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A COMPARATIVE STUDY OF CONTROL STRATEGIES IN BREAST CANCER DYNAMICS

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Abstract

The mathematical model for breast cancer dynamics is studied and to control the spread of the cancer cells optimal control strategy is employed. This control strategy is compared with the *Z*-control strategy for the same system and comparative analysis is done. To substantiate our results, numerical computation is also carried out and results are displayed graphically.

1. Introduction

Breast cancer is the most diagnosed cancer among women worldwide. It occurs in women and rarely in men. Symptoms of breast cancer include a lump in the breast, bloody discharge from the nipple and changes in the shape or texture of the nipple or breast. Depending on the stage of cancer, treatment may be application of chemotherapy, radiation, hormone therapy, surgery or combination of them.

In this study, we consider treatment as combination of chemotherapy and monoclonal antibody drugs. Ketodiet is also added as a part of the treatment. Monoclonal antibodies are basically laboratory produce molecules that mimic the immune system's attack on cancer cells and attached to chemotherapeutic agent to deliver the treatment directly to the cancer cells instead of healthy cells (normal cells) [13]. Ketodiet also plays 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

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body instead of glucose [8].

2. Preliminaries

A following mathematical model proposed by the authors in [2] related to breast cancer dynamics represents competition between cancer cells (C) and Normal cells (N) and combine effect of chemotherapy and monoclonal antibody drugs (M) and Ketodiet [1, 2].

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

where $N > 0$, $C > 0$ and $M > 0$.

The explanation of each term is given below.

- $a_1 N\left(1-\frac{N}{b_1}\right)$: constitutes logistic growth of normal cells. It naturally grows in normal cells accompanied by division rate a_1 and carrying capacity b_1.
- $d_1 NC$: constitutes competition 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 represents absorption of normal cells due to combination of chemotherapy and monoclonal antibody drugs at rate e_1.
- $a_2 C\left(d-\frac{c}{b_2}\right)$: constitutes logistic growth of cancer cells. It naturally increase in cancer cells accompanied by division rate a_2 and carrying capacity b_2. Here cancer cells growth is also affected by kitodiet at constant rate d.
- $d_2 NC$: constitutes competition between cancer cells and Normal cells at rate d_2.

- $\frac{e_2CM}{f_2 + C}$: 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 : constitutes cancer cells death due to kitodiet effect.
- g : Ingrain rate of Chemotherapy agent and Monoclonal antibody drugs.
- hM : represents rinsed rate of Monoclonal antibody drugs and Chemotherapy agent at rate h.
- $\frac{j_1NM}{f_1 + N}$: This term constitutes 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.
- $\frac{j_2CM}{f_2 + C}$: constitutes 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.

In [2], the authors have proved following sufficient conditions for the existence of cancer.

Theorem 1. *Sufficient conditions for existence of cancer are* [2]

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

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

Theorem 2. *If* $a_1^{-1}ge_1 < hf_1$ *admit then the equilibrium point* $G_N(N^*, 0, M^*)$ *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. [2]

Theorem 3. *Under the condition* $ge_2 < hf_2(a_2d - u)$, *the equilibrium*

point $G_C(0, C^*, M^*)$ *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. [2]

3. Optimal Control Theory

In this study, optimal control theory is used to control the growth of cancer cells. We introduce two optimal control strategies one is about concentration of combination of chemotherapy and monoclonal anti-body drugs denoted as u_1 and another control strategy is about ketodiet denoted as u_2 in the system of non-linear ordinary differential equations given by (1). The system of equations after the introduction of the controls is as follows.

$$\frac{dN}{dt} = a_1N\left(1 - \frac{N}{b_1}\right) - d_1NC - \frac{e_1NM}{f_1 + N} + (1 - u_1)C$$

$$\frac{dC}{dt} = a_2C\left((1 - u_2) - \frac{C}{b_2}\right) - d_2NC - \frac{e_2CM}{f_2 + C} - uC - u_1C \tag{2}$$

$$\frac{dM}{dt} = (1 - u_1)g - hM - \frac{j_1NM}{f_1 + N} - \frac{j_2CM}{f_2 + C}$$

We consider following objective function to find the optimal control for system (2).

$$J(u_1, u_2) = \int_0^T \left(\left(\frac{1}{2}\right)A_1C^2 + w_1u_1^2 + w_2u_2^2\right)dt \tag{3}$$

Where A_1 : be non-negative constant for cancer cells

w_1 : be weight constant for control u_1.

w_2 : be weight constant for control u_2.

Our goal is to determine optimal control functions (u_1^*, u_2^*), such that

$J(u_1^*, u_2^*) =$ optimize $(J(u_1^*, u_2^*)/(u_1^*, u_2^*) \in \emptyset)$ where $\emptyset$ is a control strategy set. (4)

Where control strategy set $\emptyset$ is defined as follows: $\emptyset = \{(u_1, u_2)/u_i(t)$ is Lebesgue measurable on $[0, T]$, $0 \le u_i(t) \le 1$, $i = 1, 2\}$

Theorem 4. *Consider the objective function* (3) *with* $(u_1, u_2) \in \Gamma$ *subject to the constraint state system* (2) *then there exist* $(u_1^*, u_2^*) \in \Gamma$ *such that* $J(u_1^*, u_2^*) = optimize\ (J(u_1^*, u_2^*)/(u_1^*, u_2^*) \in \emptyset)$.

Proof. The integrand, $\frac{1}{2} A_1 C^2 + w_1 u_1^2 + w_2 u_2^2$ of the objective function (3) is convex in the set $\emptyset$. According to definition, the control strategy set $\emptyset$ is also close and convex. The conditions for the existence of optimal control are satisfied (Fleming and Rishel 1975) therefore the model (2) is bounded and linear in the control variables.

We use Pontryagin's Maximum Principle to derive the optimal amount of control [12]. The associated Lagrangian function with adjoint variables, λ_1, λ_2 and λ_3 is given by,

$$L = \frac{1}{2} A_1 C^2 + w_1 u_1^2 + w_2 u_2^2 + \lambda_1 \left[a_1 N \left(1 - \frac{N}{b_1}\right) - d_1 NC - \frac{e_1 NM}{f_1 + N} + (1 - u_1) C \right]$$

$$+ \lambda_2 \left[a_2 C \left((1 - u_2) - \frac{C}{b_2} \right) - d_2 NC - \frac{e_2 CM}{f_2 + C} - uC - u_1 C \right]$$

$$+ \lambda_3 \left[(1 - u_1) g - hM - \frac{j_1 MN}{f_1 + N} - \frac{j_2 MC}{f_2 + C} \right]$$

The partial derivative of Langrangian function with respect to N, C and M are obtained as follows. The evaluation gives a adjoint equation variables $(\lambda_1, \lambda_2, \lambda_3)$ corresponding to following system.

$$\lambda_1' = -\frac{\partial L}{\partial N} = -\lambda_1 a_1 + \frac{2\lambda_1 a_1 N}{b_1} + \frac{\lambda_1 f_1 e_1 M}{(f_1 + N)^2} + \frac{\lambda_3 f_1 j_1 M}{(f_1 + N)^2} + (d_1 \lambda_1 + d_2 \lambda_2) C$$

$$\lambda_2' = -\frac{\partial L}{\partial C} = -A_1 C + (\lambda_1 + \lambda_2) u_1 - \lambda_1 - \lambda_2 u - \lambda_2 a_2 (1 - u_2) + \frac{2\lambda_2 a_2 C}{b_2}$$

$$+ \frac{\lambda_2 f_2 e_2 M}{(f_1 + C)^2} + \frac{\lambda_3 f_2 e_2 M}{(f_2 + C)^2} + (d_1 \lambda_1 + d_2 \lambda_2) N$$

$$\lambda_3' = -\frac{\partial L}{\partial M} = \frac{\lambda_1 e_1 N}{f_1 + N} + \frac{\lambda_2 e_2 C}{f_2 + C} + \lambda_3\left(h + \frac{j_1 N}{f_1 + N} + \frac{j_2 C}{f_2 + C}\right)$$

For necessary condition of an optimal control problem, Pontryagins maximum principle is used and we obtained optimal control strategies analytically as follows:

$$-\frac{\partial L}{\partial u_1} = 0, -\frac{\partial L}{\partial u_2} = 0$$

For

$$-\frac{\partial L}{\partial u_1} = 0 \Rightarrow u_1 = \frac{(\lambda_1 + \lambda_2)C + \lambda_3 g}{2w_1}$$

and for

$$-\frac{\partial L}{\partial u_2} = 0 \Rightarrow u_2 = \frac{\lambda_2 a_2 C}{2w_2}$$

and Optimal conditions given as

$$u_1^* = \max\left(0, \min\left(1, \frac{(\lambda_1 + \lambda_2)C + \lambda_3 g}{2w_1}\right)\right)$$

$$u_2^* = \max\left(0, \min\left(1, \frac{\lambda_2 a_2 C}{2w_2}\right)\right)$$

To justify the above analytical results obtained, numerical simulation is also carried out using python programming language and results are displayed graphically. The graphical results represent growth of cancer cells and normal cells with respect to time with above control strategies.

4. Numerical Simulation

Numerical simulations of system (2) are carried out under following conditions [2].

(a) Sufficient conditions described in Theorem 1 for the existence of cancer.

(b) $b_1 \leq b_2$.

(c) $N_0 > C_0$. (where N_0 is initial amount of normal cells and C_0 is initial amount of cancer cells

(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.

Table 1.

Notations	Description	Parametric value	Ref.
a_1	Division rate of normal cells	1.5	[1], [2]
a_2	Division rate of Cancer cells	10.0	[1], [2]
b_1	Carrying capacity of normal cells	1460	[1], [2]
b_2	Carrying capacity of cancer cells	2100	[1], [2]
d_1	Cancer cells kills normal cells (Competition rate)	0.0075	[1], [2]
d_2	Normal cells kills cancer cells (Competition rate)	0.005	[1], [2]
e_1	Absorption rate of Normal cells due to combine effect of chemotherapy and monoclonal antibody drugs	0.000384	Calculated from [1], [2], [10] and [12]
e_2	Absorption rate of Cancer cells due to combine effect of	0.1216	Calculated from [1],

	chemotherapy and monoclonal antibody drugs		[2], [10] and [12]
j_1	Absorption rate of chemotherapy and monoclonal antibody due to drugs normal cells	0.001152	Calculated from [1], [2], [10] and [12]
j_2	Absorption rate of chemotherapy and monoclonal antibody due to drugs cancer cells	0.1152	Calculated from [1], [2], [10] and [12]
f_1	Normal cells reach their carrying capacity without competition or absorption.	1	[1], [2]
f_2	Cancer cells reach their carrying capacity without competition or absorption.	1	[1], [2]
u	Death rate of cancer cells due to ketodiet	2.0	[2], [7]
g	Infusion rate of chemotherapy and monoclonal antibody drugs	2450	Calculated from [1], [2] and [9]
h	Washout rate of chemotherapy and monoclonal antibody drugs	9.6	Calculated from [1], [2], [10] and [12]
d	Constant rate of ketodiet	0.5	[2], [7]

To obtain the following graphs $N_0 = 500$ and $C_0 = 131$ is considered.

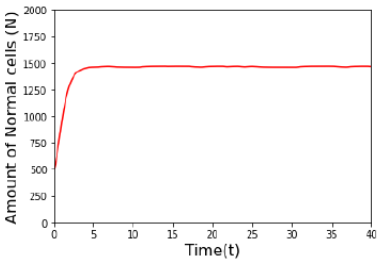

Figure 3. Growth of Normal cells with time(Days).

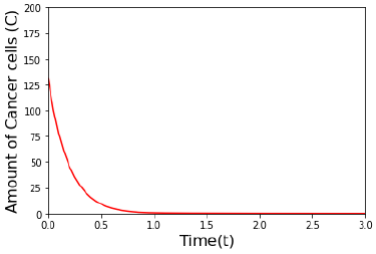

Figure 4. Growth of Cancer cells with time(Days).

At the end we compare numerical results of optimal control with the *Z*-control approach for the same system. The *Z*-control method also play significant role to get stability of the model. In *Z*-control approach the growth of cancer cells reduces to zero exponentially [2- 6].

5. Comparison between Optimal Control Strategy and *Z*-control Strategy

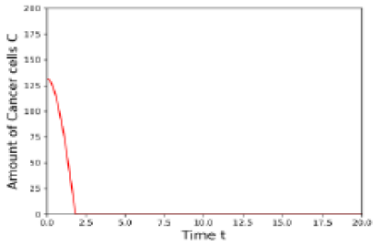

Figure 5. Z- Control effect on cancer cells.

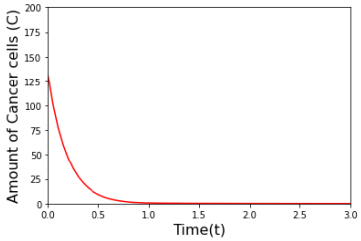

Figure 6. Optimal control effect on cancer cells.

We observe from figure (5) and figure (6) that, the cancer cells start to decrease after two days in *Z*-control approach but the cancer cells start to decrease within a day when we use optimal control approach. So according to this observation we can say that, optimal control gives better result than *Z*-control for above mentioned mathematical model.

6. Conclusion

The Mathematical model for breast cancer dynamics with treatment as combination of chemotherapy and monoclonal anti-body drugs is considered.

In this model, we designed optimal control to reduce growth of cancer cells in the body and these theoretical results are analyzed. To substantiate the theoretical results, numerical simulation is also carried out. Finally, comparison of the two control approaches one is optimal control and another is Z-control is made. We conclude from graphical observation that optimal control approach is better than Z-control approach because growth of cancer cells reduces speedily in optimal control strategy compared to Z-control strategy.

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