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Tumor Treatment Protocol by using Genetic Algorithm based Bernstein Polynomials and Sliding Mode Controller

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ABSTRACT Life threatening nature of cancer and toxic effects of chemotherapy demand for an optimal design of treatment protocol. The main objective of treatment design is to maintain adequate health of patient while administering a continuous chemo dose for effective decimation of cancer. Mathematical model adopted in this paper is first order nonlinear coupled ordinary differential equation (NCODE) relating tumor, effector immune and normal cells under effect of chemotherapy. This paper primarily utilizes the Bernstein polynomial with genetic algorithm based coefficient tuning for solution of the tumor model. Secondarily sliding mode controller (SMC) is used as optimal control for normal and immune cells boosting in addition to escalated tumor minimization. The hybrid approach used in this research produces a potent minimization of cancer. Application of SMC ensures normal cells concentration well above the critical threshold; hence a continuous treatment dose is viable. Proposed methodology enhances the effect of chemotherapy over cancer while maintaining healthy state of patient.

INDEX TERMS Bernstein polynomial (BSP), nonlinear coupled ordinary differential equation (NCODE), genetic algorithm (GA), optimization, sliding mode controller (SMC),

I. INTRODUCTION

Various forms of cancer stands among the critical life threatening diseases human race have ever seen. Core of cancer rely on unbridled growth augmented by cell division. [1] Predicts approximately 59% deaths of cancer patients by 2040 in the light of data gathered in 2018. Solid form of irregular cell growth is attributed as tumor that is classified into primary (origin) and secondary types. Primary tumor can be of cancerous or non-cancerous nature, whereas secondary tumors are cancerous by inception [2]. Among the four grades of tumor, grade-IV is the one that contains blood vessels while features rapid growth, aggressive cell division and post treatment regrowth [3].

[4] Reports nervous system tumor detection with age standardization of 0.01 to 12.7 males and 0.01 to 10.7 in females, per 100,000 people in different countries. According to [5] 12% death rate around the world due to neoplastic diseases is one of the intriguing attractions for study of dynamics and control of tumor growth. Cancerous tumor briskly grows itself exploiting nutrients supplement for normal cells (NCs). Despite the profound precedence of chemotherapy on tumor cells (TCs) , adverse effects on NCs are inevitable [6][7].

Immune system of human body launches its response upon recognition of tumor. However the sufficiency of immune system response to eliminate tumor is not always guaranteed. Immunotherapy is in regular practice to supplement the natural immune system of human body in its fight against tumor. Finding an approximate procedure for achieving optimal administration of drugs to treat tumor is active focus of researchers in recent times. The fundamental question is to find the exact dose plan along with the right technique for drug administration [8]. Combination of chemo and immunotherapies have been used with promising results to eliminate the tumor and keep NCs in healthy range [9].

It is clinically observed that the tumor size is not synchronous with dosage of chemotherapy and the phenomenon is known as temporal oscillations. Regrowth of tumor during temporal oscillation calls for optimal design of pulsed chemotherapy. Numerous studies are available in literature addressing the design of optimal controller as treatment protocol based on clinical and experimental data [10]. The treatment protocol and the tumor drug interaction phenomenon (Jeff's phenomenon) under standard pulsed chemotherapy and optimal control is

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presented by De Pillis & Radunskaya [11]. Freedman [12] discussed the mathematical tool of differential analysis, persistence theory, Hopf-Andronov-Poincare bifurcation and linear system theory to present generalized criteria for the therapeutic efficacy of Adoptive Cancer Immunotherapy (ACI).

[13] Carried out tumor reduction along with maximization of effector cells and interleukin-2 concentration using controller based on Pontryagins maximum principle followed by numerical analysis of the solution. [14] Treated mathematical model of tumor with combination of immune, vaccine and chemotherapies along with evaluation of system dynamics, stability, bifurcation analysis and detection of basins of attractions.

Rocha et al. [15] introduced a model integrating chemo-immuno therpaies with periodic radiotherapy incorporated with optimal control based on Pontryagins maximum principle. Khalili et al. [16] used steepest descent for eualvation of best rate for drug injection, while achiving stability by Lyapunov theory and Barabalat lemma. Shindi et al. [9] improved constrained multi objective optimization problem (CMOOP) solution using Pontryagins maximum principle based optimal control along with evolutionary algorithm (EA) and swarm intelligence (SI) based multi objective optimizer.

Despite the availability of diverse solutions proposed by many researchers with promising results; there is still plenty of space available for enhanced optimal solutions of given mathematical models using evolutionary algorithms and optimal controls. The main contribution of this paper is the design of treatment protocol while boosting the system of the model optimally by SMC. This work benefits from the approximation capabilities of BSP with GA tuned coefficients. Simulation is carried out with three cases without SMC and three cases with SMC applied in combination to tumor, normal and immune cells.

The paper is structured as follows. Second section is confined to the tumor model based on system of coupled differential equations followed by brief introduction of BSP, GA and SMC. Section 3 presents the proposed methodology and the design of SMC. Section 4 presents the simulation results and discussion. Conclusion is presented in section 5.

II. GOVERNING MODEL AND PROPOSED METHODOLOGY

Partial and the ordinary differential equations are the foundations of mathematical models which can mimic the dynamics of tumor and its relationship with normal and immune response of the body. Many such models are presented in literature [9], [11], [17]–[19] having their own benefits and drawbacks.

A. TUMOR MODEL

The model used in this paper is the one that is presented by De Pillis & Radunskaya [11], and modified by Shindi et al. in 2020 [9]. This model is based on of three coupled differential equations representing the cell population and fourth is the drug concentration equation. The normal, tumor and immune cells (ICs) with respect to time are represented in this model by following equations.

$$\dot{N} = r_2 N\left(1 - b_2 N\right) - c_4 TN - a_3 u \tag{1}$$

$$N\left(0\right) = N_0$$

$$\dot{T} = r_1 T\left(1 - b_1\right) - c_2 IT - c_3 TN - a_2 u \tag{2}$$

$$T\left(0\right) = T_0$$

$$\dot{I} = s + \frac{\rho IT}{\alpha + T} - c_1 IT - d_1 I - a_1 u \tag{3}$$

$$I\left(0\right) = I_0$$

$$\dot{u} = v\left(t\right) - d_2 u \tag{4}$$

With boundary conditions

$$N\left(0\right) = 0.9$$

$$T\left(0\right) = 0.25 \tag{5}$$

$$I\left(0\right) = 0.25$$

Here I, T and N are the variables used to represent the concentrations of immune, tumor and normal cells respectively. Drug concentration is denoted by u.

In equation (1), first term describes the growth term, second term for the competition between tumor and NCs and the third term is the effect of drug on NCs. In equation (2), first term is the growth of TCs, second and third terms are the immune-tumor and tumor-normal cells interactions respectively and the last term is the effect of treatment drug on tumor. In equation (3), first term is the source term, second term is the saturation control term, third term is the tumor immune interaction, fourth term is the ICs reduction naturally and the last term is the effect of chemotherapy on ICs. In equation (4), first term is the dose and the second term is the natural death rate of the drug. Other parameters manage various characteristics of the model but all of them bear positive values. Parameter r_1 and r_2 control the logistic growth rate of the model. The description and values of remaining parameters is given in Table I.

TABLE I

Parameter	Value	Description	References
a_1	0.2	I cells death rate by drug	[9], [11], [17], [18]
a_2	0.3	T cells death rate by drug	
a_3	0.1	N cells death rate by drug	
b_1, b_2	1	carrying capacity	
c_1	1	Competition term of I vs T	
c_2	0.5	Competition term of I vs T	
c_3	1	Competition term of N vs T	
c_4	1	Competition term of N vs T	
d_1	0.2	I cells natural death rate	
r_1	1.5	Growth rate of T cells	
r_2	1	Growth rate of N cells	
s	0.33	I system source	
ρ	0.01	Rate of I response	
α	0.3	Threshold rate	
d_2	1	Drug death rate	[11], [17]
$v(t)$	1	Chemotherapy source rate	

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B. BERNSTEIN POLYNOMIAL (BSP)

Russian scientist Sergei Natanovich Bernstein [20] introduced BSP, used for approximation in numerical analysis. The BSP $B_{i.n}(x)$ 'n' of the interval [0 T_a] as follows

$$B_{i,n}(x)=\binom{n}{i}\frac{x^i(T_a-x)^{n-i}}{T_a{}^n} \tag{6}$$

In this case $T_a = 1$, so

$$B_{i,n}(x)=\binom{n}{i}x^i(1-x)^{n-i} \tag{7}$$

The properties of the BSP are

$$B_{i,n}(x)=\begin{cases}0 & \forall i\neq 0\\ 1 & \forall i=0\end{cases} \tag{8}$$

$$B_{i-1,n-1}(1)=\begin{cases}0 & \forall i\neq n\\ 1 & \forall i=n\end{cases} \tag{9}$$

$$B_{i,n-1}(1)=\begin{cases}0 & \forall i\neq n\\ 1 & \forall i=n-1\end{cases} \tag{10}$$

The linear combination of lower order polynomials can be generated by using the recursive properties of higher order polynomials and their derivatives as follows:

$$B_{i,n}(x)=(1-x)B_{i,n}(x)+xB_{i,n}(x) \tag{11}$$

$$B'_{i,n}(x)=n\left(B_{i-1,n-1}(x)-B_{i,n-1}(x)\right) \tag{12}$$

Here $'$ denotes the derivative with respect to 'x' of the equations.

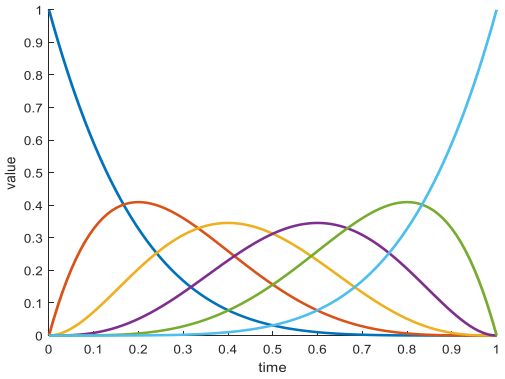

FIGURE 1. **BSP behavior**

C. GENETIC ALGORITHM

GA belongs to the clans of nature inspired algorithms. It is based on randomly generated population of chromosomes known as candidate solution [21]. The size of the chromosomes is equal to the unknown coefficients of the problem. Pair of chromosomes undergoes crossover reproduction, mutation and selection iteratively. Following steps are followed by GA in order to find the best solution.

a) Use problem specific bound for random generation of chromosomes with gene length equal to the count of unknown constants.
b) Plug in each chromosome of the population to cost function for evaluation of fitness.
c) If the fitness of best chromosome reaches a predefined value or any other termination criterion is achieved then stop, otherwise proceed to step
d) Allow the randomly selected chromosomes to reproduce new generation via crossovers and mutation and go to step (b).

D. SLIDING MODE CONTROLLER

SMC was introduced as a robust controller to locate the stability of the higher order nonlinear systems under uncertainties [22]. Application of SMC benefits in reduction of system complexity, low sensitivity to parameter fluctuation and allows decoupling of the coupled systems. The main supremacy of SMC is rejection of disturbance which is not available in other contemporary controllers like model predictive controller (MPC) and robust controller. While, applying chemotherapy treatment disturbance occurred due to uncertain condition of growth and death rate of cells. The design is quite flexible which assure stability using Lyapunov function. Apart from the advantages of SMC there exist some drawbacks; must know system states and steady state error. SMC also carry the property of finite time convergence towards the sliding manifold. SMC is applied by defining the sliding surface followed by controller design that drives the system from initial states towards the sliding surface. Controller operates by initially hitting the sliding surface and then it slides towards minimum error possible [23].

III. PROPOSED APPROACH

In this paper tumor model equations (1-3) are used to define the error function. BSP is used as basis function to find the approximate solution of the system. The coefficients of BSP are tuned by GA to minimize the error function solution of the system (1-3) subject to boundary conditions (5) is evaluated assuming linear combination given by equations (13-15).

$$\begin{aligned}N(x)&=\sum_{i=0}^{n}f_iB_{i,n}(x)\\ \dot{N}(x)&=n\left(\sum_{i=1}^{n}f_iB_{i-1,n-1}(x)-\sum_{i=0}^{n-1}f_iB_{i,n-1}(x)\right)\end{aligned} \tag{13}$$

$$\begin{aligned}T(x)&=\sum_{i=0}^{n}g_iB_{i,n}(x)\\ \dot{T}(x)&=n\left(\sum_{i=1}^{n}g_iB_{i-1,n-1}(x)-\sum_{i=0}^{n-1}g_iB_{i,n-1}(x)\right)\end{aligned} \tag{14}$$

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$$I(x)=\sum_{n=0}^{n} h_i B_{i,n}(x)$$
$$\dot{I}(x)=n\left(\sum_{i=1}^{n} h_i B_{i-1,n-1}(x)-\sum_{i=0}^{n-1} h_i B_{i,n-1}(x)\right) \quad (15)$$

Where the unknown constants f_i, g_i *and* h_i $(i = 1,2,3,\dots,n)$ are to be optimally evaluated by GA. By using initial conditions and the properties of the BSP given by equation (5) and (11)-(13) respectively the values of f_0, g_0 *and* h_0 are found us in (16-18).

$$N(0)=\sum_{i=0}^{n} f_i B_{i,n}(0)$$
$$N(0)= f_0 = 0.9 \quad (16)$$

$$T(0)=\sum_{i=0}^{n} g_i B_{i,n}(0)$$
$$T(0)= g_0 = 0.25 \quad (17)$$

$$I(0)=\sum_{i=0}^{n} h_i B_{i,n}(0)$$
$$I(0)= h_0 = 0.25 \quad (18)$$

Hence the remaining unknown constants of equations (13-15) are $\boldsymbol{f_i}$, $\boldsymbol{g_i}$ $\boldsymbol{and}$ $\boldsymbol{h_i}$ $\boldsymbol{(i = 1,2,3,\dots,n)}$. GA is applied to evaluate these unknown constants after converting NCODE (1-3) into an error minimization problem by formulating the error function.

A. THE ERROR FUNCTION

Error function is formulated for six different cases. First three cases involve combinations of immune and chemotherapies, whereas later three cases involve use of control drug in the form of SMC.

1) CASE-1

In this case the effect of tumor on NCs is studied in the absence of both immune and chemo therapies. By keeping I(t) and V(t) zero, the equations error function becomes:

$$E_N=\frac{1}{11}\sum_{j=0}^{10}\left(\dot{N}(t_j)-\left(r_2\left(1-b_2N(t_j)\right)+c_4T(t_j)\right)N(t_j)\right)^2 \quad (19)$$

$$E_T=\frac{1}{11}\sum_{j=0}^{10}\left(\dot{T}(t_j)-r_1T(t_j)\left(1-b_1T(t_j)\right)+c_3T(t_j)N(t_j)\right)^2 \quad (20)$$

$$E_{optimal}=\text{minimum}\left(E_N+E_T\right) \quad (21)$$

2) CASE-2

In this case the reaction of immune response towards tumor is deliberated in the absence of chemotherapy and the resultant error function is given as follows:

$$E_N=\frac{1}{11}\sum_{j=0}^{10}\left(\dot{N}(t_j)-r_2N(t_j)\left(1-b_2N(t_j)\right)+c_4T(t_j)N(t_j)\right)^2 \quad (22)$$

$$E_T=\frac{1}{11}\sum_{j=0}^{10}\left(\dot{T}(t_j)-r_1T(t_j)\left(1-b_1T(t_j)\right)+c_2I(t_j)T(t_j)+c_3T(t_j)N(t_j)\right)^2 \quad (23)$$

$$E_I=\frac{1}{11}\sum_{j=0}^{10}\left(\dot{I}(t_j)-s-\frac{\rho I(t_j)T(t_j)}{\alpha+T(t_j)}+c_1I(t_j)T(t_j)+d_1I(t_j)\right)^2 \quad (24)$$

$$E_{optimal}=\text{minimum}\left(E_N+E_T+E_I\right) \quad (25)$$

3) CASE-3

This case depicts the state of NCs, ICs and TCs under the effects of immune and chemo therapies. Combined error function is evaluated as follows:

$$E_N=\frac{1}{11}\sum_{j=0}^{10}\left(\dot{N}(t_j)-r_2N(t_j)\left(1-b_2N(t_j)\right)+c_4T(t_j)N(t_j)+a_3u(t_j)\right)^2 \quad (26)$$

$$E_T=\frac{1}{11}\sum_{j=0}^{10}\left(\dot{T}(t_j)-r_1T(t_j)\left(1-b_1T(t_j)\right)+c_2I(t_j)T(t_j)+c_3T(t_j)N(t_j)+a_2u(t_j)\right)^2 \quad (27)$$

$$E_I=\frac{1}{11}\sum_{j=0}^{10}\left(\dot{I}(t_j)-s-\frac{\rho I(t_j)T(t_j)}{\alpha+T(t_j)}+c_1I(t_j)T(t_j)+d_1I(t_j)+a_1u(t_j)\right)^2 \quad (28)$$

$$E_{optimal}=\text{minimum}\left(E_N+E_T+E_I\right) \quad (29)$$

4) CASE-4

In this case an SMC is designed to boost the chemotherapy effect on TCs with base configuration of case-3. SMC used as drug to exterminate the TCs is given in equation (30)

$$\mu_T(x)=-\rho_T sgn(\sigma_T)-\partial_T r_1T(1-b_1T) \quad (30)$$

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∂_T is an adjustable coefficient that is used to control tumor growth. Addition of equation (30) in tumor equation (2) results in equation (31).

$$\dot{T} = (1-\partial_T) r_1 T (1-b_1 T) - \rho_T sgn(\sigma_T) - c_2 IT - c_3 TN - a_2 u \quad (31)$$

Sliding surface and it's derivative for this case is represented by equation (32, 33)

$$\sigma_T = q_1 T + I \quad (32)$$

$$\dot{\sigma}_T = q_1 \dot{T} + \dot{I} \quad (33)$$

Here $q_1 > 0$ is the design parameter. Equation (34) is formed by multiplying σ_T on both sides of equation (33) followed by substitution of equation (3), (31) and property $\sigma_T sgn(\sigma_T) = |\sigma_T|$. Equation (37) is formed after some simplification and defining a term η_T as in equation (36).

$$\sigma_T \dot{\sigma}_T = -q_1 \rho_T |\sigma_T| + \sigma_T \left(q_1 \left((1-\partial_T) r_1 T (1-b_1 T) - c_2 IT - c_3 TN - a_2 u \right) + s + \frac{\rho IT}{\alpha + T} - c_1 IT - d_1 I - a_1 u \right) \quad (34)$$

$$\sigma_T \dot{\sigma}_T \le -|\sigma_T| \left(q_1 \rho_T - \left| q_1 \left((1-\partial_T) r_1 T (1-b_1 T) - c_2 IT - c_3 TN - a_2 u \right) + s + \frac{\rho IT}{\alpha + T} - c_1 IT - d_1 I - a_1 u \right| \right) \quad (35)$$

$$\eta_T = q_1 \rho_T - \left| q_1 \left((1-\partial_T) r_1 T (1-b_1 T) - c_2 IT - c_3 TN - a_2 u \right) + s + \frac{\rho IT}{\alpha + T} - c_1 IT - d_1 I - a_1 u \right| \quad (36)$$

$$\sigma_T \dot{\sigma}_T \le -|\sigma_T| \eta_T \quad (37)$$

Where η_T is positive by design and ρ_T evaluated from equation (36) is given in (38)

$$\rho_T = \frac{\left| q_1 \left((1-\partial_T) r_1 T (1-b_1 T) - c_2 IT - c_3 TN - a_2 u \right) + s + \frac{\rho IT}{\alpha + T} - c_1 IT - d_1 I - a_1 u \right|}{q_1} + \frac{\eta_T}{q_1} \quad (38)$$

Since $-|\sigma_T| \eta_T \le 0$ by default, therefore the system is asymptotically stable, i. e., $\sigma_T \dot{\sigma_T} \le 0$. In this case, the use of equations (1), (3) and (31) results in error function given by equations (39-42).

$$E_N = \frac{1}{11} \sum_{j=0}^{10} \left(\dot{N}(t_j) - r_2 N(t_j) \left(1 - b_2 N(t_j)\right) + c_4 T(t_j) N(t_j) + a_3 u(t_j) \right)^2 \quad (39)$$

$$E_T = \frac{1}{11} \sum_{j=0}^{10} \left(\dot{T}(t_j) - (1-\partial_T) r_1 T(t_j) \left(1 - b_1 T(t_j)\right) + \rho_T sgn(\sigma_T) + c_2 I(t_j) T(t_j) + c_3 T(t_j) N(t_j) + a_2 u(t_j) \right)^2 \quad (40)$$

$$E_I = \frac{1}{11} \sum_{j=0}^{10} \left(\dot{I}(t_j) - s - \frac{\rho I(t_j) T(t_j)}{\alpha + T(t_j)} + c_1 I(t_j) T(t_j) + d_1 I(t_j) + a_1 u(t_j) \right)^2 \quad (41)$$

$$E_{optimal} = \text{minimum}(E_N + E_T + E_I) \quad (42)$$

5) CASE-5

In this case a supplementary SMC is designed for ICs boosting to the basic framework of case-4. SMC for ICs boosting is given in equation (43).

$$\mu_I(x) = -\rho_I sgn(\sigma_I) + c_1 IT + d_1 I + a_1 u \quad (43)$$

Addition of equation (44) in ICs equation (3) results in (44)

$$\dot{I} = s + \frac{\rho IT}{\alpha + T} - \rho_I sgn(\sigma_I) \quad (44)$$

Sliding surface and its derivative for this case is given by (45, 46)

$$\sigma_I = q_2 T + q_3 I + u \quad (45)$$

$$\dot{\sigma}_I = q_2 \dot{T} + q_3 \dot{I} + \dot{u} \quad (46)$$

Here $q_2 > 0$ while $q_3 < 0$ are the design parameters.. Equation (47) is formed by multiplying σ_I on both sides of equation (46). The equations (2), (4) and (45) along with the property $\sigma_I sgn(\sigma_I) = |\sigma_I|$ is substituted afterwards Equation (50) is structured by simplification and using η_I as defined in equation (49)

$$\sigma_I \dot{\sigma}_I = -q_3 \rho_I |\sigma_I| + \sigma_I \left(q_2 \left(r_1 T (1-b_1 T) - c_2 IT - c_3 TN - a_2 u \right) + q_3 \left(s + \frac{\rho IT}{\alpha + T} \right) + v(t) - d_2 u \right) \quad (47)$$

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$$\sigma_I\dot{\sigma}_I \le -|\sigma_I|\left|\begin{array}{l} q_3\rho_I \\ -\left|\begin{array}{l} q_2\begin{pmatrix} r_1T\left(1-b_1T\right)-c_2IT \\ -c_3TN-a_2u \end{pmatrix} \\ +\ q_3\left(s+\dfrac{\rho IT}{\alpha+T}\right)+v(t)-d_2u \end{array}\right| \end{array}\right| \quad (48)$$

$$\eta_I = q_3\rho_I - \left(\begin{array}{l} q_2\begin{pmatrix} r_1T\left(1-b_1T\right)-c_2IT-c_3TN \\ -a_2u \end{pmatrix} \\ +\ q_3\left(s+\dfrac{\rho IT}{\alpha+T}\right)+v(t)-d_2u \end{array}\right) \quad (49)$$

$$\sigma_I\dot{\sigma}_I \le -|\sigma_I|\eta_I \quad (50)$$

Where $\eta_I \ge 0$ by design, ρ_I evaluated from (49) is given in equation (51).

$$\rho_I = \left(\begin{array}{l} q_2\begin{pmatrix} r_1T\left(1-b_1T\right)-c_2IT-c_3TN \\ -a_2u \end{pmatrix} \\ +\ q_3\left(s+\dfrac{\rho IT}{\alpha+T}\right)+v(t)-d_2u \end{array}\right) + \frac{\eta_I}{q_3} \quad (51)$$

The system is asymptotically stable, i. e., $\sigma_I\dot{\sigma}_I \le 0$ due to the fact that $-|\sigma_I|\,\eta_I \le 0$ by default. In this case, the use of equations (1), (31) and (44) results in the error function for case-5 represented by equations (52-55).

$$E_N = \frac{1}{11}\sum_{j=0}^{10}\left(\begin{array}{l} \dot{N}\left(t_j\right)-r_2N\left(t_j\right)\left(1-b_2N\left(t_j\right)\right) \\ +c_4T\left(t_j\right)N\left(t_j\right)+a_3u\left(t_j\right) \end{array}\right)^2 \quad (52)$$

$$E_T = \frac{1}{11}\sum_{j=0}^{10}\left(\begin{array}{l} \dot{T}\left(t_j\right) \\ -\left(1-\partial_T\right)r_1T\left(t_j\right)\left(1-b_1T\left(t_j\right)\right) \\ +\rho_T sgn\left(\sigma_T\right)+c_2I\left(t_j\right)T\left(t_j\right) \\ +c_3T\left(t_j\right)N\left(t_j\right)+a_2u\left(t_j\right) \end{array}\right)^2 \quad (53)$$

$$E_I = \frac{1}{11}\sum_{j=0}^{10}\left(\begin{array}{l} \dot{I}\left(t_j\right)-s-\dfrac{\rho I\left(t_j\right)T\left(t_j\right)}{\alpha+T\left(t_j\right)} \\ +\rho_I sgn\left(\sigma_I\right) \end{array}\right)^2 \quad (54)$$

$$E_{optimal} = \text{minimum}\left(E_N+E_T+E_I\right) \quad (55)$$

6) CASE-6

In this case, base configuration of case-5 is augmented with SMC designed to boost NCs in order to slow down their death rate. SMC used as drug to protect and boost the NCs is given in equation (56).

$$\mu_N\left(x\right) = -\rho_N sgn\left(\sigma_N\right)+c_4TN+a_3u \quad (56)$$

Addition of (56) in NCs equation (1) results in (57)

$$\dot{N} = r_2N\left(1-b_2N\right)-\rho_N sgn\left(\sigma_N\right) \quad (57)$$

Sliding surface and its derivative for this case is represented by equations (58, 59)

$$\sigma_N = q_4N+q_5T+u \quad (58)$$

$$\dot{\sigma}_N = q_4\dot{N}+q_5\dot{T}+\dot{u} \quad (59)$$

Here $q_4 > 0$ & $q_{5<0}$ are the design parameters.

Equation (61) is formed by multiplying σ_N on both sides of equation (59) followed by substitution of equations (2), (4), (57) and property $\sigma_N sgn(\sigma_N) = |\sigma_N|$. Equation (63) is formed after some simplification and defining a term η_N as in equation (62).

$$\sigma_N\dot{\sigma}_N = -q_5\rho_N|\sigma_N| + \sigma_N\left(\begin{array}{l} q_4\left(r_1T\left(1-b_1T\right)-c_2IT-c_3TN-a_2u\right) \\ +\ q_5\left(r_2N\left(1-b_2N\right)\right)+v(t)-d_2u \end{array}\right) \quad (60)$$

$$\sigma_N\dot{\sigma}_N \le -|\sigma_N|\left|\begin{array}{l} q_5\rho_N \\ -\left|\begin{array}{l} q_4\begin{pmatrix} r_1T\left(1-b_1T\right)-c_2IT \\ -c_3TN-a_2u \end{pmatrix} \\ +\ q_5\left(r_2N\left(1-b_2N\right)\right)+v(t) \\ -\ d_2u \end{array}\right| \end{array}\right| \quad (61)$$

$$\eta_N = q_5\rho_N - \left|\left(\begin{array}{l} q_4\begin{pmatrix} r_1T\left(1-b_1\right)-c_2IT-c_3TN \\ -a_2u \end{pmatrix} \\ +\ q_5\left(r_2N\left(1-b_2N\right)\right)+v(t) \\ -\ d_2u \end{array}\right)\right| \quad (62)$$

$$\sigma_N\dot{\sigma}_N \le -|\sigma_N|\eta_N \quad (63)$$

Where $\eta_N \ge 0$ by design, ρ_N evaluated from (62) is given in (64)

$$\rho_N = \left|\left(\begin{array}{l} q_4\begin{pmatrix} r_1T\left(1-b_1T\right)-c_2IT-c_3TN \\ -a_2u \end{pmatrix} \\ +\ q_5\left(r_2N\left(1-b_2N\right)\right)+v(t) \\ -\ d_2u \end{array}\right)\right| + \frac{\eta_N}{q_5} \quad (64)$$

Since $-|\sigma_N|\,\eta_N \le 0$ by default, therefore the system is asymptotically stable, i. e., $\sigma_N\dot{\sigma}_N \le 0$. The equations (31),

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(44) And (57) are utilized to evaluate the error function for case-6 represented by equations (65-68).

$$E_N = \frac{1}{11}\sum_{j=0}^{10}\left(\begin{array}{l}\dot{N}\left(t_j\right) - r_2 N\left(t_j\right)\left(1 - b_2 N\left(t_j\right)\right)\\ +\rho_N sgn\left(\sigma_N\right)\end{array}\right)^2 \quad (65)$$

$$E_T = \frac{1}{11}\sum_{j=0}^{10}\left(\begin{array}{l}\dot{T}\left(t_j\right)\\ -\left(1-\partial_T\right) r_1 T\left(t_j\right)\left(1 - b_1 T\left(t_j\right)\right)\\ +\rho_T sgn\left(\sigma_T\right) + c_2 I\left(t_j\right) T\left(t_j\right)\\ +c_3 T\left(t_j\right) N\left(t_j\right) + a_2 u\left(t_j\right)\end{array}\right)^2 \quad (66)$$

$$E_I = \frac{1}{11}\sum_{j=0}^{10}\left(\begin{array}{l}\dot{I}\left(t_j\right) - s - \dfrac{\rho I\left(t_j\right) T\left(t_j\right)}{\alpha + T\left(t_j\right)}\\ +\rho_I sgn\left(\sigma_I\right)\end{array}\right)^2 \quad (67)$$

$$E_{optimal} = \text{minimum}\left(E_N + E_T + E_I\right) \quad (68)$$

7) CONTROLLER STABILITY

Construct the Lyapunov function to prove stability of controller:

$$V_{SMC} = \frac{1}{2}\sigma^2 \quad (69)$$

$$\dot{V}_{SMC} = \sigma\dot{\sigma} \le 0 \quad (70)$$

If $\sigma\dot{\sigma} \le 0$ then the controller is asymptotically stable.

IV. NUMERICAL RESULTS AND DISCUSSION

This research has focused to develop a combination treatment protocol that can be used to effectively eliminate TCs while keeping the patient's health good enough to bear the toxic effects of chemotherapy. Several combinations are discussed in previous section from case-1 to case-6 with varying treatments and different supplements of controllers as drug.

Simulations are carried out using GA optimtool of Matlab 2018a. The unknown constants of equations (13) to (15) are approximated by keeping the following simulation parameters:

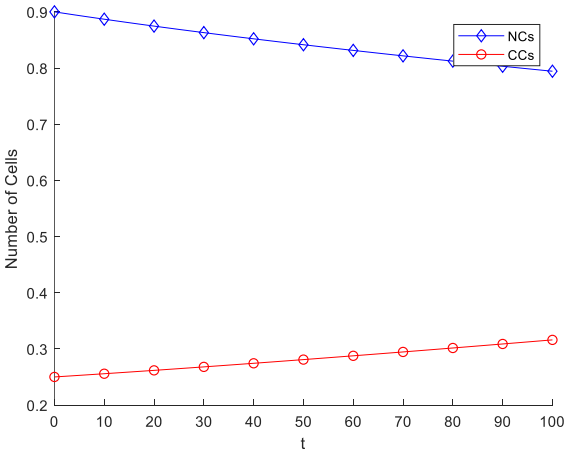
1000 generations are executed on the chromosome having 15 genes, the population size and bounds are 240 and [0 20] respectively. The approximate solution is found by BSP of degree n=5. Graphs of figure 2(a) to 2(f) represent the solutions of case-1 to case-6 with respective equations referred in Table II and parameter values from Table III.

Table II

Case	Case Equations	Objective function for GA	Approximation equations
1	(1), (2)	(21)	(13-15)
2	(1-3)	(25)	
3	(1-3)	(29)	
4	(1), (3), (41)	(42)	
5	(1), (31), (44)	(55)	
6	(31), (44), (57)	(68)	

The behavior of normal and tumor cells in the absence of chemotherapy and immunotherapy is given in figure 2(a). Without immunotherapy and chemotherapy, the TCs increase at a steady rate while the NCs decrease rapidly with the passage of time. Figure 2(b) shows that the immunotherapy decreases both the growth rate of tumor and decay rate of NCs but fail to reduce the TCs. Figure 2(c) represents the effects of chemotherapy in the presence of immunotherapy. In this case, chemotherapy eliminates TCs at a slow rate but its concomitant effects reduce both NCs and ICs to a potentially fatal level.

Figure 2(d) depicts the introduction of SMC as drug for boosting the effect of chemotherapy over tumor. Graph shows that the TCs are eliminated at a good rate but both NCs and ICs decreases to a susceptible level. Figure 2(e) shows the effect produced by supplementing SMC booster for ICs over the base structure of case-4. It is clearly evident from graph that tumor elimination is fast along with a healthy ICs concentration but the NCs concentration decreases to a considerable level. Figure 2(f) represents the final triple combination of TCs elimination and NCs and ICs booster along with chemotherapy. Graph shows the rapid elimination of TCs with an additional benefit of healthy state of patient.



(a)

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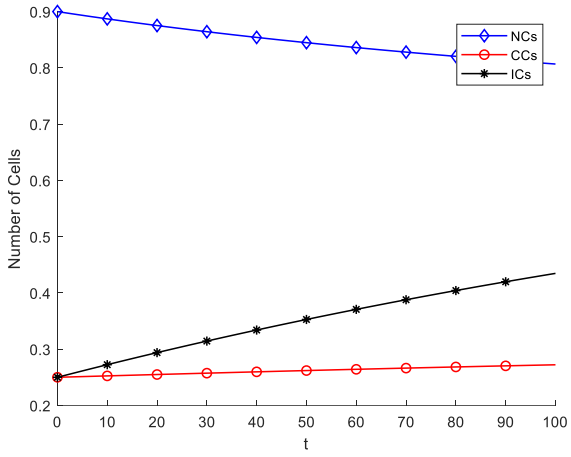

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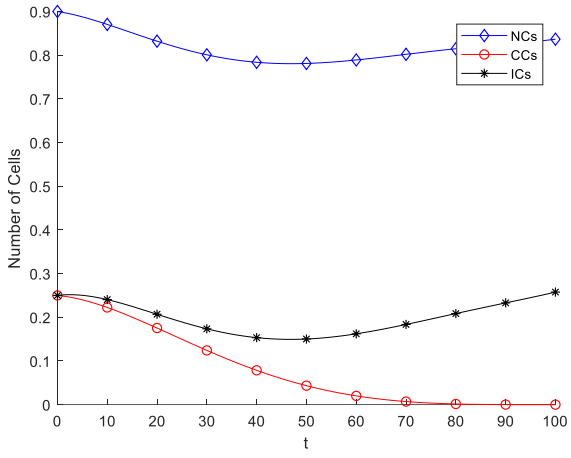
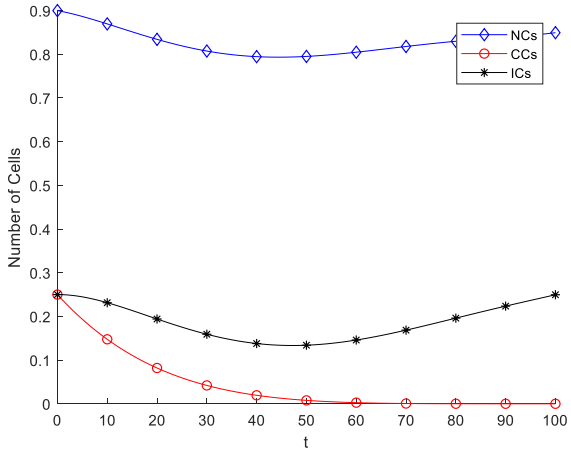
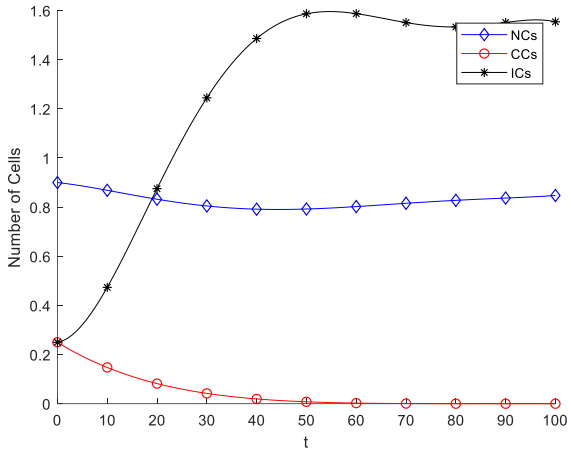


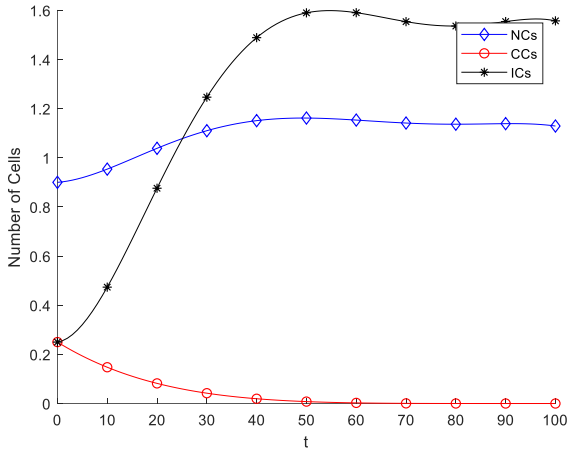
(c)



(d)



(e)



(f)

FIGURE 2. Behavior of normal, tumor and ICs with chemotherapy along with controller

The results presented in figure 2 is improved from the results presented in paper Shindi et al. [9]. Previous study showed decrement of NCs to its minimum constraint, while proposed methodology keep NCs in healthy state. The results presented in figure 3 are simulated with fixed parameter values ∂_T, $\eta's$ and $q's$; varied values of these parameters are used from Table III to analyze and manage the effects of controller drugs as per the implications of patient's health.

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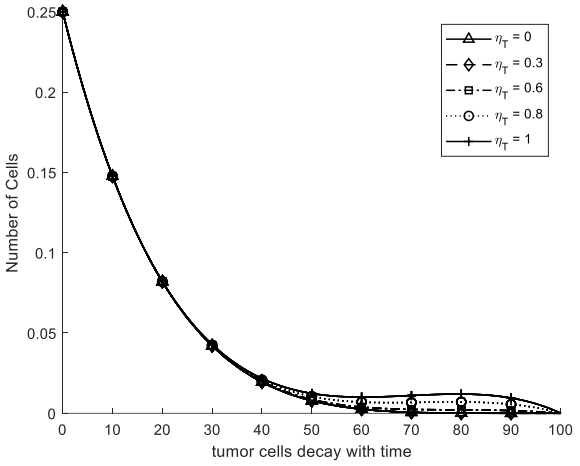
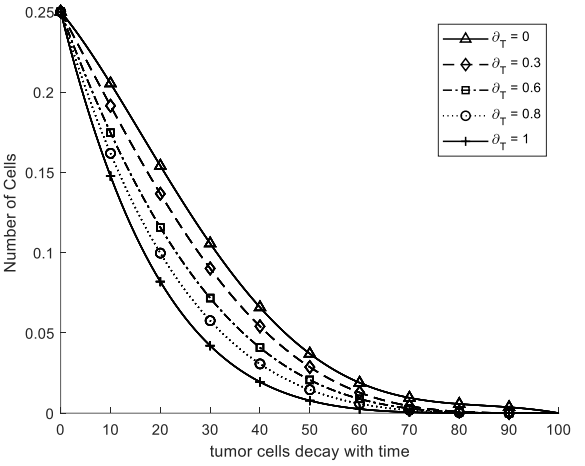
Table III

parameters	Values	Estimated
∂_T	1	0 to 1
η_N	0	0 to 0.8
η_T	0	0 to 1
η_I	0	0 to 1
q_1	1	1
q_2	1	0 to 1
q_3	-1	0 to -1
q_4	1	0 to 1
q_5	-1	-0.4 to -1.4

Figure 3(a) and 3(b) shows the effect of ∂_T and η_T on TCs under application of SMC designed to boost the tumor elimination. Figure 3(a) depicts that the large value of η_T slows down the elimination of TCs, while the small value of η_T enhances the elimination of TCs. Figure 3(b) describes that the large value of ∂_T accentuates the reduction of TCs while the small value of ∂_T slowdown the elimination of TCs. In figure 3(a) ∂_T is fixed at 1, while the η_T is varied from 0 to 1 and in figure 3(b) η_T is fixed at 0, while the ∂_T is varied from 0 to 1.



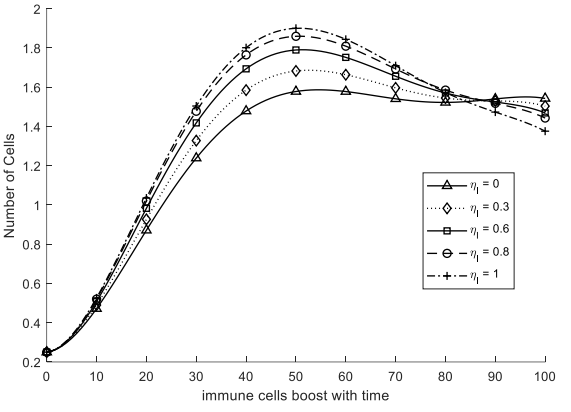
(a)



(b)

FIGURE 3. Decay of TCs on varying (a) η_T and (b) ∂_T

Figure 4(a), 4(b) and 4(c) show the behavior of ICs under the boosting effect of SMC and varied values of η_I, q_2 and q_3, whereas remaining parameters are fixed as of Table III. It is evident from figure 4(a) that for small values of η_I , ICs boosting is slow and large values of η_I results in rapid boosting of ICs. Similar effects are seen in figure 4(b) and 4(c) for various values of q_2 and q_3 .



(a)

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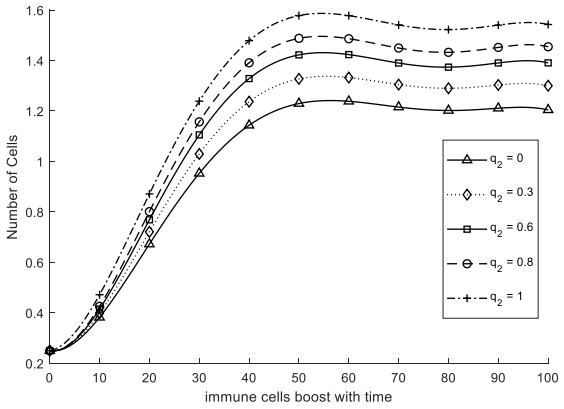
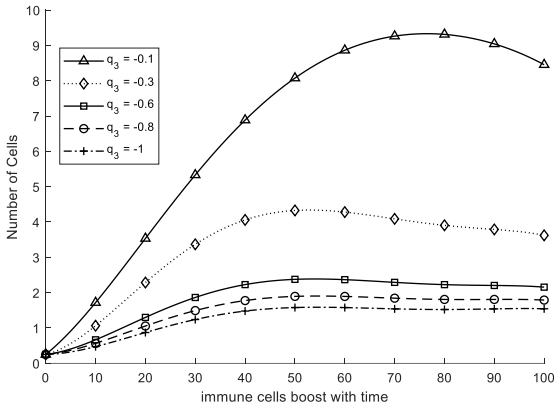


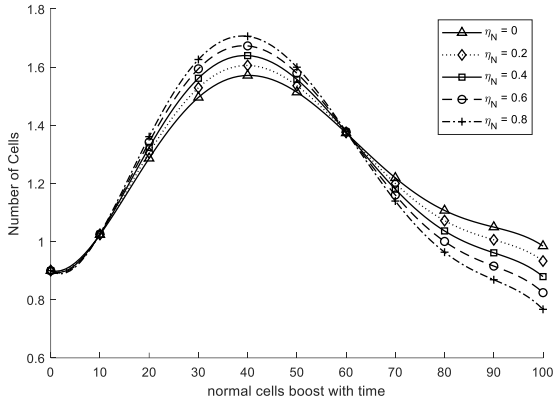
(b)



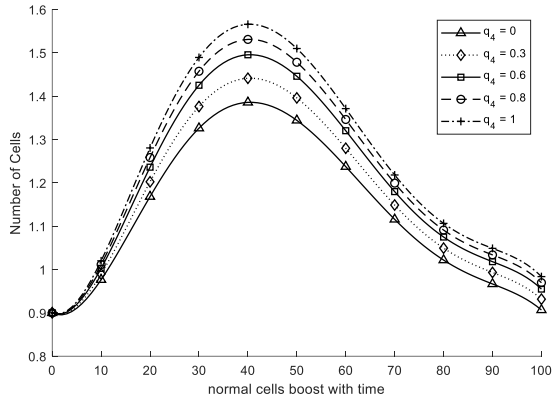
(c)

FIGURE 4. **Enhancement of ICs on different values of (a) η_I , (b) q_2 and (c) q_3**

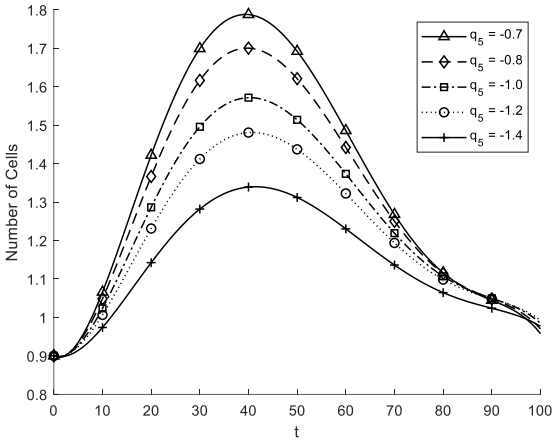
Figure 5(a), 5(b) and 5(c) show the effects of varying $\mathbf{\eta_N}$, $\mathbf{q_4}$ and $\mathbf{q_5}$ on NCs, while utilizing SMC in combination treatment of case-6. NCs boosting is initially slow for small values of $\mathbf{\eta_N}$ and fast for larger $\mathbf{\eta_N}$, but the profiles reverse after 60 days as depicted in figure 5(a). Figure 5(b) and 5(c) reveals the slow boosting for smaller and rapid boosting of NCs for larger values of $\mathbf{q_4}$ and $\mathbf{q_5}$ respectively.



(a)



(b)



(c)

FIGURE 5. **Enhancement of ICs on different values of (a) η_N , (b) q_4 and (c) q_5**

COMPARATIVE ANALYSIS

The comparison of the proposed work with some existing techniques is given in the table-IV. The table-IV shows the superiority of the proposed work while the Table V shows the values of the Objective functions.

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Table-IV: Comparison of the proposed methodology with some existing techniques

Treatment and controller	Cells	Time in days										
		0	10	20	30	40	50	60	70	80	90	100
Pulsed Chemotherapy protocol as optimal controller [11]	NCs	1.0	0.9	1.0	0.9	1.0	1.1	1.0	0.9	1.0	0.9	0.9
	TCs	0.0	0.0	0.15	0.25	0.5	0.1	0.1	0.5	0.25	0.1	0.2
	ICs	0.15	0.3	0.5	0.6	0.4	1.5	1.0	0.5	1.0	1.0	0.5
Direct collocation method to converge optimal control on continuous chemotherapy [17]	NCs	1.0	0.75	0.75	0.8	0.8	0.85	0.9	0.85	0.9	1.0	1.0
	TCs	0.3	0.25	0.2	0.2	0.15	0.1	0.025	0.0	0.0	0.0	0.0
	ICs	0.15	0.5	0.7	0.8	0.9	1.0	1.1	1.4	1.2	1.5	1.3
Traditional pulse chemotherapy [18]	NCs	1.0	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.8	0.9
	TCs	0.25	0.25	0.25	0.25	0.25	0.2	0.2	0.2	0.2	0.2	0.2
	ICs	0.15	0.4	0.6	0.6	0.6	0.6	0.6	0.65	0.7	0.7	0.75
Optimal control chemotherapy [18]	NCs	1.0	0.75	0.75	0.8	0.8	0.85	0.9	0.85	0.9	1.0	1.0
	TCs	0.3	0.25	0.2	0.2	0.15	0.1	0.025	0.0	0.0	0.0	0.0
	ICs	0.15	0.5	0.7	0.8	0.9	1.0	1.1	1.4	1.2	1.5	1.3
Optimal control theory with multi objective swarm [9]	NCs	0.9	0.75	0.75	0.85	0.9	1.0	1.0	1.0	1.0	1.0	1.0
	TCs	0.25	0.2	0.15	0.1	0.05	0.0	0.0	0.0	0.0	0.0	0.0
	ICs	0.25	0.8	0.9	1.0	1.3	1.5	1.65	1.65	1.65	1.65	1.65
SMC as an optimal controller along with chemo-immunotherapy (proposed)	NCs	0.9	0.95	1.05	1.15	1.15	1.15	1.15	1.15	1.15	1.15	1.15
	TCs	0.25	0.15	0.1	0.05	0.01	0.0	0.0	0.0	0.0	0.0	0.0
	ICs	0.25	0.45	0.9	1.3	1.5	1.55	1.55	1.55	1.5	1.5	1.5

Table V: Values of the objective functions

Objective function equations	Cells	Objective functions values										
21	NCs	0.90	0.89	0.87	0.86	0.85	0.84	0.83	0.82	0.81	0.80	0.79
	TCs	0.25	0.26	0.26	0.27	0.27	0.28	0.29	0.29	0.30	0.31	0.32
25	NCs	0.90	0.89	0.88	0.86	0.85	0.84	0.84	0.83	0.82	0.81	0.81
	TCs	0.25	0.25	0.25	0.26	0.26	0.26	0.26	0.27	0.27	0.27	0.27
	ICs	0.25	0.27	0.29	0.31	0.33	0.35	0.37	0.39	0.40	0.42	0.43
29	NCs	0.90	0.87	0.83	0.80	0.78	0.78	0.79	0.80	0.81	0.83	0.84
	TCs	0.25	0.22	0.18	0.12	0.08	0.04	0.02	0.01	0.00	0.00	0.00
	ICs	0.25	0.24	0.21	0.17	0.15	0.15	0.16	0.18	0.21	0.23	0.26
42	NCs	0.90	0.87	0.83	0.81	0.79	0.80	0.80	0.82	0.83	0.84	0.85
	TCs	0.25	0.15	0.08	0.04	0.02	0.01	0.00	0.00	0.00	0.00	0.00
	ICs	0.25	0.23	0.19	0.16	0.14	0.13	0.15	0.17	0.20	0.22	0.25
55	NCs	0.90	0.87	0.83	0.80	0.79	0.79	0.80	0.82	0.83	0.84	0.85
	TCs	0.25	0.15	0.08	0.04	0.02	0.01	0.00	0.00	0.00	0.00	0.00
	ICs	0.25	0.47	0.88	1.24	1.49	1.59	1.59	1.55	1.53	1.55	1.55
68	NCs	0.90	1.00	1.21	1.36	1.42	1.37	1.27	1.15	1.08	1.04	1.00
	TCs	0.25	0.15	0.08	0.04	0.02	0.01	0.00	0.00	0.00	0.00	0.00
	ICs	0.25	0.47	0.88	1.25	1.49	1.59	1.59	1.56	1.54	1.56	1.56

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According to De pillis et al., the NC remains in healthy state whereas TCs and ICs having oscillatory behavior. However, during the process TCs will not be removed completely [11]. Although, by using traditional pulsed chemotherapy, NCs will get reduce the normal level which is dangerous to patients' health. The treatment is halted for short period of time where NCs need recovery at this stage which causes nonlinear behavior. TCs are destroyed within 70 days but the ICs still rely on oscillatory behavior [17] [18]. The scenarios like traditional pulsed and optimal control chemotherapies are discussed in comparison table IV. Where, ICs are increased after 100 days during observation [18].

However, TCs terminated from the body while ICs will reach to higher level after 50 days [9]. Figure-2 (f) describes the proposed methodology where NCs and ICs are improved. Although, TCs are completely eliminated from patient's body using SMC. The level of NCs and ICs increases from initial condition while the TCs are vanished slowly within 45 days.

CONCLUSION AND FUTURE WORK

This research has used GA tuned BSP and SMC for designing an effective treatment protocol with combination of chemotherapy for tumor model by comparing with some existing techniques. The methodology proposed successfully eliminates tumor while maintaining patient's healthy state by keeping NCs well above the critical threshold. NCs and ICs boosting by SMC offer viability of a continuous treatment. The SMC is proposed as an anti-tumor drug, which work as an optimal treatment therapy. Varied controllers parameters allow adjustment in treatment based on patient's profile and response to tumor drug. In future different estimation functions in conjunctions with combination of controllers can be explored. This work will be extended on the mathematical model of different type not only tumor but also cancer and different diseases.

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