OPTIMAL CONTROL STRATEGY FOR IMPROVED CANCER BIOCHEMOTHERAPY OUTCOME

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ABSTRACT

A deterministic mathematical model for cancer cells dynamics in the presence of treatment is considered. The model is a system of coupled ordinary differential equations (ODEs) which describes cancer growth on a cell population level in the presence of a combination of immunotherapy and chemotherapy known as biochemotherapy. The modeled scenario is formulated as an optimal control problem with the goal of obtaining the optimal levels of each of the treatment regimen that must be adopted in order to minimize the number of a cancer cells as well as the therapy toxicity while maximizing the immune system performance. The optimality system for the optimal control problem is derived based on Pontryagin's Maximum Principle and the resulting system is solved numerically with fourth order Runge-Kunta scheme using forward-backward sweep approach. Simulations of the numerical solution were carried out and findings from the simulations show that biochemotherapy could effectively curtail the growth of the cancer cells remarkably within a reasonable short time.

Keywords: Cancer cells, Biochemotherapy, Immune system, Pontryagin's Maximum Principle, Optimality system.

Introduction

Cancer is a major cause of death worldwide. It often results from the uncontrolled growth of abnormal cells in the body. Cells are the body's building blocks, and cancer starts from the normal cells which divide to grow in order to maintain cell population equilibrium while balancing cell death. However, cancer occurs when the unbounded growth of cells in the body happens too fast. Moreover, it can also occur when cells lose their ability to die [1]. There are different kinds of

cancer depending on which organ or tissue of the body is affected. Cancer affects organs or tissues such as the lung, colon/rectum, breast, skin, bones and nerves in the body. The common feature to all forms of the cancer disease is the failure of the mechanisms that regulate normal cell growth, proliferation and cell death. Ultimately, there is progression of the resulting cancer cells from mild to severe abnormality with invasion of neighboring tissues and this eventually spread to other areas of the body. This process is referred to as Metastasis and it is a major cause of death from cancer.

Generally, cancer disease develops due to exposure of individuals to carcinogenic (cancer-causing) agents in what they inhale, eat, or drink. It may also arise as a result of DNA damages caused by certain environmental exposures. In addition, individuals infected with diseases like hepatitis B virus and human papillomavirus may also develop cancer at the severe stage of these diseases. It is important to emphasize here that the immune system plays a major role in limiting the development of cancerous cells. Particularly, the natural killer cells and $CD8^+$ killer T-cells help to directly attack and eliminate infected cells.

Cancer can be treated by chemotherapy, immunotherapy, radiation therapy, surgery, monoclonal antibody therapy, etc. The most recent therapy approach is aimed at combining immunotherapy and chemotherapy as a means of treating cancer. Chemotherapy is the treatment of cancer with one or more cytotoxic antineoplastic drug (chemotherapeutic agents) as part of standard regimens. Most forms of chemotherapy drugs act by killing cells that divide rapidly. On the other hand, the goal of immunotherapy is to strengthen the body's own natural ability to combat cancer by enhancing the effectiveness of the immune system. Immunotherapy alone is sometimes used to treat cancer, but it is often used in combination with common treatments like chemotherapy and radiation therapy. This is done in order to enhance the effectiveness of the combined therapy. One of the possible benefits of immunotherapy is that it has the potential not to be as toxic as chemotherapy, radiation therapy and surgery. The logic behind the development of a biochemotherapy is based on using as little drug as possible to effectively kill cancer cells and applying immunotherapy to support the patient's immune system. This strengthens the body's natural defenses against both the cancer cells and dangerous side effects of chemotherapy. Consequently, there have been series of research works on modeling the cancer and immune cells dynamics in the presence of therapy (See, [5, 9, 12, 18]).

Obviously, theoretical study of cancer through mathematical modeling is a very useful approach which could help better understand the dynamics of the cancer-immune cells interaction. Moreover,

optimal control theory can provide a guide on how to effectively combine the different cancer therapy options in a way that will yield improved treatment outcome for patients [2, 6, 8, 19, 21, 23]. For instance, Kuznetsov and knott [16] developed a deterministic model that describes the interplay of the cancer cells and the cytotoxic killer cells. Though, they considered only one immune cells population, they effectively discussed the mechanism of cancer growth, suppression and re-growth. In a related study, Kuznetsov and Taylor [15] presented a mathematical model for cytotoxic T lymphocytes response to the growth of an immunogenic cancer. Similarly, Kirschner and Panetta [13] proposed a different model which focuses on the cancer-immune cells interaction. They found that the dynamics among cancer cells, immune cells and the cytokine interleukin-2 can explain both short-term oscillations in cancer size as well as long-term cancer relapse. Also, Kolev [14] presented a mathematical model showing the competition between cancer cells and immune cells with emphasis on the roles of antibodies. De Pillis et al. [4] presented a model on cancer cells dynamics under the influence of immunotherapy and chemotherapy. Their simulation results show that neither chemotherapy nor immunotherapy alone was sufficient to control cancer growth while the combination of the two therapy approach could help eliminate the entire cancer cells.

In this paper, we consider the dynamics of cancer-immune cells the influence of biochemotherapy. Here, we explore the interactions of cancer cells and immune cells incorporating the effect of the therapy on the cells dynamics using a system of non-linear differential equations. We set up the scenario as an optimal control problem with the goal of minimizing the cancer cells population as well as adverse effect of therapy at the end of the treatment. Thus, the paper is structured as follows: In section 2, we discuss our proposed model with the controls. In section 3, we formulate an optimal control problem subject to the model dynamics, characterize the optimal controls, and constitute its optimality system using PMP. In section 4, we solve the resulting system numerically and discuss our results.

Proposed Mathematical Model

We proposed a deterministic model of three different cells' populations and two different drugs concentrations dynamics. They are cancer cells population (T(t)), natural killer cells (N(t)), $CD8^{+}$Tcells (L(t)), concentration of Interleukin-2 (I(t)) and concentration of interferon- α (F(t)). The model is a system of coupled ordinary differential equations expressed below:

$$\frac{dT}{dt} = (1-u_1)aT(1-bT) - cNT - c'TL - u_2 d_T T \quad (1)$$

$$\frac{dN}{dt} = \alpha_1 + \frac{gT}{h+T}N - pNT - u_2 d_N N \quad (2)$$

$$\frac{dL}{dt} = \alpha_2 - qTL - uL^2 + rNT + \frac{DT}{k+DT}L + \frac{p_i}{g_i}LI - u_2 d_L L \quad (3)$$

$$\frac{dI}{dt} = V_I(t) + kIL - \mu_I I \quad (4)$$

$$\frac{dF}{dt} = V_F(t) - \mu_F F \quad (5)$$

with initial conditions $T(0) \geq 0,\ N(0) \geq 0,\ L(0) \geq 0,\ I(0) \geq 0,\ and\ F(0) \geq 0.$

The cancerous cells growth is assumed to be logistic, since no living thing continues to grow indefinitely rather there is a stagnation/retardation on growth at the later stage of their life. Thus, this is captured by the term $aT(1-bT)$ where a represents the cancer growth rate, b is the human cancer cell's carrying capacity, c is a rate constant which denotes the rate at which cancerous cells are killed by natural killer cell, the third term represent the inactivation term for the cancerous cells due to the interaction between $CD8^+$ T- cell and cancer cell at rate c', while the interferon-α (F) also boosts the ability of immune cells to attack cancer cell and slow the growth of cancer cell directly as well as the blood vessel that the cancer cell need to grow. u_2 represents the toxicity of the therapy which implies the adverse effect of the therapy on each of the cells. d_T denotes the natural death rate of the cancer cells. However, since our model considers the dynamics of a cancer cell, setting $u_1 \equiv 0$ and $u_2 \equiv 1$ in the above equation simplifies the model to a scenario without effective therapy. This implies that $u_1 = 0$ means the therapy has no effect on the cancer growth and $u_2 = 1$ means that the therapy has no toxic effect on each of the cells under consideration. The structure of the equations guarantees non-negative solution for the state variables *T(t), N(t),L(t), I(t), F(t).*The negative terms in the above equations represent loses from the cell populations while the positive terms constitute increase in the cell populations. The other model equations (2-5) can be explained in a similar way.

Optimal Control Problem Formulation

We formulated the goal of the biochemotherapy administered on a cancer patient as an optimal control problem. We denote the positive effect of the therapy as the control variable $u_1(t)$ and its adverse effect as control variable $u_2(t)$ while the problem objective functional is defined as

$$J(u_1,u_2)=\min_{u_1,u_2}\int_0^{t_f}(\frac{1}{2}w_1u_1^2+\frac{1}{2}w_2u_2^2+T(t))dt+w_3T(t_f) \qquad (6)$$

where $w_1>0, w_2>0, w_3>0.$

subject to the state equations(1-5) with appropriate state initial conditions over the initial time t_0 up to time the terminal time t_f The control set U whose elements are Lebesgue measurable is defined as:

$$U=\{(u_1(t),u_2(t))\,|\,m_i\le u_i(t)\le M_i,\ i=1,2,\ t\in[t_0,\ t_f]\} \qquad (7)$$

the objective functional, our goal is to minimize the total cancer cells population and toxicity of the therapy over the time interval $[t_0,\ t_f]$ and also to ensure that cancerous cells remained minimal at the terminal time t_f. It is expected that effects of the drugs are non-linear, and we choose quadratic cost terms u_1^2 and u_2^2 to reflect the effectiveness of the therapy and its side-effects respectively. The coefficient w_1 and w_2 are weight constants on the controls and each of them is the relative importance of each of the control term on the therapy outcome. It is worthy to note that the higher the weight constants associated with each of the control, the more will be its impact on the model system dynamics. The salvage term $w_3T(t_f)$ is included to counter the effect of using fixed treatment time. If this term is not present, the controls could taper off earlier, and allow a rise in cancer cell count at the end of the treatment period.

The lower bounds for u_1 and u_2 correspond to no therapy. For u_1, this lower bound is $m_1=0$ and for u_2 the lower bound is $m_2=1$. We restrict $M_1<1$, as $M_1=1$ would correspond to no new cancer cell. The upper bound M_2 is greater than 1 and its impact is indirectly dependent on each of the parameter values d_T, d_N, and d_L, which are the associated death rates for each of the cell populations considered.

Existence of an Optimal Control Pair

We shall consider the sufficient conditions for the existence of a solution to our formulated optimal control problem. This will be accomplished using theorem that follows:

Theorem 1:

There exists an optimal control pair $(u_1^*,\ u_2^*)$ with a corresponding solution (T^*,N^*,L^*,I^*,F^*) to the model equations 1-5 that minimizes J(u_1, u_2) over U

Proof:

The existence of the optimal control pair (u_1^*, u_2^*) is guaranteed by the compactness of the control and state space, and convexity of the objective functional which is based on the Fleming and Rishel's theorem [10]. The non-trivial requirement of the theorem are as stated below:

(1) The set of all solutions to the model equations (1-5) and its associated initial conditions together with the corresponding controls in U is non-empty.

(2) The state system can be written as a linear function of the control variables with coefficients dependent on time and state variables.

(3) The integrand *G* in Equation (6) is convex on U and additionally satisfies

$G(t, T, N, L, I, F, u_1, u_2) \geq r_1|(u1, u2, u3)|^{\beta} - r_2$, where $r_1, r_2 > 0$ and $\beta > 1$.

Using the approach adopted in Yusuf and Benyah [24], if the solutions to the state equations are *a priori* bounded and the state equations are continuous and Lipschitz in the state variables, then there exists a unique solution corresponding to every admissible control set in U. Equally, based on the fact that for all $(T, N, L, I, T) \in \Re_+^5$, all the model state variables are bounded below and above, hence the solutions to the state equations are bounded. In addition, the boundedness of the partial derivatives with respect to the state variables in the model system of equations can be shown directly. This shows that the model system of equations is Lipschitz with respect to the state variables. Consequently, the first requirement of the theorem is satisfied.

Moreover, considering the model system of equations (1-5), it is obvious that the state variables equations are linearly dependent on the controls $u_1$and u_2. Thus, the second requirement of the theorem is satisfied too.

As for the third requirement of the theorem, we observe that the integrand G in our objective functional is convex because it is quadratic with respect to the controls. Thus, we only need to prove that G is bounded. This is proved below:

$$
\begin{aligned}
G &= \frac{1}{2}w_1u_1^2 + \frac{1}{2}w_2u_2^2 + T, \\
&\geq \frac{1}{2}w_1u_1^2 + \frac{1}{2}w_2u_2^2, \\
&\geq \frac{1}{2}w_1u_1^2 + \frac{1}{2}w_2u_2^2 - w_1; \quad \textit{because } \frac{1}{2}w_1u_1^2 - w_1 \leq 0, \qquad (8) \\
&\geq \min\ (\frac{1}{2}w_1,\ \frac{1}{2}w_2)(u_1^2 + u_2^2) - w_1, \\
&\geq W\left\|(u_1,\ u_2)\right\|^2 - w_1, \qquad W = \min(\frac{1}{2}w_1,\ \frac{1}{2}w_2).
\end{aligned}
$$

The above equation (8) establishes a bound on G. Therefore, we have a unique solution of the optimality system for small intervals due to the opposite time orientation of the state variables and the adjoint-variables equations. Furthermore, the uniqueness of the solution of the optimality system guarantees the uniqueness of the optimal control if it exists.

Characterization of the Optimal Control Pair

We characterize the optimal control u_1^* and u_2^* which gives the optimal levels for the two control variables and the corresponding states $(T^*,\ N^*,\ L^*,\ I^*,\ F^*)$. The necessary conditions for the optimal controls are obtained using the Pontryagin's Maximum Principle [20].

In order to apply the Pontryagin's Maximum Principle, we need to first defined the Hamiltonian as follows:

$$\begin{aligned} \mathrm{H} &= \frac{1}{2}w_1u_1^2 + \frac{1}{2}w_2u_2^2 + T + \lambda_1((1-u_1)aT(1-bT) - cNT - c'TL - u_2d_TT) \\ &+ \lambda_2(\alpha_1 + \frac{gT}{h+T}N - pNT - u_2d_NN) \\ &+ \lambda_3(\alpha - qTL - uL^2 + rNT + \frac{DT}{k+DT}L + \frac{p_iLI}{g_i} - u_2d_LL) \\ &+ \lambda_4(V_I + kIL - \mu_II) + \lambda_5(V_f - \mu_fF) \end{aligned} \tag{9}$$

Theorem 2 *Let* $(u_1^*, u_2^*) \in U$ be an optimal control with the corresponding states $T^*,\ N^*,\ L^*,\ I^*,\ and\ F^*$. Then, there exist the adjoint variables λ_i for $i = 1\ldots5$, which satisfy

$$\begin{aligned} \lambda_1' &= -1 - \lambda_1\left((1-u_1)(a-2abT) - cN - c'L - u_2d_T\right) \\ &+ \lambda_2\left(\frac{g(h+T)-gT}{(h+T)^2}N - pN\right) - \lambda_3\left(-qL + rN + L(\frac{(k+DT)D - D^2T}{(k+DT)^2})\right), \end{aligned} \tag{10}$$

$$\lambda_2' = \lambda_1cT - \lambda_2\left(\frac{gT}{h+T} - pT - u_2d_N\right) - \lambda_3rT\,, \tag{11}$$

$$\lambda_3' = \lambda_1c'T - \lambda_3\left(\frac{DT}{k+DT} + \frac{p_iI}{g_i} - u_2d_L - qT - 2uL\right) - \lambda_4kI\,, \tag{12}$$

$$\lambda_4' = -\lambda_3\left(\frac{p_iL}{g_i}\right) - \lambda_4(kL - \mu_I)\,, \tag{13}$$

$$\lambda_5' = \lambda_5\mu_f\,, \tag{14}$$

and the transversality conditions

$$\lambda_1(t_f) = w_3,\ \lambda_2(t_f) = 0,\ \lambda_3(t_f) = 0,\ \lambda_4(t_f) = 0,\ \lambda_5(t_f) = 0; \tag{16}$$

with the optimal control variables given as

$$\begin{aligned} u_1^* &= \min\left\{\max(0, \frac{\lambda_1 aT(1-bT)}{w_1}), u_{1\max}\right\}, \\ u_2^* &= \min\left\{\max(0, \frac{\lambda_1 d_T T + \lambda_2 d_N N + \lambda_3 d_L L}{w_2}), u_{2\max}\right\}. \end{aligned} \tag{17}$$

Proof:

Based on Pontryagin's Maximum principle (PMP), we obtained the adjoint variables equations (10-15) as follows:

$$\lambda_1' = -\frac{\partial \mathrm{H}}{\partial T} = -1 - \lambda_1\left((1-u_1)(a-2abT) - cN - c'L - u_2 d_T\right)$$
$$+ \lambda_2\left(\frac{g(h+T) - gT}{(h+T)^2}N - pN\right) - \lambda_3\left(-qL + rN + L(\frac{(k+DT)D - D^2T}{(k+DT)^2})\right),$$

$$\lambda_2' = -\frac{\partial \mathrm{H}}{\partial N} = \lambda_1 cT - \lambda_2\left(\frac{gT}{h+T} - pT - u_2 d_N\right) - \lambda_3 rT\ ,$$

$$\lambda_3' = -\frac{\partial \mathrm{H}}{\partial L} = \lambda_1 c'T - \lambda_3\left(\frac{DT}{k+DT} + \frac{p_i I}{g_i} - u_2 d_L - qT - 2uL\right) - \lambda_4 kI\ ,$$

$$\lambda_4' = -\frac{\partial \mathrm{H}}{\partial I} = -\lambda_3\left(\frac{p_i L}{g_i}\right) - \lambda_4(kL - \mu_I),$$

$\lambda_5' = -\frac{\partial \mathrm{H}}{\partial I} = \lambda_5 \mu_f$, where H is as specified in equation (9).

Moreover, the transversality condition of the PMB gives the terminal condition for each of the adjoint variables as stated in equation (16) while the imposition of its optimality conditions gives :

$$\frac{\partial \mathrm{H}}{\partial u_1} = w_1 u_1 - \lambda_1 aT(1-bT) = 0 \ \text{ at } \ u_1 = u_1^*.$$

This implies that

$$u_1^* = \frac{\lambda_1 aT(1-bT)}{w_1}.$$

Similarly,

$$\frac{\partial \mathrm{H}}{\partial u_2} = w_2 u_2 - \lambda_1 d_T T - \lambda_2 d_N N - \lambda_3 d_L L = 0 \qquad \text{at} \quad u_2 = u_2^*;$$

So, $u_2^* = \dfrac{\lambda_1 d_T T + \lambda_2 d_N N + \lambda_3 d_L L}{w_2}$.

We can then characterize the optimal control pair $(u_1^*,\ u_2^*)$ by imposing the bounds on the control variables given in equation (7) to obtain the optimal levels of the two controls as follows:

$$u_1^* = \min\left\{\max(0, \frac{\lambda_1 aT(1-bT)}{w_1}), u_{1\max}\right\},$$

$$u_2^* = \min\left\{\max(0, \frac{\lambda_1 d_T T + \lambda_2 d_N N + \lambda_3 d_L L}{w_2}), u_{2\max}\right\}.$$

Consequently, the modeled problem optimality system is obtained by substituting u_1^* and u_2^* for u_1 and u_2 respectively in the model state variables equations (1-5) with the associated initial conditions and the adjoint variables equations (10-14) with transversality conditions coupled with the control variables characterization given in equations (14).

Numerical Simulations

In this section, numerical simulations of the modeled problem is presented. The optimality system is solved numerically based on Runge-Kunta forth order scheme using forward-backward sweep approach and the results are presented graphically. This is done using the set of parameters values in Table 1 and solving the model state equations forward in time with an initial guess for the control variables and initial values for each of the state variables. The results are then used to solve the co-state equations backward in time with the derived terminal conditions on each of the co-state variables. This procedure is done iteratively until successive values of each of the variables converge.

Table 1 Estimation of population values and parameter

Parameter	Description	Unit	Value	Source
a	Tumor growth rate	day^{-1}	1.25	Estimate
d_T	Tumor death rate	day^{-1}	0.8	[22]
d_N	NK death rate	day^{-1}	0.6	[22]
d_L	$CD8^+$ T cell death rate	day^{-1}	0.6	[22]
b	Tumor carrying capacity	$cell^{-1}$	1.02×10^{-9}	[17]

c	Fractional tumor cell kill by effector cells	$day^{-1}.cell^{-1}$	6.41×10^{-11}	[17]
α	Recruitment rate	$cell.\ day^{-1}$	7.80×10^{8}	[17]
g	Maximum NK cell recruitment rate by tumor cell	day^{-1}	1.25×10^{-2}	[17]
h1	Steepness coefficient of the NK cells recruitment curve	day^{-1}	2.02×10^{7}	[16]
ρ	NK cells inactivation rate by tumor cells	$day^{-1}.cell^{-1}$	3.42×10^{-6}	[7]
ki	Steepness coefficient of the $CD8^+$ T cells recruitment curve	$cell^2$	2×10^{-4}	[7]
r	Self-regulation rate is the rate at which $CD8^+$ T cells stimulated to be produced as a result of tumor cells killed by NK cells	$day^{-1}.cell^{-1}$	1.10×10^{-7}	[4]
q	$CD8^+$ T cell inactivation by tumor cell	$day^{-1}.cell^{-1}$	1.42×10^{-6}	[16]
μ_f	Decay rate	day^{-1}	1.7	[11]
u	Regulatory function by NK cells of $CD8^+$ T cell	$day^{-1}.cell^{-1}$	3.00	Estimate
p_i	Maximum $CD8^+$ T cell recruitment rate by IL-2	day^{-1}	1.25×10^{-1}	[3]
g_i	Constant	$cell^2$	2.00	[3]
α_1	Constant source of NK cell	$(cells.day)^{-1}$	7.50×10^{8}	[17]
α_2	Constant source of $CD8^+$ T- cell	$(cells.day)^{-1}$	5.0×10^{8}	[17]
μ_I	Rate consumption IL-2 by $CD8^+$ T- cell	day^{-1}	10	[3]
D	Steepness coefficient of tumor-$CD8^+$ T cells) lysis. Primed with ligand-transduced cells	dimensionless	8.39×10^{-1}	[17]
V_F	Initial interferon	day^{-1}	1000	Estimate
C1	Rate of tumor cells inactivation by $CD8^+$ T- cell	$(cells.day)^{-1}$	4.4×10^{-9}	Estimate

W	Inactivation of IL-2 molecules by prostaglandins	(cells.day)$^{-1}$	1.8×10^{-8} Estimate

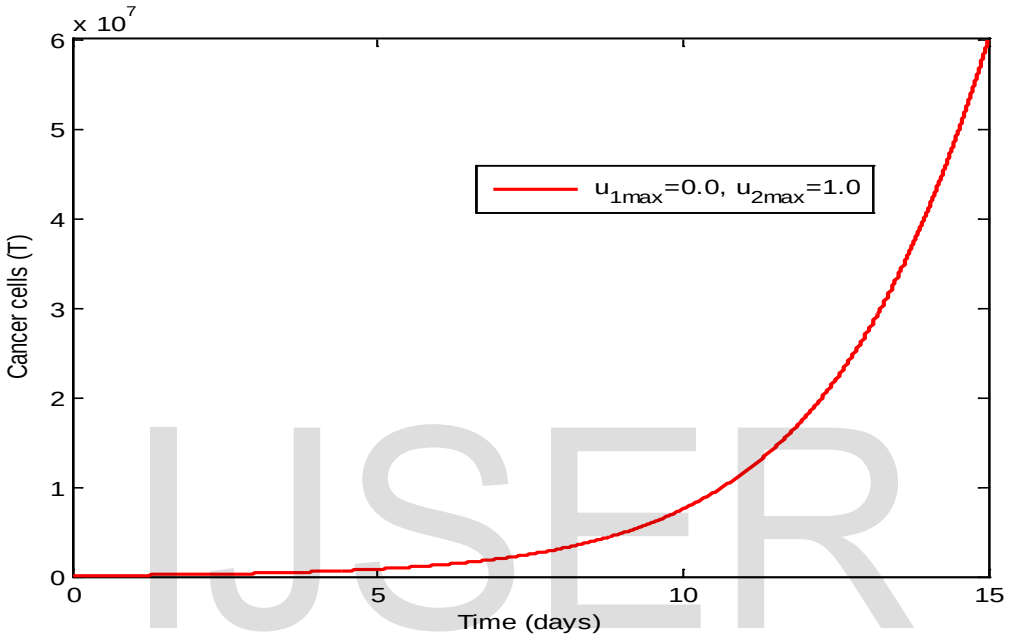

Figure 1: Cancer cells' population over time in the absence of biochemotherapy.

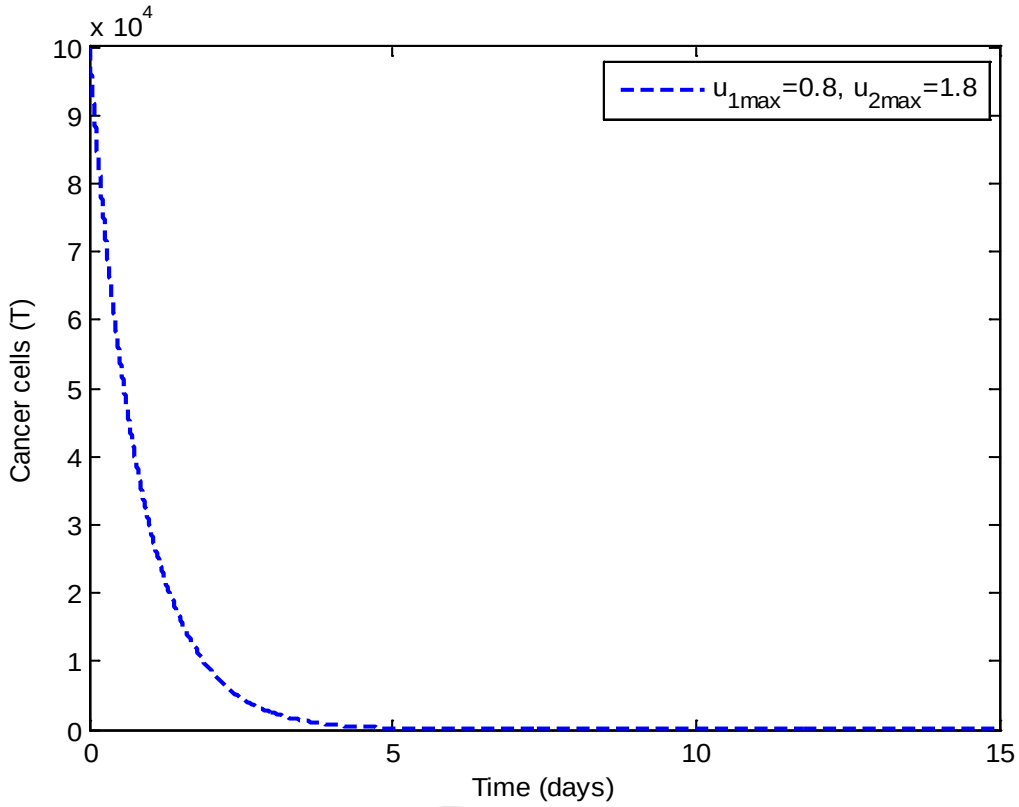

Figure 2: Cancer cells' population over time in the presence of biochemothrapy.

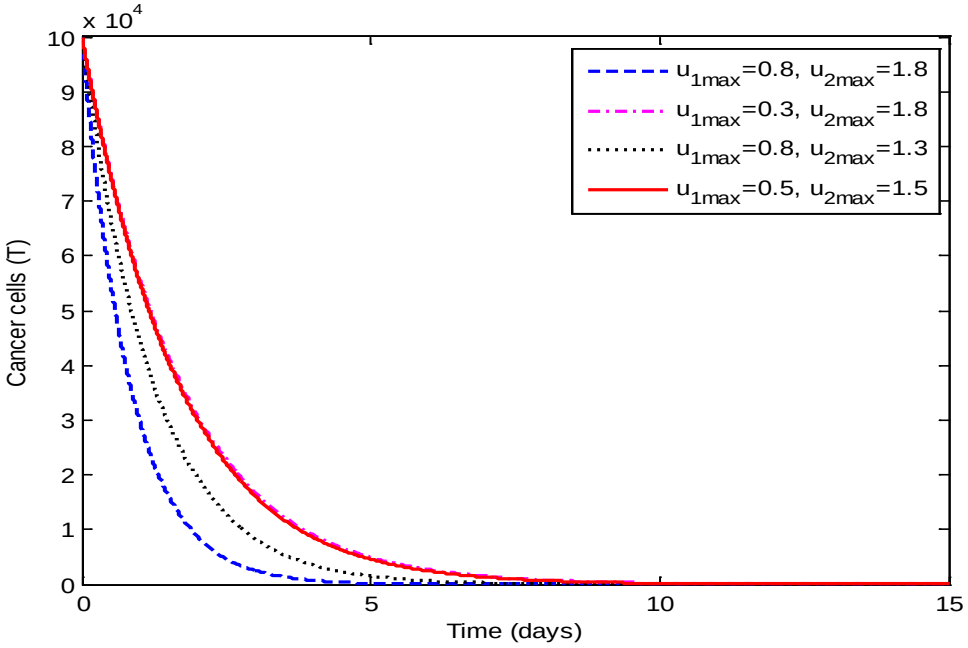

Figure 3: Cancer cells' population over time with varying combinations effectiveness and toxicity of the biochemotherapy.

Figures 1-3 above shows the dynamics of cancer cells' population with or without biochemotherapy. Figure 1 conveys that the cancer cells' population continues to increase rapidly in the absence of biochemotherapy while Figure 2 indicates that the same population decreases remarkably under biochemotherapy. However, Figure 3 shows that the more effective the biochemotherapy is , the more drastic will be the decrease in cancer cells' population although the therapy may have some side-effects on some other body cells.

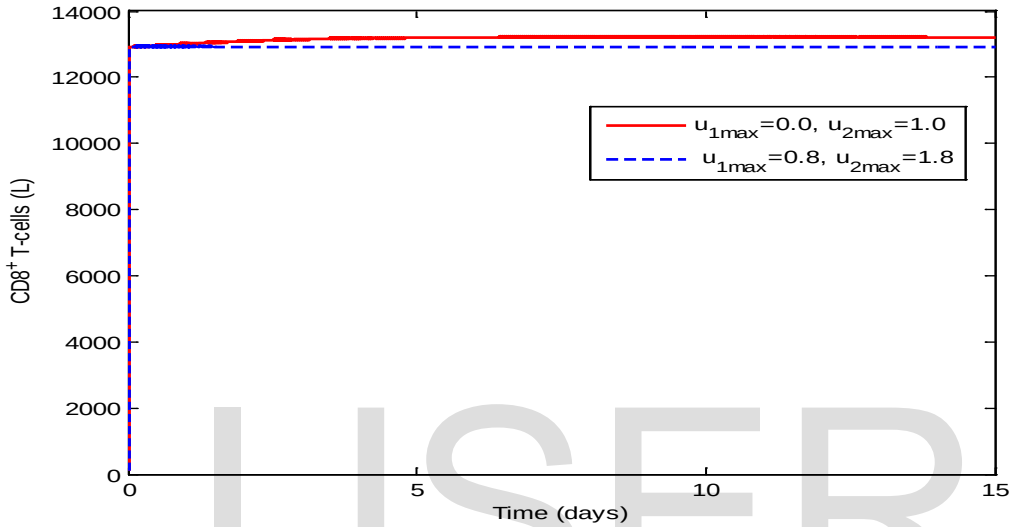

Figure 4: $CD8^+$ T-cells' population over time with and without biochemotherapy

In Figure 4, it is observed that the $CD8^+$ T-cells' population is not significantly different from one another whether with or without biochemotherapy, though the population is slightly higher in the case with biochemotherapy. This difference could be attributed to the production of more $CD8^+$ T-cells due to the therapy and this might be responsible for the sharp drop in the cancer cells' population in the presence of the therapy.

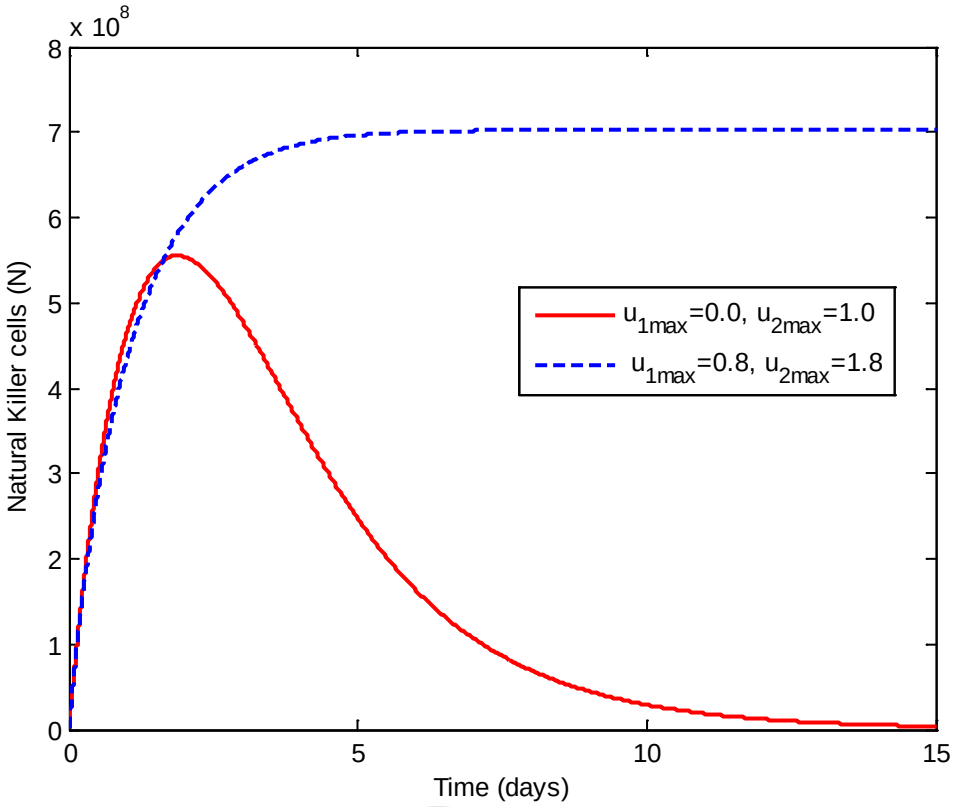

Figure 5: Natural killer cells' population over time with and without biochemotherapy.

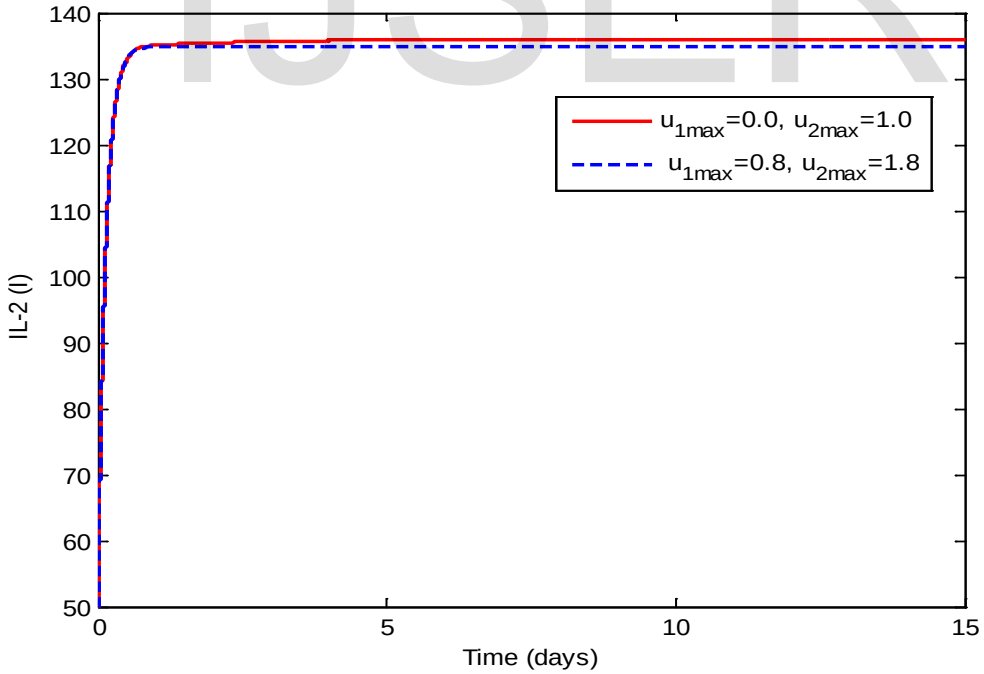

Figure 6: IL-2 population over time with and without biochemotherapy.

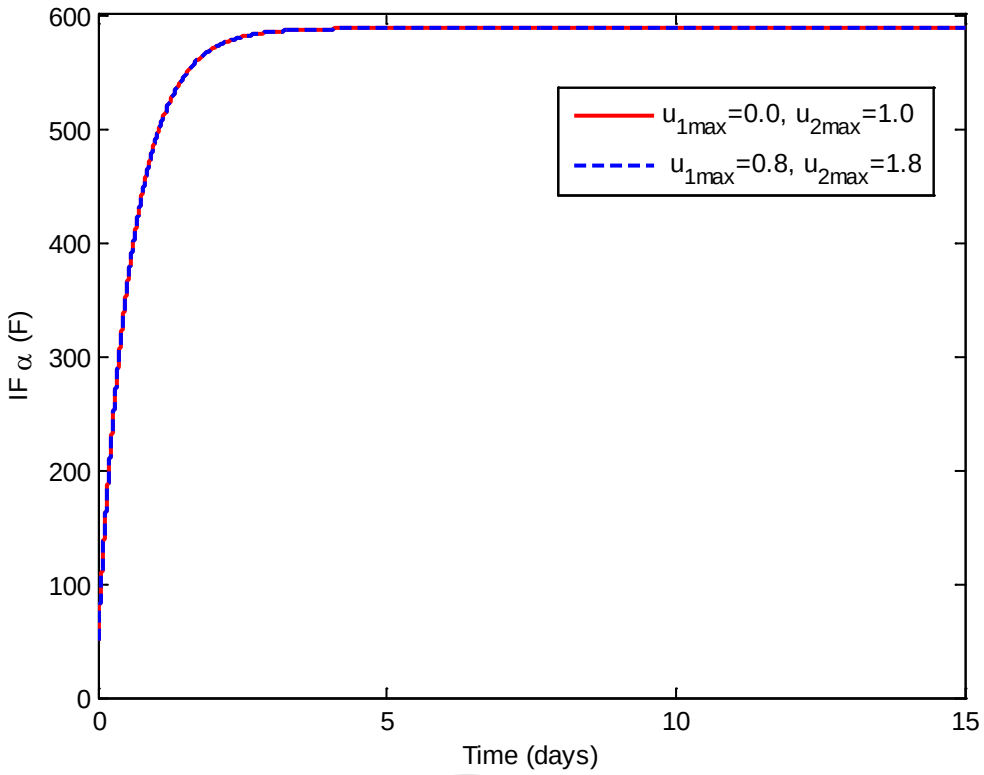

Figure 7: Interferon- alpha population over time with and without biochemotherapy

Figure 5 shows that the Natural killer cells' population grows to its carrying capacity and remains at that level over time in the presence biochemotherapy while in the case without therapy, the natural cells' population rises initially (though it does not get to the carrying capacity) but drop sharply afterwards. The sudden drop in the natural cells' population could result from substantial loss in cells' population arising from the inability of the natural killers to halt the proliferation of the cancer cells. Unlike in the case with biochemotherapy where the natural killer cells are continuously strengthened to control the growth of cancer cells.

Figure 6 and Figure 7 shows that IL-2 and interferon-alpha population profile are not significantly different in the presence or absence of biochemotherapy. It is important to mention here that the therapy may not make a difference in these two populations, they a play big role in the presence of biochemotherapy to ensure a consistent reduction of the cancer cells and enhance the performance of the immune cells.

Conclusion

In this paper, a model for the dynamics of the cancer cells and immune cells population in the presence of biochemotherapy was considered. The modelled scenarios was formulated as an

optimal control problem. The optimality system to the problem was derived using Pontryagins' maximum principle. The resulting optimality system was solved numerically using Runge-Kunta forth order scheme based on forward-backward sweep approach. Simulations of the numerical results indicated that biochemotherapy yielded drastic reduction in the cancer cells' population and it also remarkably enhanced the $CD8^+$ T-cells and natural killer cells population. Thus, resulting in improved therapy outcome for patients undergoing biochemotherapy.

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