Dynamic Modeling of the Cancer Cell Mutation with the Capability of Control Using Chemotropic Injection

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***Abstract*— in this paper the mathematical model of the mutation dynamics of the cancer cells is extracted by which the control process can be fulfilled using chemotherapy injection. The stem cells are the source of all of the tissue cells of the body and can be converted to all of the cell types of the body such as blood, cartilage, nerve cells and etc. These cells which are capable to regenerate themselves are also exist in cancer cells and have the same specifications. The development of cancer is contributed two factor of metastasis and mutation. The mathematical model and control of the former case is frequently studied so far. Considering the fact that, controlling the metastasis without taking into account the phenomenon of mutation cannot block the growth of the cancer, here it is tried to establish the mathematical dynamics of the cancer mutation. It is shown then that by the aid of this model it is possible to decrease the amount of cancer cells as a result of implementation of a proper controller and blocking the mutation process. A PD controller was performed on the cancer cell mutation model as well as chemotherapy injections as a fixed number on the model. The simulation results show that in the last days of treatment, the result of PD control, was 2.5 times faster than the control with fixed input, and in PD control, the time taken for cancer cells to zero was 10 days.**

Keywords*— *Cancer, Modeling, Stem-cells, mutation, PID, Controller

I. INTRODUCTION

Today, mathematical modeling is used in biological research. Mathematical modeling is divided into variety of field, including: tumor growth, acquired mutations, chemotherapy, and immunotherapy, as well as tumor heterogeneity. Cancer treatment with chemotherapy has been problems that have forced researchers to think of solutions in various sciences, including: mathematics and engineering. So far, researchers have used a variety of models and controllers to treat cancer, but in the case of mutations and stem cells less work has been done. Stem cell mutations are involved in tumor formation and cancer, so if it can control the mutations, an important step could be taken toward treating the cancer. This topic has not been considered by researchers so far. Here is a summary of what has been done to date in the field of Growth modeling. In 1964, Laird proposed a dynamic model for tumor growth that examines tumor growth, which is ideally a simple exponential process that ends with the exhaustion of nutritional support from the host [1]. In 2001, Andersen and Mackey were studied resonance in chemotherapy for a sample of leukemia [2]. In 2004, Jackson was proposed a mathematical model for the treatment of prostate cancer that describes pre-treatment growth and eventual return after surgery [3].

In 2006, Kohandel, Sivaloganathan, and Oza have been presented a simple mathematical model to examine the repeated effect of chemotherapy and surgical treatments [4]. In 2018, Fassoni has been 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 [5]. In [6] a review is delivered about the control of the cancer growth: In 2018,a PID controller is designed by Vivek using ISA- for optimal drug scheduling during the treatment. In 2019, Panjwani has been designed the 2DOF FOPID controller to regulate concentration and toxicity of drug [7].

Some Investigations are devoted to mutation and stem cell models: In 2007, Wodarz has been discussed the effect of stem cell turnover on protection against cancer and aging [8]. Then in 2008 Ashkenazi has been proposed a model used to detect the onset of cancer as a multistage process of accumulation of somatic mutations in tissue cells and Shows 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 [9].

Sameen, along with several other researchers, in 2015 presented a mathematical model for analyzing the behavior of KRAS mutation in colorectal cancer with respect to a combination of moAb and Chemotherapy therapies to combat drug resistance [10]. In 2017, Stiehl and Czochra developed an insight into mathematical modeling for self-regenerating

stem cells in cancer remodeling [11]. In 2019, Ascolani and Lio show by modeling how important the mutation of driver and metabolic material is in the progression of breast cancer to bone [12]. In 2020, Owolabi and Shikongo presented a mathematical model that expresses the inherent drug resistance to include the spatial effects of the cells involved, the creation of biological and asymptotic surfaces [13]. As you can see, nothing has been done to control the mutation of cancer cells. In this study the model of [9] is used, which presents a model that includes both the sequential acquisition of phenotype-modifying mutations and tissue hierarchy. This model discusses the progressive effect of accumulated mutations that ultimately lead to the induction of genetic instability. In this paper [9] a general mathematical framework for the quantitative study of carcinogenesis is presented. This model depicts key features such as the hierarchical structure of tissue and the maturation of productive cells. It clearly includes all possible modes of stem cell division in which ancestral differentiation in the existing model occurs through division, and the dynamics of each generation can be examined separately. In this article controlling of this type of cancers is discussed using the model of [9] with the mentioned features and by adding chemotherapy semester as the input of the model.

II. MODELING:

The stem cells can be divided symmetrically converting to a couple of stem cells or a couple of ordinary cells. Also it can be divided asymmetrically converting to an ordinary cell and a stem cell ("Fig. 1") [14].

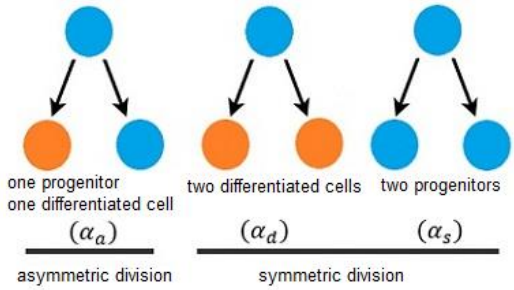

Fig. 1. Symmetric and asymmetric divisions of stem or progenitor cells.

The state space of the cancer growth dynamic without considering the mutation effect and without considering the injection input can be stated as in "Eq. (1)"[9].

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

Here S is the 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 stem cell division, assumed as generation 0) whereas that each asymmetric differentiation division contributes two progenitors to c0, but asymmetric division contribute one progenitor. , β_0 and μ_0 are the rate of division and death of the first generation of stem cells respectively and N,n denotes the number of divisions in the equation.

A. *Modeling of mutation:*

Considering the model of [9] and adding the controlling input of chemotherapy injection according to [15], the dynamics of the stem cells can be presented as follow for 3 mutations and 2 divisions show in "Eq. (2)":

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

According to [9], the natural divisions are take place with probability of $(1 - m_S)$ while the mutated divisions are take place with probability of m_S. $\{\alpha_{Si}.\alpha_{S(1-I)}.\alpha_{SI}.\alpha_{S(1-i)}\}$ 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. $\frac{dS^{(I)}}{dt}$ and $\frac{dS^{(i)}}{dt}$; i in this model denotes the mutation number 1, 2 while I denotes the third generation. p_{10} shows the rate of the death of the healthy cells by the chemotherapy drug which is equal to 1.2×10^{-7} and finally a_1 is the saturation rate of the healthy cells which is equal to 1.1.

Now the dynamic equations of natural and mutated progenitor can be expressed as in "Eq. (3)":

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

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

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

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 in "Eq. (5)":

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

Dynamics of the system is simulated here firstly without considering any controlling input. Here the constant parameters are as table 1 [9].

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

Parameters Used			
parameter	***Biological Meaning***	***Normal Value***	***Mutated Value***
S	Normal stem cells	18000	18000
α_S	Probability of symmetrically self-renewing stem cells	0.2 [16]	0.4
α_a	Probability of asymmetrically self-renewing stem cells	0.6[16]	0.425
α_d	Probability of symmetrically differentiating stem cells	0.15[16]	0.025
δ_S	Probability of stem-cell death	0.05[17]	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

B. Equilibrium point analysis

Homeostasis in physiology means that a special material is set to be constant in the body. By default, all of the limbs of the body act in a way that satisfies this condition. In [9] 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 $\alpha_s = \alpha_d + \delta_s$, thus one can conclude that the stem cells are constant during the time $S(t) = S_H$. Now the equilibrium points are as follow:

$$
\begin{aligned}
[900000, 8.93, 1.1195 \times 10^5, 4.8959 \\
\times 10^7, 3.6018, 0.1788, 0.4229, 1.7151 \\
\times 10^3, 0.0011, 2.8411 \times 10^{-5}, 6.8861 \\
\times 10^{-5}, 1.3606, 6.8591 \times 10^{-5}, 1.982 \\
\times 10^{-6}, 3.9069 \times 10^{-6}, 0.4555]
\end{aligned}
$$

III. CONTROL

A. *Pole Placement Control*

In this method, considering the equation of state, for example, “Eq. (6) " which is a linear system, we want to design the state feedback control for this system that the U of control is according to " Eq. (7) " Then We arrive by executing the control input to the system equations, to the closed-loop system equation “Eq. (8) ”.

In the design of state feedback control, according to the calculations performed, the control of the system should be determined in such a way that the poles of the closed-loop system are located in suitable and desirable places. The location of the desired system poles determines the optimal behavior of the system or the optimal performance of the system. Therefore, the desired behavior or performance is selected by choosing a suitable location for the poles of the closed-loop system.

$$\dot{x} = Ax + Bu \tag{6}$$

$$u = -kx \tag{7}$$

$$\dot{x} = [A - Bk]x \tag{8}$$

Matrix A show in “Eq. (9)”:

$$A = \begin{bmatrix} a_{11} & \cdots & a_{1m} \\ \vdots & \ddots & \vdots \\ a_{m1} & \cdots & a_{mm} \end{bmatrix} \tag{9}$$

That the size of the matrix a is 16×16 and the values of its Arrays are given in “Eq. (10)” and “Eq. (11)” and Matrix Arrays B show in “Eq. (12)”.

$$a_{11} = \frac{\partial f_1}{\partial x_1} = (1 - 2m_S)\alpha_S - \alpha_d - m_S\alpha_a - \delta_S$$

$$a_{21} = \frac{\partial f_2}{\partial x_1} = 2\alpha_d(1 - m_S) + \alpha_a(1 - m_S)$$

$$a_{22} = \frac{\partial f_2}{\partial x_2} = -(\beta_0 + \mu_0)$$

$$a_{32} = \frac{\partial f_3}{\partial x_2} = 2\beta_0(1 - m_C)$$

$$a_{33} = \frac{\partial f_3}{\partial x_3} = -(\beta_1 + \mu_1)$$

$$a_{43} = \frac{\partial f_4}{\partial x_3} = 2\beta_1(1 - m_C)$$

$$a_{44} = \frac{\partial f_4}{\partial x_4} = -\mu_2$$

$$a_{51} = \frac{\partial f_5}{\partial x_1} = (2\alpha_S + \alpha_a)m_S$$

$$a_{55} = \frac{\partial f_5}{\partial x_5} = (1 - 2m_{S1})\alpha_{S1} - \alpha_{S1} - m_{S1}\alpha_{a1} - \delta_S$$

$$a_{61} = \frac{\partial f_6}{\partial x_1} = (2\alpha_d + \alpha_a)m_S$$

$$a_{65} = \frac{\partial f_6}{\partial x_5} = (2\alpha_{d1} + \alpha_{a1})(1 - m_{S1})$$

$$a_{66} = \frac{\partial f_6}{\partial x_6} = -\left(\beta_0^{(1)} + \mu_0^{(1)}\right)$$

$$a_{76} = \frac{\partial f_7}{\partial x_6} = 2\beta_0 m_{C1} + 2\beta_0^{(1)}(1 - mC_1) \tag{10}$$

$$a_{77} = \frac{\partial f_7}{\partial x_7} = -\left(\beta_1^{(1)} + \mu_1^{(1)}\right)$$

$$a_{83} = \frac{\partial f_8}{\partial x_3} = 2\beta_1 m_C$$

$$a_{87} = \frac{\partial f_8}{\partial x_7} = 2\beta_1^{(1)}(1 - m_{C1})$$

$$a_{88} = \frac{\partial f_8}{\partial x_8} = -\mu_2^{(1)}$$

$$a_{95} = \frac{\partial f_9}{\partial x_5} = (2\alpha_{S1} + \alpha_{a1})m_{S1}$$

$$a_{99} = \frac{\partial f_9}{\partial x_9} = (1 - 2m_{S2})\alpha_{S2} - \alpha_{d2} - m_{S2}\alpha_{a2} - \delta_{S2}$$

$$a_{105} = \frac{\partial f_{10}}{\partial x_5} = (2\alpha_{d1} + \alpha_{a1})m_{S1}$$

$$a_{109} = \frac{\partial f_{10}}{\partial x_9} = (2\alpha_{d2} + \alpha_{a2})(1 - m_{S2})$$

$$a_{1010} = \frac{\partial f_{10}}{\partial x_{10}} = -\left(\beta_0^{(2)} + \mu_0^{(2)}\right)$$

$$a_{117} = \frac{\partial f_{11}}{\partial x_7} = 2\beta_0^{(1)} m_{C1}$$

$$a_{1110} = \frac{\partial f_{11}}{\partial x_{10}} = 2\beta_0^{(2)}(1 - m\_C2\ )$$

$$a_{1111} = \frac{\partial f_{11}}{\partial x_{11}} = -\left(\beta_1^{(2)} + \mu_1^{(2)}\right)$$

$$
\begin{aligned}
a_{127} &= \frac{\partial f_{12}}{\partial x_7} = 2\beta_1^{(1)} m_C \\
a_{1211} &= \frac{\partial f_{12}}{\partial x_{11}} = 2\beta_1^{(2)}(1 - m_{C2}) \\
a_{1212} &= \frac{\partial f_{12}}{\partial x_{12}} = -\mu_2^{(2)} \\
a_{139} &= \frac{\partial f_{13}}{\partial x_9} = (2\alpha_{S2} + \alpha_{a2}) m_{S2} \\
a_{1313} &= \frac{\partial f_{13}}{\partial x_{13}} = \alpha_{S3} - \alpha_{d3} - \delta_{S3} \\
a_{149} &= \frac{\partial f_{14}}{\partial x_9} = (2\alpha_{d2} + \alpha_{a2}) \\
a_{1413} &= \frac{\partial f_{14}}{\partial x_{13}} = 2\alpha_{d3} + \alpha_{a3} \\
a_{1414} &= \frac{\partial f_{14}}{\partial x_{14}} = -\left(\beta_0^{(3)} + \mu_0^{(3)}\right) \\
a_{1510} &= \frac{\partial f_{15}}{\partial x_{10}} = 2\beta_0^{(2)} m_{C2} \\
a_{1514} &= \frac{\partial f_{15}}{\partial x_{14}} = 2\beta_0^{(3)} \\
a_{1515} &= \frac{\partial f_{15}}{\partial x_{15}} = -\left(\beta_1^{(3)} + \mu_1^{(3)}\right) \\
a_{1611} &= \frac{\partial f_{16}}{\partial x_{11}} = 2\beta_1^{(2)} m_{C2} \\
a_{1615} &= \frac{\partial f_{16}}{\partial x_{15}} = 2\beta_1^{(3)} \\
a_{1616} &= \frac{\partial f_{16}}{\partial x_{16}} = -\mu_2^{(3)}
\end{aligned}
\tag{11}
$$

$$
\begin{aligned}
b_{11} &= \frac{\partial f_1}{\partial u_1} = -\frac{p_{10} S}{a_1 + S} \\
b_{21} &= \frac{\partial f_2}{\partial u_1} = -\frac{p_{10} C_0}{a_1 + C_0} \\
b_{31} &= \frac{\partial f_3}{\partial u_1} = -\frac{p_{10} C_1}{a_1 + C_1} \\
b_{41} &= \frac{\partial f_4}{\partial u_1} = -\frac{p_{10} C_2}{a_1 + C_2} \\
b_{51} &= \frac{\partial f_5}{\partial u_1} = -\frac{p_{10} S^{(1)}}{a_1 + S^{(1)}} \\
b_{61} &= \frac{\partial f_6}{\partial u_1} = -\frac{p_{10} C_0^{(1)}}{a_1 + C_0^{(1)}} \\
b_{71} &= \frac{\partial f_7}{\partial u_1} = -\frac{p_{10} C_1^{(1)}}{a_1 + C_1^{(1)}} \\
b_{81} &= \frac{\partial f_8}{\partial u_1} = -\frac{p_{10} C_2^{(1)}}{a_1 + C_2^{(1)}} \\
b_{91} &= \frac{\partial f_9}{\partial u_1} = -\frac{p_{10} S^{(2)}}{a_1 + S^{(2)}} \\
b_{101} &= \frac{\partial f_{10}}{\partial u_1} = -\frac{p_{10} C_0^{(2)}}{a_1 + C_0^{(2)}} \\
b_{111} &= \frac{\partial f_{11}}{\partial u_1} = -\frac{p_{10} C_1^{(2)}}{a_1 + C_1^{(2)}} \\
b_{121} &= \frac{\partial f_{12}}{\partial u_1} = -\frac{p_{10} C_2^{(2)}}{a_1 + C_2^{(2)}} \\
b_{131} &= \frac{\partial f_{13}}{\partial u_1} = -\frac{p_{20} S^{(3)}}{a_2 + S^{(3)}} \\
b_{141} &= \frac{\partial f_{14}}{\partial u_1} = -\frac{p_{20} C_0^{(3)}}{a_2 + C_0^{(3)}} \\
b_{151} &= \frac{\partial f_{15}}{\partial u_1} = -\frac{p_{20} C_1^{(3)}}{a_2 + C_1^{(3)}} \\
b_{161} &= \frac{\partial f_{16}}{\partial u_1} = -\frac{p_{20} C_2^{(3)}}{a_2 + C_2^{(3)}}
\end{aligned}
\tag{12}
$$

IV. Results

The results of the cancer cells in the third mutation, which include four states (state13, state14, state15, state16), are shown in “Fig. 2” to “Fig. 5”:

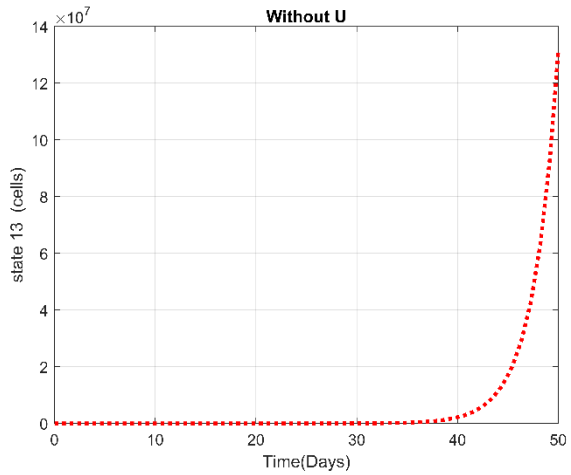

Fig. 2. State13 without U

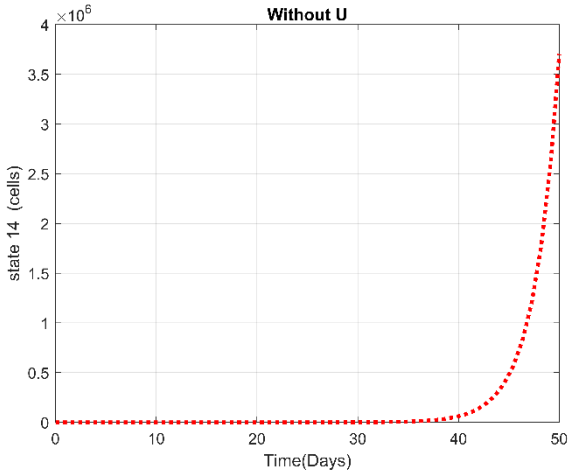

Fig. 3. State14 without

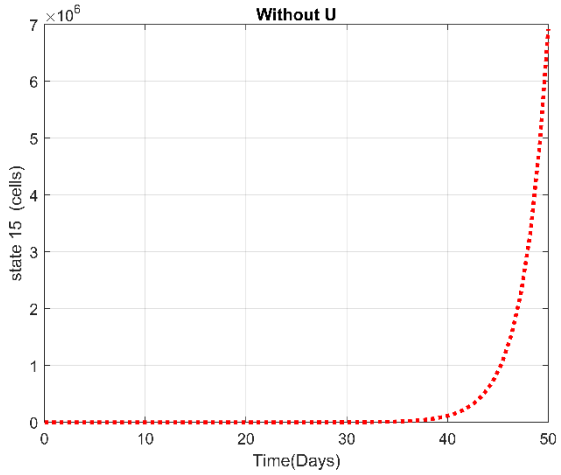

Fig. 4. State15 without U

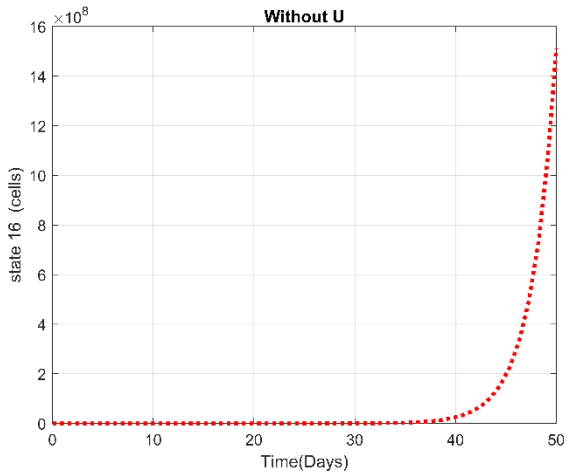

Fig. 5. State16 without U

"Fig. 2" shows state 13, which is related to the state of cancer stem cells over a 50-day period of upward trend. When cancer stem cells in the zero generation begin to divide, their number increases, as shown in "Fig. 3". "Fig. 4" shows that the first division of the cancer cells in the first generation are growing exponentially and also "Fig. 5" shows the result of the division of the cancer cells with two generations, which is also increasing over the time.

As was expected since no chemotherapy input is implemented, the number if the cancer cells tends to unconverted to infinity which means that the condition of the disease is unstable. Thus it can be concluded that the cancer cell with mutation is correctly modeled.

Now we want to compare the results obtained from 2 controllers by applying control input, one as a fixed value and the other as PID, which is shown in "Fig. 6" to "Fig. 9":

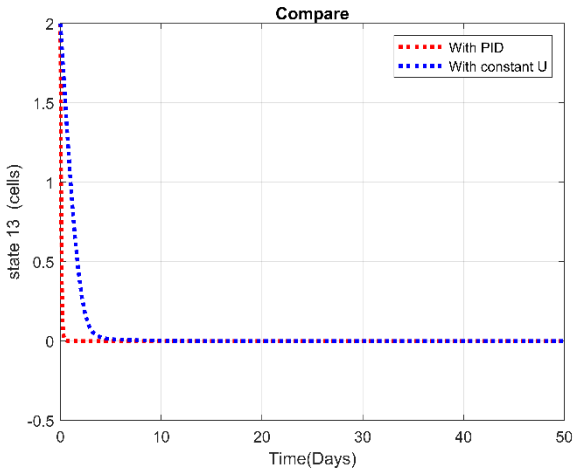

Fig. 6. State13 with controller

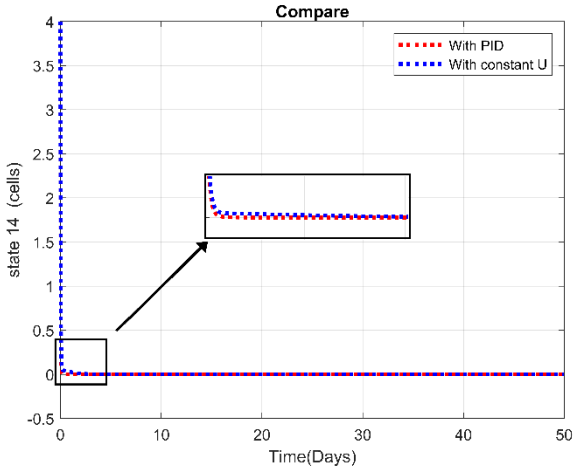

Fig. 7. State14 with controller

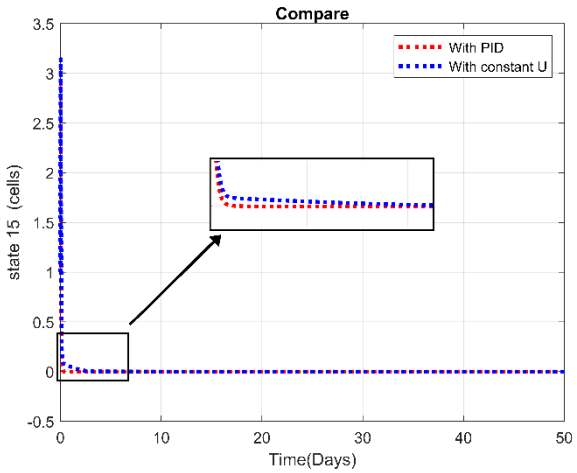

Fig. 8. State15 with controller constant and PID

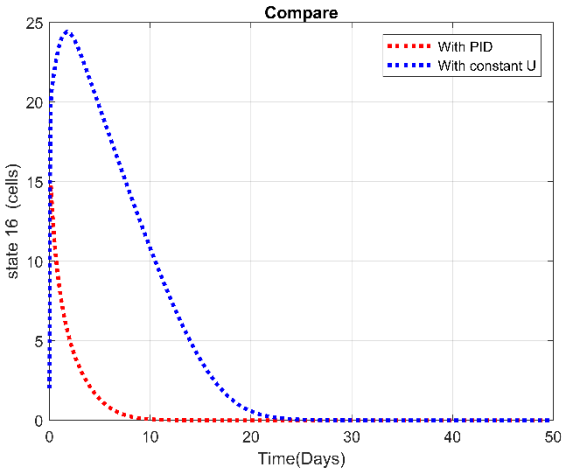

Fig. 9. State16 with controller constant and PID

It can be observed that the case in which a constant chemotropic injection is implemented, the cancer cells and mutation levels converge to zero accordingly. This phenomena shows that the controlling input is placed correctly in the model formulation. Also it can be seen that PD controller has provided a better response from the settling time and over shot points of view. As shown in "Fig. 6" to "Fig. 9", the PID controller outperforms the fixed input controller.

It can be concluded that using the PD control method, after 10 days, the cancer cells decrease until they converge to zero. Compared to the constant value control input, this time the efficiency is increased up to 2.5 times, and the results show that the person with cancer is treated properly using the employed PD controller.

The diagram shown in "Fig. 10" shows the input changes (chemotherapy injection) by day. As shown in the figure, the rate of drug injection gradually decreases to zero, and we also consider that the non-zero of this graph is not far from reality because it shows that the proposed model is only chemotherapy controls the system. Another point is that an important issue in control is the steady state process, which can ignore such details that this hypothesis has been implemented in the article [15].

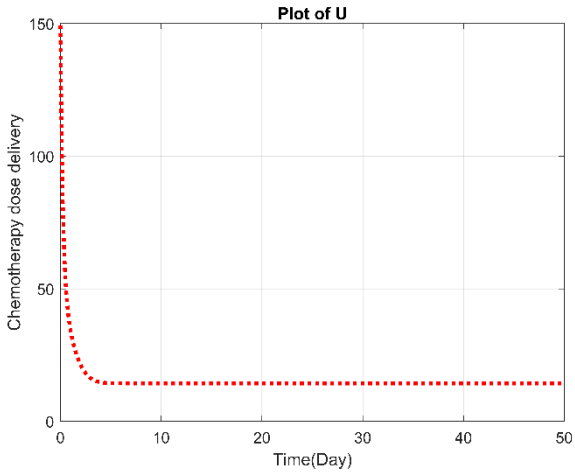

Fig. 10. Plot of U with PD

V. CORRECTNESS OF THE MODELING:

In order to check the correctness of the modeling, the response of the open loop system related to the states 1,4 are compared with the results presented in [9]:

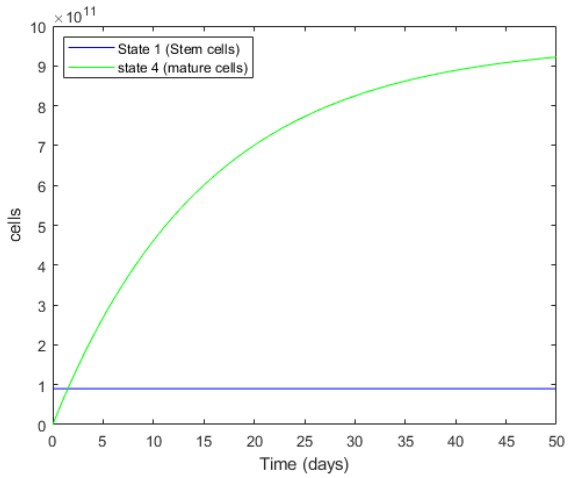

Fig. 11. The correctness of the modeling

The good compatibility of the profiles show the correctness of the model. The validity of the designed controller is also obvious since the response of the closed loop system is converged to zero.

VI. 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 [15]. Since it is supposed to control the mutation phenomena, the nonlinear state space was linearized around its stable point and the linearized state space was gained accordingly. A PD 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 shows the correctness of the modeling. Afterward a constant chemotherapy injection was implemented on the model and it was observed that the states and the cancer cells converge to zero. This result shows that the input injection is correctly place on the dynamic model of the system. Finally the controlling injection was improved using PD controller and as was expected the disease was controlled with a less settling time and overshoot. According to the results the efficiency of the closed loop system is increased up to 2.5 times. Thus it can be concluded that the cancer model with mutation phenomena can be considerably controlled using the proposed model and controller.

References:

[1] A. K. Laird, “Dynamics of tumor growth,” Br. J. Cancer, vol. 18, pp. 490-502, September 1964.

[2] L. K. Andersen and M. C. Mackey, “Resonance in periodic chemotherapy: a case study of acute myelogenous leukemia,” J. Theor. Biol. vol. 209, pp. 113-130, March 2001.

[3] T. L. Jackson, “A mathematical model of prostate tumor growth and androgen-independent relapse,” DCDS-B, vol. 4, pp. 187-201, February 2004.

[4] M. Kohandel, S. Sivaloganathan and A. Oza, “Mathematical modeling of ovarian cancer treatments: sequencing of surgery and chemotherapy,” Journal of Theoretical Biology, vol. 242, pp. 62-68, March 2006.

[5] A. C. Fassoni and H. M. Yang, “Modeling dynamics for oncogenesis encompassing mutations and genetic instability,” A Journal of the IMA, vol. 00, pp. 1-27, June 2018.

[6] P. Vivek, P. Nikhil, R. Asha and S. Vijander, “Optimal ISA-PID-based drug concentration control in cancer chemotherapy,” Instrumentation and Control Engineering Division, pp. 165-171, April 2018.

[7] B. Panjwani, V. Mohan, A. Rani and V. Singh, “Optimal drug scheduling for cancer chemotherapy using two degree of freedom fractional order PID scheme,” Journal of Intelligent & Fuzzy Systems, vol. 36, pp. 2273-2284, March 2019.

[8] D. Wodarz, “Effect of stem cell turnover rates on protection against cancer and aging,” Journal of Theoretical Biology, vol. 245, pp. 449-458, October 2006.

[9] R. Ashkenazi, S. N. Gentry and T. L. Jackson, “Pathways to tumorigenesis modeling mutation acquisition in stem cells and their progeny,” Neoplasia, vol. 10, pp. 1170-1182, November 2008.

[10] S. Sameen, R. Barbuti, P. Milazzo, A. Cerone, M. D. Re and R. Danesi, “Mathematical modeling of drug resistance due to KRAS mutation in colorectal cancer,” Journal of Theoretical Biology, vol. 389, pp. 263-273, November 2015.

[11] T. Stiehl and A. M. Czochra, “Stem cell self-renewal in regeneration and cancer: insights from mathematical modeling,” Current Opinion in Systems Biology, vol. 5, pp. 112-120, October 2017.

[12] G. Ascolani and P. Lio, “Modeling breast cancer progression to bone: how driver mutation order and metabolism matter,” BMC Medical Genomics, vol. 12, July 2019.

[13] K. M. Owolabi and A. Shikongo, “Mathematical modelling of multi-mutation and drug resistance model with fractional derivative,” Alexandria Engineering Journal, vol. 59, pp. 2291-2304, February 2020.

[14] M. Lee and V. Vasioukhin, “Cell polarity and cancer – cell and tissue polarity as a non-canonical tumor suppressor,” Journal of Cell Science, vol. 121, pp. 1141-1150, February 2008.

[15] P. Khalili, S. Zolatash and R. Vatankhah, “Fuzzy control for drug delivery in cancerous tumors chemotherapy,” Modares Mechanical Engineering, vol. 19, pp. 1467-1473, June 2019.

[16] M. Wu, H. Y. Kwon, F. Rattis, J. Blum, C. Zhao, R. Ashkenazi, T. L. Jackson, N. Gaiano, T. Oliver and T. Reya, “Imaging hematopoietic precursor division in real time,” Cell Stem Cell, vol. 1, pp. 541-554, November 2007.

[17] F. Michor, T. P. Hughes, Y. Iwasa, S. Branford, N. P. Shah, C. L. Sawyers and M. A.Nowak, “Dynamics of chronic myeloid leukaemia,” Nature, vol. 435, pp. 1267-1270, June 2005.