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Nonlinear Impulsive Control Design for Biologically Grounded NSM Tumor Growth Model Using Exact Linearized Mapping

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Abstract: This paper investigates the problem of personalized chemotherapy scheduling using a system-modeling approach based on a nonlinear impulsive control technique. In particular, this work deals with the so-called Norton-Simon-Massagué (NSM) model, a minimal biologically grounded model for controlled tumor growth, which has been accepted in clinical oncology for breast cancer treatment. In this paper, we continue this line of research, to advance the concept of closed-loop control a step further towards widespread clinical use. In the present work, the problem of chemotherapy drug scheduling is approached using an impulsive control strategy combined with a state-space observer. The technical challenges of the nonlinearity of the controlled system and the impulsive nature of control input are handled via the utilization of a novel mapping that transforms the control problem into a "simplified" linear discrete-time control problem. Theoretical guarantees regarding the sign and invertibility of the proposed transformation are demonstrated. Then, an observer-based state feedback controller is proposed for chemotherapy drug scheduling as a proof-of-concept control strategy. Simulation results showing the performance of the designed closed-loop controlled chemotherapy schedules in reducing and eradicating tumor volume are provided using model's parameters derived using real tumor data and Doxirubicin drug.

Keywords: Controlled tumor growth, Nonlinear impulsive control, Norton-Simon-Massagué (NSM) model, Exact linearized transformation, observer-based state feedback.

1. INTRODUCTION

Cancer, the uncontrolled development and proliferation of cells is one of the leading causes of death worldwide despite the tremendous efforts made during the last several years (Bray et al., 2018). Various therapeutic clinical options are available to treat cancerous tumors, e.g., surgery, chemotherapy, radiotherapy, and immunotherapy. Chemotherapy, either used alone or in combination with other therapies remains one of the most extensively utilized treatments worldwide. A revolutionary new era in the field of oncology that aims to provide more effective treatment to patients was ushered in with targeted personalized therapy. A key factor in personalized therapy is how drug schedules may be delivered in terms of amount, "how much," and injection time, "how often and when," to a given patient. This leads to the important issue of setting drug dosage and injection time in a more systematic and personalized manner, instead of being selected and chosen from a fixed set of given protocols in an ad-hoc fashion. This has led to the concept of *dynamic-decision making* (DDM) in cancer treatment (Engelhardt and Michor, 2021). In the last few decades, several mathematical models for tumor growth have been proposed. They may be divided into a broad spectrum ranging from simple macroscopic models, which usually have fewer details and fewer parameters, trying to capture the clinically observed growth of tumor volume to more sophisticated and complex models involving more details about the microscopic and/or molecular processes that contribute to tumor growth process (Wodarz and Komarova, 2014), (Araujo, 2004),(Michor and Beal, 2015). A number of

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versions of macroscopic tumor growth models based on ordinary differential equations (ODEs) exist in the literature, see, e.g., (Wodarz and Komarova, 2014), (et al., 2014) and the cited references therin. Moreover, modeling the effect of cytotoxic chemotherapy on tumor growth dynamics has seen several important developments. The log-kill hypothesis, which states that a given dose of chemotherapy kills the same fraction of tumor cells regardless of the size of the tumor at the time of administration, has for decades guided the clinical treatment of many types of cancer (Norton, 2014), (Traina and Norton, 2015). This model led to the administration of a maximum tolerated dose (MTD) of a cytotoxic agent with prolonged treatment breaks to counteract disease progression and to kill as many cancer cells as possible while allowing the body to recover from the induced treatment toxicity. Based on clinical observations many types of solid tumors were not in agreement with the outcomes of the log-kill hypothesis (Norton, 2014). Thus, the Norton–Simon (NS) hypothesis has emerged (Norton and Simon, 1986), (Norton, 2014). It states that cancer cell death in response to a chemotherapeutic drug agent is proportional to the untreated tumor growth rate at the time of treatment. This model led to the finding that not only dose intensity but also dose density is important. The major success story of "dose-densing" protocols that was the outcome of the NS hypothesis was based also on a minimal mathematical model that we will refer to as the "Norton-Simon-Massagué" (NSM) tumor growth model (Belkhatir et al., 2021).

The concept of DDM, which is an area of very active research among cancer researchers, may be considered from the standpoint of feedback or closed-loop control theory as it is related to the fundamental question of identifying the best anticancer chemotherapeutic treatment for a specific patient, which remains challenging to answer conclusively. A particular class of controllers that has received great attention in the last decade, especially in biomedical research, is impulsive control. Many research works have been proposed to deal with linear impulsive control (Wang and Lu, 2020), (Rivadeneira et al., 2018), but to a less extent nonlinear impulsive control strategies. This type of control scheme has a great potential to benefit cancer treatments. However, to make a real clinical impact and to turn the concept of impulsive closed-loop control into real clinical protocols, the formulated problem should be biologically sound and based on hypotheses and models sufficiently clear and well-accepted by clinicians. This is the main objective and contribution of this work. We propose an impulsive control strategy for chemotherapy treatment based on the NSM tumor growth model. Moreover, we propose a simplification of the nonlinear impulsive control problem by transforming it into a linear discrete-time control problem that has the potential to be more readily adopted and may be more easily implemented and tested not only in simulation but also in pre-clinical and clinical settings.

The remainder of this paper is structured as follows. Section 2 provides the NSM model both in absence and in presence of chemotherapy. In Section 3, the transformation proposed to deal with the non-linearity and impulsive nature of the control is provided along with its theoretical properties. Section 4 provides a linear observer-based state feedback controller design for designing the dosage of chemotherapy assuming that the injection times are known and set by the oncologist after each measurement time. Simulation results of the designed closed-loop controlled chemotherapy are provided in Section 5 to test the performance of the proposed transformation and control design. Conclusions and future work directions are set in Section 6.

2. THE CONTROLLED NORTON-SIMON-MASSAGUÉ (NSM) TUMOR GROWTH MODEL

In this work, we investigate the chemotherapy drug scheduling problem using the biologically grounded minimal order NSM tumor growth model with the aim of moving the concept of closed-loop control for cancer treatment a step forwards towards real clinical implementation.

The so-called NSM model given by

$$\frac{dV(t)}{dt} = aV^{\alpha}(t) - bV(t), \tag{1}$$

where $V(t)$ denotes the tumor volume, was first proposed to describe the growth of biological organisms based on basic energetic principles and then formulated and analyzed in the tumor growth context. More details can be found in (von Bertalanffy, 1957; Norton, 2005) and the references therein. The parameters a and b are the growth and death constants, respectively. Equation (1) posits that the net growth rate of an organism results from the balance of synthetic and degradative processes. While the rate of the former process follows a law of allometry (i.e., the rate is proportional to the volume $V(t)$ via the power function V^{α}), the rate of the latter process scales linearly with $V(t)$.

There are two interesting special cases of (1) that can be distinguished: (i) power law with $b = 0$, and (ii) second type growth with $\alpha = 2/3$; which was successfully applied to describe tumor growth (Vaidya and Alexandro, 1982), (Gerlee, 2013). The more general fractal case, $0 < \alpha < 1$, was introduced in (Norton and Massagué, 2006) to explain the self-seeding hypothesis. Moreover, a geometrical interpretation was hypothesized and proposed in (Norton, 2005), (et al., 2014), which relates the exponent $\alpha = d/3$ to the fractional Hausdorff dimension of the proliferative tissue, where d denotes the fractal dimension of the proliferative tissue. Furthermore, the growth model (1) was derived mechanistically in 2011, where the tumor growth was linked to the metabolic rate and vascularization properties (Herman et al., 2011). In the rest of the paper, model (1) is referred to as the *NSM tumor growth model*[1]

The problem of the continuous delivery of a cytotoxic agent using the controlled NSM model has been investigated in (Belkhatir et al., 2021) using a combined extended Kalman filtering and model predictive control approach. To the best of our knowledge, the problem of *impulsive injections* has not been previously addressed for the NSM tumor growth model, and this work is the first proof-of-concept study devoted to this purpose, and where we

[1] The NSM name was given to refer to the authors L. Norton and J. Massagué who introduced the self-seeding concept introduced, and also R. Simon who proposed with L. Norton the "Norton-Simon" hypothesis that is used in this study to model the chemotherapeutic drug agent.

will extend the previous work by treating the case of intravenous (IV) delivery, which is more frequently used in clinics. In the course of IV administration, the plasma concentration changes in under a minute, and so by considering one day as the time unit, the absorption phase may be considered to be instantaneous. Hence, it is very reasonable to consider the IV administered drug as an *impulsive* input.

The evolution of the controlled dynamic changes for the tumor volume using the NS chemotherapy modeling hypothesis is given by the following dynamical equations:

$$\begin{cases} \dot{V}(t) = (aV^{\alpha}(t) - b\,V(t))\,(1 - \xi\,C(t))\,, \\ \dot{C}(t) = -k\,C(t) + u(t), \\ V(0) = V_0, \\ C(0) = C_0, \end{cases} \tag{2}$$

where $V(t) \geq 0$ is the tumor volume (with initial condition V_0) and $C(t) \geq 0$ is the drug concentration. The rate of flow of drug into the body is represented by the control variable $u(t)$. The constants a, b, α, k, ξ are positive real parameters, with k denoting the elimination rate constant of the drug from bloodstream and ξ reflecting the sensitivity of the tumor to the drug. The linear dynamics of $C(t)$ describes the one compartment pharmacokinetics model.

Let us consider the set of execution times $\{t_h | h \in \mathbb{N}\} \subseteq \mathbb{N}$ of the control input, where $\mathbb{N}$ denotes the set of natural numbers and such that $t_{h+1} > t_h$, for all $h \in \mathbb{N}$, and $t_0 = 0$, The corresponding control input is then written as:

$$u(t) := \begin{cases} \bar{u}_h, & \text{if } t = t_h, \\ 0, & \text{otherwise}, \end{cases} \tag{3}$$

where $\bar{u}_h \geq 0$ represents the amplitude of the rate of flow of drug into the body at time t_h.

3. EXACT LINEARIZED DISCRETE TRANSFORMATION

3.1 Linearized Transformation

The dynamics (2)-(3) may be captured by the following deterministic impulsive system (Li et al., 2001):

$$\begin{cases} \dot{V}(t) = (aV^{\alpha}(t) - b\,V(t))\,(1 - \xi\,C(t))\,, \\ \dot{C}(t) = -k\,C(t), \end{cases} \quad t \in [t_h, t_{h+1}), \tag{4}$$

$$\begin{cases} V(t^+) = V(t), \\ C(t^+) = C(t) + u(t), \end{cases} \quad t = t_h. \tag{5}$$

First, we note that the state variables $V(t)$ and $C(t)$ remain positive for all times. In fact, under the assumption that $V(0) \geq 0$, $V(t)$ cannot change its sign during the continuous flow since the derivative $\dot{V}(t)$ becomes zero when $V(t) = 0$ while the discrete jumps do not affect $V(t)$. Moreover, $C(t)$ also cannot change its sign during the flows since the derivative $\dot{C}(t)$ becomes zero when $C(t) = 0$ while the value of $C(t)$ can only increase during the jumps since $u(t) \geq 0$.

Now, since the dynamics of $C(t)$ are linear and depend only on the impulsive input $u(t)$, it is straightforward to integrate (4)-(5) between t_h and $t \in [t_h, t_{h+1}]$ and write:

$$C(t_h^+) = C(t_h^-) + u(t_h), \tag{6}$$

$$C(t) = C(t_h^+)\exp(-k(t - t_h)), \quad t_h \leq t < t_{h+1}, \tag{7}$$

where $C(t_h^+)$ denotes the value of $C(t)$ right after the time t_h (after the treatment $u(t_h)$ is injected) or more formally defined as $C(t_h^+) = \lim_{\epsilon \to 0^+} C(t_h + \epsilon)$. Similarly we have $C(t_h^-) = \lim_{\epsilon \to 0^+} C(t_h - \epsilon)$.

Next, let us define the following state-dependent map that will enables the linearization of the nonlinear tumor growth model (4)-(5):

$$G(V) := a - bV^{1-\alpha}. \tag{8}$$

The following lemma studies the sign of $G(V(t))$ under the dynamics (4)-(5).

Lemma 1. Under the dynamics (4)-(5), the sign of $G(V(t))$, as defined in (8), remains constant for all times $t \geq 0$.

Proof. First, note that the nonlinear function $G(V)$ is not differentiable at $V = 0$. In view of the dynamics of $V(t)$, the time derivative of $G(V(t))$ satisfies

$$\dot{G}(V(t)) = \begin{cases} -b(1-\alpha)(1 - \xi C(t))G(V(t)) & V(t) \neq 0, \\ 0 & \text{otherwise.} \end{cases} \tag{9}$$

At $G(V(t)) = 0$, the time derivative of $G(V(t))$ satisfies $\dot{G}(V(t)) = 0$ and, therefore, the variable $G(V(t))$ cannot change its sign as this would require a non-zero derivative at $G(V(t)) = 0$.

In the next proposition, we show that it is possible to integrate the dynamics to obtain an explicit expression of $G(V(t))$ as a function of time.

Proposition 1. For all $t \in [t_h, t_{h+1}]$, one has

$$G(V(t)) = \begin{cases} \Gamma(t, t_h), & \Gamma(t, t_h) < a, \\ a, & \text{otherwise}, \end{cases} \tag{10}$$

where the function $\Gamma(t, t_h)$ is given by:

$$\Gamma(t, t_h) := G(V(t_h))\exp\left(-g(t, t_h)\right), \tag{11}$$

$$g(t, t_h) := b(1-\alpha)\big[(t - t_h) + \frac{\xi}{k} C(t_h^+)\left(\exp(-k(t - t_h)) - 1\right)\big]. \tag{12}$$

Proof. Let us assume that $V(t) \neq 0$ on the interval $[t_h, t]$ for some $t \in [t_h, t_{h+1}]$, we can integrate (9) between t_h and t. This yields

$$\begin{aligned} &\ln\left(|G(V(t))|\right) - \ln\left(|G(V(t_h))|\right) = \\ &\qquad - b(1-\alpha)\int_{t_h}^{t} (1 - \xi C(\tau))d\tau, \\ &= -b(1-\alpha)(t - t_h) + \\ &\qquad b(1-\alpha)\xi \int_{t_h}^{t} C(t_h^+)\exp(-k(\tau - t_h))d\tau, \\ &= -b(1-\alpha)(t - t_h) - \\ &\qquad b(1-\alpha)\frac{\xi}{k} C(t_h^+)\left(\exp(-k(t - t_h)) - 1\right), \\ &=: -g(t, t_h). \end{aligned}$$

Therefore, one has $|G(V(t))| = |G(V(t_h))|\exp(-g(t, t_h))$. However, in view of Lemma 1, $G(V(t))$ and $G(V(t_h))$ must have the same sign; hence $G(V(t)) = \Gamma(t, t_h)$ when $V(t) > 0$ one the interval $[t_h, t]$. Note that $V(t) > 0$

corresponds to $G(V(t)) = \Gamma(t, t_h) < a$. In the case where $V(t) = 0$ at some time in $[t_h, t]$, one has $G(V(t)) = a$ for all future times due to the fact that $V(t) = 0$ is an invariant set for the dynamics under consideration. Therefore, the expression $G(V(t)) = \Gamma(t, t_h)$ will hold only when $\Gamma(t, t_h) < a$; otherwise $G(V(t)) = a$.

3.2 Exact Integration of the Original NSM Model

We note that the inverse function of (8) is given by $G^{-1}(y) = ((a - y)/b)^{1/(1-\alpha)}$ when $y \leq a$. This along with (10) and (6)-(7) allows us to obtain an exact integration scheme for the tumor growth model (4)-(5) for any given impulsive input signal $u(t)$. This is summarized in the following Theorem whose proof directly follows from Proposition 1 and the above discussion.

Theorem 1. Given the impulsive system (4)-(5), the states $V(t)$ and $C(t)$ can be explicitly obtained via the exact integration scheme given in Algorithm 1. This integration scheme may be implemented using any desired sampling time (including continuous-time integration).

Algorithm 1 Exact Integration Scheme for the Tumor Growth Model (4)-(5)

Set the model parameters a, b, α, ξ, k.
Initialize $V(0), C(0)$ to be non-negative.
Input the impulsive control $u(t)$.
for $h \in \mathbb{N}$ **do**
  Update $V(t_h^+) = V(t_h^-)$.
  Update $C(t_h^+) = C(t_h^-) + u(t_h)$.
  for $t \in [t_h, t_{h+1})$ **do**
    Calculate $\Gamma(t, t_h) = G(V(t_h)) \exp(-g(t, t_h))$ with $g(t, t_h)$ defined in (12).
    Update $V(t) = G^{-1}(\Gamma(t, t_h))$ only if $\Gamma(t, t_h) < a$. Otherwise $V(t) = V(t^-) = 0$.
    Update $C(t) = C(t_h^+) \exp(-k(t - t_h))$.
  end for
end for
Output solutions $V(t)$ and $C(t)$

3.3 Discrete-Time System Formulation for Periodic Inputs

The nonlinear change of variable defined in (8) is upper bounded by the growth parameter a, since $V(t) \geq 0$ for all times. Moreover, without loss of generality, we may assume that $G(V(0)) \geq 0$. In fact, in the uncontrolled case with $u(t) \equiv 0$ and $C(0) = 0$, the tumor growth model reduces to

$$\dot{V}(t) = aV^{\alpha}(t) - b\,V(t) = V^{\alpha}(t)G(V(t)), \qquad (13)$$

and, hence, the tumor will grow only if $G(V(t)) \geq 0$ for all times which, according to Lemma 1, is satisfied if $G(V(0)) \geq 0$. In other words, if $G(V(0)) < 0$ the tumor will anyway decrease in the uncontrolled system.

Under the assumption of $G(V(0)) \geq 0$, let us introduce the following change of variable:

$$Z(V(t)) := -\ln\left(\frac{G(V(t))}{a}\right) = -\ln\left(1 - \frac{b}{a}V^{1-\alpha}\right). \quad (14)$$

The function $Z(V)$ maps the interval $[0, (a/b)^{1/(1-\alpha)}]$, where it is defined, to the non-negative reals in $[0, +\infty)$. Note that this new variable is well-defined since $G(V(t)) \geq 0$ for all times according to Lemma 1. Moreover, in view of (4)-(5), one has

$$\dot{Z}(t) = \begin{cases} b(1-\alpha)\,(1 - \xi\,C(t))\,. & Z(t) > 0, \\ 0 & Z(t) = 0. \end{cases} \qquad (15)$$

This is a linear discontinuous positive system, and in view of (9), the integration of the above ODE gives:

$$Z(t) = \begin{cases} Z(t_h) + g(t, t_h), & t \in [t_h, t_{h+1}], \quad Z(t^-) \neq 0, \\ Z(t^-) = 0 & \text{otherwise.} \end{cases} \qquad (16)$$

Now, let us assume periodic drug administration, *i.e.,* we have $t_{h+1} - t_h = \delta$ for some positive parameter δ. We denote $Z(h) := Z(t_h^-)$ and $C(h) := C(t_h^-)$ the values of the state variable just before the hth treatment class and $u(h) := u_h$. In view of (6)-(7) and (16), we have

$$Z(h+1) = \begin{cases} Z(h) - \gamma_2 C(h) + \gamma_1, & \text{if } Z(h) > \\ & \min(0, \gamma_2 C(h) - \gamma_1)) \\ 0, & \text{elsewhere} \end{cases} \qquad (17)$$

$$C(h+1) = \gamma_3 C(h) + \gamma_3 u(h). \qquad (18)$$

where we have defined the following non-negative parameters:

$$\gamma_1 := b(1-\alpha)\delta, \qquad (19)$$

$$\gamma_2 := \gamma_1(1-\gamma_3)\xi\delta^{-1}k^{-1}, \qquad (20)$$

$$\gamma_3 := e^{-k\delta}. \qquad (21)$$

The state-space representation, equivalent to equations (17)-(18), is given as follows:

$$X(h+1) = \begin{cases} A\,X(h) + B\,v(h), & \text{if } X_1(h) > \\ & \min(0, \gamma_2 X_2(h)) \\ A_0 X(h) + Bv(h), & \text{elsewhere} \end{cases} \qquad (22)$$

where the state vector $X(h) \in \mathbb{R}^2$ and the matrices $A, A_0 \in \mathbb{R}^{2\times 2}$ and $B \in \mathbb{R}^2$ are given as follows:

$$X(h) = \begin{pmatrix} X_1(h) \\ X_2(h) \end{pmatrix} := \begin{pmatrix} Z(h) \\ C(h) - \dfrac{\gamma_1}{\gamma_2} \end{pmatrix}, \quad A = \begin{pmatrix} 1 & -\gamma_2 \\ 0 & \gamma_3 \end{pmatrix}, \qquad (23)$$

$$A_0 = \begin{pmatrix} 0 & 0 \\ 0 & \gamma_3 \end{pmatrix}, \quad B = \begin{pmatrix} 0 \\ \gamma_3 \end{pmatrix}, \qquad (24)$$

with $v(h) := u(h) - \gamma_4$ and $\gamma_4 := \dfrac{\gamma_1}{\gamma_2\,\gamma_3}(1 - \gamma_3)$. The obtained model in (23)-(24) is a linear discrete-time dynamical system with discontinuous right-hand side. It captures the exact evolution of the impulsive system (4)-(5) when the input is injected periodically.

4. LINEAR OBSERVER-BASED STATE FEEDBACK CONTROLLER FOR LINEARIZED NSM MODEL

In this section, we propose a linear saturated state feedback controller cascaded with a Luenberger-like observer to estimate the state vector variables. Note that the input control is practically bounded, *i.e.,* there exists $u_{\max}$ such that $0 \leq u(t) \leq u_{\max}$ for all times. The value of $u_{\max}$ can be chosen depending on the maximum safe drug concentration. Therefore, we propose to employ saturated state feedback. Many research works have dealt with the problem of state-feedback control design with constrained

inputs, e.g., (Gutman and Hagander, 1985), (Saberi et al., 1996), (Memon and Khalil, 2008) to cite few examples.

In this work, the proposed state-feedback control law takes the following form:

$$u(h) = \begin{cases} \text{sat}(-KX(h) + \gamma_4) & \text{if } X_1(h) > \\ & \min(0, \gamma_2 X_2(h)) \\ 0 & \text{otherwise} \end{cases} \quad (25)$$

where K is a feedback gain that is selected such that the eigenvalues of $(A - BK)$ lie inside the unit circle. Our proposed feedback is a discontinuous saturated linear state-feedback. The saturation function is defined as:

$$\text{sat}(u) := \begin{cases} u & \text{if } u \leq u_{\max}, \\ u_{\max} & \text{if } u \geq u_{\max}. \end{cases} \quad (26)$$

Moreover, in practice, we have measurement only of the the tumor growth $V(t)$. Therefore, it is suitable to design an output feedback for this control problem. For this purpose, we consider the following output equation:

$$y(h) = DX(h) := (1\ 0)\, X(h). \quad (27)$$

We propose the following observer for system (17)-(18):

$$\begin{cases} \hat{X}(h+1) = A\hat{X}(h) + Bv(h) + L(y(h) - D\hat{X}(h)) \\ \qquad\qquad \text{if } y(h) > 0, \\ \hat{X}(h+1) = A_0\hat{X}(h) + Bv(h) \text{ and } D\hat{X}(h) = 0 \\ \qquad\qquad \text{otherwise}, \end{cases} \quad (28)$$

where L is tuned such that the eigenvalues of the matrix $(A - LD)$ lie inside the unit circle. When the tumor growth is non-zero ($y(h) > 0$), the observer takes the form of a linear Luenberger observer. When the measured tumor growth becomes zero, we assign 0 to both the current and the future estimates of the tumor growth state (*i.e.,* $D\hat{X}(h)$ and $D\hat{X}(h+1)$ are zero). In the latter case, the observer ensures convergence in finite-time. This results in a zero output error and therefore the remaining state is updated normally using the A_0 matrix (second equation of (17)-(18)). The update step $D\hat{X}(h) = 0$ when $y(h) = 0$ is important to correct a potential *false* previous update of the estimated state $\hat{X}$ due to the fact that the condition $Z(h+1) > 0$ (which appears in (23)) is unknown at the current step and was not used in the first equation of the observer.

5. NUMERICAL SIMULATIONS

In this section, we will implement the proposed observer-based state feedback controller and test the performance of the closed-loop drug scheduling in eradicating the tumor burden. We will focus on the Doxirubicin drug treatment (DDT) that is used in the treatment of different types of cancer [2], where the dose of the drug is $DDT = 60\ mg/m^2$ given intravenously with administration time of $t_i = 1$ minute and it is provided in non-densified and densified regimens, every 3 weeks and 2 weeks. This means that maximum drug dose $u_{\max} = DDT/t_i = 150\ mg.m^{-2}.\text{day}^{-1}$. The model's parameters estimated in (Belkhatir et al., 2021) using real lung mouse data are used, with an initial volume considered to be $V_0 = 10^5\ mm^3$. Regarding the PK paramaters of the Doxirubicin drug, its half-life is between $\tau_{1/2} \approx 20 - 48$ hours leading to an elimination constant $k = \dfrac{\ln(2)}{\tau_{1/2}} \approx 0.0347 - 0.0144$ hours^{-1}. In the simulation, we considered a half time of $\tau_{1/2} = 1$ day.

The numerical implementation carried out in this section is performed using MATLAB. Figure 1 depicts the controlled tumor volume using proposed closed-loop impulsive controller in the case where the drug is administrated in a non-densified manner, every 3 weeks. However, Figure 2 shows the case of densified injections, every 14 days. We observe that the tumor is eradicated faster in the more densified regimen and given the longer break between drug injections in the non-densified regimen the relapse of tumor is higher between designed closed-loop injection. Those observations are interesting because they are matching the experiments of dose-dense protocols (Norton, 2005) even in closed-loop DDM stand point.

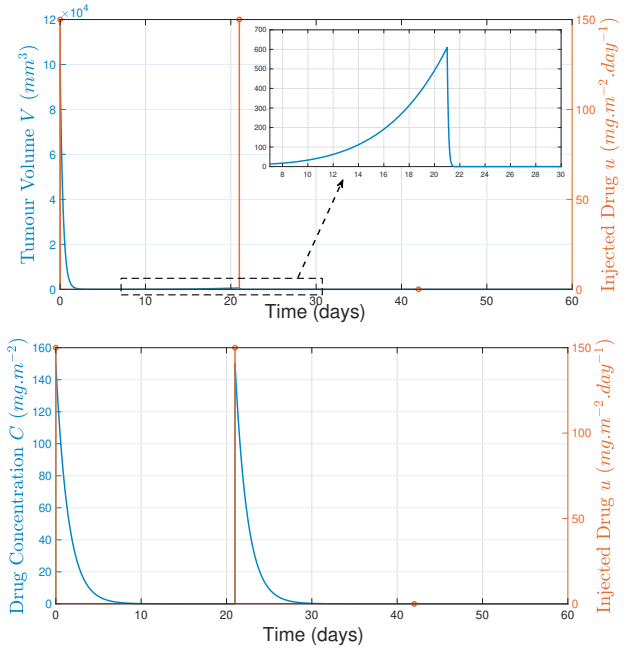

Fig. 1. Designed impulsive closed-loop drug scheduling in the non-densified regimen (injection given every 21 days) along with tumor volume (upper panel). Drug Concentration dynamics along with impulsive scheduling (lower panel). Eradication time of tumor around ~ 22 days.

6. CONCLUSION

This present paper explores the problem of chemotherapy scheduling using closed-loop output impulsive control along with a minimally biologically-grounded tumor growth model. The study aims to advance the problem of controlled cancer treatment towards clinical use by imposing constraints on the inputs and model that are clinically sound. Accordingly, we have converted a nonlinear impulsive control problem into a (discontinuous) linear discrete-time control system. This makes the real

[2] List of clinical protocols used for different types of cancer is available in: `https://www.just.edu.jo/DIC/ClinicGuidlines/Breast%20cancer%20regimens.pdf`

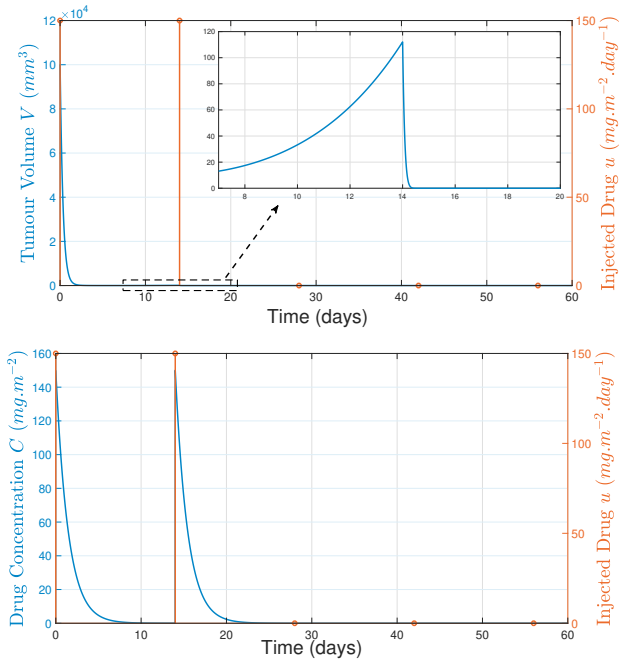

Fig. 2. Designed impulsive closed-loop drug scheduling in the densified regimen (injection given every 14 days) along with tumor volume (upper panel). Drug Concentration dynamics along with impulsive scheduling (lower panel). Eradication time of tumor around ~ 15 days.

implementation in pre-clinical and clinical studies easier and hopefully more accessible to clinicians. Moreover, we designed an observer-based state feedback controller and tested its performance against open-loop clinical schedules.

For future work, and to move deeper into real clinical practice, we plan to investigate the problem of impulsive closed-loop optimal drug scheduling and test its robustness against external and internal disturbances. Moreover, the proposed transformation is sought to be generalised for the case of non-periodic unknown injection time instants.

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REFERENCES

Araujo, R. (2004). A history of the study of solid tumour growth: The contribution of mathematical modelling. *Bull. Math. Biol.*, 66, 1039–1091.

Belkhatir, Z., Pavon, M., Mathews, J., Pouryahya, M., Deasy, J.O., Norton, L., and Tannenbaum, A.R. (2021). Stochastic norton–simon–massagué tumor growth modeling: Controlled and mixed-effect uncontrolled analysis. *IEEE Transactions on Control Systems Technology*, 29, 704 – 717.

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R.L., Torre, L.A., and Jemal, A. (2018). Global cancer statistics 2018: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *A Cancer J. Clin.*, 68, 394–424.

Engelhardt, D. and Michor, F. (2021). A quantitative paradigm for decision-making in precision oncology. *Trends in Cancer*, 7(4), 293–300.

et al., S.B. (2014). Classical mathematical models for description and prediction of experimental tumor growth. *PLoS Comput. Biol.*, 10(8).

Gerlee, P. (2013). The model muddle: In search of tumor growth laws. *Cancer Res.*, 73(8), 2407–2411.

Gutman, P.O. and Hagander, P. (1985). A new design of contrained controllers for linear systems. *IEEE Transactions on Automatic Control*, 30, 22–33.

Herman, A.B., Savage, V.M., and West, G.B. (2011). A quantitative theory of solid tumor growth, metabolic rate and vascularization. *PLoS ONE*, 6(9), e22973.

Li, Z.G., Wen, C.Y., and Soh, Y.C. (2001). Analysis and design of impulsive control systems. *IEEE Transactions on Automatic Control*, 46(6), 894–897.

Memon, A.Y. and Khalil, H.K. (2008). Output regulation of linear systems subject to input constraints. *47th IEEE Conference on Decision and Control*.

Michor, F. and Beal, K. (2015). Improving cancer treatment via mathematical modeling: Surmounting the challenges is worth the effort. *Cell*, 163(5), 1059–1063.

Norton, L. (2005). Conceptual and practical implications of breast tissue geometry: Toward a more effective, less toxic therapy. *Oncologist*, 10(6), 370–381.

Norton, L. and Massagué, J. (2006). Is cancer a disease of self-seeding? *Nature Med.*, 12(8), 875–878.

Norton, L. (2014). Cancer log-kill revisited. *Amer. Soc. Clin. Oncol. Educ. Book*, (34), 3–7.

Norton, L. and Simon, R. (1986). The norton-simon hypothesis revisited. *Cancer Treat. Rep.*, 70(1), 163–169.

Rivadeneira, P.S., Ferramosca, A., and Gonzalez, A.H. (2018). Control strategies for nonzero set-point regulation of linear impulsive systems. *IEEE Transactions on Automatic Control*, 63(9).

Saberi, A., Lin, Z., and Teel, A. (1996). Control of linear systems with saturating actuators. *IEEE Transactions on Automatic Control*, 41, 368 – 378.

Traina, T.A. and Norton, L. (2015). Log-kill hypothesis. In *Encyclopedia of Cancer*.

Vaidya, V.G. and Alexandro, F.J. (1982). Evaluation of some mathematical models for tumor growth. *Int. J. Bio-Med. Comput.*, 13(1), 19–35.

von Bertalanffy, L. (1957). Quantitative laws in metabolism and growth. *Quart. Rev. Biol.*, 32(3), 217–231.

Wang, Y. and Lu, J. (2020). Some recent results of analysis and control for impulsive systems. *Communications in Nonlinear Science and Numerical Simulation*, 20.

Wodarz, D. and Komarova, N.L. (2014). *Dynamics of Cancer: Mathematical Foundations of Oncology*. Singapore: World Scientific.