Optimal Control of Immunogenic Tumor Cells Population Growth

Morteza Nazari Monfared*, Ahmad Fakharian*,
M. B. Menhaj, Rezvan Abbasi***

**Faculty of Electrical, Biomedical and Mechatronics Engineering, Qazvin Branch, Islamic Azad University, Qazvin, Iran, (e-mail: m.n.monfared@qiau.ac.ir, ahmad.Fakharian@qiau.ac.ir, rezvan.Abbasi@qiau.ac.ir)*
*** Center of Excellence on Control and Robotics and the Department of Electrical Engineering, Amirkabir University of Technology, Tehran, Iran, (e-mail: Menhaj@aut.ac.ir)*
Corresponding Author: Ahmad Fakharian

Abstract: The optimal control of cancerous Cells proliferation is the main contribution of this paper. Chemotherapy is an efficient medical approach to eradicate malignant cells. These drugs are highly toxic and may have lethal side-effects; hence, determining an optimal drugs injection protocol has turned into a challengeable problem. To cope with the problem from the system's theory standpoint, a well-known fourth-order nonlinear dynamic model is applied to describe the system behavior.Firstly, the unique solution of the system's differential model is guaranteed by employing the Lipschitz condition. Then, to eradicate tumor cells by minimum injection of drugs, a nonlinear optimal control technique is proposed. The controller originates at the approximate polynomial solution of the Hamilton-Jacobi-Bellman (HJB) nonlinear partial differential equation (PDE). By this method, the complexity of the controller structure, based on its order, can be adjusted by the designer. Finally, some simulations are carried out to highlight the effectiveness of the controller in terms of optimality, treatment time, and enlarging of the system's domain of attraction.

Keywords: Cancer cells proliferation control, Hamilton-Jacobi-Bellman PDE, Lipschitz condition, nonlinear optimal control, polynomial approximate solution.

1. INTRODUCTION

Cancer, in a simplified interpretation, is a disorder in the apoptosis process and the inability of cells in receiving DNA's commands to stop dividing. This uncontrolled proliferation of cells results in forming tumors that can have deadly consequences. This uninhibited population of cells interacts dynamically with the population of other cells. Mathematical modelling helps to have a better understanding of these interplays. There are several proposed mathematical models in papers based on the mutual effects of different cells and treatment approaches (Adam and Bellomo, 2012). The utilized dynamic model in this paper is formed based on the interplay of tumor-immune-host cells and chemotherapy treatment (De Pillis and Radunskaya, 2003). The given model is validated by employing the Lipschitz condition to check the solution existence and uniqueness of the system differential equations (Khalil and Grizzle, 2002). These properties have not been investigated before to the best of our knowledge.

These malignant cells should be eradicated by therapies like chemotherapy, radiotherapy, and so on. Another significant arisen problem is the treatment protocol. Lethal side effects due to improper dosage of injected chemotherapy drugs highlight the role of determining an optimal treatment protocol, i.e., proposing a regimen that minimizes Drugs' dosage and the average population of tumor cells (Swan, 1990). There have been great efforts into proposing new optimal protocols based on the maximum principle approach (Murray, 1990), bang-bang theory (Ledzewicz and Schättler, 2002), state-dependent Riccati equation (SDRE) (Itik et al., 2010, Batmani and Khaloozadeh, 2013), and other efficient techniques (Castiglione and Piccoli, 2007).

The proposed chemotherapy regimen in this paper originates from a nonlinear optimal controller. This controller is designed based on the approximate solution of the HJB nonlinear PDEs (Kirk, 2004). Several numerical techniques have been proposed to solve these PDEs since they do not have any closed-form solution for the complex nonlinear systems (Fakharian et al., 2010; Navasca and Krener, 2000; Sassano and Astolfi, 2012; Beard et al., 1997; Hwang et al., 2009). Truncated power series expansion is an approximate technique that is utilized in this paper and its effectiveness for the system is shown from different aspects. The presented approach does not have some drawbacks of the SDRE technique (Itik et al., 2010), as another useful method, and gives a unified controller needless to a switching mechanism. For more information, see (Çimen, 2008).

The rest of this paper is organized as follows: in section 2, a description of the mathematical model and the properties of its solution are presented. Section 3 is related to the design of the optimal controller for the system. An overview of HJB PDEs and its approximate solution is presented in this section, too. The proposed approach is compared with another efficient technique in section 4. Open and closed-loop systems are simulated in section 5, where the system's performance is investigated from different considerable aspects. Finally, in section 6, the conclusion is drawn.

2. GOVERNING DYNAMIC OF CELLS INTERACTIONS

There are different supportive theories to define the mechanism of cancerous cells proliferation and interplays between them and other cells in the human body (Kirschner and Panetta, 1998; De Pillis et al., 2006). Also, these mechanisms are impressed by the nature of the tumor, diffusion or compact, its homogeneity, and development of its vasculature, angiogenesis. In this paper, the characteristics of a solid tumor model and its eradication are investigated (Araujo and McElwain, 2004). For these types of tumors, great significance is placed into the population growth dynamic. Malignant tumor and normal cells enter a competition for nourishment and space, while the competition between tumor and immune cells is in a prey-predator manner. These competitions, the mutual effects of cells, and considering chemotherapy treatment lead to forming the following model (De Pillis and Radunskaya, 2003):

$$\begin{aligned}
\dot{N} &= r_1 N\left(1-b_1 N\right) - c_1 TN - \alpha_1\left(1-e^{-v}\right)N \\
\dot{T} &= r_2 T\left(1-b_2 T\right) - c_2 IT - c_3 TN - \alpha_2\left(1-e^{-v}\right)T \\
\dot{I} &= s + \frac{\rho IT}{\alpha+T} - c_4 IT - d_1 I - \alpha_3\left(1-e^{-v}\right)I \\
\dot{v} &= -d_2 v + u
\end{aligned} \tag{1}$$

where $N = N(t)$, $T = T(t)$, and $I = I(t)$ are the number of normal, tumor, and immune cells at time t, respectively. The fourth state, $\upsilon = \upsilon(t)$, is the concentration of drug in blood and $u = u(t)$ is the dose of injected drugs as the control signal. The parameters description and their values are given in Appendix A.

Competition between the cells finally ends, and their population reaches a steady-state value. These steady values are considered as the equilibrium points (EPs) of the dynamic system (1) and are classified into three main groups: dead, coexistence, and healthy EPs. In the first group, the number of host cells is zero. In the second group, tumor cells are present. These are undesirable EPs. The number of tumor cells in healthy EP is zero, while the number of two other cells meets the healthy condition (De Pillis and Radunskaya, 2003). Reaching this point is a significant control objective.

2.1 Checking Lipschitz Condition

Consider the following nonlinear system with the following affine structure ($x \in \mathbb{R}^n$, $f(x) \in \mathbb{R}^n$, $g(x) \in \mathbb{R}^{n\times m}$, and $u = u(t) \in \mathbb{R}^m$)

$$\dot{x} = f(x) + g(x)u \;;\; x(t_0) = x_0 \tag{2}$$

where $x = x(t)$, t_0, and x_0 are the vector of the system's states, initial time, and initial state, respectively. By defining $x = \begin{bmatrix} N & T & I & v \end{bmatrix}^T$, the system (1) is rewritten as the format (2). Then, following demonstrations are applied to the open-loop version of the system (2), $u = \upsilon = 0$.

Lemma 1. [(Khalil and Grizzle, 2002), P88]. Continuity of $f(x)$ in its arguments for the initial value problem (IVP) (2) ensures that there is at least one solution for the problem.

The right-hand side of system (1) consists of polynomial continuous terms except for the Michaelis-Menten type fraction function in third dynamic, which becomes discontinuous at $T = -\alpha$. Since $\alpha \succ 0$ and the population of tumor cells cannot be negative, this discontinuity is not the case. Thus, the existence of at least one solution for the system (1) is ensured.

Theorem 1. [(Khalil and Grizzle, 2002), Theorem 3.3.] Let $f(x)$ be locally Lipschitz for all x in domain $D \subseteq R^n$. Let W be a compact set of D, $x_0 \in W$, and suppose it is known that every solution of system (2) lies in W. Then there is a unique solution that is defined for all $t \geq t_0$.

Based on the Theorem 1, a unique solution to the interval $t \geq t_0$ is ensured by these two conditions. The first condition is demonstrated by applying Lemma 3.2 (Khalil and Grizzle, 2002) to the system (1) for domain $D: 0 \leq x_i \leq \gamma$, where $i = 1,2,3$ and γ stands for the upper bound of the population of different cells. This Lemma relates satisfing the Lipschitz condition to the calculating of the upper bound L for the function $\left\| \frac{\partial f(x)}{\partial x} \right\|_\infty$, i.e., $\left\| \frac{\partial f(x)}{\partial x} \right\|_\infty \leq L$. The upper bound is obtained as

$$L = \begin{cases} r_2 + 2\left(c_2 + c_3 + r_2 b_2\right)\gamma & ;\, 0 \leq \gamma \leq 0.214 \\ \dfrac{1}{\alpha^2}\left(\alpha^2 d_1 + 2\left(c_4\alpha^2 + \rho\alpha + \alpha d_1\right)\gamma \right. & \\ \qquad \left. + \left(4c_4\alpha + d_1 + \rho\right)\gamma^2 + 2c_4\gamma^3\right) & ;\, 0.214 \leq \gamma \end{cases}$$

The calculation of the constant L is postponed to Appendix B. The second condition in terms of the nonlinear dynamic system analysis is interpreted as the existence of a domain of attraction W for the system's asymptotically stable healthy EP. The domain W can be considered as $D: 0 \leq x_i \leq \gamma$ for the system (1). By these explanations, the existence and uniqueness of the solution for the open-loop system (1) are guaranteed.

3. DESIGN OF THE POLYNOMIAL OPTIMAL CONTROLLER

Various papers have focused on designing a controller for the tumor growth system (Rokhforoz et al., 2017; Chien et al., 2009). A significant factor in the cancer treatment regimen is the sense of optimality. The problem in general structure is defined as designing an optimal feedback controller, $u^* = u^*(x)$ for the system (2), which stabilizes the system's

desirable equilibrium point asymptotically while minimizes the cost function

$$J(x,u)=\int_0^{\infty} L(x,u)\,dt \tag{3}$$

To cope with this problem, let define the scalar function $V=V(x)$ as the minimum cost function (3) and form the following Hamiltonian function

$$H(x,u,V_x)=L(x,u)+V_x.\left[f(x)+g(x)u\right] \tag{4}$$

where V_x stands for the gradient of the function $V(x)$ with respect to x. Now, the HJB PDEs are given as

$$\underset{u}{Min}\left\{L(x,u)+V_x.\left[f(x)+g(x)u\right]\right\}=0 \tag{5}$$

and

$$L(x,u^*)+V_x.\left[f(x)+g(x)u^*\right]=0 \tag{6}$$

They originates from employing nonlinear dynamic programming and principle of optimality to nonlinear continuous-time systems (Kirk, 2004). The PDE (5) can be rewritten as follows:

$$\left(\frac{\partial}{\partial u}\left[L(x,u)+V_x.f(x,u)\right]\right)\Big|_{u=u^*}=0 \tag{7}$$

Generally, these PDEs do not have any closed form solution; thus, the issue of approximate solution is arisen in facing with these PDEs. One of the efficient approximate approaches is power series expansion (PSE) (Navasca and Krener, 2000).

3.1 PSE Approximate Solution

Let the integrant of the cost function (3) has the following quadratic structure

$$L(x,u)=0.5x^TQx+0.5u^TRu \tag{8}$$

Where $Q=Q^T\geq 0$ and R=R^T>0. Suppose that the input matrix $g(x)$ in (2) is a constant matrix, $g(x)=B$. It is assumed that the vector field $f(x)$ in (2), optimal control signal u^* in (6), and $V(x)$ in (6) have the following power series expansion around the system's desirable operation point:

$$f(x)=Ax+F^{[2]}(x)+F^{[3]}(x)+\text{H.O.T.} \tag{9}$$

$$u^*(x)=Kx+u^{[2]}(x)+u^{[3]}(x)+\text{H.O.T.} \tag{10}$$

and

$$V(x)=0.5x^TPx+V^{[3]}(x)+u^{[4]}(x)+\text{H.O.T.} \tag{11}$$

where $K\in\mathbb{R}^{m\times n}$ and $P\in\mathbb{R}^{n\times n}$. Over this paper, the symbol $Z^{[i]}$ for a given function Z(x) denotes the terms of the degree i in the power expansion series and H.O.T. stands for high order terms.

By substituting (8) to (11) for corresponding functions in (6) and (7), separating terms with identical degree, and putting them equal to zero, we would have following equations for the matrices P and K, respectively:

$$A^TP+PA-PBR^{-1}B^TP+Q=0 \tag{12}$$

$$K=-R^{-1}B^TP \tag{13}$$

and for $V^{[i]}(x)$ and $k^{[i-1]}(x)$

$$\sum_{y=2}^{i-1}V_x^{[y]}\left\{F^{[i-(y-1)]}(x)+Bk^{[i-(y-1)]}(x)\right\}+V_x^{[i]}.(A+BK)x=0 \tag{14}$$

$$k^{[i-1]}(x)=-R^{-1}B^T\left(V_x^{[i]}\right)^T \tag{15}$$

respectively, where $i\geq 3$. Equations (12) and (13) are obtained by separating terms with degree two in (6) and degree one in (7). Also, equations (14) and (15) are acquired by separating terms with degree i in (6) and degree $i-1$ in (7). To obtain $V^{[i]}(x)$ from (14), it is vital to employ the following approximation

$$V_x^{[i]}(x).(A+BK)x\approx V^{[i]}(x) \tag{16}$$

therefore, (14) is rewritten as

$$V^{[i]}(x)=-\sum_{y=2}^{i-1}V_x^{[y]}.\left\{F^{[i-(y-1)]}(x)+Bk^{[i-(y-1)]}(x)\right\} \tag{17}$$

To desgin the controller, it is necessary to obtain $V^{[i]}(x)$, calculate its deravative with respect to the states, and substitute for $V_x^{[i]}(x)$ in (15). It worth noting that if the linear part of the optimal control problem is nice then such as approximate solution for the HJB PDE exist (Hunt and Krener, 2010).

3.2 Population Control of Cancerous Cells

The problem is defined as minimizing the average number of cancerous cells with minimum dosage of chemotherapy drugs in the treatment regimen. The cost function is supposed to be in the given format (3) with integrant function (8). The weighting matrices are given in Appendix C. They are selected corresponding the matrices in another paper (Itik et al., 2010). The order of the controller is confined to seventh degree, while higher orders can be calculated straightforwardly.Therefore, the polynomial expanded version of the system (1) should be acquired using truncated Taylor

series expansion at seventh order around the healthy equilibrium point.

Based on the aforementioned notes and defining $x=[N\text{-}1/b_1\ T\ I\text{-}s/d_1\ v]^T$ as the state vector of the system (1), the matrix $P=P^T>0$ in the function $V^{[2]}(x)=0.5x^TPx$ in (11) can be calculated by solving the (12). The functions $V^{[n]}(x)$, for $n=3,4,5,...,8$, are obtained from (17) as follows:

$$V^{[3]}(x)=-x^TPF^{[2]}(x) \tag{18}$$

$$\begin{aligned}V^{[4]}(x)= \ & -x^TPF^{[3]}(x)-V_x^{[3]}(x)F^{[2]}(x)\\ & +0.5V_x^{[3]}(x)BR^{-1}B^TV_x^{[3]^T}(x)\end{aligned} \tag{19}$$

$$\begin{aligned}&V^{[5]}(x)=-x^TPF^{[4]}(x)-V_x^{[3]}(x)F^{[3]}(x)\\ &-V_x^{[4]}(x)F^{[2]}(x)+V_x^{[4]}(x)BR^{-1}B^TV_x^{[4]^T}(x)\end{aligned} \tag{20}$$

$$\begin{aligned}&V^{[6]}(x)=-x^TPF^{[5]}(x)-V_x^{[3]}(x)F^{[4]}(x)\\ &+0.5V_x^{[4]}(x)BR^{-1}B^TV_x^{[4]^T}(x)-V_x^{[4]}(x)F^{[3]}(x)\\ &+0.5V_x^{[5]}(x)BR^{-1}B^TV_x^{[3]^T}(x)-V_x^{[5]}(x)F^{[2]}(x)\end{aligned} \tag{21}$$

$$\begin{aligned}&V^{[7]}(x)=-x^TPF^{[6]}(x)-V_x^{[3]}(x)F^{[5]}(x)\\ &-V_x^{[4]}(x)F^{[4]}(x)-V_x^{[5]}(x)F^{[3]}(x)-V_x^{[6]}(x)F^{[2]}(x)\\ &+V_x^{[5]}(x)BR^{-1}B^TV_x^{[4]^T}(x)+V_x^{[6]}(x)BR^{-1}B^TV_x^{[3]^T}(x)\end{aligned} \tag{22}$$

$$\begin{aligned}&V^{[8]}(x)=-x^TPF^{[7]}(x)-V_x^{[3]}(x)F^{[6]}(x)\\ &-V_x^{[4]}(x)F^{[5]}(x)-V_x^{[5]}(x)F^{[4]}(x)-V_x^{[6]}(x)F^{[3]}(x)\\ &-V_x^{[7]}(x)F^{[2]}(x)+0.5V_x^{[5]}(x)BR^{-1}B^TV_x^{[5]^T}(x)\\ &+V_x^{[6]}(x)BR^{-1}B^TV_x^{[4]^T}(x)+V_x^{[7]}(x)BR^{-1}B^TV_x^{[3]^T}(x)\end{aligned} \tag{23}$$

where the structure of the controllers $k^{[2]}(x)$, $k^{[3]}(x)$, $k^{[4]}(x)$, $k^{[5]}(x)$, $k^{[6]}(x)$, and $k^{[7]}(x)$ are calculated according to (15).The structure of the fifth-order controller in terms of population of cells is given in Appendix C.

4. COMPARISON WITH SDRE TECHNIQUE

One of another interesting optimal controller design techniques for nonlinear systems is the state dependent Riccati equation (SDRE) (Çimen, 2008). In this technique a controller is designed upon the solution of the following extended version of the well-known Riccati algebraic equation (ARE) (12) for state-dependent nonlinear system $\dot{x}=A(x)x+Bu$

$$A^T(x)P(x)+P(x)A(x)-P(x)BR^{-1}B^TP(x)=0 \tag{24}$$

which should be solved for $P(x)$. The state-dependent ARE (24) can be considered as a simplified version of the HJB PDE (6). The SDRE technique has been employed to control the population of cancerous cells (Itik et al., 2010). It is an effective approach but it has some drawbacks.

In the SDRE approach, the formulation (24) imitates the format of ARE (12) for the state-dependent nonlinear system, $\dot{x}=A(x)x+Bu$, with $V_x(x)=x^TP(x)$. This imitation imposes some conditions like positive definiteness and symmetry on the state dependent matrix $P(x)$, which originate similar conditions for P, $P=P^T>0$, in a Lyapunov function $V(x)=x^TPx$ with $V_x(x)=x^TP$ for the linear systems. These conditions are not the case for the PSE approach.

The formulation (24) should be solved to obtain $P(x)$. It is not possible to obtain $P(x)$ in a closed-form. Instead it is solved for different operation points' of the system $\dot{x}=A(x)x+Bu$. At first, it is evaluated at a series of operation points to transform it to a set of AREs (12). Then, these AREs are solved to obtain constant matrices $P_i=P(x)\big|_{x=\bar{x}_i}$, where $\bar{x}_i$ denotes the *i-th* operation point. It means that a series of constant matrices $P_i=P_i^T>0$ are obtained instead of the closed-form matrix $P(x)$. Therefore, acquiring the closed formulations for $V_x(x)=x^TP(x)$, $V(x)$, and $u^*(x)$ are not possible. By the SDRE technique, a series of linear controllers are acquired which applied to the system based on the operation point of the system. This necessitate a switching mechanism.

On the other hand, $V(x)$ is considered as the minimum of cost function (8), i.e.,

$$V(x)=\min_{u(x)}\int_0^\infty 0.5\left(x^TQx+u^{*T}Ru^*\right)dt \tag{25}$$

The integrant of (25) is quadratic, hence, $V(x)$ is a positive definite function and can be considered as a candidate Lyapunov function for the nonlinear system (2). According to (6) it is obvious that $\frac{dV(x)}{dt}=-L(x,u^*)$, where $\frac{dV(x)}{dt}=V_x(x).\left[f(x)+Bu^*\right]$ is the time derivative of $V(x)$ along the trajectories of close loop system (2). With respect to positive semi definiteness of $L(x,u^*)$, it can be found that $\frac{dV(x)}{dt}$ is negative semi definite; therefore, stability of the closed loop system can be proved. As a result, $V(x)$ can be utilized to analyse the stability properties of the system straightforwardly (Khalil and Grizzle, 2002). Lack of a closed formulation for $V(x)$ can be a drawback of the SDRE technique.

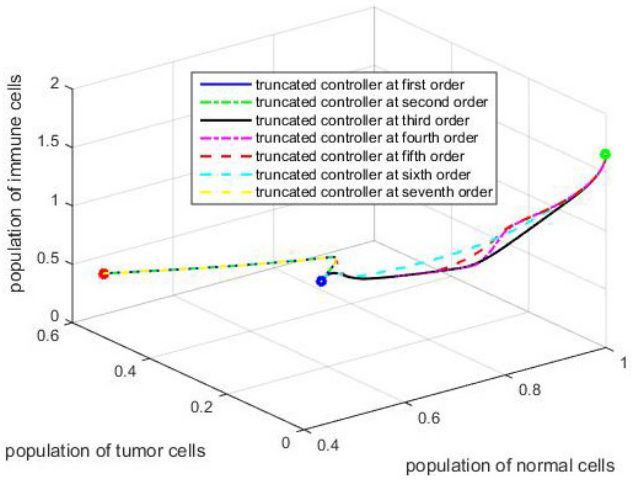

Fig. 1. Trajectory of closed-loop systems in response to an initial condition which is out of the open-loop healthy point's DOA. Green point: healthy EP, blue point: initial condition, and red point: coexistence EP.

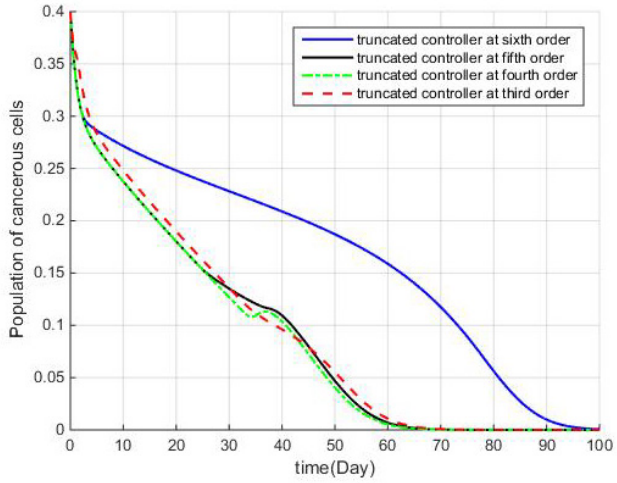

Fig. 2. Comparison between controllers for initial condition $\begin{bmatrix}0.8 & 0.4 & 0.6 & 0\end{bmatrix}^T$.

5. SIMULATION AND ANALYSIS

The open-loop system (1) based on the given values for the parameters has two stable EPs, a coexistence point and a healthy one, and three unstable EPs. Reaching a stable healthy EP is defined as the main control objective. On the other hand, from the system's theory point of view, multiple EPs implies that the domain of attraction of the healthy EP is not global and is confined by the DOA of the other EPs. Injection of chemotherapy drugs helps to enlarge the healthy EP's DOA. Mathematically, this is interpreted as forcing the system out of the basin of attraction of the stable coexistence point. This can be done by broadening the healthy point's domain of attraction. To show the efficiency of the controller in terms of enlargement domain of attraction, the closed-loop systems with truncated controllers at different orders are compared. The result of this comparison for the initial condition $\begin{bmatrix}0.625 & 0.25 & 0.625 & 0\end{bmatrix}^T$ is depicted in Fig. 1. It can be seen from Fig. 1 that the linear controller and truncated controllers at second and seventh orders do not have satisfactory performance rather than other orders. It is a reasonable possible result since applying high order terms for approximated controllers by PSE method necessarily does not lead to a wider region of attraction (Navasca and Krener, 2000).

Table1. Performance of the Closed-loop Systems.

Performance Measure	Third-Order Controller	Fourth-Order Controller
Cost Function	229.25	209.58
Treatment Time	112	109
Performance Measure	Fifth-Order Controller	Sixth-Order Controller
Cost Function	207.24	374.65
Treatment Time	110	141

The time interval of treatment process is another major factor that shows the effectiveness of the controller. The behavior of the closed-loop systems in encountring acute medical condition $\begin{bmatrix}0.8 & 0.4 & 0.6 & 0\end{bmatrix}^T$ is shown in Fig. 2. Truncated controllers at third and sixth orders are not as effective as other ones in the eradication of cancerous cells. Also, the treatment time for the fourth-order controller does not have a dramatic reduction rather than the fifth order. In Table 1, controllers are compared in terms of the cost function value and treatment time. The criteria for treatment time is $T(t) \le 1\times10^{-10}$, that means eradication of cancerous cells.

The selection between the closed-loop system by fourth and fifth-order controllers with a more desirable response is a tradeoff between the minimum value of the cost function and treatment time. In our investigation, the problem mainly is proposed based on the minimization of the cost function. A comparison between the performance of the closed-loop systems by controllers from different orders in terms of integral of square error (ISE) measure for the system's variables is reported in Table 2. It can be concluded that the truncated controller at the fifth-order has a high ability to enlarge the domain of attraction and reduction of treatment time.

Table 2. Performance of the Closed-loop Systems.

System's Variables	Normal Cells	Tumor Cells	Immune Cells	Control Signal
Fourth-Order Controller	2.6640	1.6645	42.5208	33.2367
Fifth-Order Controller	2.6694	1.7032	42.5722	28.4495

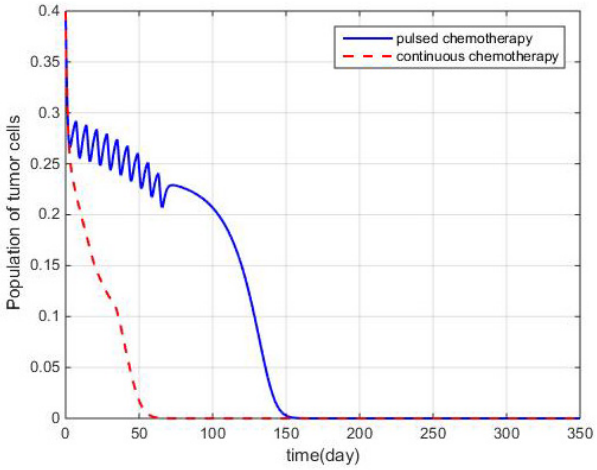

Fig. 3. Comparison between pulsed chemotherapy and continuous chemotherapy based on proposed optimal controller truncated at fifth order.

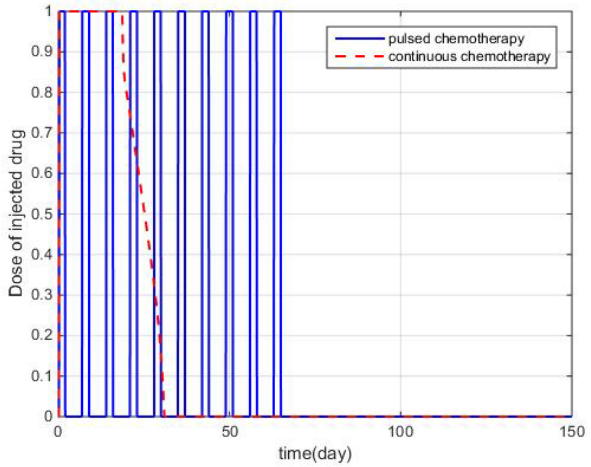

Fig. 4. Comparison between control signal of the pulsed chemotherapy and the continuous chemotherapy based on theproposed optimal controller truncated at fifth order.

In the final scenario, the problem is investigated from practical point of view. In acute medical situations with enormous growing of cancerous cells population, the first decision for the controller would be increasing the amount of the injected drugs in a continuous manner. In all of simulations the amount of the injected drugs is constrained to a unit dose. The continuous drugs injection may arose the question of practicality of the proposed controller in this paper. Since nowadays we witness great developments in hardware technologies, it seems using continuous control approaches for continual drugs injection in a specific interval is reasonable. But, to show the ability of the proposed controller, a discontinuous profile with pulsed drugs injection regimen based on the applying sampled saturated control signal is tested for the closed loop system. Fig. 3 and Fig. 4 show the response of the closed loop system and control signal to the initial condition $\begin{bmatrix}0.8 & 0.4 & 0.9 & 0\end{bmatrix}^T$, respectively. It is not unexpected that the closed loop system would have tighter domain of attraction than that of continuous drug injection.

6. CONCLUSIONS

In this paper, at first, the problem of solution existence and uniqueness using Lipschitz theory for the deterministic dynamic model governing the growth of the cancerous cells was put into perspective. A piecewise function is obtained based on the upper bound of the cells population as the Lipschitz constant. Then, the problem of determining an optimal chemotherapy regimen was addressed to inhibit the population growth of cancerous cells. The optimization measure, the cost function, for the system has a quadratic structure and is defined based on minimizing the dosage of injected drugs and the average number of tumor cells. For the determination of optimal protocol, the HJB PDE was solved approximately. The approximate solution works based on the truncated power series expansion technique. Since the optimal problem for the system was nice, the necessary condition for optimality and the existence of the approximate solution were ensured.

Controllers with different orders were designed for the system. It was shown numerically that the truncated state feedback controller at the fifth-order has a better response rather than the other six orders in our application in terms of different factors. The optimal cost function and treatment time for an initial acute medical condition, in which the population of tumor cells is very large, reduces considerably by the fifth-order controller. Also, the domain of attraction is broadened. Besides, the effectiveness of the controller from the practical point of view was shown by comparing it with conventional pulsed chemotherapy. It has dramatic effects on the reduction of the treatment time.

REFERENCES

Adam, J. A. and Bellomo, N. 2012. *A survey of models for tumor-immune system dynamics*, Springer Science & Business Media.

Araujo, R. P. and Mcelwain, D. S. 2004. A history of the study of solid tumour growth: the contribution of mathematical modelling. *Bulletin of mathematical biology,* 66**,** 1039-1091.

Batmani, Y. and Khaloozadeh, H. 2013. Optimal chemotherapy in cancer treatment: state dependent Riccati equation control and extended Kalman filter. *Optimal Control Applications and Methods,* 34**,** 562-577.

Beard, R. W., Saridis, G. N. and Wen, J. T. 1997. Galerkin approximations of the generalized Hamilton-Jacobi-Bellman equation. *Automatica,* 33**,** 2159-2177.

Castiglione, F. and Piccoli, B. 2007. Cancer immunotherapy, mathematical modeling and optimal control. *Journal of theoretical Biology,* 247**,** 723-732.

Chien, T.-L., Chen, C.-C. and Huang, C.-J. 2009. Feedback linearization control and its application to MIMO cancer immunotherapy. *IEEE Transactions on Control Systems Technology,* 18**,** 953-961.

Çimen, T. 2008. State-dependent Riccati equation (SDRE) control: A survey. *IFAC Proceedings Volumes,* 41**,** 3761-3775.

De Pillis, L. G., Gu, W. and Radunskaya, A. E. 2006. Mixed immunotherapy and chemotherapy of tumors: modeling, applications and biological interpretations. *Journal of theoretical biology,* 238**,** 841-862.

De Pillis, L. G. and Radunskaya, A. 2003. The dynamics of an optimally controlled tumor model: A case study. *Mathematical and computer modelling,* 37**,** 1221-1244.

Fakharian, A., Hamidi Beheshti, M. and Davari, A. 2010. Solving the Hamilton–Jacobi–Bellman equation using Adomian decomposition method. *International Journal of Computer Mathematics,* 87**,** 2769-2785.

Hunt, T. and Krener, A. J. Improved patchy solution to the Hamilton-Jacobi-Bellman equations. 49th IEEE Conference on Decision and Control (CDC), 2010. IEEE, 5835-5839.

Hwang, I., LI, J. and Du, D. 2009. Differential transformation and its application to nonlinear optimal control. *Journal of dynamic systems, measurement, and control,* 131.

Itik, M., Salamci, M. U. and Banks, S. P. 2010. SDRE optimal control of drug administration in cancer treatment. *Turkish Journal of Electrical Engineering & Computer Sciences,* 18**,** 715-730.

Khalil, H. K. and Grizzle, J. W. 2002. *Nonlinear systems*, Prentice hall Upper Saddle River, NJ.

Kirk, D. E. 2004. *Optimal control theory: an introduction*, Courier Corporation.

Kirschner, D. and Panetta, J. C. 1998. Modeling immunotherapy of the tumor–immune interaction. *Journal of mathematical biology,* 37**,** 235-252.

Ledzewicz, U. and Schättler, H. 2002. Optimal bang-bang controls for a two-compartment model in cancer chemotherapy. *Journal of optimization theory and applications,* 114**,** 609-637.

Murray, J. 1990. Optimal control for a cancer chemotheraphy problem with general growth and loss functions. *Mathematical Biosciences,* 98**,** 273-287.

Navasca, C. L. and Krener, A. J. Solution of hamilton jacobi bellman equations. Proceedings of the 39th IEEE Conference on Decision and Control (Cat. No. 00CH37187), 2000. IEEE, 570-574.

Rokhforoz, P., Jamshidi, A. A. and Sarvestani, N. N. 2017. Adaptive robust control of cancer chemotherapy with extended Kalman filter observer. *Informatics in Medicine Unlocked,* 8**,** 1-7.

Sassano, M. and Astolfi, A. 2012. Dynamic approximate solutions of the HJ inequality and of the HJB equation for input-affine nonlinear systems. *IEEE Transactions on Automatic Control,* 57**,** 2490-2503.

Swan, G. W. 1990. Role of optimal control theory in cancer chemotherapy. *Mathematical biosciences,* 101**,** 237-284.

Appendix A. DEFINITION OF THE SYSTEMS PARAMETERS

Table 3. Description and values of parameters for dynamic competition differential model (1).

Parameter	Description	Value
r_1	Per unit growth rate (Normal cells)	1
r_2	Per unit growth rate (Tumor cells)	1.5
b_1	Carrying capacity (Normal cells)	1
b_2	Carrying capacity (Tumor cells)	1
c_1	Competition coefficient (Nomal-Tumor cells)	1
c_2	Competition coefficient (Tumor-Immune cells)	0.5
c_3	Competition coefficient (Tumor-Normal cells)	1
c_4	Competition coefficient (Immune-Tumor cells)	1
α_1	Fraction cell kill (Normal cells)	0.1
α_2	Fraction cell kill (Tumor cells)	0.3
α_3	Fraction cell kill (Immune cells)	0.2
s	Immune source rate	0.33
ρ	Immune response rate	0.01
α	Immune threshold rate	0.3
d_1	Per capita death rate (Immune cells)	0.1
d_2	Per capita death rate (Drug)	1

Appendix B. CALCULATING LIPSCHITZ CONSTANT

$$\left\|\frac{\partial f(x)}{\partial x}\right\|_\infty = \max_{x1,x2,x3}\left(\left|\sum_{j=1}^{3}\left(\frac{\partial f(x)}{\partial x}\right)_{1j}\right|,\left|\sum_{j=1}^{3}\left(\frac{\partial f(x)}{\partial x}\right)_{2j}\right|,\left|\sum_{j=1}^{3}\left(\frac{\partial f(x)}{\partial x}\right)_{3j}\right|\right)$$

By considering $0 \le x_m \le \gamma$, for $m = 1,2,3$, without loss of generality we would have

$$\left|\sum_{j=1}^{3}\left(\frac{\partial f(x)}{\partial x}\right)_{1j}\right| = \left|r_1 - 2r_1b_1x_1 - c_1x_2\right| + \left|-c_1x_1\right|$$

$$\le r_1 + \left(2r_1b_1 + c_1\right)\left|x_1\right| + c_1\left|x_2\right| \le r_1 + 2\left(r_1b_1 + c_1\right)\gamma = h_1^*(\gamma)$$

and

$$\left|\sum_{j=1}^{3}\left(\frac{\partial f(x)}{\partial x}\right)_{2j}\right| = \left|-c_3x_2\right| + \left|r_2 - 2r_2b_2x_2 - c_2x_3 - c_3x_1\right| + \left|-c_2x_1\right|$$

$$\le r_2 + c_3\left|x_1\right| + \left(c_3 + 2r_2b_2 + c_2\right)\left|x_2\right| + c_2\left|x_3\right|$$

$$\le r_2 + 2\left(c_2 + c_3 + r_2b_2\right)\gamma = h_2^*(\gamma)$$

$$\left|\sum_{j=1}^{3}\left(\frac{\partial f(x)}{\partial x}\right)_{3j}\right|$$

$$= \left|\frac{-c_4\left(\alpha^2x_3 + x_2^2x_3 + 2\alpha x_2x_3\right) + \rho\alpha x_3}{\left(\alpha + x_2\right)^2}\right|$$

$$+ \left|\frac{-\alpha d_1 - \left(d_1 + c_4\alpha + \rho\right)x_2 - c_4x_2^2}{\alpha + x_2}\right|$$

$$= \left|\frac{1}{\left(\alpha + x_2\right)^2}\right|\left\{\left|\left(-\alpha d_1 - \left(d_1 + c_4\alpha + \rho\right)x_2 - c_4x_2^2\right)\left(\alpha + x_2\right)\right|\right.$$

$$\left. + \left|-c_4\left(\alpha^2x_3 + x_2^2x_3 + 2\alpha x_2x_3\right) + \rho\alpha x_3\right|\right\}$$

$$\le \max_{x_1,x_2,x_3} \frac{1}{(\alpha+x_2)^2}\left\{\alpha^2 d_1+\left(c_4\alpha^2+\rho\alpha\right)|x_3|+\left(2d_1\alpha+c_4\alpha^2+\rho\alpha\right)|x_2|\right.$$
$$\left.+2c_4\alpha|x_2||x_3|+\left(2c_4\alpha+d_1+\rho\right)|x_2|^2+c_4|x_2|^2|x_3|+c_4|x_2|^3\right\}$$
$$=\max_{x_1,x_2,x_3} h_3(x_1,x_2,x_3)$$

Maximum of $h_3=h_3(x_1,x_2,x_3)$ as its strict upper bound can be obtained by solving a set of algebraic equations $\frac{\partial h_3}{\partial x_k}=0$, for $k=1,2,3$, which stem from putting the gradient h_3 equal to zero. Instead of this procedure which is not straightforward, we can obtain a conservative upper bound for h_3 as follows:

$$\max_{x_1,x_2,x_3} h_3(x_1,x_2,x_3)$$
$$\le \frac{1}{\min_{x_2}\left\{(\alpha+x_2)^2\right\}}.\max_{x_1,x_2,x_3}\left\{\alpha^2 d_1+\left(c_4\alpha^2+\rho\alpha\right)|x_3|+\right.$$
$$\left(2d_1\alpha+c_4\alpha^2+\rho\alpha\right)|x_2|+2c_4\alpha|x_2||x_3|+\left(2c_4\alpha+d_1+\rho\right)|x_2|^2$$
$$\left.+c_4|x_2|^2|x_3|+c_4|x_2|^3\right\}$$
$$\le \frac{1}{\alpha^2}\left\{\alpha^2 d_1+2\left(c_4\alpha^2+\rho\alpha+\alpha d_1\right)\gamma\right.$$
$$\left.+\left(4c_4\alpha+d_1+\rho\right)\gamma^2+2c_4\gamma^3\right\}=h_3^*(\gamma)$$

Hence we would have for the Lipschitz constant $L=\max_{\gamma}\left(h_1^*(\gamma),h_2^*(\gamma),h_3^*(\gamma)\right)$. Maximum value between the functions $h_1^*(\gamma)$, $h_2^*(\gamma)$, and $h_3^*(\gamma)$ can be found by comparing their inclination, initial distance from origin, and calculating the their intersection points. Based on the quantification of parameters according to [10], we would have

$$L=\begin{cases}\left\{h_2^*(\gamma)\right. & ;\quad 0<\gamma<\gamma^*\\ h_3^*(\gamma) & ;\quad \gamma>\gamma^*\end{cases}$$

Where $\gamma^*=0.214$.

Appendix C. REQUIRED FUNCTIONS FOR DESIGNING CONTROLLER AND THE CONTROLLER STRUCTURE

$$A=\begin{bmatrix}-1 & -1 & 0 & -0.1\\ 0 & -0.325 & 0 & 0\\ 0 & -1.595 & -0.2 & -0.33\\ 0 & 0 & 0 & -1\end{bmatrix};$$

$$F^{[2]}(x)=\begin{bmatrix}-0.1x_1^2-x_1x_2-0.1x_1x_4+0.05x_4^2\\ -1.5x_2^2-0.5x_2x_3-x_1x_2-0.3x_2x_4\\ 0.183x_2^2-0.966x_2x_3-0.2x_3x_4+0.165x_4^2\\ 0\end{bmatrix};$$

$$F^{[3]}(x)=\begin{bmatrix}0.05x1x_4^2-0.016x_4^3\\ 0.15x_2x_4^2\\ 0.611x_2^3-0.111x_2^2x_3+0.099x3x_4^2-0.054x_4^3\\ 0\end{bmatrix};$$

$$F^{[4]}(x)=\begin{bmatrix}-0.016x_4^3x_1+0.004x_4^4\\ -0.05x_2x_4^3\\ -2.037x_2^4+0.370x_2^3x_3-0.033x_4^3x_3+0.103x_4^4\\ 0\end{bmatrix};$$

$$F^{[5]}(x)=\begin{bmatrix}0.004x_1x_4^4-0.0008x_4^5\\ 0.012x_2x_4^4\\ 6.79x_2^5-1.234x_3x_2^4+0.008x_3x_4^4-0.002x_4^5\\ 0\end{bmatrix};$$

$$Q=\begin{bmatrix}0 & 0 & 0 & 0\\ 0 & 200 & 0 & 0\\ 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0.2\end{bmatrix};$$

$$R=2.4;$$

$$P=\begin{bmatrix}0 & 0 & 0 & 0\\ 0 & 307.69 & 0 & 0\\ 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0.980\end{bmatrix}$$

$$u^*(N,T,I,v)=\left\{-1.0408v\right\}+\left\{-0.092v^2+13402.34T^2\right\}$$
$$+\left\{-0.103v^3-55599.179T^3-0.083Nv^2-27190.319T^2N\right.$$
$$\left.-779.33vT^2-8897.627IT^2+0.13v^2J-0.2609Tv^2\right\}$$
$$+\left\{-0.051v^4+77126.568T^4+19130.768T^2N^2+0.104N^2v^2\right.$$
$$\left.+0.096v^3I+2296.153T^2I^2-0.04Tv^3\right\}+\left\{29225.28T^3I\right.$$
$$+67307.88T^3N-0.041v^2J^2+0.0041v^3N$$
$$\left.+3078.568T^3v\right\}+\left\{11123.076T^2JN+345.64T^2vN\right.$$
$$-1426.85T^2v^2+722.37T^2vJ+0.265Tv^2J+0.08NTv^2$$
$$-36565.477T^5-0.041N^3v^2-21435.89N^2T^3$$
$$+0.00138N^2v^3+-230.769T^2I^3+0.028v^4I$$
$$-23253.61T^4I-4306.743T^3J^2-0.022v^3J^2$$
$$+0.004v^4N+30.89T^2v^3+9556.41T^4v+1597.9T^3v^2$$
$$-0.08Tv^2J^2-3692.3T^2JN^2+402.502T^2v^2J$$
$$-1307.69T^2J^2N-1056.08T^3vN+873.368T^2v^2N$$
$$+67.62820342N^2T^2v-0.041N^2Tv^2+0.022Tv^3J$$
$$-142.948T^2vJ^2-1213.15T^3vJ+0.0069Tv^3N$$
$$-16398.71T^3JN-248.717T^2vJN-0.006v^5$$
$$\left.-4615.38N^3T^2-41001.921T^4N\right\}$$