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The Application of Power Series Expansion to Optimal Control of an Immune-Oncology Nonlinear Dynamic Problem

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ABSTRACT: This paper is concerned with the eradication of tumor cells in the human body by defining an optimal protocol using a polynomial approximation technique for the injection of chemotherapy drugs. The dynamics of the system are described based on immune-oncology. Variation of host, tumor, and immune cells' populations are studied in the model during the injection of the chemotherapeutic drugs. The objective is the minimization of cancerous cells' average population by minimum drug injection to avoid the destructive side-effects of these chemotherapeutic substances. It should be done by stabilizing the population of host and immune cells around a free-tumor desirable health condition. This optimization problem by considering the nonlinear model of the system makes applying nonlinear optimal control inevitable. Solving Hamilton-Jacobi-Bellman (HJB) nonlinear partial differential equation (PDE) for the system is put into our perspective to cope with this problem. Since the dynamics of the system are not polynomial, it comprises fractional terms, this PDE cannot be solved straightforwardly. We take advantage of the power series expansion technique to approximate the solution of the PDE with satisfactory accuracy. Finally, a series of simulations are carried out to prove the capability of the controller in terms of robustness and sensitivity, increasing convergence rate for the elimination of cancerous cells, and enlargement of the domain of attraction.

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1- INTRODUCTION

Cancerous tumors emerge when the cells lose their ability to stop dividing. This leads to the formation of tumors. Malignant tumors can bring impairment for the operation of side organs or attack to other organs by angiogenesis [1]. Cancer disease is known as one of the most fatal ones. Hence, there is a wide range of researchers in different fields to cure it. The treatment approaches include surgery, chemotherapy, immunotherapy, virotherapy, radiotherapy, etc.

One of these research areas is mathematical modeling and systems control. Addressing the cancerous tumors proliferation problem from the system's theory viewpoint makes it possible for researchers to reveal various interplays between different types of cells and cells with drugs or have a more comprehensive understanding of them [2]. It also helps to take advantage of control techniques to propose effective treatment protocols and test them initially by computer simulations instead of clinical trials and errors.

The immune system of the body is a defensive organ and it reacts against the presence of malignant immunogenic cells. Based on a series of assumptions and theories which are obtained from observation of cells behavior and their interaction in vitro or in vivo, there have been proposed various types of models [2-4]. Methods of treatment and their effects on different cells are other factors that should be considered in mathematical modeling of the system. The initial model in [5] is a fifth-order one in which two out of five dynamics are not coupled with others, hence, the model is reduced to a third-order one. Also, one of the three coupled dynamics has fast variation rather than that of two others, therefore, the model is presented by a second-order differential equation which is considered as the base model for a wide range of other presented models in papers.

In [6, 7], the dynamics are extended to a fourth-order model by considering the competition of tumor-host cells and the chemotherapy treatment method. This model becomes complicated by inclusion a dynamic that governs the toxicity of chemotherapy drugs in [8] , but it is not coupled with other states. Therefore the basic model is a fourth-order one. In [9], the immunotherapy treatment by injection of Interleukin-2 (IL-2) and Adoptive cellular injection (ACI) is presented instead of chemotherapy, then, a third-order model is proposed. A model based on mixed immunotherapy and chemotherapy in presented in [10]. Also, a second-order dynamic by considering just virotherapy is presented in [11].

Chemotherapy drugs, because of their possible destructive effects need a more accurate injection protocol. Among the

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side effect, anemia, bleeding, blood clotting, kidney, and fertility problems are the most serious ones. On the side, chemotherapy is a treatment approach that is conventionally prescribed for most of the people who suffer cancer disease roughly. Compromise between the complexity of the model to comprise all cells' interactions and the simplicity of the model to analyze and determine treatment protocol is another main factor in describing models. Based on the aforementioned notes, in this paper, a well-known fourth-order nonlinear coupled ordinary differential model based on the interaction of tumor-immune cells, the competition of normal-tumor cells, and chemotherapy treatment method is exploited [7].

The main objective of any treatment regimen is inhibition of cancerous cells population growth and their eradication with minimum destructive effects on other cells and organs. It means that we are dealing with an optimization problem with a special cost function which is defined as the minimization of tumor cells' average population while the minimum dosage of the drugs is injected [12, 13]. A host number of papers, during the last decades, have focused on proposing a nonlinear controller to cope with this problem. These approaches are mainly optimal but cannot be extended to all of them [14]. Linear controllers are not the case because of the high nonlinearities of the system's dynamics and by linearization, a series of the system's properties cannot be revealed and it leads to unsatisfactory results [15]. In [8], a Lyapunov-based approach is proposed to determine the time of drug injection. Feedback linearization [16], adaptive controller [17, 18], adaptive fuzzy [19], and impulsive approach [20] are among the proposed nonlinear controllers.

The optimal nonlinear controllers are mainly formed based on potryagin's minimum principle for different cost functions [7, 21-23]. In [12], state-dependent Riccati equation (SDRE) technique is used to eradicate tumor cells for the simplified version of the model [6]. It considers mass product formulation for the effect of chemotherapeutic drugs on different cells instead of the exponential formulation. An optimal controller based on the SDRE in combination with an extended Kalman filter has been proposed for the simplified model in [24]. In this paper, we design an efficient optimal controller based on approximate solution of the Hamilton-Jacobi-Bellman (HJB) partial differential equation (PDE) [25]. It is designed in order to determine the dosage of injected chemotherapeutic drugs while satisfy the optimization conditions and stabilize the system asymptotically around the desired point. In the desired point, the population of tumor cells is zero and two other cells' populations meet the health conditions.

The PDE cannot be solved simply even for simple nonlinear systems. Proposing approximate techniques for the PDE has attracted the attention of many researchers in the fields of mathematics and control engineering even decades after presenting the HJB PDE [26-29]. Derivative and integral transforms are among the conventional tools to solve the PDEs. However, there are different proposed techniques in published papers that can solve the PDE indirectly [30, 31] . Designed Optimal controllers by solving HJB PDE have broad applications and their effectiveness have been proved in various papers [32-34]. The effective applied method in this paper, as our main contribution, is truncated power series expansion which has a fast computational procedure and makes it possible to solve a set of algebraic equations instead of PDE one. It also can determine the complexity of the controller in terms of its order based on the designer requirement and satisfying the closed-loop system desired measures. The obtained controller is in polynomial format, hence, its real implementation would be most straightforward rather than the controller with other formats. Finally, it is compared with the SDRE controller.

The rest of this paper is organized as follows: in section 2, the mathematical model is presented and analyzed in terms of placement of equilibrium point and the behavior of the open-loop system. The procedure of the controller design for the system is elaborated in section 3. An overview of the HJB PDE and its solution is presented and then it is designed for the system to eradicate tumor cells. Simulations are carried out in section 4, and finally, the conclusion is drawn in section 5.

2- IMMUNE-ONCOLOGY DYNAMICS

When a cancerous tumor is formed as a result of a malfunction in the apoptosis procedure, the immune system of the body tries to eliminate them. The immune response consists of a two-level confrontation. Innate immune system (IIS) and the adaptive immune system (AIS). IIS is the first level that responds to unnatural cells and eliminates them. It is done by natural killer (NK) cells. In the second level, AIS responds to tumor cells and eradicates them with the help of cytotoxic T-cells (CD8+). Therefore, there is an interaction between immune and tumor cells. Other cells in the host body need nutrients to survive and divide. On the other side, tumor cells do not stop dividing and need great amounts of nutrients. This leads to a competition for nutrients and space between normal (host) and tumor cells. These assumptions can be presented by the following dynamic model [6, 7]:

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

Where the population size of the normal, tumor, and immune cells at time t are presented by $N = N(t)$, $T = T(t)$, and $I = I(t)$, respectively. The control signal, the injected chemotherapy drugs, is denoted by $u = u(t)$ and its concentration in blood is specified by the fourth state $v = v(t)$.

The first terms in the first and second dynamics show the population variation of normal and tumor cells in the absence of any other cells. They are presented in a logistic form which is according to observation in vitro [35]. An overview of logistic models can be found in [36]. Instead of the logistic models, there are models can be used. A comparison between

Table 1. Description and values of parameters for the dynamic system (1) [7]

Parameter symbol	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 (Normal-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)	0.2
d_2	Per capita death rate (Drug)	1

models has been presented in [37].

Competition on nutrients for tumor-normal cells are presented by the second term in the first dynamic and the third term in the second dynamic. Immune and tumor cells have the pray-predator interaction in the Lotka-Volterra manner. The second term in the second dynamic and the third term in the third dynamic can reveal it. The presence of tumor cells makes the IIS and AIS to the response. This stimulation leads to more proliferation of immune cells which is modeled by fractional Michaelis-Menten type function in the third dynamic. Immune cells in the absence of tumor cells are produced by bone marrow constantly which is denoted by s and has a death rate equal to d_1. Injection of chemotherapy drugs increases their concentration in the blood. The effects of excessive drugs injection on cells, i.e., the effects of its toxicity, is confined by exponential terms in the first, second, and third dynamics. The concentration of drugs decreases with the rate d_2 in conditions the drug is not injected. The system's parameters and their values are described in Table 1 according to those in [7].

2-1- Analysis of the open loop dynamic systems in terms of equilibrium points

Since the system is nonlinear and highly coupled, the number of equilibrium points (EPs) of the system (1) are dependent on the values of the parameters. The number of equilibrium points has been investigated in [7]. The values of the system's parameters in this paper are selected according to Table 1. In healthy conditions, corresponding to a tumor-free version of the system (1) ($T(t)=0$ and $v(t)=0$), there are two equilibrium points $[0 \quad 1.65]^T$ and $[1 \quad 1.65]^T$ by considering $[N \quad I]^T$ as the state vector. The equilibrium points of the dynamics governing on the cells in the presence of tumor cells based on the system (1) are obtained as follows:

· The EPs for normal cells population are obtained as follows:

$$N^*(t)=0 \tag{2-a}$$

$$1-b_1N^*(t)-\frac{c_1}{r_1}T^*(t)=0 \tag{2-b}$$

· The EPs for tumor cells population are obtained as follows:

$$T^*(t)=0 \tag{3-a}$$

$$1-b_2T^*(t)-\frac{c_2}{r_2}I^*(t)-\frac{c_3}{r_2}N^*(t)=0 \tag{3-b}$$

And

· The EPs for immune cells population are obtained as follows:

$$I^*(t)=\frac{\left(a+T^*(t)\right)s}{\left(d_1+c_4T^*(t)\right)\left(a+T^*(t)\right)-\rho T^*(t)} \tag{4}$$

The system would have three to five EPs based on the solution of algebraic equations which is consisted of the combination of (2), (3), and (4). Based on the value of the parameters in Table 1., we have following EPs (The stability property of these EPs is demonstrated based on the position of eigenvalues in state matrices which are obtained by Jacobian linearization):

· Two unstable dead EPs: since the population of normal cells is zero, it is assumed that they are related to a person who is dead.

$$EP_1=\begin{bmatrix}0\\0\\1.65\end{bmatrix};\quad EP_2=\begin{bmatrix}0\\0.89\\0.3\end{bmatrix} \tag{5}$$

· Stable coexistence point: since both tumor and immune cells exist without a winner.

$$EP_3=\begin{bmatrix}0.43\\0.56\\0.43\end{bmatrix} \tag{6}$$

· Unstable coexistence point

$$EP_4=\begin{bmatrix}0.76\\0.23\\0.76\end{bmatrix} \tag{7}$$

· Stable tumor-free point: since the health of patient is guaranteed with eradication of tumor cells it is a desirable point.

$$EP_5=\begin{bmatrix}1\\0\\1.65\end{bmatrix} \tag{8}$$

A stable coexistence point means the immune system can inhibit the cancerous cells population without full eradication. Reaching this point is not desirable since the permanent existence of tumor cells in the body has a high risk of metastasizing that can have harmful effects on other organs' performance. Mathematically, this stable point has a specific domain of attraction that any patient with an initial condition in this domain cannot be cured without external drug intervention [38]. Also, the tumor-free point which corresponds to healthy point has an specific domain of attraction which has been estimated in [39]. It can arise a question that a healthy point is stable and there is no need to control the system. Chemotherapy treatment from the system's theory can be interpreted to find a control signal which can enlarge the domain of attraction of the healthy point and increases the convergence rate to cure the people, reaching to healthy condition.

3- NONLINEAR OPTIMAL CONTROL DESIGN

The HJB PDE originates from nonlinear dynamic programming [40]. The general structure for our problem is defined as stabilizing the nonlinear system (1) with following format

$$\dot{x}(t)=f\left(x(t)\right)+Gu(t) \tag{9}$$

asymptotically around the healthy point while minimizing the following cost function

$$\psi\left(x(t),u(t)\right)=\frac{1}{2}\int_0^\infty\left(\beta_1x_2^2(t)+\beta_2x_4^2(t)+\beta_3u^2(t)\right)dt \tag{10}$$

where $x=x(t)$ is the vector of state variables and is defined as $x=[N\quad T\quad I\quad v]^T$ for the system (1), $f(x)\in\mathbb{R}^4$ is according to the right hand side of the first to forth dynamics in (1), and $G\in\mathbb{R}^4$ is a constant input matrix that for the system (1) is formed as $G=[0\quad 0\quad 0\quad 1]^T$. The parameters β_z, for $z=1,2,3$, are positive weighting factors and $\psi(x,u)$ is a predefined cost function.

It is proved that by the following optimal control signal

$$u^*(x)=-\frac{1}{\beta_3}G^T\frac{\partial\psi^T\left(x,u^*(x)\right)}{\partial x} \tag{11}$$

our control objective is achievable provided to finding $\psi\left(x,u^*(x)\right)$ [25]. This function can be obtained by solution of the following HJB PDE

$$\frac{1}{2}\left(\beta_1x_2^2+\beta_2x_4^2-\frac{\partial\psi\left(x,u^*(x)\right)}{\partial x}G\frac{1}{\beta_3}G^T\frac{\partial\psi^T\left(x,u^*(x)\right)}{\partial x}\right)+\frac{\partial\psi\left(x,u^*(x)\right)}{\partial x}f(x)=0 \tag{12}$$

The equation (12) is not solvable analytically for the system (1) because of its high complexity. In the next subsection, an efficient technique based on the power series expansion is used to solve (12) for the system (1) numerically [27].

3-1- Power series expansion method

Let suppose that $f(x)$ in (9) and $\psi\left(x,u^*(x)\right)$ in (12) can be approximated by the following polynomial functions:

$$f(x)=Fx+F^{[2]}(x)+F^{[3]}(x)+\cdots \tag{13}$$

$$\psi\left(x,u^*(x)\right)=\psi(x)=\frac{1}{2}x^TPx+\psi^{[3]}(x)+\psi^{[4]}(x)+\cdots \quad (14)$$

where the matrix $P=P^T>0$. Also, $F^{[i]}(x)$ and $\psi^{[h]}(x)$ denote functions from order $i\geq 2$ and $h\geq 3$, respectively. All the functions in (13) are known and can be computed by power series expansion while the functions in (14) are unknown and should be computed by solving HJB PDE (12).

Shifting the systems from the healthy EP to origin and Substituting (13) and (14) in (12) leads to a series of algebraic equations in a polynomial formation. Now, it would be straightforward to put the summation of terms with identical degree equal to zero. Doing this procedure for the shifted system leads to the following equations for x^TPx and $\psi^{[h]}(x)$, $h=3,4$, respectively:

$$x^TPx\cong 307.7x_2^2+0.098x_4^2 \quad (15)$$

$$\psi^{[3]}(x)\cong x_2^2\left(307.6x_1+461.5x_2+153.8x_3+92.3x_4\right) \quad (16)$$

$$\psi^{[4]}(x)\cong x_2^2\left(923.07x_1^2+3880.27x_2^2+153.84x_3^2-31.5x_4^2\right) \quad (17)$$
$$x_2^2\left(2615.3x_1x_2+1302.5x_2x_3+692.3x_2x_4+400x_1x_4+615.3x_1x_3+215.3x_3x_4\right)$$

To calculate (15) to (17) it has been supposed that the constant weighting parameters are $\beta_1=200$, $\beta_2=0.2$, and $\beta_3=2.4$ according to [12]. Also, the second-layer approximation

$$V_x^{[i]}(x).(A+BK)x\approx V^{[i]}(x) \quad (18)$$

has been used in computing procedure of (16) and (17).

By substituting (14) to (17) in (11), we would have the following control signal for the shifted system (1)

$$u^*(x)\cong 26.28x_2^2x_4-166.66x_2^2x_1-288.46x_2^3-89.74x_2^2x_3-38.46x_2^2\text{-}0.04x_4 \quad (19)$$

which is consisted of the third order terms based on the state variables.

It worth noting that $\psi\left(x,u^*\right)$ can be considered as a candidate Lyapunov function for the system (1) and the optimal control signal for approximate solution procedure is sought in the area where $\psi(x)$ is positive. The derivative of $\psi(x)$ with respect to time is obtained negative semi-definite which by applying Lasalle's theorem in [15] its negative definiteness is proved.

One of the other techniques to solve (12) is SDRE. In this approach, instead of finding $\psi\left(x,u^*(x)\right)$, its derivative with respect to x, $\psi_x=\frac{\partial\psi\left(x,u^*(x)\right)}{\partial x}$, is found numerically by imitating the formulation of the algebraic Riccati equation (ARE) for the linear systems by considering $\psi_x=x^TP(x)$ as $\psi_x=x^TP$ for linear systems. In fact, $\psi\left(x,u^*(x)\right)$ is not calculated and instead ψ_x is obtained by finding $P(x)$ numerically. The function $P(x)$ is acquired by substituting $x^TP(x)$ for ψ_x in (12) and transforming it to an algebraic Riccati equation (ARE) by point to point evaluation of (12). In the SDRE method there is no closed-form solution for $\psi(x)$ and $u^*(x)$. It means that for $\psi(x)$ and $u^*(x)$ we would have a series of linear Lyapunov functions, x^TPx, and linear controllers, Kx, based on the operation point of the systems, respectively. Therefore, for Lyapunov based analyses of the closed-loop system such as estimation of the domain of attraction, there would be problems in dealing with the SDRE approach.

4- SIMULATIONS AND ANALYSIS OF THE CLOSED LOOP SYSTEM

4-1- Sensitivity Analysis

One of the effective performances of a controller is its ability to reduce the sensitivity of the system's behavior to its parameters. To investigate the ability of the proposed controller, the sensitivity equation is formed as [15]

$$\dot{S}(t)=A(t,\lambda_0)S(t)+B(t,\lambda_0);\quad S(0)=0 \quad (20)$$

Where

$$A(t,\lambda_0)=\left.\frac{\partial f(t,x,\lambda)}{\partial x}\right|_{\substack{x=x(t,\lambda_0)\\ \lambda=\lambda_0}} \quad (21)$$

$$B(t,\lambda_0)=\left.\frac{\partial f(t,x,\lambda)}{\partial \lambda}\right|_{\substack{x=x(t,\lambda_0)\\ \lambda=\lambda_0}} \quad (22)$$

where $\lambda\in\mathbb{R}^{15}$ is the vector of parameters in dynamics (1) and λ_0 is the vector λ evaluated in their nominal values, $S(t)\in\mathbb{R}^{4\times 19}$, $A(t,\lambda_0)\in\mathbb{R}^{4\times 4}$, and $B(t,\lambda_0)\in\mathbb{R}^{4\times 19}$.

In [8] it has been shown that the system (1) is very sensitive to variations of the value of the parameter c_2 in the second dynamic. To show the effectiveness of the controller in the reduction of sensitivity to the parameter c_2, a comparison between the sensitivity of the closed-loop and open-loop systems is done and depicted in Fig. 1. It is obvious that the closed-loop system shows a better performance rather than that of the open-loop stable system around healthy point. Especially, the population variation of the immune cells in the open-loop system is highly sensitive to the parameter while for the closed-loop system this sensitivity is decreased to about 20 percent of the open-loop system.

The values of the parameters for the system (1) differ from one patient to another. This problem necessitates investigating the robustness of the designed controller with the nominal values for other patients with uncertainty in the values of parameters. To check the robustness of the controller the same mechanism as [41] is employed. The controller is applied to 8 patients with different parameters' values. The parameters experience 20 percent uncertainty in some cases. The results have been depicted in Fig. 2. It is important to note that the populations of cells and values of the parameters for the dynamics (1) are normalized.

4-2- Minimization of the cost function

The control mission is defined as minimizing the cost function (10) while the behavior of the system converges to its desirable point asymptotically. Linear and truncated nonlinear optimal controllers at the second and third-orders are compared based on the predefined cost function (10) and treatment time for the initial condition $x(0)=[0.75 \quad 0.25 \quad 1 \quad 0]^T$ in Table 2.

Treatment time, i.e., the time is needed to eradicate tumor cells is a measure that can be vital in determining the performance of a proposed controller. Our measure is when the population of tumor cells meets the condition $T(t)\le 10^{-6}$. It should be noted that the minimum value for the population of tumor cells to be detected in the conventional medical tests is about $T(t)\approx 10^{-4}$ in normalized population, hence the condition $T(t)\le 10^{-6}$ is a strict measure for demonstration of the presented controller. A unit population of tumor cells is equal to 10^{11} cells that can form a sphere tumor with a radius 3 to 6 centimeters.

Fig. 3 shows the performances of closed-loop systems by different controllers and their comparison with the open-loop

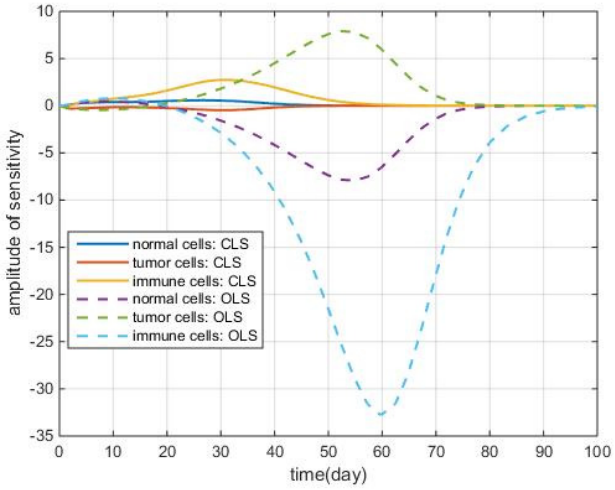

Fig. 1. Sensitivity Comparison of closed loop system (CLS) and open loop system (OLS) to parameter c_2 for initial condition $x(0)=[0.75 \quad 0.25 \quad 0.9 \quad 0]^T$.

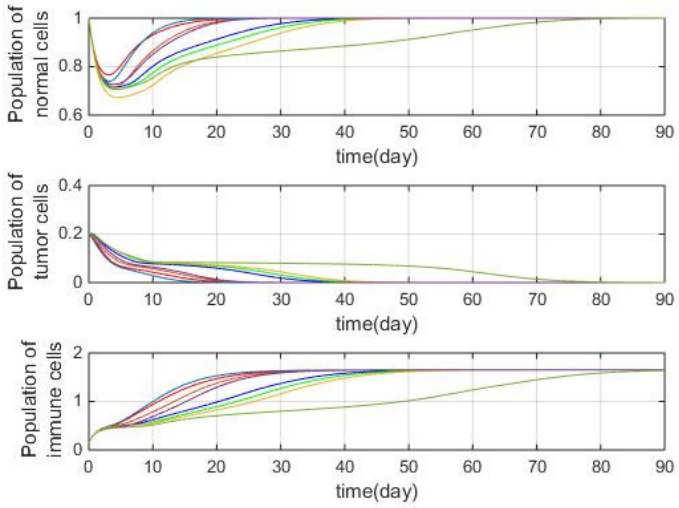

Fig. 2. Variation of cells' population with uncertainties in system's parameters in response to critical initial condition $x(0)=[1 \quad 0.2 \quad 0.15 \quad 0]^T$.

Table 2. Comparison of performance measures for closed-loop systems with truncated controllers at different orders and the open-loop system

	Open-Loop System	Linear Controller	Truncated controller at Second order	Truncated controller at Third order
Cost function value	106	106	106	70
Treatment time (day)	79	79	79	69

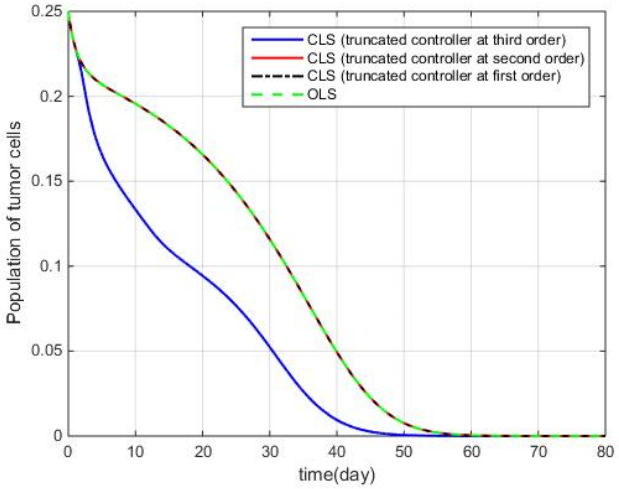

Fig. 3. Comparison of closed loop system (CLS) and open loop system (OLS) responses

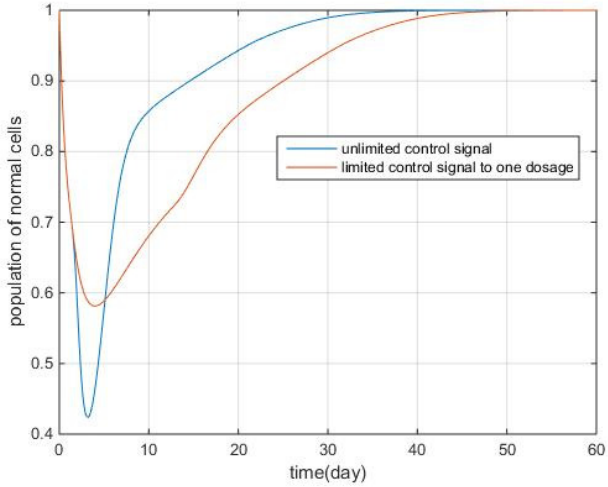

Fig. 4. Comparison between variation of normal cells' population for the closed-loop systems with limited and unlimited injection of chemotherapeutic drugs

system in response to initial condition $x(0)=[0.75 \quad 0.25 \quad 1 \quad 0]^T$. It is clear that the highest order controller has a better performance in convergence rate. But it is not a case generally. A higher order controller may show a worse behavior than that of a lower order controller [27].

In simulations, we limit the dosage of the drug to a unit. By imposing this limitation, the toxic effects of injected chemotherapy drugs on normal cells are controlled and the population of normal cells is kept around its desirable value [12]. It is demonstrated by all of the simulations. To show the positive effect of limiting dosage of the injected chemotherapeutic drugs on the population of normal cells, the performances of the closed-loop systems for the critical initial condition $[1 \quad 0.5 \quad 0.15 \quad 0]^T$ with a limitation and without it are compared in Fig. 4.

4-3- Domain of attraction

The open-loop system has two stable equilibrium points with a specific domain of attraction. The controller should be able to broaden this area for healthy EP. It can be done by eliminating the coexistence equilibrium point and other unstable EPs, which means that the closed-loop system would have a global domain of attraction. The closed-loop systems with truncated orders are compared for an initial condition $x(0)=[0.625 \quad 0.25 \quad 0.625 \quad 0]^T$ in Fig .5.

The second order controller is not capable to broad the domain of attraction of the system. One of the interesting points about designing a controller using these types of approximation techniques is that a higher-order controller does not necessarily mean better response and wider domain of attraction [27]. Since the open-loop system is stable (because of that all the processes in the body are asymptotically stable with a specific domain of attraction, convergence rate, and transient response), the truncated controllers at the first and second orders are not capable to function desirably and effectively. But, it is not the case for the third-order controller.

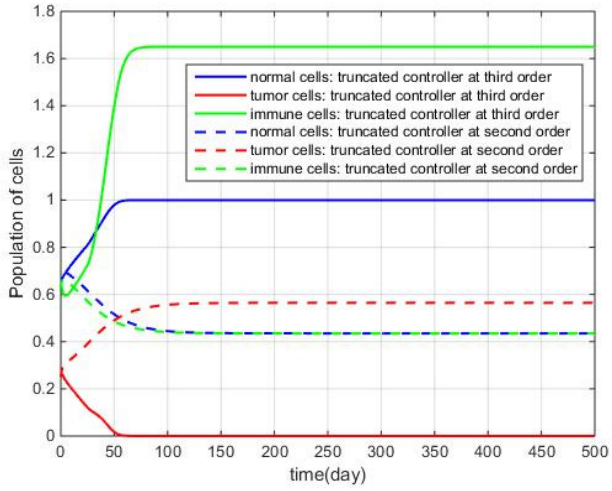

Fig. 5. Comparison of closed loop system (CLS) with truncated controllers at third and second order in terms of enlargement of domain of attraction

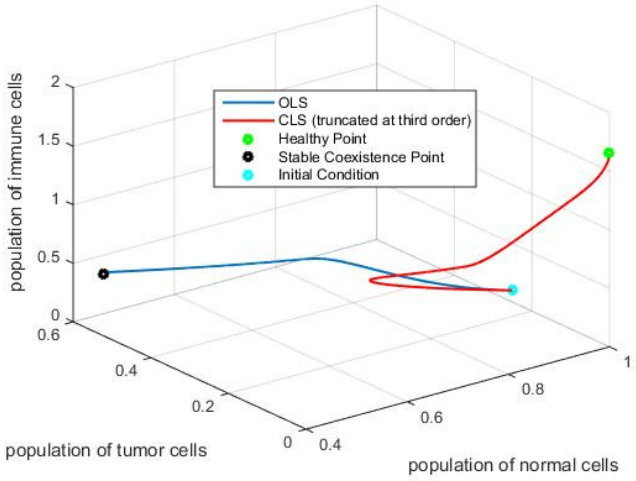

Fig. 6. Comparison of OLS and CLS in terms of enlargement of the domain of attraction

Also, the phase plane of the states $N(t)$, $T(t)$, and $I(t)$ for the closed-loop system with the truncated controller at the third order in response to the acute initial condition $[1 \quad 0.25 \quad 0.1 \quad 0]^T$ is depicted in Fig. 6. In this initial condition, the population of tumor cells is about 2.5×10^{10} cells (a sphere tumor of radius 2.85 centimeter), which is a large tumor sphere, and the number of immune cells is lower than 10% of healthy conditions. This point is in the stable coexistence point's domain of attraction. The response of the fourth state and control effort are illustrated in Fig. 7.

It is obvious that the third-order controller has more capability to extend the region of attraction. The third order controller $u^*(x)$ in (19) eliminates the stable coexistence EP of the system and two of the unstable EPs. The closed-loop system has two EPs corresponding to

$$EP_{CL,1} = \begin{bmatrix} 1 \\ 0 \\ 1.65 \\ 0 \end{bmatrix}; \quad EP_{CL,2} = \begin{bmatrix} 0 \\ 0 \\ 1.65 \\ 0 \end{bmatrix} \tag{23}$$

where the first one is healthy EP and the second one is unstable dead EP. Medically, since the second EP is related to a dead person, the closed-loop system has a global domain of attraction. From the system's theory point of view, the third-order controller enlarges the domain of attraction significantly but it is not global.

4-4- Comparison with SDRE technique

One of the well-known optimal control techniques for

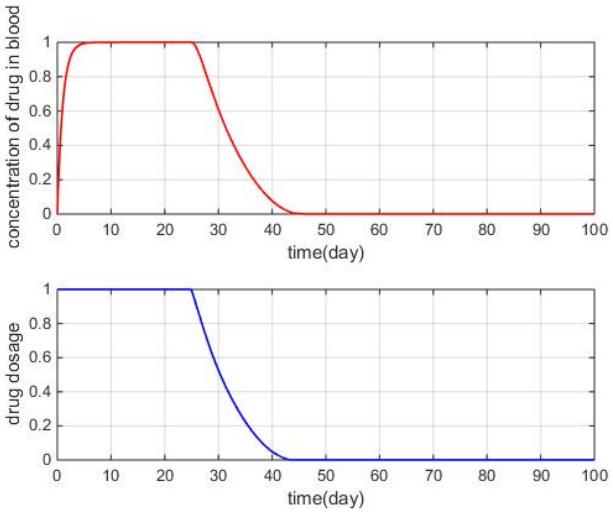

Fig. 7. Concentration of drug, the fourth state in (1), and control effort for the closed-loop system in response to acute initial condition $[1 \quad 0.25 \quad 0.1 \quad 0]^T$

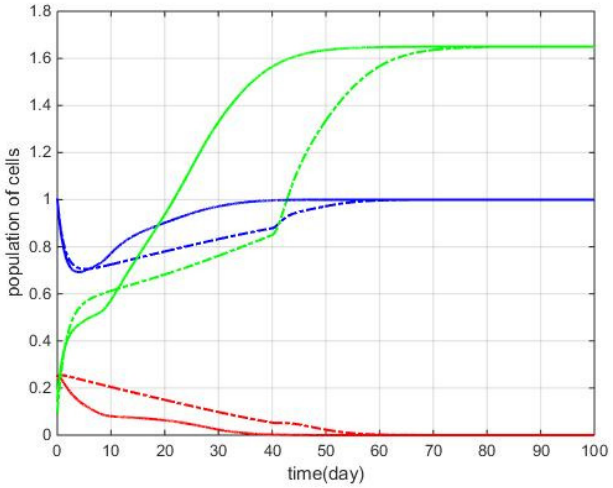

Fig. 8. Comparison between two nonlinear optimal control techniques SDRE (dash-dotted lines) and HJB approximate solution (solid lines). Population of normal, tumor, and immune cells are shown by blue, red, and green colors, respectively.

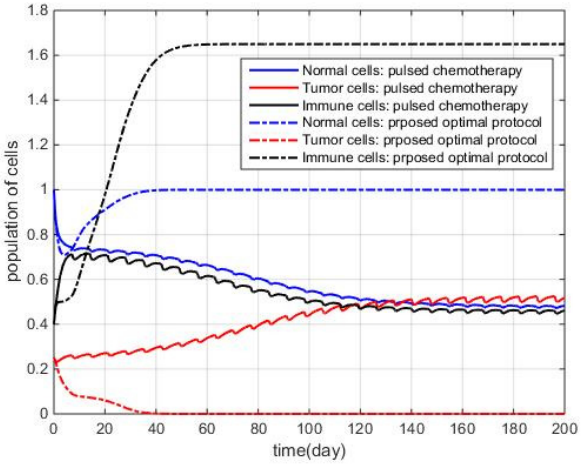

Fig. 9. Comparison between closed-loop systems with two different chemotherapeutic drugs injection protocol for initial condition $[1 \quad 0.25 \quad 0.4 \quad 0]^T$ **: pulsed chemotherapy and proposed optimal protocols.**

proposing an effective chemotherapy regimen to inhibit the proliferation of cancerous cells and eradicate them is the state-dependent Riccati equation (SDRE) approach [12]. Since it is an optimal controller, the results of employing this technique can be compared by the proposed optimal control approach (based on the HJB approximate solution) in this paper. This comparison for a critical medical initial condition $[1 \quad 0.25 \quad 0.15 \quad 0]^T$ is shown in Fig. 8. It is clear that the proposed controller leads to a better performance in facing with cancerous cells in the human body. Besides the less effectiveness of the SDRE technique rather than the proposed controller, there are some drawbacks with it. The SDRE controller is designed based on switching between linear controllers at specific times. This switching mechanism practicality may lead to instability of the closed-loop system at the instant of switching which is not the case for the proposed controller.

Also, the proposed technique is compared with prevailing clinical drugs injection protocols, pulsed chemotherapy [7]. The pulsed chemotherapy not only is not effective in broadening the domain of attraction, but also it takes far more time for treatment. Fig. 9. Shows the results of this comparison.

5- CONCLUSION

Finding a cancer treatment's optimal regimen by determining the dosage of the chemotherapeutic drugs was addressed in this paper. Generally, people who suffer cancer are cured by chemotherapy drugs alone or in combination with other approaches. These drugs may have fatal results in the health of a patient. In these cases, an optimization problem arises: minimization of tumor cells' average population with minimum drug injection. Since the model is highly nonlinear a nonlinear optimal controller was proposed. This controller was designed by solving HJB PDE. This equation can be solved by the SDRE technique which transforms the nonlinear problem into a pseudo-linear structure. It has some drawbacks. Instead, we put the direct solution of HJB PDE into our perspective. Since the PDE was not solvable in a closed form, an approximation technique based on power series expansion was applied to solve a series of dependent algebraic equations instead of the PDE. The power series expansion gives the designer the ability to truncate the controller at any order in which the closed-loop system meets predefined measures. We truncated controller at third-order where the special objective including extending the domain of attraction, faster convergence rate, reducing the sensitivity to parameters, and minimizing the cost function was fulfilled. To prove the ability of the closed-loop system a series of simulations were carried out.

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