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Variable Structure Based Control for the Chemotherapy of Brain Tumor

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ABSTRACT Brain Tumor is an unwanted mass when cells grow abnormally. It puts pressure on certain areas of the brain which dangerously affects its functioning. For severe tumors like malignant, surgery is not a good option because they do not have definite boundaries and are closely attached with the other healthy tissues of the brain. So chemotherapy is preferable in this case to avoid damaging the healthy cells. The primary intention of this research is to suggest a controller for drug injection so that the tumor cells may reach the desired reference value of zero. In this paper, variable structure based nonlinear control algorithms: sliding mode control, integral sliding mode control, double integral sliding mode control and super-twisting sliding mode controllers have been proposed to reduce the tumor cells, maintain a safe number of healthy cells, keep the immune cells above a certain value and ensure suitable amount of chemotherapy drug. Lyapunov based stability theory has been used to prove stability of SMC, ISMC, DISMC and ST-SMC. MATLAB/Simulink environment has been used to analyze the performance of the proposed controllers on the basis of chattering, rate of convergence, undershoot/overshoot etc. and on the basis of these results drug through most suitable controller is advised. Among the proposed controllers, due to its better convergence, reduced chattering and less amount of drug used, ST-SMC is suggested for the chemotherapy of brain tumor.

INDEX TERMS Brain tumor, sliding mode control (SMC), integral sliding mode control (ISMC), double integral sliding mode control (DISMC), super-twisting sliding mode control (ST-SMC), chemotherapy, cancer.

I. INTRODUCTION

Brain tumor is a life threatening problem. Although there are more than 120 types of brain tumors but they can be categorized into two major types: primary and secondary brain tumors [1]–[3]. Tumor that occurs inside the skull, is termed as primary brain tumor, while in case of a secondary brain tumor, cancer cells spread to brain from other organs, for example, lung or breast, also known as a metastatic brain tumor [1], [4]–[6]. Around the globe, millions of people register with brain tumor every year. Only in United States, some 86,970 people were diagnosed with primary brain tumors in 2019; among them 26,170 people had malignant brain tumors and 60,800 had benign brain tumors [1]. There are various methods for the treatment of brain tumors which include surgery, chemotherapy, radiation therapy etc. [4], [5]. For less severe tumors like Benign, applying surgery is advisable because they are small in size and have well defined boundaries [1]. While in case of severe tumors like Malignant, suggesting surgery is not always a good option because they do not have definite boundaries and are closely attached with sensitive tissues of the brain as clear from the MRI scan shown in Fig.1. So, in case of malignant tumors, it is preferable to go with option of chemotherapy treatment to avoid damaging healthy brain cells. Malignant brain tumors are categorized in low and high grades. The low grade tumors are further classified as grade I and grade II tumors. Grade I tumors, which are not aggressive, can be treated by surgery, radiation therapy or chemotherapy. On the other hand, grade II tumors are treated via chemotherapy or a clinical trial. For high grade tumor, the treatment techniques include chemotherapy, radiation therapy, targeted therapy, tumor treating fields etc. [1], [4], [5].

Chemotherapy has more advantages than disadvantages. Even if a patient is uncertain about initial diagnosis or recurrence, it is more beneficial to go for chemotherapy.

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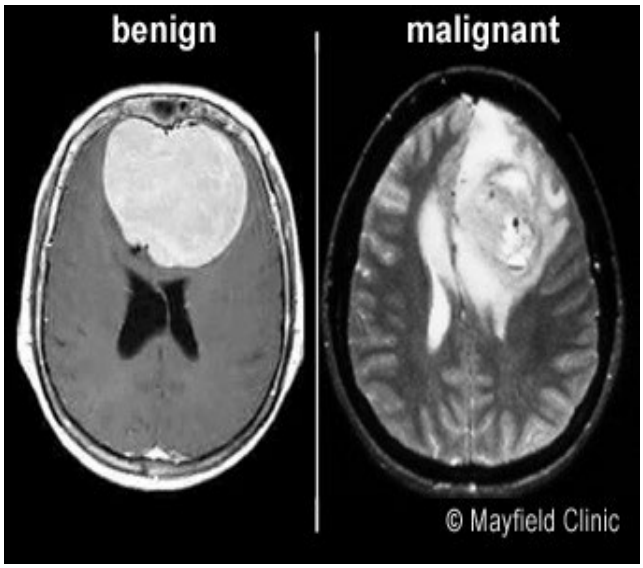

FIGURE 1. Comparison between benign and malignant tumors.

In this research, the main focus is on the treatment of Malignant tumors for which chemotherapy treatment is most suitable [7]. In this case, drugs are used to kill rapidly growing tumor cells. This dosage can be taken either orally or intravenously [4], [5], [8], [9]. The treatment of brain tumor depends upon the age of a patient, his/her overall health, medical history, size, location and type of tumor, rate at which tumor is spreading, chance of its recurrence and how a patient can tolerate certain medication or therapies [4], [5].

The first tumor mathematical model proposed by De Pillis and Radunskaya [10] but it was without interaction of drug as input. Later, El-Gohary modified this model with different parameters for brain tumor [7]. He demonstrated that a mathematical model of brain tumor can be seen as an optimal nonlinear control problem and subsequently specified the drug dosage for the patients having tumor [7]. Updated mathematical model of brain tumor in the form of state space has been proposed in [7] and [11]. It is a single input model with four states; tumor cells, healthy cells, immune cells and the amount of drug. This model under the attack of chemotherapeutic agents is solved by Pontryagin minimum principle and values of tumor cells, healthy cells and immune cells have been obtained by applying optimal dosage of drug [11].

In this paper the main contribution is to design the robust and finite time convergent nonlinear controllers for the control of brain tumor system. This type of robust nonlinear controllers have not been proposed so far in the literature. In the previous work described in [7], [10], [11] the tumor, healthy and immune cells do not achieve zero steady state error. In this paper SMC, the higher order SMC and state of the art super-twisting controllers have been proposed. The SMC is robust to internal or external perturbations/disturbances, can cater for the uncertainties in the system model, ensures parametric invariance, has a very simple implementation and is finite time convergent [12]–[17]. It is a nonlinear controller that attains the behavior of the system along a sliding surface [13], [14]. Besides other strong points as compared to Backstepping, Lyapunov redesign etc, model order reduction is also one of the feature attained in this technique. During sliding mode, problem of chattering arises which is inherent in SMC. It can considerably be reduced by the design of SMCs of greater order which uses the summation of integral in order to mitigate chattering and improve transient characteristics. SMC and higher order SMC have been implemented in the literature on different applications like four quadrant Quasi-Z-source converter, photo-voltaic system, MPPT control of stand-alone photo-voltaic system, blood glucose regulation, biometric grip force and brushless direct current motor speed control etc. [12]–[23]. Experimental verification of nonlinear controllers can also be done for biological systems as in [24], [25]. For the periodic event-triggered-scheme the proposed SMC law ensures the state trajectories to arrive at the sliding surface in a finite time in [26]. While a framework to design the model-based event-triggered SMC law is established in [27]. For delayed Markovian jump repeated scalar nonlinear systems subjected to packet dropouts SMC has been designed in [28]. In case of discrete singular systems subjected to randomly occurring mixed time-delays adaptive robust SMC is formulated in [29]. Recently, fractional sliding mode control for micro gyroscope has been implemented in [30] while fractional-order sliding-mode control with application to active power filter has been designed in [31].

Supertwisting SMC is a higher order controller which has the property to reduce chattering to almost zero [32], [33], an undesirable phenomenon unbearable especially for brain tumor system. ST-SMC also enhances the dynamic response of the system and is computationally less costly as it does not require the derivative of the sliding surface as compared to conventional sliding mode control.

In this paper four nonlinear controllers (SMC, ISMC, DISMC, ST-SMC) have been proposed in order to reduce the number of tumor cells and maintain safe amount of healthy and immune cells through automated injection of suitable amount of drug. These controllers have been designed to track all the states to their desired reference values. The proposed controllers have been compared with each other on the basis of rate of convergence and overshoots/undershoots. The remaining part of this paper has been arranged as follows: the nonlinear model of brain tumor has been described in section II. Sliding mode controller design procedure has been described in section III-B, while integral sliding mode controller in section III-C, double integral sliding mode controller in III-D, and super-twisting sliding mode controller in III-E. Linearization and controllability of tumor system is given in IV. Simulation results have been described in section V and conclusion has been described in section VI.

II. NONLINEAR MODEL OF BRAIN TUMOR

The mathematical model of brain tumor discussed by El-Gohary and De Pillis in [7] and [10] respectively, which incorporates the dynamics of tumor cells, healthy cells, immune cells and amount of drug is described as follows:

$$\frac{dy_1(t)}{dt} = y_1(t)[r_1(1-b_1y_1(t))-c_2y_3(t)-c_3y_2(t)-a_1(1-e^{-y_4(t)})] \tag{1a}$$

$$\frac{dy_2(t)}{dt} = y_2(t)[r_2(1-b_2y_2(t))-c_4y_1(t)-a_2(1-e^{-y_4(t)})] \tag{1b}$$

$$\frac{dy_3(t)}{dt} = s+y_3(t)\left[\frac{r_3y_1(t)}{\alpha+y_1(t)}-c_1y_1(t)-d_1-a_3(1-e^{-y_4(t)})\right] \tag{1c}$$

$$\frac{dy_4(t)}{dt} = v(t)-d_2y_4(t) \tag{1d}$$

where $y_1(t)$, $y_2(t)$, $y_3(t)$ and $y_4(t)$ represent the tumor cells, healthy cells, immune cells and the amount of drug respectively. d_1 and d_2 represent the death rate of the cells in the absence of tumor and death rate of drug respectively, while s represents influx rate of immune cells. r_1 and r_2 represent per capita growth rate of tumor and healthy cells respectively. b_1 and b_2 are the reciprocal carrying capacity of tumor and healthy cells respectively, while $a_1, a_2, a_3, c_1, c_2, c_3, c_4$ are the system response coefficients and $v(t)$ represents the dose of the drug in the tumor system.

El Gohary simplified this model and reduce it from twelve to eight parameters [6], which for $z_1 = T(t)$, $z_2 = H(t)$, $z_3 = I(t)$ and $z_4 = D(t)$ is as follows:

$$\dot{z}_1 = z_1\{k_1(1-z_1) - n_2z_3 - n_3z_2 - m_1(1-e^{-z_4})\} \tag{2a}$$

$$\dot{z}_2 = z_2\{k_2(1-z_2) - n_4z_1 - m_2(1-e^{-z_4})\} \tag{2b}$$

$$\dot{z}_3 = 1 + z_3\{\frac{k_3z_1}{v_1+z_1} - n_1z_1 - v_2 - m_3(1-e^{-z_4})\} \tag{2c}$$

$$\dot{z}_4 = u - z_4 \tag{2d}$$

where,

- n_1, n_2, n_3, n_4: positive real constants
- m_1, m_2, m_3: system response coefficients of respective cells
- k_1, k_2, k_3: per capita growth of respective cells

In this model, the immune cells destroy tumor cells through a kinetic process and the presence of a detectable tumor does not automatically imply that the tumor has completely escaped from active immuno surveillance. Sometimes a tumor is immuno genetic and the immune response cannot fight the tumor alone. The healthy and tumor cells are modelled by a logistic growth law [11]. It can be noted that source of the immune cells is to be outside the system so it would be reasonable to assume that the immune cells have a constant influx rate s [11]. In the absence of any tumor, the cells will die off at a per capita rate of d_1, resulting in long-term population size of s/d_1. This model contains a term (1-e^{-x_4}) which represents amount of drug to be injected. While u is control variable for amount of drug.

III. CONTROLLER DESIGN

In this section, we have considered the model given by the system of eqs. (2a)-(2d) and proposed Sliding Mode, Integral Sliding Mode, Double Integral Sliding Mode and Super-twisting Sliding Mode controllers for the chemotherapy treatment to achieve the objective of reducing chattering while converging to the reference level of tumor cells while retaining as many healthy cells as possible. The higher order SMCs have been opted for further reducing the chattering and the SSE.

A. ASSUMPTIONS

1) Gains of the sliding surface c_1, c_2, c_3, $\cdots$, c_8, c_9, d_1, d_2, d_3 are strictly positive real numbers.
2) Design coefficient k is a strictly positive constant.
3) Design parameters α and ϕ are taken between 0 and 1.
4) Lyapunov candidate function is positive definite.

B. SLIDING MODE CONTROL

In order to track all the states to their reference values, we define the errors as follows:

$$e_1 = z_1 - z_{1ref} \tag{3}$$

where e_1 is the difference between the tumor cells and their desired reference value z_{1ref},

$$e_2 = z_2 - z_{2ref} \tag{4}$$

where e_2 defines the difference between the healthy cells and the desired reference z_{2ref},

$$e_3 = z_3 - z_{3ref} \tag{5}$$

where e_3 defines the difference between the immune cells and the desired reference z_{3ref} and

$$e_4 = z_4 - z_{4ref} \tag{6}$$

where e_4 is the error difference between the amount of drug and its desired reference z_{4ref}.

Now considering a first order sliding surface that incorporates all the tracking errors mentioned in eqs. (3)-(6) as:

$$s_1 = c_1e_1 + c_2e_2 + c_3e_3 + c_4e_4 \tag{7}$$

Taking the derivative of eq.(7) with respect to time:

$$\dot{s_1} = c_1\dot{e_1} + c_2\dot{e_2} + c_3\dot{e_3} + c_4\dot{e_4} \tag{8}$$

Now, the time derivatives of all the errors as follows:

$$\dot{e}_1 = \dot{z}_1 - \dot{z}_{1ref} \tag{9a}$$

$$\dot{e}_2 = \dot{z}_2 - \dot{z}_{2ref} \tag{9b}$$

$$\dot{e}_3 = \dot{z}_3 - \dot{z}_{3ref} \tag{9c}$$

$$\dot{e}_4 = \dot{z}_4 - \dot{z}_{4ref} \tag{9d}$$

By putting values of $\dot{e}_1, \dot{e}_2, \dot{e}_3$ and $\dot{e}_4$ from eq.(9) in eq.(8), we have:

$$\dot{s}_1 = c_1(\dot{z}_1 - \dot{z}_{1ref}) + c_2(\dot{z}_2 - \dot{z}_{2ref}) + c_3(\dot{z}_3 - \dot{z}_{3ref}) + c_4(\dot{z}_4 - \dot{z}_{4ref}) \quad (10)$$

In order to make $\dot{s}_1$ negative definite, put

$$\dot{s_1} = -k|s_1|^{\alpha} sign(\frac{s_1}{\phi}) \quad (11)$$

where k is a design co-efficient and is a positive number, α is any number taken between $0 - 1$ and ϕ is used to reduce chattering and is usually a very small number. $|s|^{\alpha}$ deals with the convergence of system to the sliding surface increases.

Theorem 1: Consider the system (2), the sliding surface (7) under the assumptions given in section III-A, then the designed SMC controller will stabilize the systems asymptotically provided the condition (11) holds. Further, in presence of external disturbance $d(t)$, the designed controller ensures robustness when the condition $c_1\ d(t) \leq k|s_1|^{\alpha}$ holds.

Proof: Considering a Lyapunov candidate function to analyze the asymptotic stability of the system as [23]:

$$V = \frac{1}{2}s_1^2 \quad (12)$$

Taking the derivative of eq.(12) with respect to time, we have

$$\dot{V} = s_1\dot{s}_1 \quad (13)$$

Inserting the value of $\dot{s}_1$ from eq.(11) in eq.(13), we get:

$$\dot{V} = -s_1\ (\ k\ |s_1|^{\alpha}\ sign\ (\ \frac{s_1}{\phi}) \quad (14)$$

or

$$\dot{V} = -\ k\ |s_1|^{\alpha}\phi\frac{s_1}{\phi}\ sign\ (\ \frac{s_1}{\phi}) \quad (15)$$

The simplified value of $sign(x)$ as follows:

$$sign(x) = \frac{|x|}{x} \quad (16)$$

Since $\frac{s_1}{\phi}\ sign\ (\ \frac{s_1}{\phi}) = |\frac{s_1}{\phi}|$, we have

$$\dot{V} = -\ k\ |s_1|^{\alpha}\phi|\frac{s_1}{\phi}| \quad (17)$$

Because $|\phi| = \phi$ for $\phi > 0$, we get:

$$\dot{V} = -\ k\ |s_1|^{\alpha+1} \quad (18)$$

The final simplified value of time derivative of Lyapunov function is mentioned in eq.(18). It is clear that $\dot{V}$ is negative definite. According to Lyapunov stability theory the designed controller is stable, it ensures that the system errors reach zero in finite time, and is stable. Putting the values of $\dot{z}_1, \dot{z}_2, \dot{z}_3$ and $\dot{z}_4$ from eq.(2) in eq.(10), yields:

$$\begin{aligned}\dot{s}_1 =\ & c_1[z_1\{k_1(1-z_1)-n_2z_3-n_3z_2-m_1(1-e^{-z_4})\}-\dot{z}_{1ref}] \\ & +c_2[z_2\{k_2(1-z_2)-n_4z_1-m_2(1-e^{-z_4})\}]-\dot{z}_{2_ref}) \\ & +c_3(1+z_3\{\frac{k_3z_1}{v_1+z_1}-n_1z_1 \\ & -v_2-m_3(1-e^{-z_4})\}-\dot{z}_{3ref})+c_4(u-z_4)\end{aligned} \quad (19)$$

Solving eqs.(11) and (19) for the control input $u(t)$, we get

$$\begin{aligned}u(t) =\ & \frac{-k}{c_4}|s_1|^{\alpha}sign(\frac{s_1}{\phi}) \\ & -\frac{c_1}{c_4}[z_1\{k_1(1-z_1)-n_2z_3-n_3z_2-m_1(1-e^{-z_4})\}-\dot{z}_{1ref}] \\ & -\frac{c_2}{c_4}[z_2\{k_2(1-z_2)-n_4z_1-m_2(1-e^{-z_4})\}-\dot{z}_{2ref}]-\frac{c_3}{c_4} \\ & [1+z_3\{\frac{k_3z_1}{v_1+z_1}-n_1z_1-v_2-m_3(1-e^{-z_4})\}-\dot{z}_{3ref}]+z_4\end{aligned} \quad (20)$$

which is required control input for the chemotherapy treatment of brain tumor using SMC technique.

SMC in case of disturbance/noise can be analyzed by adding disturbance $d(t)$ in the eq.(2a) of the system as follows:

$$\begin{aligned}\dot{z}_{1n} &= z_1\{k_1(1-z_1)-n_2z_3-n_3z_2-m_1(1-e^{-z_4})\}+d(t) \\ &= \dot{z}_1+d(t)\end{aligned} \quad (21)$$

where $\dot{z}_{1n}$ represents the number of tumor cells with disturbance.

Now consider following sliding surface:

$$s_1 = c_1(z_{1n}-z_{1ref})+c_2(z_2-z_{2ref})+c_3(z_3-z_{3ref})+c_4(z_4-z_{4ref}) \quad (22)$$

Taking the time derivative of Lyapunov candidate function as mentioned by eq.(12) and using the value of sliding surface from eq.(22) in eq.(23), we get:

$$\dot{V}_1 = s_1\dot{s}_1 = s_1(c_1(\dot{z}_{1n}-\dot{z}_{1ref})+c_2(\dot{z}_2-\dot{z}_{2ref})+c_3(\dot{z}_3-\dot{z}_{3ref})+c_4(\dot{z}_4-\dot{z}_{4ref})) \quad (23)$$

Now inserting the value of $\dot{z}_4$ from eq.(2a) and $\dot{z}_{1n}$ from eq.(21) in eq.(23) to obtain the updated value of $\dot{V}_1$ as follows:

$$\dot{V}_1 = s_1(c_1(\dot{z}_1-\dot{z}_{1ref})+c_2(\dot{z}_2-\dot{z}_{2ref})+c_3(\dot{z}_3-\dot{z}_{3ref})+c_4(u-x_4-\dot{z}_{4ref})+c_1d(t)) \quad (24)$$

In order to prove the robustness of designed controller against the external disturbance, let the value of u as follows:

$$u = -\frac{c_1}{c_4}(\dot{z}_1-\dot{z}_{1ref})-\frac{c_2}{c_4}(\dot{z}_2-\dot{z}_{2ref})-\frac{c_3}{c_4}(\dot{z}_3-\dot{z}_{3ref})+(z_4+\dot{z}_{4ref})+k|s_1|^{\alpha}sign(\frac{s_1}{\phi}) \quad (25)$$

where k is a known positive gain and α is the same as defined earlier. Now putting the value of u from eq.(25) in eq.(24) to obtain the updated value of $\dot{V}_1$, we get:

$$\dot{V}_1 = s_1(-k|s_1|^{\alpha}sign(\frac{s_1}{\phi})+c_1d(t)) \quad (26)$$

Since $s_1\ sign(\frac{s_1}{\phi}) = |s_1|$, the updated value of $\dot{V}_1$ as given by eq.(26) becomes:

$$\begin{aligned}\dot{V}_1 &= -k|s_1|^{\alpha+1} + c_1 s_1 d(t) \\ &\leq -|s_1|(k|s_1|^{\alpha} - c_1 d(t))\end{aligned} \tag{27}$$

Note that $\dot{V}_1 \leq 0$ if

$$c_1|d(t)| \leq k|s_1|^{\alpha} \tag{28}$$

This proves that the designed controller is robust to external disturbance.

C. INTEGRAL SLIDING MODE CONTROL

In order to reduce chattering, we have to introduce integral actions of the errors in SMC, which for the tracking of tumor cells, healthy cells, immune cells and amount of drug respectively are as follows:

$$\begin{aligned}e_5 &= \int (z_1 - z_{1ref})\, dt \\ e_6 &= \int (z_2 - z_{2ref})\, dt \\ e_7 &= \int (z_3 - z_{3ref})\, dt \\ e_8 &= \int (z_4 - z_{4ref})\, dt\end{aligned} \tag{29}$$

The sliding surface incorporating all the errors for ISMC is taken as follows:

$$s_2 = c_1e_1 + c_2e_2 + c_3e_3 + c_4e_4 + c_5e_5 + c_6e_6 + c_7e_7 + c_8e_8 \tag{30}$$

Now taking the derivative of eq.(30) with respect to time, we have

$$\dot{s_2} = c_1\dot{e}_1 + c_2\dot{e}_2 + c_3\dot{e}_3 + c_4\dot{e}_4 + c_5\dot{e}_5 + c_6\dot{e}_6 + c_7\dot{e}_7 + c_8\dot{e}_8 \tag{31}$$

The time derivatives of e_5, e_6, e_7 and e_8 are calculated using eqs. (3)-(6) as follows:

$$\dot{e}_5 = z_1 - z_{1ref} = e_1 \tag{32a}$$
$$\dot{e}_6 = z_2 - z_{2ref} = e_2 \tag{32b}$$
$$\dot{e}_7 = z_3 - z_{3ref} = e_3 \tag{32c}$$
$$\dot{e}_8 = z_4 - z_{4ref} = e_4 \tag{32d}$$

Inserting values of the time derivative of errors from eq.(9) and eq.(32) in eq.(31), we get:

$$\begin{aligned}\dot{s_2} = {} & c_1(\dot{z}_1 - \dot{z}_{1ref}) + c_2(\dot{z}_2 - \dot{z}_{2ref}) + c_3(\dot{z}_3 - \dot{z}_{3ref}) \\ & + c_4(\dot{z}_4 - \dot{z}_{4ref}) + c_5e_1 + c_6e_2 + c_7e_3 + c_8e_8\end{aligned} \tag{33}$$

Theorem 2: Consider the system (2), the sliding surface (30) under the assumptions given in section III-A, the designed ISMC controller will stabilize the system asymptotically provided condition $\dot{s}_2 = -k|s_2|^{\alpha} sign\frac{s_2}{\phi}$ holds. The designed controller will ensure robustness to external disturbance provided condition (46) holds.

Proof: Now considering a Lyapunov candidate function to analyze the asymptotic stability of the system as follows:

$$V = \frac{1}{2}s_2^2 \tag{34}$$

By taking the derivative of eq.(34) with respect to time, we have:

$$\dot{V} = s_2\dot{s}_2 \tag{35}$$

To ensure $\dot{V}$ to be negative definite, put:

$$\dot{s}_2 = -k|s_2|^{\alpha} sign\frac{s_2}{\phi} \tag{36}$$

We have:

$$\dot{V} = -s_2(k|s_2|^{\alpha} sign(\frac{s_2}{\phi}) \tag{37}$$

or

$$\dot{V} = -\,k\,|s_2|^{\alpha}\phi\frac{s_2}{\phi}\,sign\,(\,\frac{s_2}{\phi}) \tag{38}$$

Since $\frac{s_2}{\phi}\ sign\ (\ \frac{s_2}{\phi}) = |\frac{s_2}{\phi}|$, we get:

$$\dot{V} = -\,k\,|s_2|^{\alpha}\phi|\frac{s_2}{\phi}| \tag{39}$$

or

$$\dot{V} = -\,k\,|s_2|^{\alpha+1} \tag{40}$$

Eq.(40) clearly shows that $\dot{V}$ is negative definite. According to Lyapunov stability theory, the designed controller is stable and ensures that the system errors reach zero in finite time.

Now, comparing eq.(33) and eq.(36), we get:

$$\begin{aligned}& -k|s_2|^{\alpha} sign(\frac{s_2}{\phi}) \\ &= c_1(\dot{z}_1 - \dot{z}_{1ref}) + c_2(\dot{z}_2 - \dot{z}_{2ref}) \\ &\quad + c_3(\dot{z}_3 - \dot{z}_{3ref}) + c_4(u(t) - z_4 - \dot{z}_{4ref}) \\ &\quad + c_5e_1 + c_6e_2 + c_7e_3 + c_8e_4\end{aligned} \tag{41}$$

By putting values of $\dot{z}_1$, $\dot{z}_2$, $\dot{z}_3$ and $\dot{z}_4$ from eq.(2) in eq.(41) and solving it for the value of control function $u(t)$, we have:

$$\begin{aligned}& u(t) \\ &= -\frac{k}{c_4}|s_2|^{\alpha} sign(\frac{s_2}{\phi}) - \frac{c_1}{c_4} \\ &\quad \times[z_1\{k_1(1-z_1) - n_2z_3 - n_3z_2 - m_1(1-e^{-z_4})\} \\ &\quad -\dot{z}_{1ref}] - \frac{c_2}{c_4}[z_2\{k_2(1-z_2) - n_4z_1 - m_2(1-e^{-z_4})\} - \dot{z}_{2ref}] \\ &\quad -\frac{c_3}{c_4}[1 + z_3\{\frac{k_3z_1}{v_1+z_1} - n_1z_1 - v_2 - m_3(1-e^{-z_4})\} - \dot{z}_{3ref}] \\ &\quad +z_4 + \dot{z}_{4ref} - \frac{c_5}{c_4}e_1 - \frac{c_6}{c_4}e_2 \\ &\quad -\frac{c_7}{c_4}e_3 - \frac{c_8}{c_4}e_4\end{aligned} \tag{42}$$

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

ISMC in case of disturbance/noise can be analyzed by adding Gaussian noise $d(t)$ in the eq.(2a) of the system as follows:

$$\dot{x}_{2n} = z_1\{k_1(1-z_1) - n_2 z_3 - n_3 z_2 - m_1(1-e^{-z_4})\} + d(t) \tag{43}$$

where $d(t)$ satisfies the inequality defined in eq.(21).

The sliding surface for ISMC in case of noise is same as defined by eq.(30) while the value of the error can be defined by

$$e_{2n} = z_{2n} - z_{2nref} \tag{44}$$

where, e_{2n}, z_{2n} and z_{2nref} are error for tumor cells with noise, tumors cells with noise and reference of tumor cells with noise respectively. Repeating the same process as done in the start of section III-B for the case of designing the SMC, the value of control input $u(t)$ with disturbance can be calculated as

$$\begin{aligned} u(t) &= -\frac{k}{c_4}|s_2|^{\alpha} sign(\frac{s_2}{\phi}) \\ &-\frac{c_1}{c_4}[z_1\{k_1(1-z_1) - n_2 z_3 - n_3 z_2 - m_1 \\ &\times(1-e^{-z_4})\} - \dot{z}_{1ref}] - \frac{c_2}{c_4} \\ &\times[z_2\{k_2(1-z_2) - n_4 z_1 - m_2(1-e^{-z_4})\} - \dot{z}_{2ref}] \\ &-\frac{c_3}{c_4}[1 + z_3\{\frac{k_3 z_1}{v_1+z_1} - n_1 z_1 - v_2 - m_3(1-e^{-z_4})\} \\ &-\dot{z}_{3ref}] + z_4 + \dot{z}_{4ref} - \frac{c_5}{c_4}e_1 - \frac{c_6}{c_4}e_2 \\ &-\frac{c_7}{c_4}e_3 - \frac{c_8}{c_4}e_4 - \frac{c_1}{c_4}d(t) \end{aligned} \tag{45}$$

where the stability of the controller is ensured only when

$$c_1|d(t)| \leq k|s_2|^{\alpha} \tag{46}$$

Thus, the designed controller is robust to external disturbances.

D. DOUBLE INTEGRAL SLIDING MODE CONTROL

DISMC is used to further improve the convergence of the states to their tracking references, reducing the and chattering. The addition of integral term also ensures the robustness of the controller as it eliminates the reaching phase [34]. The tracking errors in DISMC technique in addition to the errors defined by the eq.(9) and eq.(29) are as follows:

$$\begin{aligned} e_9 &= \int(\int(z_1 - z_{1ref})\,dt)\,dt \\ e_{10} &= \int(\int(z_2 - z_{2ref})\,dt)\,dt \\ e_{11} &= \int(\int(z_3 - z_{3ref})\,dt)\,dt \\ e_{12} &= \int(\int(z_4 - z_{4ref})\,dt)\,dt \end{aligned} \tag{47}$$

The sliding surface incorporating all the errors for DISMC is taken as follows:

$$\begin{aligned} s_3 &= c_1e_1 + c_2e_2 + c_3e_3 + c_4e_4 + c_5e_5 \\ &+c_6e_6 + c_7e_7 + c_8e_8 + c_9e_9 \\ &+c_{10}e_{10} + c_{11}e_{11} + c_{12}e_{12} \end{aligned} \tag{48}$$

The time derivatives of e_9, e_{10}, e_{11} and e_{12} given by eq.(47) are calculated using eq.(29) as follows:

$$\begin{aligned} \dot{e}_9 &= \int(z_1 - z_{1ref})\,dt = e_5 \\ \dot{e}_{10} &= \int(z_2 - z_{2ref})\,dt = e_6 \\ \dot{e}_{11} &= \int(z_3 - z_{3ref})\,dt = e_7 \\ \dot{e}_{12} &= \int(z_4 - z_{4ref})\,dt = e_8 \end{aligned} \tag{49}$$

The sliding surface for the DISMC is defined as follows:

$$\begin{aligned} s_3 &= c_1\dot{e}_1 + c_2\dot{e}_2 + c_3\dot{e}_3 + c_4\dot{e}_4 \\ &+c_5\dot{e}_5 + c_6\dot{e}_6 + c_7\dot{e}_7 + c_8\dot{e}_8 + c_9\dot{e}_9 \\ &+c_{10}\dot{e}_{10} + c_{11}\dot{e}_{11} + c_{12}\dot{e}_{12} \end{aligned} \tag{50}$$

Inserting values of the time derivative of errors from eq.(9), eq.(32) and eq.(49) in eq.(36), we get:

$$\begin{aligned} \dot{s}_3 &= c_1(\dot{z}_1 - \dot{z}_{1ref}) + c_2(\dot{z}_2 - \dot{z}_{2ref}) \\ &+c_3(\dot{z}_3 - \dot{z}_{3ref}) + c_4(\dot{z}_4 - \dot{z}_{4ref}) + c_5e_1 + c_6e_2 \\ &+c_7e_3 + c_8e_4 + c_9e_5 + c_{10}e_6 + c_{11}e_7 + c_{12}e_8 \end{aligned} \tag{51}$$

Theorem 3: Consider the system (2), the sliding surface (48) under the assumptions given in section III-A, the designed DISMC controller will stabilize the system asymptotically provided condition $\dot{s}_3 = -k|s_3|^{\alpha} sign\frac{s_3}{\phi}$ holds. The robustness to external disturbance is ensured by DISMC controller provided condition (64) exists.

Proof: Now considering a Lyapunov candidate function to analyze the asymptotic stability of the system as follows:

$$V = \frac{1}{2}s_3^2 \tag{52}$$

By taking the derivative of eq.(52) with respect to time, we obtain:

$$\dot{V} = s_3\dot{s}_3 \tag{53}$$

To make $\dot{V}$ negative definite, let:

$$\dot{s}_3 = -k|s_3|^{\alpha} sign\frac{s_3}{\phi} \tag{54}$$

So:

$$\dot{V} = -s_3(k|s_3|^{\alpha} sign(\frac{s_3}{\phi}) \tag{55}$$

or

$$\dot{V} = -\,k\,|s_3|^{\alpha}\phi\frac{s_3}{\phi}\,sign\,(\frac{s_3}{\phi}) \tag{56}$$

Since $\frac{s_3}{\phi}\ sign\ (\frac{s_3}{\phi}) = |\frac{s_3}{\phi}|$, we have

$$\dot{V} = -\ k\ |s_3|^{\alpha}\phi|\frac{s_3}{\phi}| \tag{57}$$

It implies that

$$\dot{V} = -\ k\ |s_3|^{\alpha+1} \tag{58}$$

It is clear from eq.(44) that $\dot{V}$ is always negative definite.

Now, comparing eq.(51) and eq.(54) and by putting values of $\dot{z}_1, \dot{z}_2, \dot{z}_3$ and $\dot{z}_4$ from eq.(2), we get:

$$\begin{aligned}
&-k|s_3|^{\alpha} sign\frac{s_3}{\phi} \\
&= c_1[z_1\{k_1(1-z_1) - n_2z_3 - n_3z_2 - m_1(1-e^{-z_4})\} \\
&\quad -\dot{z}_{1ref}] + c_2[z_2\{k_2(1-z_2) - n_4z_1 - m_2(1-e^{-z_4})\} \\
&\quad -\dot{z}_{2ref}] + c_3[1 + z_3\{\frac{k_3z_1}{v_1+z_1} - n_1z_1 - v_2 - m_3(1-e^{-z_4})\} \\
&\quad -\dot{z}_{3ref}] + c_4[u - z_4 - \dot{z}_{4ref}] + c_5e_1 + c_6e_2 \\
&\quad +c_7e_3 + c_8e_4 + c_9e_5 + c_{10}e_6 + c_{11}e_7 + c_{12}e_8
\end{aligned} \tag{59}$$

Rearranging eq.(59) to find the value of control input $u(t)$:

$$\begin{aligned}
&u(t) \\
&= -\frac{k}{c_4}|s_3|^{\alpha} sign(\frac{s_3}{\phi}) - \frac{c_1}{c_4} \\
&\quad \times[z_1\{k_1(1-z_1) - n_2z_3 - n_3z_2 - m_1(1-e^{-z_4})\} - \dot{z}_{1ref}] \\
&\quad -\frac{c_2}{c_4}[z_2\{k_2(1-z_2) - n_4z_1 - m_2(1-e^{-z_4})\} - \dot{z}_{2ref}] \\
&\quad -\frac{c_3}{c_4}[1 + z_3\{\frac{k_3z_1}{v_1+z_1} - n_1z_1 - v_2 \\
&\quad -m_3(1-e^{-z_4})\} - \dot{z}_{3ref}] + z_4 + \dot{z}_{4ref} - \frac{c_5}{c_4}e_1 - \frac{c_6}{c_4}e_2 \\
&\quad -\frac{c_7}{c_4}e_3 - \frac{c_8}{c_4}e_4 - \frac{c_9}{c_4}e_5 - \frac{c_{10}}{c_4}e_6 - \frac{c_{11}}{c_4}e_7 - \frac{c_{12}}{c_4}e_8
\end{aligned} \tag{60}$$

DISMC in case of disturbance/noise can be analyzed by adding Gaussian noise $d(t)$ in the eq.(2a) of the system as follows:

$$\dot{z}_{1n} = z_1\{k_1(1-z_1) - n_2z_3 - n_3z_2 - m_1(1-e^{-z_4})\} + d(t) \tag{61}$$

where d(t) satisfies the inequality defined in eq.(21).

The sliding surface for DISMC in case of noise is same as defined by eq.(50) while the value of the error can be defined by

$$e_{3n} = z_{3n} - z_{3nref} \tag{62}$$

where, e_{3n}, z_{3n} and z_{3nref} are error for tumor cells with noise, tumors cells with noise and reference of tumor cells with noise respectively. Repeating the same process as done in the start of section III-C for the case of designing the SMC, the value of control input $u(t)$ with disturbance can be calculated as

$$\begin{aligned}
&u(t) \\
&= -\frac{k}{c_4}|s_3|^{\alpha} sign(\frac{s_3}{\phi}) \\
&\quad -\frac{c_1}{c_4}[z_1\{k_1(1-z_1) - n_2z_3 - n_3z_2 - m_1(1-e^{-z_4})\} - \dot{z}_{1ref}] \\
&\quad -\frac{c_2}{c_4}[z_2\{k_2(1-z_2) - n_4z_1 - m_2(1-e^{-z_4})\} \\
&\quad -\dot{z}_{2ref}] - \frac{c_3}{c_4}[1 + z_3\{\frac{k_3z_1}{v_1+z_1} - n_1z_1 - v_2 - m_3(1-e^{-z_4})\} \\
&\quad -\dot{z}_{3_ref}] + z_4 + \dot{z}_{4ref}\frac{c_1}{c_4}d(t) - \frac{c_5}{c_4}e_1 \\
&\quad -\frac{c_6}{c_4}e_2 - \frac{c_7}{c_4}e_3 - \frac{c_8}{c_4}e_4 \\
&\quad -\frac{c_9}{c_4}e_5 - \frac{c_{10}}{c_4}e_6 \\
&\quad -\frac{c_{11}}{c_4}e_7 - \frac{c_{12}}{c_4}e_8
\end{aligned} \tag{63}$$

where the stability of the controller is ensured only when

$$c_1|d(t)| \leq k|s_3|^{\alpha} \tag{64}$$

Thus, the designed controller is robust to external disturbances. The behavior of tumor cells with addition of disturbance in SMC, ISMC and DISMC can be seen in the simulation results by Fig.13.

E. SUPER TWISTING SLIDING MODE CONTROL

The super-twisting sliding mode control (ST-SMC) algorithm is again based on selecting a sliding surface. We consider a first order sliding surface that incorporates all the tracking errors as:

$$\sigma = d_1e_{sw_1} + d_2e_{sw_2} + d_3e_{sw_3} + d_4e_{sw_4} \tag{65}$$

where e_{sw_1}, e_{sw_2}, e_{sw_3} and e_{sw_4} are the errors for tumor cells, healthy cells, immune cells and the amount of drug respectively. Taking the derivative of eq.(65) with respect to time:

$$\dot{\sigma} = d_1\dot{e}_{sw_1} + d_2\dot{e}_{sw_2} + d_3\dot{e}_{sw_3} + d_4\dot{e}_{sw_4} \tag{66}$$

By putting values of derivatives of errors from eq.(9) in eq.(48), we have:

$$\begin{aligned}
\dot{\sigma} &= d_1(\dot{z}_1 - \dot{z}_{1ref}) + d_2(\dot{z}_2 - \dot{z}_{2ref}) \\
&\quad +d_3(\dot{z}_3 - \dot{z}_{3ref}) + d_4(u - z_4 - \dot{z}_{4ref})
\end{aligned} \tag{67}$$

Substituting values of $\dot{z}_1$, $\dot{z}_2$, $\dot{z}_3$ and $\dot{z}_4$ from eq.(2) and putting $\dot{\sigma} = 0$ in eq.(67), we get the equivalent control u_{equ} as:

$$\begin{aligned}
&u_{equ} \\
&= -\frac{d_1}{d_4}[z_1\{k_1(1-z_1) - n_2z_3 - n_3z_2 - m_1(1-e^{-z_4})\} \\
&\quad -\dot{z}_{1ref}] - \frac{d_2}{d_4}[z_2\{k_2(1-z_2) - n_4z_1 - m_2(1-e^{-z_4})\} \\
&\quad -\dot{z}_{2_ref}] - \frac{d_3}{d_4}[1 + z_3\{\frac{k_3z_1}{v_1+z_1} - n_1z_1 - v_2 \\
&\quad -m_3(1-e^{-z_4})\} - \dot{z}_{3_ref}] + z_4
\end{aligned} \tag{68}$$

The switching control for the super-twisting sliding mode u_{sw} can be written as follows:

$$u_{sw} = -k_1\ |\ \sigma\ |^{\alpha}\ sign(\sigma) - k_2\int sign(\sigma)d\tau \tag{69}$$

where k_1 and k_2 given in [33], [35] satisfy the following inequalities:

$$k_1 \geq \frac{4\psi\Gamma_{max}(k_2+\psi)}{\Gamma^2{}_{min}\Gamma_{min}(k_2-\psi)} \tag{70}$$

and

$$k_2 > \frac{\psi}{\Gamma_{min}} \tag{71}$$

where ψ, Γ_{max} and Γ_{min} are design parameters [33], [35]. The overall control for the supertwisting sliding mode u_{ST} is given as follows:

$$u_{ST} = u_{equ} + u_{sw} \tag{72}$$

where u_{equ} and u_{sw} are the equivalent control and switching control inputs respectively.

Now substituting the values of u_{ST} from eq. (72) in eq. (67), we obtain:

$$\dot{\sigma} = -k_1 \mid \sigma \mid^{\alpha} sign(\sigma) - k_2 \int sign(\sigma)d\tau \tag{73}$$

Theorem 4: Consider the system (2), the sliding surface (65) under the assumptions given in section III-A, there exists strictly positive constants k_1 and k_2 in (70) and (71) respectively, the designed ST-SMC controller will stabilize the system asymptotically provided condition (73) holds.

Proof: Consider the following positive definite Lyapunov function to analyse the stability of the controller.

$$V = \frac{1}{2}\sigma^2 \tag{74}$$

Now taking time derivative of V using eq.(74) and putting the value of $\dot{\sigma}$ from eq.(67) in the resultant equation as follows:

$$\begin{aligned}\dot{V} &= \sigma\dot{\sigma} \\ &= \sigma(d_1(\dot{z}_1 - \dot{z}_{1ref}) + d_2(\dot{z}_2 - \dot{z}_{2ref}) \\ &\quad + d_3(\dot{z}_3 - \dot{z}_{3ref}) + d_4(u_{ST} - z_4 - \dot{z}_{4ref}))\end{aligned} \tag{75}$$

Now inserting the value of u_{ST} from eq.(72) in eq.(75) and using the values of eq.(68) and eq.(69) to obtain the resultant value of $\dot{V}$ as follows:

$$\dot{V} = -k_1 \mid \sigma \mid^{\alpha+1} -k_2\sigma \int sign(\sigma)d\tau \tag{76}$$

It is clear from eq.(76) that $\dot{V}$ is negative definite and the designed controller is stable. Stability analysis proposed in [36] proves that the proposed controller achieves the stability criteria $\dot{V} \leq 0$ which also explains the finite time convergence of all the errors to zero. The above mentioned control methods are summarized as follows:

F. SUMMARY OF CONTROL METHODS

Unlike traditional nonlinear controllers, sliding mode control utilizes an error based sliding surface that has an advantage of model order reduction and has a very simple implementation. The only problem that arises in SMC is chattering. The problem of chattering is reduced in ISMC due to the addition of integral of errors. It also has an advantage of improved convergence and less steady state error. To further reduce the chattering and improvement of transient and steady state characteristics, DISMC is designed. At last, to eliminate chattering completely the switching control for the super-twisting sliding mode is designed such that the inequalities in (70) and (71) are satisfied. ST-SMC shows fastest convergence of tracking errors to zero in finite time. All the designed controllers offer robustness to parametric in-variance and disturbance rejection.

IV. LINEARIZATION AND CONTROLLABILITY OF TUMOR SYSTEM FOR PID CONTROLLER

In this section, we have linearized the tumor model and observed the controllability of the linearized one.

By linearizing the model of tumor system given in eqs.(2a)-(2d), we get:

$$\dot{z}_1 = (k_1 - m_1)z_1 \tag{77a}$$
$$\dot{z}_2 = (k_2 - m_2)z_2 \tag{77b}$$
$$\dot{z}_3 = 1 - v_2 z_3 - m_3 z_3 \tag{77c}$$
$$\dot{z}_4 = u - z_4 \tag{77d}$$

From above model the system matrix A can be obtained as:

$$A = \begin{bmatrix} k_1 - m_1 & 0 & 0 & 0 \\ 0 & k_2 - m_2 & 0 & 0 \\ 0 & 0 & -v_2 - m_3 & 0 \\ 0 & 0 & 0 & -1 \end{bmatrix} \tag{78}$$

By using the values of constants given by the table I, we get:

$$A = \begin{bmatrix} 21 & 0 & 0 & 0 \\ 0 & 33 & 0 & 0 \\ 0 & 0 & -25 & 0 \\ 0 & 0 & 0 & -1 \end{bmatrix} \tag{79}$$

Input matrix B can be given as:

$$B = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 1 \end{bmatrix} \tag{80}$$

Controllability matrix Co of above system is given as:

$$Co = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ -1 & -1 & -1 & -1 \end{bmatrix} \tag{81}$$

Now calculating determinant of Co:

$$|Co| = 0 \tag{82}$$

Since the determinant of Co is zero, so the linearized system is uncontrollable and hence cannot be stabilized by a linear control technique.

V. SIMULATION RESULTS

The behavior of the proposed nonlinear controllers given by eqs.(20), (42), (63) and (72) using SMC, ISMC, DISMC, ST-SMC techniques respectively and their comparison with each other have been presented in this section. The simulations have been performed on Matlab/Simulink by using the values of the parameters given by table 1.

TABLE 1. Values of parameters.

Parameter	Value of Parameter	Parameter	Value of Parameter
k_1	30	k_2	48
k_3	29	n_1	2
n_2	1.3	n_3	0.47
n_4	8	m_1	9
m_2	15	m_3	4
$z_1(0)$	2.5	$z_2(0)$	0.25
$z_3(0)$	1.55	$z_2(0)$	1.35
μ	0	σ	$1 * 10^{-3}$
k	19	α	0.9

This section has been further divided into three subsections. The comparison is shown in terms of behavior of tumor cells, number of healthy cells, number of immune cells and the amount of drug. The comparison of input graphs of all control techniques are also shown in this section.

Following tracking references of the states have been used for the simulations.

$$z_{1ref} = 0, \quad z_{2ref} = 0.9, \; z_{3ref} = 18, \; z_{4ref} = 0$$

1) COMPARISON BETWEEN SMC AND ISMC

The values of the design parameters for the SMC are as follows: $c_1 = 350$, $c_2 = 20$, $c_3 = 35$, $c_4 = 40$, $k = 0.60$, $\alpha = 0.90$, $\phi = 0.70$

Whereas, the values of design parameters for ISMC are as follows: $c_1 = 300$, $c_2 = 200$, $c_3 = 30$, $c_4 = 40$, $k = 0.70$, $\alpha = 0.99$, $\phi = 0.85$

Fig.2 shows the comparison of tumor cells using SMC and ISMC techniques for chemotherapy. The convergence of tumor cells near to the desired reference is faster and the chattering is lesser in case of ISMC while it is comparatively larger using SMC.

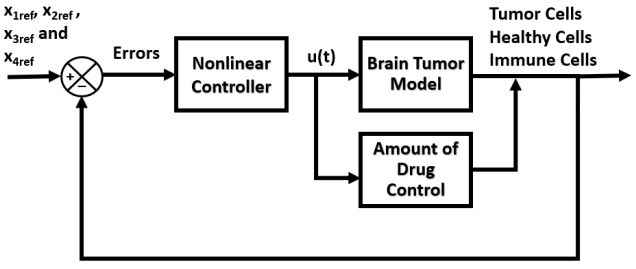

FIGURE 2. Diagram of proposed approach.

The comparison of healthy cells has been shown in Fig.3. The graph shows that they are tracked perfectly to their desired reference and final count of healthy cells are in safe

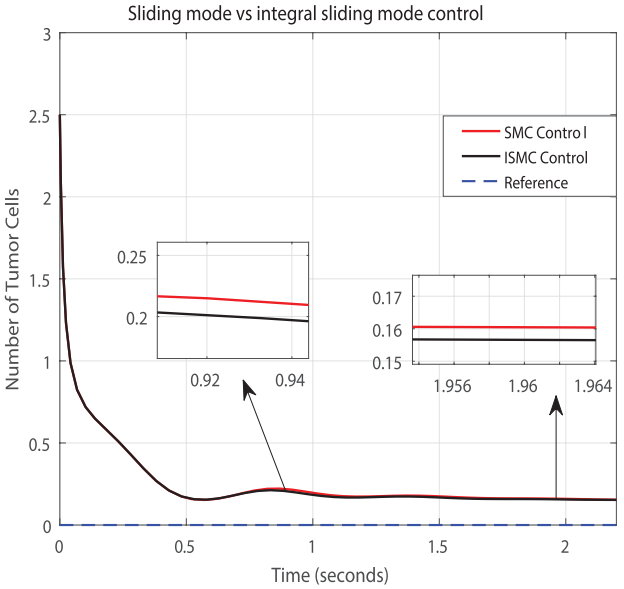

FIGURE 3. Comparison of number of tumor cells.

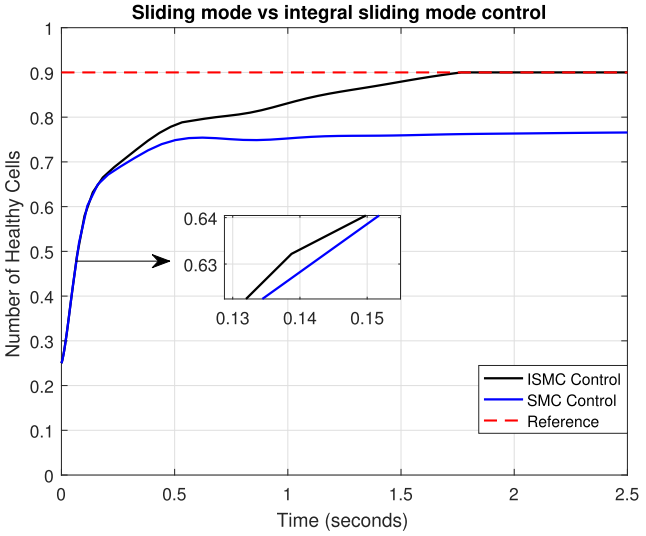

FIGURE 4. Comparison of number of healthy cells.

limit in case of ISMC. It can be seen that after 0.72 seconds healthy cells are reduced for small interval in case of SMC but some SSE has been noted. While in case of ISMC, healthy cells take more time to reach steady state value but ultimately achieve it. The control input for the SMC and ISMC have been shown in Fig.4 which is between 0 and 1. It can be seen that input effort required for ISMC is less as compare to SMC. Fig.5, has been drawn to show the comparison of immune cells for the proposed controllers. It shows that ISMC perfectly tracks the immune cells to their reference value while SMC take takes less time to reach steady state value but from 0.50 to 2.50 seconds, the growth rate of immune cells is far better in case of ISMC. The comparison of amount of drug given by area under the curve is shown in Fig.6 which for SMC is 58.4 and for ISMC is 42.2. Another integral action has

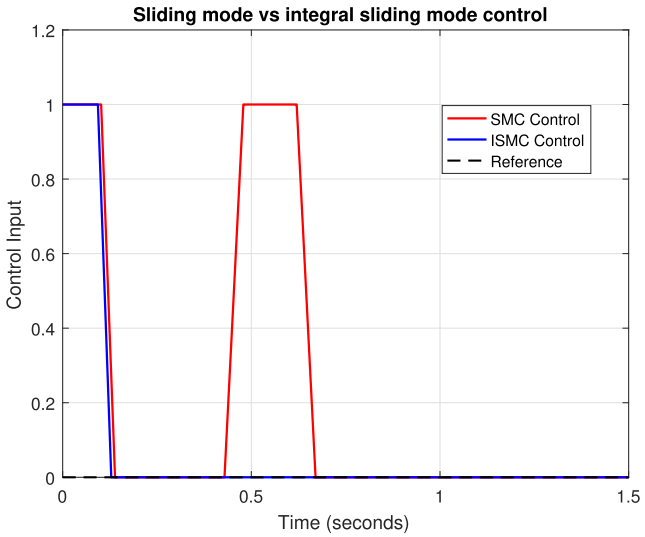

FIGURE 5. Comparison of control input.

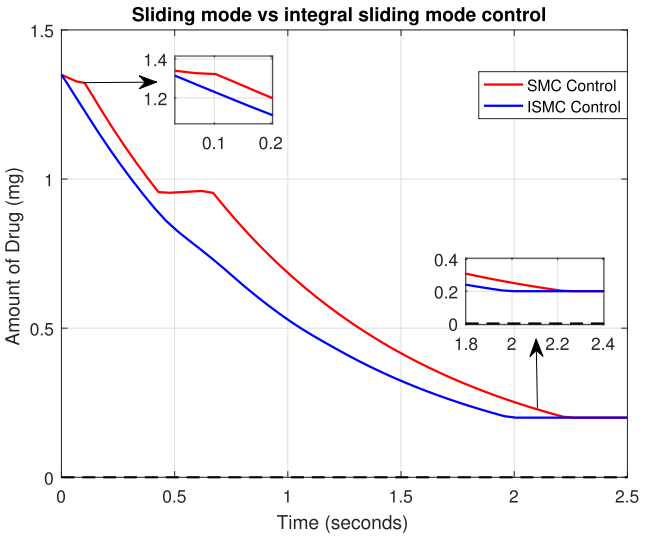

FIGURE 7. Comparison of amount of drug.

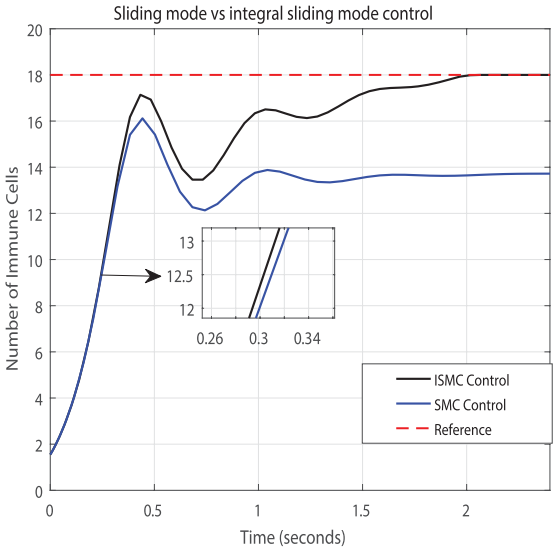

FIGURE 6. Comparison of number of immune cells.

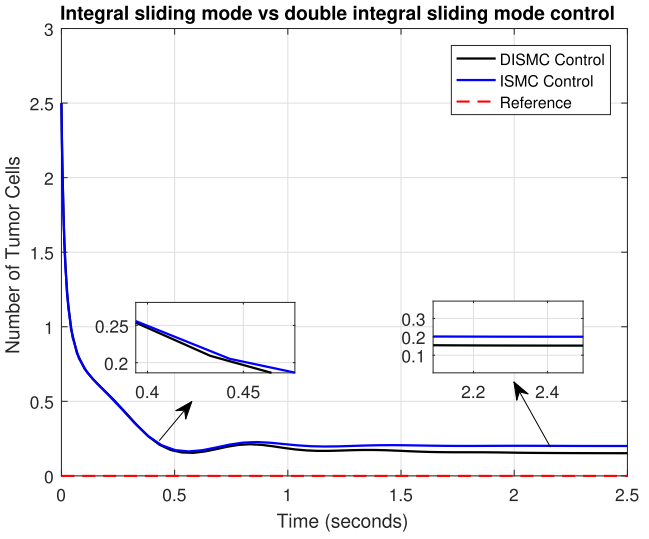

FIGURE 8. Comparison of number of tumor cells.

been added to ISMC that results in DISMC in order to further improve the responses. We compared ISMC with DISMC to suggest better control input for the tumor system on the basis of rate of convergence, chattering and amount of drug consumed in the following subsection.

2) COMPARISON BETWEEN ISMC AND DISMC

The values of the design parameters for the DISMC technique are as follows: $c_1 = 350$, $c_2 = 20$, $c_3 = 35$, $c_4 = 40$, $k = 0.50$, $\alpha = 0.99$, $\phi = 0.90$

The behavior of tumor cells has been shown in Fig.7 which shows that the convergence rate of tumor cells near to zero is almost similar for both the controllers but DISMC has an advantage over ISMC on the basis of chattering and a bit faster convergence time as clear from the zoomed portion.

The behavior of healthy cells has been shown in Fig.8 which shows that they are tracked perfectly to the desired reference 0.90 by both the controllers which satisfy the safe limit mentioned in the literature.

The comparison of immune cells given by Fig.9 shows that both ISMC and DISMC perfectly track the immune cells to their reference value, whereas immune cells in DISMC take 0.19 seconds to reach the steady state value which is less than that of ISMC's which is 0.24 seconds.

Fig.10 shows that the amount of drug used in case of ISMC is 42.2, which is more than the value being consumed in case of DISMC. The chattering and rate of convergence clearly indicate that the DISMC is better than ISMC. The control input for the ISMC and DISMC controllers have been shown in Fig.11 which is between 0 and 1. It can be seen that

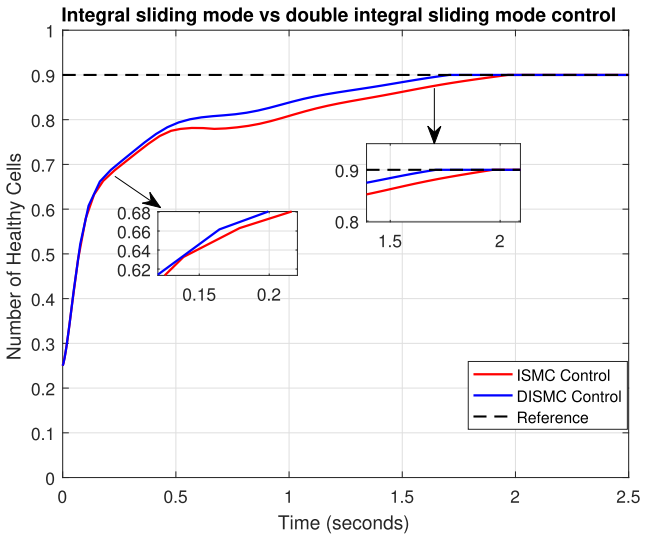

FIGURE 9. Comparison of number of healthy cells.

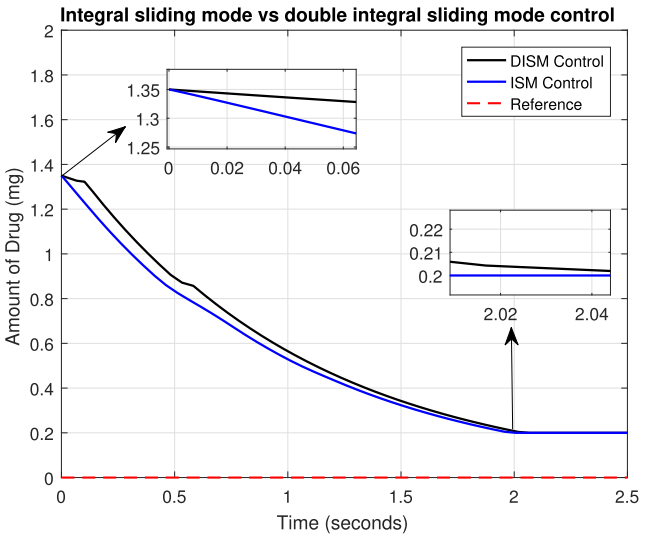

FIGURE 11. Comparison of amount of drug.

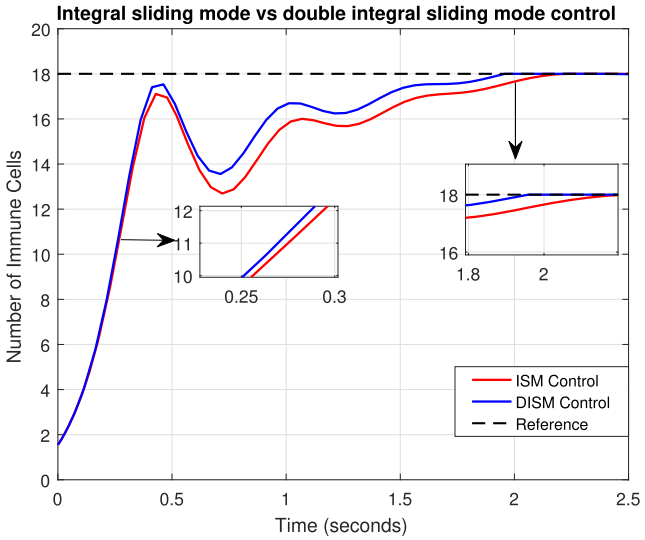

FIGURE 10. Comparison of number of immune cells.

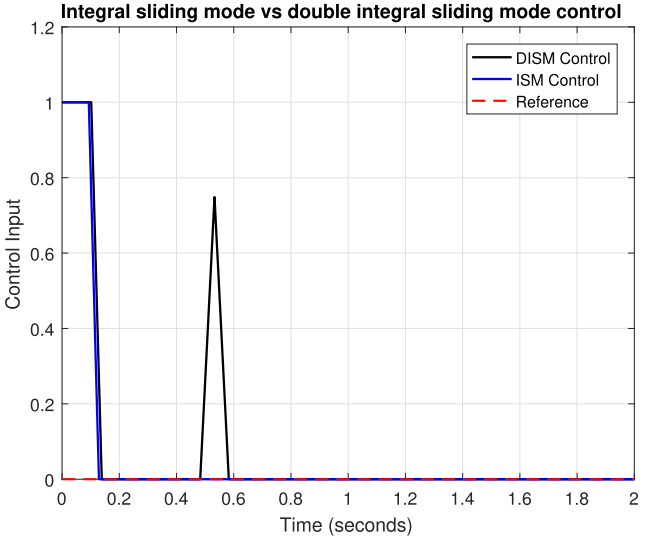

FIGURE 12. Comparison of control input.

input effort required for DISMC is less as compare to ISMC because ISMC requires more effort during 0.5-0.6 seconds.

From the above comparative analysis, it can concluded that controller designed by DISMC is better than ISMC on the basis of chattering, rate of convergence and amount of drug consumed.

The combined results of the behaviour of tumor cells by using SMC, ISMC and DISMC is shown in Fig.12. It shows that the DISMC is a bit better than both SMC and ISMC on the basis of chattering and rate of convergence. DISMC is takes lesser time to reach steady state value as compared to other proposed controllers.

Now to observe tracking ability of SMC, ISMC and DISMC by adding Gussian noise of mean $= 0$ and variance $1 * 10^{-3}$. k is an upper bound of the disturbance/noise and has value 0.9 which is greater than $1 * 10^{-3}$ satisfying the inequality (46). The behavior of tumor cells for SMC, ISMC and DISMC has been presented by Fig.14.

From the fast convergence of tumor cells with negligible chattering in the presence of external disturbance shows that DISMC is better than SMC and ISMC. It is robust and is invariant to parametric uncertainties.

3) COMPARISON BETWEEN DISMC AND ST-SMC

The values of the design parameters for the ST-SMC are as follows: $k_1 = 1$, $k_2 = 700$, $k = 0.60$, $\alpha = 0.5$, $\phi = 0.650$

Fig.15 shows the comparison of tumor cells using DISMC and ST-SMC controllers for chemotherapy. It can be seen that the convergence of tumor cells to the desired reference is faster and the chattering is negligible using ST-SMC as compared to DIMSC. So, on the basis of these results the ST-SM controller is better than DISM controller.

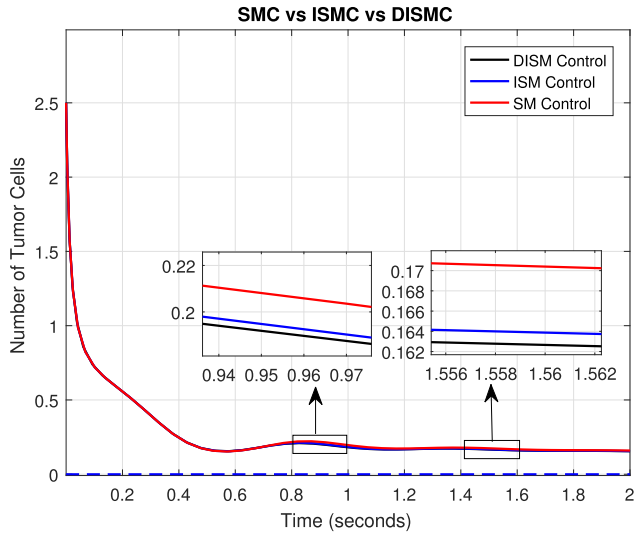

FIGURE 13. Comparison of number of tumor cells.

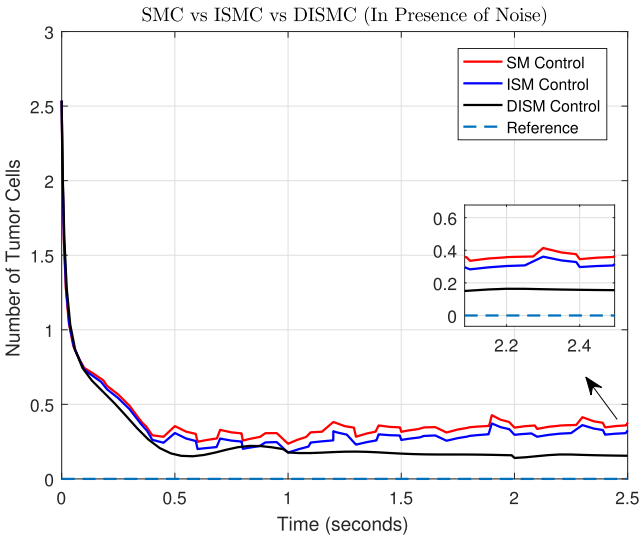

FIGURE 14. SMC, ISMC and DISMC with noise.

The comparison of healthy cells has been shown in Fig.16. The graph shows that they are tracked perfectly to their desired reference and the final count of healthy cells are in safe limit for both the proposed controllers. It can be seen that after 0.15 seconds healthy cells grow faster in case of ST-SMC as compared to DISMC. Also they take lesser time to reach steady state value in case of ST-SMC.

Fig.17 shows that the amount of drug used in case of DISMC is 39.8, which is more than the value being consumed in case of ST-SMC. The chattering and rate of convergence clearly indicate that the ST-SMC is better than DISMC.

The comparison of tumor and healthy cells on the basis of response parameters has been shown in table 2 and 3 respectively. It can be seen that ST-SMC is better among all the proposed controllers in terms of convergence and steady state error.

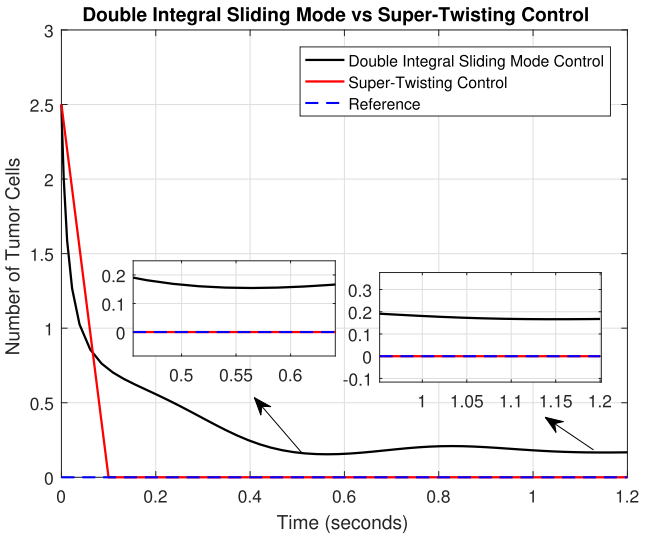

FIGURE 15. Comparison of number of tumor cells.

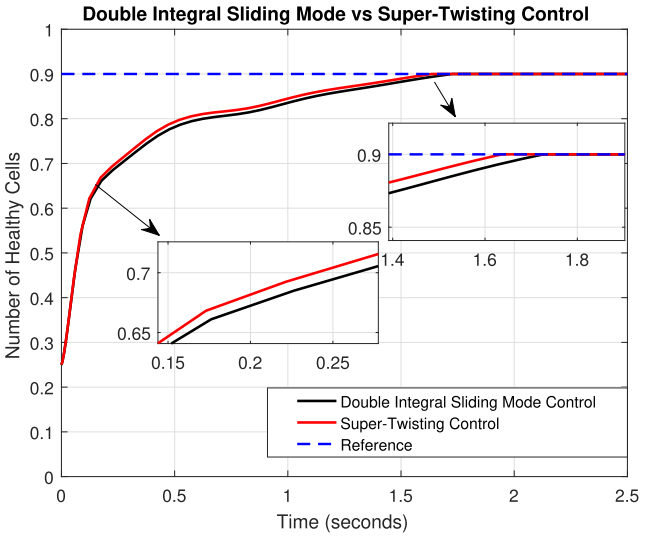

FIGURE 16. Comparison of number of healthy cells.

TABLE 2. Response of proposed controllers (Tumor Cells).

Response	SMC	ISMC	DISMC	ST-SM
Rise Time (s)	–	–	–	–
Settling Time (s)	0.9315	0.9154	0.8961	0.8959
Steady State Error (s)	0.3562	0.172	0.152	0
Peak Value	2.5	2.5	2.5	2.5
Peak Time (s)	0	0	0	0

TABLE 3. Response of proposed controllers (Healthy Cells).

Response	SMC	ISMC	DISMC	ST-SM
Rise Time (s)	1.1843	0.9735	0.9729	0.9025
Settling Time (s)	1.7813	1.7262	1.5526	1.4698
Steady State Error (s)	0	0	0	0
Peak Value	0.9	0.9	0.9	0.9
Peak Time (s)	1.9669	1.7262	1.7259	1.6363

The tumor cells in case of ST-SMC controller converge to zero in least number of seconds as indicated by settling time

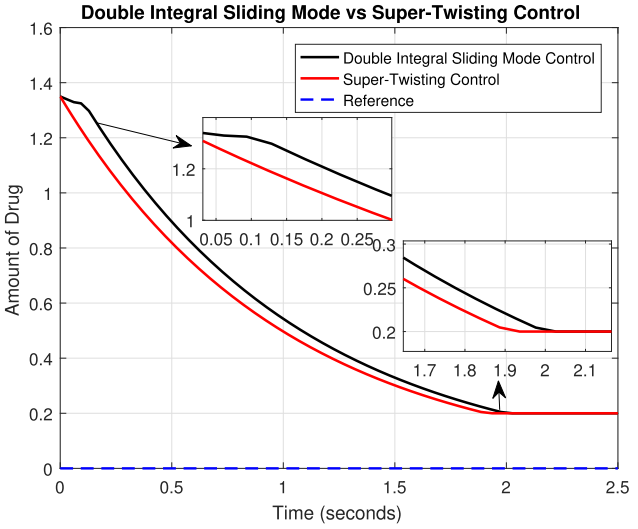

FIGURE 17. **Comparison of amount of drug consumed.**

in table 2. Moreover, the zero steady state error can only be observed in case of ST-SMC.

The transient response of healthy cells indicated by rise time, settling time and peak time is given in table 3. It shows better results in case of ST-SMC controller as compared to SMC, ISMC and DISMC controllers. Thus, ST-SMC controller is the suitable one among the proposed controllers on the basis of improved convergence rate and steady state error.

VI. CONCLUSION

In this paper, an updated model of brain tumor has been considered and four variable structure controllers named as: Sliding Mode, Integral Sliding Mode, Double Integral Sliding Mode and Supertwisting controllers have been proposed to control the amount of drug given to the patient and to reduce the number of tumor cells while retaining a safe number of healthy cells as well as immune cells. A complete mathematical analysis has been given to prove stability of the proposed controllers using Lyapunov theory. Results of these controllers are better than the previously designed optimal controller for brain tumor system. They have been compared with each other in simulation results using MATLAB/Simulink environment where it is noticed that ST-SMC controller is better than SMC, ISMC and DISMC controllers in terms of the rate of convergence, chattering and the amount of drug. So amount of drug by using super-twisting controller is advised.

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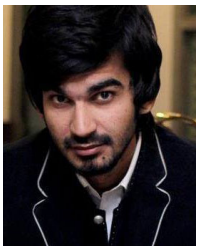

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