Optimizing Antiangiogenic Therapy for Tumor Minimization

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Abstract—In this paper, optimization of antiangiogenic therapy for tumor management is considered as a nonlinear control problem. A new technique is developed to optimize antiangiogenic therapy which minimizes the volume of a tumor and prevents it from growing using an optimum drug dose. To this end, an optimum desired trajectory is designed to minimize a performance index. Two controllers are then presented that drive the tumor volume to its optimum value. The first controller is proven to yield exponential results given exact model knowledge. The second controller is developed under the assumption of parametric uncertainties in the system model. A least-squares estimation strategy based on a prediction error formulation and a Lyapunov-type stability analysis is developed to estimate the unknown parameters of the performance index. An adaptive controller is then designed to track the desired optimum trajectory. The proposed tumor minimization scheme is shown to minimize the tumor volume with an optimum drug dose despite the lack of knowledge of system parameters.

I. INTRODUCTION

Tumor antiangiogenic therapy is an encouraging new form of cancer treatment which targets the vasculature of a growing tumor. A solid, avascular growing tumor reaches a size, a few millimeters in diameter, where it can no longer depend upon the blood vessels of the host to obtain its nutrition; thus, it starts the process of angiogenesis. This is a process where a tumor taps the surrounding mature host blood vessels to develop its own blood vessels [1]. The linings of these newly created blood vessels consist of endothelial cells. The tumor produces vascular endothelial growth factor to stimulate the endothelial cells growth along with inhibitors to suppress them [2], [3]. Antiangiogenic therapies were proposed in the early seventies by Folkman [4] to arrest this phase of tumor growth. As pointed out in [5], these treatments were enabled only after the discovery of the inhibitory mechanism of the tumor in the nineties [6]. Antiangiogenic therapies indirectly affect the tumor growth by providing external angiogenic inhibitors in the form of medication which targets the endothelial cells and block their growth; hence, a tumor is deprived of its necessary nutrition and ceases to grow. This therapy does not kill the fast replicating and mutating cancer cells, and instead targets the comparatively more stable endothelial cells. Hence, acquired drug resistance to the angiogenic inhibitors has not been observed [7]. Since the conventional chemotherapy treatments are often limited by the development of drug resistance by the tumor cells, antiangiogenic therapy has been considered as a promising treatment of tumors [8], [9].

There have been several mathematical models that describe the dynamics of angiogenesis. Some of these models attempt to fully describe the complexity of the biological processes [10], [11]. Ramanujan et al. [12] presented a model of tumor growth based on the balance of pro-angiogenic and antiangiogenic signals. More complex PDE models are also presented in [13], [14], [15]. However, these models are not tractable for mathematical analysis [16]. Mathematical models that aim to describe a tumor growth in the vascular phase including the development of the vasculature are few. A simple mathematical model which emphasizes the concept that the development of vascular network controls the tumor growth process was developed and biologically validated by Hahnfeldt et al. [17]. This two-dimensional model uses ordinary differential equations to describe the interactions between the tumor volume and the carrying capacity of the endothelial cells. The model can easily represent the effect of antiangiogenic drugs and the predictions of the model have been successfully compared with the volume response of an experimental subcutaneous tumor implanted in mice treated with drugs [18]. The underlying spatial analysis carried out in the development of the model has spawned various modifications. A modification of this model has been presented by Ergun et al. [19]. More recently, a slight variant of the model by Hahnfeldt et al. was presented by d’Onofrio and Gandolfi [18]. This model assumes the potential doubling time of the vasculature to be constant. Also, it subdivides the endothelial cell pool, which is involved in angiogenesis, into resting and proliferating cells.

Since antiangiogenic therapy is a new cancer treatment, very few researchers have worked on controlling or administrating the drugs. Ledzewicz et al. [1], [5], [16], [20], [21], have proposed optimal control theory for administrating a given amount of drug dose to realize the minimum tumor size. Ergun et al. [19] and Swierniak et al. [22] also proposed optimal control theory to address the same problem. d’Onofrio and Gandolfi proposed open-loop periodic antiangiogenic therapy in [18] and constant infusion of antiangiogenic therapy [23] for tumor reduction. To obtain effective control on tumor growth, antiangiogenic therapy has been proposed by Kerbel and Folkman as an uninterrupted and a long-term therapy [24]. Further, Cao [25], pointed out that a life-span delivery or injection of angiogenesis inhibitors to patients may be required and research is going on to develop oral angiogenic drugs for therapy. It will be shown later in the paper that the tumor as well as the vasculature carrying capacity tend to grow if the medication...
is removed; thus, the regression of tumor volume is not guaranteed.

In this paper, we present an entirely different approach for tumor minimization from the aforementioned papers where optimal control theory was utilized and the drug dose was stopped after a certain time. As mentioned previously, tumor antiangiogenic therapy may require a long-term or a life-span delivery of drugs; hence, we are motivated to develop a tumor reduction technique which keeps the tumor size at a minimum and prevents it from growing using the least possible continuous drug dose. To this end, we first formulate a performance index which will be minimized. Then, we present a nonlinear, continuous control (i.e., drug dose) to achieve the desired optimum value of the carrying capacity of the endothelial cells (and thus, the optimum size of the tumor) assuming exact model knowledge. However, it is a difficult task to exactly measure or estimate the model parameters. Thus, we develop a prediction error based least-squares estimation technique to identify the unknown parameters used in the performance index. Further, an adaptive controller is designed to track the desired optimum trajectory for the carrying capacity of endothelial cells. The optimum trajectory is obtained through an optimization algorithm which seeks the minimum of the performance index. The developed tumor minimization technique finds the optimum values of the tumor size and the carrying capacity of endothelial cells, and it prevents them from growing by maintaining an optimum drug dose.

The remainder of the paper is organized as follows: Section II describes the mathematical model considered. Section III describes the formulation of the performance index along with the control problem associated with it. Sections IV presents the development of the controller given exact model knowledge. Section V describes the development of the least-squares based estimator along with the development of an adaptive controller and an optimum trajectory generator. Finally, concluding remarks are provided in Section VI.

II. SYSTEM MODEL

In our work, we consider the model proposed by d’Onofrio and Gandolfi [18] to relate tumor growth, vascular growth, and the effect of an antiangiogenic therapy. This model allows for a detailed description of the drug effects, and it is given as follows

\[ \dot{p} = \alpha p \left( 1 - \frac{p}{q} \right) \] (1)

\[ \dot{q} = bq - dp^{2/3} - Guq \] (2)

where \( p(t) \in \mathbb{R} \) is the tumor volume in [mm]³, \( q(t) \in \mathbb{R} \) is the carrying capacity of the endothelial cells, also measured in [mm]³, and \( \alpha \in \mathbb{R} \) is a positive tumor growth parameter. In (2), the term \( bq \) accounts for the proliferation kinetics of the endothelial cells and the term \( dp^{2/3} \) models endogenous inhibition of the tumor. The exponent \( 2/3 \) arises from the geometrical argument that the inhibitors generated within the tumor are transported out of the tumor through the tumor surface, modeled as a sphere. The parameters \( b, d \in \mathbb{R} \) are positive growth constants. The positive constant \( G \in \mathbb{R} \) denotes the antiangiogenic killing parameter, and \( u(t) \in \mathbb{R} \) is the manipulated control input which corresponds to the drug dose, measured in [conc.]. A term which represents a spontaneous vasculature loss is often neglected in the literature as it is very small compared to other factors [1]; thus, it is omitted in the above model.

To investigate the steady-state properties of the system model given in (1) and (2), we calculate its equilibria corresponding to a constant drug dose \( u = u_0; u_0 \in \mathbb{R} \) being the steady-state value of \( u(t) \). To this end, we set the right-hand sides of (1) and (2) equal to zero. After some algebraic manipulations we obtain the following two equilibria

\[ p_0 = q_0 = 0 \] (3)

and

\[ p_0 = q_0 = \left( \frac{b - Gu_0}{d} \right)^{3/2} \] (4)

It should be noted that \( p_0 = q_0 = 0 \) is not an admissible point [18]. It is evident from (4) that if the control input is zero, the tumor volume \( p(t) \) along with \( q(t) \) rise and go to their respective equilibria which is \( p_0 = q_0 = 17320 \) [mm]³. This supports the previously mentioned claim that an uninterrupted or a long-term antiangiogenic therapy is required to prevent growth of the tumor. All the parameter values are taken from [18], and are given as follows

\[ \alpha = 1.08 \text{ [day] }^{-1}, \quad d = 3.63 \times 10^{-4} \text{ [day] }^{-1} \text{[mm]}^{-2}, \]
\[ b = 0.243 \text{ [day] }^{-1}, \quad G = 1.3 \text{ [day] }^{-1} \text{[conc.]}^{-1}. \] (5)

**Assumption 1:** In this work, we assume that the tumor volume \( p(t) \) along with the carrying capacity of endothelial cells \( q(t) \) are measurable. Furthermore, we restrict our analysis to a biologically realistic domain where \( p(t) > 0 \) and \( q(t) > 0 \) for all time instants.

III. CONTROL PROBLEM

The goal of this work is to design a therapy regimen for \( u(t) \) that minimizes the volume of the while minimizing the drug dose. We propose that these objectives will be met if the following performance index is minimized

\[ J = p + \left( \frac{Gu}{d} \right)^{3/2}. \] (6)

The performance index \( J(t) \in \mathbb{R} \) captures the treatment goal using the summation of tumor size and drug dose. The drug dose \( u(t) \) in the performance index is multiplied by a factor of \( G/d \) and then raised to \( 3/2 \) to obtain the same unit as \( p(t) \); thus, \( J(t) \) is expressed in [mm]³. The steady-state expression for the performance index can be written as

\[ J_0 = p_0 + \left( \frac{Gu_0}{d} \right)^{3/2} \] (7)

where \( J_0, p_0, \) and \( u_0 \) are the steady-state values of \( J(t), p(t), \) and \( u(t), \) respectively. The minimum of this performance index gives the minimum tumor volume that can be obtained and kept at that value with the minimum amount of the drug
dose $u(t)$. Figure 1 shows the plot for $J_0$ with respect to the steady-state values of $u(t)$, denoted by $u_0$. Figure 2 shows $J_0$ with respect to the steady-state values of $p(t)$ and $q(t)$. Thus, the control objective is to minimize the performance index given in (6) and drive the carrying capacity of the endothelial cells $q(t)$ to its optimum value $q^*$. From (4) and from Figure 2, it can be seen that at steady-state, $q(t)$ is equal to $p(t)$; thus, driving $q(t)$ to its optimum value makes $p(t)$ to go to its optimum value. The minimum value of the performance index at steady-state $J_0$, and the optimum values of $u(t)$, $p(t)$, and $q(t)$ at their respective steady-states can be seen in Figures 1 and 2, and are given as follows

$$J^* = 12,247 \text{ [mm]}^3 \quad u^* = 0.0938 \text{ [conc.]}$$

$$p^* = q^* = 6115 \text{ [mm]}^3.$$

(8)

IV. CONTROLLER DEVELOPMENT WITH EXACT MODEL KNOWLEDGE

In this section, a continuous nonlinear controller is presented to manipulate the drug dose $u(t)$ in order to minimize the tumor volume using the minimum drug dose. From (6), it is clear that if we have an exact knowledge of the model parameters, we can obtain the minimum value of the performance index, and the optimum values of $p(t)$ and $q(t)$ as given in (8); thus, a set-point control for $q(t)$ can be designed to achieve

$$q(t) \to q^* \text{ as } t \to \infty.$$  

(9)

As stated earlier, $p(t) = q(t)$ at steady-state; thus, if $q(t)$ goes to $q^*$ then $p(t) \to p^* = q^*$.

To facilitate the control development, we define the tracking error $e_m(t) \in \mathbb{R}$ as follows

$$e_m = q - q^*.$$  

(10)

After taking the time derivative of (10), the following expression is obtained

$$\dot{e}_m = bq - dp^{2/3}q - Guq$$  

(11)

where (2) was utilized. Based on the subsequent stability analysis, the following control law is proposed

$$u = \frac{1}{Gq} \left( bq - dp^{2/3}q + k_m e_m \right)$$  

(12)

where $k_m \in \mathbb{R}$ is a positive control gain.

Remark 1: From (1) and Assumption 1, it is clear that $\dot{p}(t) \leq 0$ when $p(t) \geq q(t)$; thus, $p(t)$ decreases. If $p(t) < q(t)$, $p(t)$ will increase until $p(t) = q(t)$, and will start to decrease again if $p(t) \geq q(t)$. Therefore, $p(t)$ is bounded as long as $q(t)$ is bounded.

A. Stability Analysis

Theorem 1: The control law given in (12) ensures that $e_m(t) \to 0$ exponentially.

Proof: After substituting (12) into (11), we obtain the following error dynamics

$$\dot{e}_m = -k_m e_m.$$  

(13)

After solving the differential equation given in (13), the following expression can be obtained

$$e_m(t) = e_m(t_0) \exp(-k_m t).$$  

(14)

It is clear from (14) that $e_m(t) \to 0$ exponentially; thus, $q(t) \to q^*$ exponentially fast.

From (14), we can infer $e_m(t) \in \mathcal{L}_\infty$; hence, from (10), it follows that $q(t) \in \mathcal{L}_\infty$. Since $q(t)$ is bounded, from Remark 1, it follows that $p(t) \in \mathcal{L}_\infty$. The control input $u(t)$ given in (12) is a function of bounded signals (i.e., $p(t)$ and $q(t)$) and known constant parameters, therefore, $u(t) \in \mathcal{L}_\infty$. 

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V. CONTROLLER DEVELOPMENT WITH UNCERTAIN MODEL KNOWLEDGE

As mentioned previously in the Introduction, in practice, it is difficult to exactly determine the model parameters for a specific patient. To address this issue, we define an estimate of the performance index given in (6), denoted by \( \hat{J}(t) \in \mathbb{R} \), as follows

\[
\dot{\hat{J}} \triangleq p + \left( \frac{\hat{G}u}{d} \right)^{3/2}
\]  

(15)

where \( \hat{G}(t), \hat{d}(t) \in \mathbb{R} \) are estimates of \( G \) and \( d \), respectively. The control objective remains the same as outlined in Section IV because of the lack of knowledge about the model parameters. To overcome this problem, we design an adaptive controller to track an optimum desired trajectory \( q_d(t) \in \mathbb{R} \) such that \( q(t) \to q_d(t) \) as \( t \to \infty \). The desired optimum trajectory is dynamically generated online using a numerical-based optimization algorithm, described later in Section V-C, to minimize the performance index given in (15), such that \( q_d(t) \to q^* \) where \( q^* \) is the optimum value of \( q(t) \) at steady-state. Thus, the overall control objective can be stated as follows

\[
q(t) \to q_d(t) \to q^* \text{ as } t \to \infty.
\]  

(16)

A. Parameter Estimation

In this subsection, we design an estimator based on the least-squares estimation technique to generate estimates of the unknown constant parameters \( b, d, \) and \( G \). The estimates \( \hat{G}(t) \) and \( \hat{d}(t) \) are then utilized in (15). To facilitate the estimator development, we parameterize (2) as follows

\[
Q = W_e \theta_e
\]  

(17)

where \( Q(t) \) denotes \( \dot{q}(t) \) and \( W_e(t) \in \mathbb{R}^{1 \times 3} \) represents a measurable regression vector which is defined as follows

\[
W_e \triangleq \left[ q \quad -p^{2/3}q \quad -uq \right].
\]  

(18)

In (17), \( \theta_e \in \mathbb{R}^3 \) is a vector of unknown constant parameters defined as follows

\[
\theta_e \triangleq \left[ b \quad d \quad G \right]^T.
\]  

(19)

To further facilitate the estimator design, we define a prediction error \( \varepsilon(t) \in \mathbb{R} \) as follows

\[
\varepsilon \triangleq Q_f - \dot{\hat{Q}}_f
\]  

(20)

where \( Q_f(t) \in \mathbb{R} \) is a filtered signal defined as follows

\[
\dot{Q}_f \triangleq -\beta Q_f + \beta Q \quad ; \quad Q_f(t_0) = 0
\]  

(21)

where \( \beta \in \mathbb{R} \) is a positive constant. Notice that (21) cannot be implemented since \( Q(t) \) is unmeasurable. The reader is referred to [26] for the implementable form of the filtered signal. In (20), \( \dot{Q}_f(t) \in \mathbb{R} \) is the estimate of \( Q_f(t) \), defined as follows

\[
\dot{Q}_f \triangleq W_f \dot{\theta}_e
\]  

(22)

where \( W_f(t) \in \mathbb{R}^{1 \times 3} \) is a filtered regression vector, written as follows

\[
W_f \triangleq -\beta W_f + \beta W_e \quad ; \quad W_f(t_0) = 0_{1 \times 3}
\]  

(23)

where \( 0_{1 \times 3} \) denotes a 1-by-3 vector of zeros and \( \beta \) was introduced in (21). In (22), \( \dot{\theta}_e(t) \triangleq \left[ b \quad d \quad \tilde{G} \right]^T \in \mathbb{R}^3 \) is the estimate of the unknown parameters. After substituting (17) into (21), the following expression can be obtained

\[
\dot{Q}_f + \beta Q_f = \beta W_e \theta_e.
\]  

(24)

The expression given in (24) can be rewritten as follows

\[
\dot{Q}_f + \beta Q_f = W_f \theta_e + \beta W_f \theta_e
\]  

(25)

where (23) was utilized. After taking the time derivative of (22), and then adding and subtracting the term \( W_f \theta_e \) to the right-hand side of the resulting expression, the following expression can be obtained

\[
\dot{\hat{Q}}_f + \beta \hat{Q}_f = \frac{d}{dt} \left(W_f \theta_e\right) + \beta W_f \theta_e
\]  

(26)

where (22) and (23) were utilized. After subtracting (26) from (25), and utilizing (20) and (23), the resulting expression can be written as follows

\[
\hat{\varepsilon} + \beta \varepsilon = \frac{d}{dt} \left(W_f \theta_e\right) + \beta W_f \theta_e
\]  

(27)

where \( \hat{\varepsilon}(t) \in \mathbb{R}^3 \) is the estimation error signal defined as follows

\[
\hat{\varepsilon} \triangleq \varepsilon - \theta_e.
\]  

(28)

From (27), it can be shown that a mathematically useful, but unrealizable, form of the prediction error \( \varepsilon(t) \) given in (20) can be written as follows [27]

\[
\varepsilon = W_f \theta_e.
\]  

(29)

Based on the subsequent stability analysis, the following continuous least-squares update law \( \hat{\theta}_e(t) \in \mathbb{R}^3 \) is employed for estimating the unknown parameters

\[
\dot{\hat{\theta}}_e \triangleq \Gamma W_f^T \varepsilon
\]  

(30)

where \( \Gamma(t) \in \mathbb{R}^{3 \times 3} \) is the least-squares estimation gain matrix which is designed as follows

\[
\hat{\theta}_e \triangleq \Gamma W_f^T \dot{\varepsilon}
\]  

(31)

Remark 2: If \( Q(t) \) is bounded, from (21), we can show that \( Q_f(t), \dot{Q}_f(t) \in \mathcal{L}_\infty \). Similarly, if \( W_e(t) \in \mathcal{L}_\infty \), from (23), we can show that \( W_f(t), \dot{W}_f(t) \in \mathcal{L}_\infty \). The reader is referred to [27] for a detailed description.

Remark 3: It should be noted that if \( \Gamma^{-1}(t_0) \) is selected to be positive definite and symmetric then \( \Gamma(t_0) \) is also positive definite and symmetric. Therefore, it follows that both \( \Gamma^{-1}(t) \) and \( \Gamma(t) \) are positive definite and symmetric. The following expression can be obtained from (31)

\[
\Gamma = -\Gamma W_f^T W_f \Gamma.
\]  

(32)

It can be easily seen from (32) that \( \Gamma(t) \) is negative semidefinite; therefore, \( \Gamma(t) \) is always constant or decreasing; hence, it follows that \( \Gamma(t) \) is bounded (for more details, the reader is referred to [28] and [29]).
B. Development of Adaptive Control Law

To proceed with the development of an adaptive control law to achieve the control objective stated in (16), we divide both sides of (2) by G to obtain the following expression

\[ \frac{1}{G} \dot{q} = \frac{b}{G} q - \frac{d}{G} q^{2/3} - uq. \]  (33)

The expression given in (33) is then parameterized as follows

\[ A \dot{q} = W_0 \theta_0 - uq \]  (34)

where \( A \triangleq G^{-1} \in \mathbb{R} \) is a positive unknown constant, and \( W_0(t) \in \mathbb{R}^{1 \times 2} \) is a measurable regression vector defined as follows

\[ W_0 \triangleq \begin{bmatrix} q & -p^{2/3}q \end{bmatrix}. \]  (35)

In (34), \( \theta_0 \in \mathbb{R}^2 \) is a vector of unknown constants, defined as follows

\[ \theta_0 \triangleq \begin{bmatrix} bA & dA \end{bmatrix}^T. \]  (36)

To facilitate the development, we define a tracking error \( e_a(t) \in \mathbb{R} \) as follows

\[ e_a \triangleq q - q_d \]  (37)

where \( q_d(t) \in \mathbb{R} \) is a subsequently designed optimum desired trajectory for \( q(t) \). The desired trajectory \( q_d(t) \) is designed such that \( q_d(t), \dot{q}_d(t) \in \mathcal{L}_\infty \) as shown later in Section V-C. After taking the time derivative of (37), and then multiplying both sides of the resulting expression by \( A \), we can write the following expression

\[ A \dot{e}_a = A \dot{q} - A \dot{q}_d. \]  (38)

After substituting (34) into (38), the following expression is obtained

\[ A \dot{e}_a = W_0 \theta_0 - uq - A \dot{q}_d \]  (39)

which can be rewritten in a parameterized form as follows

\[ A \dot{e}_a = W_0 \theta_0 - uq. \]  (40)

In (40), \( W_a(t) \in \mathbb{R}^{1 \times 3} \) is a measurable regression vector and \( \dot{\theta}_a \in \mathbb{R}^3 \) is a vector of unknown constants defined as follows

\[ W_a \triangleq \begin{bmatrix} W_0 & -\dot{q}_d \end{bmatrix} \]  (41)

and

\[ \dot{\theta}_a \triangleq \begin{bmatrix} \theta_0^T & A \end{bmatrix}^T. \]  (42)

Based on the subsequent stability analysis, the control input \( u(t) \) is designed as follows

\[ u \triangleq \frac{1}{q} \left( W_a \hat{\theta}_a + k_a e_a \right) \]  (43)

where \( \hat{\theta}_a(t) \in \mathbb{R}^3 \) is an estimate vector of \( \theta_a \), and the adaptive update law \( \hat{\theta}_a(t) \in \mathbb{R}^3 \) is designed as follows

\[ \dot{\hat{\theta}}_a \triangleq \gamma_a W_a^T e_a. \]  (44)

In (43) and (44), \( k_a, \gamma_a \in \mathbb{R} \) are positive constants.

C. Optimum Trajectory Generation

In this subsection, an optimum desired trajectory \( q_d(t) \) is designed which is fed to the adaptive controller given in Section V-B. This continuous optimum trajectory \( q_d(t) \) is designed to minimize the performance index given in (15) where the estimates for the parameters \( G \) and \( d \), obtained as described in Section V-A, are utilized. For the minimization of the estimate of the performance index, \( J(t) \), a gradient descent algorithm is employed which guesses the optimum value \( \hat{q}_d[n] \) at each time step of the optimization algorithm. The output of the algorithm, \( \hat{q}_d[n] \), is passed through a set of second-order, stable and proper, low-pass filters to generate continuous and bounded signals for \( q_d(t) \) and \( \dot{q}_d(t) \). The following filters are utilized

\[ q_d(t) = \frac{s_1}{s_2 s^2 + s_3 s + s_4} \hat{q}_d[n], \]  (45)

\[ \dot{q}_d(t) = \frac{s_1}{s_2 s^2 + s_3 s + s_4} \hat{q}_d[n] \]  (46)

where \( s_1, s_2, s_3, s_4 \in \mathbb{R} \) are positive filter constants, and \( n \in \mathbb{Z} \) is a positive integer (i.e., the iteration step of the algorithm). At step \( n \), the optimum trajectory holds the output, \( \hat{q}_d[n] \), constant until the response of the closed-loop system, \( q_t \), has reached a steady-state near \( q_d(t) \). A new target optimum \( \hat{q}_d[n+1] \) is then issued. In other words, the algorithm waits for certain thresholds to be satisfied before it proceeds to the next iteration. For instance, if \( |q(t) - q_d(t)| \leq \varepsilon_1, |\hat{q}_d[n] - q_d(t)| \leq \varepsilon_2, \) and \( |q(t) - p(t)| \leq \varepsilon_3 \) then \( n = n + 1 \) where \( \varepsilon_1, \varepsilon_2, \varepsilon_3 \in \mathbb{R} \) are threshold constants. Furthermore, the designed trajectory can be concluded to have converged when the gradient of \( J(t) \) with respect to \( q(t) \) is within a certain threshold. Once the optimization algorithm satisfies the termination criteria, it stops updating \( \hat{q}_d[n] \). As the performance index approaches its minimum value, the desired trajectory \( q_d(t) \) and \( u(t) \) approach \( \hat{q}^* \) and \( \hat{u}^* \), respectively. \( \hat{q}^* \), \( \hat{u}^* \in \mathbb{R} \) are the estimates of the optimum values of \( q(t) \) and \( u(t) \), respectively that are resulted from the optimum seeking algorithm.

As mentioned earlier, at steady-state \( p(t) = q(t) \); therefore, \( p(t) \rightarrow p_d(t) \rightarrow \hat{p}^* \) as \( q(t) \rightarrow q_d(t) \rightarrow \hat{q}^* \) where \( p_d(t) = q_d(t) \) and \( \hat{p}^* = \hat{q}^* \). Then \( \hat{p}^* \) is the estimated optimum tumor volume that can be realized by applying the estimated optimum drug dose \( \hat{u}^* \).

D. Stability Analysis

Theorem 2: The update law defined in (30) ensures that \( ||\hat{\theta}_e(t)|| \rightarrow 0 \) as \( t \rightarrow \infty \) provided that the following Persistency of Excitation (PE) condition [30] holds

\[ \kappa_1 I_3 \leq \int_{t_0}^{t_0+\delta} W_f^T(\tau)W_f(\tau)d\tau \leq \kappa_2 I_3 \]  (47)

where \( \kappa_1, \kappa_2, \delta \in \mathbb{R} \) are positive constants, and \( I_3 \) is a standard 3-by-3 identity matrix.

Proof: See [26].

Remark 4: The PE condition given in (47) can be fulfilled by guaranteeing that the signals in the regression matrix vary...
in a sufficiently independent manner within a time-window. The reader is referred to [31] for a detailed explanation.

Theorem 3: The control law \( u(t) \) given in (43) and the adaptive update law defined in (44) guarantee that \( e_q(t) \to 0 \) as \( t \to \infty \).

Proof: See [26].

Remark 5: From Theorem 3 and the optimum seeking algorithm described in Section V-C, it can be concluded that \( q(t) \to q_0(t) \) as \( t \to \infty \) and \( q_0(t) \to \hat{q}^* \). From the simulation results shown in [26], it can be further seen that if \( \hat{q}^* = q^* \) then \( q^* = u^* \) resulting in an optimal solution. However, if the optimization algorithm does not locate the exact optimal values, the solution results into one of a sub-optimal nature.

VI. CONCLUSION

A novel approach to optimize antiangiogenic therapy for tumor minimization was presented. We considered the mathematical problem to minimize the tumor volume and prevent it from growing using a continuous optimum drug dose. A performance index was formulated which was minimized in order to obtain the optimum value of the tumor volume. It was shown that given exact model knowledge, the tumor volume can be driven to its optimum value exponentially fast. In the absence of model knowledge, a least-squares estimation strategy was presented which facilitated the estimation of the performance index. An optimum trajectory generator was presented which seeks the unknown minimum of the performance index while ensuring that the desired trajectory remains bounded and sufficiently differentiable. An adaptive controller was then developed to track the desired trajectory in the presence of uncertainties in the model in order to minimize the tumor volume with an optimum dose of drug. It was proven that the least-squares estimation errors are driven to zero upon the satisfaction of a PE condition. The developed technique minimizes the tumor volume along with the carrying capacity of endothelial cells with an optimum drug dose despite the lack of knowledge about the sytem model.

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