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Derivation of an optimal trajectory and nonlinear adaptive controller design for drug delivery in cancerous tumor chemotherapy

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ABSTRACT

Numerous models have investigated cancer behavior by considering different factors in chemotherapy. The subject of a controller design approach for these models in order to find the best rate of drug injection during the course of treatment has recently attracted much attention. The rate of drug injections is very important in chemotherapy, as it not only causes cancer cells to die, but also kills healthy cells. On the other hand, by modeling tumor growth behavior in each patient, different parameters for the dynamics of the system should be considered. In this study, optimal control signals were obtained for the most recent model of chemotherapy, using the steepest descent method. The logic of the solution was biologically compared to the experimental results. Then an adaptive controller, considering this path as the desired optimal trajectory, directs the system towards it. The global stability of the closed-loop system is achieved by means of the Lyapunov stability theory and Barbalat lemma. It is worth noting that some of the system parameters are estimated using an online recursive estimation method. Simulation results indicate the performance and effectiveness of the designed controller. The estimation parameters are also verified using experimental data from available studies.

1. Introduction

In a healthy body, the rate of cell division and cell death are balanced. A biological cause can disturb this process, which is called cancer. One of the most effective methods of treating cancer is through the injection of certain medications, called chemotherapy medicines. These drugs are injected into the body during predetermined sessions after diagnosis of cancer. The main purpose of these drugs is to eliminate the cancerous cells in the patient with minimal damage to healthy tissues. Different mathematical models are presented for simulating the behavior of cancer dynamics with consideration of various factors. The main goal of these models is to find an effective drug program for treatment. These models have been proposed in this regard, each with its own advantages and disadvantages.

The initial models are very simple and use a first order ordinary differential equation for describing the growth rate of cancer cells and their destruction by chemotherapy, such as log-kill [1], E_{max} [2] and Norton-Simon hypothesis [3]. However, these models gradually advanced and involved several other factors in order to make them even more precise. For example, the model proposed in Ref. [4] is able to compare different strategies of drug delivery to tumor tissue. The computational results show that nanoparticles improve the efficacy of chemotherapy during treatment sessions. After presenting each model, various nonlinear and optimal controllers were used to find the injection rate of the drug (control signal). From this perspective, there are some differences between mathematical models and control aims which will be discussed in the following sections.

It is entirely reasonable to assume that the basis of cancer mathematical models should be consistent with the biological assumptions. For example, cell growth can be considered a continuous process due to the large number of cells. Thus, cellular growth in cancer mathematical models is more often referred to as differential equations [5] and especially ordinary differential equations (ODEs) [6]. Magni and coworkers [7], presented differential equations with five variables, three for the description of untreated growth and two for describing the effect of medicine in the body. The model is based on mouse experiments as a part of drug research and development. The proposed model is able to evaluate a drug in the prediction and the ability of tumor growth in response to various treatments.

In another study, by considering the masses of healthy cells, tumor, blood vessels in the tumor and chemotherapy as states, a dynamic model with four differential equations was presented. Liu and Freedman [8] also introduced the delay effect in their proposed dynamics. Mathematical analysis of the system without treatment was verified due to the necessity of non-negativeness of all system variables, limitation of the answers, the nature of equilibrium points and stability

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and global stability of the system. Other effects, such as the metastasis phenomenon, which is the spread of cancer cells from the tissue of origin to other bodily tissues through blood vessels, was considered in the model proposed in Ref. [9]. That model consists of six ODEs in the state-space form: three states of healthy cells, cancer cells and chemotherapy on the first side and the same on the second side. The effect of the delayed metastatic phenomenon and the competition of healthy and cancerous cells for survival were also considered in the equations. The existence and stability of the system around the equilibrium points as well as the dynamic analysis of the system, were carried out analytically and numerically. The general behavior of the model for different values of parameters was also investigated.

Typically, normal (healthy), immune and cancer cells are the key states of the dynamics of cancer. In many models, these states, along with chemotherapy, are considered the main variables. One of the most comprehensive studies in this field was proposed by De Pillis and Radunskaya [10]. They analyzed the dynamics of the system and examined the mathematical and biological concepts of each equilibrium point. Their results showed that the equilibrium points divide positive 3-D space in twelve regions. Now, if the control signal approaches the system into the region of attraction of a healthy and stable equilibrium point (no tumor or a safe amount of cancer cells), then it is no longer necessary to inject the drug and the body will recover over time. They also applied an optimal controller and compared their results with the pulse controller in prior works. They concluded that the total amount and the highest amount of injection did not differ significantly between the two controllers, and the only difference was in the management of drug injection time.

Finding the optimal solution for the dynamics of cancer is very important. Thus, this is an interesting field for researchers. However, finding the right type of optimal control is challenging, because of the dynamic complexity of cancer. The use of State-Dependent-Riccati-Equations (SDRE) in the optimal control for nonlinear models, including cancer dynamics, can be very useful. In Ref. [11], a control signal is obtained from this method, and the effect of different weights in the cost function was examined. In another work [12], the optimal control signal was calculated with the same method and compared with different adaptation rates for control signals. It's worth-mentioning that optimal algorithms are also used to investigate other optimal treatments, such as hyperthermia, to improve the efficacy of chemotherapy, like [13] using a Genetic Algorithm to find the optimal solution for thermal damage to cancer tissue.

One of the major problems in cancer models is the existence of variety coefficients that may vary in each patient, or even during the treatment of one person. One idea that can be used in this field is the design of an optimal control scheme with known coefficients to find the optimal path of a reference model, and then design an adaptive controller for the reference model for each patient with unknown coefficients. In Ref. [14], the optimal control signal is calculated from the SDRE method and the parameters are then obtained using adaptive control methods and the Lyapunov theorem. The results of this combined controller for the dynamics of cancer show that the dynamic system of each patient with unknown coefficients is well adapted to the reference model.

Nowadays, obesity is one of the fundamental problems in peoples' lives. The main problem is where the fat itself causes or worsens some diseases, including cancer. For the first time, the mathematical relations of the interactions between immune, normal and cancer cells and fat were considered in Ref. [15]. In order to find the effect of fat on the progression of cancer in the body, this variable (in addition to immune, cancer and normal cells) was added to ODEs. The dynamic model without drug injection and bifurcations related to the discussed coefficients, and the stability of the equilibrium points in different intervals of the parameters are described in detail. In 2017, the effect of drug injection was added into the equations, and by defining a cost function to reduce cancer cells at the end of the treatment, optimal control was applied on the cancer system [16]. The optimal rate of drug injection in two low and high caloric diets in two thirty and sixty day of treatments were compared. The results showed that weight loss promoted a faster recovery of cancer in chemotherapy. In other words, for a weight-loss patient, a better control signal is obtained with an increase in weight gain. In 2018, a robust sliding mode controller was applied to the same system as the first nonlinear controller designed for the cancer system in the presence of fat effect [17]. By considering the optimal path derived in Ref. [16] as the reference signal, the sliding mode controller was designed to slide the system on this desire trajectory.

Another drug that is used in mathematical models in chemotherapy treatment is anti-angiogenic. This drug prevents the production of new blood vessels around the tumor, which are caused by the tumor itself. In experimental results, a collaboration between chemotherapy and anti-angiogenic drugs has been recognized to be more effective than chemotherapy alone [18]. In the model proposed in 1999, tumor growth was assumed to be directly related to the oxygen and food that reaches the tumor through blood vessels [19]. That model was proposed based on experimental tests, and parameters of the model were obtained by matching the experimental data. The results indicated that the tumor was in equilibrium over a specific period and its growth was stopped by an anti-angiogenic drug. The model was improved in Ref. [20] to further improve its efficacy.

In 2009, considering an anti-angiogenic drug and chemotherapy as cancer treatments, a dynamic model was presented with four first-order ordinary differential equations [21]. The variables in the state-space form of the system included: the maximum stable size of the tumor that can exist at any moment, the size of the tumor at any moment, chemotherapy and anti-angiogenic drugs. After analyzing the proposed dynamic model, the optimal chemotherapy doses were obtained with the aim of minimizing the maximum tumor size (the first state) in the last day of treatment, such that the anti-angiogenic dose of the drug had the same pattern as in Ref. [22]. The most comprehensive mathematical model, including the simultaneous effects of these two drugs, has been studied in Ref. [23]. In this model, the effects of five variables of normal, cancer and endothelial cells, along with chemotherapy and anti-angiogenesis drugs in the body have been considered. The mathematical analysis of the model without treatment showed that if no treatment is performed, the system tends to increase cancer cells and reduce normal cells, which leads to death. This suggested that the immune system of the patient's body cannot cure cancer alone, and one of the cancer treatments is necessary. If an anti-angiogenic drug, which only affects the endothelial cells, is injected alone, the patient will not be cured, which is in accordance with laboratory data. In some cases, if chemotherapy is used alone, the patient can be cured under specific circumstances. Through mathematics, this model proved that if both drugs are used simultaneously, the chance of a person's recovery is greater.

In recent cancer mathematical models, the complexity of the governing equations requires a strong nonlinear controller with the capability of proving stability. In the present paper, a novel approach for personalizing the optimal drug injection in chemotherapy by considering the effect of anti-angiogenics is proposed. The idea is to obtain the optimal drug injections for an individual and adapt the system on the optimal trajectory using a proposed nonlinear adaptive controller. Since the parameters in the model may be different for each patient and may also vary for patients during chemotherapy treatment, it is important to know how they change during chemotherapy sessions. Thus, several parameters of the model are unknown and are estimated simultaneously using an online recursive method. It is worth noting that this model is chosen for the first time to follow controlled aims. So far, no controller has been applied to this system. Since the effect of the

anti-angiogenic is considered in addition to chemotherapy, the results are more complete than prior models in this field. Although the optimal controller is open-loop, the adaptive controller is closed-loop, which means that the amounts of control signals in the next step are influenced by the changes in each state of the previous timepoint. This makes the closed-loop system more reliable, as every state does not always react as we expect, and thus, precautions must be taken.

The first step is to apply the steepest descent method to obtain an optimal trajectory of the model, considering the rates of injection of both chemotherapy and anti-angiogenic as control signals. In the next step, this path is chosen as the desired trajectory, and an adaptive controller, despite the existence of uncertainties in the dynamics of the system, is designed and forces the system to follow the desired path. In other words, by changing the amount of drug injection, the volume of the tumor is adjusted to its optimal value. This procedure is able to control and adapt the system to its desire. It is worth noting that in this method, the global asymptotic stability is mathematically achieved by the Lyapunov stability theory and Barbalat lemma. The parameter estimation procedure is accomplished in such a way that the global stability of the system is guaranteed independently of the initial conditions.

This paper is organized as follows: section 2 reviews the mathematical model considered in this study. All assumptions and the concepts of coefficients are explained. The meaning of sub-models in the absence of each drug is also described briefly. In section 3, the assumptions of the optimal problem are investigated, and the cost function is defined accordingly. Furthermore, the steepest descent method is used, and the optimal path is calculated and compared with experimental data in section 3. In section 4, the adaptive controller is used to attain the control signals. To do so, the Lyapunov stability theory and Barbalat lemma are utilized to guarantee the global stability of the system. Section 5 illustrates the computer simulation results of the closed-loop system, which are compared with laboratory data. In section 6, the results are discussed and the reasons why this model and control method can supply more thorough results compared to prior works are explained. Finally, section 7 concludes the paper.

2. Mathematical model

In this section we briefly discuss the cancer model chosen in this paper; but first the facts that anti-angiogenic drug is also important in cancer treatment, are explained. The production of new blood vessels is a natural phenomenon that is essential for the growth and repair of tissues in the body. This is called angiogenesis. In the early observations, it was demonstrated that when the size of the tumor reaches about 3 mm, signals were released by tumor, causing the blood vessels (Endothelial cells) to branch out in order to provide nutrients and oxygen for the survival of cancer cells [24]. In other words, with angiogenesis there is a competition between normal and cancer cells to use nutrients in blood [25]. Anti-angiogenic is the drug which controls this procedure. It's worth-noting that it slows down the process; but do not stop the spreading procedure. This is due to the fact that blood along with chemotherapy drug must reach the tumor in order to destroy it. It should be noted that anti-angiogenic drugs do not kill the tumor and only keep it hungry. The use of chemotherapy is a way to eliminate cancer cells. The mathematical model considering the effects of both drugs, which is also used in this paper, is reviewed in the following section.

As mentioned earlier, five variables are taken as the main states in the model in Ref. [23]: Normal cells (NCs), Cancer cells (CCs), Endothelial cells (ECs), chemotherapy agent (CA) and anti-angiogenic agent (AA) in body indicated by x_1, x_2, x_3, y and w, respectively. In this section, only the non-dimensional dynamic is written, which is shown in Equation (1).

Table 1
Concepts and normalized values of coefficients in Equation 1.

Coefficient	Concept	Normalized value
α_1	NCs proliferation rate	0.0068 day^{-1}
α_2	CCs proliferation rate	0.01 day^{-1}
α_3	ECs proliferation rate	0.002 day^{-1}
q_1	Competitive rate of NCs	0.00702 day^{-1}
q_2	Competitive rate of CCs	0.00072 day^{-1}
γ	Coefficient of ECs for blood supply to the tumor	0.1615
β	CCs production rate due to ECs	0.00371 day^{-1}
a_1	Saturation rate on NCs	1.10 day^{-1}
a_2	Saturation rate on CCs	4.6205 day^{-1}
a_3	Saturation rate on ECs	4.6666 day^{-1}
d_1	CA combination rate with NCs	0.0002 day^{-1}
d_2	CA combination rate with CCs	0.032 day^{-1}
d_3	AA combination rate with ECs	0.032 day^{-1}
p_{10}	NCs loss rate by CA	1.2E-07 day^{-1}
p_{20}	CCs loss rate by CA	0.2051 day^{-1}
p_3	ECs loss rate by AA	1.7143 day^{-1}
p_{11}	Rate of ECs cooperation on CA for NCs	4.2E-08 day^{-1}
p_{12}	Rate of AA cooperation on CA for NCs	1.0E-07 day^{-1}
p_{21}	Rate of ECs cooperation on CA for CCs	0.00431 day^{-1}
p_{22}	Rate of AA cooperation on CA for CCs	19.4872 day^{-1}

$$
\begin{aligned}
\dot{x}_1 &= \alpha_1 x_1(1-x_1) - q_1 x_1 x_2 - p_1(x_3, w)\frac{x_1 y}{a_1 + x_1}\\
\dot{x}_2 &= \alpha_2 x_2\left(1 - \frac{x_2}{1+\gamma x_3}\right) - q_2 x_1 x_2 - p_2(x_3, w)\frac{x_2 y}{a_2 + x_2}\\
\dot{x}_3 &= \beta x_2 + \alpha_3 x_3(1-x_3) - \frac{p_3 x_3 w}{a_3 + x_3}\\
\dot{y} &= \delta - \left(\xi + d_1\frac{x_1}{a_1 + x_1} + d_2\frac{x_2}{a_2 + x_2}\right)y\\
\dot{w} &= \phi - \left(\eta + d_3\frac{x_3}{a_3 + x_3}\right)w
\end{aligned}
\tag{1}
$$

The concept of each coefficient along with normalized value of each parameter is given in Table 1. In the above equation, $p_i(x_3, w) = p_{i0} + p_{i1}x_3 + p_{i2}w$ is defined with $i = 1,2$. It is worth noting that p_{i0} indicates the x_i's rate of death by CA in the absence of x_3 and $w(i = 1,2)$, and p_{ij} is the x_i's rate of destruction by CA per concentration of x_3 $(j = 1)$ and $w(j = 2)$.

The model assumptions are listed briefly as follows:

- Since cell growth is very fast and its exact number is very large and uncountable, it is entirely reasonable to consider the model as a continuous system. Thus, the governing equations are ODEs in which states vary with time.
- There is a homogeneous distribution of cells in the tissues of the body which are affected by drugs. CA does not purify cells. In other words, it eliminates both NCs and CCs with different rates.
- The effect of CA on ECs can be ignored.
- x_1 and x_2 present logistic proliferation rates and compete for living.
- x_3 is duplicated due to the chemical behavior of angiogenesis based on CCs and its own logistic proliferation rates, but its growth rate is less than x_1 or x_2.
- y acts as a fatal agent with different coefficients on x_1 and x_2. w only destroys x_3. These terms have appeared in the form of a saturation function relative to x_is in ODEs. In other words, the maximum effect of the drug on cells is one as x_i tends to infinity.
- y and w have a direct relationship with the continuous injection rate of each drug (incremental factor).
- Due to the half-life of drugs, medications are lost in the patient's body. Also, cells in the body kill them (decrement factors).

As mentioned earlier, one of the strengths of this model is its mathematical proofs that state variables are always limited to the positive region, since all the initial conditions are non-negative or positive. In other words, all the possible answers starting from positive region remain in the same region; and any response outside this area in

the non-negative area at the initial time will be entered into this region in finite time.

The full dynamic analysis is accomplished mathematically in Ref. [23]. Here, we just mention the main results. To verify the validity of the model, the system was considered in four cases:

Case 1. No treatment: According to experimental results, CCs always win the competition from NCs. In other words, the immune system of body cannot cope with this disease alone and ultimately leads to death. By eliminating CA and AA from Equation (1), the equilibrium point of the system is $\lim_{t\to\infty}(x_1(t), x_2(t)) = (0,1)$ which is equivalent to death.

Case 2. No CA: In this case, $y \equiv 0$ and $\delta \equiv 0$. By considering the first two equations and compare them with Case 1, it's concluded that NCs tend to zero and CCs become larger than Case 1. Thus, AA cannot cure cancer alone and leads to death. This also matches experimental data.

Case 3. No AA: Investigating the stability of the equilibrium point (if exists), nonlinear system should be linearized around this point. For this purpose, the Jacobian matrix around the equilibrium point was written and the eigenvalue of the equation regarding to CCs was considered. It's shown that CA is able to make this eigenvalue negative under some conditions. The conclusion that can be drawn from this result is that chemotherapy is able to cure the patient under some circumstances.

Case 4. CA & AA: With the same procedure explained in Case 3, it's concluded that in conditions where CA cannot cure the patient alone, AA with the aid of CA can eliminate CCs. This type of cancer is called Chemo-Resistant tumors. This point was derived from laboratory results [26], which indicates the validity of this model.

Other dynamic analyses were accomplished in details in Ref. [23]. As the final digest, we briefly review the main results of this model:

- CCs cannot be killed by AA alone.
- In the case of Chemo-Resistant tumor, CA cannot cure the patient alone. But in other cases, CA may eliminate CCs under some conditions.
- Cooperation of CA and AA is more effective on reducing CCs compared to CA alone.

3. Optimal controller

Due to the wide variety of problems that are solved by optimal control method, the preliminaries of the article should be thoroughly investigated and the cost function must be written accordingly. In order to use optimal control, the state space form of the dynamical equations of the system is required (Equation (1)). The details of model were fully described in Section 2. As described, the control signals are rates of injection of CA (δ) and AA (ϕ).

To define the cost function, the main goal of the system must be clarified, and that is, to reduce CCs. But it should be noted that if we only consider this variable in the cost function, it is obvious that the numerical value of the control signals would be large. With the increase in the rate of injection of CA, NCs are also destroyed since the drug does not distinguish between CCs and NCs. Therefore, reducing the amount of control signals are considered as one of the targets.

Since chemotherapy is usually prescribed by a doctor before treatment started, it is possible to consider the duration of chemotherapy known in this problem.

According to the above assumptions and [27], Hamiltonian can be written as follows,

$$H = k_1 x_2^2(t) + k_2\delta^2 + k_3\phi^2 + \sum_{i=1}^{i=5} P_i\dot{x}_i(t) \tag{2}$$

where P_is are co-states and k_is are positive constants that determine the effects or weights of their respective variables in Hamiltonian.

The next step is to extract the equations of co-states. According to Ref. [27], they all must satisfy the set of ODEs, $\dot{P}_i = -\frac{\partial H}{\partial x_i}$, which are derived below.

$$\begin{aligned}
\dot{P}_1 &= -P_1\left(\alpha_1(1-x_1) - \alpha_1 x_1 - q_1 x_2 - \frac{p_1 x_4}{a_1+x_1} + \frac{p_1 x_1 x_4}{(a_1+x_1)^2}\right) + P_2 q_2 x_2 \\
&\quad + P_4\left(\frac{d_1}{a_1+x_1} - \frac{d_1 x_1}{(a_1+x_1)^2}\right)x_4 \\
\dot{P}_2 &= -2k_1 x_2 + P_1 q_1 x_1 - P_2\left(\alpha_2\left(1 - \frac{x_2}{1+\gamma x_3}\right) - \frac{\alpha_2 x_2}{1+\gamma x_3} - q_2 x_1 - \frac{p_2 x_4}{a_2+x_2}\right. \\
&\quad \left. + \frac{p_2 x_2 x_4}{(a_2+x_2)^2}\right) - P_3\beta + P_4\left(\frac{d_2}{a_2+x_2} - \frac{d_2 x_2}{(a_2+x_2)^2}\right)x_4 \\
\dot{P}_3 &= -\frac{P_2\alpha_2 x_2^2\gamma}{(1+\gamma x_3)^2} - P_3\left(\alpha_3(1-x_3) - \alpha_3 x_3 - \frac{p_3 x_5}{a_3+x_3} + \frac{p_3 x_3 x_5}{(a_3+x_3)^2}\right) \\
&\quad + P_5\left(\frac{d_3}{a_3+x_3} - \frac{d_3 x_3}{(a_3+x_3)^2}\right)x_5 \\
\dot{P}_4 &= \frac{P_1 p_1 x_1}{a_1+x_1} + \frac{P_2 p_2 x_2}{a_2+x_2} - P_4\left(-\xi - \frac{d_1 x_1}{a_1+x_1} - \frac{d_2 x_2}{a_2+x_2}\right) \\
\dot{P}_5 &= \frac{P_3 p_3 x_3}{a_3+x_3} - P_5\left(-\eta - \frac{d_3 x_3}{a_3+x_3}\right)
\end{aligned} \tag{3}$$

Each differential equation of states and co-states is solved with a boundary condition. Although the conditions for states are defined in the initial time, the conditions for the co-states are expressed in final time [27]. Boundaries for the states can be taken from Ref. [23], which is $x_1(0) = 0.6,\ x_2(0) = 0.6,\ x_3(0) = y(0) = w(0) = 0$, and based on the optimal control theory, the numerical value of all co-states are zero in the final time.

After obtaining the states' and co-states' ODEs along with their boundary conditions, the problem of solving them together simultaneously, comes up. The difficulties with its possible solutions are discussed in the following section.

3.1. Steepest descent method

The numerical solution of ODEs in the previous section is an important challenge. Based on optimal theories, there exist three sets of equations: Algebraic equations ($\partial H/\partial u_i = 0$), and two sets of ODEs ($\dot{x}_i = \partial H/\partial P_i$ and $\dot{P}_i = -\partial H/\partial x_i$). Since for the numerical solution of ODEs, a certain boundary condition is needed, and regarding to the point that the conditions for the states are in initial time and for co-states are in final time, the use of an analytic solution for complicated nonlinear problems seems to be impossible and it is necessary to look for numerical solutions of these equations.

In general, there are five categories of equations and conditions (two sets of ODEs, a set of algebraic equations and two sets of boundary conditions) for optimal control. Different numerical methods are used to solve such problems, each solving one or more equations and for the rest, initial guesses are needed. Afterwards, the calculated values are compared with their guesses and then corrected in the next step. In this paper, the Steepest Descent method is used, which is discussed in the following.

In the Steepest Descent method, the initial trajectory for control signals is guessed. Afterwards, ODEs of states are obtained from the beginning to the end, and co-states are solved from the final time to initial time, separately. According to the Pontyagin principle, the goal is to find a control signal such that minimizes the amount of Hamiltonian. Therefore, the control signals are corrected with the concept of gradient vectors and replaced with the initial guesses [27]. This process will continue until the stopping criteria are satisfied. Eventually, the control signals are calculated at each time step for the injection rate of CA from,

$$\delta^{(i+1)}(t) = \delta^{(i)}(t) - \tau_1(2k_2\delta^{(i)} + P_4) \tag{4}$$

and for AA,

$$\phi^{(i+1)}(t) = \phi^{(i)}(t) - \tau_2(2k_3\phi^{(i)} + P_5) \tag{5}$$

where τ_1 and τ_2 are time constants. The numerical value of these

constants affects the convergence or divergence of the problem. As the values would be large, it approaches more quickly to the answer (extremum of the cost function); as much as these values would be small, the convergence speed of the problem would be very low. For this reason, it is quite logical that in first steps there should be a large time constant so that the problem approaches the answer as closely as possible, and over time this amount would be reduced. By repeating the above process in MATLAB, the best answer is achieved with $\tau_1 = 1/(iteration)^{0.3}$ and $\tau_2 = 1/iteration$, such that the denominator of each is the number of the steps.

3.2. Derivation of optimal trajectories

Considering the steps described in the previous sections, the control signals are updated according to Equations (4) and (5). In this paper, 400 steps are considered for the convergence of answer. An appropriate biological and convergent response is found for values of $k_1 = 0.043$, $k_2 = 0.5$ and $k_3 = 0.001$ in Hamiltonian (Equation (2)) using trial and error method. Because of the large variation in the duration of chemotherapy, a 250-day time period has been chosen to examine the results. The reason for using this number is that according to the data taken from the hospital, the length of treatment is almost six months. To further examine the states, a longer period is considered. The coefficients are also extracted from Ref. [23] which are available in Table 1.

Let's start with the trajectory of states which is shown in Fig. 1. Their behavior must be physically logical. Regarding Fig. 1, it is observed that NCs tend to be close to value one (desire value in healthy state). The reason is that CCs are reduced. If more days are considered, the final value will be closer to one.

The downward trend of CCs is one of the criteria which indicates that the control goal is satisfied, but has not reached zero. Regarding the stages of treatment for cancerous tumors, patients undergo chemotherapy (or CA along with AA) or radiotherapy sessions, or a combination of all of them, in order to slow down the progression of the disease after diagnosis. After completing the courses, the patient undergoes surgery and the tumor remains (if exists) will be removed from the patient's body. Thus, the steady state of the amounts of CCs in final days is indicated that CCs progression is controlled by the injection of CA and AA, that means the behavior of this state is reasonable and the system's goal is satisfied.

ECs during the course of treatment have an increasing and then decreasing trend, but have not reached zero, which is acceptable due to

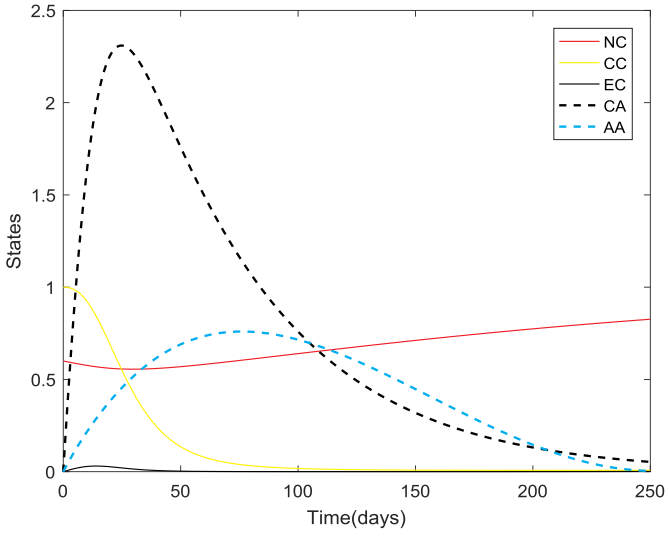

Fig. 1. The optimal time evaluation of NCs, CCs, ECs, CA and AA using parameters from Table 1. Initial conditions are $x_1(0) = 0.6,\ x_2(0) = 0.6,\ x_3(0) = y(0) = w(0) = 0$

the delivery of CA in order to destroy CCs through ECs. On the other hand, its proliferation rate is slower than NCs, which is true due to model assumptions explained in Section 2.

The amounts of CA and AA remaining in the body are the last two states. The two are initially ascending (to cope with cancer) and then have a downward trend (due to the steady state). More details about the amounts of these two and the control signals are discussed later. The only remaining point is the final amounts of the two drugs. It should be noted that each drug has a half-life, thus, if one left in the body, it will eventually disappear due to its half-life, and is not a concern [28].

The behavior of all co-states is shown in Fig. 2A with respect to time. According to the selection of Hamiltonian and boundary conditions in Section 3, the final value of all co-states is zero, which is well illustrated in this figure. For more clarity, the behavior of the three variables is drawn up separately (Fig. 2B). The reason for the calculation of these variables, according to Equations (4) and (5), is that the control signals of each step are updated by P_4 and P_5. Obtaining these two requires the solution of the ODEs of Equation (3). Since the co-states values are functions of time, the optimal control signals obtained are the open-loop system responses.

This system is controlled by the two control signals, δ and ϕ, the variation with time of which are shown in Fig. 3. Both will reach zero in the final days of treatment, which is valid. The next point is its numerical values. In general, the numerical value of CA injection is higher than AA, because it causes the tumor to disappear. Thus, the remaining of CA in the body must be larger than AA, which is also shown in Fig. 1. According to Ref. [26], which has done experimental tests for the injection rates of the two drugs, the reasonable ratio of injections of CA to AA is about 14. This ratio is also observed in Ref. [23] with the difference that in this article these two control signals are considered constant, but are varied in our investigation.

To examine this issue, first, the behavior of control signals is plotted, which is shown in Fig. 3A (δ) and 3B (ϕ). Both signals reach zero in the final time, which is reasonable, because the dynamics reach a steady state that drug injections are no longer effective. To investigate the behavior of the two drugs relative to each other during treatment, the ratio δ/ϕ is illustrated in Fig. 4 to compare the obtained optimal response with experimental data. As it's shown, this ratio starts at around 22 and ultimately tends to zero, which is quite reasonable. Because the system finally reaches a stable state and the injection rates are reduced.

Remark 1. The only point is the value of this ratio in the final time. However, according to Fig. 3, both control signals reach zero at this time. This can be counted as the small amounts of control signals at this time, so that the ratio is quite large and can be ignored.

According to the results described above, the optimal solution is justified logically. The next step is to examine the convergence of the optimal answer. As described in Section 3.1, there should be a stopping point for obtaining control signals. In this work, variations of $\partial H/\partial\delta$ and $\partial H/\partial\phi$ with respect to the step number are considered as stopping criteria. As shown in Fig. 5A and B, these two values reach zero at the initial stages, which indicates the rapid convergence of the response. For more clarity, the amount of the two ratios are shown to the step number of forty.

Remark 2. It's important to draw attention to check continuous control signals during treatment. It may be a bit far from reality that the two control signals have been considered continuous throughout this time. The idea in this paper is the process of drug injection and ultimately its use to estimate some parameters of the system despite the uncertainties. For this reason, the steady-state system and continuous signals were considered in order to use them in stability theorems. This assumption has been widely used in many other papers to examine and compare various control methods and different models such as, [11,12,14,29–31].

So far, an optimal control signal is obtained such that the behavior

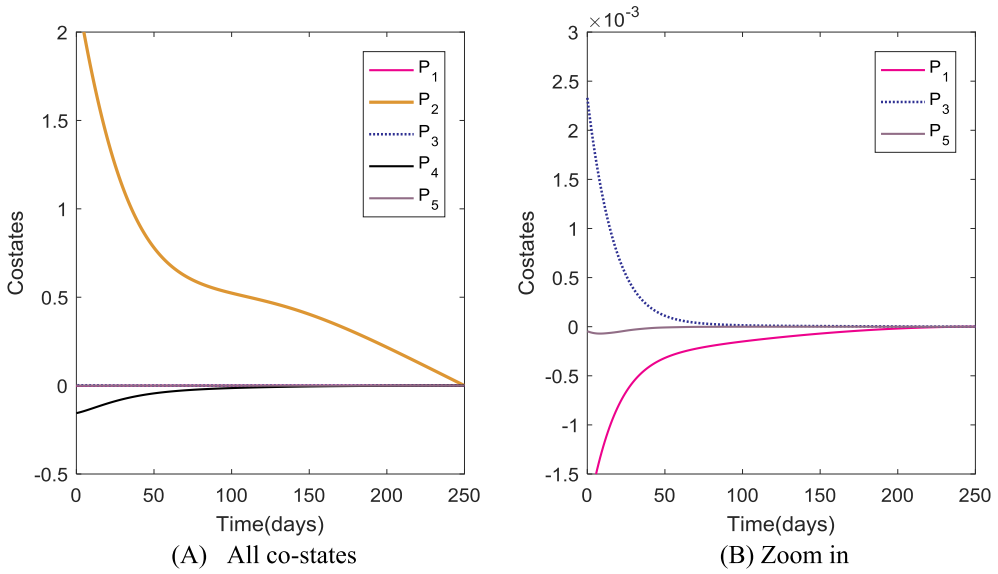

Fig. 2. The behavior of co-states (P_i, $i = 1, 2, 3, 4, 5$) during chemotherapy treatment based on Equation (3). Final conditions are.$P_1(250) = P_2(250) = P_3(250) = P_4(250) = P_5(250) = 0$.

of states is logical and reasonable. Additionally, this solution is convergent from the mathematical aspect. Therefore, this answer can be considered as a possible optimal path or a reference trajectory for an adaptive nonlinear controller. In the following section, a nonlinear adaptive control scheme is designed and applied in order to adapt an arbitrary system to the selected optimal path.

4. Adaptive controller design and parameters estimation

In this section, the control signals are designed using a nonlinear adaptive control scheme. As mentioned earlier, the optimal path is a possible and desirable trajectory to track. The aim of designing adaptive controller is to lead the system on this path. The first step is to rewrite the equations of the dynamical system based on control signals. According to Equation (1), the cancer model has two control signals: injection rate of CA and AA as,

$$\delta = \dot{y} + \xi y + d_1 \frac{x_1 y}{a_1 + x_1} + d_2 \frac{x_2 y}{a_2 + x_2}, \tag{6}$$

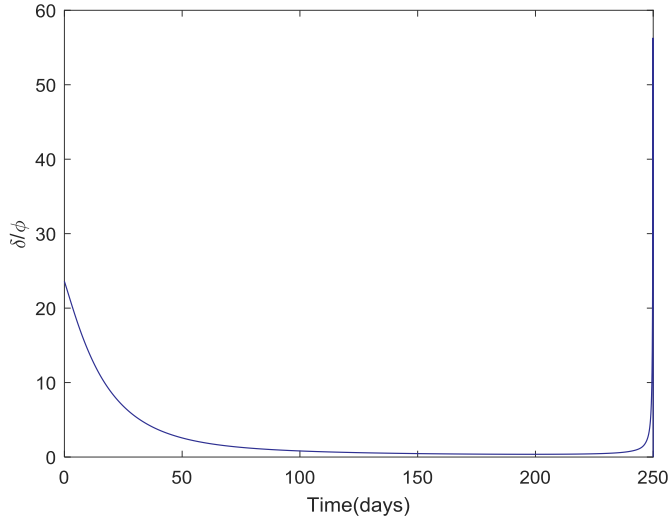

Fig. 4. The ratio of injection rates of CA to AA during treatment.

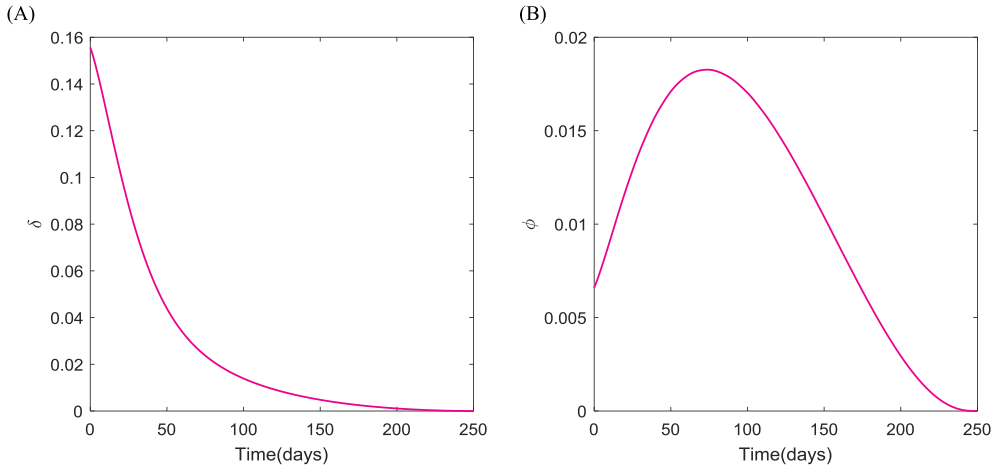

Fig. 3. A, injection rate of CA (δ); B, injection rate AA (ϕ) during chemotherapy treatment.

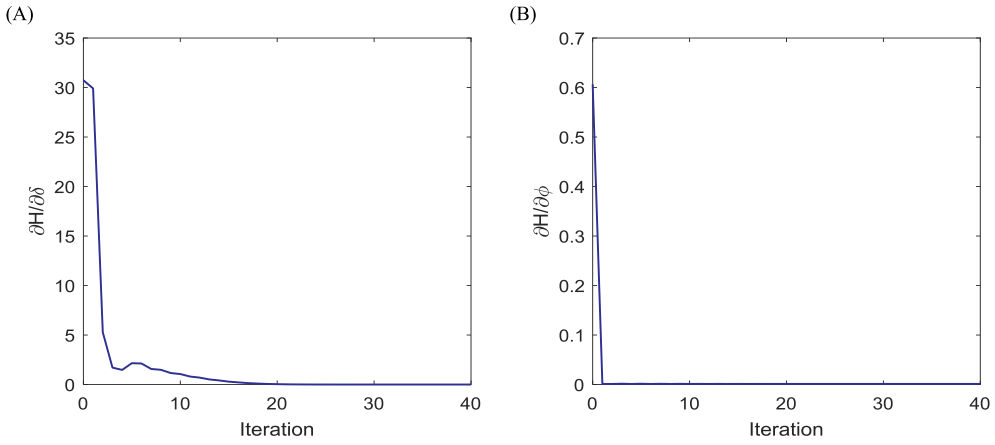

Fig. 5. Variation of Hamiltonian relative to the injection rates of CA (A) and AA (B) with respect to the number of repeat steps.

$$\phi = \dot{w} + \eta w + d_3 \frac{x_3 y}{a_3 + x_3}. \tag{7}$$

Considering above relationships, control signals can be rewritten as follows

$$\delta = \psi_1 + Z_1 \Theta_1, \tag{8}$$

$$\phi = \psi_2 + Z_2 \Theta_2. \tag{9}$$

such that, ψ_1 and ψ_2 are alternatives for $\dot{y}$ and $\dot{w}$, respectively, with the definition of,

$$Z_1 = \left[y \quad \frac{x_1 y}{a_1 + x_1} \quad \frac{x_2 y}{a_2 + x_2} \right], \quad \Theta_1 = [\xi \;\; d_1 \;\; d_2]^T \tag{10}$$

$$Z_2 = \left[w \quad \frac{x_3 y}{a_3 + x_3} \right], \quad \Theta_2 = [\eta \;\; d_3]^T. \tag{11}$$

By assuming $\tilde{y} \triangleq y - y_d$ and $\tilde{w} \triangleq w - w_d$, ψ_1 and ψ_2 are designed as follows.

$$\psi_1 = \dot{y}_d - \lambda_1 \tilde{y}, \tag{12}$$

$$\psi_2 = \dot{w}_d - \lambda_2 \tilde{w}, \tag{13}$$

where λ_1 and λ_2 are control gains. The system control rules will be rewritten by specifying the estimated parameters by $\hat{}$, as follows

$$\delta = (\dot{y}_d - \lambda_1 \tilde{y}) + Z_1 \hat{\Theta}_1, \tag{14}$$

$$\phi = (\dot{w}_d - \lambda_2 \tilde{w}) + Z_2 \hat{\Theta}_2. \tag{15}$$

By substituting Equations (14) and (15) in the dynamics of the system, Equation (1), two below equations are obtained

$$\dot{\tilde{y}} = -\lambda_1 \tilde{y} + Z_1 \tilde{\Theta}_1, \tag{16}$$

$$\dot{\tilde{w}} = -\lambda_2 \tilde{w} + Z_2 \tilde{\Theta}_2. \tag{17}$$

By means of Theorem 1 and Barbalat lemma, which are dealt with in the following, global stability and tracking convergence of the closed-loop system are guaranteed by taking Equations (14) and (15) as control rules, and Equations (18) and (19) as adaptation laws

$$\dot{\hat{\Theta}}_1^T = -\Gamma_1 Z_1 \tilde{y}, \tag{18}$$

$$\dot{\hat{\Theta}}_2^T = -\Gamma_2 Z_2 \tilde{w}. \tag{19}$$

where Γ_1 and Γ_2 are symmetric positive definite constant matrices.

Theorem 1. Consider the following positive definite function as the Lyapunov candidate,

$$\mathrm{V} = \frac{1}{2}[\tilde{y}^2 + \tilde{w}^2 + \tilde{\Theta}_1^T \Gamma_1^{-1} \tilde{\Theta}_1 + \tilde{\Theta}_2^T \Gamma_2^{-1} \tilde{\Theta}_2], \tag{20}$$

the error dynamics of cancer model, is globally stable by control laws, Equations (14) and (15), along with adaptation laws, Equations (18) and (19).

Proof. By considering the Lyapunov candidate of Equation (20), its derivative with respect to time will be,

$$\dot{V} = \dot{\tilde{y}}\tilde{y} + \dot{\tilde{w}}\tilde{w} + \dot{\hat{\Theta}}_1^T \Gamma_1^{-1} \tilde{\Theta}_1 + \dot{\hat{\Theta}}_2^T \Gamma_2^{-1} \tilde{\Theta}_2. \tag{21}$$

By inserting the Equations (16) and (17), the time derivative relation is simplified as follows

$$\dot{V} = -\lambda_1 \tilde{y}^2 - \lambda_2 \tilde{w}^2 + \tilde{y} Z_1 \tilde{\Theta}_1 + \tilde{w} Z_2 \tilde{\Theta}_2 + \dot{\hat{\Theta}}_1^T \Gamma_1^{-1} \tilde{\Theta}_1 + \dot{\hat{\Theta}}_2^T \Gamma_2^{-1} \tilde{\Theta}_2. \tag{22}$$

Now, by substituting Equations (18) and (19) as adaptation laws into Equation (22), the time derivative of the Lyapunov function will become

$$\dot{V} = -\lambda_1 \tilde{y}^2 - \lambda_2 \tilde{w}^2. \tag{23}$$

By considering the positive definiteness of the Lyapunov function and the negative semi-definiteness of its time derivative, it cannot be concluded that the system is globally stable from the Lyapunov stability theorem [32]. Unless it is concluded that the Lyapunov function is zero only when the time is infinity. Barabalat Lemma helps us to conclude this. Different expressions have been expressed for this lemma, which one them is described below.

Barbalat lemma. If function g is continuous and uniform, and the limit of expression $\lim_{t\to\infty} \int_0^t g(\xi) d\xi$ exists and is finite, the following statement can be deduced [32],

$$\lim_{t\to\infty} g(t) = 0. \tag{24}$$

Now if function g is chosen as $-\dot{V}$, by integrating it from zero to infinity with respect to time, we get the following relation.

$$V(0) - V(\infty) = \lim_{t\to\infty} \int_0^t g(\xi) d\xi \tag{25}$$

Since the time derivative of the Lyapunov function is negative semi-definite, the value of the Lyapunov function is always decreasing or constant with time. Thus, it can be concluded that the left-hand-side of Equation (25) is positive and has a finite value. According to the above descriptions, and Barbalat lemma, the following relation can be obtained.

$$\lim_{t\to\infty} (\lambda_1 \tilde{y}^2 + \lambda_2 \tilde{w}^2) = \lim_{t\to\infty} (-\dot{V}) = 0 \tag{26}$$

In other words, by considering the decrement of time derivative of

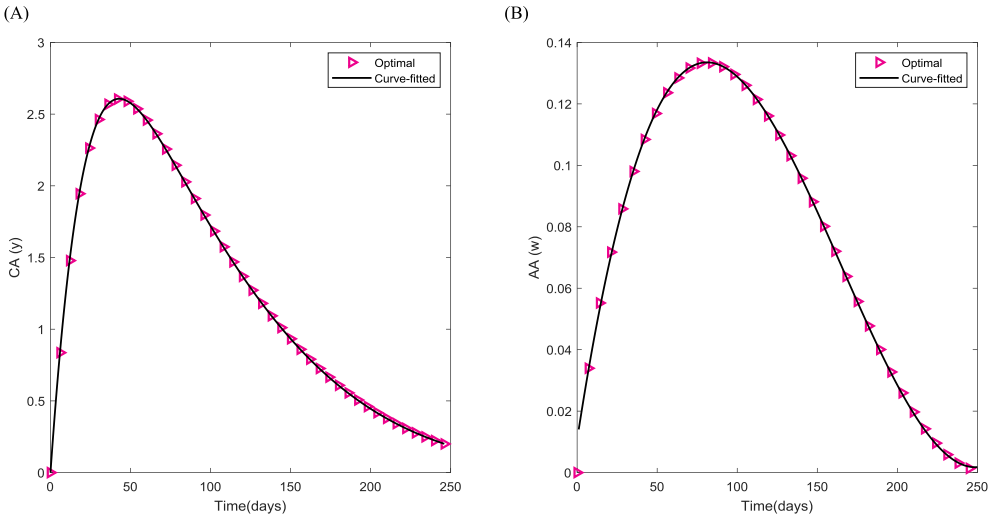

Fig. 6. Optimal chemotherapy (A) and anti-angiogenic (B) variation in body during treatment (based on the data extracted from Fig. 1) along with the fitted curves (Equations (27) and (28)).

Table 2
Adaptation and control gains.

Adaptation gain	$\Gamma_1(1,1) = 0.01$	$\Gamma_1(2,2) = 0.08$	$\Gamma_1(3,3) = 0.1$
	$\Gamma_2(1,1) = 5$		$\Gamma_2(2,2) = 0.5$
Control gain	$\lambda_1 = 1.03$		$\lambda_2 = 1$

the Lyapunov function, the value of the Lyapunov function reaches zero at infinity. Besides that, from the positive definiteness of the Lyapunov function, it can be concluded that according to the Lyapunov stability theory and Barbalat lemma, the system with control laws of Equations (14) and (15) has global stability. In other words, $\tilde{y}$ and $\tilde{w}$ reaches zero at infinity, which implies that $y \to y_d$ *and* $w \to w_d$ *as* $t \to \infty$.

Remark 3. The advantage of using an adaptive controller in this work is that cancer models usually includes coefficients which may vary with each individual or even during the course of treatment for one patient. This choice for the controller, not only adapts the closed-loop system on its optimal path, but also estimates the parameters. In other words, unique optimal control laws can be designed for each patient for any initial conditions.

5. Simulation results

In this section the validity of the proposed controller is verified. Regarding the control laws (Equations (14) and (15)), first we have to consider the optimal trajectories for the CA (y) and AA (w) remaining in the body. The purpose of this paper is to use the optimal paths as desired trajectories. For this reason, optimal trajectories of these two states are considered from Section 3.2. Since the time derivative of the two states is needed, two curves are fitted to their obtained optimal data. Equations (27) and (28) indicate the form of the fitted curves, and Fig. 6A and B shows their graphs along with their optimal data, which are well-adapted,

$$y_d = 5.613\, e^{-\left(\frac{t+114.8}{197.7}\right)^2} - 36.01\, e^{-\left(\frac{t+95.93}{-64.77}\right)^2}, \tag{27}$$

$$w_d = 10^{-8}(5.6246928t^3 - 2780.1474476t^2 + 339942.7196355t + 1067181.5480709). \tag{28}$$

Considering the control and adaption laws, the dynamics of cancer is simulated. The validity of the numerical values and the rationality of the optimal paths are explained in detail in Section 3.2. Therefore, this section discusses only the results of the designed adaptive controller on this path. The non-estimated parameters are still selected from Table 1 and the values for the five estimated parameters (the ones in the adaptation laws) are considered as their initial conditions. In order to verify the strength of the designed adaptive controller, initial conditions for states are assumed as follows: $x_1(0) = 0.5,\ x_2(0) = 0.7,\ x_3(0) = 0.01,\ y(0) = w(0) = 0,$ which is a worse situation compared to the optimal paths. In comparison with initial conditions of the optimal controller stated in Section 3, NCs are considered lower and CCs are assumed to be larger in the adaptive controller. ECs are also assumed to have a nonzero value in this controller, which indicates that the ECs proliferation has started before treatment begins. Other states are still zero, because at the beginning of treatment CA and AA have not been injected to the body yet. Control and adaptation gains are given in Table 2. It should be noted that Γ_1 and Γ_2 are diagonal matrices, and only the values of the main diameter are given in this table.

Fig. 7 illustrates the behavior of the closed-loop system in comparison with the optimal path: The first three states (NC, CC and EC) are plotted separately along with their optimal data (Fig. 7A, B and 7C, respectively); and, the last two states (CA and AA) are drawn with their optimal desired trajectories (Fig. 7D and E). Since the initial conditions of the first three are chosen differently from the optimal controller, the beginning of the figures are not matched with the optimal data, but have the same trend. The behavior of each state is discussed and compared with its optimal trajectory in the following.

The optimal initial condition for NCs was 0.6. When treatment began, they decreased because of the existence of a tumor, and then increased to reach the value one (see Section 3.2). This shows that the patient is getting back to the healthy state as CCs reduced [23]. The same behavior happens when the adaptive controller is applied, but they start from 0.5; decrease at the beginning of treatment and then increase to be close to the value one in final days. It should be noted that the final value of NCs in both controllers depends on the initial condition. Since the initial value in the adaptive controller is assumed to be lower than optimal, its final value is lower than the optimal path which makes sense.

It was assumed that CCs start from a greater value in the first day of treatment (a worse case comparing to the optimal condition). Thus, its final value is a bit larger than optimal trajectory in the final days, as shown in Fig. 7B, which is reasonable. CCs also have the same behavior as their optimal path: They decrease and eventually have a constant value in final days. It's worth noting that this state is the critical state the behavior of which is indicative of the controller's goal [11,12,14,16,29,30,33], which is satisfied in both optimal and adaptive

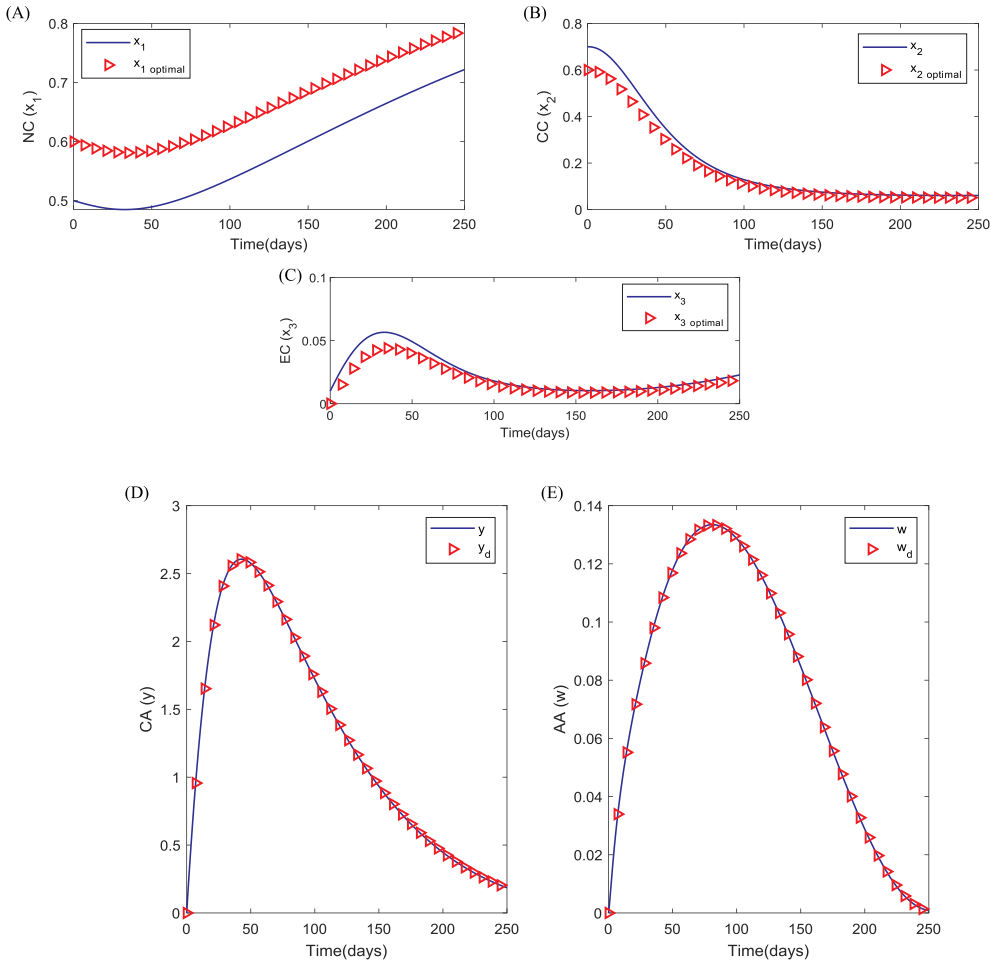

Fig. 7. Changes in states during the course of treatment using the proposed adaptive controller (thick line) along with the optimal trajectories of NC (A); CC (B); EC (C) and the desired amounts of CA (D); AA (E) residual in the body (triangle markers). Initial conditions are considered to be $x_1(0) = 0.5,\ x_2(0) = 0.7,\ x_3(0) = 0.01,\ y(0) = w(0) = 0$.

controllers as discussed.

ECs' behavior in the optimal and the closed-loop adaptive controller is almost the same. The difference between the two curves is their values in the initial days. Since it was assumed that the ECs' proliferation has started before chemotherapy sessions in the adaptive controller, their initial value is greater than the optimal condition. However, as expected, they gradually follow the optimal path (See Section 3.2) and have larger value comparing with an optimal curve in the final days. The last point about ECs is its little increase in the final days. It could be concluded that by considering the fact that CCs have controlled by CA and AA injections (Fig. 7B), the ECs growth in final days can be counted as a natural phenomenon in patient's body, not as a result of the existence of a cancerous tumor [34].

As shown in Fig. 7D and E, the last two states are exactly matched with their optimal data as the considered desired paths for the adaptive controller design. The adaptation is well done, although the controller initial conditions are worse than the optimal ones. Thus, the behavior of CA and AA are exactly like their optimal ones and the explanations about their behavior in Section 3.2 are still valid here.

The control signals along with their optimal data are plotted in Fig. 8. The system has successfully adapted itself to the optimal path. There is a small fluctuation in the rate of injection of CA (δ), which is due to the rapid adaptation of the system to its desire. Since the degree of these fluctuations is very small with respect to variation range, they can be ignored. As the behavior of the control signals is very much like their optimal trends, their evaluations with respect to time are the same as the one stated in Section 3.2.

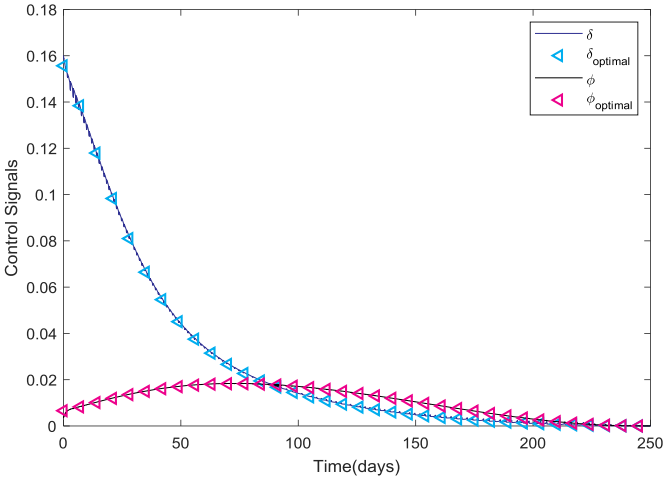

Fig. 8. Control signals obtained from the designed adaptive controller (thick line) and optimal control data (triangle markers).

As already mentioned, one of the aims of using an adaptive controller is to estimate some of the unknown parameters. In this case, five parameters are assumed to be unknown. The diagram of their variation during the treatment can be seen in Fig. 9. Their biological concepts are described in Table 1. In this section, the numerical and experimental values are compared. As is shown in these five charts, the values of the

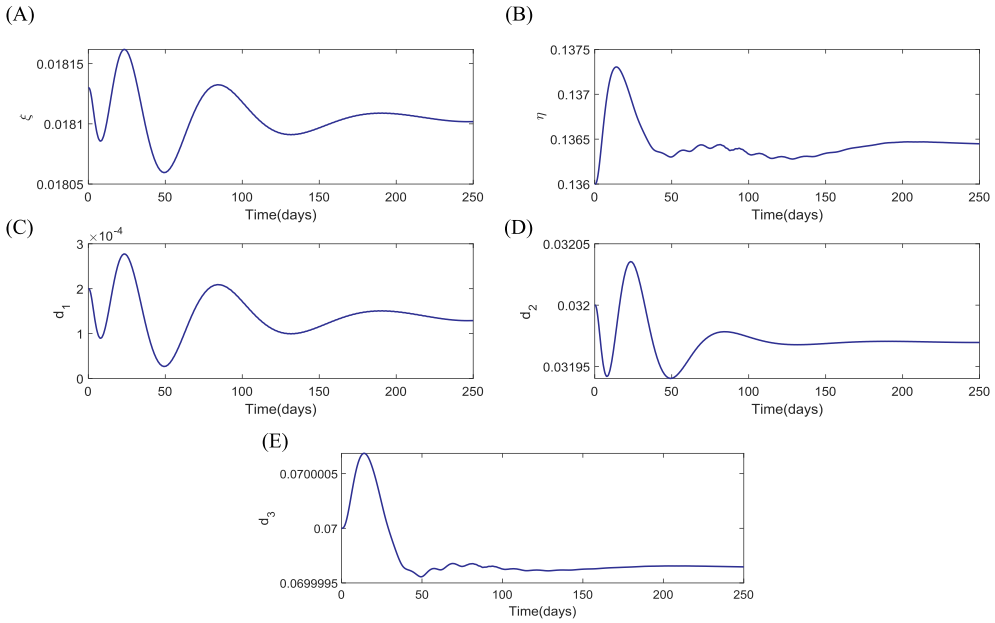

Fig. 9. Estimated parameters during treatment: A, CA half-life (ξ); B, AA half-life (η); C, CA combination rate with NCs (d_1); D; CA combination rate with CCs (d_2); E, AA combination rate with ECs (d_3).

Table 3
Initial and final values of the estimated parameters.

	η	ξ	d_1	d_2	d_3
Initial value	0.13600	0.01813	0.002	0.03200	0.07000
Final value	0.13645	0.01810	1.12889E-04	0.03197	0.06999

five parameters are always positive and do not change much, and eventually, each of them reaches a desired value. Their initial and final values are given in Table 3.

As stated earlier, d_1 and d_2 are the effects of CA on NCs and CCs, respectively, and d_3 is the effect of AA on ECs. According to the experiments of the effect of AA against angiogenesis phenomenon, d_3 has the largest numerical value among them. d_2 is also within its range, but d_1 is much smaller than the other two values [35]. This point is completely matching the results of the adaptive control in Fig. 9C, D and 9E.

The ranges of destruction rate of CA (ξ) and AA (η) in the body based on their half-lives are not large, which indicates that the final values are also valid (Fig. 9A and B, respectively). However, to make sure, we also consider another factor. The destruction rates of the two drugs have been studied in Ref. [36]. For more clarity, another criterion is considered for the validation of the results shown in Fig. 9. In Ref. [23], the ratio η/ξ is taken about 7.5 from the experimental results. Since these two parameters are estimated, it's reasonable to observe the behavior of this ratio during treatment (Fig. 10A). As illustrated, the variation range is less than 0.1, and the ratio tends to about 7.54. Comparing with laboratory data, this trend is a suitable and acceptable answer.

The last point to investigate is the injection rates of CA to AA (δ/ϕ), which was mentioned earlier in Section 3.2 and is illustrated in Fig. 10B. Except for the initial and the final values of the figure, the rest has the exact behavior as the one in Fig. 4. The initial value can be ignored because of the inequality of initial conditions. In the last days of treatment, oscillations could be seen. One of the reasons is the fluctuations of the control signal δ in Fig. 8. This fluctuation is clearer in the smallest amounts of δ and ϕ in the ratio, especially when they are close to zero. As stated earlier, since the range of the oscillations of δ is small, the oscillations of this ratio in final days can be ignored, too. It is

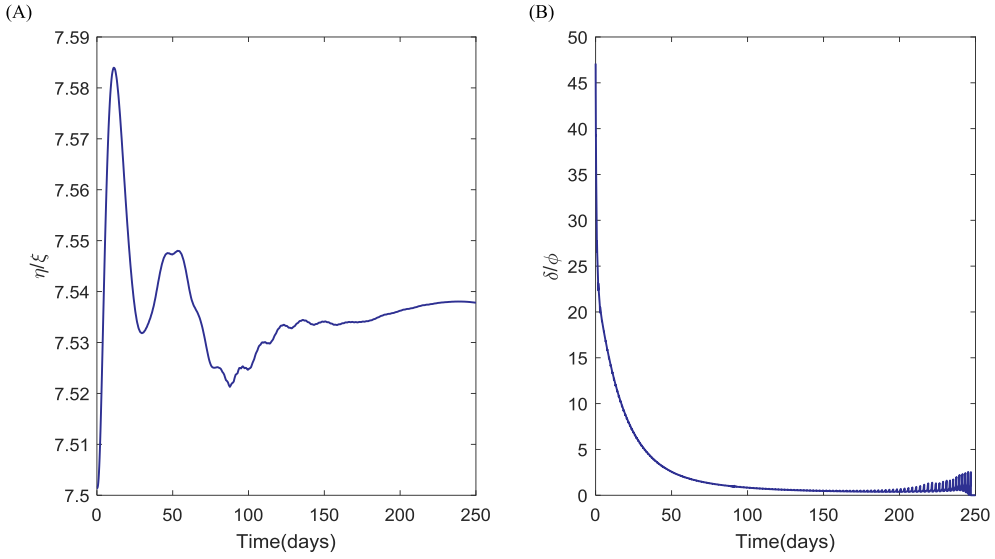

Fig. 10. Estimated ratios during treatment: A, η/ξ; B, δ/ϕ.

important that this ratio generally has a decreasing trend and ultimately reaches zero, which is reasonable.

6. Discussion and comparison with the prior works

Among various mathematical cancer models presented in the chemotherapy field, the model proposed by Pinho in Ref. [23] is chosen to investigate the behavior of the system by the presented optimal adaptive controller. Some major remarks about the selected model and comparison of this investigation with the prior works are indicated in the following:

- The selected dynamic model involves AA as an aid for CA. As stated in the introduction, there are models which consider only CA as the main treatment [8–10,15]. But, Pinho entered AA in order to propose a more comprehensive model. They analyzed each sub-model in the absence of CA and AA, and the general form of the dynamics. Their mathematical proofs were successful in justifying cancer's behavior in all sub-models and the general model (See Section 2).
- There are some papers focusing on designing of controller for the cancerous tumors growth dynamic model presented by De Pillis [10] or the extended one proposed by Ku-Carrillo [15]. Refs. [11,12,14,16,37,38] are just examples of such studies. To the best knowledge of the authors, control methods have not been applied to the selected model in the last investigations. Therefore, it provides a good opportunity to investigate the behavior of the model by applying a closed-loop controller.
- There are mathematical proofs confirming that the model is capable of simulating cancer's behavior. Additionally, the states for a cure can be reachable under special circumstances.
- In this study, the effects of two treatments, chemotherapy and anti-angiogenic, are considered in the dynamic model which makes the presented model more reliable. Other models, however, mainly have one control signal, chemotherapy injection rate, along with the states of system that are usually three to five [8,10,15].
- Some studies have just investigated the optimal solution of the cancerous tumor growth model. For instance Ref. [16], considers optimal control schedules of chemotherapy for the model presented in Ref. [15], with the effect of fat in the dynamics. Their results showed that weight gain can slow down the reduction of CCs. [39] is another example which used an optimal control method to investigate the immune resistance state in cancer therapy. [11] also utilized SDRE to compare the behavior of the cancer dynamics with different weighting matrices in the cost function.

However, there are other studies that applied more complicated controllers on cancer's dynamics. For example [29], utilizes optimal robust control in order to compare the behavior of the three basic cancer dynamics: Log-kill, E_{max} and Norton-Simon. Another study considered the three basic models with the existencine of uncertainties the ODEs [30]. One of the important methods is to use SDRE in order to obtain an optimal solution and then design a Model Reference Adaptive Control (MRAC) to track the optimal path [12,14]. Learning based methods using Q-learning [40] and Genetic Algorithm [13] are other algorithms used to find the best drug dosage. Another powerful method has been used in Ref. [41] by mixing the idea of predictive control and moving horizon estimation.

In the present study, the controller is applied such that.

1. The optimal path is calculated by using calculus of variations by defining a proper cost function based on the system's aims,
2. The adaptive controller is designed using the Lyapunov stability theory and Barbalat lemma to steer the closed-loop system's response towards the obtained optimal trajectory,
3. Some parameters are meanwhile estimated based on the system's stability.

The procedure proposed in this paper is a blend of the objectives of other studies in this field: First, the cost function chosen for the optimal controller design includes the critical state (CC) and two control signals. Such thorough cost function rarely used in the literature. The advantage of putting control signals in the cost function is that the optimal procedure limits their values in each time step. Since CA could eliminate both NC and CC, the patient may suffer from the excessive death of NC. Thus, putting control signals in cost function is a suitable way to limit the increase of control signals. Second, the global stability of the closed loop system is achieved mathematically using an adaptive nonlinear controller design, which is one of the advantages of the proposed controller. Third, some parameters of the system are estimated, and this would give us a chance to observe the behavior of the parameters during chemotherapy. As reviewed earlier, this is for the first time that an optimal adaptive controller design is accomplished for the cancerous tumor growth under above-mentioned conditions. Additionally, since the model chosen in this paper had a powerful mathematical background with two control signals, the obtained results are more comprehensive and reliable in comparison with other similar works in the literature.

7. Conclusions and future work

In this study, a dynamic model of cancer in which chemotherapy and anti-angiogenic are selected as the two simultaneous treatments is studied. Among various models that have been proposed for cancer, the one in which NC, CC, EC, CA and AA are taken as the states in the dynamic model is chosen in this paper. After reviewing the dynamic analysis of the model, optimal paths are extracted as possible and logical trajectories. To do so, due to the urgency of the problem and its constraints, the cost function is defined based on the considered biological assumptions and the optimal control is applied by means of Steepest Descent method. Obtained results show that the most important goal of optimal control, which is to reduce the amount of CCs during treatment, is achieved and all the states are changed logically.

Afterwards, as the first nonlinear controller, an adaptive control is designed. Then, the control laws (for controlling the system) and adaptive laws (for the estimation of parameters) are obtained. It is attained, by using the Lyapunov stability theory and Barbalat lemma, that the global stability of the closed-loop system can be achieved by the chosen control and adaptive laws. Five parameters are also estimated based on adaptive laws. The results are compared with experimental data and, the comparison shows there is a good agreement between the obtained results and the available results in the literature. Thus, it can be concluded, from numerical simulations, that the introduced optimal and adaptive control methods are very efficient methods for controlling the dynamics of cancer. These methods can be used for personalizing drug injection in chemotherapy treatment in order to make sure the rates of injections are possible and optimal.

The results also show that the amounts of CCs left in the body after chemotherapy sessions, is mainly dependent on its initial value. It could be concluded that if a patient visits a doctor with the existence of cancerous tumor in the body for a long time and the treatment begins late, the likelihood of a person's improvement decreases.

In other words, an early stage cancerous tumor is more likely to be cured successfully. It should be noted that the exception always exists in medical science. One may die even if the treatment starts quickly, while another will ultimately stay healthy in spite of the severity of the tumor. These issues mainly depend on the strength of the body and its conditions when it is exposed to the illness. Exceptions such these are neglected in most of the dynamic models in this field. These models, mostly pay attention to the process of total variation of variables, not the exceptions.

It's worth noting that the considered case for examining the efficiency of the designed adaptive controller is assumed to be worse comparing to optimal conditions (See Section 5); and the optimal initial

conditions were written according to Ref. [23]. In general, the proposed control algorithm is able to steer the closed-loop system' response towards the desire optimal path. This means that the theory of personalizing the drug injection program to find the optimal path first, and then makes the system follows it via designing the proposed adaptive controller for an individual, is successful. In order to make this theory more applicable, the effects of the resistance of the patient's body against the tumor, gender, age, weight, the location of the tumor, the necessity of surgery, immunotherapy or radiotherapy during or after chemotherapy and etc. must be considered to strengthen the treatment procedure. Afterwards, the extracted results must be examined in the laboratory in every possible case study to make sure that this method will definitely work on humans. In other words, this paper can be the beginning of this long journey that we hope to lead us to more optimal treatment of this deadly disease in the near future.

In future works, other assumptions can be considered that are closer to reality. Other than personalizing the optimal drug delivery for each patient, the reaction of the body is almost predictable. In the future, radiotherapy could be added to find the best optimal solution for the dosage of CA and AA simultaneously. Another suggestion is to use a closed-loop optimal control, in such a way that when disturbances happen, the optimal control would still be able to find the optimal trajectory for the rest of the treatment.

Conflicts of interest

None Declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.compbiomed.2019.04.011.

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