Informatics in Medicine Unlocked 8 (2017) 1–7

Contents lists available at ScienceDirect

Informatics in Medicine Unlocked

journal homepage: www.elsevier.com/locate/imu

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

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ARTICLE INFO

Keywords:
Cancer
Chemotherapy
Robust control
Kalman filter.

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

☆ This work is partially supported by University of Tehran and Behnam Daheshpour Charity Organization. Any opinions, findings, and conclusions or recommendations expressed in this material are those of the authors and do not necessarily reflect the views of University of Tehran nor Behnam Daheshpour Charity Organization.

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http://dx.doi.org/10.1016/j.imu.2017.03.002
Received 18 January 2017; Received in revised form 3 March 2017; Accepted 11 March 2017
Available online 05 April 2017

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