Dynamic Modelling and Robust Control of Cancer Mutation Employing Sliding Mode Based Chemotherapy

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Abstract: Mutation dynamics of the cancer growth is modelled here analytically considering the chemotherapy injection as its controlling input. Controlling the metastasis of cancer cells without considering the mutation challenge, results in drug resistance and failure of the treatment. In order to implement the required corrections on the injection dosage of the input, the model of the closed loop system of the cancer growth is required considering the mutation phenomenon. Thus the analytic model of the cancer mutation for which the chemotherapy can be employed as its controlling input is extracted in this paper. Considering the fact that the model of a biological system is always an approximate of the real system, robust sliding mode controller is designed then and implemented as its controlling strategy. It is shown that by the aid of the proposed model and controlling strategy, not only the cancer cells can be converted to zero, but also its probable mutation risk will be blocked and the treatment process consequently will be accomplished in a stable mode. Verification of the developed model is performed by comparing the results with previous studies and the efficiency of the designed controller is evaluated by conducting some comparative simulation scenarios in MATLAB.

Keywords: Cancer Dynamics, Mutation modelling, Robust control, drug resistance, Stem-cells.

1. Introduction

Millions of people yearly die as the result of cancer and tumor growth. Although some progress are achieved toward the treatment of this disease, complete restrain of this challenge is not yet possible. The main popular remedies toward decelerating the cancer growth consist chemotherapy, radiotherapy, immunotherapy, surgery and etc. However, it is inevitable that these treatments have not been completely successful so far. The main obstacle toward the fundamental eradication of this phenomenon is drug resistance. This is contributed to the fact that most of the cancer cells are able to start a genetic mutation process. A cancer tumour has two main characteristics. The first one is known as metastasis which is the progressive and unstable division of the cells and subsequently drastically growth of the tumour. This effect is significantly controllable by the aid of the mentioned custom treatments. However, the main obstacle toward restraining the cancer growth which is called drug resistance is related to the second characteristics of the cancer which

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is the mutation of its corresponding cell genome. Mutation of cancer cell causes that the predetermined chemotherapy drug becomes ineffective on the tumour which consequently results to relapse of the disease and sudden metastasis of the tumour. This challenge however has not been resolved properly so far. The reason is contributed to this fact that the future types of mutation related to the cancer cell is not predictable. It should be noted that extracting the mathematical model of the cancer and its related mutation process is the key point to solve this puzzle. The model can be derived mathematically or using a numerical tool. This model not only should consist the dynamic of the cancer metastasis, but also has to define its related mutation. As a result, both the metastasis and mutation characteristics of the cancer can be modeled simultaneously by the aid of a general state space by which the mutation process is predictable and thus the proper injection input of the chemotherapy can be determined as a function of time. This time dependent chemotherapy injection can avoid the drug resistance and block the mutation phenomenon.

The first studies related to this field initiated by simple models of the cancer tumor. Solyanik et al. have analyzed the mathematical model of the kinetic of the cancer cell growth as a function of the whole cells consisting the proliferating and stunted cells (in terms of division) or early growth with a mathematical model. Proliferating and stunted cells (in terms of division) or early growth with a mathematical model. The proposed model considers the cell division model, their death and their transmission processes. This model also can be employed for predicting and measuring the re-growth of the tumor cells after different stages of their initial growth and extreme hypoxie [1]. According to the research of Bortolussi et al. a systematic approach was delivered for mathematical modelling the population of the cancer cells at different stages of the prostate cancer progression. In this approach, the proper hormone therapy can be determined for each cancer. However the challenge of this model was the observable noise of the recorded data which were not properly justifiable [2].Mirzaei et al. have proposed a mathematical model describing the progress of breast cancer [3]. Here Linear Quadratic Regulator (LQR) method is employed to analyze the parameters and predict the states' response. In [4] the fractional order model is opted to model the patient's tumor and the system parameters are estimated using the Least Square Regression. Ali et al. have developed a novel mathematical model of tumor using Partial Differential Equations (PDEs) in [5]. Ghafari et al then delivered a new mathematical model by which the relation between the cancer cells and the ordinary ones can be extracted according to the environmental parameters and the life style. They showed that in order to achieve an acceptable treatment for the cancer, it is required to change their corresponding dynamics instead of decreasing the population of the cancer cells [6]. Afterwards, the same authors proposed another model of the tumor growth considering the drug resistance. Here the optimal control based on chemotherapy and radiotherapy was extracted using the State Dependent Riccati Equation (SDRE) approach. Employing the mentioned optimal control, the minimum drug delivery was realized [7]. Mathematical tools are also employed in [8,9] for predicting the dynamics of cancerous cells and study the effect of treatments such as radiotherapy on them. If the cancer cells could not be properly inhibited, these cells can destroy their adjacent cells resulting in metastasis. At the stated studies, just the first aspect of the cancer cells is modelled which is metastasis while as explained, ignoring the mutation process will result in drug resistance and even relapsing the disease [10]. Thus some researches have tried to model this phenomenon. In [11] two kinds of cellular populations are considered. It is

explained here that the stem cells can be infinitely divided while the cancer cells cannot be divided and have low life duration. Thus it is concluded accordingly that not stimulating the cancer stem cells individually nor banding their divisions cannot be efficient by themselves. In [12] a new model of tumor is investigated in which an independent state is considered for drug resistant cells. Here also the mutation rate is engaged in the mentioned modelling and the related numerical solution is delivered.

In [13] a mutation model is presented in which the aggregation of the mutant cells and ordinary cells can be studied. Here the roll of the cancer stem cells on the disease progression is explained and it is shown that the more mutant cells aggregation results in faster development of metastasis. In 2016, a mathematical model was delivered by [14] for analysing the mutation behavior of KRAS related to colon cancer which is supposed to be treated by the aid of moAb. Two kinds of mutant cells including KRAS and wild-type are considered in this study. However, this model is just applicable for patients with strong immune system. In [15] a mathematical model is delivered for studying the multi drug resistance of cancer. It is shown here that this phenomenon is also dependent to mutation. In 2008, Ashkenazi et al. delivered a mathematical model for starting and progressing of the cancer. This model explains symmetric and asymmetric divisions while the stems cells and mutation is also considered [16]. The mentioned research just focuses on modelling the metastasis or mutation while controlling the cancer cells are missed. Following studies have proposed some remedies to control the growth of the cancer cells. One of the earliest drug model was proposed as the chemotherapy in 1964 by Skipper et al. In this model a mathematical equation was delivered to estimate the required chemotherapy based injection as a function of tumor size [17]. Villasana et al. then proposed a new method to optimize the chemotherapy process using the drugs which are efficient in one specific stage of cell cycle. This model is dependent to a mathematical equation related to tumor growth by which the efficient protocols can be extracted for input prescription. This process is performed here in a way that the tumor can be blocked and the immune of the system could be maintained at its high level [18]. Another therapy is immunotherapy for which in [19] a related model is delivered. In this study by the aid of a series of numerical experiments it is shown that an optimal control by the aid of this method contrary to chemotherapy can stabilize the cancer growth. A new approach is chemotherapy using fuzzy logic control method. In [20] this method is proposed considering the related limitations of the treatment. Required drug input for the instantaneous state of the tumor can be calculated here using fuzzy controller. In [21] nonlinear and fuzzy controllers are designed for controlling the tumor cells of a cancer model and the performance and efficiency of the proposed controllers if different situations are investigated. A cancer model of order 4 is developed in [22] in which an independent state is considered for drug resistant cells. Afterwards, nonlinear controller is implemented in order to block the progress of cancerous cells in the presence of parametric uncertainties. In [23,24] fuzzy and optimal controllers are employed toward detection and restrain of the cancer. In [25] a new back stepping model is proposed for which a sliding mode controller is applied to stabilize the response of the system. A new composite controller based on back–stepping method with sliding approach is also added to increase the convergence of the system response. This model is robust against uncertainties. The superiority of the proposed model and controller is verified in this paper by applying it for an immunotherapy on an integer-order model of a tumor. It is shown that the

settling time of the proposed controller is less than integer-order models with ordinary fuzzy back stepping controllers. A new nonlinear mathematical model is presented in [26] for which the cancerous cells are controlled using optimal controller. Numerical approach of Lagrange and repetitive optimal controller are used here to perform the related simulations.

In [27] by the aid of new mathematical model and implementation of sliding mode control, the cancerous cells are decreased. Four controlling strategies are employed in [28] in order to cure prostate cancer using hormone therapy. It is shown that using the proposed method, the androgen can be decreased which leads to decrease the cancerous cells consequently.

As can be seen, controlling the dynamics of the cancer growth considering the mutation phenomenon is not properly studied. Thus in this article, the dynamic model of the cancer tumour considering the mutation is represented and the effect of the chemotherapy and its related controlling input on the corresponding state space is extracted. In this model the mutation challenge is considered by assuming a separate state space. Afterwards, a robust nonlinear control of sliding mode is designed and implemented on the tumour. At the next section, the analytic model of the cancer growth considering the mutation is represented and its dynamic is extracted in the presence of chemotherapy input. In section three two controlling methods of State Vector Feedback Control (SVFC) and Sliding Mode Control (SMC) are designed and implemented on the cancer. At section four, the correctness of the proposed model is verified by the aid of previous research and the efficiency of the proposed controlling strategy is proved by the aid of some analytic and comparative simulation scenarios in MATLAB. It is shown that sliding mode provides a better performance for biological dynamic systems in which the model is not completely determined and there are some parametric uncertainties. Also it is shown that the proposed controller can successfully control the growth of the cancer cells as well as blocking the mutation process and drug resistance.

2. Modelling of the Mutation with chemotherapy

2.1. Metastasis model

According to [16] the cell behaviour and its related number of population can be presented as a differential equation. Here the stem cells and their corresponding divisions are also added to the mentioned model. As we know, the stem cells can be divided symmetrically or asymmetrically According to Fig 1.

As it can be seen, in asymmetrical division, a stem cell will be divided into a stem cell and an ordinary one, while in symmetric division, the production of the division is of a similar type which can be stem cell or ordinary one. According to the mentioned division process, the general cell division model can be stated as the following mathematical equation without considering the effect of mutation:

$$\begin{aligned}
&\frac{ds}{dt} = (\alpha_S - \alpha_d - \delta_S)S \\
&\frac{dC_0}{dt} = (2\alpha_d + \alpha_a)S - (\beta_0 - \mu_0)C_0 \\
&\frac{dC_n}{dt} = 2\beta_{n-1}C_{n-1} - (\beta_n + \mu_n)C_n \\
&\frac{dC_N}{dt} = 2\beta_{N-1}C_{N-1} - \mu_N C_N
\end{aligned} \tag{1}$$

Here *S* is the number of the stem cells, α_S is the rate of the symmetrically self-renewing stem cells, α_d is the rate of the symmetrically differentiating stem cells and α_a is the rate of the asymmetrically self-renewing stem cells. Also δ_S is the rate of the death of the stem cells, C_0 is the result of stem cell divisions, which is considered as generation 0 (zero), β_0 and μ_0 are the rate of the division and death of the first generation of the stem cells respectively and *N*, *n* denote the number of the divisions in the equations that, N shows the last division of the equation.

2.2. Model of mutation

Here considering [16] the model of the cell divisions is improved considering the mutation phenomenon. According to the supposed assumption in this article, three generations of mutation are considered for which two first generations are healthy while the third one is cancerous. In order to provide the possibility of controlling the metastasis and also stabilizing the mutation process, the model is promoted so that the effect of chemotherapy input can be studied. To cover this goal, the input is implemented on the extracted modified model, according to the Pinho model [29]. Moreover, here in order to observe the density of the delivered drug in the blood, the proposed model of Li is employed [30]. Consequently, the finalized model of the natural stem cells and their corresponding mutated ones can be developed as equation 2.

$$\begin{aligned}
&\frac{dS}{dt} = ((1-2m_S)\alpha_S - \alpha_d - m_S\alpha_a - \delta_S)S - \frac{p_{10}S}{a_1 + S}M \\
&\frac{dS^{(i)}}{dt} = (2\alpha_{S(i-1)} + a_{a(i-1)})m_{S(i-1)}S^{(i-1)} + ((1-2m_{Si})\alpha_{Si} - \alpha_{di} - m_{Si}\alpha_{ai} - \delta_{Si})S^{(i)} - \frac{p_{10}S^{(i)}}{a_1 + S^{(i)}}M \\
&\frac{dS^{(I)}}{dt} = (2\alpha_{S(I-1)} + a_{a(I-1)})m_{S(I-1)}S^{(I-1)} + (\alpha_{SI} - \alpha_{dI} - \delta_{SI})S^{(I)} - \frac{p_{20}S^{(I)}}{a_2 + S^{(I)}}M
\end{aligned} \tag{2}$$

In the above equations, it is supposed that the mutant divisions in the stem cells are taking place with the probability of m_S, while the natural divisions take places with the probability of $(1-m_S)$ The parameters of $\{\alpha_{Si}, \alpha_{S(I-1)}, \alpha_{SI}, \alpha_{a(i-1)}\}$ are the modified rate of the new symmetrically self-renewing divisions, $\{\alpha_{dI}, \alpha_{di}\}$ are the modified rates of symmetrically differentiation and $\{\alpha_{dI}, \alpha_{di}\}$ are the modified rate of asymmetrically divisions. The index *i* shows the generation of mutation. $S^{(i-1)}$ denotes the stem cell in its previous mutation. In controlling term, p_{10} indicates the rate of death of healthy cells by the aid of the employed chemotherapy injection while p_{20} is the rate of

death of cancerous ones. a_1 and a_2 are in turn the saturation rate of the healthy and cancerous cells. Finally, *M* denotes the density of the chemotherapy drug in the blood.

Thus the related differential equations of the natural and mutated progenitors can be presented as equation 3.

$$\begin{aligned}
&\frac{dC_0}{dt} = (2\alpha_d\left(1-m_S\right)+\alpha_a\left(1-m_S\right))S-(\beta_0+\mu_0)C_0-\frac{p_{10}C_0}{a_1+C_0}M\\
&\frac{dC_0^{(i)}}{dt} = (2\alpha_{d(i-1)}+\alpha_{a(i-1)})m_{S(i-1)}S^{(i-1)}+(2\alpha_{di}+\alpha_{ai})(1-m_{Si})S^{(i)}\\
&\qquad -(\beta_0^{(i)}+\mu_0^{(i)})C_0^{(i)}-\frac{p_{10}C_0^{(i)}}{a_1+C_0^{i}}M\\
&\frac{dC_0^{(I)}}{dt} = (2\alpha_{d(I-1)}+\alpha_{a(I-1)})m_{S(I-1)}S^{(I-1)}+(2\alpha_{dI}+\alpha_{aI})S^{(I)}\\
&\qquad -(\beta_0^{(I)}+\mu_0^{(I)})C_0^{(I)}-\frac{p_{20}C_0^{(I)}}{a_2+C_0^{(I)}}M
\end{aligned} \tag{3}$$

In the above equations $C_0^{(i)}$ and $C_0^{(I)}$ denote the cells with no division. The equations of the cells' number resulted from the first division is as equation 4.

$$\begin{aligned}
&\frac{dC_{(n=1)}}{dt} = 2\beta_{n-1}\left(1-m_C\right)C_{n-1}-(\beta_n+\mu_n)-\frac{p_{10}C_n}{a_1+C_n}M\\
&\frac{dC_{(n=1)}^{(i)}}{dt} = 2\beta_{n-1}^{(i-1)}m_{C(i-1)}C_{n-1}^{(i-1)}+2\beta_{n-1}^{(i)}\left(1-m_{Ci}\right)C_{n-1}^{(i)}\\
&\qquad -(\beta_n^{(i)}+\mu_n^{(i)})C_n^{(i)}-\frac{p_{10}C_n^{(i)}}{a_1+C_n^{(i)}}M\\
&\frac{dC_{(n=1)}^{(I)}}{dt} = 2\beta_{n-1}^{(I-1)}m_{C2}C_{n-1}^{(I-1)}+2\beta_{n-1}^{(I)}C_{n-1}^{(I)}-(\beta_n^{(I)}+\mu_n^{(I)})C_n^{(I)}-\frac{p_{20}C_n^{(I)}}{a_2+C_n^{(I)}}M
\end{aligned} \tag{4}$$

In this equation $\beta_{n-1}^{(i-1)}$, $\beta_{n-1}^{(I-1)}$, $C_{n-1}^{(i-1)}$ and $C_{n-1}^{(I-1)}$ are related to the previous mutation. Thus the equations related to the last division (*N*) can be extracted as bellow in which the mutation is also considered:

$$\begin{aligned}
&\frac{dC_{(N=2)}}{dt} = 2\beta_{N-1}\left(1-m_C\right)C_{N-1}-\mu_nC_n-\frac{p_{10}C_N}{a_1+C_N}M\\
&\frac{dC_{(N=2)}^{(i)}}{dt} = 2\beta_{N-1}^{(i-1)}m_{C(i-1)}C_{N-1}^{(i-1)}+2\beta_{N-1}^{(i)}(1-m_{Ci})C_{N-1}^{(i)}-\mu_N^{(i)}C_N^{(i)}-\frac{p_{10}C_N^{(i)}}{a_1+C_N^{(i)}}M\\
&\frac{dC_{(N=2)}^{(I)}}{dt} = 2\beta_{N-1}^{(I-1)}m_{C(I-1)}C_{N-1}^{(I-1)}+2\beta_{N-1}^{(I)}C_{N-1}^{(I)}-\mu_N^{(I)}C_N^{(I)}-\frac{p_{20}C_N^{(I)}}{a_2+C_N^{(I)}}M
\end{aligned} \tag{5}$$

Here $\beta_{N-1}^{(i-1)}$,$C_{N-1}^{(i-1)}$, $\beta_{N-1}^{(I-1)}$ and $C_{N-1}^{(I-1)}$ are again related to the previous mutations. In order to observe the density of the chemotherapy in the blood as the physical input of the system, the following ODE equation can be defined:

$$\frac{dM}{dt} = -\gamma M + u_M(t) \tag{6}$$

Here it is supposed that the injected chemotherapy drug during the time is proportional to its related density which is $-\gamma M$ Leaves the body. The biological meaning of γ in this equation is the rate of decreasing the drug in the body. Also it should be noted that in this article it is supposed that the number of the cells just changes as the result of division or fatality. In addition, $u_M(t)$ is external injection of chemotherapy.

As was seen, in the proposed controlling model, all of the mutating generations achieve a specific dosage of chemotherapy drug according to its mutation level. If the mutation model would not be considered for controlling the cancer system, the chemotherapy input will be designed for the first generation and other states related to the mutant states will not gain the drug input. This condition which is called drug resistance can be described by the following state space and as will be seen in simulation section, can be compensated by the aid of the proposed model of equation 1:

$$
\begin{aligned}
\dot{S} &= \left(\left(1-2m_S\right)\alpha_S - \alpha_d - m_S\alpha_S - \delta_S\right)S - \frac{p_{10}S}{a_1+S}M \\
\dot{C}_0 &= \left(2\alpha_d\left(1-m_S\right)+\alpha_a\left(1-m_S\right)\right)S - \left(\beta_0+\mu_0\right)C_0 - \frac{p_{10}C_0}{a_1+C_0}M \\
\dot{C}_1 &= 2\beta_0\left(1-m_C\right)y_2 - \left(\beta_1+\mu_1\right)C_1 - \frac{p_{10}C_1}{a_1+C_1}M \\
\dot{C}_2 &= 2\beta_1\left(1-m_C\right)C_1 - \mu_2 C_2 - \frac{p_{10}C_2}{a_1+C_2}M \\
\dot{S}^{(1)} &= \left(2\alpha_S+\alpha_a\right)m_S S + \left(\left(1-2m_{S1}\right)\alpha_{S1} - \alpha_{s1} - m_{S1}\alpha_{a1} - \delta_S\right)S^{(1)} - \frac{p_{10}S^{(1)}}{a_1+S^{(1)}}M \\
\dot{C}_0^{(1)} &= \left(2\alpha_d+\alpha_a\right)m_S S + \left(2\alpha_{d1}+\alpha_{a1}\right)\left(1-m_{S1}\right)S^{(1)} - \left(\beta_0^{(1)}+\mu_0^{(1)}\right)C_0^{(1)} - \frac{p_{10}C_0^{(1)}}{a_1+C_0^{(1)}}M \\
\dot{C}_1^{(1)} &= 2\beta_0 m_{C1}C_0^{(1)} + 2\beta_0^{(1)}\left(1-m_{C1}\right)C_0^{(1)} - \left(\beta_1^{(1)}+\mu_1^{(1)}\right)C_1^{(1)} - \frac{p_{10}C_1^{(1)}}{a_1+C_1^{(1)}}M \\
\dot{C}_2^{(1)} &= 2\beta_1 m_C C_1 + 2\beta_1^{(1)}\left(1-m_{C1}\right)C_1^{(1)} - \mu_2^{(1)}C_2^{(1)} - \frac{p_{10}C_2^{(1)}}{a_1+C_2^{(1)}}M \\
\dot{S}^{(2)} &= \left(2\alpha_{S1}+\alpha_{a1}\right)m_{S1}S^{(1)} + \left(\left(1-2m_{S2}\right)\alpha_{S2} - \alpha_{d2} - m_{S2}\alpha_{a2} - \delta_{S2}\right)S^{(2)} - \frac{p_{10}S^{(2)}}{a_1+S^{(2)}}M \\
\dot{C}_0^{(2)} &= \left(2\alpha_{d1}+\alpha_{a1}\right)m_{S1}S^{(1)} + \left(2\alpha_{d2}+\alpha_{a2}\right)\left(1-m_{S2}\right)S^{(2)} - \left(\beta_0^{(2)}+\mu_0^{(2)}\right)C_0^{(2)} - \frac{p_{10}C_0^{(2)}}{a_1+C_0^{(2)}}M \\
\dot{C}_1^{(2)} &= 2\beta_0^{(1)}m_{C1}C_0^{(1)} + 2\beta_0^{(2)}\left(1-m_{C2}\right)C_0^{(2)} - \left(\beta_1^{(2)}+\mu_1^{(2)}\right)C_1^{(2)} - \frac{p_{10}C_1^{(2)}}{a_1+C_1^{(2)}}M \\
\dot{C}_2^{(2)} &= 2\beta_1^{(1)}m_C C_1^{(1)} + 2\beta_1^{(2)}\left(1-m_{C2}\right)C_1^{(2)} - \mu_2^{(2)}C_2^{(2)} - \frac{p_{10}C_2^{(2)}}{a_1+C_2^{(2)}}M \\
\dot{S}^{(3)} &= \left(2\alpha_{S2}+\alpha_{a2}\right)m_{S2}S^{(2)} + \left(\alpha_{S3} - \alpha_{d3} - \delta_{S3}\right)S^{(3)} - \frac{p_{20}S^{(3)}}{a_2+S^{(3)}}M \\
\dot{C}_0^{(3)} &= \left(2\alpha_{d2}+\alpha_{a2}\right)m_{S2}S^{(2)} + \left(2\alpha_{d3}+\alpha_{a3}\right)S(3) - \left(\beta_0^{(3)}+\mu_0^{(3)}\right)C_0^{(3)} - \frac{p_{20}C_0^{(3)}}{a_2+C_0^{(3)}}M \\
\dot{C}_1^{(3)} &= 2\beta_0^{(2)}m_{C2}C_0^{(2)} + 2\beta_0^{(3)}C_0^{(3)} - \left(\beta_1^{(3)}+\mu_1^{(3)}\right)C_1^{(3)} - \frac{p_{20}C_1^{(3)}}{a_2+C_1^{(3)}}M \\
\dot{C}_2^{(3)} &= 2\beta_1^{(2)}m_{C2}C_1^{(2)} + 2\beta_1^{(3)}C_1^{(3)} - \mu_2^{(3)}C_2^{(3)} - \frac{p_{20}C_2^{(3)}}{a_2+C_2^{(3)}}M \\
\dot{M} &= -\gamma M + u_M(t)
\end{aligned}
\tag{7}
$$

Here the cancer plant itself is of order 16 for which *M* that is the density of chemotherapy is considered as the related controlling input. However, the controlling system itslef has a first order dynamics in which the relation between the chemotherapy density and chemotherapy injection u_M can be estimated by the aid of equation 6. Thus here the *M* will be determined using the proposed controlling steratgies and it will be realised by the aid of the proper dosage of chemotherapy injection by the aid of the equation 6.

2.3. Analysis of equilibrium points

In physiology, homeostatic means to maintain the materials of the body in a stable level. All of the limbs of the body tries to meet the condition of the homeostatic. This phenomenon is also valid for the stem cells of the body and this is equal to $\frac{dS}{dt}=0$ and here, *s* is considered equal to 900000. The employed Parameters for normal and mutant cells are as Table 1.

Since the operating point of the body is its Now considering the values of Table (1) the equilibrium points of the state space in which the mutation is modelled can be extracted as follow:

$$\begin{aligned}&[S;C_0;C_1;C_2;S^{(1)};C_0^{(1)};C_1^{(1)};C_2^{(1)};S^{(2)};C_0^{(2)};C_1^{(2)};C_2^{(2)};S^{(3)};C_0^{(3)};C_1^{(3)};C_2^{(3)}]=\\&\quad[900000;8.93;1.1195\times10^{5};4.8959\times10^{7};3.618;0.1788;0.4229;1.7151\times10^{3};\\&\quad0.0011;2.8411\times10^{-5};6.8861\times10^{-5};1.3606;6.8591\times10^{-5};1.982\times10^{-6};\\&\quad3.9069\times10^{-6};0.4555]\end{aligned} \tag{8}$$

Linearization around the above equilibrium points can be conducted as follow:

$$f(x)=f(x_0)+\left.\frac{df(x_0)}{dx}\right|_{x=x_0}(x-x_0)+\dots \tag{9}$$

Considering the above Taylor equation, one can conclude the following linearized state space about the mentioned equilibrium points:

$$\begin{aligned}
\dot{S} &= -1\times10^{-6}S-1.2\times10^{-4}M-0.9014\\
\dot{C}_0 &= 0.9S-9.07\times10^{4}C_0-1.068\times10^{-4}M+48.9987\\
\dot{C}_1 &= 1.81\times10^{5}C_0-14.47C_1-1.2\times10^{-4}M+1.6227\times10^{3}\\
\dot{C}_2 &= 28.77C_1-0.07C_2-1.2\times10^{-4}M+0.002\\
\dot{S}^{(1)} &= 1\times10^{-6}S+0.225S^{(1)}-9.1926\times10^{-5}M+1.7094\\
\dot{C}_0^{(1)} &= 9\times10^{-7}S+0.72S^{(1)}-19.13C_0^{(1)}-1.6778\times10^{-5}M-0.0172\\
\dot{C}_1^{(1)} &= 56.3C_0^{(1)}-23.8C_1^{(1)}-3.3323\times10^{-5}M+0.001\\
\dot{C}_2^{(1)} &= 2\times10^{-5}C_1+47.54C_1^{(1)}-0.014C_2^{(1)}-7.311\times10^{-5}M-1.6686\\
\dot{S}^{(2)} &= 1.2\times10^{-4}S^{(1)}+0.41S^{(2)}-1.1988\times10^{-5}M+7.0579\times10^{-4}\\
\dot{C}_0^{(2)} &= 7.2\times10^{-5}S^{(1)}+0.5S^{(2)}+28.5C_0^{(2)}-3.0993\times10^{-9}M+0.0016\\
\dot{C}_1^{(2)} &= 0.004C_0^{(1)}+56.36C_0^{(2)}-33.16C_1^{(2)}-7.5116\times10^{-9}M+3.2961\times10^{-3}\\
\dot{C}_2^{(2)} &= 0.005C_1^{(1)}+65.65C_1^{(2)}-0.005C_2^{(2)}-6.6355\times10^{-5}M-9.229\times10^{-4}\\
\dot{S}^{(3)} &= 0.014S^{(2)}+0.22S^{(3)}-3.044\times10^{-6}M-4.1507\times10^{-6}\\
\dot{C}_0^{(3)} &= 0.005S^{(2)}+1.01S^{(3)}-37.85C_0^{(3)}-8.7979\times10^{-8}M-1.243\times10^{-6}\\
\dot{C}_1^{(3)} &= 0.57C_0^{(2)}+75.7C_0^{(3)}-42.5C_1^{(3)}-1.7342\times10^{-7}M-1.7851\times10^{-6}\\
\dot{C}_2^{(3)} &= 0.66C_1^{(2)}+85.1C_1^{(3)}-8.3\times10^{-4}C_2^{(3)}-0.0184M-0.2094\\
\dot{M} &= -0.9M+u_M
\end{aligned} \tag{10}$$

The required feedback signals for the above mentioned controlling treatment can be estimated using surface acoustic waves and MZI-IDA sensors. The former measurement tool detects the point mutations in cancer-related DNA [34]. Mass and viscosity signals can be measured by this sensor [34]. Moreover, as described in reference [35], the MZI-IDA sensor system can be employed to detect mutations accurately and efficiently in clinical specimens.

3. Controlling the mutation model using chemotherapy

In order to control the dynamic of the cancer growth, it is first required to show the controllability of the system. This controllability is verified here for the linearized state space of the cancer model around its stability condition. Thus the system is rewritten in the format and the controllability matrix of equation $\dot{x} = Ax + Bu$ is established. The system is controllable if the columns of this matrix span the space of order of n which means that the matrix is full rank. Here the matrices A and B are as:

$$
\begin{aligned}
&A_{1,1} = -1\times10^{-6}; A_{2,1} = 0.9\\
&A_{2,2} = -9.07\times10^{4}\\
&A_{3,2} = 1.81\times10^{-5}; A_{3,3} = -14.47\\
&A_{4,3} = 28.77; A_{4,4} = -0.07\\
&A_{5,1} = 1\times10^{-6}; A_{5,5} = 0.225\\
&A_{6,1} = 9\times10^{-7}; A_{6,5} = 0.72; A_{6,6} = -19.13\\
&A_{7,6} = 56.3; A_{7,7} = -23.8\\
&A_{8,3} = 2\times10^{-5}; A_{8,7} = 47.54; A_{8,8} = -0.014\\
&A_{9,5} = 1.2\times10^{-4}; A_{9,9} = 0.41\\
&A_{10,5} = 7.2\times10^{-5}; A_{10,9} = 0.5; A_{10,10} = 28.5\\
&A_{11,6} = 0.004; A_{11,10} = 56.36; A_{11,11} = -33.16\\
&A_{12,7} = 0.005; A_{12,11} = 65.65; A_{12,12} = -0.005\\
&A_{13,9} = 0.014; A_{13,13} = 0.22\\
&A_{14,9} = 0.005; A_{14,13} = 1.01; A_{14,14} = -37.85\\
&A_{15,10} = 0.57; A_{15,14} = 75.7; A_{15,15} = -42.5\\
&A_{16,11} = 0.66; A_{16,15} = 85.1; A_{16,16} = -8.3\times10^{-4}
\end{aligned}
$$

$$
\begin{aligned}
&B_{1,1} = -1.2\times10^{-4}\\
&B_{2,1} = -1.068\times10^{-4}\\
&B_{3,1} = -1.2\times10^{-4}\\
&B_{4,1} = -1.2\times10^{-4}\\
&B_{5,1} = -9.1926\times10^{-5}\\
&B_{6,1} = -1.6778\times10^{-5}\\
&B_{7,1} = -3.3323\times10^{-5}\\
&B_{8,1} = -7.311\times10^{-5}\\
&B_{9,1} = 1.1988\times10^{-5}\\
&B_{10,1} = -3.0993\times10^{-9}\\
&B_{11,1} = -7.5116\times10^{-9}\\
&B_{12,1} = -6.6355\times10^{-5}\\
&B_{13,1} = -3.044\times10^{-6}\\
&B_{14,1} = -8.7979\times10^{-8}\\
&B_{15,1} = -1.7342\times10^{-7}\\
&B_{16,1} = -0.0184
\end{aligned}
\qquad (11)
$$

Calculating the Rank of the controllability matrix around its stability point results in 16 which means the system is full rank and consequently controllable.

3.1. SVF control by pole placement gain tuning

In order to decrease the cancer cells and prevent the mutation process from reaching to its third generation which is cancerous here, two controlling strategies are employed and implemented on the system and their related performance are compared and analysed. For the former controller which is SVFC, the system should be first linearized. Afterward, it is possible to tune the related

gains using pole placement method to achieve negative Eigen values for all of the states and provide the stability condition of the system. Since the system is linearized about its stable point, it is possible to use pole placement to tune the related feedback gains. Considering the fact that SVFC approach is used to calculate the controlling input, it is possible to place the poles of all of the states. The linearized state space will be as follow:

$$\dot{x} = Ax + Bu \tag{12}$$

where *x* is the related states, *u* is the controlling input, *A* is the state gain matrix, *B* is the input gain matrix, and for the presented cancer state space of this paper, the values of *A* and *B* are given in equation 11.

This matrix has 16×16 size and the rest of elements are zero. . Matrix B is also as above which is a 16 element vector. Now the controlling input according to SVFC algorithm can be defined as follow:

$$u = -kx \tag{13}$$

k is the controlling gains which are tuned here using pole placement method. Here -1 is opted as the desired pole of all of the states since its real value is negative and thus guarantees the stability of all of the states. Also the imaginary part is set to be zero to ensure the exponential response of the states. Thus we have:

$$|SI - A + Bk| = (S+1)^{16} \tag{8}$$

Thus one can conclude that:

$$\begin{aligned} &m_{16}\times S^{16} + m_{15}\times S^{15} + m_{14}\times S^{14} + m_{13}\times S^{13} + m_{12}\times S^{12} + m_{11}\times S^{11} \\ &+m_{10}\times S^{10} + m_9\times S^9 + +m_8\times S^8 + m_7\times S^7 + m_6\times S^6 + m_5\times S^5 \\ &+m_4\times S^4 + m_3\times S^3 + m_2\times S^2 + m_1\times S^1 + m\times Cons\tan t = S^{16} \end{aligned} \tag{9}$$

where *m* to m_{16} are constant values. Thus the proper controlling gain vector can be calculated as follow:

$$\begin{aligned} [k_1,\ldots,k_{16}] = \\ &[-8438.857, 850438007.4594, 2.329, -1.343\times10^{-6}, -296.621, 10356.635, \\ &-727.4526, -2.8735\times10^{-4}, 186420.8587, 6024953.3165, -888589.5202, \\ &-0.0316162, 61350443.71259, -2665511177.9622, 261372845.3094, \\ &9.16955\times10^{-4}] \end{aligned} \tag{10}$$

3.2. Sliding Mode Controller

Since the SVFC is just applicable for linear systems, and also it is not robust against the parametric uncertainties especially for such biological systems, the above designed controller is just valid

around the operating point of the equilibrium zone with an exact model. Thus for the case that the cancer is in critical stage and its states are far from its corresponding stable condition, this controller is not efficient. Moreover, we know that the exact estimation of the model of the biological systems is not ideally possible. Thus a proper controller should be robust enough to neutralize the destructive effect of model uncertainty. Therefor sliding mode controller is designed and implemented as the modified controller here. This controller is an efficient approach for controlling the nonlinear systems, which is also robust against the parametric uncertainties. Thus sliding mode is employed here since it is robust against the parametric uncertainties and disturbances. This method as mentioned can compensate the parametric uncertainties related to the challenges of modeling a biological system and also other environmental disturbing effects which can play the role of input besides the chemotherapy injection. However, considering the drawback of this method which is chattering, a filter such as *tanh* can be employed to dissipate the chattering.

Here it is first required to determine the sliding surface and afterward the corresponding controlling input should be calculated accordingly. The sliding surface is considered here as follow:

$$\begin{aligned} s = {} & k_1 S + k_2 C_0 + k_3 C_1 + k_4 C_2 + k_5 S^{(1)} + k_6 C_0^{(1)} + k_7 C_1^{(1)} + k_8 C_2^{(1)} + k_9 S^{(2)} \\ & + k_{10} C_0^{(2)} + k_{11} C_1^{(2)} + k_{12} C_2^{(2)} + k_{13} S^{(3)} + k_{14} C_0^{(3)} + k_{15} C_1^{(3)} + k_{16} C_2^{(3)} + k_{17} M \end{aligned} \tag{11}$$

The controlling input should be defined in a way that the following Lyapunov function which is a function of sliding surface would be stable:

$$V = \frac{1}{2} s^2 \tag{12}$$

Thus the derivation of this function should be negative:

$$\begin{aligned} \dot{V} = s\dot{s} = s(& k_1 \dot{S} + k_2 \dot{C}_0 + k_3 \dot{C}_1 + k_4 \dot{C}_2 + k_5 \dot{S}^{(1)} + k_6 \dot{C}_0^{(1)} + k_7 \dot{C}_1^{(1)} + k_8 \dot{C}_2^{(1)} \\ & + k_9 \dot{S}^{(2)} + k_{10} \dot{C}_0^{(2)} + k_{11} \dot{C}_1^{(2)} + k_{12} \dot{C}_2^{(2)} + k_{13} \dot{S}^{(3)} + k_{14} \dot{C}_0^{(3)} + k_{15} \dot{C}_1^{(3)} + k_{16} \dot{C}_2^{(3)} \\ & + k_{17} \left(-\gamma y + u_{eq}(t) \right)) \end{aligned} \tag{13}$$

To assure the asymptotical stability of the system this condition $\dot{V} = s\dot{s} \le 0$ should be satisfied. Now the nonlinear terms can be linearized globally by the aid of the following controlling input:

$$U = u_{eq}(t) + u_r \tag{14}$$

By equalizing the $\dot{V}$ to zero, the corresponding u_{eq} can be achieved by which the Lyapunov stability can be assured:

$$\begin{aligned} u_{eq}(t) = & -\left(\frac{k_1 \dot{S} + k_2 \dot{C}_0 + k_3 \dot{C}_1 + k_4 \dot{C}_2 + k_5 \dot{S}^{(1)} + k_6 \dot{C}_0^{(1)} + k_7 \dot{C}_1^{(1)} + k_8 \dot{C}_2^{(1)}}{k_{17}} \right) \\ & -\left(\frac{k_9 \dot{S}^{(2)} + k_{10} \dot{C}_0^{(2)} + k_{11} \dot{C}_1^{(2)} + k_{12} \dot{C}_2^{(2)} + k_{13} \dot{S}^{(3)} + k_{14} \dot{C}_0^{(3)} + k_{15} \dot{C}_1^{(3)} + k_{16} \dot{C}_2^{(3)} - k_{17} \gamma y}{k_{17}} \right) \end{aligned} \tag{21}$$

While u_r which assures the finite time convergence onto the surface, should be set as bellow:

$$u_r = -k_s Sign(s) \tag{15}$$

Thus the final controlling input based on the sliding mode is as follow for which *s* can be substituted by the aid of equation 17:

$$U = u_{eq} - K_s sign(s) \tag{16}$$

Block diagram of the proposed controlling method for the cancer mutation according to chemotherapy can be seen as Fig. 2.

The stability of sliding mode method is approved in [36]. Since the origin is on the selected surface, it is provable that all of the states converge to zero through the selected surface.

4. Simulation and Verification

Correctness of the improved model and efficiency of the designed controller are investigated in this section.

4.1. Verification of the model:

In order to verify the correctness of the modeling, the profile of the stem cell numbers without mutation with two divisions is depicted and compared with the same parameter of paper [16]. This profile is for the system with not chemotherapy input. Firstly, according to Fig. 3, as was expected the number of the cells diverges since no injecting input is employed. Moreover, the same trend of these profiles shows the correctness of the present modeling.

The third generation of the mutant cells which are cancerouse can be seen as Fig. 4. Here the state 13 is related to ($S^{(3)}$ Cells), state 14 shows ($C_0^{(3)}$ Cells), stated 15 represents ($C_1^{(3)}$ Cells) and state 16 is ($C_2^{(3)}$ Cells). All of the state responces is corresponding to open loop tumore behaviour in which no chemotherapy input is employed.

As can be seen the number of cells are exponentially increasing to instability which shows that the censer will overcome if no proper input would be injected.

4.2. Drug resistance verification:

As stated, the main purpose of modeling the mutation is to eliminate the effect of drug resistance in the cancer treatment process. For a model in which the mutation is not considered, a unique input chemotherapy input usually results in drug resistance and the states related to mutant cells diverges to instability condition. Here in order to show the necessity of modeling the mutation dynamics, the proposed model that is a more realistic model for which the phenomenon of the mutations is also engaged, is imposed to two controlling strategies. The first one is a unique chemotherapy input which is estimated considering a simple model in which the mutation is not

considered while the second one is related a controller which evaluates different controlling input for each mutation generation. Actually, the plant for both approaches is the same which is a realistic model with mutation but at the former system the controller is designed based on a simple model with metastasis states while in the latter vase the controller is also based on the proposed improved model of the cancer with consideration of mutation. For the former case the response of the states is extracted as Fig. 5 and Fig. 6.

It can be seen that as expected, the states related to the first mutation are stabilized and controlled while the other states diverge to instability. This is shown that the condition of drug resistance is realized and thus a more realistic model is required for the feedforward portion of the control block. At bellow it is shown that employing the proposed model and providing the proper chemotherapy input for each mutation can compensate the above mentioned syndrome.

4.3. Efficiency of the designed SMC controller:

Afterwards, constant chemotherapy input of 12.5 drug dosage is injected for all of the mutating generations with various controlling gains and as can be seen as follow, the states are controlled and stabilized around their related equilibrium point. Here the employed controlling gain of the first 16 gains are the same as equation 16 in order to provide a better comparative study between the proposed controllers and also we have $k_s = k_{17} = -1$.

Two feedback based controllers of SVFC and sliding mode that are designed in the previous section are also implemented and their corresponding performance are studied and compared in Fig. 7.

As can be observed, the state 13, which is related to the cancerous stem cells in its third mutation, $S^{(3)}$ is stabilized and converged to zero using these controlling inputs. However, the settling time of SVFC is less than constant input while the best response is related to sliding mode by which 66% improvement is occurred respect to SVFC and 95% improvement can be seen respect to constant input. State 15 shows the cell division of the cancerous stem cells of the third mutation in first generation ($C_0^{(3)}$).State 16 shows the divisions of the cancerous stem cells in the third mutation in first generation $C_1^{(3)}$. And finally profile of state 16 is related to the divisions of the cancerous stem cells in the third mutation in second generation $C_2^{(3)}$ According to these data, it can be concluded that the best control on the cancer is realized using Sliding mode and the settling time is decreased somewhere up to about 91% respect to constant input and by about 87% respect to SVF controller.

Comparing the required chemotherapy injection for these three cases can be observed in Fig. 8.

Thus it can be concluded that using the mentioned controlling strategy it is possible to control the tumor metastasis within 50 days and consequently the cancerous mutation is accordingly blocked. According to the profile of chemotherapy input and its comparison for different controlling strategy, it can be seen that the required chemotherapy input is not vanishes after the stabilizing the disease which is related to the necessity of continuation of the treatment. This is contributed to the fact that using these therapies, the disease can just be controlled during the therapy and it won't

be disappeared without using the chemotherapy since the mutation phenomenon will restart the metastasis after stopping the therapy. However, it is noticeable that contrary to the two first controlling strategies, the sliding mode is able to completely block the mutation after 400 days and its required injection decreases to zero after this time period. This improvement is related to the robust nature of the presented sliding mode controller.

4.4. Robustness analysis of the proposed closed loop model of tumor against uncertainties:

As explained, a biological model cannot be perfectly modeled without any uncertainty. Here in order to show the robustness of the proposed sliding mode controller against the parametric uncertainties, the response of the tumor is simulated in the presence of some parametric uncertainties while it is controlled by the aid of the designed robust controller: The employed biological parameters, their considered values and the rate of their uncertainty are as Table 2.

The responses of the cancer cells for the similar scenario of the previous section are compared between the two designed controllers in Fig. 9. Here the model suffers from the above mentioned uncertainties.

As can be seen, in the third generation of mutation in which the cells are cancerous, the SVFC is not able to control the metastasis in the presence of parametric uncertainties and the cells numbers diverges to infinity. However, the designed robust controller of SMC has successfully controlled the tumour growth and its mutation which shows the superiority of the proposed robust controller for the tumor. Related comparison of the required chemotropic input injection for these two controllers can be seen in Fig. 10.

Here it can be seen that the required increase of chemotherapy drug has been implemented by the aid of SMC to neutralize the destructive effect of the presence of uncertainties while this improvement is missed for the SVFC. Thus it can be concluded that for a biological system such as tumor especially with mutation syndrome a robust controller such as SMC is a better choice.

The robustness of SMC can be observed in Fig. 11 in which the response of the closed loop system with SMC is compared for the simple system and uncertain one. It can be observed that the closed loop system equipped by robust controller of SMC has a little delay to stabilize the tumor. This delay is contributed to the required time for the controller to compensate the uncertainty and adapt the system according to the real system.

The related comparison for the drug injection can be also seen in Fig. 12.

It is illustrated in Fig. 12 that as expected, the robust controller of SMC has automatically increased its input to compensate the uncertainty of the system and is more trustable for cancer system with mutation syndrome.

5. Conclusion

In this paper, a new dynamic model was delivered for mutation process of cancer cells for which chemotherapy input can be employed as its related controlling input. It was explained that since the mutation is involved in cancer growth, this phenomenon was added to the dynamic of the

cancer metastasis to provide the possibility of stabilizing the performance of the treatment according to [16]. Also since the cancer growth is supposed to be restrained by the aid of chemotherapy injection, the effect of the input on the extracted state space was developed. Considering the fact that the extracted state space as the result of its biological nature, has definitely some parametric uncertainties, a robust control was then designed according to a sliding surface and was implemented on the extracted mutation dynamics. It was shown by the aid of simulation in MATLAB that the biological system of tumour diverges to instability if no controlling input would be employed which shows the correctness of modelling the mutation. Also the drug resistance phenomenon was observable for the cancer system in which the chemotherapy input is just adjusted for the first mutation. It was seen that the third generation of cancer cells diverges to instability if the input would be calculated for the first generation. Afterwards a constant chemotropic injection was used for all of the mutating generations and it was seen that the growth of the cancer cells is stopped and the mutation of the cells to the third generation of cancerous mode is blocked which shows the validation of the input embedding on the proposed state space. The efficiency of the designed robust controller was examined then by comparing the rate of convergence of the cancer cells to zero between the chemotherapy which is according to the designed sliding mode controller and the treatment which is based on a constant dosage of chemotherapy injection and SVFC. It was observed that the settling time of the closed loop system is decreased by about 94.28% respect to the constant input and 80% respect to SVFC. Also in order to show the robustness of the proposed treatment, a predetermined parametric uncertainty about 50% was considered at the tumour plant and the performance of the designed robust controller was compared with simple SVF controller. It was seen that the robust sliding mode can control the tumour and its mutation in the presence of implemented uncertainty by increasing the injection by about 20% while SVF controller fails to stabilize the disease condition. In all of the mentioned simulations, the reduction of cancer growth was the result of prevention of triggering the third mutation process which shows the importance of mutation modelling. As the result, it can be concluded that by the aid of the proposed state space, the mutation process can be predicted and by the aid of the designed robust controller its triggering and subsequently the cancer cell growth can be properly blocked.

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Biography:

H. Tourajizadeh was born in Tehran, Iran on October 30, 1984. He received his B.Sc. in Mechanical Engineering from KNT University of Technology in 2006. He has obtained his M.Sc. from Iran University of Science and Technology in 2008 in the field of applied mechanical design. He also has obtained his Ph.D. from Iran University of Science and Technology in 2012 in the same field, branch of control and vibration. More than 65 journal papers, 25 accepted conference papers, 1 published book, 1 chapter book and 4 booked inventions are the results of his researches so far. He has been involved in teaching and research activities for more than 15 years in the field of control and dynamics in different Universities and he is now associate professor of Kharazmi University. His research interests include robotic systems, automotive engineering, control and optimization, parallel manipulators, industrial automation and mechatronic systems.

Z. Goorkani was born in Kerman, Iran on june 8, 1994. She received her B.Sc. in Mechanical Engineering from Jiroft University in 2018. She has been studying for a M.Sc. at KHU since 2018 in the field of vibration control.

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Table 1

Parameters	Biological meaning	Numerical values	Unit
S	Stem cells	900000	Cell
α_S	Probability of symmetrically self-renewing stem cells	0.2 [32]	%
α_a	Probability of asymmetrically self-renewing stem cells	0.6 [32]	%
α_d	Probability of symmetrically differentiating stem cells	0.15 [32]	%
δ_S	Probability of stem-cell death	0.05 [33]	%
m_C	Probability of mutated divisions of progenitors	10^{-6}	%
m_S	Probability of mutated divisions in stem cells	10^{-6}	%
β_0	The division rate in this population	9.697	Per day
β_1	Stem cells division rates in the first generation	14.388	Per day
μ_0	The death rate in this population	0.1006	Per day
μ_1	Mortality rate in the first generation	0.083	Per day
μ_2	Second generation mortality rate	0.00658	Per day
p_{10}	Rate of destruction of healthy cells by chemotherapy drug	$1.2*10^{-7}$	Per day
p_{20}	Rate of cancer cells death by chemotherapy drug	0.2051	Per day
a_1	Proliferation rate of the normal cells	1.1	Per day
a_2	Proliferation rate of the cancer cells	4.6205	Per day
γ	Rate of chemotherapy drug decay	0.9 [31]	Per day

Table 2

Parameters	Biological meaning	Numerical values	Changed value
α_{S1}	Probability of symmetrically self-renewing stem cells in first generation	0.4	0.6
α_{d2}	Probability of asymmetrically self-renewing stem cells in second generation	0.5	0.7
m_C	Probability of mutated divisions of progenitors	10^{-6}	10^{-4}
μ_0	The death rate in this population	0.1006	0.15
β_0	The division rate in this population	9.697	8.2

Fig 1

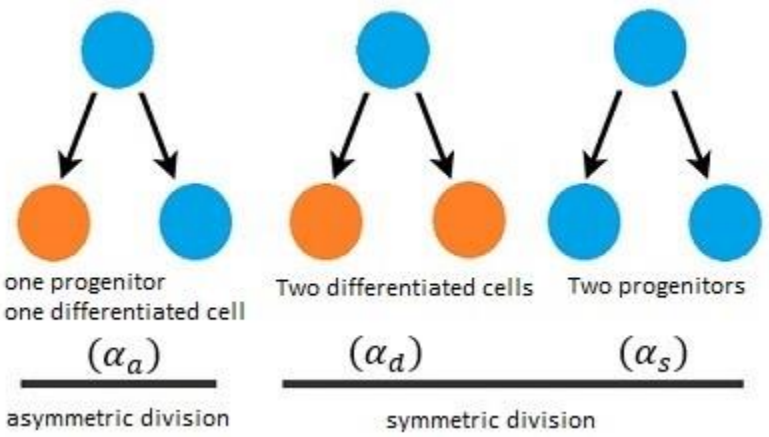

one progenitor
one differentiated cell
Two differentiated cells
Two progenitors
(α_a)
(α_d)
(α_s)
asymmetric division
symmetric division

Fig 2

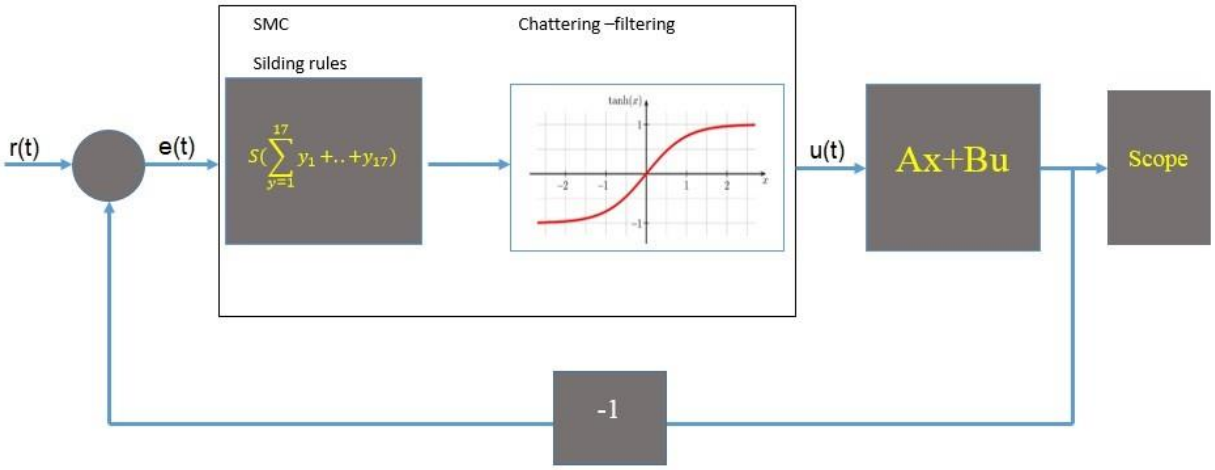

SMC
Chattering –filtering
Silding rules
r(t)
e(t)
$S(\sum_{y=1}^{17} y_1 + .. + y_{17})$
u(t)
Ax+Bu
Scope
-1

Fig 3

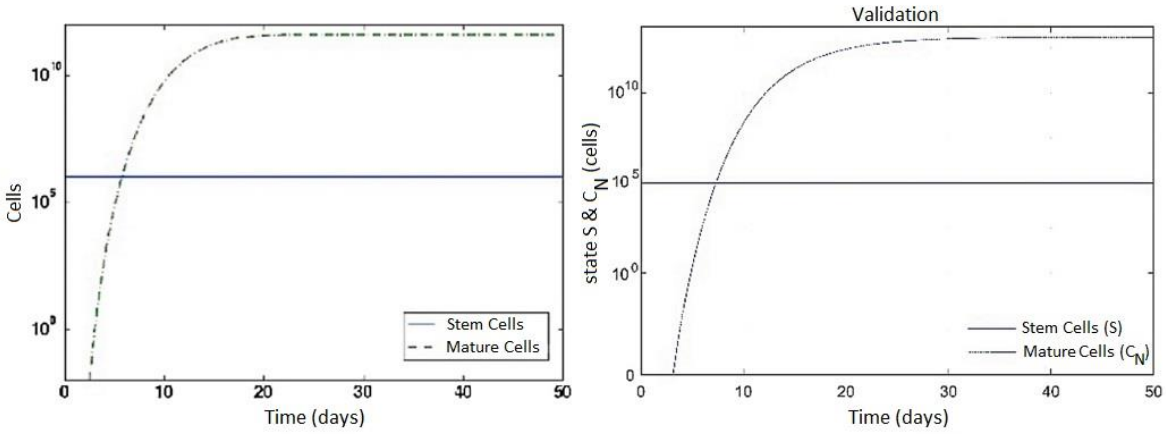

Cells
Time (days)
Stem Cells
Mature Cells
Validation
state S & C_N (cells)
Time (days)
Stem Cells (S)
Mature Cells (C_N)

Fig 4

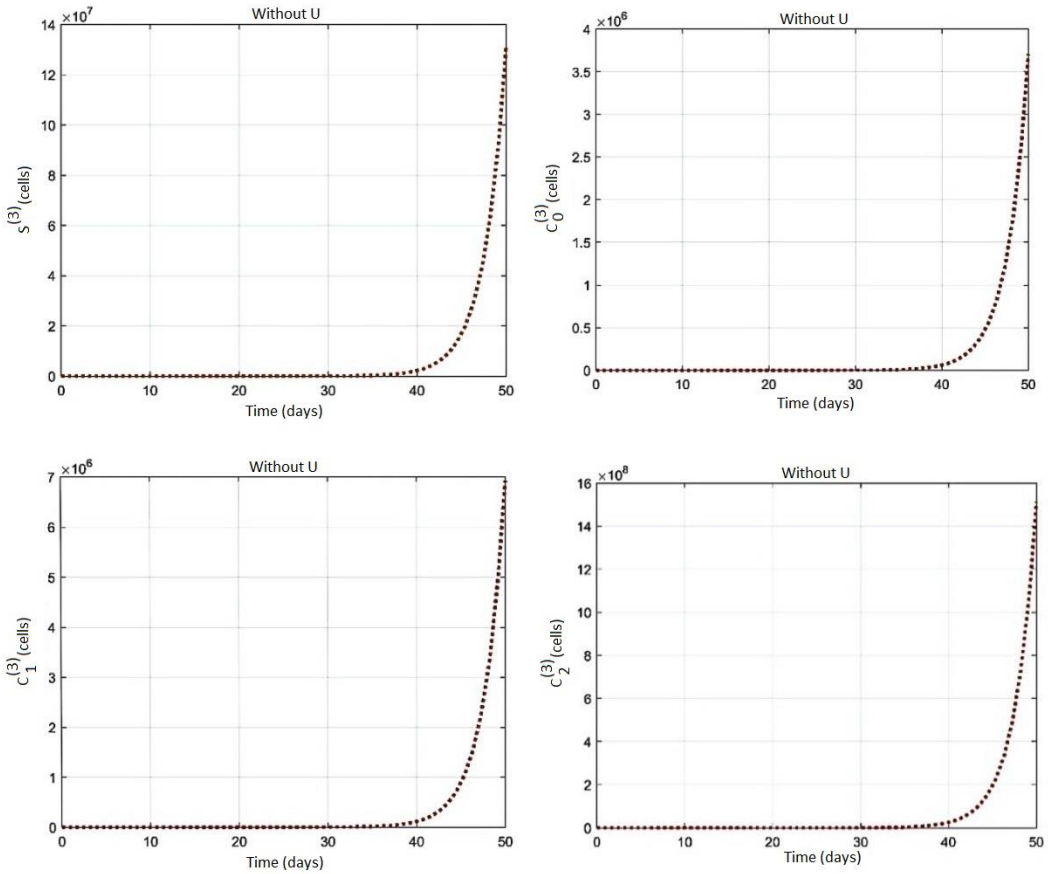

Without U
$S^{(3)}$ (cells)
Time (days)
Without U
$C_0^{(3)}$ (cells)
Time (days)
Without U
$C_1^{(3)}$ (cells)
Time (days)
Without U
$C_2^{(3)}$ (cells)
Time (days)

Fig 5

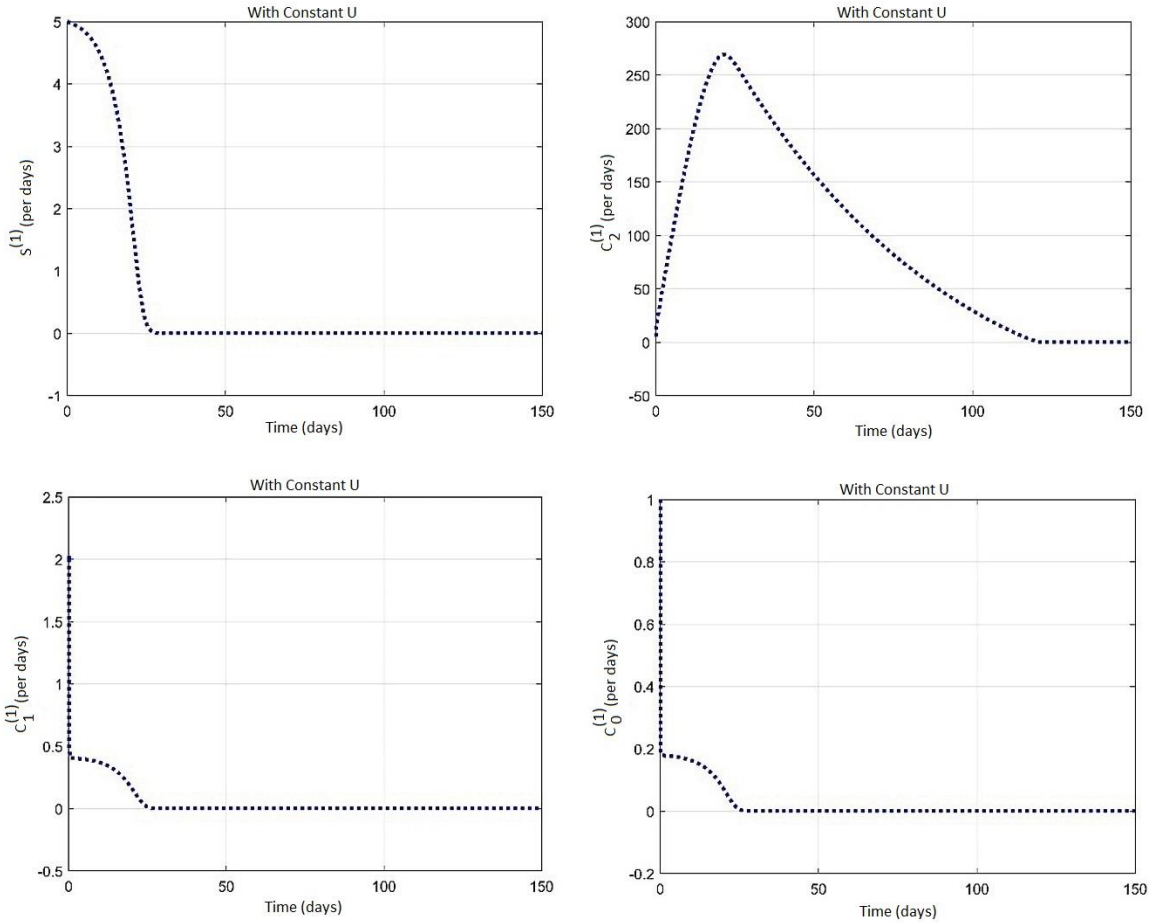

With Constant U
$S^{(1)}$ (per days)
Time (days)
With Constant U
$C_2^{(1)}$ (per days)
Time (days)
With Constant U
$C_1^{(1)}$ (per days)
Time (days)
With Constant U
$C_0^{(1)}$ (per days)
Time (days)

Fig 6

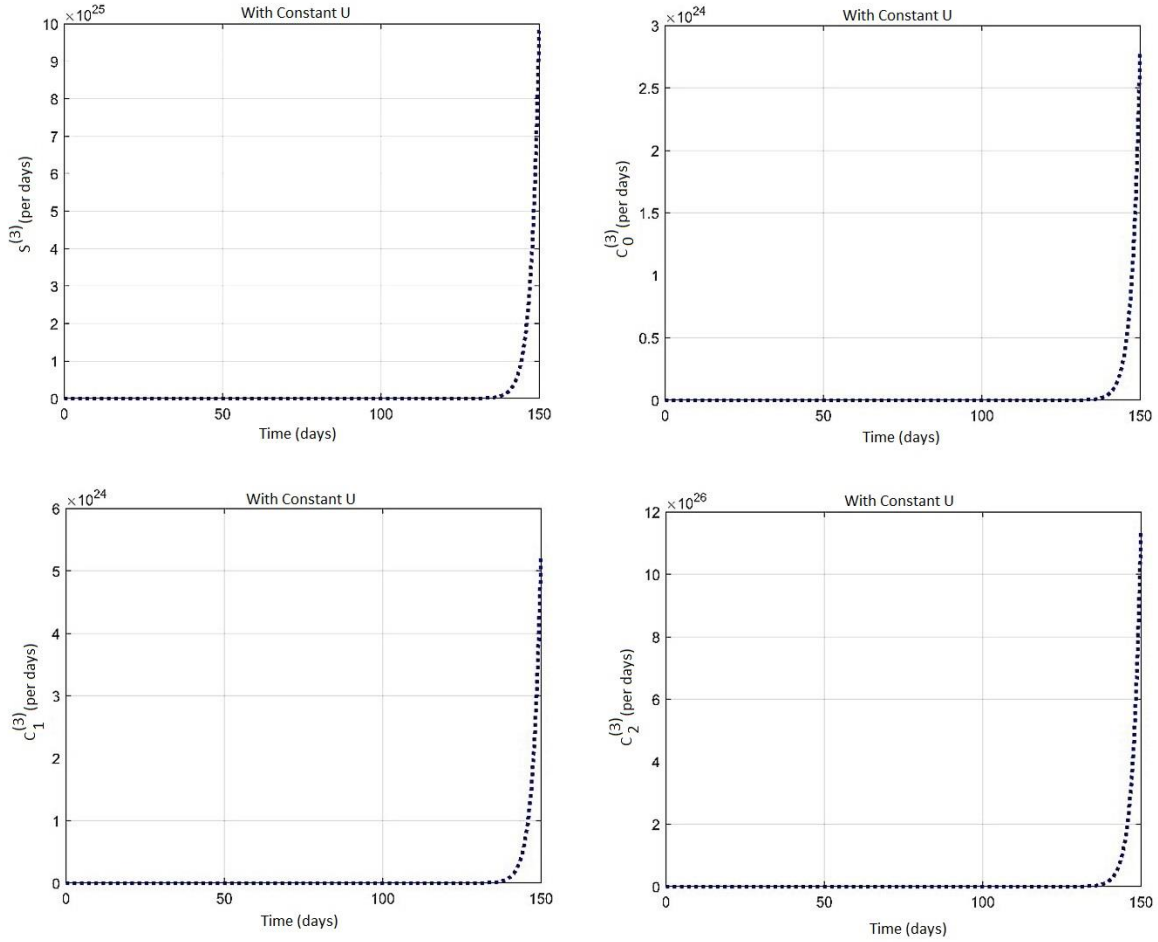

With Constant U
×10^25
S^(3) (per days)
Time (days)
With Constant U
×10^24
C_0^(3) (per days)
Time (days)
With Constant U
×10^24
C_1^(3) (per days)
Time (days)
With Constant U
×10^26
C_2^(3) (per days)
Time (days)

Fig 7

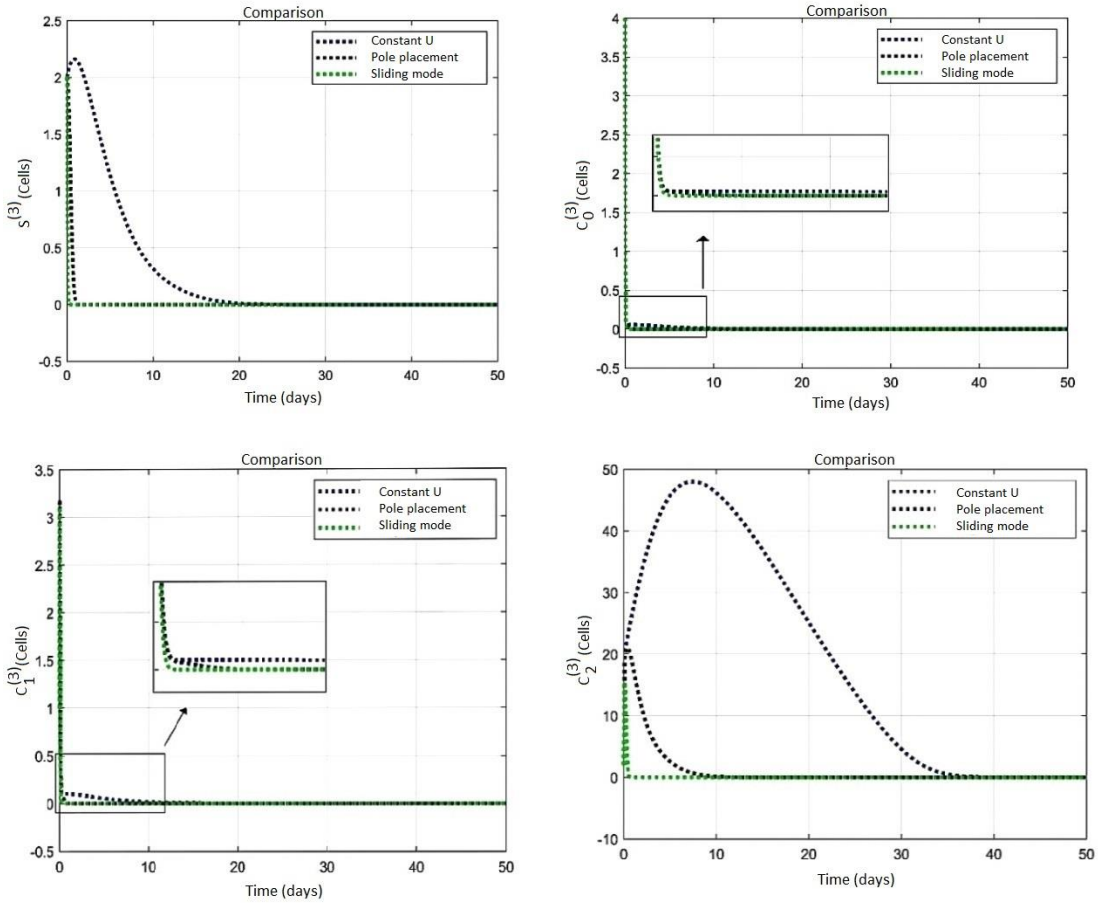

Comparison
Constant U
Pole placement
Sliding mode
$S^{(3)}$(Cells)
Time (days)
Comparison
Constant U
Pole placement
Sliding mode
$C_0^{(3)}$(Cells)
Time (days)
Comparison
Constant U
Pole placement
Sliding mode
$C_1^{(3)}$(Cells)
Time (days)
Comparison
Constant U
Pole placement
Sliding mode
$C_2^{(3)}$(Cells)
Time (days)

Fig 8

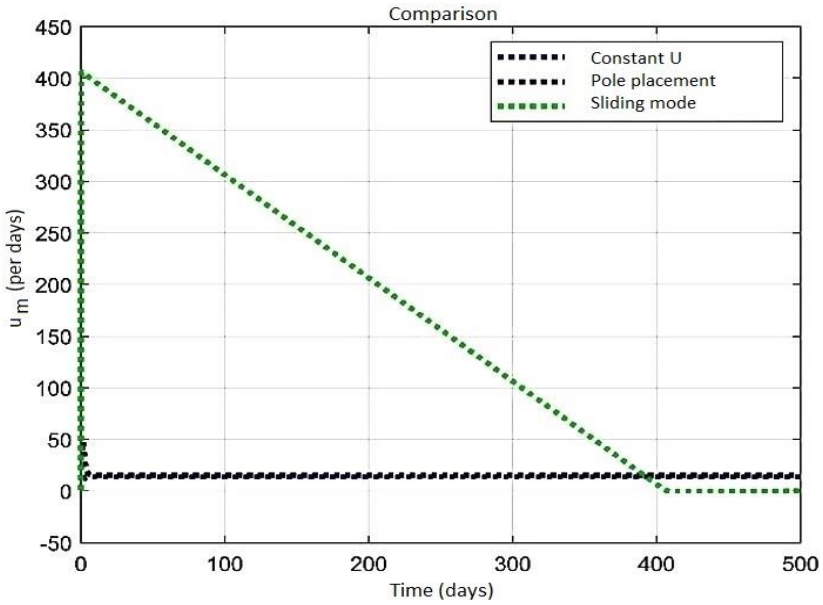

Comparison
Constant U
Pole placement
Sliding mode
u m (per days)
Time (days)
450
400
350
300
250
200
150
100
50
0
-50
0
100
200
300
400
500

Fig 9

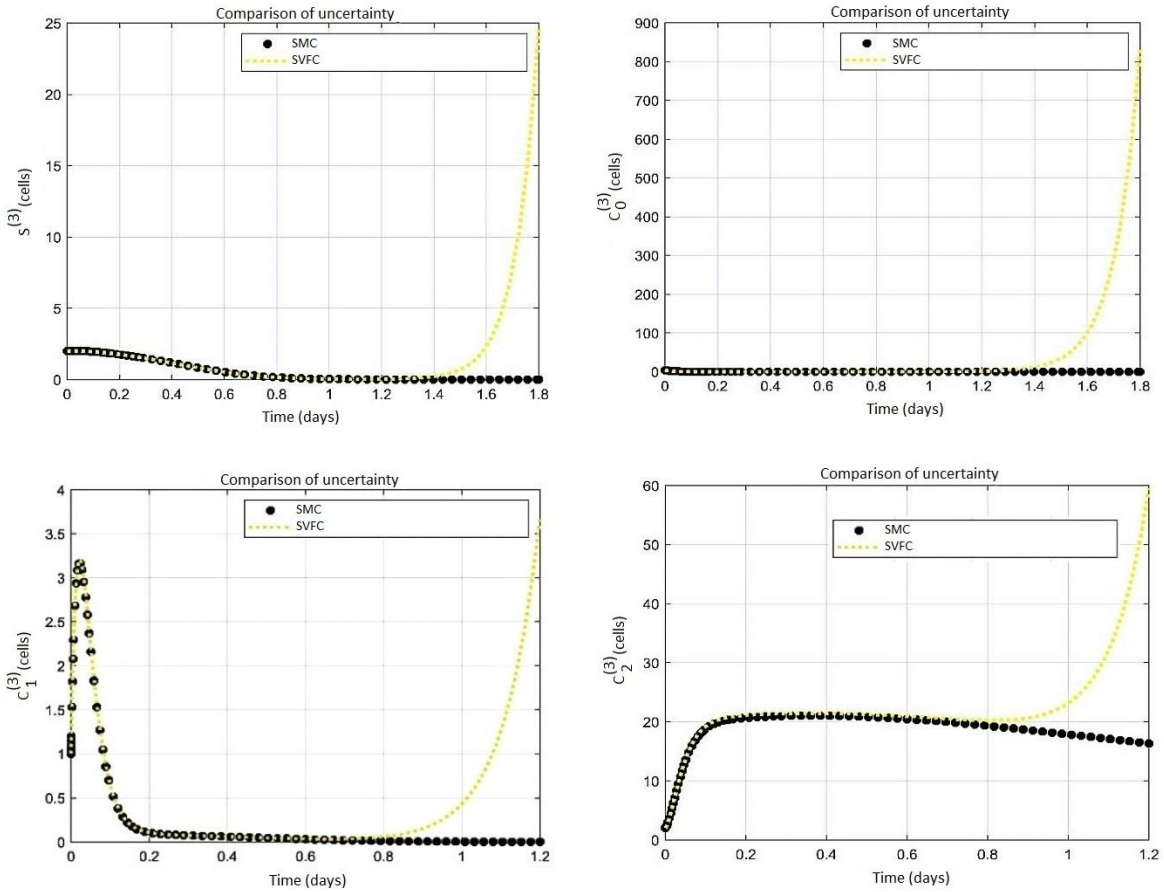

Comparison of uncertainty
SMC
SVFC
$S^{(3)}$(cells)
Time (days)
Comparison of uncertainty
SMC
SVFC
$C_0^{(3)}$(cells)
Time (days)
Comparison of uncertainty
SMC
SVFC
$C_1^{(3)}$(cells)
Time (days)
Comparison of uncertainty
SMC
SVFC
$C_2^{(3)}$(cells)
Time (days)

Fig 10

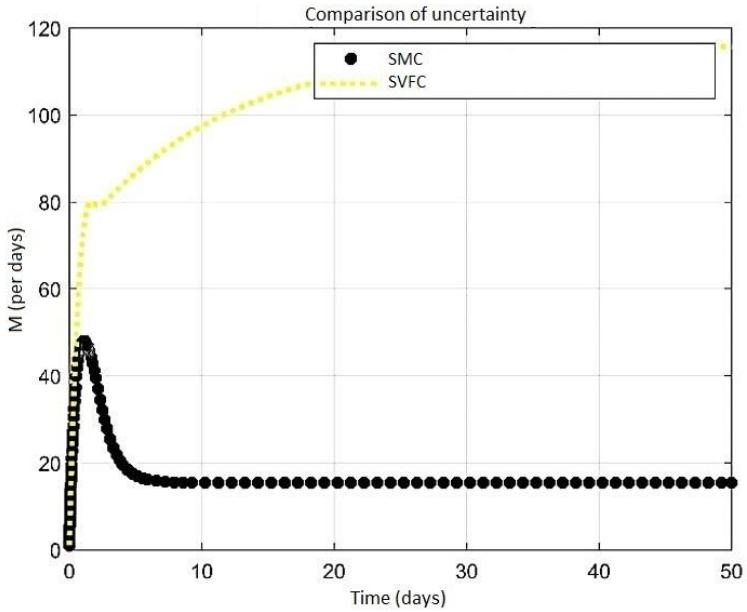

Comparison of uncertainty
SMC
SVFC
M (per days)
Time (days)
0
20
40
60
80
100
120
0
10
20
30
40
50

Fig 11

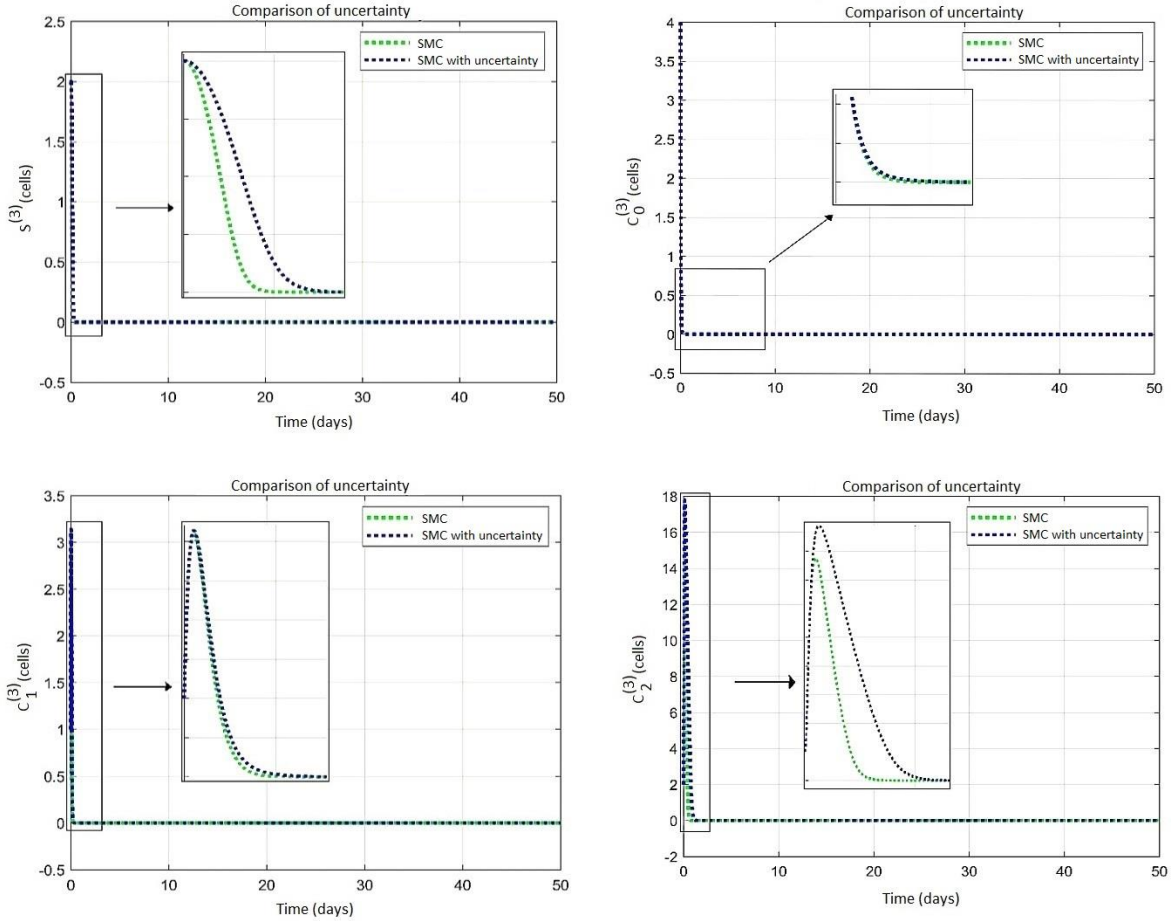
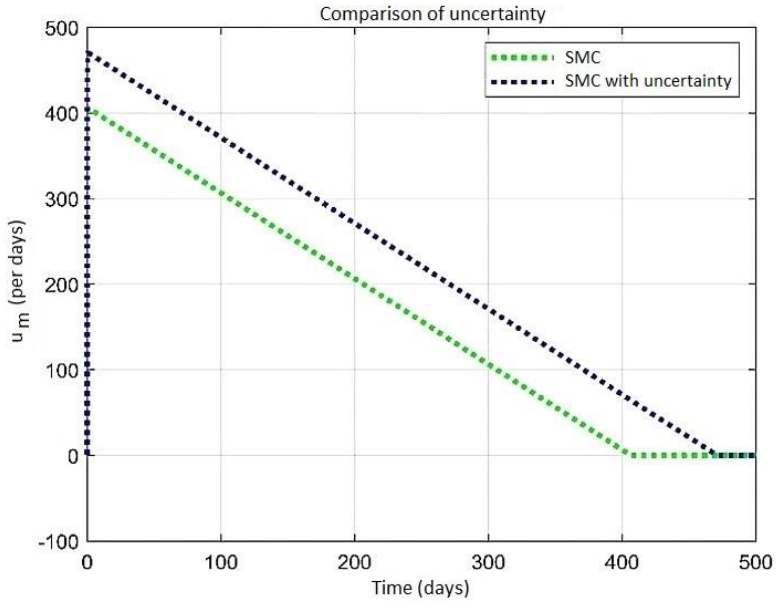

Comparison of uncertainty
SMC
SMC with uncertainty
$S^{(3)}$ (cells)
Time (days)
Comparison of uncertainty
SMC
SMC with uncertainty
$C_0^{(3)}$ (cells)
Time (days)
Comparison of uncertainty
SMC
SMC with uncertainty
$C_1^{(3)}$ (cells)
Time (days)
Comparison of uncertainty
SMC
SMC with uncertainty
$C_2^{(3)}$ (cells)
Time (days)

Fig 12


Comparison of uncertainty
SMC
SMC with uncertainty
500
400
300
200
100
0
-100
0
100
200
300
400
500
u m (per days)
Time (days)