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Adaptive robust control of cancer chemotherapy with extended Kalman filter observer☆

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ABSTRACT

In this paper we control the amount of three major biological cell types (normal, immune and tumor cells) under uncertainty in cancer model parameters, using different chemotherapy drug dosages. To achieve this goal, an adaptive robust controller is proposed for a third order nonlinear model, which consists of the interaction between normal, immune and tumor cells. We adjust the drug dosages to control the tumor growth and maintain immune and normal cells in their desired values. Due to tumor micro-environmental and biological changes and measurement inaccuracies, the exact quantity of the model parameters is not available. Therefore, it is necessary to design the controller in a way that it is robust against parameters uncertainty and variations, the proposed robust adaptive controller manipulates the drug dosages and estimates the parameters of the model, simultaneously. The resulting system is robust against parameters uncertainty and variations. The global stability and tracking convergence of the controller is proved using time-varying Lyapunov function. Moreover, extended Kalman filter observer is applied to estimate the immune cells, due to the difficulty measuring them during the biological in vivo experiments. The performance of the proposed controller and observer are investigated by computational results. Computational results show the desired effect of drug dosage injections on the normal, immune and tumor cells. We observe that the controller guarantees the robust performance against the parameters uncertainty. The extended Kalman filter observer has effective performance and estimates the immune cells with high accuracy. This approach could impact robust tumor control using appropriate drug dosages while the parameters of the model change over time in a patient and across different patients.

1. Introduction

Cancer is one of the most important diseases that caused human death in the world. There are many ways to treat cancer, such as surgery, radiotherapy, chemotherapy, hormone therapy, and immunotherapy [1]. Among the various treatment methods, chemotherapy is very important and widely used in practice. During this procedure some normal cells may be killed in addition to cancer cells [2].

Chemotherapy has many different side effects such as disturbing frequent dividing cells. The rate of division in cancer cells is more than normal cells. Hence, cancer cells are more sensitive to chemotherapy. In some tissues such as skin, hair and nails cell division happens more frequently therefore, chemotherapy may damage these kind of cells [3]. But, normal cells repair the damage because of their intact protective system. Genes which make chromosomes in nucleus, are the regulators of cell activity. Genes are copied exactly in each cell division and chemotherapy have potential to damage genes in different phases of this process [4–6]. Normal cells located in a rest phase of cell cycle may protect from chemotherapy damage [7,8]. Nowadays, to reduce chemotherapy side effects, scientists suggested to combine chemotherapy drugs in different stages of treatment. In this case there is more chance to kill more cancer cells.

Mathematical modeling provides a low-cost approach to evaluate different control strategies in cancer treatment, and shows the relationship between the population of cancer cells, normal cells and drug resistance, [9]. The general area of mathematical modeling of cancer have been evolved recently and there are many papers about cancer modeling in the literature, see e.g., [10] and [11]. Many mathematical models have been proposed to evaluate the effects of a drug on tumor behavior, [12–15]. To show the chemotherapy response to tumor

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growth, a simple mathematical model which consists of three differential equations associated with the normal cells, cancer cells and chemotherapy drug, is presented in [16]. The effect of chemotherapy on normal and cancer cells follow Michaelis-Menten saturation function as described in [17]. Various control strategies have been proposed to reduce the side effects of drugs, see e.g., [18]. Especially, it is important to know the effects of chemotherapy drugs on tumor growth, [19]. Many control strategies have been proposed to control the tumor size. In [20] optimal singular control in chemotherapy is presented. In [21] a stochastic model of cancer chemotherapy is considered and optimal controller is designed for this model. A tumor model with immune resistance and drug therapy is presented in [22] and optimal control is used to control the tumor growth.

There are various sources of uncertainty associated with chemotherapy which prevents the above mentioned approaches to guarantee the robust performance of the controller. To guarantee a robust performance in the presence of uncertainties, the robust control approach have been proposed in [23]. In [24], two control strategies are studied to make the system performance robust against uncertainties. Theses methods are: optimal linear regulation and H_∞ robust control. H_∞ controller has the best performance for system with uncertainties; however its design is difficult. To design optimal linear regulation, see e.g., [25], the nonlinear model should be linearized around its operating point. Therefore, the performance of the controller depends on the operating point and it performs well only around this point. To solve this problem a nonlinear adaptive control strategy is developed in [26]. In this work a first order nonlinear model of tumor that only considers tumor cells have been used.

In this paper, a nonlinear robust adaptive control strategy is developed for a third order nonlinear model. This model consists of normal cells, immune cells, tumor cells, and the effect of chemotherapy treatment. In our work, the tumor size, the amount of normal and immune cells are controlled by adaptive variation of drug dosages. The controller is designed based on Lyapunov stability theorem, and guarantees the global stability and tracking convergence. Unlike, the linear controllers that require the model of nonlinear system to be linearized around the operating point, the proposed nonlinear controller does not require any linearization. Moreover, the parameters of the model have been estimated in the control loop, and the controller is robust against parameters uncertainties associated with the model dynamics. In addition, since the measurement of immune cells is difficult in experimental labs an extended Kalman filter observer is applied to estimate the immune cells.

This paper is organized as follows: Section 2 resents the nonlinear cancer model used in work. Section 3 explains the design of our control strategy and its stability. Section 4 describes the design of extended Kalman filter observer to estimate the immune cells. Section 5 shows the computational results and the convergence behavior of the controller. Section 6 provides comparison with related work in the literature and concluding remarks are made in Section 7.

2. Mathematical model of chemotherapy

There are many mathematical models for describing the chemotherapy process, see, e.g., [27,28]. Since, the goal of this paper is to propose a nonlinear control method which is robust against parameters uncertainty. We have used a minimal order model of chemotherapy to investigate the performance of this control strategy. We chose the chemotherapy model of [29], which is widely used in the literature, see e.g., [9]. This model includes the interaction of tumor cells with normal and immune cells in a dynamical system. This nonlinear model is presented below;

$$\dot{I} = s + \frac{\rho IT}{\alpha + T} - c_1 IT - d_1 I - a_1 u_1 I, \tag{1}$$

$$\dot{T} = r_1 T(1 - b_1 T) - c_2 IT - c_3 TN - a_2 u_2 T, \tag{2}$$

$$\dot{N} = r_2 N(1 - b_2 N) - c_4 TN - a_3 u_3 N. \tag{3}$$

$N(t)$, $T(t)$ and $I(t)$ represent the number of normal, tumor and immune cells at time t, respectively. The drug injections are considered as the control input in the model. $u_1(t)$, $u_2(t)$ and $u_3(t)$ denote the effect of chemotherapy drugs. This model assumes a type of immune cell that can cause the reduction of tumor size through a kinetic process. Also this model includes immunes cells that their growth is stimulated by the presence of the tumor such as T-cells. In this model, we assume that all cell populations are killed by chemotherapy drug with different ratios.

Several resources such as bone marrow and lymph nodes could create a constant source for immune cells, s, which is shown in the first term of Eq. (1). The second term is the saturation function with the positive parameters ρ and α, that represents the immune cells are stimulated by tumor cells. The competition among immune and tumor cells, that cause the loss of immune cells is shown in the third term. The forth term shows that Immune cells die at the natural death rate d_1. The fifth term is the loss of immune cells due to the drug injection.

The growth of tumor cell population is shown in the first term of Eq. (2) as the logistic term with growth rate r_1 and maximum carrying capacity b_1^{-1}. The logistic growth term models the competition between proliferation and death rate [30]. The competition among immune and tumor cells, that cause the loss of tumor cells is shown in the second term. The competition among tumor and normal cells, that cause the loss of tumor cells is shown in the third term. The loss of tumor cells due to the drug injection is shown in the forth term.

The growth of normal cell population is shown in the first term of Eq. (3) as the logistic term with growth rate r_2 and maximum carrying capacity b_2^{-1}. The competition among normal and tumor cells, that cause the loss of normal cells is shown in the second term. The third term is the loss of normal cells due to the drug injection.

The effect of chemotherapy on killing cell populations are represented by a_1, a_2 and a_3, [31]. The values of different parameters are listed in Table 1.

3. Robust adaptive control

In this section, a robust adaptive control strategy is proposed for the third order nonlinear model described in Section 2. The objective of this controller is that the tumor, normal and immune cells track their desired values. To achieve this goal, the volume of the biological cells (tumor, normal and immune) are compared with their desired values, the error signals are created, and the drug dosages are recommended accordingly. Moreover, to make the control system robust against

Table 1
Nominal parameters of the chemotherapy model [31].

Parameter	Description	Value
a_1	Fractional normal cell kill by chemotherapy	0.05
a_2	Fractional tumor cell kill by chemotherapy	0.15
a_3	Fractional immune cell kill by chemotherapy	0.1
b_1^{-1}	Tumor cell carrying capacity	1.0
b_2^{-1}	Normal cell carrying capacity	1.0
c_1	Fractional tumor cell kill by immune cells	1.0
c_2	Fractional immune cell kill by tumor cells	0.5
c_3	Fractional tumor cell kill by normal cells	1.0
c_4	Fractional normal cell kill by tumor cells	1.0
d_1	Death rate of immune cells	0.2
r_1	Tumor cell growth rate	1.5
r_2	Normal cell growth rate	1.0
s	Steady source rate for immune cells	0.33
α	Immune threshold rate	0.3
ρ	Immune response rate	0.01

parameters uncertainty, the parameters of the model are estimated and used in the control loop.

Lets begin with the third order model of tumor that is described in Eqs. (1), (2) and (3) and rewrite the model in the regressor format as what follows:

$$\begin{bmatrix}\dot{I}\\ \dot{T}\\ \dot{N}\end{bmatrix}=\begin{bmatrix}1 & 0 & 0\\ \frac{IT}{\alpha+T} & 0 & 0\\ -IT & 0 & 0\\ -I & 0 & 0\\ 0 & T & 0\\ 0 & -T^2 & 0\\ 0 & -IT & 0\\ 0 & -TN & 0\\ 0 & 0 & N\\ 0 & 0 & -N^2\\ 0 & 0 & -TN\end{bmatrix}^T\begin{bmatrix}s\\ \rho\\ c_1\\ d_1\\ r_1\\ r_1b_1\\ c_2\\ c_3\\ r_2\\ r_2b_2\\ c_4\end{bmatrix}-\begin{bmatrix}a_1Iu_1\\ a_2Tu_2\\ a_3Nu_3\end{bmatrix}. \tag{4}$$

Rearrange Eq. (4) to the following form:

$$\begin{bmatrix}u_1\\ u_2\\ u_3\end{bmatrix}=\begin{bmatrix}\frac{1}{I} & 0 & 0\\ \frac{T}{\alpha+T} & 0 & 0\\ -T & 0 & 0\\ -1 & 0 & 0\\ \frac{-\dot{I}}{I} & 0 & 0\\ 0 & 1 & 0\\ 0 & -T & 0\\ 0 & -I & 0\\ 0 & -T & 0\\ 0 & \frac{-\dot{T}}{T} & 0\\ 0 & 0 & 1\\ 0 & 0 & -N\\ 0 & 0 & -T\\ 0 & 0 & \frac{-\dot{N}}{N}\end{bmatrix}^T\begin{bmatrix}\frac{s}{a_1}\\ \frac{\rho}{a_1}\\ \frac{c_1}{a_1}\\ \frac{d_1}{a_1}\\ \frac{1}{a_1}\\ \frac{r_1}{a_2}\\ \frac{r_1b_1}{a_2}\\ \frac{c_2}{a_2}\\ \frac{c_3}{a_2}\\ \frac{1}{a_2}\\ \frac{r_2}{a_3}\\ \frac{r_2b_2}{a_3}\\ \frac{c_4}{a_3}\\ \frac{1}{a_3}\end{bmatrix} \tag{5}$$

Lets define the regressor vectors as:

$$Y_1=\begin{bmatrix}\frac{1}{I} & \frac{T}{\alpha+T} & -T & -1 & \frac{-\dot{I}}{I}\end{bmatrix},$$
$$Y_2=\begin{bmatrix}1 & -T & -I & -N & \frac{-\dot{T}}{T}\end{bmatrix},$$
$$Y_3=\begin{bmatrix}1 & -N & -T & \frac{-\dot{N}}{N}\end{bmatrix}. \tag{6}$$

To consider the uncertainty in the model, the parameters of the model are replaced with their estimated values and we arrive at the following parameters vectors:

$$\hat{\theta}_1=\begin{bmatrix}\frac{\hat{s}}{\hat{a}_1} & \frac{\hat{\rho}}{\hat{a}_1} & \frac{\hat{c}_1}{\hat{a}_1} & \frac{\hat{d}_1}{\hat{a}_1} & \frac{1}{\hat{a}_1}\end{bmatrix}^T,$$
$$\hat{\theta}_2=\begin{bmatrix}\frac{\hat{r}_1}{\hat{a}_2} & \frac{\hat{r}_1\hat{b}_1}{\hat{a}_2} & \frac{\hat{c}_2}{\hat{a}_2} & \frac{\hat{c}_3}{\hat{a}_2} & \frac{1}{\hat{a}_2}\end{bmatrix}^T,$$
$$\hat{\theta}_3=\begin{bmatrix}\frac{\hat{r}_2}{\hat{a}_3} & \frac{\hat{r}_2\hat{b}_2}{\hat{a}_3} & \frac{\hat{c}_4}{\hat{a}_3} & \frac{1}{\hat{a}_3}\end{bmatrix}^T. \tag{7}$$

Moreover, to make the system stable and states (normal, immune and tumor cells) track their desired values, we consider the states derivative in the following format:

$$\begin{aligned}\dot{I} &= \dot{I}_d-\gamma_1(I-I_d),\\ \dot{T} &= \dot{T}_d-\gamma_2(T-T_d),\\ \dot{N} &= \dot{N}_d-\gamma_3(N-N_d).\end{aligned} \tag{8}$$

Where γ_1, γ_2 and γ_3 are positive constants, I_d and $\dot{I}_d$ are desired values and the derivative of immune cells, T_d and $\dot{T}_d$ are desired values and the derivative of tumor cells, and N_d and $\dot{N}_d$ are desired value and the derivative of normal cells, respectively. By substituting Eq. (8) in Eq. (6) we get,

$$\begin{aligned}Y_1(\dot{I}_d-\gamma_1(I-I_d),I,N,T) &= \begin{bmatrix}\frac{1}{I} & \frac{T}{\alpha+T} & -T & -1 & \frac{-\dot{I}_d-\gamma_1(I-I_d)}{I}\end{bmatrix},\\ Y_2(\dot{T}_d-\gamma_2(T-T_d),I,N,T) &= \begin{bmatrix}1 & -T & -I & -N & \frac{-\dot{T}_d-\gamma_2(T-T_d)}{T}\end{bmatrix},\\ Y_3(\dot{N}_d-\gamma_3(N-N_d),I,N,T) &= \begin{bmatrix}1 & -N & -T & \frac{-(\dot{N}_d-\gamma_3(N-N_d))}{N}\end{bmatrix}.\end{aligned} \tag{9}$$

According to the regressor form of system equations, the following control law is considered.

$$\begin{cases}u_1=Y_1\hat{\theta}_1,\\ u_2=Y_2\hat{\theta}_2,\\ u_3=Y_3\hat{\theta}_3.\end{cases} \tag{10}$$

Where $\hat{\theta}_1$, $\hat{\theta}_2$ and $\hat{\theta}_3$ are the estimating vector parameters. The adaptation law for estimating vector parameters is expressed as,

$$\begin{cases}\dot{\hat{\theta}}_1=\tilde{I}I\Gamma_1Y_1^T\mathrm{sign}(a_1),\\ \dot{\hat{\theta}}_2=\tilde{T}T\Gamma_2Y_2^T\mathrm{sign}(a_2),\\ \dot{\hat{\theta}}_3=\tilde{N}N\Gamma_3Y_3^T\mathrm{sign}(a_3),\end{cases} \tag{11}$$

where Γ_1, Γ_2 and Γ_3 are symmetric positive definite constant matrices. $\tilde{I}$, $\tilde{T}$, and $\tilde{N}$ are the error vectors of the immune, tumor, and normal cells, respectively and are defined as:

$$\begin{aligned}\tilde{I} &= I-I_d,\\ \tilde{T} &= T-T_d,\\ \tilde{N} &= N-N_d.\end{aligned} \tag{12}$$

In the next section, using the Lyapunov stability theorem, we show that the adaptation law in Eq. (11) makes the system stable in the presence of parameters uncertainties.

3.1. Lyapunov stability analysis

To prove the stability and tractability of the states (amount of immune, tumor and normal cells) a Lyapunov function is used, [32]. We choose the following positive definite candidate Lyapunov function.

$$V=\frac{1}{2}(\tilde{I}^2+\tilde{T}^2+\tilde{N}^2+|a_1|\tilde{\theta}_1^T\Gamma_1^{-1}\tilde{\theta}_1+|a_2|\tilde{\theta}_2^T\Gamma_2^{-1}\tilde{\theta}_2+|a_3|\tilde{\theta}_3^T\Gamma_3^{-1}\tilde{\theta}_3). \tag{13}$$

Where $\tilde{\theta}_1$, $\tilde{\theta}_2$ and $\tilde{\theta}_3$ are the error vectors defined below:

$$\begin{aligned}\tilde{\theta}_1 &= \hat{\theta}_1-\theta_1,\\ \tilde{\theta}_2 &= \hat{\theta}_2-\theta_2,\\ \tilde{\theta}_3 &= \hat{\theta}_3-\theta_3.\end{aligned} \tag{14}$$

According to Eq. (13), the Lyapunov function is always positive definite. The time derivative of Lyapunov function is obtained in the following form,

$$\begin{aligned}\dot{V} = {} & \tilde{I}(\dot{I}-\dot{I}_d)+\tilde{T}(\dot{T}-\dot{T}_d)+\tilde{N}(\dot{N}-\dot{N}_d)\\ & +|a_1|\dot{\hat{\theta}}_1^T\Gamma_1^{-1}\tilde{\theta}_1+|a_2|\dot{\hat{\theta}}_2^T\Gamma_2^{-1}\tilde{\theta}_2+|a_3|\dot{\hat{\theta}}_3^T\Gamma_3^{-1}\tilde{\theta}_3).\end{aligned} \tag{15}$$

Substituting the dynamic of the three equation model,

$$\begin{aligned}\dot{I} &= s + \frac{\rho IT}{\alpha + T} - c_1 IT - d_1 I - a_1 u_1 I,\\ \dot{T} &= r_1 T(1 - b_1 T) - c_2 IT - c_3 TN - a_2 u_2 T,\\ \dot{N} &= r_2 N(1 - b_2 N) - c_4 TN - a_3 u_3 N,\end{aligned} \tag{16}$$

in to Eq. (15), the time derivative of Lyapunov function is obtained as:

$$\begin{aligned}\dot{V} = {} & \tilde{I}(s + \frac{\rho IT}{\alpha + T} - c_1 IT - d_1 I - a_1 u_1 I - \dot{I}_d)\\ & + \tilde{T}(r_1 T(1 - b_1 T) - c_2 IT - c_3 TN - a_2 u_2 T - \dot{T}_d)\\ & + \tilde{N}(r_2 N(1 - b_2 N) - c_4 TN - a_3 u_3 N - \dot{N}_d)\\ & + |a_1|\hat{\theta}_1^T \Gamma_1^{-1}\tilde{\theta}_1 + |a_2|\hat{\theta}_2^T \Gamma_2^{-1}\tilde{\theta}_2 + |a_3|\hat{\theta}_3^T \Gamma_3^{-1}\tilde{\theta}_3).\end{aligned} \tag{17}$$

Substituting the control law of Eq. (10) in Eq. (17), results in,

$$\begin{aligned}\dot{V} = {} & \tilde{I}\Bigg(s + \frac{\rho IT}{\alpha + T} - c_1 IT - d_1 I - a_1\Bigg(\frac{1}{\hat{a}_1}\Bigg(\frac{1}{I}(\hat{s}) + \frac{T}{\alpha + T}(\hat{\rho}) - T(\hat{c}_1)\\ & - \hat{d}_1 - \frac{\dot{I}}{I}\Bigg)\Bigg)I - \dot{I}_d\Bigg) + \tilde{T}\Bigg(r_1 T(1 - b_1 T) - c_2 IT - c_3 TN\\ & - a_2\Bigg(\frac{1}{\hat{a}_2}\Bigg(\hat{r}_1 - T(\hat{r}_1\hat{b}_1) - I(\hat{c}_2) - N(\hat{c}_3) - \frac{\dot{T}}{T}\Bigg)\Bigg)T - \dot{T}_d\Bigg)\\ & + \tilde{N}\Bigg(r_2 N(1 - b_2 N) - c_4 TN - a_3\Bigg(\frac{1}{\hat{a}_3}\Bigg(\hat{r}_2 - N(\hat{r}_2\hat{b}_2) - T(\hat{c}_4)\\ & - \frac{\dot{N}}{N}\Bigg)\Bigg)N - \dot{N}_d\Bigg) + |a_1|\hat{\theta}_1^T \Gamma_1^{-1}\tilde{\theta}_1 + |a_2|\hat{\theta}_2^T \Gamma_2^{-1}\tilde{\theta}_2 + |a_3|\hat{\theta}_3^T \Gamma_3^{-1}\tilde{\theta}_3).\end{aligned} \tag{18}$$

By adding and subtracting $\gamma_1\tilde{I}^2$, $\gamma_2\tilde{T}^2$ and $\gamma_3\tilde{N}^3$ and rearranging Eq. (18) we get:

$$\begin{aligned}\dot{V} = {} & -\gamma_1\tilde{I}^2 - \gamma_2\tilde{T}^2 - \gamma_3\tilde{N}^2\\ & - a_1\tilde{I}I\begin{bmatrix}\frac{1}{I} & \frac{T}{\alpha + T} & -T & -1 & \frac{-\dot{I}}{I}\end{bmatrix}\tilde{\theta}_1\\ & - a_2\tilde{T}T\begin{bmatrix}1 & -T & -I & -N & \frac{-\dot{T}}{T}\end{bmatrix}\tilde{\theta}_2\\ & - a_3\tilde{N}N\begin{bmatrix}1 & -N & -T & \frac{-\dot{N}}{N}\end{bmatrix}\tilde{\theta}_3\\ & + |a_1|\hat{\theta}_1^T \Gamma_1^{-1}\tilde{\theta}_1 + |a_2|\hat{\theta}_2^T \Gamma_2^{-1}\tilde{\theta}_2 + |a_3|\hat{\theta}_3^T \Gamma_3^{-1}\tilde{\theta}_3).\end{aligned} \tag{19}$$

Substituting the adaptation law of Eq. (11) in Eq. (19), and the fact that Γ_1, Γ_2 and Γ_3 are symmetric, i.e., $\Gamma_1 = \Gamma_1^T$, $\Gamma_2 = \Gamma_2^T$ and $\Gamma_3 = \Gamma_3^T$, the Lyapunov time derivative is obtained as:

$$\dot{V} = -\gamma_1\tilde{I}^2 - \gamma_2\tilde{T}^2 - \gamma_3\tilde{N}^2 \leq 0. \tag{20}$$

As one can observe from Eq. (20), derivative Lyapunov function is negative semi definite, and the proposed control method guarantees the stability of the system. The immune, tumor and normal cells converge to their desired values if the control law that is obtained from Eq. (10) is implemented.

Using the Barbalat's lemma, [33], and differentiating Eq. (20) we get:

$$\ddot{V} = -2(\gamma_1\tilde{I}\dot{\tilde{I}} + \gamma_2\tilde{T}\dot{\tilde{T}} + \gamma_3\tilde{N}\dot{\tilde{N}}). \tag{21}$$

Since $\tilde{I}, \tilde{T}, \tilde{N}, \dot{\tilde{I}}, \dot{\tilde{T}}$, and $\dot{\tilde{N}}$ are bounded, Eq. (21) is bounded, thus $\dot{V}$ is uniformly continues. According to Barbalat's lemma, the parameters estimation error are bounded and the tracking errors of immune, tumor and normal cells converge to zero.

4. Extended Kalman filter observer

Since, the measurement of immune cell is difficult in the lab environment and require complex experiments, we use a nonlinear observer to estimate the immune cells. We use the estimated value instead of its measurement values in the adaptive controller. In this section, an observer is designed to estimate the immune cells.

There are many ways to design an observer, such as Kalman filter, sliding mode, MRAS (model reference adaptive system) and extended Kalman filter. Since, the tumor growth represents nonlinear behavior, a nonlinear observer must be used. Among the nonlinear observers, the implementation of extended Kalman filter is easier. Therefore, we use an extended Kalman filter to estimate the amount of immune cells. The extended Kalman filter algorithm is provided in the following steps.

A discrete time nonlinear system is considered as:

$$\begin{aligned}x_k &= f(x_{k-1}, u_{k-1}) + w_k,\\ y_k &= Hx_k + v_k.\end{aligned} \tag{22}$$

Where w_k and v_k are process and measurement noise, respectively. They are assumed to be zero mean white Gaussian noise with R and Q covariance matrices, i.e.,

$$\begin{aligned}\{w_k w_j^T\} &= Q\delta_{kj}\ Q > 0,\\ \{v_k v_j^T\} &= R\delta_{kj}\ R > 0,\\ \{w_k v_j^T\} &= 0.\end{aligned} \tag{23}$$

In Eq. (22), x_k's are the states of the system (the amount of immune, normal, and tumor cells) and y_k is the measurement vector that contains normal and tumor cells, these vectors are defined as:

$$\begin{aligned}x_k &= [I_k\ \ T_k\ \ N_k]^T,\\ y_k &= [T_k\ \ N_k]^T,\end{aligned} \tag{24}$$

f is obtained from the cancer chemotherapy model that is described in the Eqs. (1), (2) and (3). Since we assume the uncertainty in the model parameters, we use the estimated values of parameters which are obtained by Eq. (11), in the extended Kalman filter observer. Hence, the f is defined as:

$$f = \begin{bmatrix}\hat{s} + \frac{\hat{\rho} I_k T_k}{\hat{\alpha} + T_k} - \hat{c}_1 I_k T_k - \hat{d}_1 I_k - \hat{a}_1 u_{1_k} I_k\\ \hat{r}_1 T_k(1 - \hat{b}_1 T_k) - \hat{c}_2 I_k T_k - \hat{c}_3 T_k N_k - \hat{a}_2 u_{2_k} T_k\\ \hat{r}_2 N_k(1 - \hat{b}_2 N_k) - \hat{c}_4 T_k N_k - \hat{a}_3 u_{3_k} N_k\end{bmatrix}. \tag{25}$$

Extended Kalman filter estimates various states using the following procedure:

Prediction

The one-step prediction of $\hat{x}_{k|k-1}$ and its corresponding error covariance matrix $P_{k|k-1}$ are defined as:

$$\begin{aligned}\hat{x}_{k|k-1} &= f(\hat{x}_{k-1}),\\ P_{k|k-1} &= F_k P_{k-1} F_k^T + Q_k,\\ F_k &= \frac{\partial f(x)}{\partial x}|_{x=\hat{x}_{k-1}}.\end{aligned} \tag{26}$$

Update

The estimation of state $\hat{x}_k$ and estimation error covariance matrix P_k calculated as;

$$\begin{aligned}\hat{x}_k &= \hat{x}_{k|k-1} + k_k(y_k - H_k\hat{x}_{k|k-1}),\\ k_k &= P_{k|k-1}H_k^T(H_k P_{k|k-1}H_k^T + R_k)^{-1},\\ P_k &= (P_{k|k-1}^{-1} + H_k^T R_k^{-1} H_k)^{-1},\end{aligned} \tag{27}$$

where k_k is the Kalman gain, [34].

We estimate the immune cells using Eqs. (26) and (27).

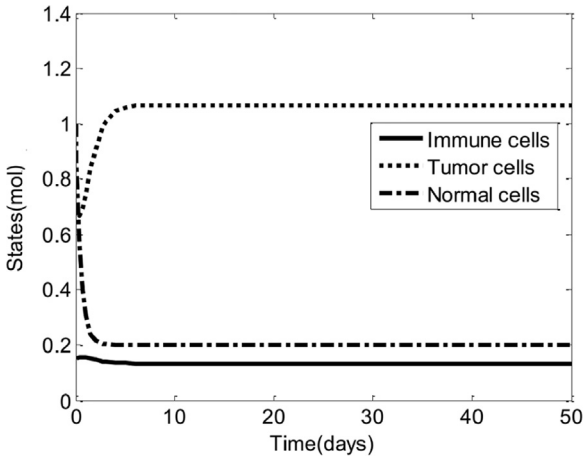

Fig. 1. Response of the system without controller with the initial values of ($I(0) = 0.15$, $T(0) = 0.7$, $N(0) = 1$).

5. Computational results

To investigate the performance of the proposed controller, we have carried out a few computational experiments. In these experiments we use the parameters that are listed in Table 1 and are reported in [31]. We have carried out three experiments on the system without the controller, with the adaptive controller and with both the adaptive controller and the nonlinear observer.

Case 1: System without controller

In this case, we simulate the tumor dynamical system without the presence of control signal (drug injection). In this experiment we assume the initial state value to be ($I(0) = 0.15$, $T(0) = 0.7$, $N(0) = 1$).

The time response of the system states (immune, tumor and normal cells) is shown in Fig. 1. According to this figure, the tumor cells growth increases, while the immune and normal cells populations decrease. Clearly, in this case the system does not have a desirable outcome.

Case 2: System with adaptive controller

In this case, the controller that is derived in Eq. (10), is implemented. We assume that the parameters of model have uncertainty, and are estimated using Eq. (11). These estimated values are used in the control law.

The initial value of state vector is assumed to be ($I(0) = 0.15$, $T(0) = 0.7$, $N(0) = 1$). The initial values of the parameters are assumed to be ($r_1 = 0.51$, $b_1 = 1$, $c_2 = 0.8$, $c_3 = 2.5$, and $a_2 = 0.15$). Time response of the system states and the parameters estimation of Eq. (2) are shown in Figs. 2 and 4, respectively. The control signals are shown in Fig. 5.

The interaction between immune, tumor and normal cells, in the three dimensional graph, is shown in Fig. 3. The desired and initial values of the immune, tumor and normal cells are ($I_d = 1.7$, $T_d = 0$, and $N_d = 1$) and ($I(0) = 0.15$, $T(0) = 0.7$, and $N(0) = 1$), respectively.

According to Figs. 2 and 3, when drugs are injected the tumor cells population decreases. After an initial decrease of the normal cells, the drug dosages cause the normal cells population increases to reach its desired value. Immune cells populations grows and plays an important role in killing the tumor cells.

As one can observe from Fig. 5, the drug dosages are bounded and when the tumor cells are reduced, the drug dosages are decreased. Fig. 4, shows the estimated parameters. This figure shows that the estimated parameters converge to their actual values and the system is robust against the assumed uncertainty. The actual values of parameters are described in Table 1.

Case 3: System with an extended Kalman filter observer

In this case, the controller with an extended Kalman filter is implemented. Immune cells are estimated, and the estimated values are used in the control process. The initial parameters of an observer in Eqs. (26) and (27) are assumed to be: $P = 100I_3$, $Q = 0.001I_3$, $R = I_2$.

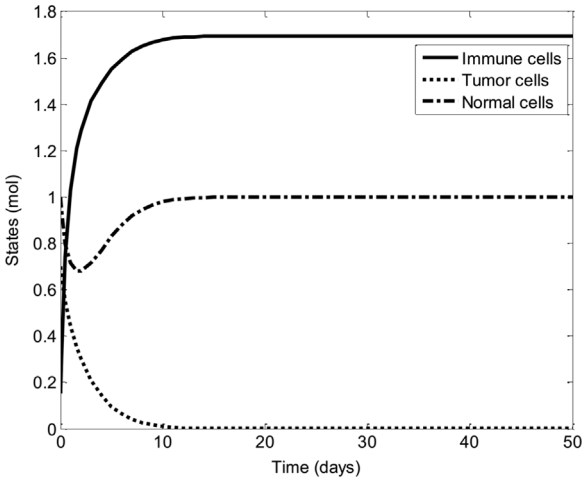

Fig. 2. The system response in presence of the robust adaptive controller. Desired values are ($I_d = 1.7$, $T_d = 0$, and $N_d = 1$) and the state initial values are ($I(0) = 0.15$, $T(0) = 0.7$, and $N(0) = 1$). Using the controller, the states are tracking their desired values.

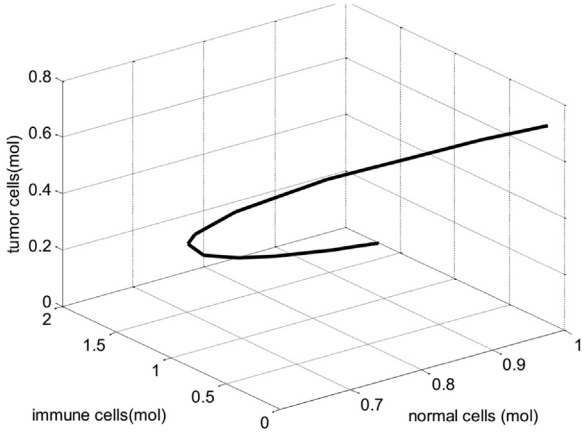

Fig. 3. The interaction between immune, tumor and normal cells, in the three dimensional graph, in presence of the robust adaptive controller. Desired values are ($I_d = 1.7$, $T_d = 0$, and $N_d = 1$) and the state initial values are ($I(0) = 0.15$, $T(0) = 0.7$, and $N(0) = 1$).

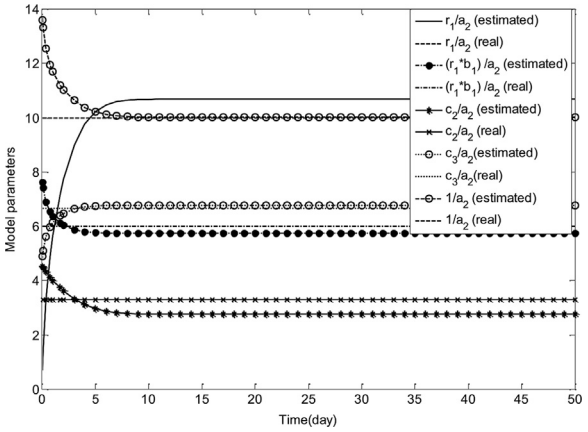

Fig. 4. Estimated and real values of the parameters of tumor dynamics in the presence of the controller.

The initial values of the estimated parameters are assumed to be (δ, $b_1 = 1$, $c_2 = 0.8$, $c_3 = 2.5$, and $a_2 = 0.15$). The initial values of states are assumed to be ($I(0) = 0.15$, $T(0) = 0.7$, and $N(0) = 1$) and the desired values are ($I_d = 1.7$, $T_d = 0$, and $N_d = 1$). The estimated values of immune cells are shown in Fig. 6.

The time response of the system states is shown in Figs. 7.

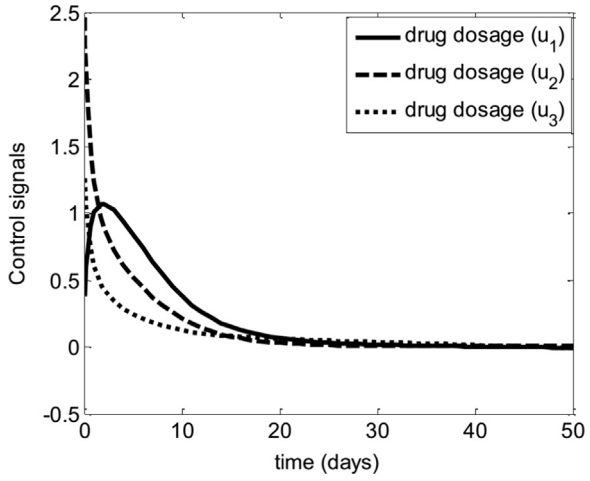

Fig. 5. The chemotherapy drug dosages u_1, u_2 and u_3 that make the immune, tumor and normal cells converge to their desired values. The dosage of u_2 is greater than the dosages of u_1 and u_3.

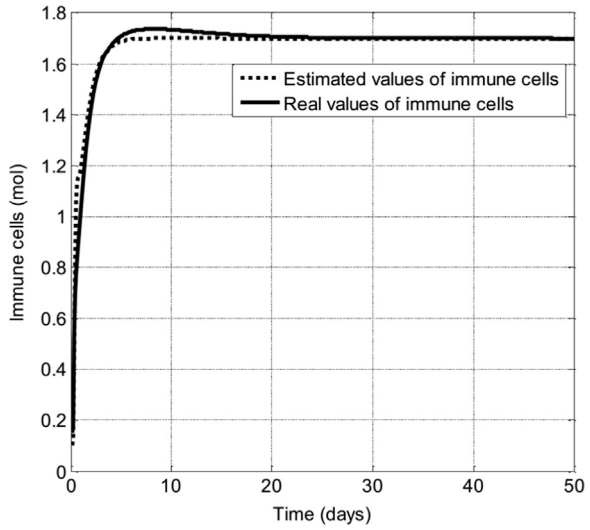

Fig. 6. Estimated values of immune cells using extended Kalman filter. The initial values of the observer are ($P = 100I_3$, $Q = 0.001I_3$, $R = I_2$), and the initial value of the states are ($I(0) = 0.15$, $T(0) = 0.7$, and $N(0) = 1$).

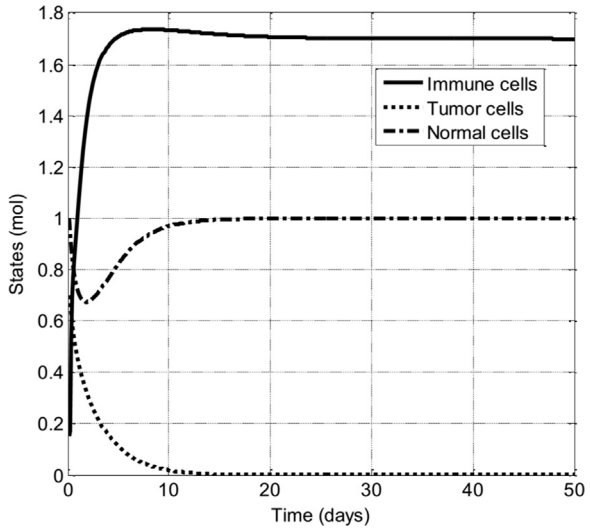

Fig. 7. Response of the system with robust adaptive control and extended Kalman filter. Desired values are ($I_d = 1.7$, $T_d = 0$, and $N_d = 1$) and the initial values are ($I(0) = 0.15$, $T(0) = 0.7$, and $N(0) = 1$), using the controller, the states track their desired values.

According to Fig. 6, the estimated values of immune cells are converged to their real values. Real values of immune cells are generated by the differential equations of cancer chemotherapy model that are described in Eqs. (1), (2) and (3). The parameter values of these equations are described in Table 1. As one can observe from Fig. 7, when these estimated values are used in the controller, the states track their desired values. This shows that the system is stable in the presence of the designed observer.

6. Comparison to the prior work

In this section, we will discuss a comparison between our work and similar prior work. The optimal control has been widely used in many papers, such as [31], and is the most popular method to control the tumor growth. This method provides the tracking performance of biological cells (tumor, immune and normal cells) to their desired values. Moreover, in this approach the amount of calculated drug dosage is within an acceptable range and does not have a damaging effect on normal cells. But this approach assumes the model parameters are known, and as a result is not robust against parameters uncertainty. Adaptive and robust control are two important approaches, that solve this problem. The robust control approach, (see e.g., [24]), is robust control based on μ-synthesis, which assumes an appropriate cost function, that minimizes the amount of drug dosages while the tumor growth is reduced. This method is robust against models uncertainty. However, the model parameters are not estimated in the control loop. Adaptive robust controller is another approach that is robust against parameters uncertainty, and also estimates the model parameters in the control loop which is the most similar work to ours [26]. In this paper, the adaptive robust control have been used, but the first order nonlinear model that only uses tumor cells, is considered. In this paper three nonlinear models, including log-kill hypothesis, Norton-Simon hypothesis and E_{max} hypothesis are considered. The log kill hypothesis model that is used in this paper is expressed as:

$$\dot{x} = -rxln(x) - \delta xu(t), \tag{28}$$

where r is the tumor growth rate and δ is the constant coefficient. The values of these parameters are listed in Table 2.

The control signal that is obtained in this paper is,

$$u = Y\hat{\theta}. \tag{29}$$

where Y is the regressor vector that is defined as following;

$$Y = \left[-\frac{\phi}{x} \quad -lnx\right], \tag{30}$$

and ϕ is expressed as:

$$\phi = \dot{x}_d - \alpha(x - x_d). \tag{31}$$

In Eq. (29), $\hat{\theta}$ is the estimation parameters vector and is obtained by,

$$\dot{\hat{\theta}} = \tilde{x}x\Gamma Y^T \text{sign}(\delta). \tag{32}$$

The initial value of tumor cell is assumed to be $x_0 = 0.9$, and the desired values of tumor cell is $x_d = 0$. The initial values of parameters which are estimated by Eq. (32) are assumed to be ($\delta = 0.55$, $r = 0.12$).

According to the computational results in this paper, tumor cells populations are controlled, but the normal and immune cells are not considered in the model, so they are not controlled by the adaptive robust controller. If high

Table 2
Nominal parameters of the model.

Parameter	Value
r	0.1
δ	0.45

drug dosage is injected to the system, more toxicity is generated and as a result more normal cells are killed. In our work a third order nonlinear model is considered and we control the immune, normal and tumor cells, simultaneously, and the problem of killing the normal cells is solved.

7. Conclusion

In this paper, an adaptive robust control strategy with an extended Kalman filter observer is developed. This controller adjusts the drug dosages and controls the tumor, immune and normal cells in chemotherapy. In this approach, the Lyapunov stability theorem is used to prove the stability and convergence of process. The parameters of model are estimated in the control loop, and the controller is robust against parameters uncertainty. Since, measuring the immune cell is difficult in practice, a nonlinear extended Kalman filter observer is used to estimate this value.

Computational results show the efficiency of adaptive control in the presence of extended Kalman filter. According to the computational results, after implementation of the controller, the tumor, normal and immune cells are tracking their desired values. This approach guarantees the estimation of model parameters within an acceptable error bound and the observer estimates the immune cells well. The estimation error of immune cells converges to zero. Moreover, our approach achieves the same performance as optimal control, with the advantage that the optimal control is not robust against parameters uncertainty. Thus, the adaptive robust control is more efficient than the optimal control approach in this problem.

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