Modelling and Control of Mutation Dynamics of the Cancer Cells Employing Chemotherapy

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Abstract: In this paper, the analytic model of the mutation dynamics related to the cancer cells which is under the control of chemotherapy is developed and its corresponding metastasis is controlled using chemotherapy method. The progress of a cancer tumours is contributed to two main factors including metastasis and mutation. It is observed that controlling the metastasis dynamic without considering the mutation phenomenon is doomed to fail. In this paper, the mathematical model of the cancer dynamic is improved considering the mutation of the stem cells and the effect of chemotherapy injection as the corresponding controlling signal is investigated in the extracted state space. Controlling the cancer growth and its mutation process is accomplished here using PID controller and State Feedback Control (SVFC) method. It is shown that by the aid of the proposed model of this paper, not only the number of the cancer cells can be converted to zero, but also the mutation process can be blocked since the feedback of the mutated cells are also engaged in the state space of the system. Verification of the model is conducted by the aid of simulation in the MATLAB and comparing the results with previous studies.

Keywords: Cancer Modelling, Dynamics of Mutation, Metastasis Controlling, Stem-cells

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Biographical notes: Hami Tourajizadeh was born in Iran. He received his PhD from IUST in Mechanical Engineering in 2012. More than 40 journal papers, 15 conference papers, 2 published books and 2 booked inventions are the results of his researches so far. His research interests include roboticis, control and optimization. **Zahra Goorkani Zarandi** was born in Iran. She received her MSc from KHU in 2021 in the field of control**. Zakieh Farboudi** was born in Iran. She received her MSc in control from KHU in 2021. **Ehsan Sadeghi Ghasemabadi** was born in Iran. He is currently studying PhD in Electrical Engineering at USB. He received his MSc in Electrical Engineering from Shahed University in 2019.

1 INTRODUCTION

Mathematical model is extremely useful in different fields and nowadays it is also employed in biological research. Dynamic model of a system can predict the behavior of a system by the aid of its related analytic differential equations and thus provides a good prerequisite for controlling the response of the system. Some examples of the biological plants which can be modelled analytically using the mentioned differential equations are tumor growth, metastasis dynamics, chemotherapy, immunotherapy, and tumor heterogeneity. Cancer treatment using chemotherapy in its traditional form has some challenges such as extreme side effects and also mutation syndrome. One of the proposed solution toward neutralizing the mentioned deficiencies is modeling the dynamics of the cancer growth and estimating the proper controlling input. So far, researchers have used variety of models and controllers to treat the cancer. Most of the previous research are related to cancer metastasis while mutations and stem cells which are effectively engaged in cancer dynamics are ignored. Stem cell mutations causes tumor formation and cancer progress. Thus if the mutation could be modeled and consequently controlled properly, the efficiency of threatening can be increased enormously. The main studies in the field of growth modeling of cancer cells are as follow.

Cancer is considered as a genetic disease in [1]. Here the dynamic of rich signalling is presented and its effect on the cancer cells and drug resistance is discussed. In 2011, Andasari analyzed a mathematical model in which the attack of the cancer cells on the Extra Cellular Matrix (ECM) and tissue was also considered, and its task was to activate the urokinase plasminogen system [2]. In this article, a mathematical model was numerically examined based on the invasion of the cancer cells into tissues. Cell-specific GEMs was employed in [3] to prevent the growth of cancer cells. Differences of cancer cell lines and the related metabolic systems were also studied here. This article studies the differences of the cell line metabolism as well as the anti-growth factors using CL-GEM which inhibits the growth of the cancer cells. In 2004, Jackson proposed a mathematical model for the treatment of the prostate cancer that describes pre-treatment growth of cancer cells and eventual return after surgery [4].

In 2006, Kohandel, Sivaloganathan, and Oza presented a simple mathematical model to examine the repeated effect of chemotherapy and surgical treatments [5]. In 2018, Fassoni proposed a mathematical model for the onset and development of cancer that considers three hallmarks of cancer, including self-sufficiency in growth signals, insensitivity to anti-growth signals, and escape from apoptosis [6]. At the mentioned studies, the cancer is modelled but no controlling signal is designed to cure the tumour. Considering the fact that the cancer is modeled, proper controlling input can be designed to stabilize the tumor growth. Shuo Wang in 2016, proposed a cancer treatment using chemotherapy which considers an optimal control with the aim of reducing the combination of tumor volume and side effects of chemotherapy [7].

A new control plan was developed by Garawany considering the therapeutic limitations of cancer in the delivery system of chemotherapy drugs [8]. Kozusko et. al proposed a mathematical model related to the growth of the cancer cells and then its related response to the treatment with the antimitotic agent curacin was analyzed [9]. The dependency of chemotherapy to the cell cycle is investigated in [10]. Here the model is categorized according to the employed drug and the optimum control is selected according to the specified category. The proposed model is used to estimate the growth of the cancer cells in vitro for the growth and treatment of the cancer cells A2780 and MCF-7 and LY2 by the aid of chemotherapy. In 2006, Dingli introduced a mathematical model that considers the dynamics of the cancer cell population. It also examined the equilibrium points for complete cure of the disease in terms of relative treatment and treatment inadequacy [11]. In 2018, Vivek designed an ISA-PID controller for optimal drug scheduling during the treatment [12].

In [13], it is explained that the main obstacles against a successful chemotherapy are the dependency of the cell cycle to treatment and also the resistance of the cancerous cell to cytotoxic. Optimal control is supposed in this research to overcome the mentioned challenges. According to their proposed thesis, the models should include division of the cell cycle into subphases and/or the mechanisms of drug resistance. Oke et. al has investigated a mathematical model of breast cancer which consists of a series of differential equations, chemotherapy and ketogenic diet. They employed optimal control in order to extract different combinations of chemotherapy drug and ketogenic diet and find out the optimum injection of drug dosage toward decreasing the cancer cells [14]. In 2019, it was shown in [15] that it is possible to postpone the drug resistance of chemotherapy of a tumor by the aid of optimal control. The proposed model divides the tumors to two sections including sensitive and resistant and includes a flow between compartments due to genetic mutations.

A non-standard objective functional including a penalty for resistant phenotype is introduced here. Panjwani designed a two Degrees Of Freedom (DOF) fractional order PID controller to regulate concentration and toxicity of the drug [16]. Dunne et. al used human adipose tissue-derived extracellular matrix (hDAM) as a three-dimensional cell culture to grow and treat the breast cancer [17]. hDAM has been used here to study

the migration / invasion growth, morphology, and drug outcome of the cancer cells. In 2019, Khalili used a fuzzy controller to control the injection of the chemotherapy drugs [18]. For cancer and healthy cells, a fixed fuzzy control input was obtained in this article, by which the rate of the chemotherapy injection using a fuzzy controller can be achieved. The mentioned research just focusses on metastasis while as mentioned the main challenge in cancer progress is mutation. Few studies have considered this phenomenon so far. In 2007, Wodarz discussed the effect of stem cell turnover on protection against the cancer and aging [19]. Samuels theoretically studied PIK3CA, which is mutated in various human cancers, by eliminating two common mutations in colon cancer [20]. The results of this method show that PIK3CA mutations amplify the neoplastic cells. Then in 2008, Ashkenazi proposed a model used to detect the onset of cancer as a multistage process of accumulation of somatic mutations in tissue cells and showed how the sequence of mutations and phenotypic changes in mutant cells affect the rate of carcinogenesis. This model predicts that the details of cancer growth dynamics are governed by the specific effect of mutations that lead to cell transformation. Also, differences in the dynamics of different cell populations have determined the accumulation of mutations and their physiological expression in a specific order [21]. Sameen, together with several other researchers, in 2015 presented a mathematical model for analysing the behaviour of KRAS mutation in colorectal cancer with respect to a combination of moAb and Chemotherapy therapies to combat drug resistance [22]. In 2017, Stiehl and Czochra developed an insight into mathematical modelling for self-regenerating stem cells in cancer remodelling [23]. In 2019, Ascolani and Lio showed by modelling that how important the mutation of driver and metabolic material is in the progression of breast cancer to bone [24-25]. In 2020, Owolabi and Shikongo presented a mathematical model that expresses the inherent drug resistance to include the spatial effects of the cells involved and the creation of biological and asymptotic surfaces [26].

As can be seen, controlling the mutation of cancer cells is not studied so far in the literature. In this study, by the aid of the proposed model of [21], the mentioned gap of mutation control is covered. In this model, both the sequential acquisition of phenotype-modifying mutations and tissue hierarchy are considered. Also the progressive effect of accumulated mutations that ultimately lead to the induction of genetic instability is studied in this model. As a result, a general mathematical framework for the quantitative study of the carcinogenesis is presented. This model considers key points of biological modelling such as the hierarchical structure of tissue and the maturation of productive cells. Moreover, all possible modes of stem cell divisions are included here, and the dynamics of each generation can be studied separately. The effect of the chemotherapy input is also investigated on the model and using the model of Pinho. PID controller is employed then to converge the cancer cells to zero. Also the related gains are tuned using pole placement method SVFC. It is shown by the aid of the extracted model and also conducting some simulation scenarios that the control of this type of cancer can be realized with the proposed controlling strategy and the mutation process can be blocked successfully by the aid the chemotherapy input according to the proposed controlling algorithm. At the next section, the proposed analytic model of the cancer mutation is presented and the related controlling input is added to the dynamics of the system. At section three, the controlling strategy according to PID and pole placement is implemented on the model. In section four, a simulation scenario is conducted in which the third mutation of cancer cells is controlled. The correctness of modelling is shown by comparing the results with previous simulations while the efficiency of the designed controller is validated by checking the applicability of the proposed chemotherapy schedule to block the mutation process. It will be concluded that using the mentioned model and control strategy, the mutation phenomenon can be successfully controlled by which the metastasis and cancer cells can be consequently stabilized.

2 MODELING

According to the presented model of [27], the stem cells can be divided symmetrically to a couple of stem cells or a couple of ordinary cells. Asymmetrically division is also possible which results in an ordinary cell and a stem cell as shown in "Fig. 1".

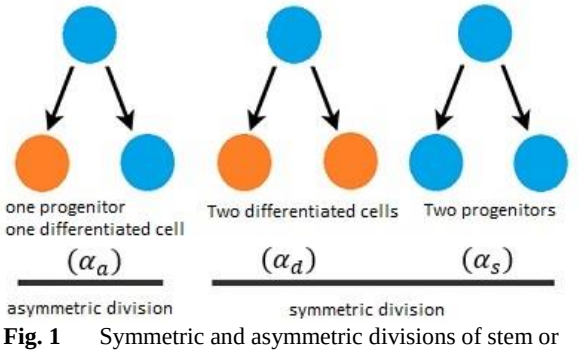

Fig. 1 Symmetric and asymmetric divisions of stem or progenitor cells.

Based on this model, the state space related to the dynamics of the cancer growth without considering the mutation and controlling input can be presented as in "Eq. (1)":

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

Here, S is the stem cells, α_S is the rate of the symmetrically self-renewing stem cells, α_d is the rate of symmetrically differentiating stem cells and α_a is the rate of the asymmetrically self-renew Stem cells. Also δ_S is the rate of the death of the stem cells, C_0 is the rate of change in the number of earliest progenitors (the direct effect of the stem cell division, which is considered as the generation 0). Here each asymmetric differentiation division contributes two progenitors, while the asymmetric ones contribute one progenitor. β_0 and μ_0 are the rate of division and death of the first generation of the stem cells respectively and N,n denotes the number of the divisions in the equations.

2.1. Modeling of Mutation:

According to [18], the controlling input as the chemotherapy injection rate can be added to the presented model of [22] as "Eq. (2)". Here the dynamics of the stem cells is presented for 3 mutations with 2 divisions:

$$\frac{dS}{dt} = \left((1-2m_S)\alpha_S - \alpha_d - m_S\alpha_a - \delta_S\right)S - \frac{p_{10}\,S}{a_1 + S}U$$
$$\frac{dS^{(i)}}{dt} = \left(2\alpha_{S(i-1)} + \alpha_{a(i-1)}\right)m_{S(i-1)}S^{(i-1)} + \left((1-2m_{Si})\alpha_{Si} - \alpha_{di} - m_{Si}\alpha_{ai} - \delta_{Si}\right)S^{(i)} - \frac{p_{10}\,S^i}{a_1 + S^i}U \qquad i = 1.2$$
$$\frac{dS^{(I)}}{dt} = \left(2\alpha_{S(I-1)} + \alpha_{a(I-1)}\right)m_{S(I-1)}S^{(I-1)} + (\alpha_{SI} - \alpha_{dI} - \delta_{SI})S^{(I)} - \frac{p_{20}\,S^I}{a_2 + S^I}U \qquad I = 3 \quad (2)$$

It should be noticed that here, the natural divisions are take place with probability of $(1 - m_S)$ while the mutated divisions are taken place with probability of m_S. Also $\{\alpha_{Si}.\alpha_{S(1-I)}.\alpha_{SI}.\alpha_{S(1-i)}\}$ are the improved rate of symmetrically self-renewing stem cells, $\{\alpha_{dI}.\alpha_{di}\}$ are the improved rate of symmetrically differentiating stem cells and $\{\alpha_{ai}.\alpha_{a(I-1)}.\alpha_{a(i-1)}\}$ are the improved rate of symmetrically self-renew stem cells. i in the equations $\frac{dS^{(I)}}{dt}$ and $\frac{dS^{(i)}}{dt}$ denotes the mutation number 1, 2 respectively while I denotes the third generation of the stem cells division. p_{10} shows the rate of the death of the normal cells by the chemotherapy drug which is equal to 1.2×10^{-7} and finally a_1 is the proliferation rate of the normal cell which is 1.1. Now the dynamic equations of the natural and mutated progenitor can be stated as "Eq. (3)":

$$\frac{dC_0}{dt} = \left(2\alpha_d(1-m_S) + \alpha_a(1-m_S)\right)S - (\beta_0 + \mu_0)C_0 - \frac{p_{10}\,C_0}{a_1 + C_0}U$$
$$\frac{dC_0^{(i)}}{dt} = \left(2\alpha_{d(i-1)} + \alpha_{a(i-1)}\right)m_{S(i-1)}S^{(i-1)} + (2\alpha_{di} + \alpha_{ai})(1-m_{Si})S^{(i)} - \left(\beta_0^{(i)} + \mu_0^{(i)}\right)C_0^{(i)} - \frac{p_{10}\,C_0^i}{a_1 + C_0^i}U \qquad i = 1.2$$
$$\frac{dC_0^{(I)}}{dt} = \left(2\alpha_{d(I-1)} + \alpha_{a(I-1)}\right)m_{S(I-1)}S^{((I-1))} + (2\alpha_{dI} + \alpha_{aI})S^{(I)} - \left(\beta_0^{(I)} + \mu_0^{(I)}\right)C_0^{(I)} - \frac{p_{20}\,C_0^I}{a_2 + C_0^I}U \qquad I = 3 \quad (3)$$

Here $C_0^{(i)}$ and $C_0^{(I)}$ show the number of the cells which are not engaged in any division and I, i denote the mutation. Also p_{20} shows the rate of the cancer cells death by chemotherapy drug where I is equal to 0.2051 and a_2 is the rate of cancer cells' saturation which is equal to 4.6205. The rate of the changes in the mutated cells in the first division can be presented as "Eq. (4)":

$$\frac{dC_1}{dt} = 2\beta_{n-1}(1-m_C)C_{n-1} - (\beta_n + \mu_n)C_n - \frac{p_{10}\,C_n}{a_1 + C_n}U \qquad n = 1$$
$$\frac{dC_1^{(i)}}{dt} = 2\beta_{n-1}^{i-1}m_{C(i-1)}C_{n-1}^{(i-1)} + 2\beta_{n-1}^{(i)}(1-mC_i)C_{n-1}^{(i)} - \left(\beta_n^{(i)} + \mu_n^{(i)}\right)C_n^{(i)} - \frac{p_{10}\,C_n^i}{a_1 + C_n^i}U \quad n = 1\ \&\ i = 1,2$$
$$\frac{dC_1^{(I)}}{dt} = 2\beta_{n-1}^{(I-1)}m_{C2}C_{n-1}^{(I-1)} + 2\beta_{n-1}^{(I)}C_{n-1}^{(I)} - \left(\beta_n^{(I)} + \mu_n^{(I)}\right)C_n^{(I)} - \frac{p_{20}\,C_n^I}{a_2 + C_n^I}U \quad n = 1\ \&\ I = 3 \quad (4)$$

In the above equations, $n = 1$ shows the first division and the production of the last division which is shown by N can be expressed as follow:

$$\begin{aligned}
\frac{dC_N}{dt} &= 2\beta_{N-1}(1-m_C)C_{N-1} - (\beta_N + \mu_N)C_N \\
&\quad - \frac{p_{10}\, C_N}{a_1 + C_N}U \qquad N = 2 \\
\frac{dC_N^{(i)}}{dt} &= 2\beta_{N-1}^{(i-1)} m_{C(i-1)} C_{N-1}^{(i-1)} \\
&\quad + 2\beta_{N-1}^{(i)}(1-m_{Ci})C_{N-1}^{(i)} - \mu_N^{(i)} C_N^{(i)} \\
&\quad - \frac{p_{10}\, C_N^i}{a_1 + C_N^i}U \qquad i = 1,2 \;\; \& \;\; N = 2 \\
\frac{dC_N^{(I)}}{dt} &= 2\beta_{N-1}^{(I-1)} m_{C(I-1)} C_{N-1}^{(I-1)} \\
&\quad + 2\beta_{N-1}^{(I)} C_{N-1}^{(I)} - \mu_N^{(I)} C_N^{(I)} \\
&\quad - \frac{p_{20}\, C_N^I}{a_2 + C_N^I}U \qquad I = 3 \;\; \& \;\; N = 2
\end{aligned} \tag{5}$$

Dynamics of the system is simulated in two scenarios. In the first scenario, no controlling input is considered. Here the constant parameters are as "Table 1" [21].

Table 1 The parameters used in MATLAB for normal cells and the Maturity Structured model of mutation

Parameter	Biological Meaning	Normal Value	Mutated Value
S	Normal stem cells	18000 (cells)	18000 (cells)
α_S	Probability of symmetrically self-renewing stem cells	0.2 [28]	0.4
α_a	Probability of asymmetrically self-renewing stem cells	0.6 [28]	0.425
α_d	Probability of symmetrically differentiating stem cells	0.15[28]	0.025
δ_S	Probability of stem-cell death	0.05[29]	0.025
m_c	Probability of mutated divisions of progenitors	10^{-6}	10^{-4}
m_S	Probability of Mutated divisions in stem cells	10^{-6}	10^{-4}
β_0	The division rate in this population	9.697	19.08
μ_0	The death rate in this population	0.1006	0.0484
p_{10}	Rate of destruction of healthy cells by chemotherapy drug	1.2×10^{-7}	–
p_{20}	Rate of cancer cells death by chemotherapy drug	0.2051	–
a_1	Proliferation rate of the normal cells	1.1	–
a_2	Proliferation rate of the cancer cells	4.6205	–

2.2. Linearization Around the Operating Point

Since the cancer cells are supposed to be destroyed, their number is around the equilibrium points of the extracted state space in the stable condition. Thus the equilibrium points are calculated here to linearize the state space around them as the related operating point. As a result it is possible then to control the system using a simple and strong controller of PID.

According to homeostasis phenomenon, any material is set to be constant in the body for all of the limbs. In [21] it is supposed that this condition is realized by the aid of a constant number of stem cells, i.e. $\frac{dS}{dt} = 0$. Thus if the rate of the asymmetric division and death would be non-zero they should be balanced accordingly. Thus we have $\alpha_s = \alpha_d + \delta_s$, which means that the stem cells are constant during the time $S(t) = S_H$. As a result, the equilibrium points can be extracted as follow:

$$\begin{aligned}
&[900000; 8.93; 1.1195\times10^{5}; 4.8959\times10^{7}; \\
&3.618; 0.1788; 0.4229; 1.7151\times10^{3}; \\
&0.0011; 2.8411\times10^{-5}; 6.8861\times10^{-5}; \\
&1.3606; 6.8591\times10^{-5}; 1.982\times10^{-6}; \\
&3.9069\times10^{-6}; 0.4555]
\end{aligned} \tag{6}$$

Linearizing the mentioned state space of the cancer dynamics results in:

$$\frac{dS}{dt} = -1 \times 10^{-6} S - 1.2 \times 10^{-4} u - 0.9014$$
$$\frac{dC_0}{dt} = 0.9S - 9.07 \times 10^{4} C_0 - 1.068 \times 10^{-4} u + 48.9987$$
$$\frac{dC_1}{dt} = 1.81 \times 10^{5} C_0 - 14.47 C_1 - 1.2 \times 10^{-4} u + 1.6227 \times 10^{3}$$
$$\frac{dC_2}{dt} = 28.77 C_1 - 0.07 C_2 - 1.2 \times 10^{-4} u + 0.002$$
$$\frac{dS^{(1)}}{dt} = 1 \times 10^{-6} S + 0.225 S^{(1)} - 9.1926 \times 10^{-5} u + 1.7094$$
$$\frac{dC_0^{(1)}}{dt} = 9 \times 10^{-7} S + 0.72 S^{(1)} - 19.13 C_0^{(1)} - 1.6778 \times 10^{-5} u - 0.0172$$
$$\frac{dC_1^{(1)}}{dt} = 56.3 C_0^{(1)} - 23.8 C_1^{(1)} - 3.3323 \times 10^{-5} u + 0.001$$
$$\frac{dC_2^{(1)}}{dt} = 2 \times 10^{-5} C_1 + 47.54 C_1^{(1)} - 0.014 C_2^{(1)} - 7.311 \times 10^{-5} u - 1.6686$$
$$\frac{dS^{(2)}}{dt} = 1.2 \times 10^{-4} S^{(1)} + 0.41 S^{(2)} - 1.1988 \times 10^{-5} u + 7.0579 \times 10^{-4}$$
$$\frac{dC_0^{(2)}}{dt} = 7.2 \times 10^{-5} S^{(1)} + 0.5 S^{(2)} + 28.5 C_0^{(2)} - 3.0993 \times 10^{-9} u + 0.0016$$
$$\frac{dC_1^{(2)}}{dt} = 0.004 C_0^{(1)} + 56.36 C_0^{(2)} - 33.16 C_1^{(2)} - 7.5116 \times 10^{-9} u + 3.2961 \times 10^{-3}$$
$$\frac{dC_2^{(2)}}{dt} = 0.005 C_1^{(1)} + 65.65 C_1^{(2)} - 0.005 C_2^{(2)} - 6.6355 \times 10^{-5} u - 9.229 \times 10^{-4}$$
$$\frac{dS^{(3)}}{dt} = 0.014 S^{(2)} + 0.22 S^{(3)} - 3.044 \times 10^{-6} u - 4.1507 \times 10^{-6}$$
$$\frac{dC_0^{(3)}}{dt} = 0.005 S^{(2)} + 1.01 S^{(3)} - 37.85 C_0^{(3)} - 8.7979 \times 10^{-8} u - 1.243 \times 10^{-6}$$
$$\frac{dC_1^{(3)}}{dt} = 0.57 C_0^{(2)} + 75.7 C_0^{(3)} - 42.5 C_1^{(3)} - 1.7342 \times 10^{-7} u - 1.7851 \times 10^{-6}$$
$$\frac{dC_2^{(3)}}{dt} = 0.66 C_1^{(2)} + 85.1 C_1^{(3)} - 8.3 \times 10^{-4} C_2^{(3)} - 0.0184 u - 0.2094 \quad (7)$$

3 CONTROL

3.1. PID Control using Pole Placement Tuner

PID controlling strategy is supposed to be employed in this paper to stabilize the growth of cancer cells and consequently its related mutation process. In order to guarantee the convergence of the cancer cells to zero and blocking the mutation, the corresponding Eigen values are set to be negative using pole placement method. To cover this goal, considering the linearized equation of the system state space, the gains of the feedback controlling signal should be set in such a way that the poles of the closed-loop system would be located at the left side of the imaginary axis. The location of the desired poles determines the optimal performance of the system. Therefore, by choosing a suitable location for the poles of the closed-loop system, the required controlling gains can be extracted for achieving the stable condition of the cancer growth and mutation. The linearized state space and the related input of the system is:

$$\dot{x} = Ax + Bu \quad (8)$$

$$u = -kx \quad (9)$$

Here matrix B is a 16 × 1 vector which is as follows:

$$\begin{aligned}
B_{1,1} &= -1.2 \times 10\text{^} - 4 \\
B_{2,1} &= -1.068 \times 10\text{^} - 4 \\
B_{3,1} &= -1.2 \times 10\text{^} - 4 \\
B_{4,1} &= -1.2 \times 10\text{^} - 4 \\
B_{5,1} &= -9.1926 \times 10\text{^} - 5 \\
B_{6,1} &= -1.6778 \times 10\text{^} - 5 \\
B_{7,1} &= -3.3323 \times 10\text{^} - 5 \\
B_{8,1} &= -7.311 \times 10\text{^} - 5 \\
B_{9,1} &= 1.1988 \times 10\text{^} - 5 \\
B_{10,1} &= -3.0993 \times 10\text{^} - 9 \\
B_{11,1} &= -7.5116 \times 10\text{^} - 9 \\
B_{12,1} &= -6.6355 \times 10\text{^} - 5 \\
B_{13,1} &= -3.044 \times 10\text{^} - 6 \\
B_{14,1} &= -8.7979 \times 10\text{^} - 8 \\
B_{15,1} &= -1.7342 \times 10\text{^} - 7 \\
B_{16,1} &= -8.3 \times 10\text{^} - 4
\end{aligned} \quad (10)$$

And matrix A is 16 × 16 and is a lower triangular matrix the values of its elements are given in "Eq. (10)". The elements which are not mentioned here are zero.

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

Here the desired poles of all of the states are supposed to be placed on "-1" using State Vector Feedback Control (SVFC). Equalizing the actual characteristic equation by the one which is extracted using the desired poles, one can concluded that:

$$
|SI - A + Bk| = (S-1)^{16} \tag{12}
$$

which results in:

$$
\begin{aligned}
&m16\times S^{16} + m15\times S^{15} + m14\times S^{14} \\
&+m13\times S^{13} + m12\times S^{12} + m11\times S^{11} \\
&+m10\times S^{10} + m9\times S^{9} + +m8\times S^{8} \\
&+m7\times S^{7} + m6\times S^{6} + m5\times S^{5} \\
&+m4\times S^{4} + m3\times S^{3} + m2\times S^{2} \\
&+m1\times S^{1} + m\times Cons\tan t = S^{16}
\end{aligned}
\tag{13}
$$

The parameters {m, m1, m2, …, m16} are the product of coefficients $|SI - A + Bk|$. Thus the required controlling gains (k) can be tunes as follow:

$$
\begin{aligned}
&[k_1; \ldots; k_{16}] \\
&= [-8440.13; 8.5059 \times 10^{8}; 7.3252; 3.5641 \\
&\times 10^{-12}; -552.25; 19328.403; -14341.511; 2.555 \\
&\times 10^{-12}; 247507.122; 1.0189 \times 10^{7}; -1.4508 \\
&\times 10^{7}; 2.1782 \times 10^{-11}; 8.8709 \times 10^{7}; -3.860 \\
&\times 10^{9}; 3.825 \times 10^{8}; -2.8772 \times 10^{-14}]
\end{aligned}
\tag{14}
$$

4 SIMULATION AND VERIFICATION

In order to show the correctness of modeling, the profile of the cancer cells growth during the days are depicted for the open loop system in which no chemotherapy injection is employed, and its response is compared with [21] ("Fig. 2"):

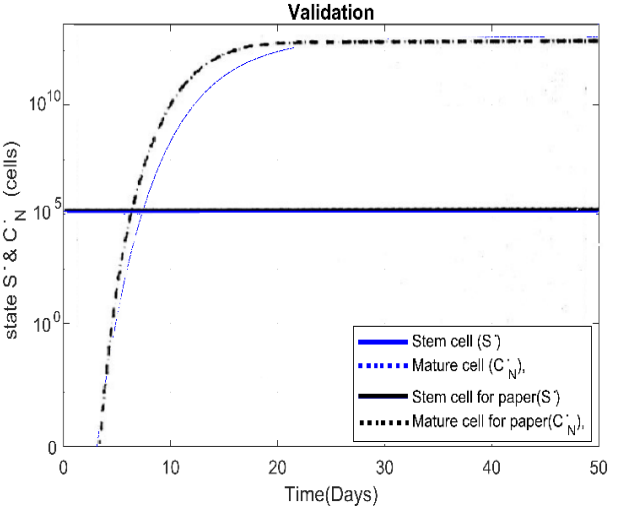

Fig. 2 Stem and cancer cells, obtained with MATLAB and reference [21].

As was expected, not only the number of cancer cells are growing up exponentially, but also switching between the generations as the result of mutation results in converting the normal cells to cancer ones at the third generation of the stem cell division. Also the good compatibility of the profiles shows the validity of the modeling. Here the cancer is controlled in an open loop way by applying a constant value of 11.50 as the chemotherapy dosage input. The related block diagram of the system with constant input is as follow shown in "Figs. 3 to 7".

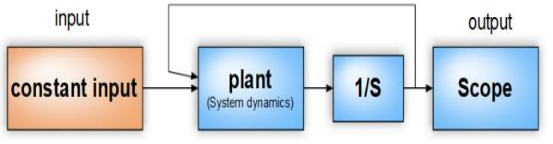

Fig. 3 Open loop system block diagram.

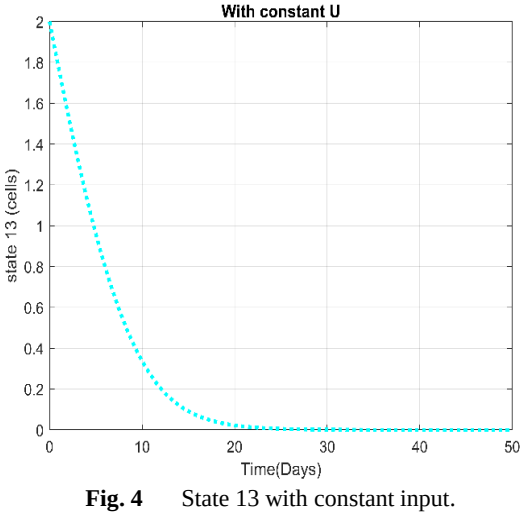

Fig. 4 State 13 with constant input.

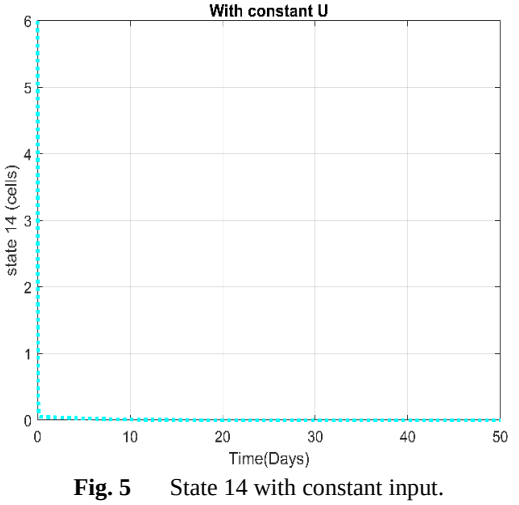

Fig. 5 State 14 with constant input.

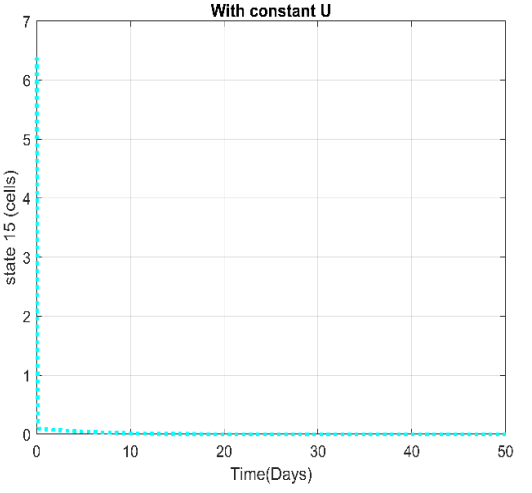

Fig. 6 State 15 with constant input.

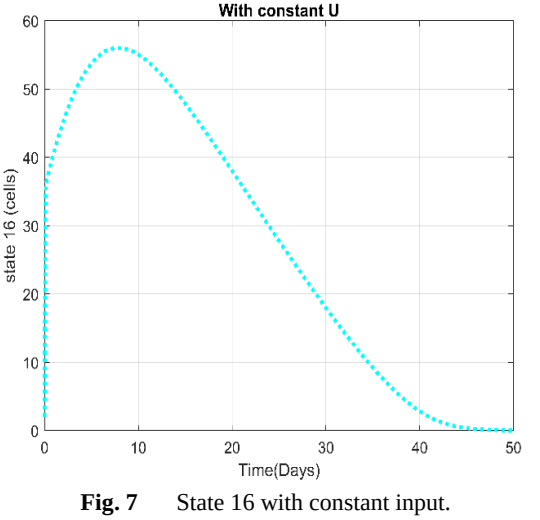

Fig. 7 State 16 with constant input.

It can be seen that the number of cancer cells at the third generation of the stem cell division decreases rapidly which shows the efficiency of the proposed closed loop model of the cancer mutation. The number of cancer cells are converged to zero within 50 days.

To show the performance of the designed controller, the treatment process of the patient is compared between three cases; constant input of injection, injection using PID controller with manual gains and the one which is tuned using pole placement method. The related block diagram of the cancer mutation which is under the therapy of the proposed closed loop controller is as shown in "Fig. 8".

The comparison of the cancer performance for the mentioned cases can be seen in "Figs. 9 to 12".

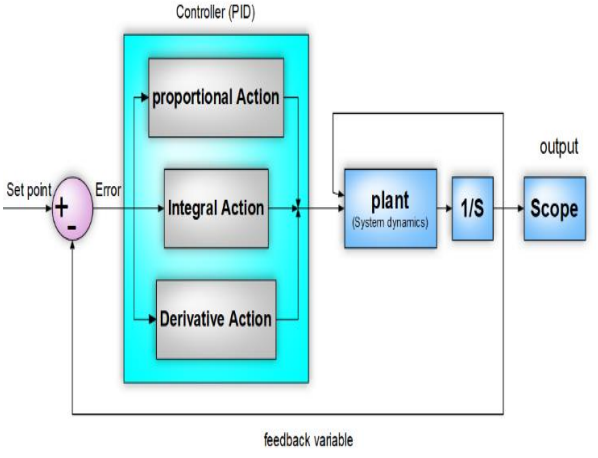

Fig. 8 Block diagram for PID Controller.

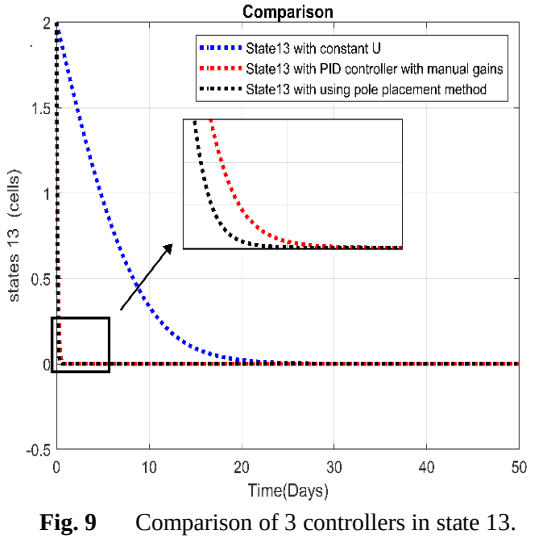

Fig. 9 Comparison of 3 controllers in state 13.

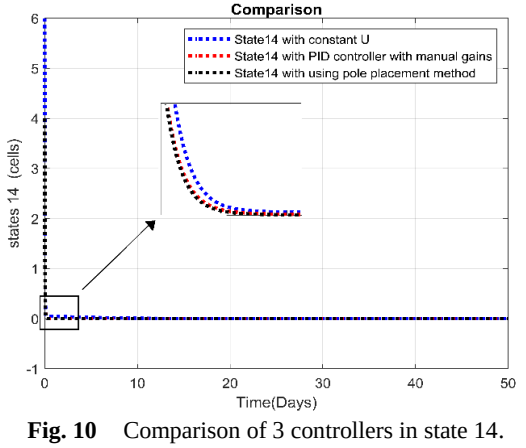

Fig. 10 Comparison of 3 controllers in state 14.

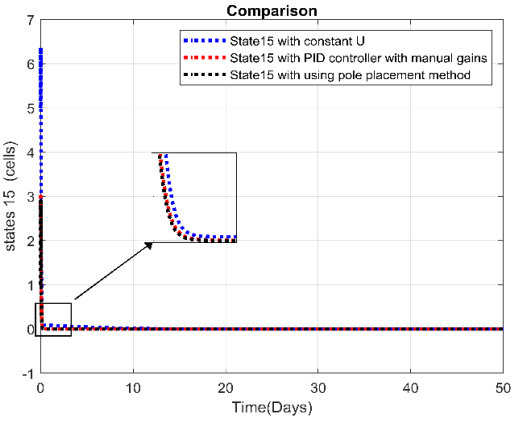

Fig. 11 Comparison of 3 controllers in state 15.

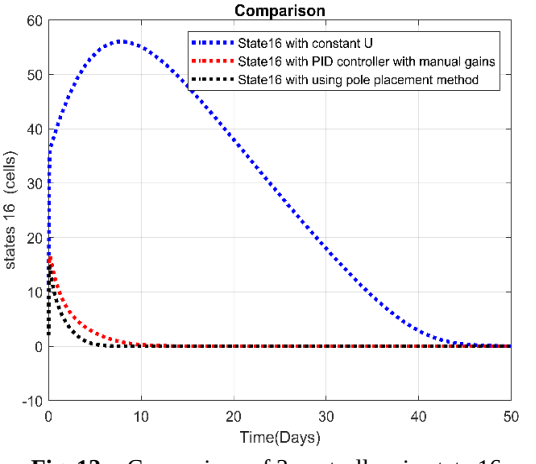

Fig. 12 Comparison of 3 controllers in state 16.

Here the following controlling gains are employed for the PID controller:

$$kP = 7; kI = 1; kD = 0.6 \tag{15}$$

It can be observed that the rate of recovery is significantly increased for the system in which the chemotherapy drug is determined using PID controller compared to constant case. This improvement is even strengthened for the case in which the gains are tuned by the aid of pole placement method. It can be observed that, the settling time of the closed loop system is decreased by about 80% for the critical state 16 compared to the open loop system. Also the PID controller for which the gains are tuned, has decreased the settling time for about 50% compared to the system in which the gains are tuned manually. This study shows that, the mutation process and generating the cancer cells can be significantly blocked by the aid of modeling the dynamic of cancer mutation and design its proper controller for chemotherapy regime.

The diagram shown in "Fig. 13" shows the input changes (chemotherapy injection) by day. As shown in the figure, the rate of drug injection gradually decreases to zero. According to the weight, 10 mg of chemotherapy drug should be received by patient per 1 kilogram of his weight.

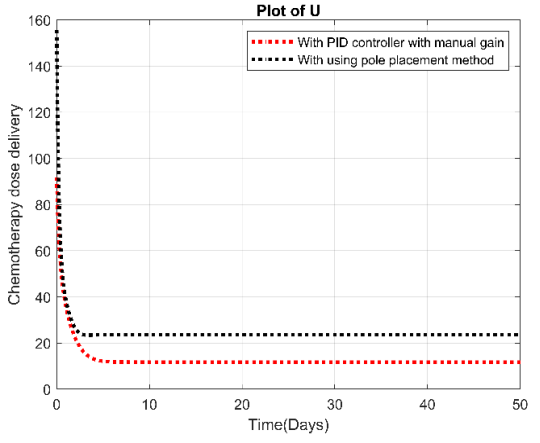

Fig. 13 Chemotherapy input obtained from two PID methods.

It should be noticed that the chemotherapy input is decreased as the cancer cells are converged to zero, but its value is not ended to absolute value of zero and it is converged to a little constant dosage. This is contributed to the fact that, here pole placement method is used to control the cancer and this method is based on state vector feedback control in which the error of all of the states are involved. Although, here the cancer cells which are corresponding to the third mutation of the cancer cells are converged to zero, the other states are not decreased to absolute value of zero and the decrease of some of them to zero last for about 100 days. This means that the chemotherapy input should not be truncated immediately after the elimination of the cancer cells. This important conclusion shows the effect of mutation dynamics on treatment process. It means that considering the mutation phenomenon, the chemotherapy should be continued till the first generations of the cell states which are not cancerous and have a longer treatment duration would be also destroyed completely, otherwise the metastasis will be again relapsed [18].

5 CONCLUSION

The dynamic of cancer cell growth was extracted considering its corresponding mutation. The related nonlinear state space was formed then and the controlling input was implemented on this space according to the chemotherapy injection model of Pinho [18]. Since it is supposed to control the mutation phenomenon, the nonlinear state space was linearized around its stable point and the linearized state space was gained accordingly. The PID controller was then designed and implemented on the mutation model of the cancer cells using pole placement method. It was shown by conducting some simulation scenarios that the cancer cells according to the extracted model of this paper grows exponentially to instability condition if no controlling input would be injected. This growth of cancer cells and progress of mutation levels which is similar to previous research shows the correctness of the modeling. Afterward a constant chemotherapy injection was implemented on the model and its was observed that the states and the cancer cells converge to zero within 50 days. This result shows that the input injection is correctly placed on the dynamic model of the system. Finally the controlling injection was improved using PID controller and as was expected the disease was controlled with a less settling time and overshoot. The settling time is decreased by about 80 percent for the closed loop system and this improvement is even strengthened by about 50 percent by tuning the gains effectively. Also it was concluded that the main effect of consideration of mutation dynamics is that here, in order to prevent the relapse of metastasis, the chemotherapy and input injection should be continued even after the destroy of the mutant generation of the cancerous cells, till the first generations of risky cells would be also completely vanished. Thus it can be concluded that the cancer model with mutation phenomenon can be considerably controlled using the proposed model and controller.

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