



Model based smooth super-twisting control of cancer chemotherapy treatment

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ABSTRACT

Chemotherapy is one of the most efficient methods for treating cancer patients. Chemotherapy aims to eliminate cancer cells as thoroughly as possible. Delivering medications to patients' bodies through various methods, either oral or intravenous is part of the chemotherapy process. Different cell-kill hypotheses take into account the interactions of the expansion of the tumor volume, external drugs, and the rate of their eradication. For the control of drug usage and tumor volume, a model based smooth super-twisting control (MBSSTC) is proposed in this paper. Firstly, three nonlinear cell-kill mathematical models are considered in this work, including the log-kill, Norton-Simon, and $E_{\max}$ hypotheses subject to parametric uncertainties and exogenous perturbations. In accordance with clinical recommendations, the tumor volume follows a predefined trajectory after chemotherapy. Secondly, the MBSSTC is applied for the three cell-kill models to attain accurate trajectory tracking even in the presence of uncertainties and disturbances. Compared to conventional super-twisting control (STC), the non-smooth term is introduced in the proposed control to enhance the anti-disturbance capability. Finally, simulation comparisons are performed across the proposed MBSSTC, conventional STC, and proportional-integral (PI) control methods to show the effectiveness and merits of our designed control method.

1. Introduction

Cancer has recently become the second factor of death after cardiovascular disease, resulting in one out of six fatalities worldwide [1,2]. Cancer may be treated with a variety of different treatment methods, such as radiotherapy, surgery, chemotherapy, and immunotherapy, and frequently treatment involves a combination of methods. These methods are used to eliminate or reduce cancerous cells in the human body. With chemotherapy, however, frequently non-cancerous (healthy) cells in the body are also impacted, whilst the drug dosage is delivered to the cancer cells [3–5]. This, therefore, encourages the exploration of new control techniques to enhance the effectiveness of killing cancer cells, whilst reducing the drug's impact on healthy cells [3–5].

Biomedical engineering researchers have investigated a number of different methods for tumor treatment, such as back-stepping control, sliding mode control, parameter estimation and fuzzy control [2].

Sarhaddi and Yaghoobi [2] introduced a sliding mode based on an adaptive fuzzy back-stepping controller applied to a cancerous tumor system, to address the convergence rate and to achieve robustness against uncertainties. This system is modeled as a nonlinear fractional-order multi-input, multi-output model using a fuzzy controller. Their results illustrated that the proposed control reduced tumor cells to zero with a higher convergence rate in contrast to the adaptive fuzzy conventional back-stepping and integer-order model control schemes. Azarbakhsh and Mazinan [6] noted that chemotherapy, whilst a standard treatment method for cancer, has disadvantageous side-effects during transportation of the drug through the blood to the cells. Therefore, they investigated the application of a super-twisting sliding mode control, as applied to a nonlinear mathematical model of a brain tumor cancer system, in order to stabilize the closed loop system, reject the uncertainties and disturbance, reduce the chattering, and optimize the

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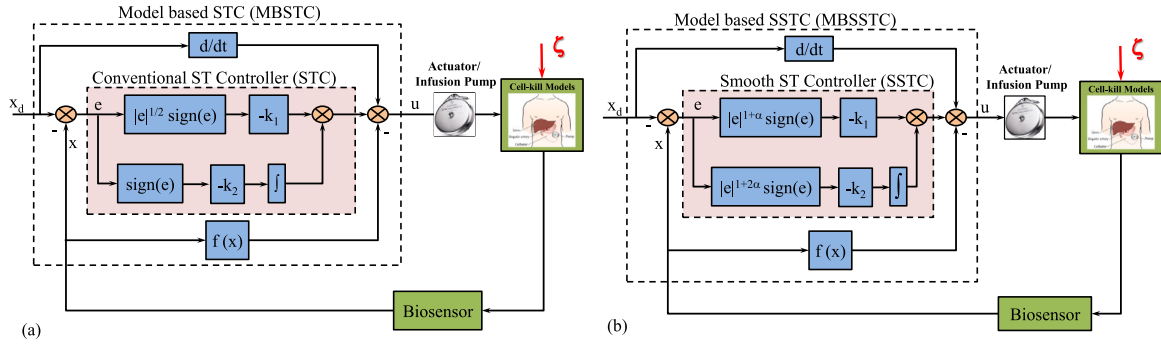


Fig. 1. Block diagram of tumor volume responses under. (a) Conventional STC controller. (b) MBSSTC controller.

drug dose. Their simulation results show that the injection rate could be effective on a patient's cells by adjusting the interleukin concentration rate, in the presence of system uncertainties and disturbances.

Shahri, et al. [7] present a Lyapunov stability theory-based sliding mode control applied to a nonlinear tumor growth model system subject to uncertainties to identify the active dose in the application of immunotherapy, in which recurrent neural networks are employed for the identification process of a mathematical model of a particular cancer. An appropriate sliding variable in the sliding mode control was constructed to achieve the desired values of tumor size. Their results showed that a small amount of error of the identification is helpful to achieve precision of the proposed identification technique as applied on a virtual patient under uncertainties to reach the desired dose, and reduce tumor cell count to zero. Ebrahimi et al. [8] proposed a novel, model-free, data-driven sliding mode controller for a non-linear single input and single output based on input and output data, and an optimization approach validated experimentally. The results of their simulations on a given cancer model showed that uncertainties and external disturbances acting on the model were actively addressed to achieve a rapid speed of convergence with transient response property.

To investigate the tumor growth reduction using different mathematical models and to compare healthy cells with tumorous ones requires including the effect of the immune system in these studies. Accordingly, Itik et al. [9] presented a nonlinear cancer drug therapy system to construct optimal control techniques, in which the system is verified for global system dynamics and within small disturbances about the equilibrium points. The results proved that the cancerous cells were eradicated in a very short time with a limited amount of drug combined with an optimal therapy administration. Studies examined, different nonlinear mathematical cell-kill models for investigating the behavior of cancer using different treatments [5,10–12]. These studies focused on chemotherapy treatment by proposing three mathematical cell-kill models, including log-kill hypothesis, Norton and Simon hypothesis and $E_{\max}$ hypothesis. The mathematical models are proposed to find the best transient time of drug injection during chemotherapy treatment to eliminate or minimize the toxicity risk of the drug [10]. Moradi et al. [5] designed a robust adaptive control for these three nonlinear models, log-kill, Norton and Simon and $E_{\max}$, to compensate for uncertainties and the effect of the treatment period using the Lyapunov stability theory. The results show that the amount of drug usage in the Norton and Simon approach is less than in the log-kill and $E_{\max}$ models, since the control input is a relatively large quantity around the small values of tumor volume. In addition to that, Dey et al. [12] used a theoretical super-twisting sliding mode control (SMC) for the cell-kill hypotheses log-kill, Norton-Simon, and $E_{\max}$ subjected to external perturbations to control and track a predefined trajectory of tumor volume after application of chemotherapy for a specific period to compensate the external disturbance and uncertainties using nonlinear models. In their study, they took the treatment period for 15 days. The simulation results for these cell-kill models verified their methodology based on an in-silico environment validation. In light of the analysis

presented above, a novel model-based smooth super-twisting control (MBSSTC) scheme is proposed for the cell-kill models in the cancer chemotherapy system in this correspondence. A non-smooth term is used to swap the function of discontinuous switching hidden over the integration that exists in the standard STC algorithm to improve an inadequate performance of the STC caused by this hidden discontinuous function behind the integration. Comparisons by simulations are made among the commonly employed PI, traditional STC, and the proposed MBSSTC schemes. Consequently, the following three aspects encapsulate the major contributions of this correspondence:

1. The proposed MBSSTC replaces the discontinuous switching function used in the conventional STC algorithm with a non-smooth term, reducing the effect of the chattering on the tracking performance of the cancer chemotherapy system and making it more useful in most cancer treatment applications.
2. By appropriately adjusting the parameters of our designed controller, the error, being the difference between the tumor volume reduction and the real tumor volume can approach to an arbitrarily small region, guaranteeing that the cancer chemotherapy system exhibits superior tracking effectiveness.
3. The designed MBSSTC can be regarded as a sort of non-smooth control method between the PI controller and the STC. The necessary antidisturbance capability and tumor volume performance can be obtained by choosing the suitable parameter α for the particular circumstances.

The current paper is organized into seven sections, commencing with this, the Introduction section. Section 2 presents the models of cell-kill hypotheses encapsulating cancer chemotherapy. In Section 3, the control objective in this research is stated. The conventional STC design is revisited in Section 4. The construction of the proposed control algorithm, with its rigorous stability analysis, is described in Section 5. Section 6 presents all supporting simulated results of the proposed controller. Finally, the paper conclusion is given in Section 7.

2. Cell-Kill hypotheses models in cancer chemotherapy

In this section, we consider three models of cell-kill hypotheses: log-kill hypothesis (named Model 1), Norton-Simon hypothesis (named Model 2), and $E_{\max}$ hypothesis (named Model 3). Dynamics of those three models are expressed by the following differential equations [5]

$$\text{Model 1 : } \frac{dx}{dt} = -rx \ln(x) - \delta x u(t) \quad (1)$$

$$\text{Model 2 : } \frac{dx}{dt} = -\ln(x) [rx - \delta u(t)] \quad (2)$$

$$\text{Model 3 : } \frac{dx}{dt} = -rx \ln(x) - \frac{\delta x}{\lambda + x} u(t) \quad (3)$$

where x refers to the volume of tumor, r is the rate of tumor volume growth, δ is the model constant coefficient associated to the drug usage magnitude, and λ stands for the constant of the model, which is observed clinically. In addition, $u(t)$ is the concentration (density)

of the chemotherapy drug. In the plasma compartment, if the drug concentration is absent when $u(t) = 0$, whereas $u(t) > 0$ means that the drug usage is strengthened. For the sake of simplicity, instead of the concentration drug, the drug usage is adopted in the next formulas, simulation results and discussions. Furthermore, the tumor volume dynamics in (1)–(3) have the initial condition of $x(0) = x_0$ specified clinically by the following range $0 < x_0 < 1$.

Note that the mathematical models of the cell-kill hypothesis presented in (1)–(3) are used in several studies in [5,12–14] to investigate the performance of rate reduction of tumor volume, in which the model parameters based on the aforementioned hypothesis are realistically verified via clinical observations on different cancer types [15]. The verification was performed by using different drug doses for tumor reduction of ovarian and breast cancers.

3. Control objective

Clinical observations suggest that when a patient receives chemotherapy, the tumor volume should decrease until it reaches a safe level. The standard practice recommends a particular length of treatment to achieve this. Therefore, for the three cell-kill models (1)–(3), the main objective of the control is to maintain a target tumor growth trajectory, $x_d(t)$, despite perturbations and parametric uncertainties.

4. Design of conventional STC with its analysis

For the three cancer cell-killing models (1)–(3) mentioned above, the generalized form of the chemotherapy process can be expressed as

$$\dot{x}(t) = f(x) + b(x)u(t) \quad (4)$$

where $x(t) \in \mathbb{R}$ is the tumor size and $u(t) \in \mathbb{R}$ represents the control input. If $\zeta(t) \in \mathbb{R}$, represents an unidentified non-vanishing disturbance, which affects the aforementioned system. Then, the dynamics (4) can be reformulated as

$$\dot{x}(t) = f(x) + b(x)u(t) + \zeta(t) \quad (5)$$

with

$$\text{Model 1 : } f(x) = -rx \ln(x); \quad b(x) = \delta x$$

$$\text{Model 2 : } f(x) = -rx \ln(x); \quad b(x) = \delta \ln(x)$$

$$\text{Model 3 : } f(x) = -rx \ln(x); \quad b(x) = -\frac{\delta x}{\lambda + x}.$$

Assumption 1. 1: The non-vanishing disturbance $\zeta(t)$ in the dynamical models (5) is differentiable. The time derivative of the disturbance $\dot{\zeta}(t)$ has its upper bound given by $|\dot{\zeta}| \leq D$, where D is the known positive constant.

Let us now introduce the tracking error of the tumor volume as

$$e(t) = x(t) - x_d(t) \quad (6)$$

where x_d is the desired reference of tumor growth, which is assumed to be differentiable up to one.

From the first derivative of (5) and (6), we obtain

$$\dot{e}(t) = f(x) + b(x)u(t) + \zeta(t) - \dot{x}_d(t). \quad (7)$$

For the dynamics in (7), the control law u can be given by the following conventional STC algorithm

$$\begin{cases} u = b(x)^{-1} [-f(x) - k_1 |e|^{1/2} \text{sign}(e) + u_1 + \dot{x}_d], \\ \dot{u}_1 = -k_2 \cdot \text{sign}(e) \end{cases} \quad (8)$$

where k_1 and $k_2 \in \mathbb{R}^+$ are the adjustable gains. In the control law formula (8), if we also choose k_1 large enough, in addition, the $k_2 > D$ is a necessary condition for convergence, controller (8) ensures a finite-time convergence of $e = \dot{e} = 0$.

Based on [16,17], the Lyapunov theorem and geometric approach, respectively, have been utilized in proving the finite-time convergence

and stability of the STC algorithm. Thus, the proof of the closed-loop stability (7)–(8) is skipped over in this section. The structure of the conventional STC is displayed in Fig. 1(a).

5. Applicability and design procedure of MBSSTC method

5.1. Applicability of the proposed control

The clinical applicability of the proposed control scheme is shown in the closed-loop control systems of the chemotherapy treatment in Fig. 1(a) and (b), typically having three elements: an actuator, a sensor, and an active control strategy. The essential components of a closed-loop drug delivery system usually comprise a pump, biosensor, controller, and supercomputer. The control action $u(t)$ of the proposed scheme (uploaded on the supercomputers) actuates an infusion pump that is an electronically controlled personal mechanical pump through an integrated wireless mechanism. The amount of the cancer drug is stored in an integrated reservoir of the infusion pump implemented in the patient's body, which is delivered to the patients via catheters with a low flow rate and high precision. This drug amount administered depends on the coil current of the infusion pump generated by the proposed controller. The controlled current automatically opens the pump valve to inject, with the proper flow rate of the drug to patients.

Moreover, a biosensor may be implanted along with the infusion pump either locally or remotely in location, which is used in designing the closed-loop cancer drug system to measure the actual output data of tumor parameters from patients. The signal recorded from the sensor is fed back to the pump to confirm whether the drug action has produced enough reduction or not. For reducing the risk of sensor damage, long-term implantable sensors are preferable. In this general configuration, the controlled system acts as an intermediate connection between the biosensor and the drug infusion pump mechanism. For more details, one can refer to the review paper in [18] and the thesis in [19]. The procedure of the proposed control design and its stability shall be stated and examined in the subsequent sections.

The proposed MBSSTC scheme with finite time property works based on the ideal cancer mathematical model hypothesis and the feedback recorded from an implementable biosensor, leading to the tracking error difference between the desired tumor volume reduction predefined in advance by doctors and the actual volume reduction. The tracking error is aimed at converging quickly to zero in a finite time even in the application of some uncertainties compared to the ideal models. The amount of drug delivery under the proposed control will be calculated based on the tracking difference.

5.2. Control design of MBSSTC scheme

To alleviate the inevitable chattering problem in the sliding mode control (SMC), the discontinuous function in the following term $k_2 \cdot \text{sign}(e)$ is put behind the integration, although the control chattering still exists in the traditional STC approach (8). This will not only cause some unwanted chattering, but it will also have an impact on the cancer chemotherapy system's steady-state performance. Therefore, it is an urgent matter to figure out how to substitute a continuous term for the discontinuous term in the traditional STC algorithm.

For removing the discontinuous function influence in the term of $k_2 \cdot \text{sign}(e)$ in the standard STC scheme, the MBSSTC approach is designed as follows

$$\begin{cases} u = b(x)^{-1} [-f(x) - k_1 |e|^{1+\alpha} + u_1 + \dot{x}_d] \\ \dot{u}_1 = -k_2 |e|^{1+2\alpha} \end{cases} \quad (9)$$

where k_1 and k_2 stand for the tunable positive gains and $\alpha \in (-\frac{1}{2}, 0)$ is constant. Fig. 1(b) displays the block diagram of the proposed MBSSTC algorithm.

Substituting the MBSSTC controller (9) into error dynamics (7), one has

$$\begin{cases} \dot{\eta}_1 = \eta_2 - k_1 |\eta_1|^{1+\alpha} \\ \dot{\eta}_2 = -k_2 |\eta_1|^{1+2\alpha} + \dot{\zeta}(t) \end{cases} \quad (10)$$

where $\eta_1 = e$ and $\eta_2 = \zeta(t) - k_2 \int_0^t |\eta_1|^{1+2\alpha} d\mu$.

5.3. Useful definition and lemmas

To complete the stability analysis of the MBSSTC algorithm, a definition and four useful lemmas are given as follows:

Definition 1 ([20]). Let fixed states variables $(v_1, v_2, \dots, v_n) \in R^n$ and given real numbers $\varepsilon_i > 0$, $i = 1, \dots, n$. One possesses $\Psi(e^{\varepsilon_1} v_1, e^{\varepsilon_2} v_2, \dots, e^{\varepsilon_n} v_n) = e^{\rho} \Psi(v_1, v_2, \dots, v_n)$, if a real number $\rho \in R$ exists such that for $\forall e > 0$ and $\forall v \in R^n \setminus \{0\}$. Then, the function $\Psi : R^n \rightarrow R$ is known as homogeneous of degree ρ , where $(\varepsilon_1, \varepsilon_2, \dots, \varepsilon_n)$ are the weights of the states.

Lemma 1 ([21]). The function $\Phi(v) : R^n \rightarrow R$ and the positive-definite function $\Psi(v) : R^n \rightarrow R$ are supposed to have the same homogeneity of degree with respect to the same dilation weight. Then, one can obtain a constant $\bar{N} > 0$, such that $\Phi(v) \leq \bar{N} \Psi(v)$. Moreover, if $\Phi(v)$ is positive-definite, one has $\underline{N} \Psi(v) \leq \Phi(v)$, where $\underline{N}$ is a positive constant.

Lemma 2 ([22]). Assume that $0 < c \leq 1$, then for $\forall v, w \in R$,

$$|v|^c - |w|^c \leq 2^{1-c} |v - w|^c.$$

Lemma 3 ([21]). For $c_1 > 0$ and $c_2 > 0$ and let $h(v, w) > 0$ is a function of v and w . Then, for $\forall v, w \in R$, we have

$$|v|^{c_1} |y|^{c_2} \leq \frac{c_1}{c_1 + c_2} h(v, w) |v|^{c_1 + c_2} + \frac{c_2}{c_1 + c_2} h(v, w)^{-\frac{c_1}{c_2}} |w|^{c_1 + c_2}$$

Lemma 4 ([23]). Let $n \geq 1$. Then the following holds for $\forall v, w \in R$

- $||v|^n - |w|^n| \leq b(2^{n-2} + 2)(|v - w|^n + |v - w||w|^{n-1})$.
- $||v|^n - |w|^n| \geq 2^{1-n} |v - w|^n$.

5.4. Stability proof

We will design the Lyapunov function in this subsection to verify that the states of the system σ_1 and σ_2 will approach to the following region:

$$\begin{aligned} \Omega = & \left\{ (\sigma_1, \sigma_2) : |\sigma_1| \leq \kappa_2^{\frac{1}{2+\alpha}} \left(\frac{2}{1+\alpha} \right)^{\frac{1}{2}} \left(\frac{\kappa_1 D}{k_1(1-\phi)} \right)^{\frac{1}{1+2\alpha}} \right. \\ & \left. + 2^{\frac{1}{2}} \kappa_2^{\frac{1}{2+\alpha}} \left(\frac{\kappa_1 D}{k_1(1-\phi)} \right)^{\frac{1}{1+2\alpha}} \right. \\ & \left. |\sigma_2| \leq \kappa_1 \kappa_2^{\frac{1+\alpha}{2+\alpha}} \left(\frac{2}{1+\alpha} \right)^{\frac{1+\alpha}{2}} \left(\frac{\kappa_1 D}{k_1(1-\phi)} \right)^{\frac{1+\alpha}{1+2\alpha}} \right\} \end{aligned} \quad (11)$$

where κ_1 and κ_2 are positive constants and $\phi \in (0, 1)$ is a constant that has to be sufficiently small.

Remark 1. It is obvious that the system state σ_1 is bounded by the value $\left[\kappa_2^{\frac{1}{2+\alpha}} \left(\frac{2}{1+\alpha} \right)^{\frac{1}{2}} + 2^{\frac{1}{2}} \kappa_2^{\frac{1}{2+\alpha}} \right] \left(\frac{\kappa_1 D}{k_1(1-\phi)} \right)^{\frac{1}{1+2\alpha}}$, i.e., the tumor volume error e is bounded. The tumor volume error e can be reduced to an arbitrarily small number by appropriately adjusting the parameters k_1 and α , ensuring the accuracy of the cancer chemotherapy process.

Defining $x_1 = \sigma_1$ and $x_2 = \frac{1}{k_1} \sigma_2$, system dynamics (10) can be reformulated as

$$\begin{cases} \dot{x}_1 = m_1 (x_2 - [x_1]^{1+\alpha}) \\ \dot{x}_2 = -m_2 [x_1]^{1+2\alpha} + \frac{\dot{\zeta}(t)}{m_1} \end{cases} \quad (12)$$

where $m_1 = k_1$ and $m_2 = \frac{k_2}{k_1}$.

For the purpose of simplification, let

$$\begin{aligned} z_1 &= x_2 - [x_1]^{1+\alpha}, \quad z_2 = -[x_2]^{\frac{2\alpha+1}{\alpha+1}} \\ z_3 &= [x_2]^{\frac{2\alpha+1}{\alpha+1}} - [x_1]^{1+2\alpha}, \quad z_4 = [x_2]^{\frac{1}{\alpha+1}} - x_1. \end{aligned} \quad (13)$$

Next, the reconstruction of the system dynamics (12) is

$$\begin{cases} \dot{x}_1 = m_1 z_1, \\ \dot{x}_2 = m_2 (z_2 + z_3) + \frac{\dot{\zeta}(t)}{m_1} \end{cases} \quad (14)$$

The reliance on Lemma 2 and the fact $0 < \frac{1+2\alpha}{1+\alpha} < 1$ leads to the conclusion that

$$|z_3| \leq 2^{\frac{-\alpha}{1+\alpha}} |z_1|^{\frac{1+2\alpha}{1+\alpha}}. \quad (15)$$

Lemma 4 (a) is used to result in

$$\begin{aligned} |z_4| &= -x_1 + |x_2|^{\frac{1}{1+\alpha}} \leq \frac{1}{1+\alpha} \left(2 + 2^{\frac{1}{1+\alpha}-2} \right) \\ &\quad \times \left(|x_2 - [x_1]^{1+\alpha}| |x_2|^{\frac{1}{1+\alpha}-1} + |x_2 - [x_1]^{1+\alpha}|^{\frac{1}{1+\alpha}} \right) \\ &= \Gamma \left(|z_1| \cdot |x_2|^{\frac{-\alpha}{1+\alpha}} + |z_1|^{\frac{1}{1+\alpha}} \right) \end{aligned} \quad (16)$$

where $\Gamma = \frac{1}{1+\alpha} (2^{\frac{-1-2\alpha}{1+\alpha}} + 2)$.

Motivated by [24], to ensure the system stability (14), the Lyapunov function is selected as follows

$$V(x_1, x_2) = M_1(x_1, x_2) + M_2(x_2) \quad (17)$$

where $M_1(x_1, x_2) = \frac{1}{2} (x_1 - [x_2]^{\frac{1}{1+\alpha}})^2$ and $M_2(x_2) = \frac{1+\gamma}{2} |x_2|^{\frac{2}{1+\gamma}}$. Meanwhile, along system (14), $V(x_1, x_2)$ is differentiated with respect to time as follows

$$\dot{V}(x_1, x_2)|_{(14)} = \dot{M}_2(x_2)|_{(14)} + \dot{M}_1(x_1, x_2)|_{(14)}. \quad (18)$$

Using $\frac{\partial M_2(x_2)}{\partial x_2} = -[x_2]^{\frac{1-\gamma}{1+2\gamma}}$ and selecting $m_2 \geq 2$ yield

$$\begin{aligned} \dot{M}_2(x_2)|_{(14)} &= \frac{\partial M_2(x_2)}{\partial x_2} \dot{x}_2|_{(14)} \\ &= -[x_2]^{\frac{1-\alpha}{1+2\alpha}} (m_2 z_2 + m_2 z_3) + \frac{\partial M_2(x_2)}{\partial x_2} \cdot \frac{\dot{\zeta}(t)}{m_1} \\ &\leq -2|x_2|^{\frac{2+\alpha}{1+2\alpha}} - m_2 [x_2]^{\frac{1-\alpha}{1+2\alpha}} z_3 + \frac{\partial M_2(x_2)}{\partial x_2} \cdot \frac{\dot{\zeta}(t)}{m_1}. \end{aligned} \quad (19)$$

By means of Lemma 3 and (15), we obtain

$$\begin{aligned} m_2 |x_2|^{\frac{1-\alpha}{1+2\alpha}} z_3 &\leq m_2 |x_2|^{\frac{1-\alpha}{1+2\alpha}} 2^{\frac{-\alpha}{1+\alpha}} |z_1|^{\frac{1+2\alpha}{1+\alpha}} \\ &= m_2 2^{\frac{-\alpha}{1+\alpha}} |x_2|^{\frac{1+\alpha}{1+2\alpha}} \cdot \frac{1-\alpha}{1+\alpha} |z_1|^{\frac{1+2\alpha}{1+\alpha}} \\ &\leq \frac{1}{2} |x_2|^{\frac{2+\alpha}{1+2\alpha}} + \gamma_1 |z_1|^{\frac{2+\alpha}{1+\alpha}} \end{aligned} \quad (20)$$

where $\gamma_1 > 0$ is a constant.

Eq. (20) is substituted into (19), obtains

$$\dot{M}_2(x_2)|_{(14)} \leq -\frac{3}{2} |x_2|^{\frac{2+\alpha}{1+2\alpha}} + \gamma_1 |z_1|^{\frac{2+\alpha}{1+\alpha}} + \frac{\partial M_2(x_2)}{\partial x_2} \cdot \frac{\dot{\zeta}(t)}{m_1}. \quad (21)$$

Similarly, one can rewrite $\dot{M}_1(x_1, x_2)|_{(14)}$ that is the second term in (17) as follows

$$\begin{aligned} \dot{M}_1(x_1, x_2)|_{(14)} &= -\frac{1}{1+\alpha} |x_2|^{\frac{-\alpha}{1+\alpha}} \left(-[x_2]^{\frac{1}{1+\alpha}} + x_1 \right) \dot{x}_2 + \left(-[x_2]^{\frac{1}{1+\alpha}} + x_1 \right) \dot{x}_1 \\ &= \frac{1}{1+\alpha} |x_2|^{\frac{-\alpha}{1+2\alpha}} m_2 (z_3 + z_2) z_4 + \left(-[x_2]^{\frac{1}{1+\alpha}} + x_1 \right) m_1 z_1 \\ &\quad + \frac{\dot{\zeta}(t)}{m_1} \cdot \frac{\partial M_1(x_1, x_2)}{\partial x_2}. \end{aligned} \quad (22)$$

One can simply calculate the following

$$\begin{aligned} |z_4| &\leq \Gamma |z_1|^{\frac{1}{1+\alpha}} + \Gamma |z_1| \cdot |z_2|^{\frac{-\alpha}{1+\alpha}} \\ &\leq \Gamma |z_1|^{\frac{1}{1+\alpha}} + \Gamma |z_1| \cdot |z_2|^{\frac{-\alpha}{1+2\alpha}}. \end{aligned} \quad (23)$$

Based on Lemma 3, we get

$$\begin{aligned} &\frac{1}{1+\alpha} |z_2|^{\frac{-\alpha}{1+2\alpha}} m_2 z_2 z_4 \\ &\leq \frac{1}{1+\alpha} m_2 \Gamma |z_1|^{\frac{1}{1+\alpha} \times 1} \cdot |z_2|^{\frac{1}{1+2\alpha} \cdot (1+\alpha)} \\ &+ \frac{1}{1+\alpha} m_2 \Gamma |z_1|^{\frac{1}{1+\alpha} \cdot (1+\alpha)} \cdot |z_2|^{\frac{1}{1+2\alpha} \times 1} \\ &\leq \gamma_2 |z_1|^{\frac{2+\alpha}{1+\alpha}} + \frac{1}{4} |z_2|^{\frac{2+\alpha}{1+2\alpha}} \end{aligned} \quad (24)$$

where $\gamma_2 > 0$ is a constant.

Similarly, we find

$$\begin{aligned} &\frac{1}{1+\alpha} |z_2|^{\frac{-\alpha}{1+2\alpha}} m_2 z_3 z_4 \\ &\leq \frac{1}{1+\alpha} |z_2|^{\frac{-\alpha}{1+2\alpha} \cdot 2} |z_1|^{\frac{1+2\alpha}{1+\alpha}} \\ &\times m_2 \Gamma \left(|z_1|^{\frac{1}{1+\alpha}} + |z_1| \cdot |z_2|^{\frac{-\alpha}{1+2\alpha}} \right) \\ &= \frac{2}{1+\alpha} m_2 \Gamma |z_2|^{\frac{1}{1+2\alpha} \cdot (-\alpha)} |z_1|^{\frac{1}{1+\alpha} \cdot (2+2\alpha)} \\ &+ \frac{2}{1+\alpha} m_2 \Gamma |z_2|^{\frac{1}{1+2\alpha} \cdot (-2\alpha)} |z_1|^{\frac{1}{1+\alpha} \cdot (2+3\alpha)} \\ &\leq \frac{1}{4} |z_2|^{\frac{2+\alpha}{1+2\alpha}} + \gamma_3 |z_1|^{\frac{2+\alpha}{1+\alpha}} \end{aligned} \quad (25)$$

where $\gamma_3 > 0$ is a constant.

Furthermore, by Lemma 4(b) and with the assistance of the fact $\frac{1}{1+\alpha}$, it is clear that

$$\begin{aligned} &\left(-|x_2|^{\frac{1}{1+\alpha}} + x_1 \right) m_1 z_1 \\ &= m_1 \left(-|x_2|^{\frac{1}{1+\alpha}} + x_1 \right) \left(x_2 - |x_1|^{1+\alpha} \right) \\ &= -m_1 \left| |x_2|^{\frac{1}{1+\alpha}} - |x_1|^{(1+\alpha) \cdot \frac{1}{1+\alpha}} \right| \cdot |x_2 - |x_1|^{1+\alpha}| \\ &\leq -m_1 2^{\frac{\alpha}{1+\alpha}} \left| x_2 - |x_1|^{1+\alpha} \right|^{\frac{2+\alpha}{1+\alpha}} \\ &= -m_1 2^{\frac{\alpha}{1+\alpha}} |z_1|^{\frac{2+\alpha}{1+\alpha}}. \end{aligned} \quad (26)$$

Putting (24), (25), and (26) into (22) results in

$$\begin{aligned} M_1(x_1, x_2)|_{(14)} &\leq \frac{1}{2} |z_2|^{\frac{2+\alpha}{1+2\alpha}} + \left(\gamma_2 + \gamma_3 - m_1 2^{\frac{\alpha}{1+\alpha}} \right) |z_1|^{\frac{2+\alpha}{1+\alpha}} \\ &+ \frac{\partial M_1(x_1, x_2)}{\partial x_2} \cdot \frac{\dot{\zeta}(t)}{m_1}. \end{aligned} \quad (27)$$

Based on (21) and (27), one can rewrite (18) by

$$\begin{aligned} &\dot{V}(x_1, x_2)|_{(14)} \\ &\leq -|z_2|^{\frac{2+\alpha}{1+2\alpha}} + \left(\gamma_3 + \gamma_2 + \gamma_1 - m_1 2^{\frac{\alpha}{1+\alpha}} \right) |z_1|^{\frac{2+\alpha}{1+\alpha}} \\ &+ \frac{\dot{\zeta}(t)}{m_1} \cdot \frac{\partial V(x_1, x_2)}{\partial x_2}. \end{aligned} \quad (28)$$

Moreover, the constant m_1 can be selected according to

$$m_1 \geq 2^{\frac{-\alpha}{1+\alpha}} (\gamma_1 + \gamma_2 + \gamma_3 + 1). \quad (29)$$

Putting (29) into (28) obtains

$$\dot{V}(x_1, x_2)|_{(14)} \leq -G(x_1, x_2) + \frac{\dot{\zeta}(t)}{m_1} \cdot \frac{\partial V(x_1, x_2)}{\partial x_2} \quad (30)$$

where $G(x_1, x_2) = |z_2|^{\frac{2+\alpha}{1+2\alpha}} + |z_1|^{\frac{2+\alpha}{1+\alpha}}$.

Assumption 1, one obtains

$$\dot{V}(x_1, x_2)|_{(14)} \leq -G(x_1, x_2) + \frac{D}{m_1} \cdot \left| \frac{\partial V(x_1, x_2)}{\partial x_2} \right|. \quad (31)$$

The region Ω that will then be approached in a finite amount of time is proved by using the next two steps.

Step 1. we will prove that $\dot{V}(x_1, x_2)|_{(14)}$ is a negative function in this step, if $(x_1, x_2) \notin R_1$ and the region R_1 is constructed as

$$R_1 = \left\{ (x_1, x_2) : |z_2|^{\frac{2+\alpha}{1+2\alpha}} + |z_1|^{\frac{2+\alpha}{1+\alpha}} \leq \left(\frac{\kappa_1 D}{m_1(1-\phi)} \right)^{\frac{2+\alpha}{1+2\alpha}} \right\}.$$

Because of $(x_1, x_2) \notin R_1$, we have

$$|z_1|^{\frac{2+\alpha}{1+\alpha}} + |z_2|^{\frac{2+\alpha}{1+2\alpha}} > \left(\frac{\kappa_1 D}{m_1(1-\phi)} \right)^{\frac{2+\alpha}{1+2\alpha}}.$$

Now, we obtain both $G^{\frac{1-\alpha}{2+\alpha}}(x_1, x_2)$ and $\left| \frac{\partial V(x_1, x_2)}{\partial x_2} \right|$ are homogeneous of degree $1-\gamma$ with regard to the dilation weight $(1, 1+\alpha)$.

By using Lemma 1, one can conclude that

$$\left| \frac{\partial V(x_1, x_2)}{\partial x_2} \right| \leq \kappa_1 G^{\frac{1-\alpha}{2+\alpha}}(x_1, x_2). \quad (32)$$

Eq. (32) is substituted into (31) to obtain

$$\dot{V}(x_1, x_2)|_{(14)} \leq -G(x_1, x_2) + \frac{\kappa_1 D}{m_1} G^{\frac{1-\alpha}{2+\alpha}}(x_1, x_2). \quad (33)$$

According to the fact $G(x_1, x_2) = |z_1|^{\frac{2+\gamma}{1+\gamma}} + |z_2|^{\frac{2+\gamma}{1+2\gamma}} > \left(\frac{\kappa_1 D}{m_1(1-\phi)} \right)^{\frac{2+\gamma}{1+2\gamma}}$, Eq. (33) can be reformulated as

$$\dot{V}(x_1, x_2)|_{(14)} < -\alpha G(x_1, x_2) < 0.$$

But, once $\forall (x_1, x_2) \in R_1$, $\dot{V}(x_1, x_2)|_{(14)} < 0$ will not be ensured, that is, the system coordinate may go away from the neighborhood R_1 .

Thus, a larger region R_2 should be determined. For any initial state $(x_1(0), x_2(0)) \in R_2$, this region ensures that a finite time T exists such that $(x_1, x_2) \in R_2, \forall t \leq T$. The region R_2 is designed as

$$R_2 = \left\{ (x_1, x_2) : V(x_1, x_2) \leq H; H = \kappa_2^{\frac{2}{2+\alpha}} \left(\frac{\kappa_1 D}{m_1(1-\phi)} \right)^{\frac{2}{1+2\alpha}} \right\} \supset R_1.$$

Step 2. Based on the analysis above, provided that it can be demonstrated that R_1 is a subset of R_2 , the result $\dot{V}(x_1, x_2)|_{(14)} < 0, (x_1, x_2) \notin R_2$ is deduced.

Considering Definition 1, one finds both $G(x_1, x_2)$ and $V^{\frac{2+\alpha}{2}}(x_1, x_2)$ are homogeneous of degree $2+\alpha$ with regard to the dilation weight $(1, 1+\alpha)$. With using Lemma 1, one can conclude that

$$V^{\frac{2+\alpha}{2}}(x_1, x_2) \leq \kappa_2 G(x_1, x_2). \quad (34)$$

As $G(x_1, x_2) > \left(\frac{\kappa_1 D}{m_1(1-\phi)} \right)^{\frac{2+\alpha}{1+2\alpha}}, (x_1, x_2) \in R_1$, (34) is reformulated as

$$\begin{aligned} V^{\frac{2+\alpha}{2}}(x_1, x_2) &\leq \kappa_2 \cdot \left(\frac{\kappa_1 D}{m_1(1-\phi)} \right)^{\frac{2+\alpha}{1+2\alpha}} \\ &\leq \left(\kappa_2^{\frac{2}{2+\alpha}} \left(\frac{\kappa_1 D}{m_1(1-\phi)} \right)^{\frac{2}{1+2\alpha}} \right)^{\frac{2+\alpha}{2}} = H^{\frac{2+\alpha}{2}}. \end{aligned} \quad (35)$$

Thus, it can be concluded from (35) that $(x_1, x_2) \in R_2$, that is, $R_1 \subset R_2$.

Alternatively stated, a finite time T exists, such that $V(x_1, x_2) \leq H$ for $\forall t \geq T$.

Once $t \geq T$, one obtains

$$M_2(x_2) = \frac{1+\alpha}{2} |x_2|^{\frac{2}{1+\alpha}} \leq V(x_1, x_2) \leq H. \quad (36)$$

As $x_2 = \frac{1}{k_1} \eta_2$ and $m_1 = k_1$, from (36), one has

$$|\eta_2| \leq k_1 \kappa_2^{\frac{1+\alpha}{2+\alpha}} \left(\frac{2}{1+\alpha} \right)^{\frac{1+\alpha}{2}} \left(\frac{\kappa_1 D}{k_1(1-\phi)} \right)^{\frac{1+\alpha}{1+2\alpha}}. \quad (37)$$

On the contrary, once $t \geq T$, we get

$$M_1(x_1, x_2) = \frac{1}{2} \left(-[x_2]^{\frac{1}{1+\alpha}} + x_1 \right)^2 \leq V(x_1, x_2) \leq H.$$

Keeping $x_1 = \eta_1$ in mind, one consequently obtains that

$$\begin{aligned} |\eta_1| &\leq \left| [x_2]^{\frac{1}{1+\alpha}} \right| + \left| -[x_2]^{\frac{1}{1+\alpha}} + x_1 \right| \\ &\leq \kappa_2^{\frac{1}{2+\alpha}} \left(\frac{2}{1+\alpha} \right)^{\frac{1}{2}} \left(\frac{\kappa_1 D}{k_1(1-\phi)} \right)^{\frac{1}{1+2\alpha}} \\ &\quad + 2^{\frac{1}{2}} \kappa_2^{\frac{1}{2+\alpha}} \left(\frac{\kappa_1 D}{k_1(1-\phi)} \right)^{\frac{1}{1+2\alpha}}. \end{aligned} \quad (38)$$

Thus, it can simply deduced from (37) and (38) that the system coordinates η_1 and η_2 will be driven and approach to the region Ω in an instance of finite-time.

Remark 2. It is worthy to mention that the fraction power parameter α can be chosen from $\frac{-1}{2}$ to 0, excepting $\frac{-1}{2}$ and 0. The MBSSTC scheme reduces to the standard STC scheme when $\alpha = \frac{-1}{2}$. At $\alpha = 0$, the MBSSTC scheme degenerates into the PI control. In light of this, our designed MBSSTC can be regarded as a sort of non-smooth control between the conventional STC and the PI control.

Remark 3. The traditional STC controller, which has a discontinuous switching function, theoretically has a strong capability of disturbance rejection. However, the switching function causes the inescapable chattering phenomena that may negatively impact the cancer chemotherapy system's long-term performance. Additionally, the antidisturbance property of the STC may not be superior to the non-smooth controller in actual situations because of the impact of sampling time on the digital application of the control method. Due to the careful selection of the parameter α , the proposed MBSSTC controller not only has a smaller drug usage oscillation than a standard STC but also displays stronger antidisturbance performance.

Remark 4. It is worth mentioning that the proposed control could be a better candidate for different potential clinical applications of various diseases such as Leukemia, Type 1 diabetes, COVID-19, anesthesia, HIV/AIDS, hepatitis B virus (HBV), Androgen deprivation, SEIAR influenza, p53 protein, etc. [25–40]. In the existing literature, many control feedback control strategies have been employed for clinical therapies, treatments, and trials of the aforementioned diseases such as PID, fractional-order PID, optimal controls, model predictive controls, backstepping controls, sliding mode controls, and super-twisting controls. However, the two main drawbacks of the aforementioned control schemes are: First, slow convergence of the output of those clinical treatments with respect to the desired/reference input prescribed by doctors or physicians specialized in those treatments. Second, the non-smoothness drug delivery is generated by bioactuators activated by the above controllers. These two drawbacks can be tackled by the proposed control that can have possible clinical uses for different diseases. Unlike the aforementioned control methods, the fast convergence rate and the smoothness of the drug delivery are the main contributions of the current work, which are guaranteed by using the continuous terms with the fraction power in (9).

Remark 5. It is worth mentioning that the suggested control gains should be carefully chosen for the safe implementation of the considered cancer chemotherapy treatment, as the drug regulation performance is usually influenced by control drug delivery smoothness, cancer model uncertainties, initial conditions, and external disturbances. The corresponding gains selection criteria of the proposed control given in (9) are: (i) Generally, the control parameters k_1 and k_2 should be large positive values to compensate for the influence of the lumped disturbance and uncertainty. Too large control parameters could cause

Table 1

Nominal system parameters of log-kill, Norton-Simon, and $E_{\max}$ hypothesis represented by Model 1, Model 2, and Model 3, respectively.

Symbol	Model 1	Model 2	Model 3
r	0.1	0.1	0.1
δ	0.45	4	0.225
λ			0.25

Table 2

Control parameters of the proposed, STC, and PI scheme for Model 1, Model 2, and Model 3.

Method	Model	Parameters
MBSSTC (9)	Model 1	$k_1 = 6, k_2 = 17.6, \alpha = -0.38$
	Model 2	$k_1 = 34.04, k_2 = 566.5, \alpha = -0.33$
	Model 3	$k_1 = 11.1243, k_2 = 60.5, \alpha = -0.36$
STC (8)	Model 1	$k_1 = 2.1213, k_2 = 2.2$
	Model 2	$k_1 = 5.8095, k_2 = 16.5$
	Model 3	$k_1 = 3.3541, k_2 = 5.5$
PI (Go to Remark 2)	Model 1	$k_1 = 21.319, k_2 = 222.2$
	Model 2	$k_1 = 134.2898, k_2 = 8.8165e+03$
	Model 3	$k_1 = 67.1658, k_2 = 2.2055e+03$

the control chattering of the infusion pump, leading to non-smooth drug delivery, while too small parameters slow down the convergence rate of the tumor volume reduction concerning the required volume; (ii) the fractional power α should be within the range as defined in (9) and have two special reduction cases as stated in Remark 2. The proper value of α should regard the trade-off between the convergence speed of the tumor size reduction and the drug usage smoothness.

Remark 6. Due to the rapid convergence, smoothness, and robustness properties, the fractional power of the proposed cancer chemotherapy controller plays a pivotal role in improving clinical significance including maximum tumor cell killing (best tumor size reduction), minimum toxicity (smallest required drug doses usage), and short period of treatment. However, the selection of the fractional power should be careful, having a trade-off between convergence and smoothness, affecting clinical tumor size reduction and the amount of toxicity, respectively. To be specified, the low value of the exponent leads to the maximum tumor cell killing and short treatment schedule, but at the level of toxicities and damage to the drug infusion pump used in the chemotherapy treatment. Thus, it is desirable to ensure an optimal trade-off between those clinical specifications.

6. Simulation results

Realistic model parameters are used from [15] for simulating and investigating the effect of the proposed MBSSTC algorithm, and are provided in Table 1. Those parameters, which were established through experimental tests of various types of cancers, are scaled as non-dimensional numbers (in which for the reduction of ovarian and breast cancer, different drugs like Taxol have been employed). With the theoretical analysis mentioned in the previous section, the MBSSTC algorithm and comparative controllers (STC and PI schemes) for the generalized cell-kill hypothesis are constructed in the MATLAB/Simulink environment. To ensure fairness in the comparison, the proposed and comparative controls parameters are adjusted as listed in Table 2 such that the control performance should be better for all those controls.

For all three cell-kill hypotheses, the results of simulative tests are provided in this section. In all models mentioned previously, the volume of the tumor is normalized so that $0 \leq x \leq 1$. In the simulation results, two treatment durations are considered: $t_{f1} = 15$ and $t_{f2} = 30$ days. As recommended by a cancer doctor, there are two ideal scenarios for tumor reduction that can be expressed as

$$x_d = (x_0 - b) \exp(-at) + b \quad (39)$$

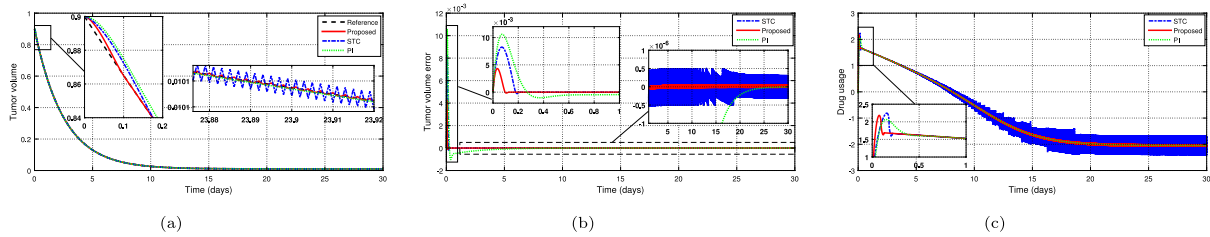


Fig. 2. Tracking responses of log-kill hypothesis with initial condition of $x_0 = 0.9$ (Sim 1). (a) Tumor volume. (b) Tumor volume error. (c) Required drug usage.

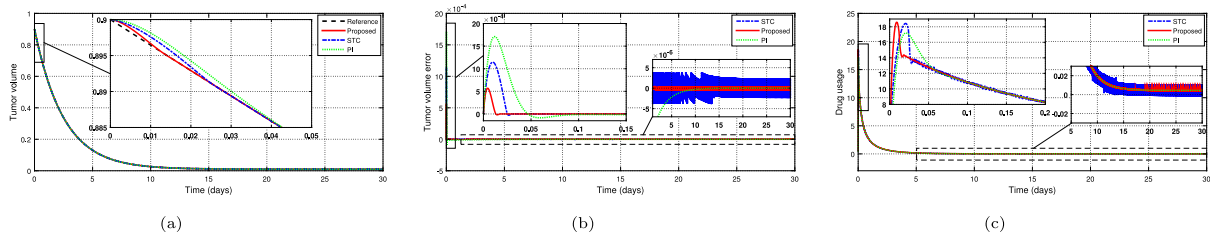


Fig. 3. Tracking responses of Norton-Simon hypothesis with initial condition of $x_0 = 0.9$ (Sim2). (a) Tumor volume. (b) Tumor volume error. (c) Required drug usage.

where x_d is the desired reference of tumor volume reduction, x_0 is initial condition of tumor volume, a refers to the convergence rate of the reduction of the tumor volume in cancer chemotherapy, and b is the desired final value of the steady state for tumor size, which should be set by the cancer doctor as the final value.

It should be noted from (39) that the function of exponent for decreasing the tumor size is taken into account, which are consistent with the cases employed in the prior optimal controllers such as [13, 15, 41, 42]. Without losing generality, other functions can be used to reduce the desired tumor volume. For examining the proposed control scheme, in the following, we will study four cases for tumor reduction of the three models of chemotherapy system.

6.1. The effect of carrying capacity on the control performance (Case 1)

In this case, the initial condition of three models used to characterize the cell-kill hypothesis as modeled in Section 2 is changed from $x_0 = 0.9$ and $x_0 = 0.5$ by varying the carrying capacity from 90 and 50% in (39). Accordingly, we test the proposed control efficiency for the chemotherapy system with three models under two desired references of tumor volume reduction and system initial conditions, comparing with PI controller and STC scheme. Under the variations of the desired reference and carrying capacity, the simulation results for three models are shown in Figs. 2 to 7, are labeled by Sim 1 to Sim 6, respectively. For initial condition $x_0 = 0.9$ as 90% of carrying capacity, Figs. 2 to 4 show the tracking curves of log-kill, Norton-Simon, and $E_{\max}$ models which are represented as nominal cases of those models in Sim 1, Sim 2, and Sim 3. More clearly, the left, middle, and right side of the figures represent the tumor volume profile, tracking error of tumor reduction, and control input of drug usage, respectively.

It can be seen that the tracking trajectory of the tumor volume reduction of the three models under the proposed control scheme is fastest in the transient, compared to PI and STC schemes. Also, the tracking error of the proposed control has the smallest value of 0.2 day, in contrast to those comparative controllers. Furthermore, the proposed control can smooth out the drug delivery, whereas the STC scheme suffers from the control chattering in Sim 1, Sim 2, and Sim 3 for both the transient and steady state regions.

For 50% of carrying capacity (initial condition $x_0 = 0.5$), simulation results of the three models are shown in Figs. 5, 6 and 7 labeled by Sim

4, Sim 5, Sim 6. As observed, the proposed control in three models of the cancer chemotherapy can rapidly track the desired reduction of the tumor volume trajectory. For all three models in Sim 4, 5, and 6, the proposed control still exhibits the smallest tracking error and converges to zero quickly in the transient, and has the highest precision in the steady state. The control input of drug usage for the three models under the proposed control scheme is smoother than the counterpart STC that generates non-smooth drug usage due to having a discontinuous switching function.

6.2. The effect of tumor reduction rate on the control performance (Case 2)

In Case 2, the rate of tumor reduction in (39) is readjusted from nominal value of 0.4 to 0.15, whilst keeping the rest parameters of the desired reference of tumor size reduction such as $x_0 = 0.9$, and $b = 0.01$. Accordingly, the new desired scenario of tumor size is obtained from (39), which is considered in Case 2 to show the influence of the variety of desired reference changed by the value of a . The Case 2 is implemented for the three models, and the simulation results of those models under the variation of a are shown in Fig. 8, 9, and 10.

The simulation results show that tracking time response of tumor volume in the three models is faster than the STC and PI scheme. In contrast to the STC and PI methods, the tracking error of the proposed control scheme converges to zero quickly and exhibits high precision in the steady state region. The continuity of the proposed control can be ensured due to the adoption of smooth term, but the STC causes chattering in the control signal.

6.3. The influence of parametric system uncertainties on the control efficiency of cell-kill models (Case 3)

In this subsection, as a real scenario, the impact of parametric uncertainties of the three models plants is investigated to show the robustness performance of the proposed control methodology. Case 3 is tested on log-kill, Norton-Simon, and $E_{\max}$ as labeled by Sim 10, 11, and 12. In this Case, the uncertain system parameters are varied with 50% of the nominal corresponding values as

$$(1 - \varphi)\bar{r}_i < r_i < (1 + \varphi)\bar{r}_i$$

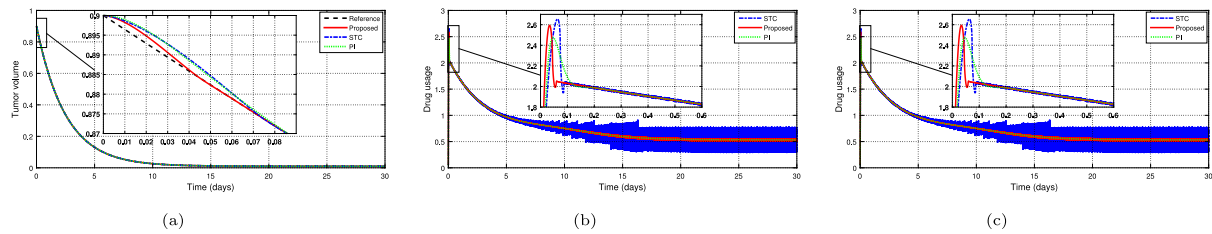


Fig. 4. Tracking responses of $E_{\max}$ hypothesis with initial condition of $x_0 = 0.9$ (Sim3). (a) Tumor volume. (b) Tumor volume error. (c) Required drug usage.

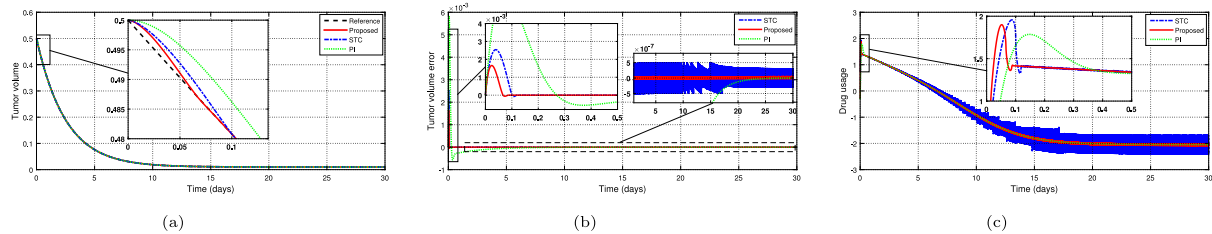


Fig. 5. Tracking responses of log-kill hypothesis with initial condition of $x_0 = 0.5$ (Sim4). (a) Tumor volume. (b) Tumor volume error. (c) Required drug usage.

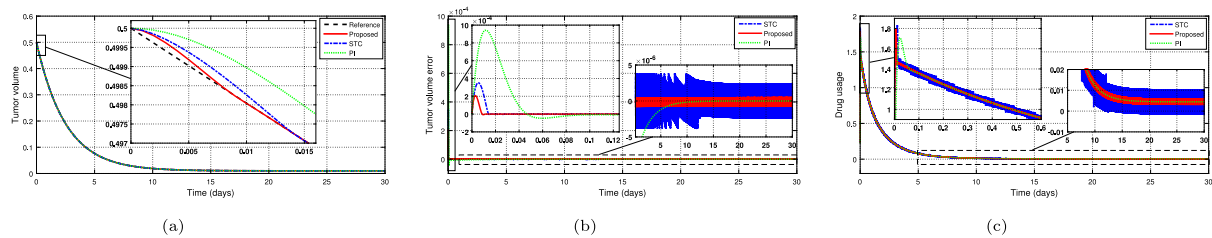


Fig. 6. Tracking responses of Norton-Simon hypothesis with initial condition of $x_0 = 0.5$ (Sim5). (a) Tumor volume. (b) Tumor volume error. (c) Required drug usage.

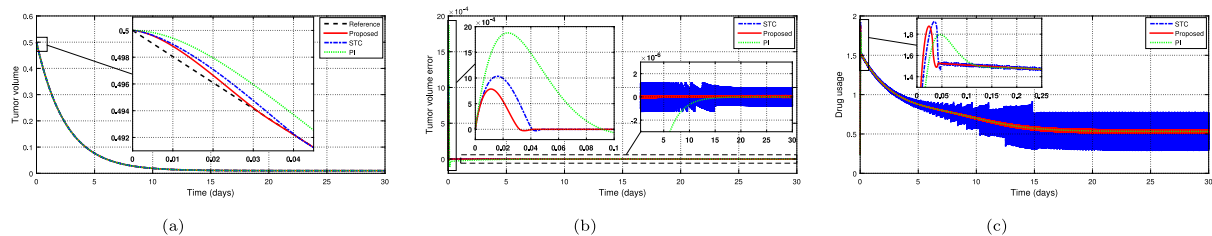


Fig. 7. Tracking responses of $E_{\max}$ hypothesis with initial condition of $x_0 = 0.5$ and (Sim6). (a) Tumor volume. (b) Tumor volume error. (c) Required drug usage.

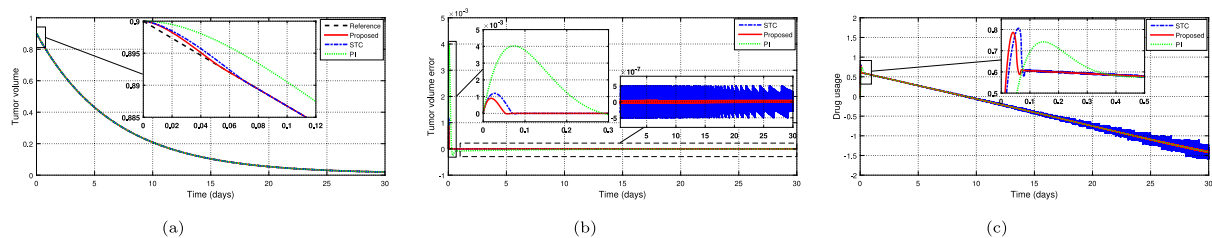


Fig. 8. Tracking responses of log-kill hypothesis with initial condition of $x_0 = 0.9$ and $a = 0.15$ (Sim7). (a) Tumor volume. (b) Tumor volume error. (c) Required drug usage.

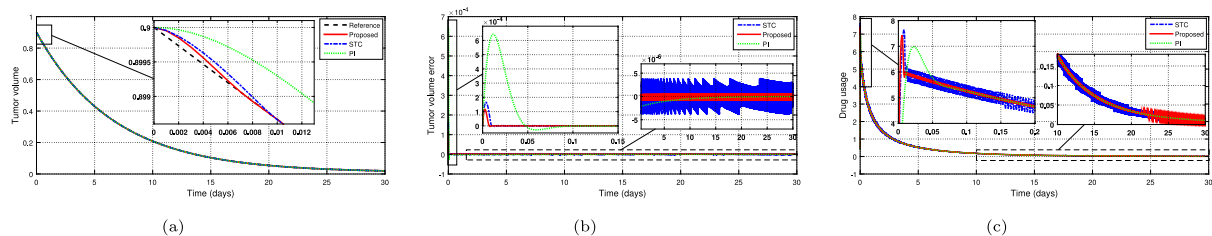


Fig. 9. Tracking responses of Norton-Simon hypothesis with initial condition of $x_0 = 0.9$ and $a = 0.15$ (Sim8). (a) Tumor volume. (b) Tumor volume error. (c) Required drug usage.

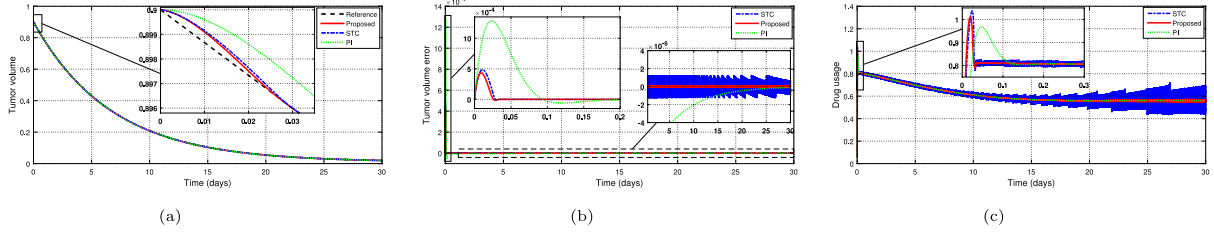


Fig. 10. Tracking responses of $E_{\max}$ hypothesis with initial condition of $x_0 = 0.9$ and $a = 0.15$ (Sim9). (a) Tumor volume. (b) Tumor volume error. (c) Required drug usage.

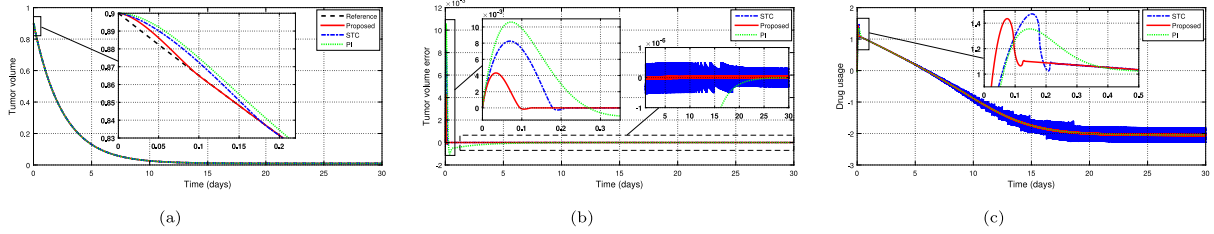


Fig. 11. Tracking responses of log-kill hypothesis with initial condition of $x_0 = 0.9$ and system uncertainties (Sim10). (a) Tumor volume. (b) Tumor volume error. (c) Required drug usage.

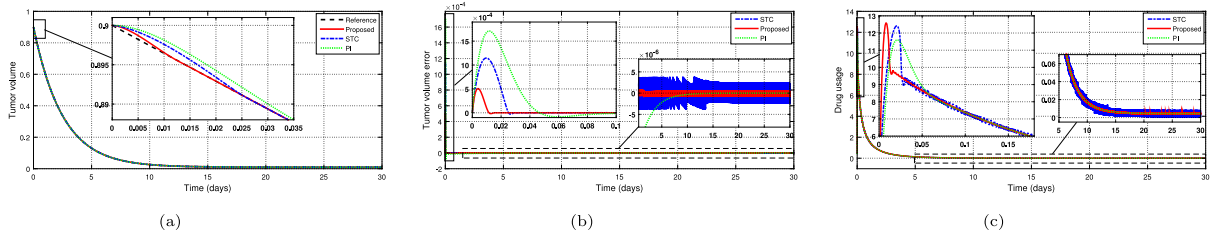


Fig. 12. Tracking responses of Norton-Simon hypothesis with initial condition of $x_0 = 0.9$ and system uncertainties (Sim11). (a) Tumor volume. (b) Tumor volume error. (c) Required drug usage.

$$(1 - \varphi)\bar{\delta}_i < \delta_i < (1 + \varphi)\bar{\delta}_i, i = 1, 2, 3 \text{ and } \varphi = 0.5 \quad (40)$$

$$(1 - \varphi)\bar{\lambda}_i < \lambda_i < (1 + \varphi)\bar{\lambda}_i$$

where r_i , $\bar{\delta}_i$, and $\bar{\lambda}_i$ are the nominal values of the respective parameter given in Table 1. In Case 3, the uncertain parameters of the actual models $\bar{r}_i$, $\bar{\delta}_i$, and $\bar{\lambda}_i$ are assumed to be equal to $(1 + \varphi)\bar{r}_i$, $(1 + \varphi)\bar{\delta}_i$, and $(1 + \varphi)\bar{\lambda}_i$, respectively, while keeping the initial desired tumor volume as $x_0 = 0.9$.

Accordingly, in the presence of a given amount of parametric uncertainties (50% uncertainty) introduced by (40), simulation results, including tracking tumor volume reduction, tracking error, drug consumption, for the three cell-kill models are shown in Figs. 11, 12, and 13. The simulation results show that, based on our control objective stated in Section 3 and in the presence of 50% uncertainty, the proposed control can track the desired tumor quickly in comparison to the STC and PI scheme.

In addition, the tracking error of tumor volume under the proposed control design converges to zero quickly in the transient region and can be achieved with high precision in the steady state region compared with other comparative controllers. It should be noted that with 50% uncertainty in the model parameters, the tracking error gets worse in contrast to nominal cases as investigated in Sim 1, 2 and 3. Fortunately, the proposed scheme can attain the smallest tracking error.

Furthermore, to compensate 50%, a remarkable increase in the drug consumption is required compared with Sim 1, 2 and 3, which is better with the proposed controller in Sim 10, 11, and 12. Thus, the proposed controller in Sim 10, 11, and 12 is smoother in terms of chattering control input and robust against the parameters variations compared with the STC and PI controllers.

6.4. The effect of system external disturbances on the control performance of cell-kill models (Case 4)

In this subsection, the effectiveness of the proposed control is examined with the existence of bounded disturbance in all three cancer chemotherapy models to resemble a realistic process of chemotherapy. For the sake of brevity, the robustness against the external disturbance is presented with the initial desired volume of patient tumor $x_0 = 0.9$. In Case 4, the bounded disturbances acting on all three models studied in this work is as $\zeta(t) = 0.01 - 0.01\sin(t)$ for ensuring a robustness performance of the proposed method over those disturbances.

To analyze the influence of the external disturbance, simulation results of the cell-kill models subject to the external disturbance are shown in Fig. 14, 15, and 16 labeled by Sim 13, 14, and 15, respectively. The results show that for all three models, the desired tumor proposed control can be tracked quickly, compared with the STC and PI. This is indicated by the fact that the tracking error of the actual tumor reduction volume under the proposed work is faster to converge to zero with high accuracy. However, the tracking error of the PI control suffers from high deviations around zero, while the STC is affected by the chattering control input of drug usage. Note that, due to the existence of the disturbances, the tracking error of the three models in Sim 13, 14, and 15 is compared to the nominal cases in Sim 1, 2 and 3.

According to the summary of the simulation results, the proposed strategy can offer outstanding clinical benefits as follows:

1. The close and precise tracking performance is accomplished as the desired tumor size rate reduction that oncology clinicians require even in different scenarios of the initial percentage of

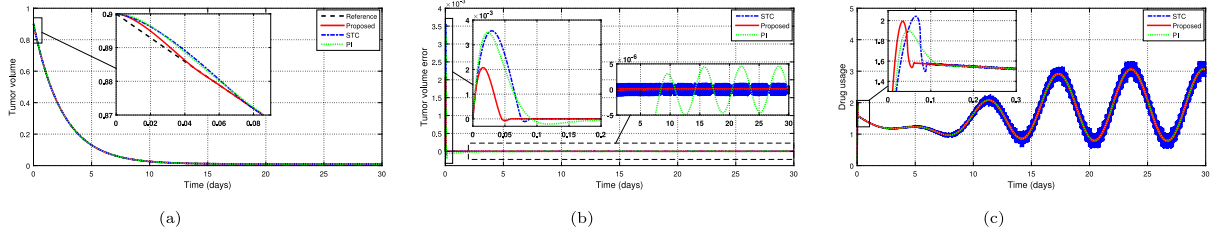


Fig. 13. Tracking responses of $E_{\max}$ hypothesis with initial condition of $x_0 = 0.9$ and system uncertainties (Sim12). (a) Tumor volume. (b) Tumor volume error. (c) Required drug usage.

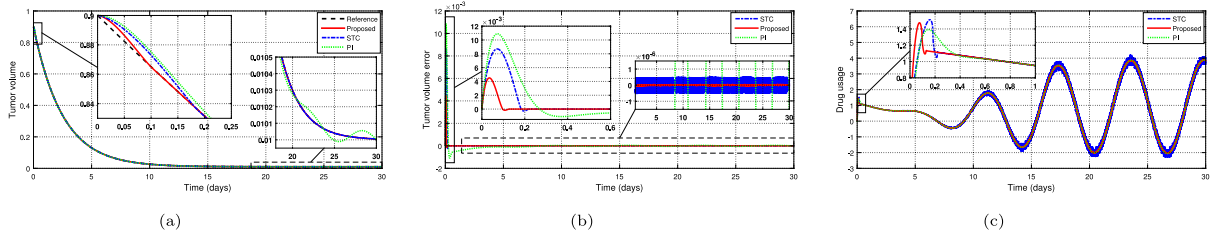


Fig. 14. Tracking responses of log-kill hypothesis with initial condition of $x_0 = 0.9$ and external disturbance (Sim13). (a) Tumor volume. (b) Tumor volume error. (c) Required drug usage.

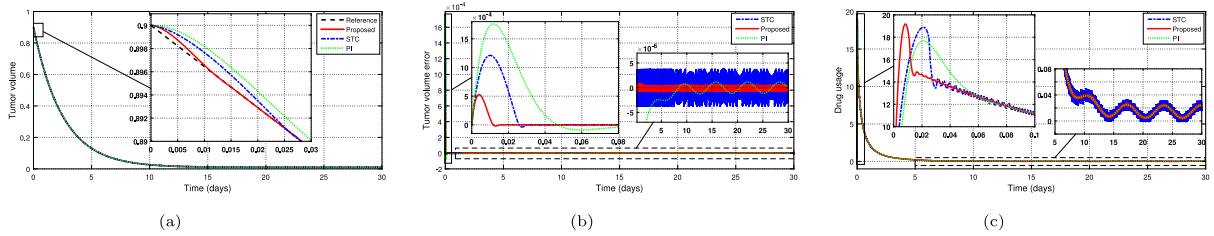


Fig. 15. Tracking responses of Norton-Simon hypothesis with initial condition of $x_0 = 0.9$ and external disturbance (Sim14). (a) Tumor volume. (b) Tumor volume error. (c) Required drug usage.

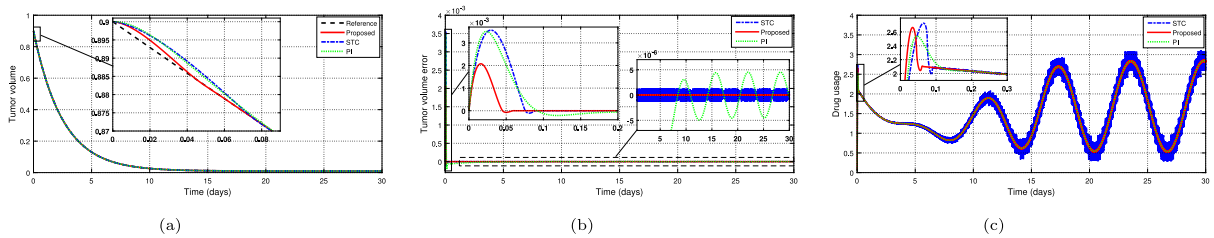


Fig. 16. Tracking responses of $E_{\max}$ hypothesis with initial condition of $x_0 = 0.9$ and external disturbance (Sim15). (a) Tumor volume. (b) Tumor volume error. (c) Required drug usage.

tumor carrying capacity and parametric uncertainties of the three cell-kill models.

- Due to the finite time rate convergence property, the reduction rate of tumor size of patients becomes fast, leading to a short interval period of the chemotherapy treatment to which patients are exposed.
- A lower level of drug delivery is generated by the infusion pump, generally used in chemotherapy treatments, that is actuated by the proposed technique.
- Patient safety under the proposed clinical application of drugs in chemotherapy treatment, is a prime concern for clinicians and doctors, can which can be improved to a large extent due to the continuity of the proposed control that generates smooth actuation of drug delivery. However, the discontinuous actuation of the infusion pump may damage the pump itself and shorten

its life. Furthermore, it will require energy consumption of the power supply used in this electronic pump-based control, which will be another significant challenge.

The main new direction extracted from the current application of the chemotherapy treatment is the patient safety improvement against any pump malfunctions that could generate another side effect on patients.

Remark 7. Generally, the standard super-twisting control abbreviated by the STC is designed according to the fundamental control theory concepts, including finite time convergence and chattering reduction properties. Inspired by these properties, from the existing outcomes of the chemotherapy control applications, the STC algorithm has been

already applied to the cancer chemotherapy models in [6,12] for regulation problems of tumor volume reduction and dose delivery. Thus, we are inspired by these fundamental concepts to design the proposed controller by improving the finite-time convergence rate of tumor size reduction and the chattering suppression of the drug usage injected from the infusion pump. Correspondingly, the primary contribution extracted from this research is to construct a smooth STC (SSTC), in which its working principle is to inject an appropriate and smooth dose by the proposed controller that enforces the initial tumor size of patients from any value to follow the desirable reduction advised by cancer doctors. As a result of the conducted simulative outcomes, the continuity and smoothness of the dose injection can ensure the safety factor for both patients and infusion actuators.

7. Conclusions

In this paper, to effectively treat cancer patients with chemotherapy, a composite model-based smooth super-twisting control (MBSSTC) scheme observer has been newly designed for the three cell-kill models under the parametric system uncertainties and external disturbances. This paper concerns the three mathematical models of the cell-kill system based on log-kill, Norton-Simon, and $E_{\max}$ hypotheses. Utilizing the model-based STC controller to form the composite controller, can avoid unsatisfactory transient and steady performance caused by the discontinuous switching function existing in the standard STC. Also, with the proposed controller techniques presented, the variation of initial and steady-state parameters of the desired reduction rate of tumor volume has been adequately addressed. In addition, parametric system uncertainties and unknown external disturbances are well compensated for, compared with the conventional STC and PI. Furthermore, the continuity of chemotherapeutic drugs over time intervals in the existing treatment is guaranteed, definitely guiding cancer physicians and doctors to decide on drug dosage and delivery following a specified duty cycle. Thus, the drug diagnostics in cancer chemotherapy treatment are enhanced by the proposed algorithm. The simulation results have verified that the proposed controller is more effective than the conventional STC and PI.

Our future vision for developing the proposed closed-loop chemotherapy control drug delivery is to overshadow the time delay that may be induced by transmission channels of infusion pump used in the chemotherapy treatment, from toxicity absorption of tumor cells, from wireless communication used in smart drug delivery pump devices, or from other causes. Since this time delay exhibits adverse impacts on any closed control system, the effectiveness of our suggested control chemotherapy system can be limited by these impacts. Furthermore, the optimal time derivation of tuning optimal parameters of the proposed controller will be investigated in the coming work by employing an appropriate optimization technique.

CRediT authorship contribution statement

Kamal Rsetam: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. **Mohammad Al-Rawi:** Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing, Formal analysis. **Zhenwei Cao:** Supervision, Writing – review & editing, Investigation, Methodology. **Abeer Alsadoon:** Investigation, Methodology, Writing – review & editing. **Lulu Wang:** Methodology, Visualization, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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