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Robust Control of Cancer Chemotherapy through Time Delayed Estimation Philosophy

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ABSTRACT Chemotherapy, a vital cancer treatment, operates by delivering drugs to target and eliminate cancer cells in the patient body. Mathematical models like the log-kill, Norton-Simon, and $E_{\max}$ hypotheses describe the growth/shrinking of the cancerous tumor due to the interaction and administration of the drugs with the tumor. This paper proposes a robust control approach based on artificial time-delayed theory to track the desired rate of change in tumor volume under model uncertainties and disturbances. The proposed algorithm relaxes the assumption on a priori knowledge of disturbance bound and its derivative. Unlike traditional methods, the control structure is simple, and the total disturbance is estimated by analyzing the previous input and output of the feedback state and control variables. Thus, robustness is ensured without relying on high-frequency switching or high gain. The stability analysis of the proposed scheme is investigated based on the Lyapunov theory. Moreover, extensive simulation results with comparative analysis affirm the efficacy of the proposed approach.

INDEX TERMS Cancer Chemotherapy, Cell-kill hypotheses, Robust Control, Trajectory tracking, Time-delayed Control.

I. INTRODUCTION

The severe disease of cancer, which is one of the most potent killers of humans worldwide, is characterized by imbalances in the processes of cellular growth (proliferation) and programmed cell death, also known as apoptosis [1]. This imbalance, if untreated, leads to the development of cancerous malignancies, such as out-of-control tumors, blood-borne illness, and organ failure, among others. This may result in the ultimate demise of the human due to these anomalies. Thus, effective treatment options for cancer are a widely explored area in literature and practice for their potential to save countless human lives [2]–[6]. Although the size of a malignant mass is frequently described with reference to the number of cells, nonetheless, cancer cells generally multiply exponentially. The size of the cancerous mass is assessed empirically as a volume, and numerous methods of treating cancer patients have developed over time. Surgery, chemotherapy, radiation, and immunotherapy are all used to tackle and manage cancer in humans. These can be used separately or in conjunction with one another [7]. However, clinical chemotherapy is one of the most popular and effective cancer treatment options that has grown in popularity and significance over the past several years. Chemotherapy for cancer seeks to minimize the presence of malignant cells after a specific amount of time or perhaps completely eliminate them. A predefined amount of drugs is

injected into the patient's body during chemotherapy, either intravenously or orally. The goal of chemotherapy is to either totally eliminate cancer cells or lower their number to a safe minimum.

Chemotherapy is a powerful treatment that can have side effects. The chemotherapy medications have an immediate adverse effect of raising the body's toxicity levels, which damages healthy, normal cells. Therefore, choosing the right medication dose is essential for the chemotherapy procedure to destroy cancer cells effectively, and save as many healthy and normal cells as possible. The use of control strategies to develop effective approaches for cancer treatment has gained traction in the last decade, as can be seen from [7]–[9]. Model-based control techniques are crucial for manipulating drug consumption, which in turn, directly affects the volume of the tumor in cancer treatment. In such approaches, designing an efficient feedback controller is impossible without a thorough comprehension of the process dynamics that has to be regulated. Developing a mathematical model that can accurately represent the physical process is crucial. However, comprehending the complicated biochemical interplay between chemotherapy medications, immune cells, healthy cells, and dangerous tumor cells is difficult. The literature uses a variety of mathematical models to illustrate these intricate biological connections. Several models have been created for the chemotherapy process's destruction of malignant tumor cells. Among these, widely used cell-kill models include the nonlinear mathematical models of log kill [10], Norton-Simon [11], and $E_{\max}$ [12], which are discussed in this work. Each approach (Log-kill, Norton-Simon, $E_{\max}$) has unique strengths suited to different scenarios. The best choice depends on the specific question and the patient's situation. For instance, the log-kill model might be the most fitting for estimating initial tumor reduction. The Norton-Simon model could be ideal when predicting treatment response based on tumor size and dosage. To optimize drug dosing while minimizing toxicity, the $E_{\max}$ model offers a more realistic perspective.

Open loop unconstrained and constrained control have been devised in [13], [14], and based on these selected theories, viable treatment plans vary in these study papers. As a constrained medication delivery control for nonlinear models, the bang-bang control approach has been applied in [13], and it has also been demonstrated how to apply a closed-loop scheme with a quadratic performance objective. In [14], [15], the optimal control issue is reconstructed as a straightforward numerical problem where the control variable is approximated by a constant value over a predetermined time. Such open-loop control strategies are employed during the chemotherapy procedure. Numerous studies investigating the chemotherapy treatment process use optimal control methodologies, as seen from [16], [17]. However, it is of utmost importance that analysis and control design must take into account the uncertainties impacting cancer models in order to ascertain the most effective medication administration therapy. Process parameters, parasitic/unmodeled dynamics, and unknown external perturbations are the sources of these uncertainties. Thus, it is highly possible that some of the described control strategies won't work effectively under a range of operating situations and in the face of uncertainty. Optimal and robust control strategies are explored for cancer treatment in [18], [19] using model predictive and LMI-based control, respectively. However, these methods are model-based control. In [20], the effects of three cancer chemotherapeutic strategies: optimal linear regulation, optimal control based on the variation of extremals, and H_∞ robust control have been reported. Based on a linearized cell kill model, these controllers were proposed, and therefore, only within a small radius of the operating point where the nonlinear cell kill models are linearized can the performance of these controllers be assured.

Various robust control techniques are also investigated for cancer treatment procedures, namely, adaptive control [21], sliding mode control (SMC) [22], fractional order control [23], fuzzy control [24], extended Kalman filter [25], etc. In [26], an adaptive and robust control technique is developed that can effectively modify drug delivery schedules, with the potential to reduce tumor growth. Further, a model reference adaptive control (MRAC) strategy for personalized drug delivery protocols in cancer treatment is proposed in [27]. Through state-dependent Riccati equations (SDRE) within the MRAC framework, optimal drug delivery strategies are determined for a particular patient with unknown parameters. In [28], an adaptive control strategy is developed to reduce the volume of cancerous cells and identify tumor parameters online during the chemotherapy process. A fuzzy logic-based finite time backstepping control for delivering cancer immunotherapy drugs is proposed in [29]. This scheme uses fuzzy logic to handle patient response uncertainties and achieves faster tumor reduction. In [21], an enhanced Kalman filter observer with an adaptive control technique is reported. The controller modifies the medication dosages in chemotherapy procedures and regulates the state of tumor, immune, and normal cells. In the proposed study, three kinds of cell-kill hypotheses are investigated. The control scheme aims to follow a predetermined reference value of tumor volume following chemotherapy administration for a set amount of time. Further, the controller needs to tackle exogenous disturbances and model uncertainties.

Utilizing the traditional control methodologies to design an effective approach for tackling the problem of tumor growth management under the effect of uncertainties and having a highly nonlinear structure is difficult. The use of nonlinear controllers in the biomedical field has increased significantly. SMC is one such nonlinear control method that is simple in design, achieves faster system response, and attenuates parametric uncertainties and external disturbances. The SMC has been incorporated in various biomedical research, such as the regulation of human blood sugar [30], [31], artificial pancreas in type 1 diabetes patients [32], cancer chemotherapy treatment [33]–[36], etc. However, the major issue with the SMC is input chattering due to the

switching function in the control law. The higher-order SMC techniques were incorporated in [34]–[36] to address the chattering problem. However, the formulation of control scheme then becomes complex as it employs the exact differential observers to estimate the higher-order state variables [37]. Besides, the SMC schemes in [33]–[35] assume a priori upper bound knowledge of disturbance for designing the control law, which is not always practically feasible.

In this regard, the technique of time-delayed estimation (TDE) is proposed to estimate the uncertainties and the unmodelled dynamics of the considered system to design a time-delayed control (TDC) methodology [38]–[41]. This approach alleviates the conservative assumption of apriori knowledge of upper bounds and also of bounded uncertainties, provided the uncertainties are slowly varying with respect to the control cycle. In the TDC strategy, the uncertainties along with the unknown parts of the system dynamics are effectively estimated utilizing the data from prior instant through the use of an artificial delay, which is introduced for the control law formulation in an otherwise delay-free system.

The primary contributions of this work can be listed as

- Unlike the aforementioned model-based control schemes, the proposed time delay-based control structure for the nonlinear cell-kill models is model-free. With the use of immediate past input and output information, the proposed control is devised.
- The controller design doesn't require prior information about the bounds of uncertainties and disturbances. Therefore, it relaxes the restrictive assumption of uncertainties in the system model. Further, to establish the efficacy of the proposed control design, it has been analyzed on multiple hypotheses of cancer chemotherapy.
- A comprehensive theoretical stability analysis is presented using Lyapunov theory, which ensures tracking capabilities and robustness against various uncertainties. Further, Lyapunov analysis affirms a uniformly ultimately bounded (UUB) stability.
- A detailed comparison with the state-of-the-art super-twisting algorithm for the discussed problem is also included in this work.

The rest of the paper is organized as follows: The considered model is described in Section II, followed by the formulation of the control law in Section III. The stability analysis and the results are reported in Section IV and V, respectively, while the conclusion is presented in Section VI.

II. MODEL DESCRIPTION

Mathematical modeling plays a pivotal role in cancer research by providing a rigorous tool that can be utilized to influence and enhance the efficacy of cancer treatment. Thus, the chemotherapy process has been modeled in the literature using dynamical systems as presented in [14], [42]. Also, based on in-vitro research, cell death was contemplated to be proportional to the tumor population in some studies [10]. Instead of a fixed quantity, a constant percentage of the tumor population was eliminated by a particular dosage of medications. Therefore, it may be deduced that a malignant tumor's volume decreases more quickly when it has a big population than when it has a relatively small population.

The log-kill mechanism is an alternate term for this cell-killing theory, however this technique was unable to adequately demonstrate the nature of cell death for humans and certain experimental solid tumors. The growing process of a tumor volume is expressed in the study using a particular growth function (Gompertzian growth curve [43]). There is an occurrence of a paradox with the log-kill hypothesis regarding acute lymphoblastic leukemia and Hodgkin's disease, where the decrease in tumor volume was seen to obey a completely different function [11]. An alternative theory was devised by [11], which suggested that the cell-kill was related to the rate of tumor population growth.

Another theory put out in [12] that suggested an enzyme should assimilate the tumor volume before chemotherapy medications are delivered. The theory is known as the $E_{\max}$ hypothesis. The metabolic process produces a saturable function of cell-kill. Following is the generalized dynamics of a cell-kill model:

$$\frac{dx}{dt} = rx\Psi(x) - \Gamma(x,t) \tag{1}$$

where, x is the tumor volume, r is the rate at which x is expanding, $\Psi(x)$ is the generalized growth function, and $\Gamma(x,t)$ stands for the drug's pharmacodynamic effects. Here, the Gompertzian type growth function is considered, and mathematically it is stated as,

$$\Psi(x) = \ln(k/x) \tag{2}$$

with k being the scaling factor. The mathematical expressions of the $\Gamma(x,t)$ for the three cell-kill hypotheses are as follows:

$$\Gamma(x,t) = \frac{\delta x}{k}u(t), \text{ for log-kill hypothesis,} \tag{3a}$$
$$\Gamma(x,t) = \delta\Psi(x)u(t), \text{ for Norton-Simon hypothesis,} \tag{3b}$$
$$\Gamma(x,t) = \frac{\delta x}{x+\lambda}u(t), \text{ for } E_{\max} \text{ hypothesis} \tag{3c}$$

where $u(t)$ represents the controlled usage of chemotherapeutic medicines, constant λ is clinically observed, and δ is a constant proportional to the amount of drug use. For ease of expression, the following transformations are employed:

$$\bar{x} = x/k,\ \bar{\delta} = \delta/k,\ \bar{\lambda} = \lambda/k. \tag{4}$$

The aforementioned hypotheses (1), (2), and (3) can be rewritten in terms of the transformed variable as:
For log-kill hypothesis,

$$\frac{d\bar{x}}{dt} = -r\bar{x}\ln(\bar{x}) - \delta\bar{x}u(t). \tag{5}$$

For Norton-Simon hypothesis,

$$\frac{d\bar{x}}{dt} = -\ln(\bar{x})\left(r\bar{x} - \delta u(t)\right). \tag{6}$$

And for $E_{\max}$ hypothesis,

$$\frac{d\bar{x}}{dt} = -r\bar{x}\ln(\bar{x}) - \frac{\delta\bar{x}}{\bar{x}+\lambda}u(t). \tag{7}$$

The clinically determined starting condition for the tumor volume is $\bar{x}(0) = x_0$.

III. CONTROLLER DESIGN

This section investigates a robust control strategy using TDC for the cancer treatment procedure with cell-kill hypothesis. According to clinical findings, a patient's tumor volume should decrease or reach a risk-free limit after chemotherapeutic treatment. The standard practice recommends a set amount of time for therapy. The tumor volume $x(t)$ should decrease along a targeted trajectory during the course of treatment.

Control Objective: Given the three cell-kill models (5)–(7), the proposed controller aims to track the reference tumor growth trajectory $\bar{x}_r(t)$ in the presence of perturbations and model uncertainties without knowing their upper bounds.

The equations of three cell-kill based cancer chemotherapy process models (5)–(7) can be expressed in a more generalized way as:

$$\dot{\bar{x}} = f(\bar{x}) + g(\bar{x})u \tag{8}$$

where $\bar{x} \in \mathbb{R}$ is the tumor volume and $u \in \mathbb{R}$ is the controlled drug input. Moreover, in the presence of unmodelled dynamics and/or unknown non-dissipating disturbance (let's say $d(t) \in \mathbb{R}$), the system model (8) can be redefined as

$$\dot{\bar{x}} = f(\bar{x}) + g(\bar{x})u + d(t) \tag{9}$$

Assumption 1: The disturbance $d(t)$ is bounded with an unknown bound.

A. TIME-DELAYED CONTROL LAW

This section presents a robust tracking scheme such that the tumor volume $\bar{x}(t)$ at time t follows a reference trajectory represented as $\bar{x}_r(t)$. For that, we first denote the error in tumor volume as $\sigma = \bar{x} - \bar{x}_r$. Differentiating σ with respect to time and substituting the expression for $\dot{\bar{x}}$ as (9), the error dynamics is:

$$\dot{\sigma} = f(\bar{x}) + g(\bar{x})u + d(t) - \dot{\bar{x}}_r \tag{10}$$

A function that merges the states and uncertainties is taken as $\bar{f}(\bar{x}) = f(\bar{x}) + d - \dot{\bar{x}}_r$. The error dynamics (10) now is expressed as

$$\dot{\sigma} = \bar{f}(\bar{x}) + g(\bar{x})u \tag{11}$$

Considering $g(\bar{x}) \neq 0$, let us assume $\bar{g}(\bar{x}) = g^{-1}(\bar{x})$ and multiply $\bar{g}(\bar{x})$ to the both sides of (11) to obtain

$$\bar{g}(\bar{x})\dot{\sigma} = g_1(\bar{x}) + u \tag{12}$$

where $g_1(\bar{x}) = \bar{g}(\bar{x})\bar{f}(\bar{x})$. Adding and subtracting $h(\bar{x})\dot{\sigma}$ in (12), we obtain,

$$h(\bar{x})\dot{\sigma} = \bar{g}_1(\bar{x}) + u \tag{13}$$

where $\bar{g}_1(\bar{x}) = \bar{g}(\bar{x})\bar{f}(\bar{x}) + [h(\bar{x}) - \bar{g}(\bar{x})]\dot{\sigma}$ and $h(\bar{x})$ is a user-defined positive function, which is discussed more in detail in later section. The arguments of functions for (13) are henceforth dropped in this work for the purposes of brevity. Further, the parameters, which are explicit functions of time, would from now on be represented as $h(t)$ and $\bar{g}_1(t)$ instead of $h(\bar{x})$ and $\bar{g}_1(\bar{x})$. Therefore, (13) now is:

$$h(t)\dot{\sigma}(t) = \bar{g}_1(t) + u(t). \tag{14}$$

For deriving the stabilizing control, $u(t)$ for (14), an artificial time-delay philosophy has been utilized as

$$u(t) = h(t)v(t) - \hat{g}_1(t), \tag{15}$$

where the estimated value of $\bar{g}_1(t)$ is represented as $\hat{g}_1(t)$ and the auxiliary input $v(t)$, which is the closed loop feedback control law is given as

$$v(t) = -K\sigma(t) \tag{16}$$

where K is the gain designed for the controller. Now, utilizing (15) and (16), (14) can be re-written as

$$\begin{aligned} h(t)[\dot{\sigma}(t) + K\sigma(t)] &= \bar{g}_1(t) - \hat{g}_1(t) \\ \Rightarrow \dot{\sigma}(t) + K\sigma(t) &= h^{-1}(t)[\bar{g}_1(t) - \hat{g}_1(t)] \end{aligned} \tag{17}$$

Hence, the closed loop error dynamics is obtained as

$$\dot{\sigma}(t) + K\sigma(t) = \xi(t) \tag{18}$$

where $\xi(t) = h^{-1}(t)[\bar{g}_1(t) - \hat{g}_1(t)]$. It should be noted that when $\xi(t)$ goes to zero, by selecting an appropriate controller gain K, the closed loop system can be steered to the origin. This would lead to an ideal tracking behavior of $\bar{x}_r(t)$. However, as $\bar{g}_1(t)$ is estimated by $\hat{g}_1(t)$, the estimation error denoted by $\xi(t)$ appears in (18). Also, $\bar{g}_1(t)$ can be expressed by using (14) as

$$\bar{g}_1(t) = h(t)\dot{\sigma}(t) - u(t) \tag{19}$$

The TDE approach is used in this study to complete the necessary estimation. The approach calculates the estimated value $\hat{g}_1(t)$ using input-output measurement data and knowledge of system dynamics. The ideal estimation is obtained when $\hat{g}_1(t)$ is computed utilizing measurement data of the current time instant t, as can be seen from the expression (19). Such a need, however, shows the presence of control input and other state measurements at that specific instant in time. In a real-world setting, such an implementation is not possible, and instead, it is possible to predict the consequences of uncertainties by using measurement data from the immediate previous instant of time. Without a doubt, such an approach leads to a near-perfect estimate as the time difference between the present and earlier timestamps approaches zero. The estimated value is then represented as a time-delayed version of the preceding instant as follows:

$$\hat{g}_1(t) \approx \bar{g}_1(t - \gamma) \tag{20}$$

where γ is a small delay introduced artificially, representing the difference between two consecutive time instances. From

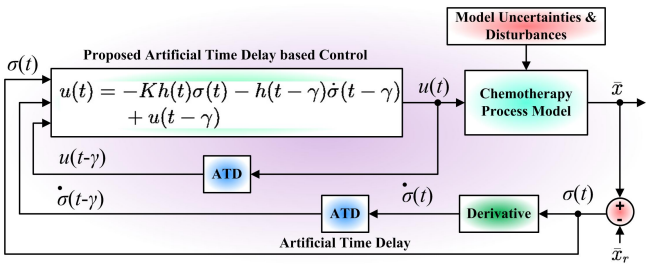


FIGURE 1: Block diagram for the proposed ATDC scheme.

(20), it can be intuitively concluded that introducing a time-delay γ, which is small enough, would ultimately result in a relatively smaller estimation error $\xi(t)$. Since, in practical applications, the sampling interval of the onboard processor is the smallest time realizable. Thus, the time-delay γ is also chosen to be the same for this work. Thus, the estimate in time-delayed estimation philosophy is computed as

$$\hat{g}_1(t) \approx \bar{g}_1(t-\gamma) = h(t-\gamma)\dot{\sigma}(t-\gamma) - u(t-\gamma) \quad (21)$$

Finally, for closed loop system (18), the control law is obtained by utilizing (20) and (21) in (15) as

$$u(t) = h(t)v(t) - h(t-\gamma)\dot{\sigma}(t-\gamma) + u(t-\gamma). \quad (22)$$

The schematic diagram for the proposed ATDC algorithm is shown in Fig. 1. In this block representation, the innermost loop gives the information of the immediate past value of input $u(t-\gamma)$. While the middle loop updates the controller with the immediate past value of error derivative term $\dot{\sigma}(t-\gamma)$. The proposed controller also uses the current error value $\sigma(t)$, which is fed through the outermost loop. The chemotherapy process is under the influence of model uncertainties and disturbances as well.

IV. STABILITY ANALYSIS

The stability analysis for the error system in (18) on application of the TDC law in (22), is derived in this section. The following assumption has to be taken into consideration for the implementation of the TDC-based control law.

Assumption 2: The lumped uncertainties $\bar{f}(\bar{x}(t))$, vary slowly with time for the error dynamics described in (11) and any variation appearing in $v(t)$, which is the feedback auxiliary input is bounded between successive instants of time.

In real-time cases, a tumor in the human body does not exhibit a sudden abrupt growth in a very short span of time. By taking practical scenarios into consideration, it can be concluded that Assumption 2 is a realistic constraint that has been considered in this work. Such an assumption leads to the boundedness of estimation error under the proposed robust philosophy, which has been presented in the following lemma.

Lemma 1: With Assumption 2 being satisfied, the estimation error $\xi(t)$ at any time instant t obtained as a result of implementation of TDE scheme (20) and robust control law (22), remains bounded when the following condition holds

$$\left\|\bar{g}^{-1}(t)h(t) - 1\right\| < 1, \ \forall\, t \geq 0. \quad (23)$$

Proof: In terms of auxiliary input $v(t)$, Equation (18) is re-written to represent the estimation error $\xi(t)$ as

$$\xi(t) = \dot{\sigma}(t) - v(t). \quad (24)$$

With a factor $\bar{g}(t)$ multiplied to both sides of (24) and using (12), the above expression appears as

$$\bar{g}(t)\xi(t) = g_1(t) + u(t) - \bar{g}(t)v(t). \quad (25)$$

Now consider the input $u(t)$ designed using TDC law (22) with $u(t-\gamma)$ replaced with time-delayed version of equation (12) as $u(t-\gamma) = \bar{g}(t-\gamma)\dot{\sigma}(t-\gamma) - g_1(t-\gamma)$, to yield

$$u(t) = h(t)v(t) - \big\{h(t-\gamma) - \bar{g}(t-\gamma)\big\}\dot{\sigma}(t-\gamma) - g_1(t-\gamma). \quad (26)$$

Next, the control input $u(t)$ represented as (26) is used to modify equation (25) as follows

$$\begin{aligned}\bar{g}(t)\xi(t) =& \big\{h(t) - \bar{g}(t)\big\}v(t) + g_1(t) - g_1(t-\gamma) \\ &- \big\{h(t-\gamma) - \bar{g}(t-\gamma)\big\}\dot{\sigma}(t-\gamma). \quad (27)\end{aligned}$$

The term $\{h(t) - \bar{g}(t)\}\, v(t-\gamma)$ is added and subtracted to further modify the above expression as

$$\begin{aligned}\bar{g}(t)\xi(t) =& \big\{h(t) - \bar{g}(t)\big\}\big\{v(t) - v(t-\gamma)\big\} + g_1(t) \\ &- g_1(t-\gamma) - \big\{h(t-\gamma) - \bar{g}(t-\gamma)\big\}\dot{\sigma}(t-\gamma) \\ &+ \big\{h(t) - \bar{g}(t)\big\}v(t-\gamma). \quad (28)\end{aligned}$$

Note the auxiliary input in time-delayed form can be obtained from (24) as $v(t-\gamma) = \dot{\sigma}(t-\gamma) - \xi(t-\gamma)$. Replacing the expression of $v(t-\gamma)$ in the last term of the above expression, equation (28) is achieved as

$$\begin{aligned}\bar{g}(t)\xi(t) =& -\big\{h(t) - \bar{g}(t)\big\}\xi(t-\gamma) + g_1(t) - g_1(t-\gamma) \\ &+ \big\{\bar{g}(t-\gamma) - \bar{g}(t) + h(t) - h(t-\gamma)\big\}\dot{\sigma}(t-\gamma) \\ &+ \big\{h(t) - \bar{g}(t)\big\}\big\{v(t) - v(t-\gamma)\big\}. \quad (29)\end{aligned}$$

Recall that the control law $u(t)$ stands for the amount of chemotherapeutic medicine that is required to be injected into a patient body. Consecutive injection of two dosages of drugs into the patient's body and corresponding bodily response in zero time duration is physically impossible, and hence, the smallest time interval between two consecutive drug injections should be a small scalar, at least in the time unit of minutes. Thus, the possible selection of the time delay γ should also be considered accordingly. In such a scenario, the error system can be represented in the discrete-time domain with time instant t and $(t-\gamma)$ denoted as k^{th} and $(k-1)^{th}$ time instant, respectively. In discrete-time domain, the expression for ξ using (29) appears as

$$\begin{aligned}\bar{g}(k)\xi(k) =& -\big\{h(k) - \bar{g}(k)\big\}\xi(k-1) + g_1(k) - g_1(k-1) \\ &+ \big\{\bar{g}(k-1) - \bar{g}(k) + h(k) - h(k-1)\big\}\dot{\sigma}(k-1) \\ &+ \big\{h(k) - \bar{g}(k)\big\}\big\{v(k) - v(k-1)\big\}. \quad (30)\end{aligned}$$

The factor $\bar{g}^{-1}(k)$ is multiplied to the left and right sides of (30) to yield

$$\begin{aligned}\xi(k) = &-\{\bar{g}^{-1}(k)h(k)-1\}\xi(k-1)\\ &+\{\bar{g}^{-1}(k)h(k)-1\}\mu_1(k-1)\\ &-\mu_2(k-1)\{\bar{g}(k-1)^{-1}h(k-1)-1\}\mu_3(k-1)\\ &+\{\bar{g}^{-1}(k)h(k)-1\}\mu_3(k-1)+\mu_4(k-1) \quad (31)\end{aligned}$$

where

$$\mu_1(k-1) = \{v(k)-v(k-1)\}, \quad (32a)$$
$$\mu_2(k-1) = \bar{g}^{-1}(k)\bar{g}(k-1), \quad (32b)$$
$$\mu_3(k-1) = \dot{\sigma}(k-1), \quad (32c)$$
$$\mu_4(k-1) = \bar{g}^{-1}(k)\{g_1(k)-g_1(k-1)\}. \quad (32d)$$

Assumption 2 bounds the functions $\mu_1(k-1)$ and $\mu_2(k-1)$. The user chooses the reference attitude trajectory $\bar{x}_r(k)$ and can design it to keep the reference time derivative $\dot{\bar{x}}_r(k)$ bounded. With this in mind, Assumption 2 ensures that the error in the rate of tumor growth in volume $\mu_3(k-1)$ is bounded using equation (11). Additionally, slowly varying uncertainties, as considered in the TDE methodology, ensure that $\mu_4(k-1)$ is bounded. Thus, one arrives at the following condition that affirms the boundedness of the estimation error $\xi(k)$.

$$\left\|\bar{g}^{-1}(k)h(k)-1\right\| < 1, \quad \forall \quad k \in \mathbb{Z}^+. \quad (33)$$

The subsequent stability theorem is derived from Lemma 1, which is stated as follows.

Theorem 1: The error dynamics (11) under the application of the control (22) remains UUB stable.

Proof: Considering Lyapunov function as

$$V = \frac{1}{2}\sigma^2. \quad (34)$$

The first time derivative of the above equation provides

$$\dot{V} = \sigma\dot{\sigma}. \quad (35)$$

By replacing $\dot{\sigma}$ with the closed-loop error dynamics (18), equation (35) is seen to evolve as

$$\begin{aligned}&\dot{V} = \sigma(-K\sigma+\xi),\\ \Rightarrow\ &\dot{V} = -K\sigma^2+\sigma\xi,\\ \Rightarrow\ &\dot{V} \le -K\|\sigma\|^2+\|\sigma\|\,\|\xi\|. \quad (36)\end{aligned}$$

Note that Lemma 1 already confirms that the estimation error ξ obtained as a result of the implementation of time-delayed estimation (20) philosophy remains bounded. Thus, $\dot{V}$ can be shown to be negative definite if the following condition is satisfied

$$\begin{aligned}K\|\sigma\|^2 &> \|\sigma\|\,\|\xi\|,\\ \|\sigma\| &> \frac{\|\xi\|}{K} = \mho. \quad (37)\end{aligned}$$

The closed-loop system (18) has UUB stability as it is affirmed by the condition (37), and the stability bound is given by $\mho$.

Remark 1: The residual bound $\mho$ is a function of estimation error ξ and controller gain K. Consequently, increasing the value of K and/or decreasing the sampling time γ can further reduce $\mho$.

Remark 2: For accurate time delay estimation, it's advisable to choose γ as small as possible. However, there's a practical limit to how fast a processor can actually take samples. Therefore, γ is selected as the processor's sampling time. It's important to remember that faster sampling (smaller γ) typically comes with a higher cost for the processor. Therefore, γ is selected to be the sampling instant for the processor. It is to be noted that the shorter the sampling time of the processor, the higher its cost will be. There's a trade-off between accuracy and cost.

Remark 3: With low-cost processors having large sampling intervals, it will become necessary to raise the controller gains under the proposed scheme. However, it's important to recognize that setting the controller gain too high can lead to excessive transients, potentially pushing systems toward instability.

V. NUMERICAL ANALYSIS

This section demonstrates the simulation analysis of the proposed TDC scheme for the aforementioned cell-kill hypotheses (5)-(7). Moreover, this work compares the efficacy of the proposed approach with the powerful super twisting variant of the well-established robust control technique of sliding mode control presented in [33]. Depending on the recommendations made by medical professionals, various therapy lengths can be suggested. For this study, a 15-day chemotherapy treatment course is adopted.

The desired tumor volume decay has the following form [33]:

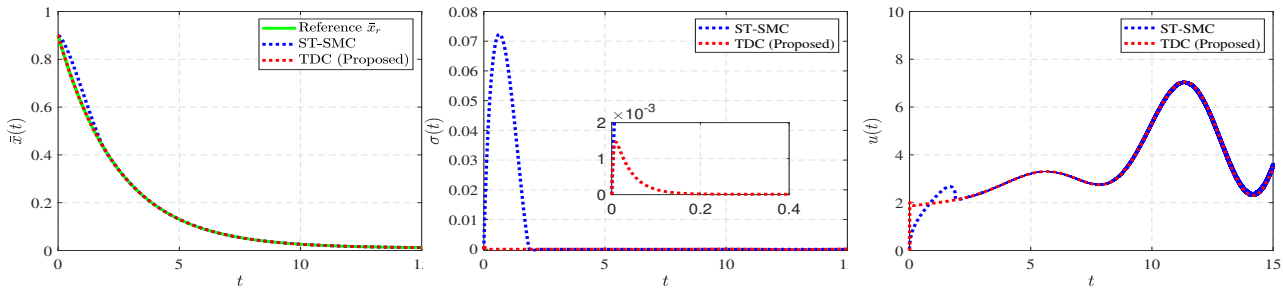
$$\bar{x}_r(t) = b + (\bar{x}(0)-b)e^{-at} \quad (38)$$

with a being the rate of tumor volume reduction and b being the required steady-state level. These constant reference values in (38) depend on how long a patient is treated. In [33], parameter values of a and b are chosen as $a = 0.4$ and $b = 0.01$ based on the chemotherapy treatment period of 15 days. Other parameters of all cell-kill models are tabulated in Table 1. The expression of exogenous disturbance for the cell-kill system is taken as $d = 10^{-2} \times (1-\sin(t))$ [33].

TABLE 1: Model parameters

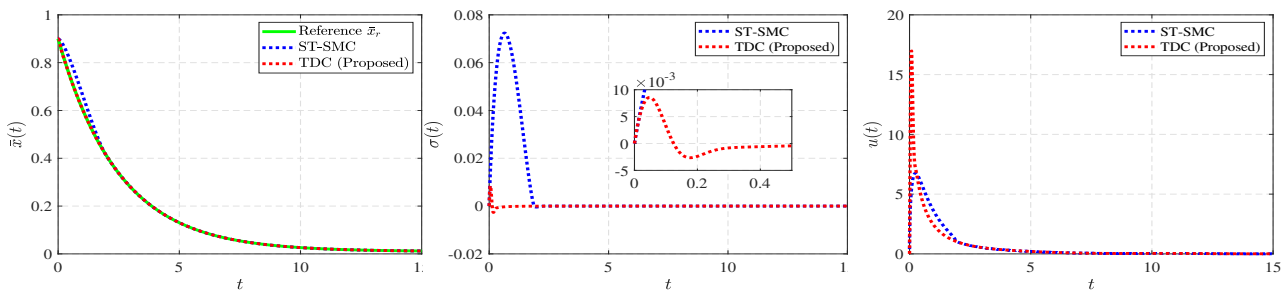
Description	Symbol	Value
Initial normalized tumor volume	$\bar{x}(0)$	0.9
Normalized parameter of drug usage	$\bar{\delta}$	0.225
Clinically observed normalized value	$\bar{\lambda}$	0.25
Period of chemotherapy	t_f	15 days
Tumor growth rate	r	0.1

The control parameter values of the proposed TDC approach and the ST-SMC approach under different hypotheses are illustrated in Table 2. The sampling time of the processor has been considered to be $\gamma = 0.01$ sec.



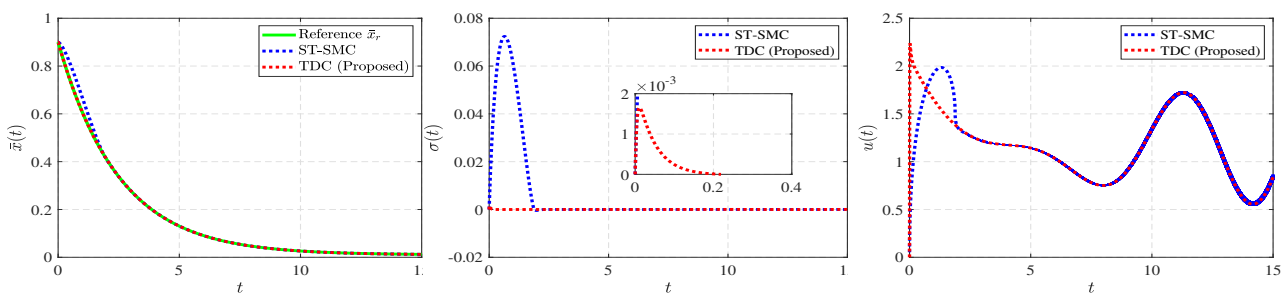
(a) Tumor volume response (b) Tracking error response (c) Chemotherapeutic drugs usage

FIGURE 2: For log-kill hypothesis



(a) Tumor volume response (b) Tracking error response (c) Chemotherapeutic drugs usage

FIGURE 3: For Norton-Simon hypothesis



(a) Tumor volume response (b) Tracking error response (c) Chemotherapeutic drugs usage

FIGURE 4: For $E_{\max}$ hypothesis

TABLE 2: Parameter values of controls under different hypotheses

Scheme	Log-kill	Norton-Simon	$E_{\max}$
TDC	$K = 25$	$K = 20$	$K = 30$
[33]	$k_1 = 0.8$, $k_2 = 1$	$k_1 = 0.6$, $k_2 = 0.5$	$k_1 = 0.3$, $k_2 = 1$

A. COMPARATIVE PERFORMANCE WITH LOG-KILL HYPOTHESIS

The performance of the TDC and ST-SMC strategies under the log-kill hypothesis is compared in this subsection. The behavior of tumor volume in a log-kill chemotherapy procedure under ST-SMC and TDC schemes is demonstrated in Fig. 2(a). The tumor volume tracking response in the proposed TDC method has a faster convergence with a lower maximum overshoot value than the ST-SMC design. The tracking error response in Fig. 2(b) also validates the superior performance of the TDC approach, where the error state converges to zero within 0.2 days. Figure 2(c) displays the control input or chemotherapeutic medication given to the patient under two control approaches. Moreover, other performance measures, like the amount of drug usage (calculated through the area under the curve of Fig. 2(c)), maximum overshoot, and convergence bound, are tabulated in Table 3. These performance indices also indicate better results for the proposed algorithm with the same amount of drug usage.

TABLE 3: Performance comparison for log-kill hypothesis

Measures	ST-SMC	TDC
Total amount of drug dosage	52.86	52.86
Max. overshoot from desired dosage	0.092	0.0015
Error convergence bound	5.85×10^{-4}	1.06×10^{-4}

B. COMPARATIVE PERFORMANCE WITH NORTON-SIMON HYPOTHESIS

The simulation results of both the control schemes under the Norton-Simon hypothesis are illustrated in Fig. 3. The tracking performance of tumor volume under the proposed controller is quicker with better transient error response than the ST-SMC design, as shown in Fig. 3(a) and Fig. 3(b). Moreover, the amount of medication usage (control input) is also lesser in the TDC approach, as seen from Fig. 3(c) and Table 4. Likewise, the TDC design performs better in other measures as well, which are depicted in Table 4.

TABLE 4: Performance comparison for Norton-Simon hypothesis

Measures	ST-SMC	TDC
Total amount of drug dosage	9.42	9.28
Max. overshoot from desired dosage	0.092	0.0086
Error convergence bound	5.85×10^{-4}	9.3×10^{-7}

C. COMPARATIVE PERFORMANCE WITH $E_{\max}$ HYPOTHESIS

Figure 4 illustrates the comparative performance of TDC and ST-SMC under $E_{\max}$ procedure. In the case of TDC design, tumor volume reaches the desired trajectory more quickly than ST-SMC, as shown in Fig. 4(a), and has a better transient error behavior, as shown in Fig. 4(b). The controlled medication input for the TDC and ST-SMC is shown in Fig. 4(c). The comparative measure in Table 5 also indicates a more proficient performance of the proposed controller over TDC. The control response under all three cell-kill-based models shows that the tracking of tumor volume is successful even under the influence of unknown disturbance.

TABLE 5: Performance comparison for $E_{\max}$ hypothesis

Measures	ST-SMC	TDC
Total amount of drug dosage	17.61	17.64
Max. overshoot from desired dosage	0.092	0.0017
Error convergence bound	5.85×10^{-4}	3.22×10^{-5}

VI. CONCLUSION

The quantity of cancer cells within a patient's body determines how serious their cancer is. Therefore, reducing these cancer cell numbers is a primary goal of most therapeutic methods. In this paper, three cell-kill based models for cancer chemotherapy were investigated using the proposed time-delayed control methodology to reduce the cancer cells to zero. The designed control approach effectively compensates for the effects of unknown disturbances and the ambiguous parametric effect without knowing their bounds. The performance of the proposed control approach gives the predicted satisfactory results to the simulations of three cell-kill models for cancer treatment function. In a physical treatment method, chemotherapy medicines are never administered continuously. However, the trajectory of continuous-time control input will indeed be directed toward choosing the medicine dose and distribution method intermittently after a certain duty cycle. Thus inspiring a new concept of hybrid chemotherapy treatment modeling in the future. The extension of this research work will focus on the effect of measurement noise on the performance of cancer therapy medication diagnoses. The future extension of this work will also explore the scalability of the proposed algorithm to more complex scenarios with practical real-time datasets.

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