Constrained RMPC algorithms for time delay systems with parametric uncertainties: Application to the cancer combined therapy

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Abstract— **In this paper, a new MPC formulation for systems with known delayed states and a new iterative algorithm of robust model predictive control (RMPC) subject to polytopic-type parameter uncertainties and input constraints is presented. Control of delayed systems with parameter uncertainties is usually more complicated in presence of input constraints. MPC is an appropriate approach to handle this type of problems. Unlike existing MPC techniques, the main advantage of the proposed MPC algorithms is that they are simple to construct and therefore can be simply implemented in real applications. Combined chemotherapy and anti-angiogenic treatment is a novel medical approach used for cancer treatment in recent years. The paper shows the performance of proposed algorithms for tumor volume reduction in combined therapy subject to the necessary constraints on drugs dosage. In order to be more realistic, we consider model with delays in states that describe the process of angiogenesis- the growth of new blood vessels by budding from pre-existing vessels - and uncertainty in parameters. Finally, the simulation results illustrate the performance of the proposed algorithms.**

Keywords; Model predictive control (MPC), Delays, Polytopic uncertainties, cancer combined therapy

I. INTRODUCTION

In practice, many of dynamic systems have time delays. Delay phenomena have been recognized in biological systems for the first time. Then, they have been found in many engineering systems such as communication networks, chemical process, mechanical systems and etc. Also, there are many factors that can create uncertainties in the dynamic model parameters. Such factors are different clinical situations, measurement errors and the approximations made because of estimation of unavailable state variables. These unavoidable uncertainties and delays in systems motivate researchers to design a robust controller in order to achieve more realistic results. Therefore, in recent years many control researches have studied delayed systems with uncertainties [1-3]. Among existing control techniques, MPC is an appropriate and popular tool for controlling systems with time delays, uncertainties and constraints. The robust model predictive control methods have

been the subject of many researches [8-10]. One of these methods utilized in this paper is Max-Min MPC.

These time delays and uncertainties cause performance degradation and instability [4]. In [2], a novel constrained RMPC method has been designed for uncertain systems and the ability to extend the method for delayed systems has been demonstrated. In [5], a MPC algorithm for unknown delayed systems with polytopic uncertainties is achieved. They relaxed one defined optimization problem on two other optimization problems by finding an upper bound on the cost function. One of the optimization problems is solvable. Then, they improved MPC algorithm by considering relaxation procedures of the assumption and stabilizes the closed-loop system.

Kown and et al. formulated an optimal problem for state delayed systems into an optimal problem for delay free ordinary systems by utilizing MPC technique. However, this method couldn't guarantee the stability [6].

In [3] by utilizing MPC optimization and Lyapunov stability theory combined with linear matrix inequalities (LMIs) techniques, a novel method was introduced for multiple uncertain time-delayed linear uncertain systems and input constraint.

In this paper we propose a new state-space formulation of MPC for systems with known and multiple state-delays. This method can be applied to a wide class of time-varying delay systems. The success of MPC depends on the model accuracy while in reality; the modeling process exerts some inherent uncertainties to the model. Also this study presents a new iterative algorithm for solving the Max-Min optimization problem for systems with polytopic parameter uncertainties. These methods can be applied for a wide class of time delay systems. Compared with other works in the literature, we illustrate a simple but reasonably and applicable MPC algorithm for multiple time delays and uncertain systems.

The focus of this research is on cancer combined chemotherapy and anti-angiogenic treatment. To design the realistic controller, the model parameters are supposed with delays and 10 and 20 percent uncertainties. The effect of

proposed algorithm is investigated over the determining drugs dosages and tumor volume reduction.

The rest of the paper is organized as follows. Section 2, states target systems and assumptions. Describing the formulation of MPC for delayed systems and introduces a novel iterative algorithm Min-Max MPC in section 3. In section 4, simulations illustrate the achieved results and the efficiency of theses methods for combined anti-angiogenic and chemotherapy. Finally, conclusions are given in section 5.

II. PROBLEM FORMULATIOM

Let us consider the following discrete-time system with a delayed state and polytopic parameter uncertainties:

$$x(k+1) = A(k)x(k) + \sum_{\tau=1}^{m} A_{d\tau}(k)x(k-d_\tau)$$

$$+B(k)u(k)$$

$$x(0) = \varphi(l), \ l \in [-d_m, 0] \tag{1}$$

Subject to constraints on control input:

$$u_{min} \leq u(k) \leq u_{max} \tag{2}$$

where $\varphi(l)$ is initial conditions of system and $d\tau > 0$ ($\tau = 1, \ldots$, m) denotes the various delays in system, with $d_1 < d_2 < \ldots < d_m$.

Where the matrices $\left[A(k), \underbrace{A_{d1}(k)\ldots A_{dm}(k)}_{A_\tau(k)}, B(k) \right]$ are

unknown but contained in a polytope Ω at all times k. That is:

$$[A(k), A_\tau(k), B(k)] \in \Omega$$
$$= Co\{[A_1(k), A_{\tau1}(k), B_1(k)], [A_2(k), A_{\tau2}(k), B_2(k)],$$
$$\ldots, [A_L(k), A_{\tau L}(k), B_L(k)]\} \tag{3}$$

Co denotes the convex hull and $\left[A_j(k), A_{\tau j}(k), B_j(k) \right]$, $j = 1:L$ are vertices of the convex hull.

In the following, an objective function is defined constituting the difference between the predicted and the desired output as well as the control effort. The MPC control signal is obtained by the following min–max problem, which is considered at each time k:

$$\min_{u(k+i)\epsilon U, i\geq 0} \max_{[A(k+i) \ A_\tau(k+i) \ B(k+i)]\in\Omega} J(k)$$

Subject to:

$$J(k) \triangleq \sum_{i=0}^{N_p} \left(y(k+i|k) - y_d \right)^T W_{ii} \left(y(k+i|k) - y_d \right)$$

$$+u^T(k+i|k)Q_{ii}u(k+i|k)$$

$$x(k+1+i|k) = A(k)x(k+i|k)$$

$$+\sum_{\tau=1}^{m} A_{d\tau}(k)x(k-d_\tau+i|k) + B(k)u(k+i|k)$$

$$u_{min} \leq u(k+i|k) \leq u_{max} \tag{4}$$

Where W_{ii} and Q_{ii} are strictly positive definite symmetric weighting matrices. N_P denotes the length of the prediction horizon.

In the proceeding sections a method for solving time delayed systems with parameter uncertainty is introduced. Our case study for proposed method is optimal dosing of drugs for cancer combined therapy.

III. PROPOSED METHOD

A. Nonlinear Model predictive control

In MPC, we use system model to minimize an objective function in order to obtain control signal. The following steps, determines the control signal in each iteration:

1. Discretizing continuous time state space.

2. Linearizing model around operating point and design the MPC controller for the linear system.

3. Apply control signal to nonlinear system.

4. At the next sampling time, go to first step.

Note that the problem is now in the quadratic form which cannot be solved analytically in the presence of constraints on the input. So, we used quadratic programming (QP) algorithm to find the optimal solution.

B. New state-space formulation of MPC for delayed systems:

In this section, we introduce new state-space formulation of model predictive control for model with multiple delays in states.

Consider the following system:

$$x(k+1) = f\left(x(k), x(k-1), \ldots, x(k-m), u(k)\right) \tag{5}$$

The system is linearized according to the different delayed state as follows:

$$x(k+1) = A_1(k)x(k) + A_2(k)x(k-1) + \ldots$$
$$A_m(k)x(k-m) + B(k)u(k) \tag{6}$$

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Based on the state-space model the future states are predicted for Np (prediction horizon) number of samples as follow:

$$for \quad i = 0 \Rightarrow x(k+1|k) = A_1(k)x(k) +$$

$$A_2(k)x(k-1) + A_3 x(k)(k-2) + \ldots$$

$$+ A_{m+1}(k)x(k-m) + B(k)u(k)$$

$$x(k+1|k) = [\underbrace{A_1(k) \quad A_2(k) \quad \ldots \quad A_{m+1}}_{\bar{A}_1}(k)] \underbrace{\begin{bmatrix} x(k) \\ x(k-1) \\ \vdots \\ x(k-m) \end{bmatrix}}_{X_0}$$

$$\underbrace{+ B(k)u(k)}_{\bar{B}_1},$$

$$x(k+2|k) =$$

$$\underbrace{\left[A_1(k)^2 + A_2(k) \quad A_1(k)A_2(k) + A_3(k) \quad \ldots \quad A_1(k)A_{m+1}(k) \right]}_{\bar{A}_2} X_0$$

$$+ \underbrace{[A_1(k)B(k) \quad B(k)]}_{\bar{B}_2} \begin{bmatrix} u(k) \\ u(k+1|k) \end{bmatrix} \qquad (7)$$

$\bar{A}_2$ and $\bar{B}_2$ can be written as follows:

$$\bar{A}_2 = A_1(k)\bar{A}_1 + [A_2(k) \quad A_3(k) \quad \ldots \quad A_{m+1}(k)]$$

$$\bar{B}_2 = A_1(k)[\bar{B}_1 \quad 0] + [0 \quad B(k)] \qquad (8)$$

If we continue sequentially, for $x(k+N_p|k)$ we have:

$$x(k+N_p|k) = \bar{A}_{N_p} X_0 + \bar{B}_{N_p} \underbrace{\begin{bmatrix} u(k) \\ u(k+1|k) \\ \vdots \\ u(k+N_p-1|k) \end{bmatrix}}_{U} \qquad (9)$$

$\bar{A}_{N_p}$ and $\bar{B}_{N_p}$ are calculated as following:

$$\bar{A}_{N_p} = A_1(k)\bar{A}_{N_p-1} + A_2(k)\bar{A}_{N_p-2} + \ldots + A_{N_p-1}(k)\bar{A}_1$$

$$+ \left[A_{m+1}(k) \quad 0 \quad \ldots \quad 0 \quad 0 \quad 0 \right]_{n \times n^{(m+1)}}$$

$$\bar{B}_{Np} = A_1(k)\left[\bar{B}_1 \quad 0 \quad \ldots \quad 0 \right]_{n \times n} + A_1(k)\left[0 \quad \bar{B}_2 \quad \ldots \quad 0 \right]_{n \times n}$$

$$+ \ldots + \left[0 \quad 0 \quad \ldots \quad B(k) \right]_{n \times n}$$

Thus, the system output will be as follows:

$$\rightarrow y = \underbrace{\begin{bmatrix} C(k)\bar{A}_1 X_0 \\ \vdots \\ C(k)\bar{A}_{N_p} X_0 \end{bmatrix}}_{y_0} + \begin{bmatrix} C(k)B(k)u(k) \\ \vdots \\ C(k)\sum_{i=1}^{N_p} A_1(k)^{j-i} B(k)u(k+i-1|k) \end{bmatrix}$$

hence, we have:

$$y = y_0 + GU$$

$$G = \begin{bmatrix} CB & 0 & 0 & 0 & \cdots & 0 \\ CA_1 B & CB & 0 & 0 & \ldots & 0 \\ CA_1^2 B & CA_1 B & CB & 0 & \ldots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ CA_1^{N_p-1}B & CA_1^{N_p-2}B & CA_1^{N_p-3}B & CA_1^{N_p-4}B & \ldots & CB \end{bmatrix}$$

$$(10)$$

where $C = C(k)$, $B = B(k)$ and $A_1 = A_1(k)$. Then, to solve steady space MPC problem, we consider the obtained equation (10) for output y, in the cost function (4).

C. Iterative Min-Max MPC algorithm

The RMPC control problem is generally formulated as the Min-Max problem to be able to handle the worst case scenario. This is done through solving the following optimization problem:

$$\min_{u \in U} \max_{\theta \in \Omega} J(u, \theta) \qquad (11)$$

The function to be minimized is actually the maximum value of an error norm representing how well the reference trajectories are tracked by the output. In the following, a new iterative scheme is suggested to design a robust NMPC (Min-Max MPC) for a class of nonlinear multivariable systems with linear parametric uncertainties.

Remark 1: If a function is convex and is defined over a convex set, then its maximum will occur on one of the corner points of this space. Since the proposed cost function $J(u,\theta)$ is convex with respect to u and proved to be convex in θ as well, then to solve the problem, it only remains to evaluate the cost function in the corner points of the uncertainty set.

Briefly, the algorithm is defined in the following:

1. At time k, find u_k by solving the following optimization problem with random uncertainty $\theta^* \triangleq \theta_{old}$ and set flag =1.

$$u_k = \min_{u \in U} J(u, \theta_{old}), \quad \theta_{old} \in \Omega \qquad (12)$$

2. To be sure the calculated control signal is for the maximum value of $J(u(k), \theta)$, the corner point in which cost function takes its maximum value is found and named θ_{new}. Hence :

$$\theta_{new} = \arg \max_{\theta \epsilon \Omega} J(u_K, \theta) \qquad (13)$$

If $\theta_{old} = \theta_{new}$ then finish algorithm. Otherwise go to step 1 and set $\theta_{old} = \theta_{new}$ and set flag=flag+1.

3. At the next sample time, set flag =1and repeat these steps.

The iterative Min-Max MPC algorithm is summarized in a Flow chart that is shown in Fig. 1.

IV. SIMULATIONS AND RESULTS

In this section, the effectiveness of the proposed MPC algorithms is shown for the cancer combined therapy with time delay and parameter uncertainties in the model.

Combined chemotherapy and anti-angiogenic treatment is a novel medical approach used to reduce the side effects of chemotherapy and increase the effectiveness of the treatment.

In the model presented by Ledzewicz the effects of angiogenesis on tumor size (N) and the vascular carrying capacity or endothelial cells volume (K) are chosen as model variables and described using a second order dynamic model. This model was validated using medical data in Harvard University medical school [10].

Most biological populations need some time to detect changes and adapt to them. So we focus on the developed model by d'Onofrio and Gandolfi in [11]   with two discrete delays as follows:

$$\dot{N}(t) = \beta N(t) ln(K(t-\tau_1) / N(t-\tau_1)) - \psi(\frac{K(t)}{N(t)}) N(t) v(t)$$

$$\dot{K}(t) = K(t) \left[\gamma \left(\frac{N(t-\tau_2)}{K(t-\tau_2)} \right) - \lambda N^{2/3}(t) - \mu - \eta u(t) - \xi v(t) \right]$$

$$(14)$$

The discrete delays τ1 and τ2 represent the time lags in processes of tumor growth and vessels formation, respectively. Both delays represent the time lags process of tumor angiogenesis.

Where u and v are the anti-angiogenic inhibitor and chemotherapy agent dosage, β is the tumor growth rate, γ and λ are angiogenesis stimulation and inhibition parameters respectively, μ is the normal endothelial cells death rate and η and ζ are constants describing the lethality of anti-angiogenic and chemotherapy drugs for endothelial cells.

In this model, the effect of vascular pruning using anti-angiogenic agents and the effect of vascular density $\left(\frac{K(t)}{N(t)} \right)$ on the effectiveness of chemotherapy drugs is described as:

$$\psi(\frac{K(t)}{N(t)}) = \frac{\bar{\gamma} N(t)}{1 + \left(\frac{K(t)/N(t) - \rho_m}{\sigma} \right)^2} \qquad (15)$$
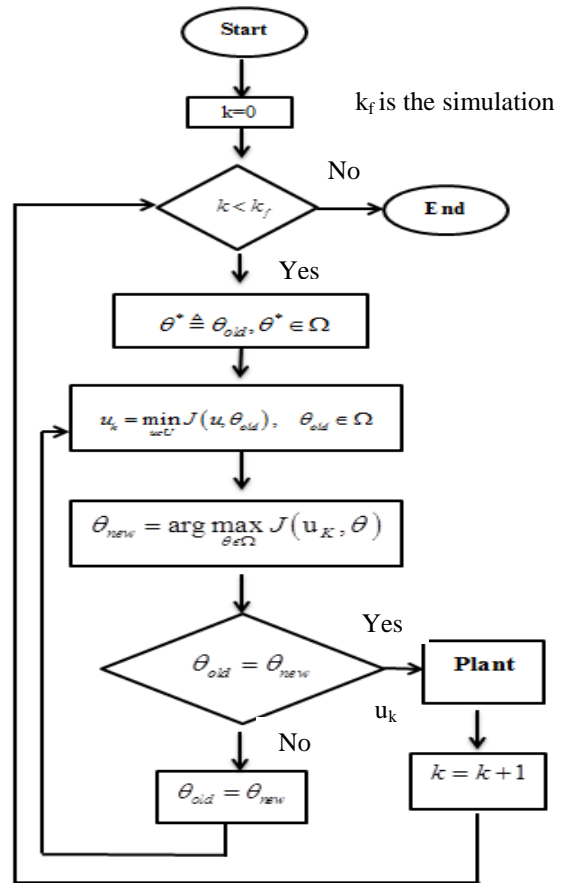

k_f is the simulation time

Figure 1.   Iterative Min-Max MPC algorithm

where, $\psi(\frac{K(t)}{N(t)})$ is the constant describing the cytostatic killing parameter for cancer cells. The parameter values and constraints value used in the simulations which are the same as those of [10] are shown in Table 1. The initial conditions used in the simulations (N_0 =12000, K_0 =15000). Based on this analysis in [11], the maximal values of τ1 and τ2 could not be

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greater than 0.2685 day and 0.2565 day, respectively. Fig.2 shows the dynamic of tumor growth and endothelial cells volume in the presence of delay without any treatment.

In all the simulations, the system model is discretized with a small sampling time (t=0.001). Period of treatment is fixed to 15 days. In all cases, the chemotherapy control v is found to be in its full dose from the beginning of the treatment period. Also in all simulations, we consider constraints on the control signal variation rates which result in the prevention of the chattering phenomena and rendering the results clinically reasonable.
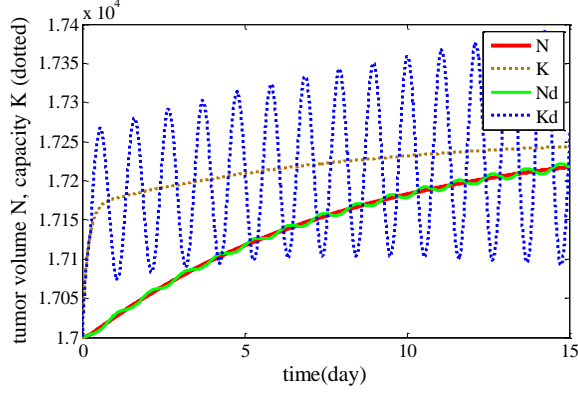

Figure 2. Behavior the systems in absence of therapy:tumor volume (N) and capacitya(K) the dynamic of system ,(Nd)and(Kd) the dynamic of delayed system.

TABLE I. PARAMETERS USED IN SIMULATION [10]

Symbol	Units	Value
β	day^{-1}	0.192
γ	day^{-1}	5.85
λ	day^{-1}	0.00873
μ	day^{-1}	0.02
η	kg mg^{-1}	0.15
ξ	kg mg^{-1}	0.26
ψ	kg mg^{-1}	$\bar{\gamma}$ =0.3, ρ_m =2, σ=0.35
u_{max}	$\left[\frac{mg\ of\ dose}{kg}\right]$	75
v_{max}	$\left[\frac{mg\ of\ dose}{kg}\right]$	2

The nonlinear time-delay system (14) was linearized at each sampling time and A, $A_{\tau 1}$, $A_{\tau 2}$ are obtained. Fig.3 show the application of MPC control method is capable of effective reduction of the tumor volume and endothelial cells volume whilst observing states delayed in model and the

constraints on maximally allowable drugs dosage. It is seen from Fig.3 that the proposed delay-dependent MPC method outperforms the MPC designed on the systems without delays. Fig. 4 shows that the control effort for the delayed system is less than the system without delays. Biological system models are not typically very accurate which makes estimating their parameters from gathered data a complex and difficult process. Hence, a robust control strategy becomes essential
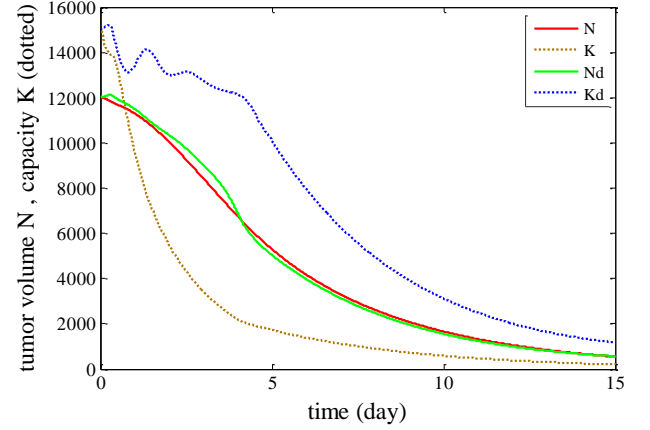

Figure 3. tumor volume and capacity during combined therapy process (N,K) MPC designed without consideration of delay, (Nd, Kd) Proposed delay-MPC method.
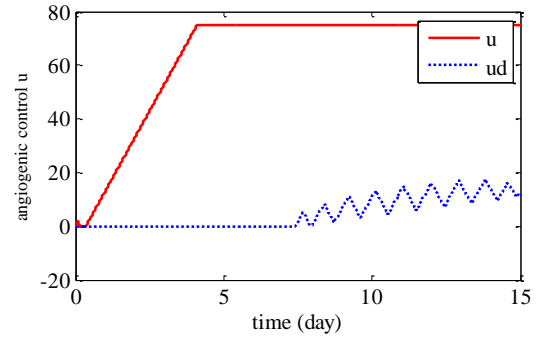

Figure 4. The optimal controls u (anti-angiogenic agnt) during cancer combined therapy process .(u) MPC designed without consideration of delay, (ud) Proposed delay-MPC method.

.To clarify the robustness of the proposed Iterative Min-Max algorithm, the model parameters β, μ, γ, η, ξ, λ, σ, $\bar{\gamma}$ are considered to have 10 and 20 percent uncertainties which are added to their nominal values as:

$$(1-\chi)\bar{r}_i < r_i < (1-\chi)\bar{r}_i \quad , \; \chi = 0.1, 0.2 \qquad (16)$$

where r_i is any of the above parameter the proposed methods are ability to reduce the tumor size even in the presence of uncertainties and state delays but as the uncertainties become more prominent, the tumor size reduction becomes less significant, Figs (5- 7) shows results of robust MPC in presence of delays in the system (14) that contain reduction tumor value, capacity and antigenic control respectively.

V. Conclusion

This paper presented a new state space formulation of MPC for systems with multiple known delayed states. The simulation result illustrate the proposed MPC algorithm is superior to the
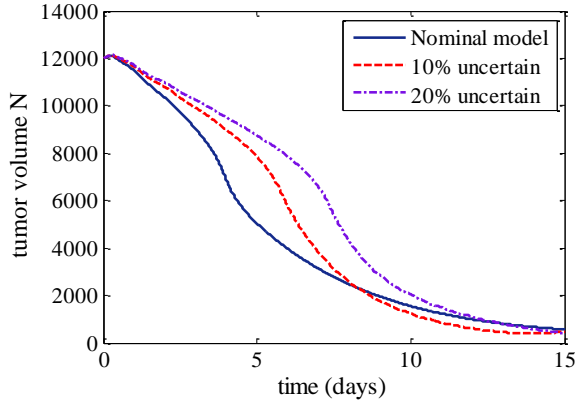

Figure 5. tumor volume during combined therapy process with nominal plant (blue solid line) and uncertain plants with 10% (red dashed line), 20% (violet dashed– dot line) in the presence of delays in model.
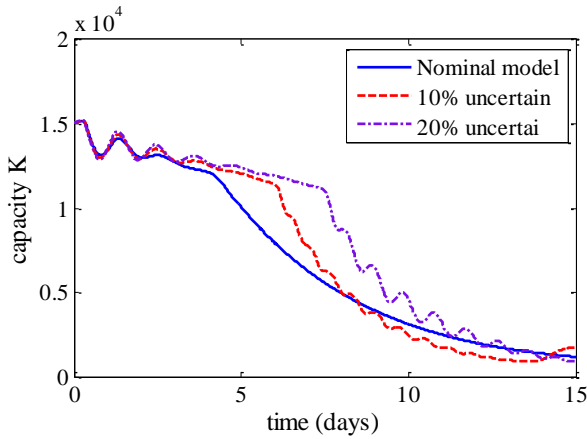

Figure 6. The endothelial cells volume, during combined therapy process with nominal plant (blue solid line) and uncertain plants with 10% (red dashed line), 20% (violet dashed– dot line) in the presence of delays in model.

MPC algorithm without considering state-delay. Then new iterative algorithm of robust model predictive control (RMPC) is presented for systems with polytopic-type parameter uncertainties and input constraints. Comparing with a previous delay-dependent MPC and Min-Max methods, the main advantage of our method is that they are simple to construct and therefore can be simply implemented in real applications. At the end, benefits of proposed algorithms are illustrated on cancer combined chemotherapy and anti-angiogenic treatment. To obtain more realistic results, we consider uncertainties for model parameters and also in spite of uncertainty and delays, we observed tumor reduction. The results of this paper can be extended for systems with both state- and input- time varying delays.
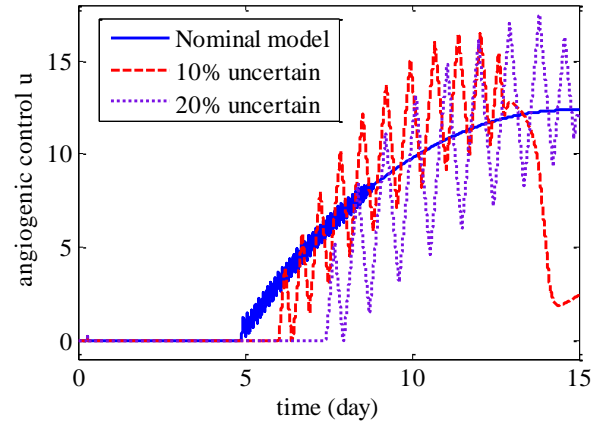

Figure 7. The optimal controls u (anti-angiogenic agnt) during cancer combined therapy process with nominal plant (blue solid line) and uncertain plants with 10% (red dashed line), 20% (violet dashed– dot line) in the presence of delays in model.

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