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Adaptive robust control of cancer chemotherapy in the presence of parametric uncertainties: A comparison between three hypotheses

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ABSTRACT

In this paper, an adaptive robust control strategy is developed for the manipulation of drug usage and consequently the tumor volume in cancer chemotherapy. Three nonlinear mathematical cell-kill models including log-kill hypothesis, Norton–Simon hypothesis and E_{max} hypothesis are considered in the presence of uncertainties. The Lyapunov stability theorem is used to investigate the global stability and tracking convergence of the process response. For the first time, performance of the uncertain process is investigated and compared for three nonlinear models. In addition, the effects of treatment period, initial value of tumor volume (carrying capacity) and the uncertainty amount on dynamic system behaviour are studied. Through a comprehensive evaluation, results are presented and compared for three cell-kill models. According to the results, for a wide range of model uncertainties, the adaptive controller guarantees the robust performance. However, for a given treatment period, more variation in drug usage is required as the amount of model uncertainty increases. Moreover, for both the nominal and uncertain models, less drug usage is required as the treatment period increases.

1. Introduction

During the drug delivery process in chemotherapy, normal healthy cells may be killed in addition to the cancer cells [1,2]. Some control strategies have been proposed for the effective killing of cancer cells and minimizing the negative aspects of drugs on healthy cells. For this purpose, drugs delivery must be regularly scheduled to maintain a specific level of the drug dosage in the body. Therefore, understanding the effects of chemotherapeutic drugs on tumors behaviour is important in development of efficient treatment strategies.

Several models have been presented for the killing of cancer tumor cells in chemotherapy process. In log-kill hypothesis as an early model, it was shown that cell killing (using the chemotherapeutic drug) is proportional to the tumor population [3]. Thus, it is shown in this hypothesis that the volume of larger tumors is reduced more rapidly than smaller tumors for a fixed dose of drug [3]. After that, in some clinical observations, the predictions of log-kill hypothesis fail in some cases such as Hodgkin's disease and acute lymphoblast leukemia (in these cases, larger tumors reduce slower than the similar smaller tumors) [4–6]. Consequently, Norton Simon hypothesis was proposed [4,5], in which the cell-kill was considered to be proportional to the tumor growth rate. Finally, in E_{max} hypothesis, the cell-kill rate was assumed to be proportional to a saturable function of tumor mass [7]. This hypothesis is obtained from the fact that chemotherapy drugs must be metabolized by an enzyme before their activation. However, this metabolism is saturable because the amount of enzyme is fixed in the body.

For the above-mentioned hypotheses, open loop unconstrained and constrained control methods have been proposed [6,8–11]. As a constrained drug delivery control, bang-bang control strategy has been used for the nonlinear models. The application of feedback control with a quadratic performance criterion for the mathematical models of cancer chemotherapy has been studied in the early works [8,9]. In other researches [10,11], considering normal and tumor cells under the hypotheses of Gompertzian and logistic growth, the rate of drugs administration was controlled.

Another open-loop control strategy utilized for chemotherapy process is the control parameterization technique. In this method, optimal control problem is transformed into a numerical problem and the control variables are approximated with the constant values in specified time intervals [12,13]. Using this optimal control strategy, the dosage of specific drugs (e.g., paclitaxel) has been determined for the reduction of breast and ovarian cancers [14]. Moreover, it is concluded that treating with repeated shorter periods allows more drug to be given without excess damage to the bone marrow [14,15].

Mathematical details of optimal control techniques and their therapeutic performances in different cell-kill hypothesis including

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treatment schedules have been studied in other researches, e.g., [6]. Moreover, some other approaches have also been investigated, such as: optimal singular control in chemotherapy [16,17], the influence of fixed and free final time of treatment on optimal chemotherapeutic protocols [18], optimal control for a stochastic model of cancer chemotherapy [19], optimal control for the tumor model with immune resistance and drug therapy [20], a comparison between linear and quadratic controls [21] and a comparison between optimal control for different models [22]. In some other researches, model simulation and experimental validation of intratumoral chemotherapy using multiple polymer implants [23], sensor-based cell and tissue screening for personalized cancer chemotherapy [24] have been accomplished. A multi-objective optimal chemotherapy control model for cancer treatment [25] has also been proposed.

It should be noted that chemotherapy processes similar to other dynamic systems are potentially accompanied with various sources of uncertainty. The dynamic model inaccuracies are in the form of structured and unstructured uncertainties; described through parametric or model (non-parametric) uncertainties, respectively. These uncertainties are due to either sensor fusion systems (direct measurement) or observers algorithms (indirect measurement). As a result, previous control strategies may not guarantee a robust performance in the presence of uncertainties and for a wide range of operating conditions, e.g., [8–14,16–22].

In a recent study [26], for achieving the robust performance against uncertainties, three control approaches including optimal linear regulation, nonlinear optimal control based on variation of extremals and H_∞-robust control were developed. It was shown that H_∞ controller has the most efficient performance for the uncertain plants; however its conceptual design is rather complex. For some previous linear controllers, e.g., [8–14,16–22] and two other linear controllers recently proposed in [26] (H_∞-robust and optimal linear regulation), the nonlinear model should be linearized around its operating points. Therefore, choosing these operating points affects the performance of the controller, and the controller has desired performance only in the areas close to these operating points.

In this research, a nonlinear adaptive control strategy is developed for the chemotherapy process described through log-kill hypothesis, $E_{\max}$ hypothesis and Norton–Simon hypothesis. The nonlinear adaptive controllers are designed based on Lyapunov stability theorem which guarantees the global stability and tracking convergence of the problem. Unlike the linear controllers in [8–14,16–22,26] that require the linearization around the operating points, the proposed nonlinear controller does not require linearization and its performance is not related to some operating points or areas. As a result, the nonlinear controller could achieve to its goal with the desired performance independent from the points (or states) during the process.

Moreover, unlike the previous works, parametric uncertainties associated with the dynamic models are also included. It should be mentioned that the linear controllers [8–14,16–22,26] are affected from the parameters of the original nonlinear model and their uncertainties especially in linearization procedure. However, for the proposed nonlinear adaptive controller, the nonlinear model parameters are considered to be completely uncertain and their magnitudes do not affect the controller design. The amount of tumor volume is manipulated by adaptive variation of drug usage. For the first time, performance of the uncertain process is investigated and compared for three nonlinear models (with an adaptive controller). In addition, the effects of treatment period, initial value of tumor volume (carrying capacity) and the uncertainty amount on dynamic system behaviour are studied. Results are presented and compared for three cell-kill models.

2. Cell-kill models in cancer chemotherapy process

As it is mentioned, several approaches have been developed for modeling the process of tumor cells killing; which is also called chemotherapeutic induced cell-kill. In an early work by Schabel, Skipper and Wilcox, it was hypothesized that cell-kill due to a chemotherapeutic drug was proportional to the tumor population [3]. This hypothesis was obtained based on in-vitro studies in the murine leukemia cell-line L1210. According to this hypothesis, a specified dose of drug kills a constant fraction of the cells independently from the tumor size. Moreover, there is a relationship between the drug dosage and the percentage of the killed leukemia cells. Consequently, large tumors are diminished more rapidly than smaller tumors with a specific dosage of drug. This proposed hypothesis is called as the log-kill mechanism in the literature. This model is valid for experimental leukemia because the growth dynamics of the cancer is constant during the course of observation. However, it failed when applied to the experimental solid tumors of human in which tumor size approached a plateau level (in which tumor dynamics is approximated by Gompertzian growth curves) [27,28].

After that, Norton and Simon [4,5] found that the log-kill model contradicts some clinical observations, such as acute lymphoblastic leukemia and Hodgkin's disease. In these cases, reduction in small tumors was histologically faster than in similar larger tumors. Consequently, Norton and Simon hypothesized that the cell-kill is proportional to the growth rate of the tumor (e.g., as an exponential, logistic, or Gompertzian functions). In a recent work, a simple realistic biophysical model of tumor growth in the presence of a constant continuous chemotherapy is studied, and it was shown that if an extended Norton–Simon hypothesis holds, the system may have multiple equilibria [29]. Therefore, the tumor carrying capacity and/or the drug pharmacodynamics (and/or the drug pharmacokinetics) are affected by the bounded stochastic fluctuations which cause the transition from a small equilibrium to a far larger one, not compatible with the life of the host. Finally, in another hypothesis, it was mentioned that some chemotherapeutic drugs must be metabolized by an enzyme before being activated. Due to the fixed amount of enzyme, this reaction is saturable. Accordingly, Holford and Sheiner [7] proposed $E_{\max}$ hypothesis in which the cell-kill is described in terms of a saturable function of Michaelis–Menton form. The concentration effects of drugs is essentially considered and discussed in $E_{\max}$ model. This model introduces theoretical support from the physicochemical principles (by inclusion the law of mass action); governing the binding of drug to the receptor [30].

In this section, Skipper's log-kill hypothesis (called Model 1), $E_{\max}$ hypothesis (called Model 2) and Norton–Simon hypothesis (called Model 3) are considered. General dynamics of these systems is presented through differential equations as [3–6]:

$$\frac{dx}{dt} = rxF(x) - G(x,t) \tag{1}$$

where x is the tumor volume, r is the tumor growth rate, $F(x)$ is the generalized growth function and $G(x,t)$ describes the pharmacokinetic and pharmacodynamic effects of the drug. While the tumor burden and toxicity level are defined as the time-integral of the drug concentration, the Growth function (Gompertzian) is expressed as:

$$F(x) = \ln\left(\frac{\Theta}{x}\right) \tag{2}$$

where Θ is the constant of scaling. For the mentioned hypotheses, $G(x,t)$ is described as:

$$\text{For log} - \text{kill hypothesis (Model 1)} : G(x,t) = \delta\left(\frac{x}{\Theta}\right) u(t) \qquad (3-1)$$

For $E_{\max}$ hypothesis (Model 2) : $G(x,t)=\dfrac{\delta x\, u(t)}{x+\lambda}$ (3 – 2)

For Norton – Simon hypothesis (Model 3) : $G(x,t)=\delta\, F(x)\, u(t)$ (3 – 3)

where λ and δ are constant coefficients of the model and $u(t)$ is the chemotherapy drug concentration (density); e.g., in the plasma compartment. $u(t)=0$ means the absence of drug effect and $u(t)>0$ denotes the amount or strength of the drug effect. It should be mentioned that for simplicity in next formulations, simulation results and discussions, 'drug usage' is used instead of 'drug concentration'. Using $\tilde{x}=x/\Theta$, $\tilde{\lambda}=\lambda/\Theta$ and $\tilde{\delta}=\delta/\Theta$ for scaling the models given by Eq. (3-1) and dropping the '$\sim$' in the quantity $\tilde{\chi}$, $\chi=x,\ \lambda,\ \delta$; the following differential equations are obtained [6]:

(Model 1) $\dfrac{dx}{dt}=-rx\ln(x)-\delta\, x\, u(t)$ (4 – 1)

(Model 2) $\dfrac{dx}{dt}=-rx\ln(x)-\dfrac{\delta\, x}{\lambda+x}u(t)$ (4 – 2)

(Model 3) $\dfrac{dx}{dt}=-\ln(x)\,[rx-\delta\, u(t)]$ (4 – 3)

with the initial condition of $x(0)=x_0$; where the tumor volume is normalized by using the mentioned change of variables as $0<x_0<1$.

3. Development of adaptive control strategy for cell-kill hypotheses

In this section, the adaptive control strategy is developed for proposed cell-kill hypotheses in cancer chemotherapy process. The goal of adaptive control strategy is tracking the desired volume of the cancer tumor (defined by the chemotherapy physician), while the cell-kill models are associated with uncertainties. The feedback signal used in these controllers is the volume of tumor. Using the Lyapunov theorem, the stability of closed-loop control systems (for all three models) and the convergence of tumor volume reduction to the desired value (x_d) are presented. Moreover, it is shown that using the adaptation law for updating the estimated parameters of the system, the estimation error of model parameters is remained bounded. A schematic of the cancer chemotherapy process using proposed nonlinear adaptive controllers for drug delivery of different tumor models is shown in Fig. 1.

3.1. Adaptive control design in log-kill hypothesis

Dynamics of the log-kill hypothesis (Model 1, Eq. (4-1)), can be rewritten as:

(Model 1) $-\dfrac{1}{\delta}\dfrac{\dot{x}}{x}-\dfrac{r}{\delta}\ln(x)=u(t)$ (5)

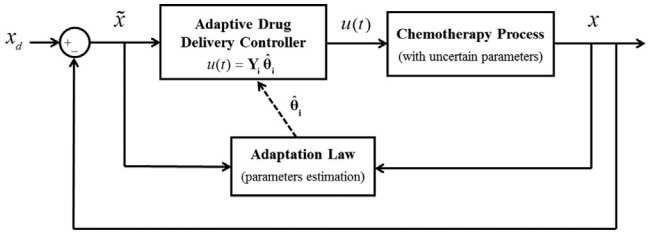

Fig. 1. Nonlinear adaptive control of drug delivery in cancer chemotherapy process for cell-kill models with parametric uncertainty.

Property. The left-hand side of Eq. (5), by considering an arbitrary variable ϕ instead of $\dot{x}$, is linearly parameterized in terms of the system parameters as [31]:

$$-\frac{1}{\delta}\frac{\phi}{x}-\frac{r}{\delta}\ln(x)=\mathbf{Y_1}(\phi,\ x)\,\boldsymbol{\theta_1} \tag{6}$$

The regressor matrix $\mathbf{Y_1}$ and the vector $\boldsymbol{\theta_1}$ contain known functions and unknown parameters of the system, respectively as:

$$\mathbf{Y_1}=\left[-\frac{\phi}{x}\quad -\ln(x)\right];\boldsymbol{\theta_1}=\left[\frac{1}{\delta}\quad \frac{r}{\delta}\right]^{\mathrm{T}} \tag{7}$$

The adaptive control law is defined as:

$$u(t)=-\frac{1}{\hat{\delta}}\frac{(\dot{x}_d-\alpha\tilde{x})}{x}-\frac{\hat{r}}{\hat{\delta}}\ln(x) \tag{8}$$

The accent $\wedge$ is used for estimated values of parameters. $\hat{\delta}$ and $\hat{r}$ are estimates of the system parameters δ and r, respectively. These estimated parameters are obtained via an adaptation law, as will be presented next. $\tilde{x}=x-x_d$ is the error vector for the tumor volume with respect to the desired volume (x_d), and α is a positive constant. Using *Property*, and substituting $\phi=\dot{x}_d-\alpha\tilde{x}$ in Eq. (6), the control law (Eq. (8)) is rewritten as:

$$u(t)=\mathbf{Y_1}(\dot{x}_d-\alpha\tilde{x},\ x)\ \hat{\boldsymbol{\theta}}_1 \tag{9}$$

where $\hat{\boldsymbol{\theta}}_1$ is the vector of estimated parameters. Now, the adaptation law for updating the vector of estimated parameters is introduced as:

$$\dot{\hat{\boldsymbol{\theta}}}_1=\tilde{x}\,x\,\Gamma\,\mathbf{Y_1}^{\mathrm{T}}\mathrm{sgn}(\delta) \tag{10}$$

where Γ is a symmetric positive definite constant matrix. It will be shown in the following Lyapunov stability proof that the adaptation law by Eq. (10) provides the tracking performance in the presence of parametric uncertainties. The Lyapunov theorem [31] is used for proving the stability of the system and asymptotic tracking of the desired tumor volume (x_d) during chemotherapy. For this purpose, a Lyapunov function candidate is used as:

$$V=\frac{1}{2}\,(\tilde{x}^{\,2}+|\delta|\ \tilde{\boldsymbol{\theta}}_1^{\,\mathrm{T}}\,\Gamma^{-1}\,\tilde{\boldsymbol{\theta}}_1) \tag{11}$$

where $\tilde{\boldsymbol{\theta}}_1=\hat{\boldsymbol{\theta}}_1-\boldsymbol{\theta}_1$ is the error vector for parameters estimation. According to Eq. (11), the Lyapunov function is always positive ($V\geq 0$). The time derivative of V is obtained as:

$$\dot{V}=\tilde{x}\ (\dot{x}-\dot{x}_d)+|\delta|\ \dot{\hat{\boldsymbol{\theta}}}_1^{\,\mathrm{T}}\,\Gamma^{-1}\,\tilde{\boldsymbol{\theta}}_1 \tag{12}$$

where $\dot{\tilde{\boldsymbol{\theta}}}_1=\dot{\hat{\boldsymbol{\theta}}}_1$, because $\boldsymbol{\theta}_1$ is the vector of the constant actual parameters and therefore $\dot{\boldsymbol{\theta}}_1=0$. Substituting the dynamics of Model 1, Eq. (4-1) in Eq. (12), yields:

$$\dot{V}=-r\,\tilde{x}\,x\ln(x)-\delta\,\tilde{x}\,x\,u(t)-\tilde{x}\,\dot{x}_{desired}+|\delta|\ \dot{\hat{\boldsymbol{\theta}}}_1^{\,\mathrm{T}}\,\Gamma^{-1}\,\tilde{\boldsymbol{\theta}}_1 \tag{13}$$

Substituting the control law (given by Eq. (8)) in Eq. (13) yields:

$$\dot{V}=-r\,\tilde{x}\,x\ln(x)+\delta\frac{\hat{r}}{\hat{\delta}}\tilde{x}\,x\ln(x)+\frac{\delta}{\hat{\delta}}\tilde{x}\,\dot{x}_d-\frac{\delta}{\hat{\delta}}\alpha\,\tilde{x}^{\,2}-\tilde{x}\,\dot{x}_d+|\delta|\ \dot{\hat{\boldsymbol{\theta}}}_1^{\,\mathrm{T}}\,\Gamma^{-1}\,\tilde{\boldsymbol{\theta}}_1 \tag{14}$$

By adding and subtracting $\alpha\,\tilde{x}^{\,2}$, and arranging Eq. (14), it can be written as:

$$\dot{V}=-\alpha\,\tilde{x}^{\,2}-\delta\,\tilde{x}\,x\left[-\frac{(\dot{x}_d-\alpha\tilde{x})}{x}\quad -\ln(x)\right]\ \tilde{\boldsymbol{\theta}}_1+|\delta|\ \dot{\hat{\boldsymbol{\theta}}}_1^{\,\mathrm{T}}\,\Gamma^{-1}\,\tilde{\boldsymbol{\theta}}_1 \tag{15}$$

Substituting $\phi=\dot{x}_d-\alpha\tilde{x}$ in Eqs. (6) and (15) is modified as:

$$\dot{V}=-\alpha\,\tilde{x}^{\,2}-\delta\,\tilde{x}\,x\,\mathbf{Y_1}(\dot{x}_d-\alpha\tilde{x},\ x)\,\tilde{\boldsymbol{\theta}}_1+|\delta|\ \dot{\hat{\boldsymbol{\theta}}}_1^{\,\mathrm{T}}\,\Gamma^{-1}\,\tilde{\boldsymbol{\theta}}_1 \tag{16}$$

Then, using the adaptation law given by Eq. (10) and $\Gamma=\Gamma^{\mathrm{T}}$ in Eq. (16), the time derivative of Lyapunov function is obtained as:

$$\dot{V}=\ -\alpha\,\tilde{x}^{\,2}\ \leq 0 \tag{17}$$

According to Lyapunov stability theorem, through Eqs. (11) and (17), the proposed control method guarantees the global stability and tracking convergence ($\tilde{x}\to 0$ or $x\to x_d$ as $t\to\infty$). In other word, if the drug is consumed according to the law suggested by the controller, the actual volume of tumor (x) converges to its desired value (x_d).

Proof. The Lyapunov function V in Eq. (11) is positive definite in $\tilde{x}$ and $\tilde{\boldsymbol{\theta}}_{\mathbf{1}}$. Since $\dot{V}$ is negative definite ($\dot{V}\le 0$), V is also bounded and therefore, $\tilde{x}$ and $\tilde{\boldsymbol{\theta}}_{\mathbf{1}}$ are bounded. We know that the desired tumor volume (x_d) and its time derivative ($\dot{x}_d$) are bounded. Therefore, according to $\tilde{x}=x-x_d$, x is bounded and consequently according to system dynamics by Eq. (4-1), $\dot{x}$ is also bounded. As a result, $\dot{\tilde{x}}=\dot{x}-\dot{x}_d$ is bounded from the boundedness of $\dot{x}$ and $\dot{x}_d$. Finally, to apply Barbalat's lemma [31], the uniform continuity of $\dot{V}$ should be checked. Differentiating Eq. (17) with respect to time, yields:

$$\ddot{V}=-2\alpha\,\tilde{x}\,\dot{\tilde{x}} \tag{18}$$

This implies that $\ddot{V}$ is bounded since $\tilde{x}$ and $\dot{\tilde{x}}$ are bounded. Thus, $\dot{V}$ is uniformly continuous. Using Barbalat's lemma, it is proved that $\tilde{x}\to 0$ as $t\to\infty$ and the vector of parameters estimation error $\tilde{\boldsymbol{\theta}}_{\mathbf{1}}$ remains bounded. Using Eq. (7), the estimation error of two parameters of the model ($\tilde{\delta}$ and $\tilde{r}$) will be remained bounded. Therefore, the objective of the proposed adaptive controller (tracking convergence, $\tilde{x}\to 0$) is achieved; while, the identification of the actual parameters is not obtained (which is not a goal for the controller).

3.2. Adaptive control design in $\mathbf{E_{max}}$ hypothesis

Dynamics of the $E_{\max}$ hypothesis (Model 2, Eq. (4-2)), can be rewritten as:

$$\text{(Model 2)}\ -\frac{1}{\delta}\left(1+\frac{\lambda}{x}\right)\dot{x}-\frac{r}{\delta}(x+\lambda)\ln(x)=u(t) \tag{19}$$

Similarly, using the same ***Property*** given in previous section, the left-hand of Eq. (19) can be linearly parameterized in terms of the system parameters as:

$$-\frac{1}{\delta}\left(1+\frac{\lambda}{x}\right)\phi-\frac{r}{\delta}(x+\lambda)\ln(x)=\mathbf{Y_2}(\phi,\,x)\,\boldsymbol{\theta}_{\mathbf{2}} \tag{20}$$

where the regressor matrix $\mathbf{Y_2}$ and the vector $\boldsymbol{\theta}_{\mathbf{2}}$ contain known functions and unknown parameters of the system, respectively as:

$$\mathbf{Y_2}=\left[\begin{array}{cccc}-\phi & -\frac{\phi}{x} & -x\ln(x) & -\ln(x)\end{array}\right];\boldsymbol{\theta}_{\mathbf{2}}=\left[\begin{array}{cccc}\frac{1}{\delta} & \frac{\lambda}{\delta} & \frac{r}{\delta} & \frac{r\lambda}{\delta}\end{array}\right]^{\mathrm{T}} \tag{21}$$

The adaptive control law for Model 2 is defined as:

$$u\,(t)=-\frac{1}{\hat{\delta}}\left(1+\frac{\hat{\lambda}}{x}\right)(\dot{x}_d-\alpha\tilde{x})-\frac{\hat{r}}{\hat{\delta}}(x+\hat{\lambda})\ln(x) \tag{22}$$

while $\hat{\delta}$, $\hat{\lambda}$ and $\hat{r}$ are the estimated parameters of the system (see previous section). Substituting $\phi=\dot{x}_d-\alpha\tilde{x}$ in Eq. (20), the control law is rewritten as:

$$u\,(t)=\mathbf{Y_2}(\dot{x}_d-\alpha\tilde{x},\;x)\,\hat{\boldsymbol{\theta}}_{\mathbf{2}} \tag{23}$$

where $\hat{\boldsymbol{\theta}}_{\mathbf{2}}$ is the vector of estimated parameters. The adaptation law for updating the vector of estimated parameters is introduced as:

$$\dot{\hat{\boldsymbol{\theta}}}_{\mathbf{2}}=\tilde{x}\,x\,\Gamma\,\mathbf{Y_2}^{\mathrm{T}}\mathrm{sgn}(\delta) \tag{24}$$

In this section, the following Lyapunov function candidate is used,

$$V=\frac{1}{2}\left((x+\lambda)\,\tilde{x}^2+|\delta|\tilde{\boldsymbol{\theta}}_{\mathbf{2}}{}^{\mathrm{T}}\Gamma^{-1}\tilde{\boldsymbol{\theta}}_{\mathbf{2}}\right) \tag{25}$$

where $\tilde{\boldsymbol{\theta}}_{\mathbf{2}}=\hat{\boldsymbol{\theta}}_{\mathbf{2}}-\boldsymbol{\theta}_{\mathbf{2}}$ is the error vector for parameters estimation. According to Eq. (25), since λ is a positive constant and the tumor volume is always positive ($x\ge 0$); the Lyapunov function is always positive ($V\ge 0$). The time derivative of V is obtained as:

$$\dot{V}=(x+\lambda)\tilde{x}(\dot{x}-\dot{x}_d)+\frac{1}{2}\dot{x}\,\tilde{x}^{\,2}+|\delta|\dot{\hat{\boldsymbol{\theta}}}_{\mathbf{2}}{}^{\mathrm{T}}\Gamma^{-1}\tilde{\boldsymbol{\theta}}_{\mathbf{2}} \tag{26}$$

where $\dot{\tilde{\boldsymbol{\theta}}}_{\mathbf{2}}=\dot{\hat{\boldsymbol{\theta}}}_{\mathbf{2}}$, and $\dot{\boldsymbol{\theta}}_{\mathbf{2}}=0$ (with the same reason discussed for Model 1). It is desired to reduce the tumor volume in chemotherapy process. Therefore, the time derivative of tumor volume is negative during the treatment ($\dot{x}<0$). From Eq. (26) we have:

$$\dot{V}\le(x+\lambda)\tilde{x}(\dot{x}-\dot{x}_d)+|\delta|\dot{\hat{\boldsymbol{\theta}}}_{\mathbf{2}}{}^{\mathrm{T}}\Gamma^{-1}\tilde{\boldsymbol{\theta}}_{\mathbf{2}} \tag{27}$$

Using the dynamics of Model 2 (Eq. (4-2)) in Eq. (27), we have:

$$\dot{V}\le-r(x+\lambda)\tilde{x}\,x\ln(x)-\delta\,\tilde{x}\,x\,u(t)-(x+\lambda)\tilde{x}\dot{x}_d+|\delta|\dot{\hat{\boldsymbol{\theta}}}_{\mathbf{2}}{}^{\mathrm{T}}\Gamma^{-1}\tilde{\boldsymbol{\theta}}_{\mathbf{2}} \tag{28}$$

Substituting Eq. (22) in Eq. (28), yields:

$$\begin{aligned}\dot{V}\le&-r(x+\lambda)\,\tilde{x}\,x\ln(x)+\delta\frac{\hat{r}}{\hat{\delta}}(x+\hat{\lambda})\,\tilde{x}\,x\ln(x)+\frac{\delta}{\hat{\delta}}(x+\hat{\lambda})\,\tilde{x}\,\dot{x}_d\\&-\frac{\delta}{\hat{\delta}}(x+\hat{\lambda})\,\alpha\,\tilde{x}^2-(x+\lambda)\,\tilde{x}\,\dot{x}_d+|\delta|\dot{\hat{\boldsymbol{\theta}}}_{\mathbf{2}}{}^{\mathrm{T}}\Gamma^{-1}\tilde{\boldsymbol{\theta}}_{\mathbf{2}}\end{aligned} \tag{29}$$

Adding and subtracting $(x+\lambda)\,\alpha\,\tilde{x}^{\,2}$ to Eq. (29) and its rearrangement, yields:

$$\dot{V}\le-(x+\lambda)\alpha\,\tilde{x}^2+|\delta|\dot{\hat{\boldsymbol{\theta}}}_{\mathbf{2}}{}^{\mathrm{T}}\Gamma^{-1}\tilde{\boldsymbol{\theta}}_{\mathbf{2}}-\delta\,\tilde{x}\,x\left[\begin{array}{cccc}-\phi & -\frac{\phi}{x} & -x\ln(x) & -\ln(x)\end{array}\right]\tilde{\boldsymbol{\theta}}_{\mathbf{2}} \tag{30}$$

where, $\phi=\dot{x}_d-\alpha\tilde{x}$. Substituting Eq. (20) in Eq. (30), yields:

$$\dot{V}\le-\alpha(x+\lambda)\tilde{x}^2-\delta\,\tilde{x}\,x\,\mathbf{Y_2}(\dot{x}_d-\alpha\tilde{x},x)\tilde{\boldsymbol{\theta}}_{\mathbf{2}}+|\delta|\dot{\hat{\boldsymbol{\theta}}}_{\mathbf{2}}{}^{\mathrm{T}}\Gamma^{-1}\tilde{\boldsymbol{\theta}}_{\mathbf{2}} \tag{31}$$

Using the adaptation law given by Eq. (24) and $\Gamma=\Gamma^{\mathrm{T}}$ in Eq. (31), the time derivative of Lyapunov function is obtained as:

$$\dot{V}\le-\alpha\,(x+\lambda)\,\tilde{x}^{\,2}\le 0 \tag{32}$$

Since $\lambda>0$ and the tumor volume is positive ($x\ge 0$), then $x+\lambda>0$. Therefore, according to Lyapunov stability theorem, through Eqs. (25) and (32), proposed control method guarantee the global stability and tracking convergence.

The continue of stability proof is presented in Appendix A. As it is concluded in Appendix A, the objective of the proposed adaptive controller (tracking convergence, $\tilde{x}\to 0$) is achieved; while, the identification of the actual parameters is not obtained (which is not a goal for the controller).

3.3. Adaptive control design in Norton–Simon hypothesis

Dynamics of the Norton–Simon hypothesis (Model 3, Eq. (4-3)), can be rewritten as:

$$\text{(Model 3)}\ \frac{1}{\delta}\frac{\dot{x}}{\ln(x)}+\frac{r}{\delta}x=u(t) \tag{33}$$

Similarly, using the same ***Property*** given in Section 3.1, the left-hand of Eq. (33) can be linearly parameterized as:

$$\frac{1}{\delta}\frac{\phi}{\ln(x)}+\frac{r}{\delta}x=\mathbf{Y_3}(\phi,\,x)\,\boldsymbol{\theta}_{\mathbf{3}} \tag{34}$$

where ϕ is an arbitrary variable; the regressor matrix $\mathbf{Y_3}$ and the vector $\boldsymbol{\theta}_{\mathbf{3}}$ contain known functions and unknown parameters of the system, respectively as:

$$\mathbf{Y_3}=\left[\begin{array}{cc}\frac{\phi}{\ln(x)} & x\end{array}\right];\boldsymbol{\theta}_{\mathbf{3}}=\left[\begin{array}{cc}\frac{1}{\delta} & \frac{r}{\delta}\end{array}\right]^{\mathrm{T}} \tag{35}$$

The adaptive control law for Model 3 is defined as:

$$u(t) = \frac{1}{\hat{\delta}} \frac{(\dot{x}_d - \alpha\tilde{x})}{\ln(x)} + \frac{\hat{r}}{\hat{\delta}} x \tag{36}$$

Substituting $\phi = \dot{x}_d - \alpha\tilde{x}$ in Eq. (36), the control law is rewritten as:

$$u(t) = \mathbf{Y_3}(\dot{x}_d - \alpha\tilde{x}, x)\hat{\boldsymbol{\theta}}_\mathbf{3} \tag{37}$$

where $\hat{\boldsymbol{\theta}}_\mathbf{3}$ is the vector of estimated parameters. The adaptation law for updating the vector of estimated parameters is introduced as:

$$\dot{\hat{\boldsymbol{\theta}}}_\mathbf{3} = -\tilde{x} \ln(x) \Gamma \mathbf{Y_3}^{\mathrm{T}} \mathrm{sgn}(\delta) \tag{38}$$

In this section, the following Lyapunov function candidate is used,

$$V = \frac{1}{2}\left(\tilde{x}^2 + |\delta| \tilde{\boldsymbol{\theta}}_\mathbf{3}^{\mathrm{T}} \Gamma^{-1} \tilde{\boldsymbol{\theta}}_\mathbf{3}\right) \tag{39}$$

where $\tilde{\boldsymbol{\theta}}_\mathbf{3} = \hat{\boldsymbol{\theta}}_\mathbf{3} - \boldsymbol{\theta}_\mathbf{3}$ is the error vector for parameters estimation. According to Eq. (39), the Lyapunov function is always positive ($V \geq 0$). The time derivative of V is obtained as:

$$\dot{V} = \tilde{x}(\dot{x} - \dot{x}_d) + |\delta| \dot{\hat{\boldsymbol{\theta}}}_\mathbf{3}^{\mathrm{T}} \Gamma^{-1} \tilde{\boldsymbol{\theta}}_\mathbf{3} \tag{40}$$

where $\dot{\tilde{\boldsymbol{\theta}}}_\mathbf{3} = \dot{\hat{\boldsymbol{\theta}}}_\mathbf{3}$, and $\dot{\boldsymbol{\theta}}_\mathbf{3} = 0$ (with the same reason discussed for Model 1). Substituting the dynamics of Model 3, Eq. (4-3), into Eq. (40), results in:

$$\dot{V} = -r\tilde{x}\, x \ln(x) + \delta \tilde{x} \ln(x)\, u(t) - \tilde{x}\dot{x}_d + |\delta| \dot{\hat{\boldsymbol{\theta}}}_\mathbf{3}^{\mathrm{T}} \Gamma^{-1} \tilde{\boldsymbol{\theta}}_\mathbf{3} \tag{41}$$

Substituting the control law given by Eq. (36) into Eq. (41), yields:

$$\dot{V} = -r\tilde{x}\, x \ln(x) + \delta \frac{\hat{r}}{\hat{\delta}} \tilde{x}\, x \ln(x) + \frac{\delta}{\hat{\delta}} \tilde{x}\dot{x}_d - \frac{\delta}{\hat{\delta}} \alpha \tilde{x}^2 - \tilde{x}\dot{x}_d + |\delta| \dot{\hat{\boldsymbol{\theta}}}_\mathbf{3}^{\mathrm{T}} \Gamma^{-1} \tilde{\boldsymbol{\theta}}_\mathbf{3} \tag{42}$$

Adding and subtracting $\alpha \tilde{x}^2$ to Eq. (42) and its rearrangement, yields:

$$\dot{V} = -\alpha \tilde{x}^2 + \delta \tilde{x} \ln(x) \left[\frac{(\dot{x}_d - \alpha\tilde{x})}{\ln(x)} \quad x\right] \tilde{\boldsymbol{\theta}}_\mathbf{3} + |\delta| \dot{\hat{\boldsymbol{\theta}}}_\mathbf{3}^{\mathrm{T}} \Gamma^{-1} \tilde{\boldsymbol{\theta}}_\mathbf{3} \tag{43}$$

Substituting $\phi = \dot{x}_d - \alpha\tilde{x}$ in Eq. (34), Eq. (43) is modified as:

$$\dot{V} = -\alpha \tilde{x}^2 + \delta \tilde{x} \ln(x) \mathbf{Y_3}(\dot{x}_d - \alpha\tilde{x}, x)\tilde{\boldsymbol{\theta}}_\mathbf{3} + |\delta| \dot{\hat{\boldsymbol{\theta}}}_\mathbf{3}^{\mathrm{T}} \Gamma^{-1} \tilde{\boldsymbol{\theta}}_\mathbf{3} \tag{44}$$

Using the adaptation law given by Eq. (38) and $\Gamma = \Gamma^{\mathrm{T}}$ in Eq. (44), the time derivative of Lyapunov function is obtained as:

$$\dot{V} = -\alpha \tilde{x}^2 \leq 0 \tag{45}$$

According to Lyapunov stability theorem, through Eqs. (39) and (45), proposed control method guarantee the global stability and tracking convergence.

Proof. The Lyapunov function V is positive definite in terms of $\tilde{x}$ and $\tilde{\boldsymbol{\theta}}_\mathbf{3}$ (Eq. (39)). Since $\dot{V}$ is negative definite ($\dot{V} \leq 0$), V is also bounded and therefore, $\tilde{x}$ and $\tilde{\boldsymbol{\theta}}_\mathbf{3}$ are bounded. With a similar reasoning presented for the Model 1 in Section 3.1, the variables x, $\dot{x}$, $\tilde{x}$ and $\dot{\tilde{x}}$ are bounded. Differentiating $\dot{V}$ given by Eq. (45), with respect to time, yields:

$$\ddot{V} = -2\alpha\, \tilde{x}\, \dot{\tilde{x}} \tag{46}$$

Table 1
Nominal parameters for the log-kill hypothesis (Model 1), $E_{\max}$ hypothesis (Model 2) and Norton–Simon hypothesis (Model 3) [6].

	Model 1	Model 2	Model 3
r_i	0.1	0.1	0.1
δ_i	0.45	0.225	4
λ		0.25	

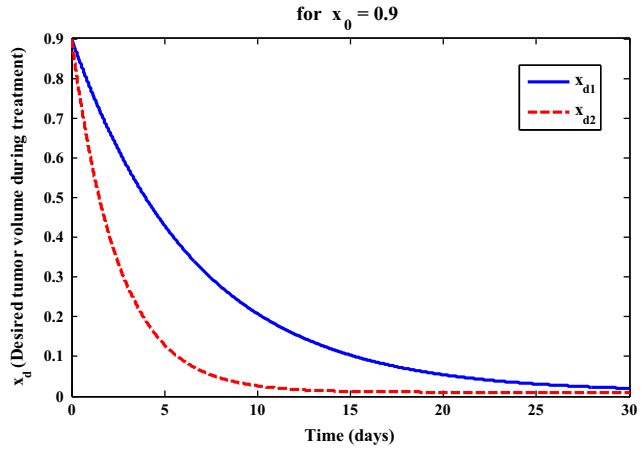

Fig. 2. Desired tumor volume during cancer chemotherapy process with 30 days, $t_{f1} = 30$ days (x_{d1}) and 15 days, $t_{f2} = 15$ days (x_{d2}) treatment period, for 90% of carrying capacity, $x_0 = 0.9$.

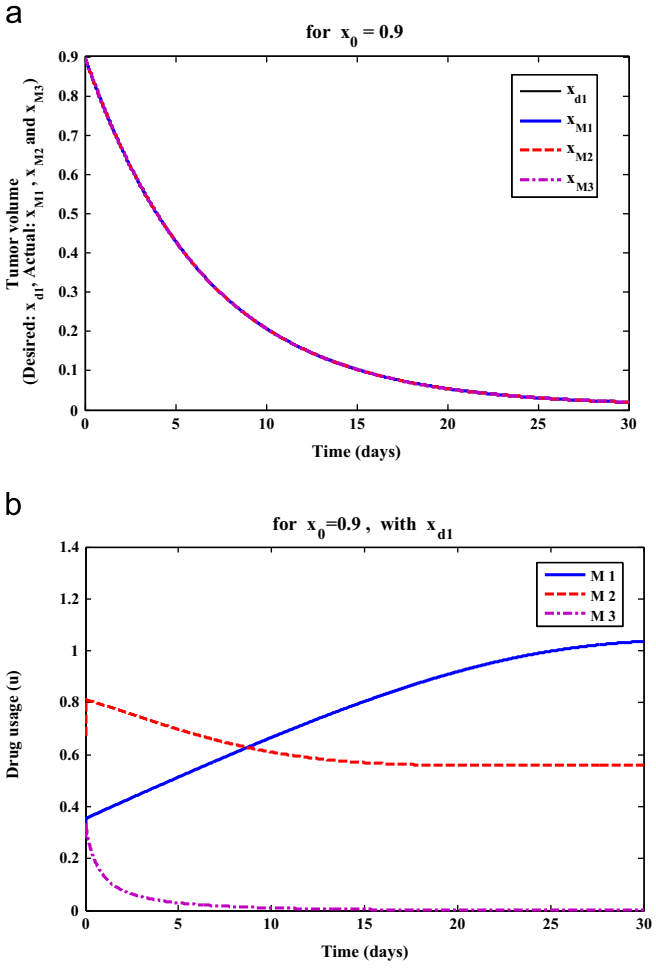

Fig. 3. Required drug usage for Model 1 (log-kill), Model 2 ($E_{\max}$) and Model3 (Norton–Simon) after implementation of the adaptive controller in tracking the desired tumor volume reduction for 30 days treatment period (x_{d1}) with 90% of carrying capacity, $x_0 = 0.9$.

This implies that $\ddot{V}$ is bounded since $\tilde{x}$ and $\dot{\tilde{x}}$ are bounded. Thus, $\dot{V}$ is uniformly continuous. Using Barbalat's lemma, it is proved that $\tilde{x} \to 0$ as $t \to \infty$ and the error vector for parameters estimation $\tilde{\boldsymbol{\theta}}_{\mathbf{3}}$ remains bounded. Using Eq. (35), the estimation error of two parameters of the model ($\tilde{\delta}$ and $\tilde{r}$) will be remained bounded. Therefore, the objective of the proposed adaptive controller (tracking convergence, $\tilde{x} \to 0$) is achieved; while, the identification of the actual parameters is not obtained (which is not a goal for the controller).

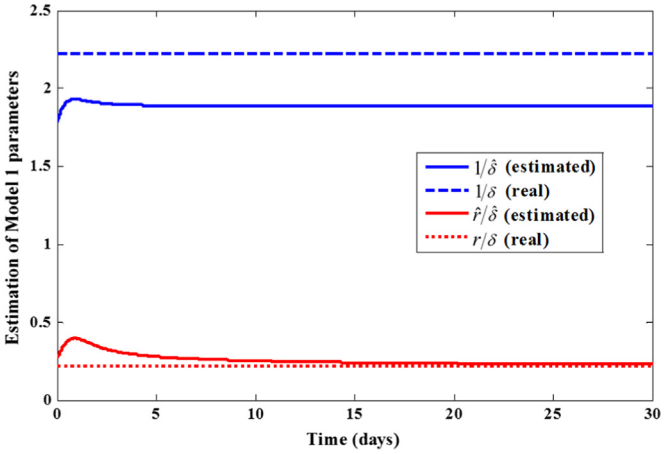

Fig. 4. Estimated and real values of parameters $1/\delta$ (upper blue solid and dashed lines) and r/δ (lower red solid and dot lines) for Model 1 (log-kill) with bounded error during the chemotherapy process using the presented adaptation law. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

4. Simulations, results and discussion on adaptive control in cell-kill hypotheses

For the problem simulation and investigation the effect of designed adaptive controllers, realistic model parameters are adopted from [6], as listed in Table 1. These parameters are scaled as non-dimensional values; obtained via experimental observations on different kinds of cancers (in which various drugs such as Taxol for the reduction of breast and ovarian cancers have been used). The adaptive control algorithms are developed in MATLAB with the procedure discussed in previous section. Tumor volume is normalized such that $0 \le x \le 1$ in all mentioned models. Results are presented for two interval times of treatment as $t_{f1} = 30$ days and $t_{f2} = 15$ days. Two desired scenarios for tumor reduction are considered as (can be prescribed by the cancer physician):

$$x_d = (x_0 - b)\ \exp(-a\,t) + b \tag{47}$$

where a is the rate of tumor reduction in cancer chemotherapy that should be adjusted by the physician and b is the desired steady state value for tumor volume (final value). x_0 and x_d are the initial and desired values of tumor volume, respectively. It should be mentioned that the exponential functions for reducing the tumor volume are considered (Eq. (47)) which is in accordance with the scenarios used in the previous optimal controls such as

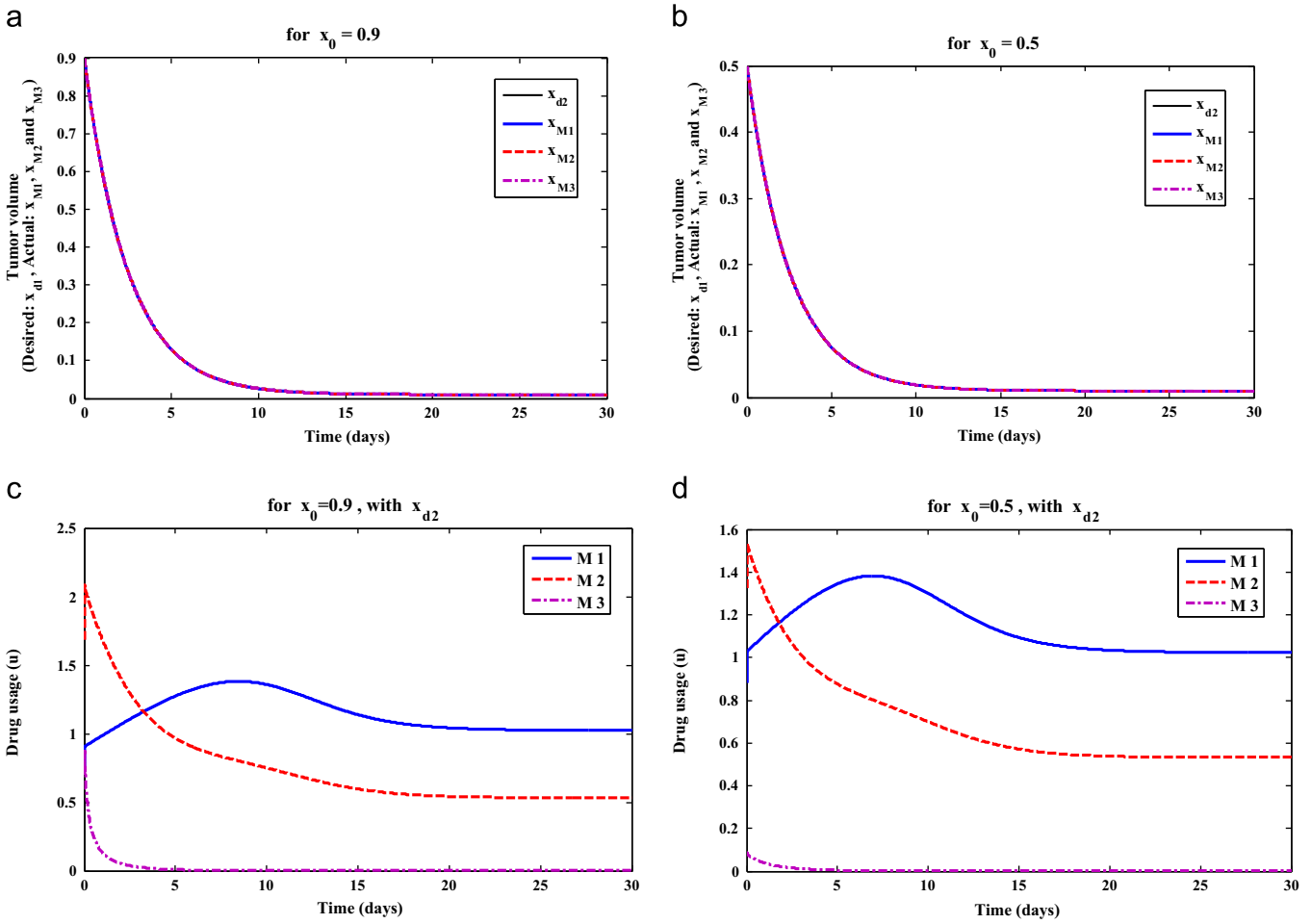

Fig. 5. Required drug usage for Model 1 (log-kill), Model 2 ($E_{\max}$) and Model3 (Norton–Simon) after implementation of the adaptive controller in tracking the desired tumor volume reduction for 15 days treatment period (x_{d2}) with (a) and (c): 90% of carrying capacity, $x_0 = 0.9$; (b) and (d): 50% of carrying capacity, $x_0 = 0.5$.

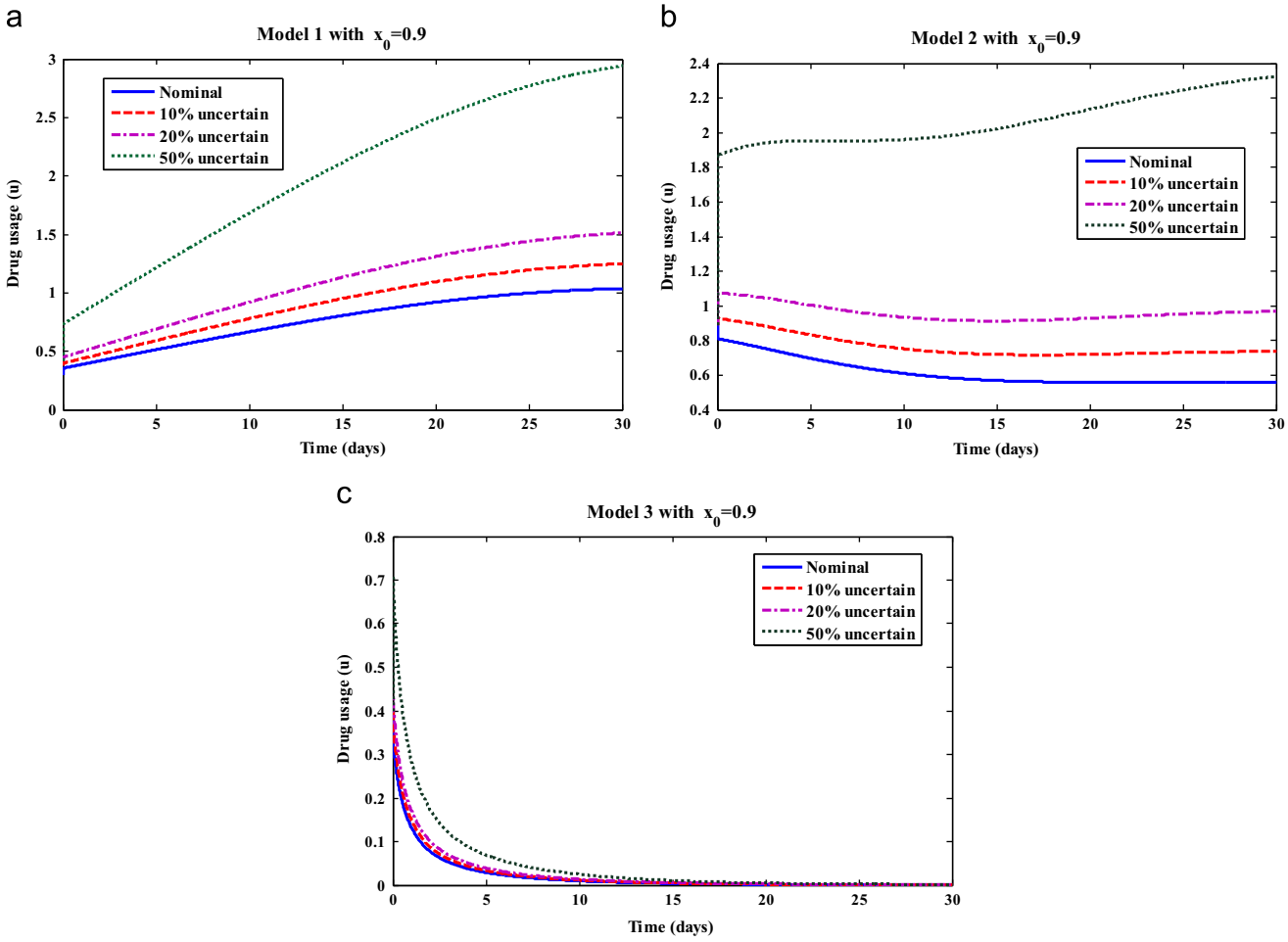

Fig. 6. Required variation of drug usage in chemotherapy process with nominal plant (blue solid line) and uncertain plants with 10% (red dashed line), 20% (violet dashed–dot line) and 50% (black dot line) uncertainty while $x_0 = 0.9$; in perfect tracking of desired tumor reduction within 30 days (x_{d1}) for (a) Model 1, log-kill, (b) Model 2, $E_{\max}$ and (c) Model 3, Norton–Simon. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

[3–6, 8–14, 26]. However, without loss of generality, other functions for desired tumor volume reduction can be used. For two scenarios with interval times of treatment $t_{f1} = 30$ days and $t_{f2} = 15$ days, these parameters are selected:

$$x_{d1}:\ a = 0.15, b = 0.01 \text{ for 30 days treatment period}$$

$$x_{d2}: a = 0.4, b = 0.01 \text{ for 15 days treatment period} \quad (48)$$

Desired scenarios for tumor reduction in interval times of $t_{f1} = 30$ days and $t_{f2} = 15$ days; and for the initial condition as 90% of carrying capacity ($x_0 = 0.9$) are shown in Fig. 2. Time response of the tumor volume in tracking of first desired scenario (x_{d1} by Eq. (48)), in treatment time of 30 days is shown in Fig. 3a, for $x_0 = 0.9$. As it is observed, after implementation of controller, desired tracking objective is obtained in all three cell-kill hypotheses. To achieve the desired tracking behaviour, the drug usage must be adjusted according to the schedules presented in Fig. 3b.

Fig. 4 shows the estimated and real values of system parameters $1/\delta$ and r/δ in Model 1, log-kill hypothesis (while an initial 20% error is assumed for each parameter). As it is observed, adaptive controller guarantees the estimation with an acceptable bounded error during the chemotherapy. Similarly, the effectiveness of adaptive control strategy in estimation of dynamic system parameters (with a bounded estimation error) can be investigated for two other models. For the sake of brevity, related results are not presented. The existence of bounded error for parameters estimation is in accordance with the Lyapunov stability analysis presented for each model in Section 3. There, it is proved for each model that the parameters estimation error ($\tilde{\boldsymbol{\theta}}_i$) has a bounded value that may not converge to zero.

Similar to Fig. 3, time response of the tumor volume in tracking of second desired scenario (x_{d2} by Eq. (48)), in treatment time of 15 days is shown in Fig. 5a and b, for $x_0 = 0.9$ and $x_0 = 0.5$, respectively. As it is observed, after implementation of the controller, desired tracking objective is obtained in all three cell-kill hypotheses. The corresponding variation in drug usage is presented in Fig. 5c and d. According to Fig. 5c and d, generally more drug usage is required for tumors with larger volume (as physically expected).

According to Figs. 3 and 5 for first and second desired scenarios, under steady state conditions, adaptive controller predicts less amount of drug usage in Norton–Simon and $E_{\max}$ hypotheses, respectively. However, in the first days of treatment, more drug usage is predicted in the $E_{\max}$ hypothesis (in comparison with log-kill). This may be an adverse effect of adaptive controller in $E_{\max}$ hypothesis, due to negative side aspect of high drug consumption in the beginning of treatment.

Finally, it should be mentioned that in both Figs. 3 and 5, the amount of drug usage in Norton–Simon hypothesis (Model 3) is significantly less than those of log-kill and $E_{\max}$ hypotheses. This is because, according to Eq. (4-3), control input $u(t)$ is multiplied by function $\ln(x)$ which itself is a large quantity around the small values of tumor volume (i.e., $\ln(x) \to \infty$ as $x \to 0$). Moreover, according to Table 1, the magnitude of δ in Model 3 is 10–20

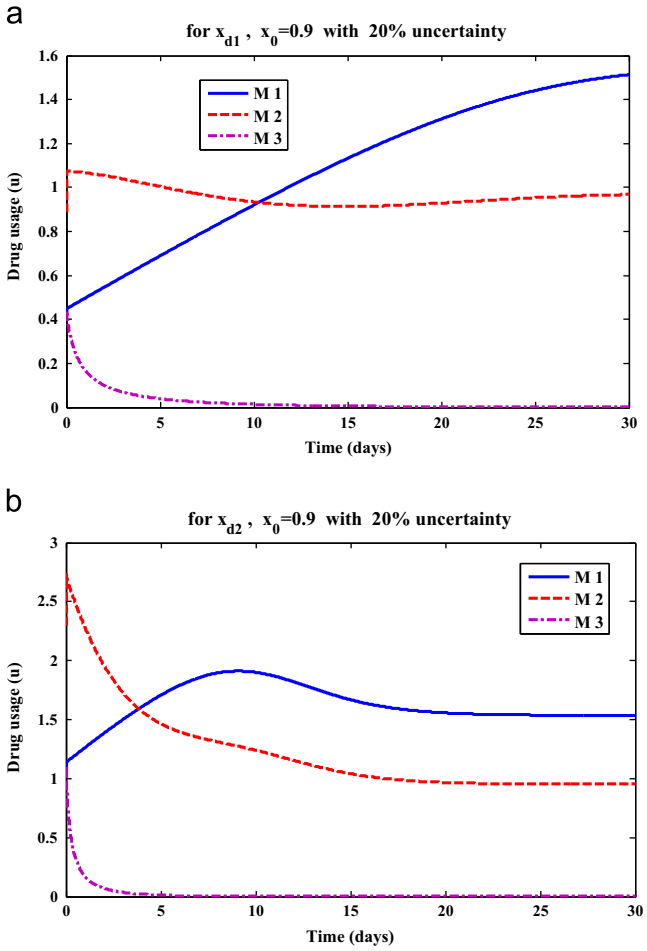

Fig. 7. Required drug usage for 20%-uncertain Model 1, log-kill (blue solid line), Model 2, E_{max} (red dashed line) and Model 3, Norton–Simon (violet dashed–dot line), for tracking the desired tumor reduction in (a) 30 days (x_{d1}) and (b) 15 days (x_{d2}) treatment period (while $x_0 = 0.9$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

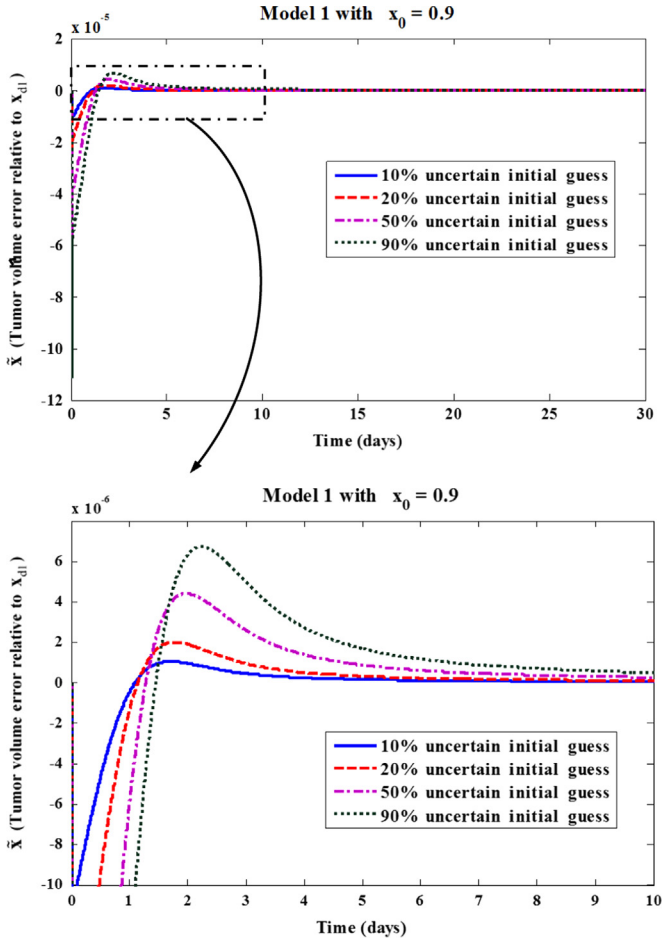

Fig. 8. The effect of 10% (blue solid line), 20% (red dashed line), 50% (violet dashed–dot line) and 90% (black dots) uncertainty in initial guess of $\boldsymbol{\theta_1}$ on error vector of tumor volume ($\tilde{x}$) in Model 1, log-kill hypothesis (while, 30 days treatment with $x_0 = 0.9$). Lower plot is the focus of upper plot around $\tilde{x} = 0$, in first 10 days. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

times of those used in Models 1 and 2. Consequently, due to these reasons, the amount of drug usage in Norton–Simon hypothesis is essentially low.

As it is shown in Figs. 3 and 5, adaptive controller guarantees the desired tracking of tumor reduction in both scenarios with 30 and 15 days of treatment. Moreover, as it is found out by comparing Figs. 3b and 5c (and physically expected), in all three models, more drug usage is required in the second scenario (x_{d2}) with shorter period of treatment (15 days) in comparison with the first scenario (x_{d1}) that has longer treatment period (30 days), both for $x_0 = 0.9$.

4.1. The effect of parametric uncertainty on dynamic behaviour of cell-kill models

To investigate the effect of uncertainties, parameters of the uncertain models are assumed to be varied with 10%, 20% and 50% of nominal values as:

$$\begin{aligned} &(1-\chi)\,\bar{r}_i < r_i < (1+\chi)\,\bar{r}_i,\\ &(1-\chi)\,\bar{\delta}_i < \delta_i < (1+\chi)\,\bar{\delta}_i, i=1,2,3,\ \chi = 0.1,\quad 0.2,\quad 0.5\\ &(1-\chi)\,\bar{\lambda} < \lambda < (1+\chi)\,\bar{\lambda} \end{aligned} \tag{49}$$

while the nominal values of $\bar{r}_i$, $\bar{\delta}_i$ and $\bar{\lambda}$ are given in Table 1. It is observed that in the presence of various amounts of uncertainties given by Eq. (49), desired tracking objectives of Fig. 2 are obtained (in all cell-kill models). For the perfect tracking of desired objective in the first scenario within 30 days (x_{d1} by Eq. (48)), drug consumption must be scheduled according to Fig. 6; for the uncertain models with $x_0 = 0.9$. For the sake of brevity, similar results for $x_0 = 0.5$ and second scenario (x_{d2}) are not presented.

In the presented simulation, the uncertain actual values of $\bar{r}_i$, $\bar{\delta}_i$ and $\bar{\lambda}$ are considered to be equal to $(1-\chi)\,\bar{r}_i$, $(1+\chi)\,\bar{\delta}_i$ and $(1+\chi)\,\bar{\lambda}$, respectively. Accordingly, as shown in Fig. 6, as the amount of uncertainty (χ) is increased, more drug usage is required to achieve the desired behaviour for tumor reduction (x_{d1}). A significant increase in drug usage is observed in the presence of 50% uncertainty (in comparison with nominal model and uncertain models with 10% and 20% uncertainty). It should be mentioned that 50% uncertainty in model parameters is a theoretical assumption that may not be occurred in practice (this case is considered for comparison purpose).

Finally, the variation of drug usage in three models and for the uncertain plants with 20% uncertainty is shown in Fig. 7; for two desired scenarios (while $x_0 = 0.9$). Due to similar behaviour, results are not presented for uncertain plants with 10% and 50% uncertainty. Again and similar to what was observed for the nominal plants in Figs. 3c and 5c; under steady state conditions, adaptive controller predicts less amount of drug usage in uncertain Norton–Simon and E_{max} models, respectively. In addition, comparing

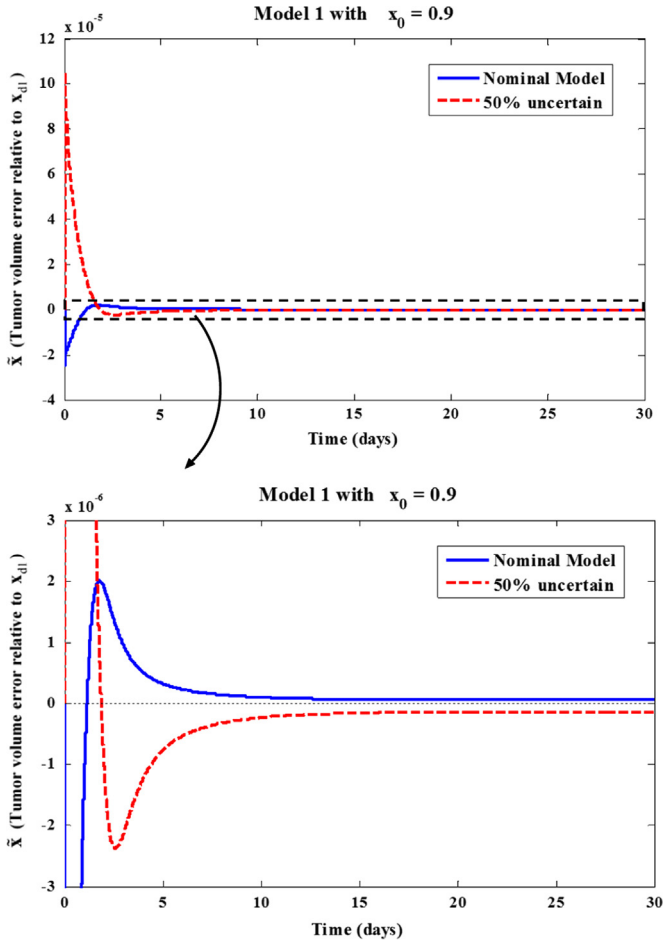

Fig. 9. Time response of the tumor volume error ($\tilde{x}$) in Model 1 (log-kill) for the nominal (blue solid line) and 50%-uncertain (red dashed line) models; with 20% uncertainty in initial guess of $\boldsymbol{\theta_1}$ (while, 30 days treatment with $x_0 = 0.9$). Lower plot is the focus of upper plot around $\tilde{x} = 0$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

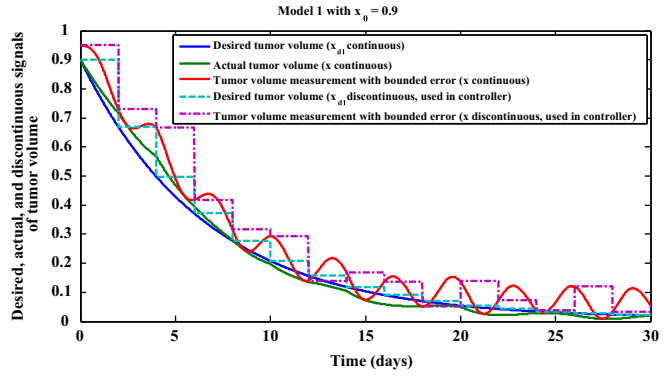

Fig. 10. The effect of discontinuous feedback (with 2-days sampling time), measurement error, and bounded disturbance on the time response of tumor volume including: The desired tumor volume, the actual tumor volume, the tumor volume with a bounded error, the discontinuous signal of desired tumor volume (used in the controller), and the discontinuous signal of the tumor volume (that has a bounded error and used in the controller) for Model 1; while, 30 days treatment (x_{d1}) is used for $x_0 = 0.9$.

Figs. 7, 3c and 5c reveals that in the presence of model uncertainties, more drug usage is required in perfect tracking of tumor reduction (in comparison with nominal plants).

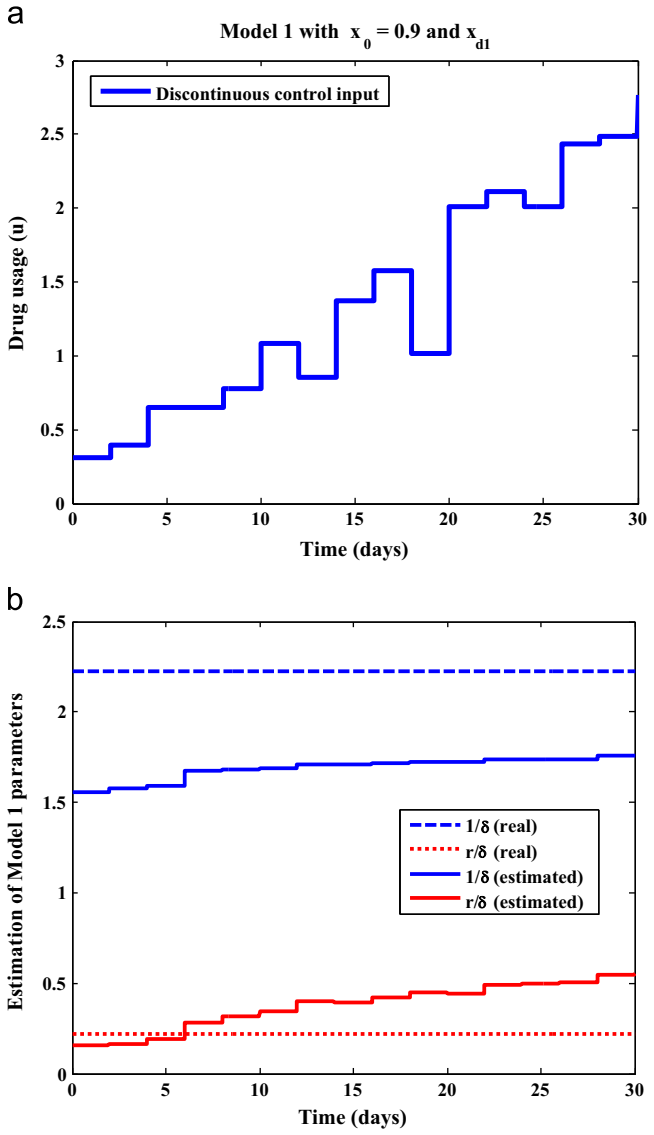

Fig. 11. The effect of discontinuous feedback (with 2-days sampling time), measurement error, and bounded disturbance on the controller performance and adaptation law including: (a) The discontinuous drug usage (control input), and (b) adaptation of parameters for Model 1; with 20% uncertainty in initial guess of parameters (while, 30 days treatment (x_{d1}) with $x_0 = 0.9$).

4.2. The effect of uncertainty in initial guess of parameters in adaptive control law

In this section, the effect of uncertainty in initial guess of parameters used in adaptive control law is investigated on dynamic response of the cell-kill models. It is assumed that there is 10%, 20%, 50% and 90% uncertainty in initial guess for parameters $\boldsymbol{\theta_i}$, $i = 1, 2, 3$, given by Eqs. (7), (21) and (35). For the sake of brevity and due to similar behaviour, the following results are only presented for Model 1 (log-kill hypothesis); with 30 days treatment. According to Fig. 8, the error vector for tumor volume ($\tilde{x} = x - x_d$) is a small value which finally converges to the zero; for various amounts of uncertainty in initial guess of $\boldsymbol{\theta_1}$ (in Fig. 8, the log-kill model itself is certain; i.e., nominal model is used).

Finally, to complete the investigation, it is assumed that the uncertainty exists in both of the model parameters (i.e., as described by Eq. (49)) and initial guess of parameters used in adaptive control law (i.e., uncertainty in $\boldsymbol{\theta_i}, i = 1, 2, 3$). Fig. 9 shows the error vector of tumor volume ($\tilde{x}$) for the nominal plant and

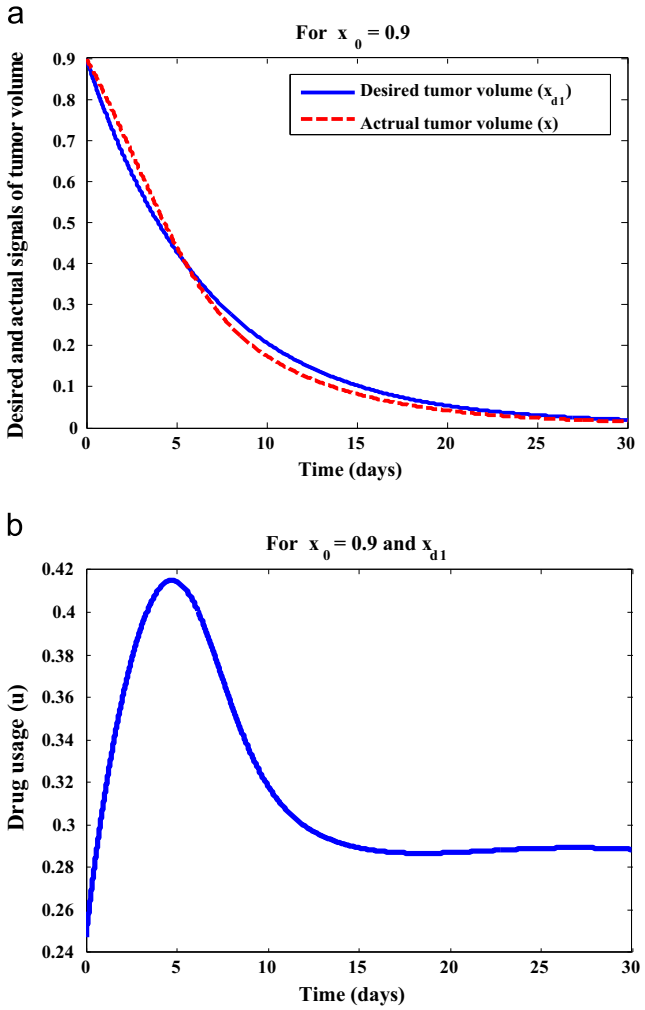

Fig. 12. The effect of modeling (non-parametric) uncertainties on the controller performance when controller designed for Model 1 is used for Model 2: (a) The desired and actual signals of tumor volume and (b) the required drug usage; in 30 days treatment (x_{d1}) with $x_0 = 0.9$.

50%-uncertain plant (i.e., $\chi = 0.5$ in Eq. (49)); in the presence of 20% uncertainty in initial guess of $\boldsymbol{\theta_1}$ with respect to the nominal model. As it is observed, in both cases, the error vector for tumor volume ($\tilde{x}$) is a small value which finally converges to the zero. Therefore, proposed control strategy is robust against the uncertainties in initial guess of parameters used in construction of control law (either for nominal plant or uncertain plants of the log-kill models). For the sake of brevity, similar results for other cases of Models 2 and 3 and other amounts of uncertainty are not presented.

4.3. The effect of sampling time, measurement noise and modelling mismatch on the controller performance

In this section, the performance of the controller is evaluated and shown using discontinuous feedback (with high sampling time) and with the existence of measurement error, and bounded disturbances and/or non-parametric uncertainties in the system; similar to a realistic chemotherapy process.

For the sake of brevity, the robustness analysis is only presented for the controller of Model 1 and with the first scenario (x_{d1}) and $x_0 = 0.9$. For this purpose, first the controller robustness is evaluated with a discontinuous feedback of tumor volume with 2 days sampling time. In other words, the volume of patient's tumor should be measured one time in every 2-days. Moreover, the bounded measurement error of tumor volume (corresponds to the sensing instrument) is considered to be a combination of a constant and time-varying terms as: $\Delta x = 0.05 + 0.05 \sin(2t)$. Accordingly, at the beginning of the chemotherapy process, shown in Fig. 10, the tumor volume is about $x \approx x_0 = 0.9$ and the maximum measurement error is more than 10% of the tumor volume. However, after 6 days of the process that the tumor volume decreases to $x \approx 0.4$, the maximum measurement error is about 25% of the tumor volume. Finally, at the end of the cell-killing process (after 20 days of treatment) that the tumor volume decreases to $x \approx 0.05$, the maximum measurement error is about 200% of the tumor volume (Fig. 10). Also, $dist = 0.01 - 0.01 \sin(t)$ is considered as a bounded disturbance (and/or modeling uncertainty) exists in the cell-kill Model 1 as: $\dot{x} = -rx \ln(x) - \delta x u(t) + dist$. 20% uncertainty is also considered in initial guess of model parameters.

The desired tumor volume, the actual tumor volume, the discontinuous signal of desired tumor volume, and the discontinuous signal of the tumor volume (that has a bounded error and used in the controller) are shown in Fig. 10. As it is shown in Fig. 10, the tumor volume is measured at the beginning of each 2 days and this measurement is used as the feedback signal in adaptive controller during 2 days. The corresponding drug usage and parameters adaptation of Model 1 are shown in Fig. 11a and b, respectively. It should be mentioned that since the dynamics of the chemotherapy (Eq. (4-1)) is slow, employing the drug usage with 2 days sampling time (Fig. 11a) can effectively control the tumor volume (Fig. 10). As it is observed in Fig. 11b, adaptive controller guarantees the estimation with an acceptable bounded error during the chemotherapy which is in accordance with the Lyapunov stability analysis presented for Model 1 in Section 3.1.

As the second part of robustness analysis of the proposed control strategy against disturbances and/or modelling uncertainties, the controller designed for Model 1 (in Section 3.1) is now used for Model 2. Since Model 2 (Eq. (4-2)) has a different structure in comparison with Model 1 (Eq. (4-1)), the performance of the controller is evaluated in the presence of model mismatch. Accordingly, using continuous feedback signal, the time response of the tumor volume in tracking of first desired scenario (x_{d1} in treatment time of 30 days), is shown in Fig. 12a for $x_0 = 0.9$. As it is observed, by implementation of controller designed for Model 1 on Model 2, the tumor volume reduction is obtained; however a bounded tracking error exists due to the model mismatch. The corresponding drug usage is also presented in Fig. 12b. Similarly, the same investigation can be performed for other cases. But, for the sake of brevity, just the performance of controller developed for Model 1 was studied on Model 2.

Next, using the discontinuous feedback signal of tumor volume (with 2-days sampling time) and a bounded measurement error ($\Delta x = 0.02 + 0.005 \sin(t)$), the performance of the controller designed for Model 1 is evaluated on Model 2. Accordingly, the desired tumor volume, the actual tumor volume, the discontinuous signal of desired tumor volume, and the discontinuous signal of the tumor volume (that has a bounded error and used in the controller) are shown in Fig. 13a for $x_0 = 0.9$ and of 30 days treatment period (x_{d1}). As shown in Fig. 13a, at the beginning of the chemotherapy process when the tumor volume is about $x \approx x_0 = 0.9$, the maximum measurement error ($\Delta x = 0.02 + 0.005 \sin(t)$) is more than 2.5% of the tumor volume. However, after 10 days of the process that the tumor volume decreases to $x \approx 0.17$, the maximum measurement error is about 15% of the tumor volume. Finally, at the end of the cell-killing process (after 20 days of treatment) that the tumor volume decreases to $x \approx 0.005$, the maximum measurement error is about 150% of the tumor volume (Fig. 13a). According to Fig. 13a, by implementation of controller designed for Model 1 on Model 2,

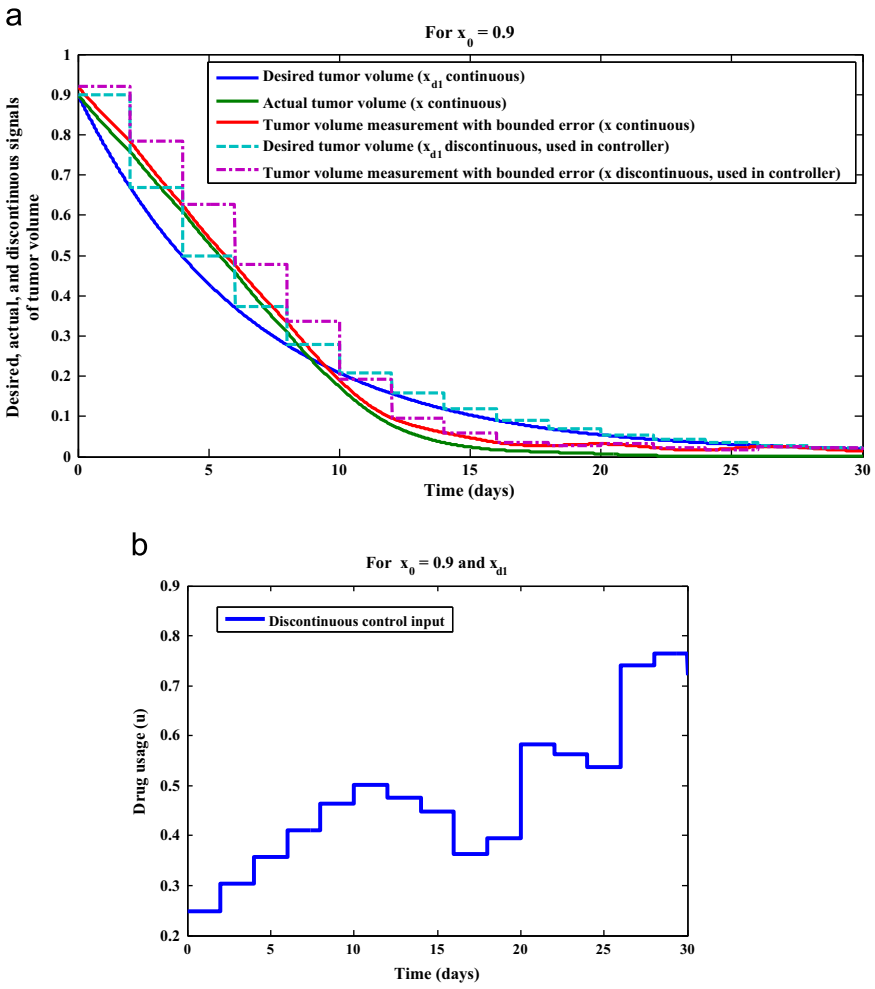

Fig. 13. The effect of modeling (non-parametric) uncertainties, discontinuous feedback (with 2-days sampling time) and measurement error on the controller performance: (a) The desired, actual and discontinuous signals of tumor volume and (b) the discontinuous drug usage, when controller designed for Model 1 is used for Model 2; in 30 days treatment (x_{d1}) with $x_0 = 0.9$.

the tumor volume reduction is obtained; however a bounded tracking error is observed due to the measurement error, discontinuous control signal and model mismatch. The corresponding drug usage with 2-days sampling time is also shown in Fig. 13b.

Therefore, according to Figs. 10–13, the robust performance of the proposed controller against discontinuous feedback (with high sampling time), measurement error, and bounded disturbance and/or modelling uncertainty is shown in addition to its previous robustness to parametric uncertainties.

5. Conclusions

In this paper, an adaptive robust control strategy is developed to adjust the drug delivery schedule and consequently tumor reduction in cancer chemotherapy. To investigate the global stability and tracking convergence of the process, Lyapunov stability theorem is used. For the first time, the efficiency of adaptive control strategy is studied on cancer chemotherapy in the presence of model uncertainties. Proposed nonlinear control approach is applied on three cell-kill models including log-kill hypothesis (Model 1), $E_{\max}$ hypothesis (Model 2) and Norton–Simon hypothesis (Model 3). In these models, cell-kill is proportional to the tumor mass, a saturable function of tumor mass and tumor growth rate, respectively.

Two desired scenarios for tumor reduction during treatment periods of 30 days and 15 days are considered. Over the treatment interval, performance of the controlled systems including the amount of drug usage and tumor volume are investigated and compared (for three nonlinear models under two desired scenarios). The effects of treatment period, initial value of tumor volume (carrying capacity) and the uncertainty amount on dynamic system behaviour are studied. Through a comprehensive evaluation, results are presented and compared for three cell-kill models. Moreover, the performance of the controller using discontinuous feedback signal and with the existence of measurement error, and bounded disturbances and/or modeling uncertainties is evaluated. According to the results, the following conclusions can be extracted:

1. After implementation of controller, desired tracking objective is obtained in all three cell-kill hypotheses for both scenarios with treatment periods of 30 days and 15 days. Moreover, this perfect tracking is also obtained for the chemotherapy process in the presence of model parametric uncertainties.
2. During the chemotherapy process, adaptive controller guarantees the estimation of model parameters with an acceptable bounded error.
3. To suppress the tumor, generally more drug usage is required for tumors with larger volume. In addition, for both nominal and uncertain plants of the cell-kill models, more drug

consumption is required in treatments of shorter periods (while the initial and final volumes of tumor are kept fixed).
4. Under steady state conditions, adaptive controller predicts less amount of drug usage in Norton–Simon and E_{max} hypotheses, respectively. However, in comparison with the log-kill model, more drug usage is predicted in the E_{max} model during the first days of treatment (which may cause a negative side aspect due to high drug consumption).
5. It is observed that the proposed adaptive controller is robust against a wide range of model uncertainties. Moreover, as the amount of uncertainty increases, more drug usage is required to achieve the desired behaviour for tumor reduction. In other words, the controller could rapidly adapt to the system uncertainties and adjust the control input.
6. The proposed control strategy is robust against the uncertainties in initial guess of parameters used in construction of control law (either for nominal plant or uncertain plants of the cell-kill models).
7. Also, the controller shows the robust performance against discontinuous feedback of tumor volume (with high sampling time), measurement error of tumor volume, and bounded disturbances and/or modelling (non-parametric) uncertainties.

Finally, it should be mentioned that the proposed robust adaptive controller can be applied on any other bioprocesses related to the chemotherapy or other similar health treatments. However, achievement of this purpose depends on the extraction of governing dynamic model.

Conflict of interest statement

Non declared.

Appendix A

In this section, the continue of the Lyapunov stability proof for Model 2 (presented in Section 3.2) is presented.

Proof. The Lyapunov function V in Eq. (11) is positive definite in $\tilde{x}$ and $\tilde{\boldsymbol{\theta}}_{\mathbf{2}}$. Since $\dot{V}$ is negative definite ($\dot{V} \le 0$), V is also bounded and therefore, x, $\tilde{x}$ and $\tilde{\boldsymbol{\theta}}_{\mathbf{2}}$ are bounded. Consequently according to system dynamics by Eq. (4-2), $\dot{x}$ is bounded. We know that the desired tumor volume (x_d) and its time derivative ($\dot{x}_d$) are bounded. Therefore, according to $\tilde{x} = x - x_d$, $\tilde{x}$ is also bounded. As a result, $\dot{\tilde{x}} = \dot{x} - \dot{x}_d$ is bounded from the boundedness of $\dot{x}$ and $\dot{x}_d$. Thus, $\mathbf{Y_2}(\dot{x}_d - \alpha\tilde{x}, x)$ is also a bounded matrix. Moreover, since the vector of actual parameters of the system ($\boldsymbol{\theta}_{\mathbf{2}}$) and the vector of parameters estimation error ($\tilde{\boldsymbol{\theta}}_{\mathbf{2}}$) are bounded, the boundedness of $\hat{\boldsymbol{\theta}}_{\mathbf{2}}$ is obtained from $\tilde{\boldsymbol{\theta}}_{\mathbf{2}} = \hat{\boldsymbol{\theta}}_{\mathbf{2}} - \boldsymbol{\theta}_{\mathbf{2}}$. If second time derivative of the desired tumor volume ($\ddot{x}_d$) is bounded, it can concluded that $\dot{\mathbf{Y}}_{\mathbf{2}}(x, \dot{x}, x_d, \dot{x}_d, \ddot{x}_d)$ is a bounded matrix. Using Eq. (32), and adding the negative term $(1/2)\dot{x}\tilde{x}^2$, $\dot{V} = -\alpha(x+\lambda)\tilde{x}^2 + (1/2)\dot{x}\tilde{x}^2 \le 0$ is obtained. By replacing $\dot{x}$ from Eq. (4-2) into the latter $\dot{V}$, yields:

$$\dot{V} = -\alpha(x+\lambda)\tilde{x}^2 + (1/2)\left(-r\,x\ln(x) - \delta\frac{x}{x+\lambda}u(t)\right)\tilde{x}^2 \tag{A.1}$$

Substituting control law $u(t)$ given by Eq. (23) into Eq. (A.1), leads to:

$$\dot{V} = -\alpha(x+\lambda)\tilde{x}^2 + \left(\frac{1}{2}\right)\left(-r\,x\ln(x) - \delta\frac{x}{x+\lambda}\mathbf{Y_2}\hat{\boldsymbol{\theta}}_{\mathbf{2}}\right)\tilde{x}^2 \tag{A.2}$$

Differentiating $\dot{V}$ with respect to time yields:

$$\ddot{V} = -\alpha\dot{x}\tilde{x}^2 - 2\alpha(x+\lambda)\tilde{x}\dot{\tilde{x}} + \left(-r\,x\ln(x) - \delta\frac{x}{x+\lambda}\mathbf{Y_2}\hat{\boldsymbol{\theta}}_{\mathbf{2}}\right)\tilde{x}\dot{\tilde{x}} + \left(\frac{1}{2}\right)\left(-r\,\dot{x}\ln(x) - r\,\dot{x} - \delta\frac{\lambda\dot{x}}{(x+\lambda)^2}\mathbf{Y_2}\hat{\boldsymbol{\theta}}_{\mathbf{2}} - \delta\frac{x}{x+\lambda}\left(\dot{\mathbf{Y}}_{\mathbf{2}}\hat{\boldsymbol{\theta}}_{\mathbf{2}} + \mathbf{Y_2}\dot{\hat{\boldsymbol{\theta}}}_{\mathbf{2}}\right)\right)\tilde{x}^2 \tag{A.3}$$

This implies that $\ddot{V}$ is bounded since x, $\dot{x}$, $\tilde{x}$, $\dot{\tilde{x}}$, $\mathbf{Y_2}$, $\dot{\mathbf{Y}}_{\mathbf{2}}$, $\hat{\boldsymbol{\theta}}_{\mathbf{2}}$ and $\dot{\hat{\boldsymbol{\theta}}}_{\mathbf{2}}$ are all bounded. Thus, $\dot{V}$ is uniformly continuous. Using Barbalat's lemma, it is proved that $\tilde{x} \to 0$ as $t \to \infty$ and the error vector for parameters estimation $\tilde{\boldsymbol{\theta}}_{\mathbf{2}}$ remains bounded. Using Eq. (21), the estimation error of three parameters of the model ($\tilde{\delta}$,$\tilde{\lambda}$ and $\tilde{r}$) will be remained bounded.

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