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Nonlinear Control for Growth of Cancerous Tumor Cells

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ABSTRACT In this research work, a Three-Dimensional Cancer model (TDCM) has been used and nonlinear controllers; Lyapunov Redesign, Synergetic and Sliding Mode based controllers have been designed in order to reduce the growth of tumor cells to a level where they become harmless, to maintain the hunting predator cells to their maximum possible value and to retain resting predator cells to 40% of the hunting predator cells. The proposed controllers have been developed for chemotherapy and their effect on different cells has been studied. Asymptotic stability of the proposed controllers has been studied using Lyapunov stability theory. Theoretical analysis has been supported by simulation results using MATLAB/Simulink. Under the proposed controllers, the system behaves very nicely even in the presence of un-modeled disturbances and noise.

INDEX TERMS Hunting and resting predator cells, Lyapunov redesign control, sliding mode control, synergetic control, tumor cells.

I. INTRODUCTION

Infectious diseases portrayed by uncontrolled cell development are called cancer. Unsatisfactory performance of immune system against chaotic tumor cells and their disordered development prompts harm and even death to patients. Tumor dormancy and escape from immune surveillance system are some unpredictable characteristics during tumor growth which must be controlled [1], [2].

There are several methodologies to treat a cancerous tumor which include surgery, radiotherapy, immunotherapy and chemotherapy. Oncologists have been using chemotherapy as one of their primary treatment for cancer patients.

Different mathematical models of cancerous tumor exist in the literature [3]. The scientists have been putting effort to study different stages of tumor development and the effect of chemotherapeutic medications on the development of tumor cells. Some models can be found in which destruction of tumor cells has been demonstrated under chemotherapeutic treatment.

Log-kill theory says that the tumor growth is proportional to the destruction of the cells [4]. Therefore, according to this hypothesis, volume of huge tumors diminishes quicker than that of smaller tumors. But there are certain diseases, like Lymphoblast Leukemia and Hodgkin's infection, the outcome contradicts to the hypotheses. Here, smaller tumors decrease quicker than sizeable tumors of a similar kind. Norton-Simon theory says that the cell destruction has been directly proportional to the rate of tumor development [5], [6].

In earlier research, unconstrained and constrained control techniques with open loop analysis have been observed in [7], [8]. In [9] a feedback controller has been presented which uses quadratic performance criterion for analysis. Optimal control on a stochastic nature model is another field of research found in the literature [5]. It used optimal control techniques for the comparison of different models. Chemotherapeutic process has also been implemented using multi-objective optimal control. Impact of parametric variations and disturbances has not been considered in most of the controllers designed in the literature. Different control strategies have also been developed to attain robustness [10]. Linear optimal regulation based on extremal variation, H_∞ control and nonlinear optimal control have been developed in [11], [12].

In one of the recent works, cell population exhibited a chaotic property which is highlighted by state-space linearization based on lie algebra using a TDCM by [1]. It included a typical population of tissue cells to perform a phase space analysis and used optimal control theory to study

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the impact of chemotherapeutic treatment [13]. It analyzed the development of tumor cell in the presence of the cytokine IL-2 and the resting predator cells. Both cells play a fundamental role to activate and simulate the immune system of the body. They concluded that antigenicity of the tumor cells does a basic job in their own recognition by the immune system. Fluctuations in the growth of tumor cells have been seen and a stable limit cycle has been observed for some of the antigenic parameters. It has been realized that chemotherapy does influence the quickly developing hunting predator cells.

One can discover different cancer-immune interaction models along with their dynamical analysis. These models incorporate distinctive cell growth and share fundamental qualities. They incorporate cancer-free equilibria, tumor existing with different cells and uncontrolled development of cancerous tumor [14]. Most of the intriguing dynamics occur when there exists an equilibrium point between tumor and other cells in a body which may produce oscillations in the growth of the cells and converge to a stable limit cycle.

In the literature, a controller has been designed for the chaotic behavior of tumor dynamics [15]. The chaos and optimal control of cancer model with totally obscure parameters together with the asymptotic stability has been studied in [16]. A nonlinear prey-predator model has been considered in [17] to demonstrate regular interaction between tumor and resting predator cells. To incorporate the characteristics of finite time convergence and enhance robustness of the controller, Sliding Mode Controllers can play a pivotal role.

In this paper we have proposed three nonlinear controllers namely; Lyapunov Redesign, Synergetic and Sliding Mode based controllers using TDCM for reducing the growth of tumor cells to a level where they become harmless, maintaining the hunting predator cells to their maximum possible value and retaining resting predator cells to 40% of the hunting predator cells.

The contents of this paper are organized as: Mathematical modeling has been discussed in section II. Controllers have been designed and detailed mathematical analysis has been discussed in section III. Simulation results using MATLAB/Simulink have been shown in section IV and section V presents the conclusion.

II. MATHEMATICAL MODEL

The model is developed for spontaneous tumor regression and progression which is an interaction between the anticancer agent cell, lymphocytes and macrophages, that are natural killer cells which destroy the malignant cells. The following assumptions have been considered:

1. The predator is T-lymphocytes and cytotoxic macrophages/natural killer cells of immune system, attacks/destroys or ingests the tumor cell.

2. The prey are the tumor cells which are attacked and destroyed by the immune cells. The predator has two states; hunting and resting, and destroys the prey. The tumor cells are caught by macrophages which can be found in all the tissues of the body and circulate round in the blood system.

3. Macrophages absorb tumor cells, eat them and release series of cytokines which activates the resting T-lymphocytes that coordinate the counter attack.

4. The resting predator cells can also be directly simulated to interact with antigens. These resting cells cannot kill tumor cells, but they are converted to a special type of T-lymphocyte cells called natural killer or hunting cells and begin to multiply and release other cytokines that simulate more resting cells.

5. This conversion between hunting and resting cells result in a degradation of the resting cells undergoing natural growth and activation of hunting cells.

6. To introduce the mathematical model, we assume that the tumor cells are being destroyed at a rate proportional to the densities of the tumor cells according to the law of mass action. We also assumed that the resting predator cells are converted to the hunting cells either by direct contacting with them or by contact with a fast diffusing substance produced by hunting cells. Once a cell is converted, it will never return to the resting stage and active cells die at constant probability per unit time.

7. All the resting predator and tumor cells are nutrient rich undergoing mitosis and the tumor cells have a proliferating advantage over the normal cells [16].

The mathematical model of the tumor uses tumor cells, hunting predator cells and resting predator cells. Equation (1) shows the ordinary differential equations of the tumor model [1].

$$\begin{cases} \dfrac{\mathrm{d}T}{\mathrm{d}t} &= r_1 T(1-\dfrac{T}{k_1}) - a_{12}TH - a_{13}TR \\ \dfrac{\mathrm{d}H}{\mathrm{d}t} &= r_2 H(1-\dfrac{H}{k_2}) - a_{21}TH \\ \dfrac{\mathrm{d}R}{\mathrm{d}t} &= (\dfrac{r_3 TR}{T+k_3}) - a_{31}TR - d_3 R \end{cases} \tag{1}$$

where $T(t)$ is the number of tumor cells, $H(t)$ is the number of hunting predator cells and $R(t)$ is the number of resting predator cells at time t. The tumor cells develop at the rate r_1 without any effect of hunting and resting predator cells with maximum carrying capacity of k_1. a_{12} and a_{13} are the rate at which tumor cells are being killed by the hunting and resting predator cells respectively. The hunting predator cells grow at the rate of r_2 with the maximum carrying capacity k_2. Hunting predator cells are being killed by the tumor cells at the rate of a_{21}. The resting predator cells are being killed by the tumor cells at the rate of a_{31} and they die naturally at the rate of d_3. Since the recognition of tumor cells by predator cells is a very complex process, let us assume that the activation of resting predator cells depends directly on the number of tumor cells with positive constants r_3 and k_3 [1].

In order to non-dimensionalize the system, lets introduce:

$$x_1 = \frac{T}{k_1}, \quad x_2 = \frac{H}{k_2}, \; x_3 = \frac{R}{k_3}$$
$$R_2 = \frac{r_2}{r_1}, \quad R_3 = \frac{r_3}{r_1}, \; D_3 = \frac{d_3}{r_1}$$

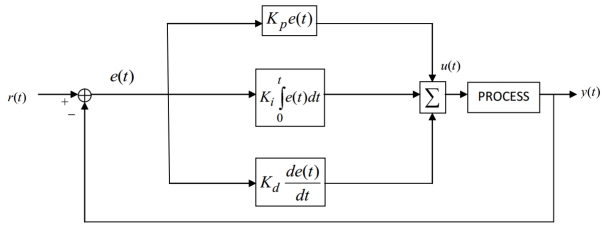

FIGURE 1. PID control logic.

$$A_{12} = \frac{a_{12}k_2}{r_1}, \quad A_{21} = \frac{a_{21}k_1}{r_1},$$
$$A_{13} = \frac{a_{13}k_3}{r_1}, \quad A_{31} = \frac{a_{31}k_1}{r_1} \tag{2}$$

Equation (1) takes the following form:

$$\begin{cases} \dot{x_1} &= x_1(1-x_1) - A_{12}x_1x_2 - A_{13}x_1x_3 \\ \dot{x_2} &= R_2x_2(1-x_2) - A_{21}x_1x_2 \\ \dot{x_3} &= \dfrac{R_3x_1x_3}{x_1+k_3} - A_{31}x_1x_3 - D_3x_3 + u \end{cases} \tag{3}$$

Equation (3) is the state space representation of dimensionless TDCM.

III. CONTROLLER DESIGN

A. PROPORTIONAL INTEGRAL DERIVATIVE (PID) CONTROLLER

PID control is a closed loop feedback control system which is very commonly used in numerous industrial automation because of its adaptability and dependability [18]. It continuously calculates the error from the feedback loop and tunes its output. It works on the structure of the PID controller, for instance, $K(s)$ being described by equation (4) [19].

$$K(s) = K_p + \frac{K_i}{s} + K_d s \tag{4}$$

$K(s)$ is the controller gain which has three parts; $K(s)$, K_i and K_d. They represents the proportional, integral and the derivative gains respectively. Desired response can be obtained by tuning these gains [18]. Figure (1) shows the block diagram of how the PID control works.

B. LYAPUNOV REDESIGN CONTROLLER

Lyapunov Redesign controller has been designed for the treatment of tumor by strengthening the immune system and destruction of cancer cells through drug injection. For this purpose, error has been introduced by taking the difference of tumor and resting predator cells with their desired reference value as follows:

$$\begin{cases} e_1 = x_1 - x_{1d} \\ e_2 = x_3 - x_{3d} \end{cases} \tag{5}$$

where x_{1d} is the desired value of tumor cells and x_{2d} is the desired value of resting predator cells; both in steady state.

Taking time derivative of equation (5) to get the following error dynamics:

$$\begin{cases} \dot{e}_1 = \dot{x}_1 - \dot{x}_{1d} \\ \dot{e}_2 = \dot{x}_3 - \dot{x}_{3d} \end{cases} \tag{6}$$

Substituting $\dot{x_2}$ and $\dot{x_3}$ from equation (3) in equation (6), we get

$$\begin{cases} \dot{e_1} = x_1(1-x_1) - A_{12}x_1x_2 - A_{13}x_1x_3 - \dot{x}_{1d} \\ \dot{e_2} = \dfrac{R_3x_1x_3}{x_1+K_3} - A_{31}x_1x_3 - D_3x_3 + u - \dot{x}_{3d} \end{cases} \tag{7}$$

x_{1d} and x_{2d} are constant references, so their derivative becomes zero. For the states x_1 and x_3 to converge to their desired values, the errors e_1 and e_2 must converge to zero. For this purpose, a positive Lyapunov candidate function is taken as:

$$V = \frac{1}{2}e_1^2 + \frac{1}{2}e_2^2 \tag{8}$$

For asymptotic stability, time derivative of V must be negative definite. For this purpose, taking time derivative of equation (8), we get

$$\dot{V} = \dot{e_1}e_1 + \dot{e_2}e_2 \tag{9}$$

By substituting the values of $\dot{e_1}$ and $\dot{e_2}$ from equation (7) in equation (9), we get

$$\dot{V} = e_1(x_1(1-x_1) - A_{12}x_1x_2 - A_{13}x_1x_3 + e_2(\frac{R_3x_1x_3}{x_1+k_3} - A_{31}x_1x_3 - D_3x_3 + u) \tag{10}$$

For $\dot{V}$ to be negative definite, we take

$$\begin{aligned} &e_1(x_1(1-x_1) - A_{12}x_1x_2 - A_{13}x_1x_3 \\ &\quad + e_2(\frac{R_3x_1x_3}{x_1+k_3} - A_{31}x_1x_3 - D_3x_3 + u) \\ &= -k_1e_1^2 - k_2e_2^2 \end{aligned} \tag{11}$$

where k_1 and k_2 are the control design parameters which are positive definite. So that $\dot{V}$ becomes

$$\dot{V} = -k_1e_1^2 - k_2e_2^2 \tag{12}$$

which will always be negative definite and the states will be asymptotic stable at the equilibrium point $(e_1, e_2) = (0, 0)$ by Lyapunov stability theory. The control input for both the resting predator and tumor cells can be obtained from the equation (11) as follows:

$$\begin{aligned} u = \frac{1}{e_2}[&-e_1(x_1(1-x_1) - A_{12}x_1x_2 - A_{13}x_1x_3) \\ &- e_2(\frac{R_3x_1x_3}{x_1+k_3} - A_{31}x_1x_3 - D_3x_3) \\ &- k_1e_1 - k_2e_2)] \end{aligned} \tag{13}$$

which is required control law using Lyapunov Redesign control technique.

C. SYNERGETIC CONTROLLER

Synergetic control emerged a few years ago and is been well used and developed by the control and automation society. Conceptually, Synergetic control works in a same manner as sliding mode controller. It works very nicely even in the presence of the disturbances and uncertainties; the advantage being chattering appears but with reduced amplitude as compared to Sliding Mode Control (SMC) [20].

The control synthesis starts by choosing a suitable macro-variable function $\delta(X, t)$ defined as:

$$\delta = C_1 e_1 + C_2 e_2 \tag{14}$$

where C_1 and C_2 are real positive constants. Taking time derivative of equation (14), we get

$$\dot{\delta} = C_1 \dot{e_1} + C_2 \dot{e_2} \tag{15}$$

The task is to track the resting predator cells to 40% of the hunting predator cells and reduce the tumor with an exponential rate under the control input. The dynamic evolution of the macro-variable is given by:

$$T\dot{\delta} + \delta = 0, T > 0 \tag{16}$$

where control parameter T is the convergence rate of the controlled states of the system. Now substituting the values of $\dot{e_1}$ and $\dot{e_2}$ from equation (6) in equation (15), we get

$$\begin{aligned}\dot{\delta} = C_1[x_1(1-x_1) - A_{12}x_1x_2 - A_{13}x_1x_3 - \dot{x}_{1d}] \\ + C_2[\frac{R_3x_1x_3}{x_1+K_3} - A_{31}x_1x_3 - D_3x_3 + u - \dot{x}_{3d}]\end{aligned} \tag{17}$$

Putting the values of δ and $\dot{\delta}$ from equations (14) and (17) respectively into (16), we get

$$\begin{aligned}T\Big(C_1\Big(x_1(1-x_1) - A_{12}x_1x_2 - A_{13}x_1x_3 - \dot{x}_{1d}\Big) \\ + C_2\Big(\frac{R_3x_1x_3}{x_1+K_3} - A_{31}x_1x_3 - D_3x_3 + u - \dot{x}_{3d}\Big)\Big) \\ + C_1e_1 + C_2e_2 = 0\end{aligned} \tag{18}$$

From equation (18), we have the following control law:

$$\begin{aligned}u = \frac{R_3x_1x_3}{x_1+K_3} - A_{31}x_1x_3 - D_3x_3 - \frac{C_1e_1}{C_2T} - \frac{e_2}{T} \\ - \frac{c_1}{c_2}x_1(1-x_1) + A_{12}x_1x_2 + A_{13}x_1x_3\end{aligned} \tag{19}$$

Asymptotic stability of the system can be proved by taking following Lyapunov candidate function as:

$$V = \frac{1}{2}\delta^2 \tag{20}$$

Taking the time derivative of equation (20), we get:

$$\dot{V} = \delta\dot{\delta} \tag{21}$$

Using equation (17), the equation (21) becomes

$$\dot{V} = -\frac{1}{T}\delta^2 \tag{22}$$

which is negative definite ensuring asymptotic stability of the system.

D. SLIDING MODE CONTROLLER

SMC controller has been designed as given in [21]. The sliding surface can be taken as:

$$s = a_1e_1 + a_2e_2 \tag{23}$$

First derivative of sliding surface can be written as:

$$\dot{s} = a_1\dot{e}_1 + a_2\dot{e}_2 \tag{24}$$

x_{1d} and x_{2d} are constant references so the derivative becomes zero. Using equation (6) we can write equation (24) as following:

$$\dot{s} = a_1\dot{x}_1 + a_2\dot{x}_3 \tag{25}$$

Using the exponential reaching law, we have

$$\dot{s} = -k \mid s \mid sign\left(\frac{s}{\psi}\right) \tag{26}$$

Control law obtained from SMC has two parts

$$u = u_{eq} + u_{dis} \tag{27}$$

where u_{eq} is the equivalent controller part which controls the reaching phase and u_{dis} is the discontinuous controller part which makes sure that the system remains on the sliding surface once arrived. u_{dis} is computed by using $\dot{s} = 0$, using equation (26) we can write

$$u_{dis} = -k \mid s \mid sign\left(\frac{s}{\psi}\right) \tag{28}$$

u_{eq} is computed using equation (3) and equation (25)

$$\begin{aligned}u_{eq} = -\frac{a_1}{a_2}(x_1(1-x_1) - A_{12}x_1x_2) \\ - \left(\frac{R_3x_1x_3}{x_1+k_3} - A_{31}x_1x_3 - D_3x_3\right)\end{aligned} \tag{29}$$

Using equation (28) and equation (27), we have the following control law:

$$\begin{aligned}u = -k \mid s \mid sign\left(\frac{s}{\psi}\right) - \frac{a_1}{a_2}(x_1(1-x_1) - A_{12}x_1x_2) \\ - \left(\frac{R_3x_1x_3}{x_1+k_3} - A_{31}x_1x_3 - D_3x_3\right)\end{aligned} \tag{30}$$

Asymptotic stability of the system can be proved by taking following Lyapunov candidate function as:

$$v = \frac{1}{2}s^2 \tag{31}$$

Taking time derivative of the equation (31) we get

$$\dot{v} = s\dot{s} \tag{32}$$

For asymptotic stability we must have $\dot{v} \leq 0$. Substituting value of $\dot{s}$ from equation (25), equation (32) can be written as:

$$\begin{aligned}s\Big(a_1\Big(x_1(1-x_1) - A_{12}x_1x_2 - A_{13}x_1x_3\Big) \\ + a_2\Big(\frac{R_3x_1x_3}{x_1+k_3} - A_{31}x_1x_3 - D_3x_3 + u\Big)\Big) \leq 0\end{aligned} \tag{33}$$

TABLE 1. Value of constants and system parameters.

Parameter	Value	Parameter	Value
R_2	0.6	R_3	4.5
D_3	0.5	A_{12}	1
A_{21}	1.5	A_{13}	2.5
A_{31}	0.2	x_{d1}	0.01
x_{d3}	0.4	-	-

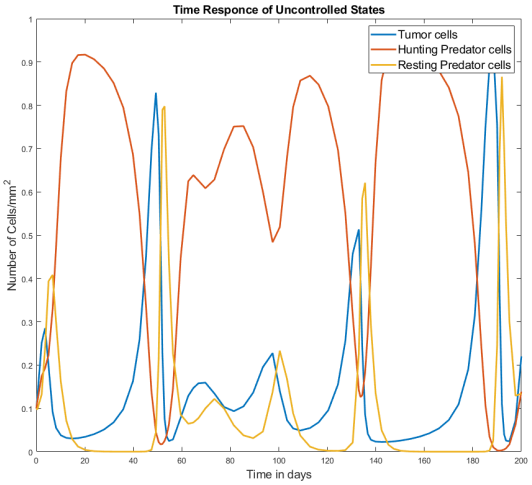

FIGURE 2. Uncontrolled response of Three Dimensional Cancer Model.

Substituting u from equation (30), we can write equation (33) as:

$$-a_2 \mid s \mid sign\left(\frac{s}{\psi}\right) \leq 0 \tag{34}$$

which is negative definite ensuring asymptotic stability of the system.

IV. SIMULATION AND RESULTS

MATLAB/Simulink has been used to simulate and study the performance of the proposed controllers. The values of the constants and system parameters have been shown in the table (1).

The uncontrolled response of the system is shown in figure (2). The response shows chaotic behavior. Figure (3) shows uncontrolled response in three-dimensional phase portrait which also shows chaotic behavior of the system. The system has initial conditions as 0.1 for all states and then the system shows chaotic behavior which is not desirable in any system.

The comparison of resting predator cells under the proposed controllers is shown in figure (4). It is clear from the figure (4) that the output of PID controller shows overshoots and undershoots before converging to the desired value with almost no steady state error. The output of Synergetic and Lyapunov Redesign controller converges to the desired value in lessor time as compared to PID controller. Synergetic controller tracks the reference value with negligible oscillations with a smaller steady state error. Lyapunov Redesign

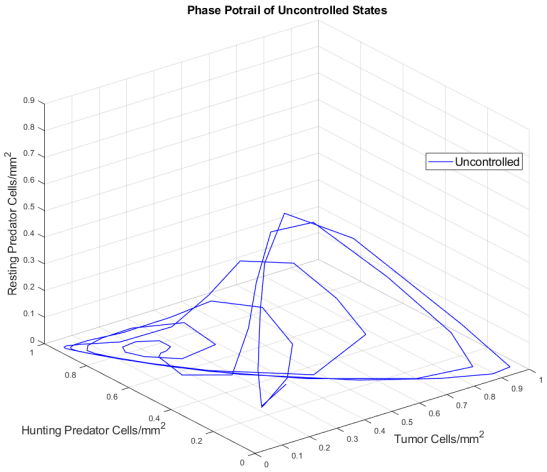

FIGURE 3. Uncontrolled response of Three Dimensional Cancer Model.

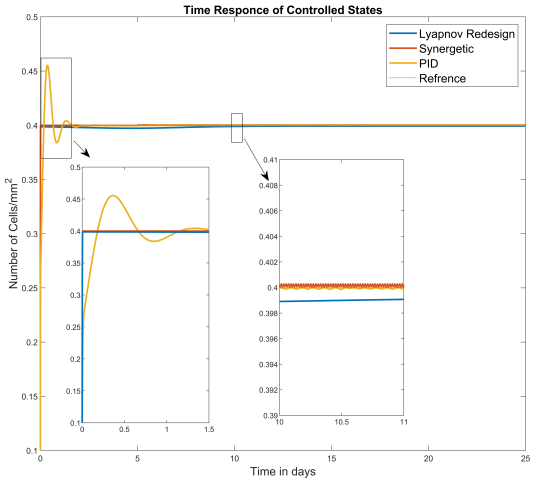

FIGURE 4. Resting predator cells: Comparison between Synergetic, Lyapunov Redesign and PID controllers.

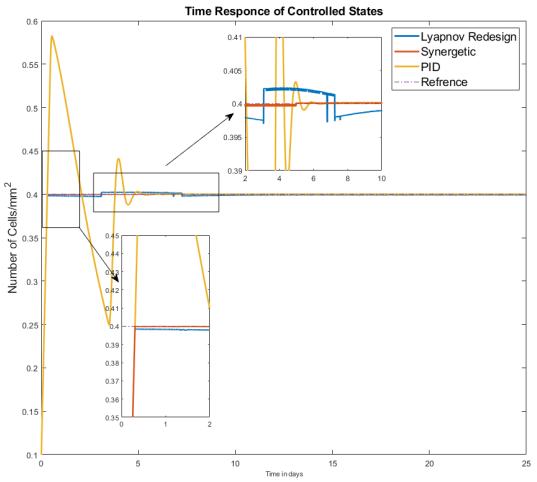

FIGURE 5. Resting predator cells with drug path blockage: Comparison between Synergetic, Lyapunov Redesign and PID controllers.

controller shows steady state error which keeps reducing with time and converges to desired value at $t = \infty$.

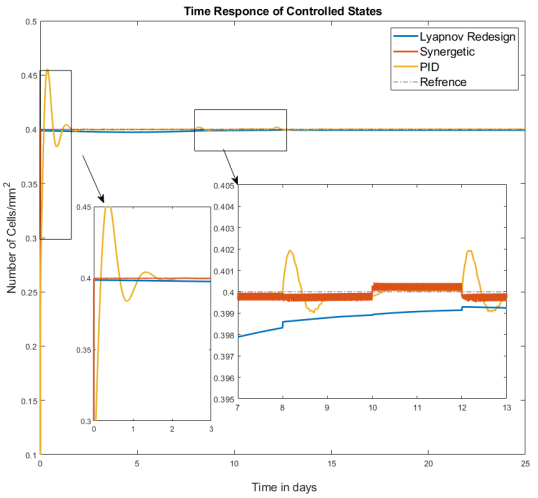

FIGURE 6. Resting predator cells with oral medication: Comparison between Synergetic, Lyapunov Redesign and PID controllers.

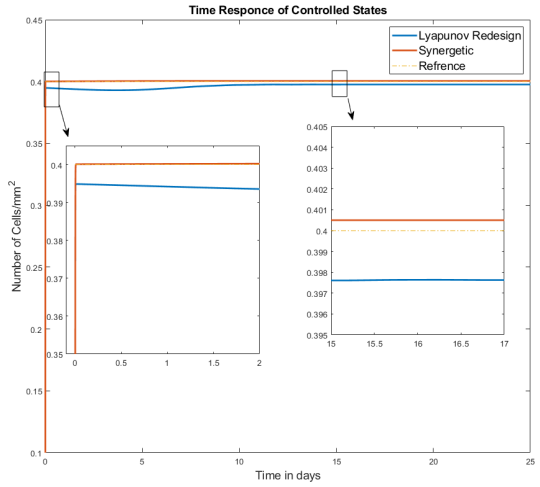

FIGURE 7. Resting predator cells with constant disturbance: Comparison between Synergetic, Lyapunov Redesign and PID controllers.

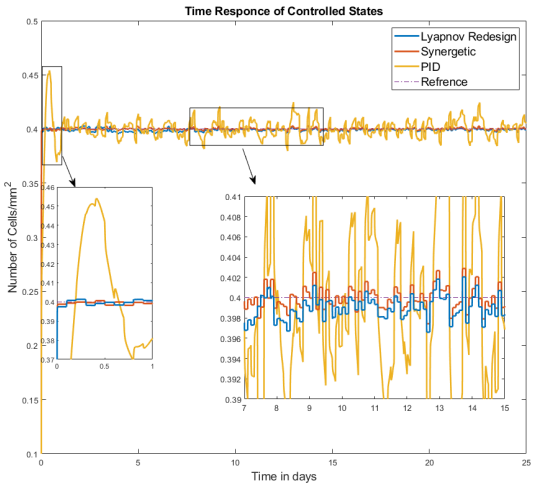

FIGURE 8. Resting predator cells with added White Noise disturbance: Comparison between Synergetic, Lyapunov Redesign and PID controllers.

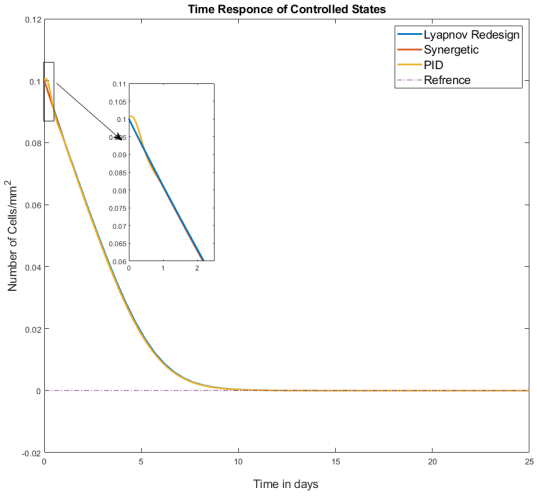

FIGURE 9. Tumor cells: Comparison between Synergetic, Lyapunov Redesign and PID controllers.

In figure (5) same comparison is shown as figure (4) but to test the stability of the controllers, drug path blockage scenario has been simulated by adding a saturation block in MATLAB/Simulink. This figure shows bigger overshoots and undershoots in the output of PID controller which takes a lot of time to converge to the desired value. Output of the Synergetic and Lyapunov Redesign controllers shows a good transient response and converges to the desired value very quickly. Output of Lyapunov Redesign deviates from the desired value in steady state response but converges back quickly while the Synergetic controller does not show any deviation in the steady state response.

The number of cells depends on various factors such as the type of food, medication and even the environment. This kind of cell behavior has been simulated by adding oral medication that will strengthen as a result of first dose whereas in second dose, it weakens the resting predator cells in the body. Figure 6 shows the output of resting predator cells under the proposed controllers. The initial response is like that of figure (4). Non-linear controllers neutralized the effect of the disturbance and the output of PID controller showed small overshoots and undershoot and took small time to converge back to the desired value when medicine has been taken by the patient.

In figure (7) a constant disturbance has been added to test the output of the proposed controllers. PID controller did not yield any output while the nonlinear controllers produced the output similar to that of figure (4).

Gaussian white noise is added to the system to simulate the natural variance occurring in the human body. Figure (8) shows the output of the Lyapunov Redesign, Synergetic and PID controllers after the addition of Gaussian white noise of power 0.01. Only PID controller has been unable to cope with the disturbances and showed a very noisy output. Synergetic and Lyapunov Redesign controllers do have small disturbances in the output but the noise observed in the output is negligible.

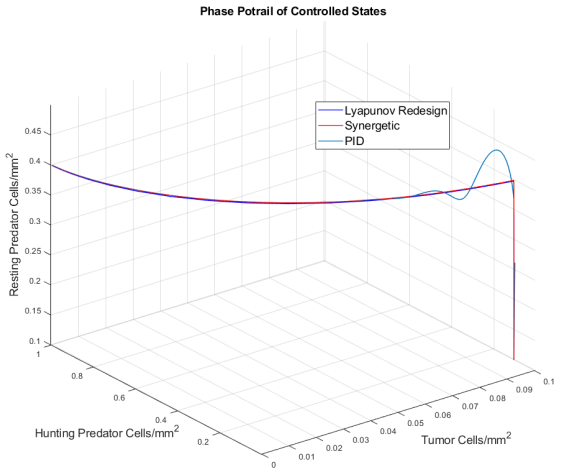

FIGURE 10. Comparison between controlled response of Three Dimensional Cancer Model.

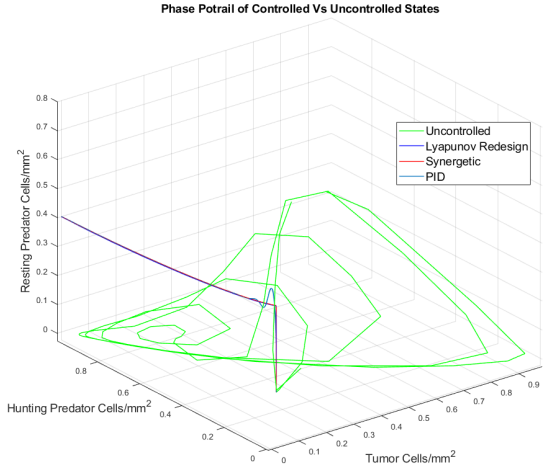

FIGURE 11. Comparison between controlled and Uncontrolled response of Three Dimensional Cancer Model.

Figure (9) shows the comparison of the proposed Lyapunov Redesign and Synergetic with each other and that with PID controller. It is clear that the tumor cells converge to zero and a small overshoot has been observed in output of the PID controller.

Figures (10) and (11) show the comparison of the controlled and un-controller phase portraits of resting predator cells using the proposed (Synergetic, Lyapunov Redesign and Sliding Mode) and PID controllers respectively. It is clear from both figures (10),(11) that the output of PID controller undergoes overshoots and undershoots.

Figure (12) shows the comparison of resting predator cells using Lyapunov Redesign, Synergetic and Sliding Mode Controllers. Both Synergetic and Lyapunov Redesign controllers start tracking the reference value right from the initial stage while the sliding mode controller starts to follow the Synergetic and Lyapunov Redesign to a certain point but gets diverted and shows delayed convergence.

Figures (13) and (14) show comparison of tumor and hunting predator cells between Lyapunov Redesign, Synergetic

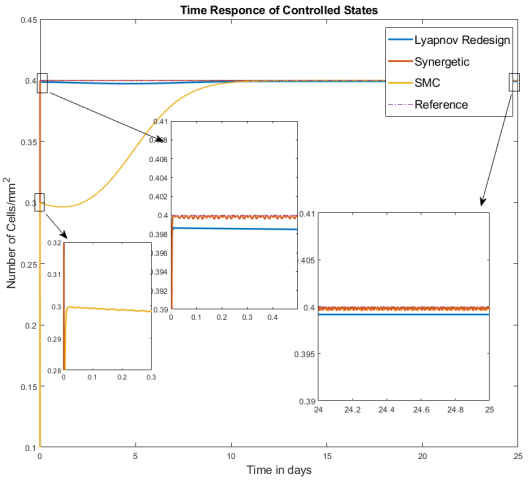

FIGURE 12. Resting predator cells: Comparison between Synergetic, Lyapunov Redesign and SMC controllers.

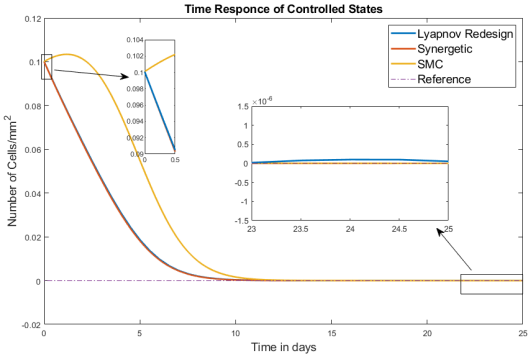

FIGURE 13. Tumor cells: Comparison between Synergetic, Lyapunov Redesign and SMC controllers.

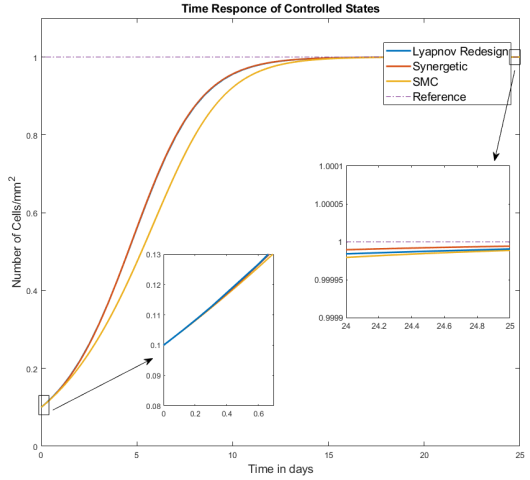

FIGURE 14. Hunting predator cells: Comparison between Synergetic, Lyapunov Redesign and SMC controllers.

and Sliding Mode Controller respectively. Sliding mode controller has negligible steady state error but starts tracking its reference with considerable delay as shown in figure (12).

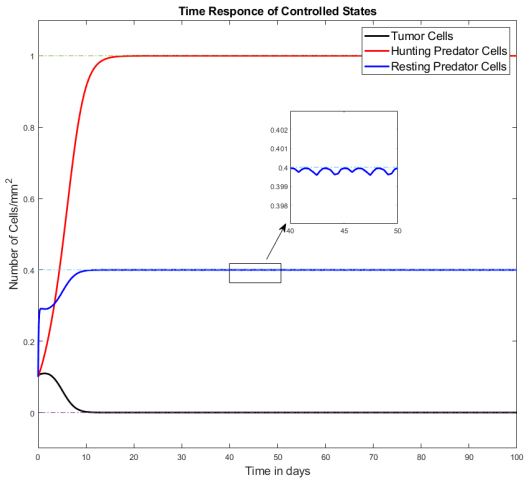

FIGURE 15. **All three cells using Sliding Mode Controller.**

Figure (13) shows overshoot in sliding mode controller and a delay in convergence to zero. Figure (14) also shows that sliding mode controller takes longer to converge to its tracking point.

Figure (15) has been drawn to show the behavior of all the 3 cells using sliding mode controller. Chattering phenomenon has been observed in zoomed-part of the figure (15) which is natural in case of sliding mode controllers.

V. CONCLUSION

In this paper, three nonlinear controllers (Synergetic, Lyapunov Redesign and Sliding Mode Controller) have been proposed to control the hunting predator, resting predator cells and to reduce tumor cells to a level where they can successfully be removed via surgery and the resting predator cells to 40% of the hunting predator cells. Proposed controllers have been compared with each other and with PID controller. Simulation results using MATLAB/Simulink show that the performance of the proposed Synergetic controller is slightly better than Lyapunov Redesign controller and Sliding Mode Controller, Sliding Mode and PID controllers in transition state and Sliding Mode Controller is slightly better than Synergetic, Lyapunov Redesign and PID controllers in steady state error. The performance of the proposed controllers has been compared based on their transient response and steady state error. It is also noted that the both proposed Sliding Mode and Synergetic controller performed slightly better than Lyapunov Redesign and far better than PID controller even in the presence of un-modeled disturbances and additive noises.

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