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RESEARCH ARTICLE

Barrier Function and Terminal Synergetic-Based Controllers for the Chemotherapy of Brain Tumor

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ABSTRACT Lumps formed by abnormal cell growth in the brain constitute brain tumors. Treatments differ depending on the specificity of the tumor and the condition of the patient; surgery, radiation therapy and targeted therapy are suggested for less severe tumors, while for severe tumors; chemotherapy is recommended. The last one, while being suggested and effective also in conjunction with surgery, has side effects that could be fatal. Therefore, it is mandatory to determine the appropriate dosage to obtain the desired effects without affecting healthy and immune cells. In this research work, advanced barrier function-based sliding mode and terminal synergetic-based controllers are designed to determine the amount of chemotherapy to eliminate tumor cells and maintain the right amount of healthy and immune cells. In particular, a barrier-based sliding mode controller is designed for dynamically controlling the chemotherapy drug for the tumor system, whereas the stability and convergence of the system are checked using the Lyapunov theory. The performance of the controller has been verified using MATLAB software based on different control parameters. The controller has remained successful in reducing the tumor cells and maintaining safe number of healthy and immune cells, showing favorable results in terms of steady-state error, over-under shoots, and rate of convergence.

INDEX TERMS Brain tumor, nonlinear control, barrier function based sliding mode control, terminal synergetic control, chemotherapy.

I. INTRODUCTION

Brain tumor has emerged as one of the most fatal diseases in recent times, witnessing a swift proliferation across diverse age groups and affecting both genders indiscriminately. This menacing condition stems from cellular anomalies within the brain, though manifestations outside the skull are also prevalent (when the tumor initiates from the other parts of the brain). However, if the tumor is located inside the skull it poses the most severe threat to human life. Such tumors are categorically divided into benign and malignant types, each with its distinct level of virulence and prognosis. In Fig.1, a comparison between benign and malignant can be observed (MRI scan of benign and malignant tumors). It is observed that a benign tumor is smaller in size with certain boundaries, while the malignant one is larger with irregular boundaries.

Across the world, many people suffer from brain tumor every year. In United States, around 1 million people were living with brain tumors in 2023, [1]. In addition to this, 94390 Americans are expected to be diagnosed with primary brain tumor this year. Further, around 18200 people lost their lives in 2022 as the survival rate for patients with malignant tumor is 35.7%, [1]. Certainly, these stats are one of the major reasons behind the motivation for this study.

The therapeutic approach to brain tumor treatment is fundamentally influenced by various factors including the tumor's dimensions, its anatomical location, the histological type, as well as patient's age, his prior medical records, the inception timing of tumor growth, proliferation rate, recurrence, and the patient's resilience to treatment modalities. In cases of low-grade malignancies, a multi-modality treatment strategy involving surgical resection, radiation therapy, and chemotherapy is typically employed, [1], [2]. On the contrary, high-grade malignancies are predominantly

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managed through more intensive chemotherapy regimens or participation in clinical trials. Chemotherapy stands as the preferred and efficacious option in the overarching treatment paradigm for brain tumors. In instances, marked by diagnostic uncertainties or concerns regarding tumor recurrence, chemotherapy substantiates itself as a versatile and practical therapeutic approach. Recent years have shown visible research to tackle this problem. In [3], the first mathematical tumor model is proposed by De Pillis, discussing the evolution of immune cells, along with the normal and tumor cells competing for available resources; optimal drug administration therapy suggested a bang-bang control. Later, improvements are proposed in [4], by El-Gohary that incorporated amount of drug as the fourth state. Then in [5], the Pontryagin principle in applied aiming at reaching the equilibrium point for the state variable, penalizing large amount of drug. Recently, the nonlinear sliding mode control and back-stepping control have been introduced for the nonlinear control of tumor, and Lyapunov stability theory has been used to prove the asymptotic stability of the system, [6], [7], [8]. Further, some recent works on chemotherapy treatment and control strategy are proposed in [9], [10], [11], [12], and [13]. The compromise that must be pursued by strategies to deal with a tumor is the reduction or elimination of tumor cells while preserving healthy cells, and simultaneously avoiding the often devastating effects of therapies. This applies to all types of tumors, as in [14] for the breast cancer. Another general characteristic of control strategies applied to cancer is the importance of combination of different strategies, such as chemotherapy and surgery or immuno-chemotherapy with gene therapy, [12], or virotherapy with chemotherapy, [11]. Furthermore, optimal chemotherapy in cancer treatment using state dependent Riccati equation control and extended Kalman filter, and optimal administration strategy in chemotherapy regimens using multi-drug cell-cycle specific tumor growth models have been explained in [15] and [16], respectively.

In this research, the treatment of severe brain tumors using the barrier function based sliding mode control (BF-SMC), [18], and terminal synergetic-based control (TSC), [20], through chemotherapy are analyzed. The aim of this research is to minimize the number of tumor cells, preserve a suitable number of immune and healthy cells and use secure drug doses at the tumor site. For this purpose, four states single input brain tumor system is used, [6], [7], [8]. The stability of both the controllers is analyzed by using Lyapunov theory, while the simulations have been performed using the MATLAB software. The obtained results have been studied on the basis of steady-state error, rate of convergence and overshoots-undershoots.

It is the first time that a barrier function-based nonlinear controller is being designed for the chemotherapy treatment of brain tumor. Due to the ability of overcoming the complexity of the system, the barrier function based controller for brain tumor system will become more practicable and

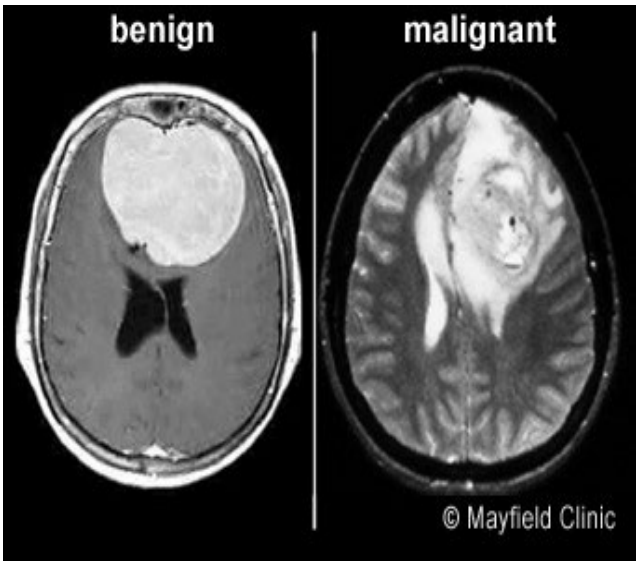


FIGURE 1. Comparison between benign and malignant tumors source: mayfield clinic, [2].

efficient. The BF-SMC would help in analyzing the response of the tumor system in efficient way because of its simple technique, lower computational cost, practical success and desired uniformity. The barrier function controller has been designed using the tumor model in the form of state space; it has been designed to control the drug dosage given to the tumor site. The study of the system is analyzed using the Lyapunov theory; the design parameters of BF-SMC can remove the uncertainties in the model. The BF-SMC ensures convergence, and also utilizes some rules to overcome any changes in the system values with time, [17]. Another feature of BF-SMC is a significant improvement of the robustness in the complex tumor system. SMC is particularly suited for systems with high degrees of uncertainty and nonlinearity, such as those encountered in modeling tumor growth and chemotherapy dynamics. In brain tumor case, the uncertainties stem from variations in patient-specific physiological parameters, such as tumor growth rate, drug clearance rates, and immune response effectiveness. Additionally, the inherent variability in chemotherapy delivery and biological responses introduces external disturbances into the system.

For the comparison purpose, another nonlinear controller TSC has been designed. Due to the fact that TSC can dynamically adjust its parameters in real-time, ensuring stable and efficient operation despite the nonlinear nature of tumor system. Furthermore, robustness analysis and simulation-based testing are crucial to validate the controller's performance and to fine-tune its parameters for desired results. By integrating sophisticated modeling techniques with advanced control strategies, TSC can effectively tackle the challenges posed by nonlinear systems, offering robust and reliable control in diverse medical applications, as the proposed one. Additionally, TSC supports comprehensive connectivity

options, enabling seamless integration with various medical equipment and systems.

The significance of utilizing the Lyapunov theory in the design and analysis of both the BF-SMC and TSC for brain tumor chemotherapy control helps in: 1. Ensuring Stability: Lyapunov theory is a powerful tool in control theory for ensuring system stability. When applied to brain tumor chemotherapy control, it helps to design control laws that ensure the drug administration system remains stable, meaning that the tumor size and other related physiological parameters remain within safe and desired bounds over time. 2. Predicting System Behavior: Lyapunov functions provide a way to predict the long-term behavior of the chemotherapy control system. By proving that a Lyapunov function decreases over time, one can show that the system will eventually converge to a desired equilibrium state, such as a stable, reduced tumor size. 3. Robustness to Disturbances: Chemotherapy treatment can be influenced by numerous uncertainties and external disturbances, such as patient-specific reactions to drugs or measurement noise. Lyapunov theory helps in designing robust control laws that can handle these uncertainties, ensuring that the system remains stable despite the presence of such disturbances. 4. Nonlinear System Analysis: Brain tumor dynamics and the effects of chemotherapy drugs are inherently nonlinear. Lyapunov theory is particularly effective in dealing with nonlinear systems. It allows the formulation of stability criteria and the design of nonlinear control laws that are tailored to the complex dynamics of tumor growth and drug interactions.

Over the years, the problem of controlling the rate of the drug at the tumor site during chemotherapy has been considered a rigorous task. Previously, the optimal and nonlinear controllers have been designed to regulate the drug in the brain tumor system with fixed values of the parameters. Now, if the parameters in the tumor system change with time, the overall dynamics of the tumor system would react differently, and the conventional controllers would be unable to act accordingly. To cater this issue, a state-of-the-art barrier function-based controller has been designed in this work.

This paper is organized as follows: the adopted nonlinear model of brain tumor is given in section II. The procedure for designing the barrier function-based and terminal synergetic-based controllers has been given in section III-A and section III-B respectively. Simulation results are shown and discussed in section IV, while the conclusion and future work are outlined in section V.

II. NONLINEAR BRAIN TUMOR MODEL

The mathematical model adopted in this paper, [4], is described as follows:

$$\frac{dT(t)}{dt} = T(t)[r_1(1 - b_1T(t)) - c_2I(t) - c_3H(t) - a_1(1 - e^{-D(t)})] \tag{1a}$$

$$\frac{dH(t)}{dt} = H(t)[r_2(1 - b_2H(t)) - c_4T(t) - a_2(1 - e^{-D(t)})] \tag{1b}$$

$$\frac{dI(t)}{dt} = s + I(t)\left[\frac{r_3T(t)}{\alpha + T(t)} - c_1T(t) - d_1 - a_3(1 - e^{-D(t)})\right] \tag{1c}$$

$$\frac{dD(t)}{dt} = v(t) - d_2D(t) \tag{1d}$$

where:

- T: Number of tumor cells
- H: Number of healthy cells
- I: Number of immune cells
- D: Amount of drug
- s: Immune cells influx rate
- d_1: Cells natural death rate
- d_2: Consumption rate of the drug
- r_1: Tumor cells growth rate
- r_2: Healthy cells growth rate
- b_1: Tumor cells replication rate
- b_2: Healthy cells replication rate
- $a_1, a_2, a_3, c_1, c_2, c_3, c_4$: control coefficients
- $v(t)$: Input (drug dose)

This nonlinear brain tumor model describes the interactions between tumor cells, healthy cells, immune cells, and the administered drug. Tumor growth is influenced by its intrinsic growth rate, limited by the carrying capacity of the environment, and suppressed by the effects of immune cells, healthy cells, and chemotherapy drugs. Healthy cell dynamics depend on their growth and carrying capacity, with negative effects from tumor cells and drug toxicity. The immune system's activity is driven by a basal influx of immune cells and their interaction with the tumor, balanced by tumor-induced suppression, natural decay, and the potential inhibitory effects of drugs. The drug concentration in the system increases with administration and decreases due to natural decay over time. This model captures the complex interplay between these components, offering insights into how control strategies like chemotherapy can balance tumor suppression, immune response, and healthy tissue preservation.

This model employs logistic growth laws to represent both tumor and host cells i.e. healthy and immune cells. Immune cells interact with tumors kinetically. In addition, the immune response alone is insufficient to counteract the rapid growth of the tumor. So, drug therapies are used to minimize final tumor cell counts. It is plausible that chemotherapy enhances the ability of immune cells characterized by a constant influx rate (s). In the absence of tumors, these immune cells undergo per capita mortality at a rate of d_1.

The model presented here can mathematically be used to represent brain cancer (as a generalized model), including malignant brain cancer. The main reason behind the focus of this study on malignant brain cancer is the fact that malignant brain cancer poses unique challenges, such as high heterogeneity of tumor growth and the blood-brain barrier, which necessitate tailored therapeutic strategies.

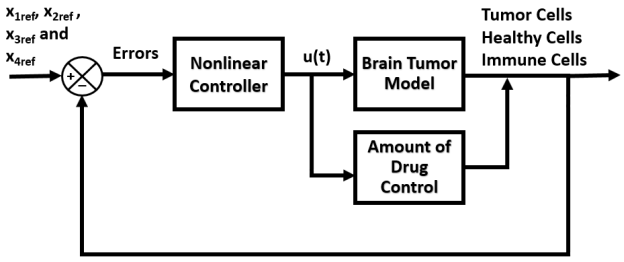


FIGURE 2. Diagram of the proposed approach.

El Gohary [4], reduced the original model of twelve parameters to eight, defining $w_1 = b_1T$, $w_2 = b_2H$, $w_3 = d_2I/s$ and $w_4 = D$. Therefore, the model (1a)-(1d) could be rewritten as follows:

$$\dot{w}_1 = w_1\{k_1(1 - w_1) - n_2w_3 - n_3w_2 - m_1(1 - e^{-w_4})\} \tag{2a}$$

$$\dot{w}_2 = w_2\{k_2(1 - w_2) - n_4w_1 - m_2(1 - e^{-w_4})\} \tag{2b}$$

$$\dot{w}_3 = 1 + w_3\left\{\frac{k_3w_1}{v_1 + w_1} - n_1w_1 - v_2 - m_3(1 - e^{-w_4})\right\} \tag{2c}$$

$$\dot{w}_4 = u - w_4 \tag{2d}$$

where:

- n_1, n_2, n_3, n_4 are positive real constants;
- m_1, m_2, m_3 are the system response coefficients of respective cells i.e. x_1, x_2, x_3;
- k_1, k_2, k_3 represent replication rates x_1, x_2, x_3

The term (1-e^{-w_4}) relates to injected amount of drug, while u represents input control.

III. CONTROLLER DESIGN

In this section, the model given by the system of eqs. (2a)-(2d) has been considered, and barrier function-based sliding mode, [6], [17], [18], [24], [25], [26] and terminal synergetic-based, [20], [21] controllers for the chemotherapy treatment of brain tumor have been designed. The objective is to reduce tumor cells while retaining as many healthy cells as possible within safe limits, [27], [28]. Further, for the sake of simplicity, the diagram of proposed approach is illustrated in Fig. 2.

This figure represents a control system designed for managing brain tumor treatment. Here's a breakdown of the components and their interactions:

Reference Values: These are mentioned on the left top corner of figure. They are the desired levels for tumor cells, healthy cells, immune cells, and amount of drug. Error Calculation: The reference values are compared with actual values, and the differences (errors) are fed into the nonlinear controller. Nonlinear Controller: This controller processes the errors and generates a control signal $u(t)$. Brain Tumor Model: The control signal $u(t)$ is applied to a model representing the dynamics of tumor cells, healthy cells, and immune cells. Amount of Drug Control: The controller also determines the appropriate amount of drug to administer, influencing the tumor model. Feedback Loop: The model's output, indicating the current state of tumor, healthy, and immune cells, is fed back into the system to adjust the control actions continuously.

The objective of the barrier control design for a tumor system is to develop a robust control strategy that ensures the tumor cell population remains within safe and therapeutically acceptable limits while minimizing adverse effects on healthy cells. This involves the following key components: 1. Safe Limits for Tumor System:

o Tumor Cell Population (T): The tumor cell population must be maintained below a maximum threshold T_{max} to prevent harmful proliferation.

o Healthy Cell Population (H): The healthy cell population must remain above a minimum threshold H_{min} to ensure normal physiological function.

o Immune Cell Population (I): The immune cell population must remain above a minimum threshold I_{min} to ensure normal physiological function.

2. Control Input Constraints:

o The control inputs, which may include drug dosage u must operate within specified safety margins to avoid toxicity and side effects.

3. Dynamic Constraints for Tumor System:

o The tumor growth dynamics, represented by the differential equations governing the tumor cells T, healthy cells H, and Immune cells I populations, must be considered. These dynamics include interactions such as proliferation rates, death rates, and the effects of control inputs in the tumor system.

A. BARRIER-BASED SLIDING MODE CONTROL

Standard SMC focuses on driving system states to a predefined sliding surface and maintaining them there, providing robustness against uncertainties. Barrier-based SMC extends standard SMC by incorporating barrier functions to enforce state constraints, ensuring the system states remain within safe limits while achieving the control objectives. For the BF-SMC, the definition of the errors for all the states in the tumor system is required. Here, w_i is representing the current state while w_{iref}, i=1,2...4 is representing the corresponding desired reference; more precisely:

$$e_1 = w_1 - w_{1ref} \tag{3}$$

where e_1 shows the gap between the tumor cells and reference w_{1ref},

$$e_2 = w_2 - w_{2ref} \tag{4}$$

where e_2 is the gap between the healthy cells and the desired reference w_{2ref},

$$e_3 = w_3 - w_{3ref} \tag{5}$$

where e_3 defines the gap between the immune cells and the desired reference w_{3ref} and,

$$e_4 = w_4 - w_{4ref} \tag{6}$$

where e_4 is the gap between the amount of drug and its desired reference w_{4ref}. As the reference values are chosen on the basis of requirement of system. In case this, have taken into account the behavior of each state of tumor system given in the literature (for instance, the healthy and immune cells are taken considering the minimum value achieved by the controller designed previously).

Now, choosing a sliding surface that uses the eqs. (3)-(6) as:

$$\Phi = g_1 e_1 + g_2 e_2 + g_3 e_3 + g_4 e_4 \tag{7}$$

the derivative of eq.(7) is given as:

$$\dot{\Phi} = g_1 \dot{e_1} + g_2 \dot{e_2} + g_3 \dot{e_3} + g_4 \dot{e_4} \tag{8}$$

The values of the derivatives of errors are:

$$\dot{e}_1 = \dot{w}_1 - \dot{w}_{1ref} \tag{9a}$$
$$\dot{e}_2 = \dot{w}_2 - \dot{w}_{2ref} \tag{9b}$$
$$\dot{e}_3 = \dot{w}_3 - \dot{w}_{3ref} \tag{9c}$$
$$\dot{e}_4 = \dot{w}_4 - \dot{w}_{4ref} \tag{9d}$$

In order to make $\dot{\Phi}$ negative definite [18], it is chosen:

$$\dot{\Phi} = -k|\Phi|^{0.5} sign(\frac{\Phi}{0.5}) \tag{10}$$

where k is a number greater than zero and:

$$sign(x) = \frac{|x|}{x} \tag{11}$$

is the signum function.

Theorem 1: Consider the system (2a-2d) and the sliding surface (7) under the assumptions given in Section III-A. The following Barrier Function-based Sliding Mode Control (BF-SMC) controller is proposed:

$$\begin{aligned} u(t) = {} & \frac{-k}{g_4}|\Phi|^{0.5} sign(\frac{\Phi}{0.5}) - \frac{g_1}{g_4}[w_1\{k_1(1-w_1) - n_2 w_3 \\ & - n_3 w_2 - m_1(1-e^{-w_4})\} - \dot{w}_{1ref}] \\ & - \frac{g_2}{g_4}[w_2\{k_2(1-w_2) \\ & - n_4 w_1 - m_2(1-e^{-w_4})\} - \dot{w}_{2ref}] \\ & - \frac{g_3}{g_4}[1 + w_3\{\frac{k_3 w_1}{v_1 + w_1} - n_1 w_1 \\ & - v_2 - m_3(1-e^{-w_4})\} - \dot{w}_{3ref}] + w_4 + \dot{w}_{4ref} \end{aligned} \tag{12}$$

Under this controller, the system stabilizes asymptotically, achieving the design goal. Specifically, if condition (10) holds, the proposed control law guarantees stability. Furthermore, when an external disturbance $d(t)$ is present, robustness is ensured as long as $c_1 d(t) \leq k|\phi|^{\alpha}$ is satisfied, thus ensuring the system's performance remains unaffected by the disturbance.

Proof: To verify the stability of the proposed controller, consider the following Lyapunov function [17]:

$$V = \frac{1}{2}\Phi^2 \tag{13}$$

This function describes the energy of the system, and its time derivative provides insight into the system's stability. Taking the derivative of V:

$$\dot{V} = \Phi\dot{\Phi} \tag{14}$$

Substituting the control law from eq. (10) into the derivative, we get:

$$\dot{V} = -k|\Phi|^{1.5} \tag{15}$$

This expression shows that $\dot{V}$ is negative definite, implying that the Lyapunov function is decreasing over time, which guarantees the system's asymptotic stability. This means that the states of the system will converge to the desired equilibrium point as time progresses.

Moreover, the introduction of barrier functions in the BF-SMC framework inherently ensures that system constraints are respected, providing an added layer of safety. These functions prevent state variables from exceeding predefined limits, thus maintaining constraint satisfaction during system operation, as detailed in [18].

Finally, by substituting the values of $\dot{w}_1$, $\dot{w}_2$, $\dot{w}_3$, and $\dot{w}_4$ from equations (2a-2d) into equation (8), and solving the resulting equations for the control input $u(t)$, we obtain the control law proposed. This control input achieves both stability and robustness against external disturbances, ensuring that the overall design objective is met. Furthermore, the asymptotic stability and robustness of the system are guaranteed by Lyapunov's stability theory, as proven above.

B. TERMINAL SYNERGETIC CONTROLLER DESIGN

For using the synergetic control method, it is required to introduce macro-variables. The selection of macro-variables depends on the number of inputs. As the tumor system has single input so selecting, say σ, as micro-variable. This macro-variable contains the tracking error for all the states [22], and it is defined as follows:

$$\begin{aligned} \sigma = {} & C_1(w_1 - w_{1ref}) + C_2(w_2 - w_{2ref}) + C_3(w_3 - w_{3ref}) \\ & + C_4(w_4 - w_{4ref}) \end{aligned} \tag{16}$$

where, as set in the previous sub-section, w_{1ref}, w_{2ref}, w_{3ref} and w_{4ref} are the reference values for tumor cells, healthy cells, immune cells and amount of drug respectively.

To track all the states to their desired reference values, the following dynamic equation is used:

$$T\dot{\sigma} + \sigma = 0 \tag{17}$$

where, $T > 0$ defines the convergence rate of states to $\sigma = 0$.

Taking time derivative of σ from eq.(16), it results:

$$\begin{aligned} \dot{\sigma} = {} & C_1(\dot{w}_1 - \dot{w}_{1ref}) + C_2(\dot{w}_2 - \dot{w}_{2ref}) + C_3(\dot{w}_3 - \dot{w}_{3ref}) \\ & + C_4(\dot{w}_4 - \dot{w}_{4ref}) \end{aligned} \tag{18}$$

Being the references w_{1ref}, w_{2ref}, w_{3ref} and w_{4ref} constant, their derivatives are zero; therefore, by using equations (2a)-(2d) in (18), it is obtained:

$$\begin{aligned}\dot{\sigma} &= C_1[w_1\{k_1(1-w_1) - n_2w_3 - n_3w_2 - m_1(1-e^{-w_4})\}] \\ &+ C_2[w_2\{k_2(1-w_2) - n_4w_1 - m_2(1-e^{-w_4})\}] \\ &+ C_3\left[1+w_3\left\{\frac{k_3w_1}{v_1+w_1} - n_1w_1 - v_2 - m_3(1-e^{-w_4})\right\}\right] \\ &+ C_4(u-w_4) \end{aligned} \tag{19}$$

By putting the value of σ and $\dot{\sigma}$ of equations (16) and eq.(19) respectively into (17) and rearranging the resultant equation for $u(t)$, it is obtained:

$$\begin{aligned} &u(t) \\ &= w_4 - \frac{1}{C_4}[C_1[w_1\{k_1(1-w_1) - n_2w_3 - n_3w_2 \\ &- m_1(1-e^{-w_4})\}] + C_2[w_2\{k_2(1-w_2) \\ &- n_4w_1 - m_2\$1 - e^{-w_4})\}] \\ &+ C_3\left[1 + w_3\left\{\frac{k_3w_1}{v_1+w_1} - n_1w_1 - v_2 - m_3(1-e^{-w_4})\right\}\right] \\ &- \frac{C_1(w_1 - w_{1ref})}{C_4T} - \frac{C_2(w_2 - w_{2ref})}{C_4T} \\ &- \frac{C_1(w_3 - w_{3ref})}{C_4T} \\ &- \frac{(w_4 - w_{4ref})}{T} \end{aligned} \tag{20}$$

which is the desired control law for chemotherapy treatment of brain tumor using synergetic control technique.

Now to check the asymptotic stability of the controller, consider a Lyapunov candidate function as follows:

$$V = \frac{1}{2}\sigma^2 \tag{21}$$

The derivative of V w.r.t. time yields:

$$\dot{V} = \dot{\sigma}\sigma \tag{22}$$

Now putting value of $\dot{\sigma}$ from eq.(17) in eq.(22), it is obtained:

$$\dot{V} = -\frac{\sigma^2}{T} \tag{23}$$

Since $\dot{V}$ is negative definite, the system is asymptotically stable by using Lyapunov stability theory. Moreover, from eq.(21):

$$\dot{V} = -\frac{2V}{T} \tag{24}$$

that is:

$$V(t) = V_0 e^{\frac{-2t}{T}} \tag{25}$$

where V_0 is the value of Lyapunov candidate function V when time $t = 0$. When $t \to \infty$, $V(t) \to 0$ then $\sigma \to 0$, which proves the exponential stability of the system. Further, for the purpose of convergence analysis it can be observed that the Lyapunov function taken, has been proved negative definite, so the states of the system would converge as the time progresses.

Now, moving towards TSC. It integrates principles from synergetic control and terminal control methodologies to guide systems towards desired final states while maintaining robust performance. It is a sophisticated control strategy designed to achieve specified performance objectives for complex dynamical systems. Further, TSC dynamically adjust its parameters by: Control Adjustment: It applies adaptive control algorithm to adjust tumor treatment parameters based on the estimated state and predefined objectives. Monitoring and Feedback: Continuously monitor the tumor system's response to treatment, updating control parameters as necessary. Robustness Check: Regularly evaluate stability using Lyapunov function and adjust control to handle disturbances and uncertainties.

Alongwith the exponential convergence of the system states, it has an additional advantage of finite time convergence [20]. The states of the system given by equations (1a)-(1d) would be driven to the specified manifold in finite time. The constraint on the manifold is defined as:

$$T\dot{\sigma_1}^{\frac{p}{q}} + \sigma_1 = 0 \tag{26}$$

where p and q are the positive odd real numbers satisfying the condition $1 < \frac{p}{q} < 2$ [20]. Note that σ_1 is the similar manifold or surface as taken in equation (16). Now, solving for the value of $\dot{\sigma_1}$ from equation (26), it results:

$$\dot{\sigma_1} = -(\frac{\sigma_1}{T})^{\frac{q}{p}} \tag{27}$$

Finally, to get the control input $u(t)$, using the choice of macro-variable as in equation (16) and by comparing the equation (18) and equation (27), it is obtained:

$$u(t) = 1/C_4[-(\frac{\sigma_1}{T})^{\frac{q}{p}} - C_1\dot{w}_1 - C_2\dot{w}_2 - C_3\dot{w}_3 + C_4w_4] \tag{28}$$

The states of the system model converge to its equilibrium point in finite time with the convergence rate depending upon the parameters p and q with the control law $u(t)$ given by the equation (28. Now to check whether the system is stable, consider a positive definite Lyapunov candidate function as:

$$W = \frac{1}{2}\sigma_1^2 \tag{29}$$

Taking time derivative of W in equation (29) gives:

$$\dot{W} = \sigma_1\dot{\sigma_1} \tag{30}$$

By substituting the value of $\dot{\sigma}$ from equation (27), it is obtained:

$$\dot{W} = \sigma_1(-\frac{\sigma_1}{T})^{\frac{q}{p}} \tag{31}$$

that yields:

$$\begin{aligned} \dot{W} &= (-\frac{1}{T})^{\frac{q}{p}}\sigma_1^{\frac{q+p}{p}} \leq -(\frac{1}{T})^{\frac{q}{p}}2^{\frac{p+q}{2p}}(\frac{1}{2}\sigma_1^2)^{\frac{p+q}{2p}} \\ \dot{W} &\leq -T_1W^{\frac{p+q}{2p}} \end{aligned} \tag{32}$$

where $T_1 = (\frac{1}{T_c})^{\frac{q}{p}} 2^{\frac{p+q}{2p}}$. It can be observed from the equation (32) that $\dot{W}$ is negative semi-definite which ensures that the macro-variable σ_1 converges to zero in finite time.

Lemma 1: Let us consider a positive definite Lyapunov function that satisfies the following inequality [20]:

$$\dot{W}(t) \leq -\beta W^{\Gamma}(t), \forall t \geq t_0, W(t_0) \geq 0 \tag{33}$$

where $\beta \geq 0$ and $0 \leq \Gamma \leq 1$ are constant values. For any t_0, $W(t)$ satisfies the following inequality:

$$W^{1-\Gamma} \leq W^{1-\Gamma}(t_0) - \beta(1-\Gamma)(t-t_0), t_0 < t < t_1 \tag{34}$$

and $W(t) \equiv 0, \forall t \geq t_1$ with the value of t_1 given by:

$$t_1 = t_0 + \frac{W^{1-\Gamma}(t_0)}{\beta(1-\Gamma)} \tag{35}$$

From lemma 1, the time t_1 at which the synergetic manifold σ_1 converges to zero at finite time can be obtained as:

$$t_1 = \frac{W^{(1-\frac{p+q}{2p})}(t_0)}{T_1(1-\frac{p+q}{2p})} \tag{36}$$

Hence, it ensures finite time convergence of system states for the TSC. So, the system is not only locally exponential stable but also finite convergent as well.

IV. SIMULATION RESULTS

The simulation results of BF-SMC and TSC for drug doses are presented. These simulations are performed by Matlab software using the model parameters given in Table 1 obtained from range of values mentioned in [3], [4], and [5]. Moreover, the values of gains for BF-SMC and TSC have been obtained by using hit and trial method, are given in Table 2 and Table 3 respectively. The behaviour of tumor cells, healthy cells, immune cells and the amount of drug is determined, comparing all states on the basis of steady state error, over-under shoot, and rate of convergence. The values g_1,g_2,g_3,and g_4 are the gains for BF-SMC, while C_1,C_2,C_3,and C_4 are the gains for TSC. These are selected as per the desired requirement of system behaviour. For instance, in tumor case it is considered that the gains must be such that the tumor cells should decrease with time, while healthy and immune cells remain above desired limit.

Fig.3 represents the evolution of the number of tumor cells by using BF-SMC and TSC techniques for chemotherapy. The error in figure 3 is decreasing with time, and it is achieving a steady state value after certain time. Further, the error in figure 3 shows the better results comparing it with the past [3], [4], [5]. Also, the convergence rate of tumor cells is faster and the chattering is lower in case of BF-SMC.

The performance of healthy cells has been represented in Fig.4. It shows that they are tracked perfectly and the final value of healthy cells is within the safe limit [4] in case of BF-SMC. The safe limits for healthy and immune cells in a tumor system can be understood within the context of maintaining normal physiological function and an effective immune response while managing the tumor. The limit is generally influenced by the specific dynamics of the tumor-immune interaction, the type of cancer, and treatment protocols. The safe limit for healthy cells in this case is above 0.9×10^6. It can be seen that after few weeks healthy cells are reduced for small intervals in the case of BF-SMC but some steady state error has been noted. In the case of TSC, healthy cells require more time to reach steady state value but ultimately they achieve it. So, BF-SMC outsmarts TSC on the basis of steady state error and rate of convergence of healthy cells. Further, BF-SMC shows negligible overshoots/undershoots as compared to TSC that shows a value around 0.14×10^6. Defining safe limits for a barrier-based method in a tumor system is important to make sure that the system works within the set boundaries and stays away from unsafe conditions. Further, if the system approaches the constraint boundary, it will show an infinite control effort. State constraints have

TABLE 1. Values of parameters.

Parameter	Value of Parameter
$w_1(0)$	$2.5mgL^{-1}s^{-1}$
$w_2(0)$	$0.25mgL^{-1}s^{-1}$
$w_3(0)$	$1.55mgL^{-1}s^{-1}$
$w_4(0)$	$0mgL^{-1}s^{-1}$
n_1	2
n_2	1.3
n_3	0.47
n_4	8
k_1	$30d^{-1}$
k_2	$48d^{-1}$
k_3	$29d^{-1}$
m_1	$9d^{-1}$
m_2	$15d^{-1}$
m_3	$4d^{-1}$
v_1	0.25
v_2	10
u	10

TABLE 2. Values of parameters for barrier function-based sliding mode approach.

Parameter	Value of Parameter
g_1	350
g_2	30
g_3	100
g_4	10
k	1
α	0.95
ϕ	0.5

TABLE 3. Values of parameters for terminal synergetic approach.

Parameter	Value of Parameter
C_1	330
C_2	20
C_3	80
C_4	35
α	0.95
ϕ	0.5

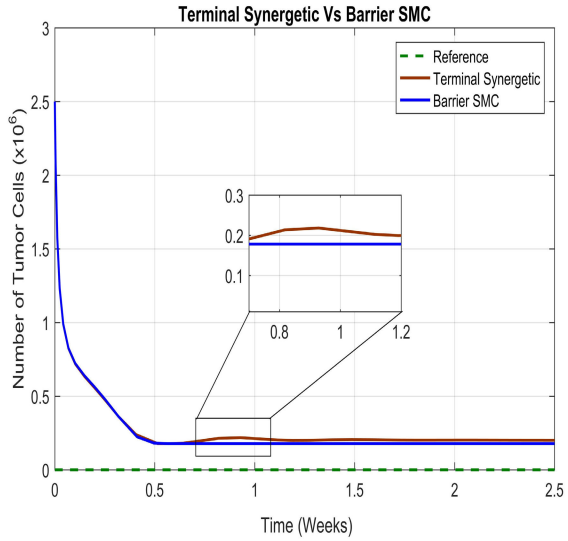


FIGURE 3. Comparison of the number of tumor cells.

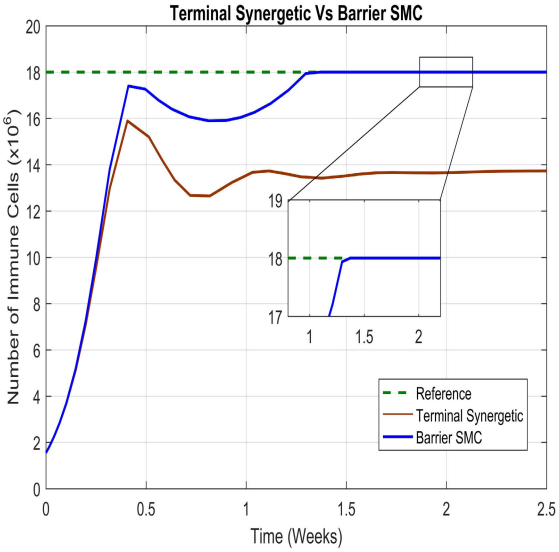


FIGURE 5. Comparison of the number of immune cells when using terminal synergetic and barrier SMC approaches.

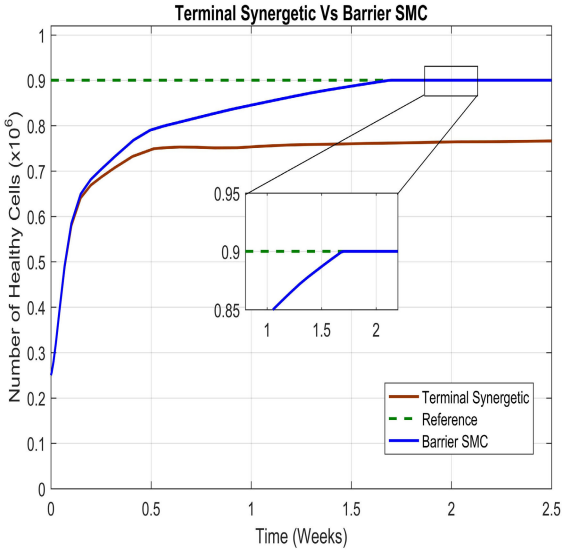


FIGURE 4. Comparison of the number of healthy cells when using terminal synergetic and barrier SMC approaches.

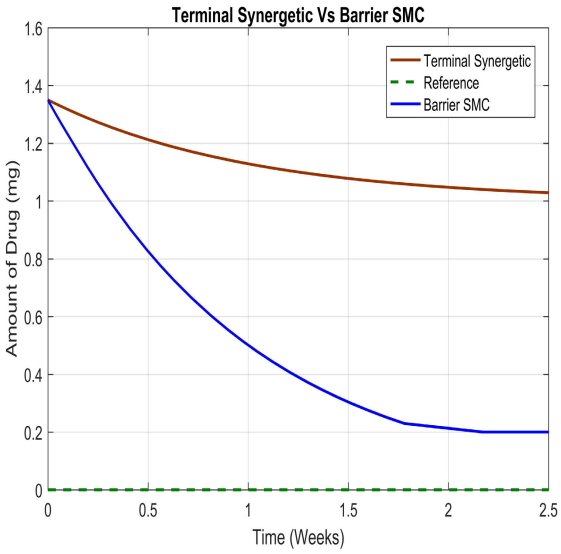


FIGURE 6. Comparison of the required amount of drug when using terminal synergetic and barrier SMC approaches.

been used in the simulations by means of the logarithmic barrier functions.

The Fig. 5 has been drawn to show the comparison of the number of immune cells for the proposed controllers. It shows that BF-SMC perfectly tracks the immune cells to their reference value while TSC takes less time to reach steady state value. Also, from 0.50 weeks onwards, the growth rate of immune cells is far better in case of BF-SMC.

The two approaches are also compared with respect to the total amount of drug by studying the *area under the curve*, Fig. 6; for TSC it is 56.4 whereas for BF-SMC this value is 39.2; due to side effects of chemotherapy it is important to stress that the control effort required decreases as the time progresses, confirming an effective control action by the barrier SMC approach related to the addition of barrier action.

As a first conclusion, it can be summarized that:

- BF-SMC shows better settling time, better rate convergence and least steady state overshoot/undershoot values
- the control input effort required for BF-SMC shows that the control effort required decreases as the time progresses as can be seen in the Fig. 7
- the chattering is reduced

In addition to this, the BF-SMC ensures convergence through the use of a sliding mode control strategy and robust handling of constraints with a barrier function. It is designed to be robust against disturbances and uncertainties

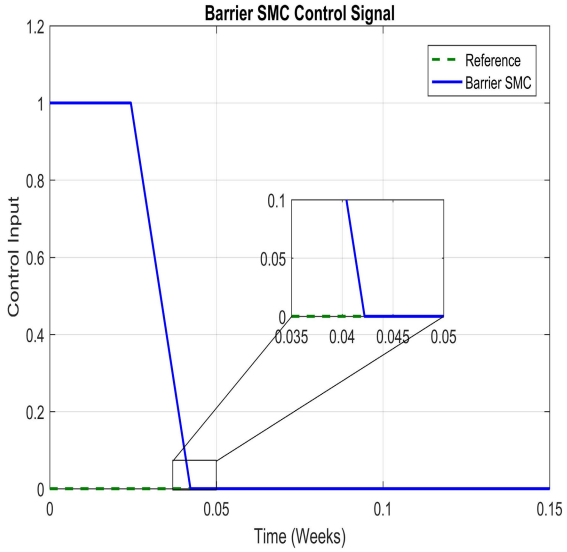


FIGURE 7. Control input of barrier function SMC.

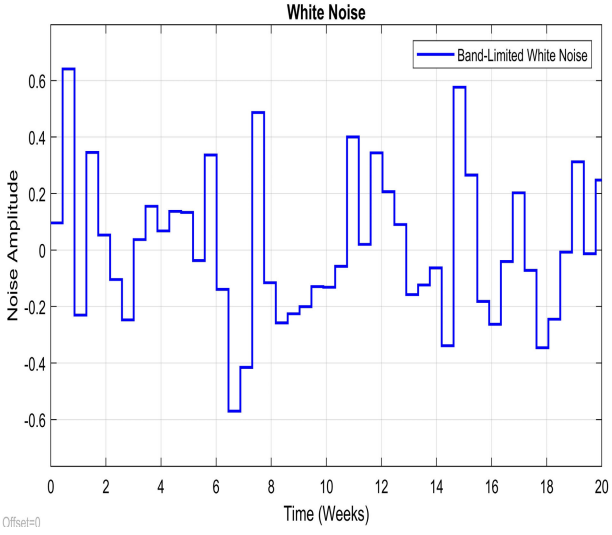


FIGURE 8. White noise.

by maintaining system states on a sliding surface and adapting to constraints. On the other hand, TSC ensures convergence through synergetic control principles focused on achieving terminal performance goals. Its robustness is centered around optimizing control strategies for final outcomes but may not always address intermediate states or disturbances as effectively as BF-SMC.

Also, a quantitative comparison between BF-SMC and TSC on the basis of settling time, steady state error and overshoots/undershoots for healthy cells is given in Table 4. It further confirms the satisfactory performances already observed in the figures.

Further, in the context of tumor dynamics involving tumor, healthy, and immune states, the selection of sampling time can be important to understand the system's behavior. This can be done by considering the biological relevance,

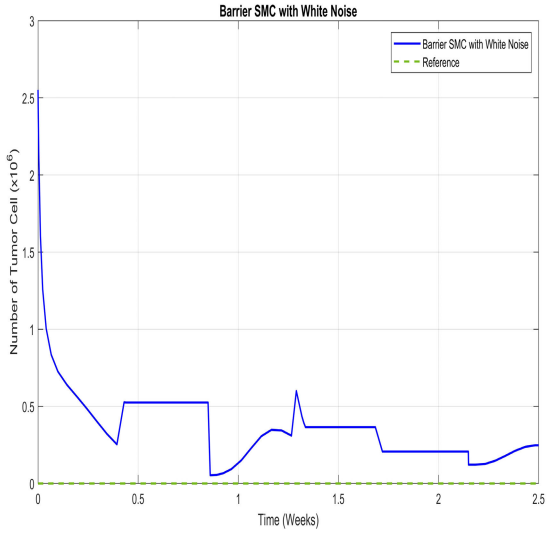


FIGURE 9. Barrier SMC with white noise.

TABLE 4. Performance comparison of BF-SMC and terminal synergetic for healthy cells.

Controller	Settling Time (weeks)	Steady State Error	Overshoots/ Undershoots ($x10^6$)
Barrier Function SMC	1.6 or less	No	0
Terminal Synergetic	2.5 or greater	Yes	0.14

controller performance, and empirical validation. In addition to this, real-time continuous measurement only may not be handful, periodic measurements are feasible and sufficient for practical implementation. The control algorithm can utilize periodic updates instead of relying on continuous state measurements. This approach eliminates the immediate need for an observer. The proposed control framework is designed to handle uncertainties and variations in state measurements. By incorporating periodic measurements of T, H, and I, the controller can still maintain its robustness and effectiveness.

Furthermore, the robustness of the proposed controller has been checked by the addition of band limited white noise in the system. The white noise is illustrated in Fig. 8 with the parametric values power 0.031 dB, and seeding value 23341. The performance of the proposed controller BF-SMC under the addition of white noise is shown in Fig. 9. It has been observed that the BF-SMC is performing well in the presence of such noise, is capable to cope the disturbance due to noise and is tracking its reference without any steady state error.

V. KEY PARAMETERS

This section will underscore the critical role of the principal parameters and their effect on tumor dynamics.

A. INFLUX RATE OF IMMUNE CELLS (S)

- **Role:** s represents the rate at which immune cells infiltrate the tumor microenvironment. A higher influx rate indicates a stronger immune response.

- **Impact:**
  - Increased s enhances the immune system's ability to suppress tumor growth (r_1).
  - However, excessive immune activity may inadvertently affect healthy cells (r_2).
- **Results:** The system demonstrates robustness in maintaining tumor suppression without compromising healthy cell populations, thanks to the sliding mode controller's adaptive nature.

B. GROWTH RATES OF TUMOR AND HEALTHY CELLS (R_1, R_2)

- **Role:**
  - r_1: Reflects tumor aggressiveness.
  - r_2: Represents tissue repair and maintenance capacity.
- **Impact:**
  - Higher r_1 leads to faster tumor growth, challenging the control system.
  - Higher r_2 supports healthy tissue recovery, aiding in maintaining homeostasis.
- **Results:** The controller effectively balances aggressive tumor growth (r_1) and healthy cell preservation (r_2) through dynamic adjustments in chemotherapy dosing.

C. CARRYING CAPACITIES (B_1, B_2)

- **Role:**
  - b_1: Maximum tumor cell population sustainable by the environment.
  - b_2: Maximum healthy cell population sustainable in the tissue.
- **Impact:**
  - Variations in b_1 affect the ultimate tumor load, while changes in b_2 influence healthy cell resilience.
- **Results:** The system maintains stability despite variations in carrying capacities, emphasizing the controller's robustness.

D. INTERACTION COEFFICIENTS (A_1, A_2, A_3)

- **Role:**
  - a_1: Rate of immune cell attack on tumor cells.
  - a_2: Negative impact of tumor cells on healthy cells.
  - a_3: Contribution of healthy cells to tumor cell dynamics.
- **Impact:**
  - Higher a_1 suppresses tumor growth more effectively.
  - Increased a_2 leads to greater healthy cell damage, requiring tighter control.
  - a_3 determines the interaction between healthy and tumor cells.
- **Results:** The sliding mode controller adapts to varied a_1, a_2, and a_3, ensuring effective tumor suppression and healthy cell protection.

E. DRUG EFFECT COEFFICIENTS (C_1, C_2, C_3, C_4)

- **Role:**
  - c_1: Effectiveness of the drug on tumor cells.
  - c_2: Side effects of the drug on healthy cells.
  - c_3: Interaction between the drug and immune cells.
  - c_4: Overall systemic impact of the drug.
- **Impact:**
  - Higher c_1 leads to stronger tumor suppression.
  - Increased c_2 risks damaging healthy cells.
  - Variations in c_3 and c_4 affect immune modulation and systemic stability.
- **Results:** The barrier functions incorporated into the controller mitigate excessive drug-induced toxicity, maintaining therapeutic efficacy and safety.

VI. CONCLUSION

An updated model of brain tumor has been considered and the advanced barrier function-based and terminal synergetic-based nonlinear controllers have been designed to monitor drug dose in the tumor system. The state-of-the-art BF-SMC has been designed to eliminate tumor cells and retain safe number of healthy as well as immune cells. A complete mathematical analysis has been given to prove the stability of the proposed controllers using the Lyapunov theory. Results of the BF-SMC and TSC have been verified by performing MATLAB simulations where it is noticed that BF-SMC controller for tumor system works satisfactorily and outsmarts TSC in terms of the rate of convergence, steady state error and over/under shoots. Hence, for the chemotherapy of given tumor system the BF-SMC is advised.

Future effort can be in following directions; first, an extensive comparison with control methods known in the literature. Second, great effort will be devoted in directly identifying the model on real data referring to specific brain tumor; there will be analysed the influence of different kinds of noise in the model identifying the most realistic representation. It will be possible to compare the therapeutic protocols currently in use with the proposed approach, thus properly tuning the parameters of the barrier function-based sliding mode. In addition to this, cellular-level models can be integrated with tissue-level models to capture the complex interactions within the tumor micro-environment.

REFERENCES

[1] T. Halkin. (2023). *Brain Tumor Facts & Figures, December 2023: In, mortality, and Survival in 2023*. Nat. Brain Tumor Soc. [Online]. Available: https://braintumor.org/brain-tumorinformation/

[2] *Mayfield, Brain and Spine*. [Online]. Available: http://www.mayfieldclinic.com/

[3] L. G. De Pillis and A. Radunskaya, "The dynamics of an optimally controlled tumor model: A case study," *Math. Comput. Model.*, vol. 37, pp. 1221–1244, Jun. 2003, doi: 0.1016/S0895-7177(03)00133-X.

[4] A. El-Gohary, "Chaos and optimal control of equilibrium states of tumor system with drug," *Chaos, Solitons Fractals*, vol. 41, no. 1, pp. 425–435, Jul. 2009, doi: 10.1016/j.chaos.2008.02.003.

[5] S. A. Alavi, J. Norabadi, and M. Arjmand, "Optimal control brain tumor system with drog and its stability," *J. Math. Comput. Sci.*, vol. 4, no. 3, pp. 473–486, Apr. 2012, doi: 10.22436/jmcs.04.03.22.

[6] M. Zubair, I. Ahmad, and Y. Islam, "Backstepping and synergetic controllers for the chemotherapy of brain tumor," *Int. J. Control, Autom. Syst.*, vol. 19, no. 7, pp. 2544–2556, Jul. 2021, doi: 10.1007/s12555-020-0426-5.

[7] M. Zubair, I. Ahmad, Y. Islam, and A. Islam, "Lyapunov based nonlinear controllers for the chemotherapy of brain tumor," *Biomed. Signal Process. Control*, vol. 68, Jul. 2021, Art. no. 102804, doi: 10.1016/j.bspc.2021.102804.

[8] M. Zubair, I. A. Rana, Y. Islam, and S. A. Khan, "Variable structure based control for the chemotherapy of brain tumor," *IEEE Access*, vol. 9, pp. 107333–107346, 2021, doi: 10.1109/ACCESS.2021.3091632.

[9] A. Das, K. Dehingia, H. K. Sarmah, and K. Hosseini, "An optimally controlled chemotherapy treatment for cancer eradication," *Int. J. Model. Simul.*, vol. 44, no. 1, pp. 44–59, Jan. 2024, doi: 10.1080/02286203.2022.2155601.

[10] K. Dehingia, S.-W. Yao, K. Sadri, A. Das, H. K. Sarmah, A. Zeb, and M. Inc, "A study on cancer-obesity-treatment model with quadratic optimal control approach for better outcomes," *Results Phys.*, vol. 42, Nov. 2022, Art. no. 105963, doi: 10.1016/j.rinp.2022.105963.

[11] A. Das, H. K. Sarmah, D. Bhattacharya, K. Dehingia, and K. Hosseini, "Combination of virotherapy and chemotherapy with optimal control for combating cancer," *Math. Comput. Simul.*, vol. 194, pp. 460–488, Apr. 2022, doi: 10.1016/j.matcom.2021.12.004.

[12] K. Dehingia, H. K. Sarmah, K. Hosseini, K. Sadri, S. Salahshour, and C. Park, "An optimal control problem of immuno-chemotherapy in presence of gene therapy," *AIMS Math.*, vol. 6, no. 10, pp. 11530–11549, 2021, doi: 10.3934/math.2021669.

[13] K. Dehingia, Y. Alharbi, and V. Pandey, "A mathematical tumor growth model for exploring saturated response of M2 macrophages," *Healthcare Analytics*, vol. 5, Jun. 2024, Art. no. 100306, doi: 10.1016/j.health.2024.100306.

[14] A. Das, K. Dehingia, E. Hinçal, F. Özköse, and K. Hosseini, "A study on the dynamics of a breast cancer model with discrete-time delay," *Phys. Scripta*, vol. 99, no. 3, Mar. 2024, Art. no. 035235, doi: 10.1088/1402-4896/ad2753.

[15] Y. Batmani and H. Khaloozadeh, "Optimal chemotherapy in cancer treatment: State dependent Riccati equation control and extended Kalman filter," *Optim. Control Appl. Methods*, vol. 34, no. 5, pp. 562–577, Sep. 2013, doi: 10.1002/oca.2039.

[16] P. Qods, J. Arkat, and Y. Batmani, "Optimal administration strategy in chemotherapy regimens using multi-drug cell-cycle specific tumor growth models," *Biomed. Signal Process. Control*, vol. 86, Sep. 2023, Art. no. 105221.

[17] S. Laghrouche, M. Harmouche, Y. Chitour, H. Obeid, and L. M. Fridman, "Barrier function-based adaptive higher order sliding mode controllers," *Automatica*, vol. 123, Jan. 2021, Art. no. 109355, doi: 10.1016/j.automatica.2020.109355.

[18] K. Shao, J. Zheng, R. Tang, X. Li, Z. Man, and B. Liang, "Barrier function based adaptive sliding mode control for uncertain systems with input saturation," *IEEE/ASME Trans. Mechatronics*, vol. 27, no. 6, pp. 4258–4268, Dec. 2022, doi: 10.1109/TMECH.2022.3153670.

[19] Z. Wu, F. Albalawi, Z. Zhang, J. Zhang, H. Durand, and P. D. Christofides, "Control Lyapunov-barrier function-based model predictive control of nonlinear systems," *Automatica*, vol. 109, Nov. 2019, Art. no. 108508, doi: 10.1016/j.automatica.2019.108508.

[20] S. A. Babar, I. A. Rana, I. S. Mughal, and S. A. Khan, "Terminal synergetic and state feedback linearization based controllers for artificial pancreas in type 1 diabetic patients," *IEEE Access*, vol. 9, pp. 28012–28019, 2021, doi: 10.1109/ACCESS.2021.3057365.

[21] A. Hachana and M. N. Harmas, "Terminal synergetic control for blood glucose regulation in diabetes patients," *J. Dyn. Syst., Meas., Control*, vol. 140, no. 10, Oct. 2018, Art. no. 100801, doi: 10.1115/1.4039716.

[22] M. Bilal, I. Ahmad, S. A. Babar, and K. Shahzad, "State feedback and synergetic controllers for tuberculosis in infected population," *IET Syst. Biol.*, vol. 15, no. 3, pp. 83–92, May 2021, doi: 10.1049/syb2.12013.

[23] C. Kunusch, P. F. Puleston, M. A. Mayosky, and J. Riera, "Sliding mode strategy for PEM fuel cells stacks breathing control using a super-twisting algorithm," *IEEE Trans. Control Syst. Technol.*, vol. 17, no. 1, pp. 167–174, Jan. 2009, doi: 10.1109/tcst.2008.922504.

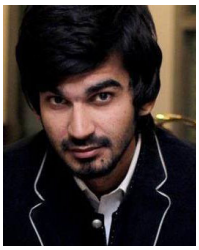
[24] H. Obeid, L. M. Fridman, S. Laghrouche, and M. Harmouche, "Barrier function-based adaptive sliding mode control," *Automatica*, vol. 93, pp. 540–544, Jul. 2018.

[25] V. H. P. Rodrigues, L. Hsu, T. R. Oliveira, and L. Fridman, "Adaptive sliding mode control with guaranteed performance based on monitoring and barrier functions," *Int. J. Adapt. Control Signal Process.*, vol. 36, no. 6, pp. 1252–1271, Jun. 2022, doi: 10.1002/acs.3278.

[26] Z. Liu and H. Pan, "Barrier function-based adaptive sliding mode control for application to vehicle suspensions," *IEEE Trans. Transport. Electrific.*, vol. 7, no. 3, pp. 2023–2033, Sep. 2021, doi: 10.1109/TTE.2020.3043581.

[27] M. Zubair, D. Iacoviello, and Y. Islam, "Adaptive super-twisting SMC and adaptive terminal SMC of brain tumor via chemotherapy," in *Proc. 26th Int. Conf. Syst. Theory, Control Comput. (ICSTCC)*, Oct. 2022, pp. 225–230, doi: 10.1109/ICSTCC55426.2022.9931763.

[28] M. Zubair, D. Iacoviello, and I. S. Mughal, "Fuzzy logic controller for the chemotherapy of brain tumor," in *Proc. 9th Int. Conf. Control, Decis. Inf. Technol. (CoDIT)*, Jul. 2023, pp. 1942–1947, doi: 10.1109/codit58514.2023.10284502.



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