Advances and Applications in Mathematical Sciences
Volume 21, Issue 1, November 2021, Pages 343-363

STABILITY ANALYSIS AND Z-CONTROL OF BREAST CANCER DYNAMICS

DRASHTI K. DAVE and TRUPTI P. SHAH

Department of Applied Mathematics
The Maharaja Sayajirao University
of Baroda, India
E-mail: drashti26@gmail.com

Abstract

In this paper, we propose and analyze a mathematical model representing the breast cancer dynamics by considering the cancer treatment as combination of chemotherapy and monoclonal antibody drugs. The stability analysis of the system is carried out extensively. The Z-control technique is applied to compute a control which minimizes the growth of cancer cells significantly. To substantiate our theoretical results, numerical computation is also carried out and results are displayed graphically.

1. Introduction

Cancer is a condition, in which some cells in the body grow uncontrollably and, in some cases, spread and invade organs in other parts of the body. This abnormal growth is harmful because it does not just replace healthy cells in organs, but also causes changes in our body's biochemistry that can lead to weight loss and a compromised immune system thereby, leading to death. There are over 200 different types of cancers, some of which are far more common worldwide that are lungs and breast cancer. Breast cancer is the most prevalent form of cancer. This disease has become a major problem all across the world, but it is one of the treatable form of cancer [13].

The goal of our paper is to introduce a system of non-linear ordinary differential equations which shows competition between cancer cells and Normal cells in present of the treatment of chemotherapy in combination with monoclonal antibody drugs and keto diet. Few researches say that diet

2020 Mathematics Subject Classification: 92-XX.
Keywords: Chemotherapy, Monoclonal antibody drugs, Z-control.
Received May 8, 2021; Accepted August 16, 2021

play effective role in cancer treatment. These diets have high digestible fat, low or moderate protein and very low carbohydrates. These all are helpful to burn fat in the body instead of glucose [7].

We focus on main treatment which is combination of chemotherapy and monoclonal antibody drugs. Monoclonal antibodies are basically laboratory produce molecules that mimic the immune system's attack on cancer cells. Monoclonal antibodies are attached to chemotherapeutic agent in order to deliver the treatment directly to the cancer cells instead of healthy cells [11].

2. Mathematical Model

We propose following mathematical model, representing competition between cancer cells (C), normal cells (N) and combine effect of chemotherapy and monoclonal anti-body drugs (M). In the model, we also consider effect of keto diet on existing cells and birth rate of cancer cells [1].

$$\begin{aligned}
\frac{dN}{dt} &= a_1 N\left(1-\frac{N}{b_1}\right) - d_1 NC - \frac{e_1 NM}{f_1+N},\\
\frac{dC}{dt} &= a_2 C\left(d-\frac{C}{b_2}\right) - d_2 NC - \frac{e_2 CM}{f_2+C} - uC, \qquad (1)\\
\frac{dM}{dt} &= g - hM - \frac{j_1 NM}{f_1+N} - \frac{j_2 CM}{f_2+C},
\end{aligned}$$

where N, C and M are positive.

The detailed description of each term is given below.

- $a_1 N\left(1-\frac{N}{b_1}\right)$: represents logistic growth of normal cells. It shows natural in-crease in normal cells with division rate a_1 and carrying capacity b_1.

- $d_1 NC$: represents rivalry between cancer cells and normal cells with rate d_1.

- $\frac{e_1 NM}{f_1 + N}$: This term is holling type-II term which shows absorption of normal cells due to combination of chemotherapy and monoclonal antibody drugs at rate e_1.

- $a_2 C\left(d - \frac{c}{b_2}\right)$: represents logistic growth of cancer cells. It shows natural increase in cancer cells with division rate a_2 and carrying capacity b_2. Here cancer cells growth is also affected by kito diet at constant rate d.

- $d_2 NC$: represents rivalry between cancer cells and Normal cells at rate d_2.

- $\frac{e_2 CM}{f_2 + C}$: represents holling type-II term which show absorption of Cancer cells due to combination of chemotherapy and monoclonal antibody drugs at rate e_2.

- uC : represents cancer cells death due to kito diet effect.

- g : Infusion rate of Chemotherapy agent and Monoclonal antibody drugs.

- hM : represents washout rate of Monoclonal antibody drugs and Chemotherapy agent at rate h.

- $\frac{j_1 NM}{f_1 + N}$: This term represents absorption of monoclonal antibody drug and chemo-therapy agent due to normal cells at rate j_1 which is also represented by holling type-II term and f_1 be Without competition and absorption normal cells reaches at carrying capacity.

- $\frac{j_2 CM}{f_2 + C}$: represents absorption of monoclonal antibody drugs and chemotherapy agent due to cancer cells at rate j_2 which is also of holling type-II term and f_2 be Without competition and absorption cancer cells reaches at carrying capacity.

3. Stability Analysis

Basic (Treatment free) Model 3.1. The treatments free model (i.e. No chemotherapy and monoclonal antibody drugs, No Kito diet are not present) is represented by following system of nonlinear differential equations.

$$\frac{dN}{dt} = a_1 N\left(1 - \frac{N}{b_1}\right) - d_1 NC,$$

$$\frac{dC}{dt} = a_2 C\left(1 - \frac{C}{b_2}\right) - d_2 NC. \tag{2}$$

Equilibrium Points

The following equilibrium points of above system (2) are obtained.

(i) $E_0(0, 0)$ – Shows that there is no cancer cell and normal cell exist in body

(ii) $E_N(b_1, 0)$ – Represents that only normal cells exist and its amount is b_1, which are its maximum carrying capacity and cancer cells are absent.

(iii) $E_C(0, b_2)$ – Represents only cancer cells exist and its amount is b_2 which is its maximum carrying capacity and normal cells are absent.

(iv) $E_{NC}(N^*, C^*)$ – Represents that there exist N^* amount of normal cells and C^* amount of cancer cells in the body which is not of much interest.

Local stability of Equilibrium Points 3.1.1.

In this section, we derive sufficient conditions for existence of cancer. The Jacobian matrix for system (2) is computed as follows.

$$J = \begin{pmatrix} a_1\left(1 - \frac{2N}{b_1}\right) & -d_1 N \\ -d_2 C & a_2\left(1 - \frac{2C}{b_2}\right) - d_2 N \end{pmatrix}.$$

Evaluating the value of Jacobian at each of the above-mentioned equilibrium points, following results regarding the stability are obtained.

At $E_0(0, 0)$, Jacobian matrix is given by

$$J_0 = \begin{pmatrix} a_1 & 0 \\ 0 & a_2 \end{pmatrix}.$$

We see that the Eigen values of J_0 are

$$\lambda_{10} = a_1 > 0$$

$$\lambda_{20} = a_2 > 0.$$

Hence E_0 is not stable.

For the equilibrium point $E_N(b_1, 0)$ and Jacobian matrix about it is,

$$J_N = \begin{pmatrix} -a_1 & -d_1 b_1 \\ 0 & a_2 - d_2 b_1 \end{pmatrix}.$$

The Eigen values of J_N are,

$$\lambda_{1N} = -a_1 < 0$$

$$\lambda_{2N} = a_2 - d_2 b_1.$$

Hence if $\lambda_{2N} = a_2 - d_2 b_1 > 0$ then $E_N(b_1, 0)$ is unstable and if $\lambda_{2N} = a_2 - d_2 b_1 < 0$ then $E_N(b_1, 0)$ is stable.

Similarly for the equilibrium point $E_C(0, b_2)$ and Jacobian matrix about it is,

$$J_C = \begin{pmatrix} a_1 - d_1 b_2 & 0 \\ -d_2 b_2 & -a_2 \end{pmatrix}.$$

The Eigen values of J_C are,

$$\lambda_{1C} = a_1 - d_1 b_2$$

$$\lambda_{2C} = -a_2 < 0.$$

Hence if $\lambda_{1C} = a_1 - d_1 b_2 > 0$ then $E_c(0, b_2)$ is unstable and if $\lambda_{1C} = a_1 - d_1 b_2 < 0$ then $E_c(0, b_2)$ is stable Hence we state the following theorem.

Theorem 1. *For basic model* (2), *the sufficient conditions for the existence of cancer are* $a_1 < d_1 b_2$ *and* $a_2 < d_2 b_1$.

Complete Model (Including Treatments) 3.2. The similar stability analysis for complete model is carried out and conditions for cancer and cancer free states are obtained. We denote equilibrium points by G. Some equilibrium points are non-practicable. The equilibrium points of above system are obtained and listed as follows:

(i) $G_0(0, 0, gh^{-1})$: represents existence no cancer cells and no normal cells but only gh^{-1} amount of monoclonal antibody drug and chemotherapy drug agent present in the body.

(ii) $G_N(N^*, 0, M^*)$: This point represents no cancer cells but only N^* amount of normal cells and M^* amount of treatment agent present.

(iii) $G_C(0, C^*, M^*)$: This type of point says that there are no normal cells but there exists only C^* amount of cancer cells and M^* amount of treatment agent.

(iv) $G_{NC}(N^*, C, M^*)$: Represents the state where all the three components are present.

Consider the points $G_N(N^*, 0, M^*)$ and $G_C(0, C^*, M^*)$. The equilibrium G_N exists provided that the following algebraic system has positive solutions.

$$a_1 N^* \left(1 - \frac{N^*}{b_1}\right) - \frac{e_1 N^* M^*}{f_1 + N^*} = 0$$

$$g - hM^* - \frac{j_1 N^* M^*}{f_1 + N^*} = 0. \tag{3}$$

By solving system (3) we get quadratic equation,

$$(h + j_1)N^{*2} + [hf_1 - b_1(h + j_1)]N^* + b_1(a_1^{-1} g e_1 - hf_1) = 0. \tag{4}$$

Above equation has a positive solution if,

$$\frac{b_1(a_1^{-1} g e_1 - hf_1)}{(h + j_1)} < 0$$

$$\Rightarrow a_1^{-1} ge_1 - hf_1 < 0 \ (\because \frac{b_1}{(h + j_1)} > 0)$$

$$\Rightarrow a_1^{-1} ge_1 < hf_1. \tag{5}$$

The equation (4) has two positive solutions if

$$\frac{[hf_1 + b_1(h + j_1)]^2}{4(h + j_1)b_1} > \frac{ge_1}{a_1} \tag{6}$$

$$\frac{ge_1}{a_1} > hf_1. \tag{7}$$

Now combining equations (6) and (7) we get,

$$hf_1 < \frac{ge_1}{a_1} < \frac{[hf_1 + b_1(h + j_1)]^2}{4(h + j_1)b_1}. \tag{8}$$

Theorem 2. *If* $a_1^{-1} ge_1 < hf_1$ *admit then* $G_N(N^*, 0, M^*)$ *exists uniquely and if* $hf_1 < \frac{ge_1}{a_1} < \frac{(hf_1 + b_1(h + j_1))^2}{4(h + j_1)b_1}$ *admit, then there exists two distinct equilibria of type* G_N.

Similarly, the equilibrium $G_C(0, C^*, M^*)$ exists provided that the following algebraic system has positive solutions.

$$a_2 C^* \left(d - \frac{C^*}{b_2} \right) - \frac{e_2 C^* M^*}{f_2 + C^*} - uC^* = 0$$

$$g - hM^* - \frac{j_2 C^* M^*}{f_2 + C^*} = 0. \tag{9}$$

By solving system (9) we get quadratic equation,

$$a_2(h + j_2)C^{*2} + [hf_2 a_2 - b_2(a_2 d - u)(h + j_2)]C^* + b_2[ge_2 - hf_2(a_2 d - u)]. \tag{10}$$

Above equation has a positive solution if,

$$\frac{b_2[ge_2 - hf_2(a_2 d - u)]}{a_2(h + j_2)} < 0$$

$$\text{i.e. } ge_2 - hf_2(a_2d - u) < 0 \left(\because \frac{b_2}{a_2(h + j_2)} > 0\right)$$

$$\text{i.e. } ge_2 < hf_2(a_2d - u). \tag{11}$$

And equation (10) has two positive solutions so for that condition is,

$$\frac{[hf_2a_2 - b_2(a_2d - u)(h + j_2)]^2}{4a_2(h + j_2)b_2} > ge_2 \tag{12}$$

$$ge_2 > hf_2(a_2d - u). \tag{13}$$

Now combining equations (12) and (13) we get,

$$hf_2(a_2d - u) < ge_2 < \frac{[hf_2a_2 - b_2(a_2d - u)(h + j_2)]^2}{4a_2(h + j_2)b_2}. \tag{14}$$

Theorem 3. *If* $ge_2 < hf_2(a_2d - u)$ *admit then* $G_C(0, C^*, M^*)$ *exists uniquely and if* $hf_2(a_2d - u) < ge_2 < \frac{((hf_2a_2 - b_2(a_2d - u)(h + j_2))^2}{4a_2(h + j_2)b_2}$ *admit then there exists two distinct equilibria of type* G_C.

The equilibrium point $G_{NC}(N^*, C^*, M^*)$ may exist but it is difficult to explain analytically.

Local stability of Equilibrium Points 3.2.1. In this section we study the stability of the points G_N and G_C. The Jacobian matrix related to system (1) is

$$J = \begin{pmatrix} J_{11} & -d_1N & \frac{-e_1N}{(f_1 + N)} \\ -d_2C & J_{22} & \frac{-e_2C}{(f_2 + C)} \\ \frac{-j_1f_1M}{(f_1 + N)^2} & \frac{-j_2f_2M}{(f_2 + C)^2} & J_{33} \end{pmatrix},$$

where $J_{11} = a_1\left(1 - \frac{2N}{b_1}\right) - d_1C - \frac{e_1f_1M}{(f_1 + N)^2}$

$$J_{22} = a_2\left(d - \frac{2C}{b_2}\right) - d_2N - \frac{e_2f_2M}{(f_2 + C)^2} - u$$

$$J_{33} = -(h + \frac{j_1N}{(f_1 + N)} + \frac{j_2C}{(f_2 + C)}).$$

Analysis at point $G_N(N^*, 0, M^*)$: The Jacobian matrix at this point is as follows:

$$J_N = \begin{pmatrix} a_1\left(1 - \frac{2N^*}{b_1}\right) - \frac{e_1f_1M^*}{(f_1 + N^*)^2} & -d_1N^* & \frac{-e_1N^*}{(f_1 + N^*)} \\ 0 & a_2d - d_2N^* - u - \frac{e_2M^*}{f_2} & 0 \\ \frac{-j_1f_1M^*}{(f_1 + N^*)^2} & \frac{-j_2M^*}{f_2} & -\left(h + \frac{f_1N^*}{(f_1 + N^*)}\right) \end{pmatrix}.$$

Out of three eigen values of J_N, one eigen value is

$$\lambda_2 = a_2d - d_2N^* - u - \frac{e_2M^*}{f_2}$$

Now for sign of remaining two eigen values $(\lambda_1 \text{ and } \lambda_3)$ we use Routh-Hurwitz (R-H) criteria [12]. For that we consider the following matrix

$$A = \begin{pmatrix} C_0 & C_1 \\ C_2 & C_3 \end{pmatrix}$$

where

$$C_0 = a_1\left(1 - \frac{2N^*}{b_1}\right) - \frac{e_1f_1M^*}{(f_1 + N^*)^2}$$

$$C_1 = \frac{-e_1N^*}{(f_1 + N^*)}$$

$$C_2 = \frac{-j_1f_1M^*}{(f_1 + N^*)^2}$$

$$C_3 = -\left(h + \frac{j_1 N^*}{(f_1 + N^*)}\right).$$

According to R-H criteria, if $\text{Trace}(A) < 0$ and $\det(A) > 0$. then remaining two eigen values $(\lambda_1 \text{ and } \lambda_3)$ are negative. Here

$$\text{Trace}(A) = c_0 + c_3$$

$$= a_1\left(1 - \frac{2N^*}{b_1}\right) - \frac{e_1 f_1 M^*}{(f_1 + N^*)^2} - \left(h + \frac{j_1 N^*}{(f_1 + N^*)}\right).$$

So we can easily say that

$$1 - \frac{2N^*}{b_1} < 0$$

$$\text{i.e. } b_1 - 2N^* < 0$$

$$\text{i.e. } N^* > \frac{b_1}{2}. \tag{15}$$

$$\text{And } \det(A) = -\left(h + \frac{j_1 N^*}{f_1 + N^*}\right)\left[a_1\left(1 - \frac{2N^*}{b_1}\right) - \frac{e_1 f_1 M^*}{(f_1 + N^*)^2}\right] - \frac{e_1 f_1 j_1 N^* M^*}{(f_1 + N^*)^3}$$

$$\text{i.e. } \det(A) = -\left(h + \frac{j_1 N^*}{f_1 + N^*}\right)a_1\left(1 - \frac{2N^*}{b_1}\right) + \frac{h e_1 f_1 M^*}{(f_1 + N^*)^2}$$

$$\text{i.e. } \det(A) = -\left(h + \frac{j_1 N^*}{f_1 + N^*}\right)a_1\left(1 - \frac{2N^*}{b_1}\right) + \frac{h e_1 f_1 g}{(f_1 + N^*)[hf_1 + (h + f_1)N^*]}.$$

$$\left(\because M^* = \frac{g(f_1 + N^*)}{[hf_1 + (h + f_1)N^*]}\right)$$

So from above we can say that

$$1 - \frac{2N^*}{b_1} < 0$$

$$\text{i.e. } b_1 - 2N^* < 0$$

$$\text{i.e. } N^* > \frac{b_1}{2}. \tag{16}$$

Theorem 4. *If* $N^* > \frac{b_1}{2}$ *then the real parts of eigen values* $(\lambda_1 \text{ and } \lambda_3)$ *are negative.*

Theorem 5. *Suppose that* $N^* > \frac{b_1}{2}$ *and* $a_2 d > d_2 N^* + u + \frac{e_2 M^*}{f_2}$ *then* G_N *is unstable and if* $N^* > \frac{b_1}{2}$ *and* $a_2 d < d_2 N^* + u + \frac{e_2 M^*}{f_2}$ *then it is asymptotically stable.*

Now for $G_C(0, C^*, M^*)$, the Jacobian matrix about it is as follows:

$$J_C = \begin{pmatrix} a_1 - \frac{e_1 M^*}{a_1} - d_1 C^* & 0 & 0 \\ -d_2 C^* & a_2\left(d - \frac{2C^*}{b_2}\right) - \frac{e_2 M^* f_2}{(f_2 + C^*)} - u & \frac{-e_2 C^*}{(f_2 + C^*)} \\ \frac{-j_1 M^*}{a_1} & \frac{-f_2 j_2 M^*}{(f_2 + C^*)^2} & -\left(h + \frac{j_2 C^*}{(f_2 + C^*)}\right) \end{pmatrix}.$$

One of the eigen value of J_C is

$$\lambda_1 = a_1 - \frac{e_1 M^*}{a_1} - d_1 C^*.$$

Again the signs of remaining two eigen values $(\lambda_1 \text{ and } \lambda_3)$ are decided by Routh-Hurwitz (R-H) criteria as follows. Consider the matrix

$$B = \begin{pmatrix} d_0 & d_1 \\ d_2 & d_3 \end{pmatrix}$$

where

$$d_0 = a_2\left(d - \frac{2C^*}{b_2}\right) - \frac{e_2 f_2 M^*}{(f_2 + C^*)^2} - u$$

$$d_1 = \frac{-e_2 C^*}{(f_2 + C^*)}$$

$$d_2 = \frac{-j_2 f_2 M^*}{(f_2 + C^*)}$$

$$d_3 = -\left(h + \frac{j_2 C^*}{(f_2 + C^*)}\right).$$

According to R-H criteria, if $\text{Trace}(B) < 0$ and $\det(B) > 0$ then remaining two eigen values $(\lambda_2 \text{ and } \lambda_3)$ are negative. Here

$$\text{Trace}(B) = d_0 + d_3$$

$$= a_2\left(d - \frac{2C^*}{b_2}\right) - \frac{e_2 f_2 M^*}{(f_2 + C^*)^2} - u - \left(h + \frac{j_2 C^*}{(f_2 + C^*)}\right)$$

$$\text{If } d - \frac{2C^*}{b_2} < 0$$

$$\text{i.e. } db_2 - 2C^* < 0$$

$$\text{i.e. } C^* > \frac{b_2 d}{2}. \tag{17}$$

$$\text{And } \det(B) = -\left(h + \frac{j_2 C^*}{f_2 + C^*}\right)\left[a_2\left(d - \frac{2C^*}{b_2}\right) - \frac{e_2 f_2 M^*}{(f_2 + C^*)^2} - u\right] - \frac{e_2 f_2 j_2 C^* M^*}{(f_2 + C^*)^3}$$

$$\text{i.e. } \det(B) = -\left(h + \frac{j_2 C^*}{f_2 + C^*}\right) a_2\left(d - \frac{2C^*}{b_2}\right) + \frac{h e_2 f_2 M^*}{(f_2 + C^*)^2}$$

$$\text{i.e. } \det(B) = -\left(h + \frac{j_2 C^*}{f_2 + C^*}\right) a_2\left(d - \frac{2C^*}{b_2}\right) + \frac{h e_2 f_2 g}{(f_2 + C^*)[hf_2 + (h + f_2)C^*]}$$

$$\left(\because M^* = \frac{g(f_2 + C^*)}{[hf_2 + (h + f_2)C^*]}\right).$$

So from above we can say that

$$d - \frac{2C^*}{b_2} < 0$$

$$\text{i.e. } db_2 - 2C^* < 0$$

$$\text{i.e. } C^* > \frac{db_2}{2} \tag{18}$$

Theorem 6. *If* $C^* > \frac{db_2}{2}$ *then the real parts of eigen values* $(\lambda_2 \text{ and } \lambda_3)$ *are negative.*

Theorem 7. *If* $C^* > \frac{db_2}{2}$ *and* $a_1 > d_1C^* + \frac{e_1M^*}{f_1}$ *then* G_C *is unstable and if* $C^* > \frac{db_2}{2}$ *and* $a_1 < d_1C^* + \frac{e_1M^*}{f_1}$ *then it is asymptotically stable.*

Theorem 8. *Conditions for existence of cancer are*

(a) $C^* > \frac{db_2}{2}$ *and* $a_1 < d_1C^* + \frac{e_1M^*}{f_1}$ *or* (19)

(b) $N^* > \frac{b_1}{2}$, *if* $a_2d > d_2N^* + u + \frac{e_2M^*}{f_2}$. (20)

Now for the Jacobian matrix about $G_0(0, 0, h^{-1}g)$ the eigen values are

$$\lambda_1 = a_1 - (f_1h)^{-1}e_1g$$

$$\lambda_2 = a_2d - (f_2h)^{-1}e_2g$$

$$\lambda_3 = -h < 0.$$

Theorem 9. *If* $a_1 < (f_1h)^{-1}e_1g$ *and* $a_2d < (f_2h)^{-1}e_2g$ *then* $G_0(0, 0, h^{-1}g)$ *is asymptotically stable and if any of the eigen value i.e.* $a_1 > (f_1h)^{-1}e_1g$ *or* $a_2d > (f_2h)^{-1}e_2g$ *then* $G_0(0, 0, h^{-1}g)$ *is unstable.*

Global stability 3.2.2. We study the global stability of the equilibrium point $G_N(N^*, 0, M^*)$ using Lyapunov function defined as follows:

$$L^*(t) = \frac{1}{2}(N - N^*)^2 + k_1C + \frac{1}{2}k_2(M - M^*)^2.$$

Where k_1 and k_1 are positive constants.

So,

$$\frac{dL^*}{dt} = \frac{\partial L^*}{\partial N}\frac{dN}{dt} + \frac{\partial L^*}{\partial M}\frac{dC}{dt} + \frac{\partial L^*}{\partial M}\frac{dM}{dt}$$

i.e. $$\frac{dL^*}{dt} = (N - N^*)\left[a_1 N\left(1 - \frac{N}{b_1}\right) - d_1 NC - \frac{e_1 NM}{f_1 + N}\right]$$

$$+ k_1\left[a_2 C\left(d - \frac{C}{b_2}\right) - d_2 NC - \frac{e_2 CM}{f_2 + C} - uC\right]$$

$$+ k_2(M - M^*)\left[g - hM - \frac{j_1 NM}{f_1 + N} - \frac{j_2 CM}{f_2 + C}\right]$$

According to LaSalle's invariant principle, the $G_N(N^*, 0, M^*)$ equilibrium point is globally stable if

$$\frac{dL^*}{dt} < 0$$

i.e. if the conditions $a_1 N\left(1 - \frac{N}{b_1}\right) < d_1 NC + \frac{e_1 NM}{f_1 + N}$,

$$a_2 C\left(d - \frac{C}{b_2}\right) < d_2 NC + \frac{e_2 CM}{f_2 + C} - uC, \tag{21}$$

$$g < hM - \frac{j_1 NM}{f_1 + N} - \frac{j_2 CM}{f_2 + C},$$

are satisfied. The conditions described in (21) are sufficient for cancer Free State.

4. Numerical Simulations

For Basic model 4.1. Numerical simulations of system (2) are carried out under following conditions.

(a) $a_1 < d_1 b_2$ and $a_2 > d_2 b_1$ which are sufficient conditions for the existence of cancer.

(b) $b_1 \le b_2$.

(c) $N_0 > C_0$, where N_0 and C_0 are initial values of N and C.

(d) Cancer cells grow faster than Normal cells.

Table 1.

Notations	Description	Parametric value	Ref.
a_1	Division rate of normal cells	1.5	[1]
a_2	Division rate of Cancer cells	10.0	[1]
b_1	Carrying capacity of normal cells	1460	[1]
b_2	Carrying capacity of cancer cells	2100	[1]
d_1	Cancer cells kills normal cells (Competition rate)	0.0075	[1]
d_2	Normal cells kills cancer cells (Competition rate	0.005	[1]

Initial conditions are $N_0 = 1460$ and $C_0 = 0.01$.

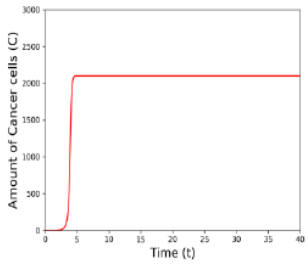

Figure 1. Growth of Cancer cells with time.

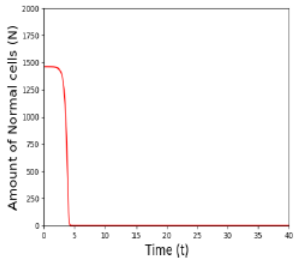

Figure 2. Growth of Normal cells with time.

For Complete model 4.2. Numerical simulations of system (1) are carried out under following conditions.

(a) Sufficient conditions described in equations (19) and (20) for the existence of cancer.

(b) $b_1 \leq b_2$.

(c) $N_0 > C_0$.

(d) Cancer cells grow faster than Normal cells.

(e) The drug is more potent against the tumor cells than against the normal cells.

(f) $j_2 > j_1$.

(g) $a_1^{-1} g e_1 < h f_1$ which guarantees the existence of G_N as per theorem 2 and as per theorem 3, $g e_2 < h f_2 (a_2 d - u)$ which guarantees the existence of G_C.

The rates for a_1, a_2, b_1, b_2, d_1 and d_2 are taken from table 1.

Table 2.

Notations	Description	Parametric value	Ref.
e_1	Absorption rate of Normal cells due to combine effect of chemotherapy and monoclonal antibody drugs	0.000384	Calculated from [1], [9] and [10]
e_2	Absorption rate of Cancer cells due to combine effect of chemotherapy and monoclonal antibody drugs	0.1216	Calculated from [1], [9] and [10]
j_1	Absorption rate of chemotherapy and monoclonal antibody due to drugs normal cells	0.001152	Calculated from [1], [9] and [10]
j_2	Absorption rate of chemotherapy and monoclonal antibody due to drugs cancer cells	0.1152	Calculated from [1], [9] and [10]
f_1	Without competition and absorption normal cells reaches at carrying capacity	1	[1]
f_2	Without competition and absorption cancer cells reaches at carrying capacity	1	[1]
u	Death rate of cancer cells due to kito diet	2.0	[6]

g	Infusion rate of chemotherapy and monoclonal antibody drugs	2450	Calculated from [8], [1]
h	Washout rate of chemotherapy and monoclonal antibody drugs	9.6	Calculated from [1], [9] and [10]
d	Constant rate of kito diet	0.5	[6]

With Initial conditions are $N_0 = 500$ and $C_0 = 100$ the following plots are obtained.

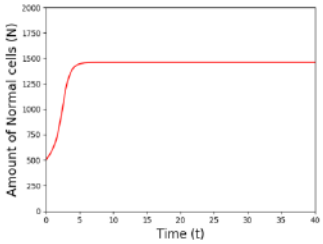

Figure 3. Growth of Normal cells with time.

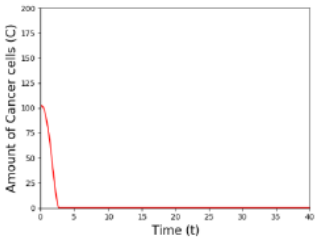

Figure 4. Growth of Cancer cells with time.

With initial conditions are $N_0 = 500$ and $C_0 = 131$.

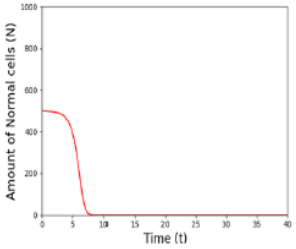

Figure 5. Growth of Normal cells with time.

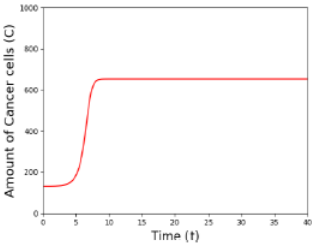

Figure 6. Growth of Cancer cells with time.

We could see that in the present of medications with the infusion rate mentioned in table 2, up to $C_0 = 130$, growth of cancer cells decrease with time but when $C_0 = 131$, immediately the effect of medications is not seen. We achieve this by applying Z-control to the system in the following section.

5. Z-Control for Breast Cancer

Now the controllability of system (1) is studied using the approach of Z-Control (ref. [2]-[5]). We introduce Z-Control $u_1(t)$ on the system (1) as follows.

$$\frac{dN}{dt} = a_1 N\left(1 - \frac{N}{b_1}\right) - d_1 NC - \frac{e_1 NM}{f_1 + N}$$

$$\frac{dC}{dt} = a_2 C\left(d - \frac{C}{b_2}\right) - d_2 NC - \frac{e_2 CM}{f_2 + C} - uC \tag{22}$$

$$\frac{dM}{dt} = g - hM - \frac{j_1 NM}{f_1 + N} - \frac{j_2 CM}{f_2 + C} - u_1(t)M.$$

Where $u_1(t)$ is the indirect control variable for chemotherapy treatment and monoclonal antibody drugs.

Z-Control method:

Z-Control method plays very important role to get the stability of the model. It is very useful to reduce difference between actual output $O(t)$ and desired output $O_d(t)$. This objective is achieved by forcing the error function $e(t) = O(t) - O_d(t)$ to converge exponentially to zero when it satisfied the following equation

$$e'(t) = -\lambda e(t) \text{ for } \lambda > 0 \tag{23}$$

Equation (23) is also known as the design formula and λ is the design parameter.

Now to compute Z-Control which exponentially reduces the cancer cells to zero. For that we define first error function $e_1(t) = C(t) - C_d(t)$. Hence from equation (23) we get

$$C'(t) - C'_d(t) = -\lambda[C(t) - C_d(t)]. \tag{24}$$

Since $u_1(t)$ cannot be derived explicitly from (24), we define second error function as

$$e_2 = e'_1 + \lambda e_1 = C'(t) - C'_d(t) + \lambda[C(t) - C_d(t)]. \tag{25}$$

But according to (23),

$$e_2'(t) = -\lambda e_2(t)$$

$$\text{i.e. } [C''(t) - C_d''(t)] + \lambda[C'(t) - C_d'(t)] = -\lambda[C'(t) - C_d'(t) + \lambda(C(t) - C_d(t))]$$

$$\text{i.e. } \left[a_2 C'\left(d - \frac{C}{b_2}\right) + a_2 C\left(-\frac{C'}{b_2}\right) - d_2 N'C - d_2 NC' - \frac{e_2 CM'}{f_2 + C} - \frac{e_2 C'M}{f_2 + C} \right.$$

$$\left. + \frac{e_2 C'CM}{(f_2 + C)^2} - uC' - C_d''(t) \right] + \lambda[C'(t) - C_d'(t)]$$

$$= -\lambda[(C'(t) - C_d'(t)) + \lambda(C(t) - C_d(t))]$$

$$\text{i.e. } \frac{e_2 CM'}{f_2 + C} = \left[a_2 C'\left(d - \frac{C}{b_2}\right) + a_2 C\left(-\frac{C'}{b_2}\right) - d_2 N'C - d_2 NC' - \frac{e_2 CM'}{f_2 + C} - \frac{e_2 C'M}{f_2 + C} \right.$$

$$\left. + \frac{e_2 C'CM}{(f_2 + C)^2} - uC' - C_d''(t) \right] + \lambda[C'(t) - C_d'(t)]$$

$$+ \lambda[(C'(t) - C_d'(t)) + \lambda(C(t) - C_d(t))]$$

$$\text{i.e. } M' = \left(\frac{f_2 + C}{e_2 C}\right)[a_2 C'\left(d - \frac{C}{b_2}\right) + a_2 C\left(-\frac{C'}{b_2}\right) - d_2 N'C - d_2 NC' - \frac{e_2 C'M}{f_2 + C}$$

$$+ \frac{e_2 C'CM}{(f_2 + C)^2} - uC' - C_d''(t) + \lambda[C'(t) - C_d'(t)]$$

$$+ \lambda[(C'(t) - C_d'(t)) + \lambda(C(t) - C_d(t))].$$

But from (22),

$$M' = g - hM - \frac{j_1 NM}{f_1 + N} - \frac{j_2 CM}{f_2 + C} - u_1(t)M$$

$$\text{i.e. } \frac{M'}{M} = \frac{g}{M} - h - \frac{j_1 N}{f_1 + N} - \frac{j_2 C}{f_2 + C} - u_1(t).$$

So, we get the Z-Controller as

$$\text{i.e. } u_1(t) = \left(-\frac{f_2 + C}{e_2 CM}\right)\left[a_2 C'\left(d - \frac{C}{b_2}\right) + a_2 C\left(-\frac{C'}{b_2}\right) - d_2 N'C - d_2 NC' - \frac{e_2 C'M}{f_2 + C} \right.$$

$$+\frac{e_2C'CM}{(f_2+C)^2}-uC'-C_d''(t)+\lambda[C'(t)-C_d'(t)]$$

$$+\lambda[(C'(t)-C_d'(t))+\lambda(C(t)-C_d(t))]+\frac{g}{M}-h-\frac{j_1N}{f_1+N}-\frac{j_2C}{f_2+C}.$$

This control $u_1(t)$ reduces the cancer cells exponentially to zero. To support this analytical result, we draw following plots by taking data from table 1 and 2, with initial condition $N_0 = 500$ and $C_0 = 131$.

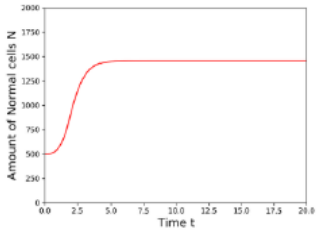

Figure 7. Control effect on normal cells.

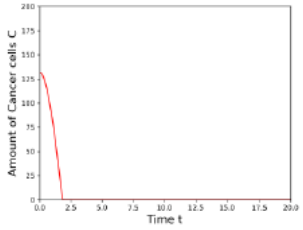

Figure 8. Control effect on cancer cells.

We see the effect of $u_1(t)$ on both normal cells and cancer cells. We observe that the cancer cells reduce to zero very rapidly.

6. Conclusion

The mathematical model for the breast cancer dynamics along with the treatment of chemotherapy with monoclonal antibody drugs is proposed. The stability analysis of treatment free model and with treatment model is discussed extensively. Global stability of the equilibrium point is studied using Lypaunov function. To control the growth of the cancer cells, Z-Control approach is used. The control $u_1(t)$ is computed analytically. To support the analytical results, numerical computation is also carried out using python programming language and results are displayed graphically.

References

[1] S. T. R. Pinho, H. I. Freedman and F. Nani, A chemotherapy model for the treatment of cancer with metastasis, Math. Comput. Model. 36 (2002), 773-803.

[2] Y. Zhang, X. Yan, B. Liao, Y. Zhanga and Y. Ding, Z-type control of populations for Lotka-Volterra model with exponential convergence, Math. Biosci. 272 (2016), 15-23. https://doi.org/10.1016/j.mbs.2015.11.009.

[3] D. Lacitignola, F. Diele, C. Marangi and A. Provenzale, On the dynamics of a generalized predator–prey system with Z-type control, Math. Biosci. 280 (2016), 10-23. https://doi.org/10.1016/j.mbs.2016.07.011.

[4] B. Liao and Y. Zhang, Different complex ZFs leading to different complex ZNN models for time-varying complex generalized inverse matrices, IEEE Trans. Neural Networks Learn. Syst. 25 (2014), 1621-1631. https://doi.org/10.1109/TNNLS.2013.2271779.

[5] S. Samanta, Study of an epidemic model with Z-type control, Int. J. Biomath. 11 (2018), 1-21. https://doi.org/10.1142/S1793524518500845.

[6] S. Isaac Oke, M. Matadi and S. Xulu, Optimal control analysis of a mathematical model for breast cancer, Math. Comput. 23 (2018), 1-28. https://doi.org/10.3390/mca23020021.

[7] B. G. Allen, S. K. Bhatia, C. M. Anderson, J. M. Eichenberger-Gilmore, Z. A. Sibenaller, K. A. Mapuskar, J. D. Schoenfeld, J. M. Buatti, D. R. Spitz and M. A. Fath, Ketogenic diets as an adjuvant cancer therapy: History and potential mechanism, Redox Biol. 2 (2014), 963-970. https://doi.org/10.1016/j.redox.2014.08.00.

[8] J. J. M. A. Hendrikx, J. B. A. G. Haanen, E. E. Voest, J. H. M. Schellens, A. D. R. Huitema and J. H. Beijnen, Fixed dosing of monoclonal antibodies in oncology, Oncologist 22 (2017), 1212-1221. https://doi.org/10.1634/theoncologist. 2017-0167.

[9] C. Bernard-Marty, F. Lebrun, A. Awada and M. J. Piccart, Monoclonal antibody-based targeted therapy in breast cancer: Current status and future directions, Drugs 66 (2006), 1577-1591. https://doi.org/10.2165/00003495-200666120-00004.

[10] EPERC homepage https://www.mywhatever.com/cifwriter/library/eperc/fastfact/ff99.html

[11] Mayo clinic homepage https://www.mayoclinic.org/diseases-conditions/cancer/in-depth/monoclonal-antibody/art-20047808.

[12] Maths 24 homepage https://www.math24.net/routh-hurwitz-criterion/.

[13] First post homepage https://www.firstpost.com/tech/science/world-cancer-day-2019.