

Mixed Immunotherapy and Chemotherapy of Tumors: Optimal Control Approach

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Abstract

The aim of this work is to apply optimal control theory to certain cancer treatment strategies which based on combination of multiple cancer therapies, in the form of a system of ordinary differential equations (ODEs), governing cancer growth on cell population level with more than one of therapy, in order to determine the best mix of treatments that minimizes both tumor mass and negative effects upon the health of the patient. Numerical simulations of mixed chemotherapy and immunotherapy shows that neither chemotherapy nor immunotherapy alone are effective in treating the cancer, but in combination the therapies are able to eliminate the entire tumor.

Key words: *chemotherapy, immunotherapy, optimal control theory, Pontryagin's Maximum principle.*

1 Introduction

Cancer is the second cause of death in the world, there were an estimated 12.7 million cancer cases around the world in 2008, of these 6.6 million cases were in men and 6.0 million in women. This number is expected to increase to 21 million by 2030, according to World cancer research fund international[39]. Radiotherapy, chemotherapy, hormone therapy, immunotherapy, gene therapy are the effective treatments for cancer patients. The more recent approach aim is looking into combining immunotherapy and chemotherapy as a way to treat the cancer. The goal of immunotherapy is to strengthen the body's own natural ability to combat cancer by enhancing the effectiveness of the immune system, the use of conventional cancer chemotherapy in combination with immunotherapy was previously not thought to be appropriate because chemotherapy generally reduces immunity and could cancel out the benefits of immunotherapy when given together, although many researchs and theoretical studies and mathematical works showed that combining chemotherapy with immunotherapy can have complementary effects that increases cancer treatment effectiveness, (See for example[1],[40],[41]). The logic behind the development of a combination chemo-immunotherapy strategy is based on using as little chemotherapy drug as possible to effectively kill tumor cells and applying immunotherapy to support the patient's immune system, thus strengthening the body's natural defenses against both the tumor cells and the dangerous side effects of the chemotherapy.

When cancer infects a human cells, the first human body line of defense is the natural killer (NK) cell : white blood cells that actively scan the body for abnormal cells, once found, the fighting strats and the strongest survives. As part of the specific immune response, CD8+ cytotoxic T lymphocytes (CTLs) intervenes to kill the tumor cells. In this work we use an existing model, taken from [1] which describes the interaction of tumor cells, NK cells, CD8+T cells, and Circulating lymphocyte cells, under a combined immunotherapy and chemotherapy, then we apply the method of optimal control theory with quadratic control.

Optimal control has been effectively applied to mathematical models incorporating the interaction between tumors and treatments; for example,[36,37,38] have utilized control theory to maximize the effectiveness of chemotherapy against tumor cell and minimize the toxic effects of treatments, also [42,43] have contributed research on applications to immunotherapy strategies for cancer and HIV. In addition, in the works by de Pillis and radunskaya[44], and de Pillis et al.[1,45] the authors explore various approaches to combining chemo-and immunotherapies through numerical simulation and the implementation of numerical linear controls. The interest in applying quadratic control to this model is determining the best mix of therapy that minimizes both tumor mass and negative effects of such treatments.

There are several different types of immunotherapy which use contrasting methods for fighting off tumor cells, they fall into three main categories: immune response modifiers, monoclonal antibodies, and vaccines (see, for example, [46]). The first category contains substances that affect immune response, such as interleukins (including IL-2), interferons, tumor necrosis factors (TNF), colony-stimulating factors (CSF), and B-cell growth factors. In the next category, monoclonal antibodies are currently being developed to target specific cancer antigens. In the third category are vaccines, which are generally used therapeutically, and are created from tumor cells. In this work, we implement treatment from the first category in the form of mathematical terms that represent IL-2 and tumor infiltrating lymphocyte (TIL) injections.

The outline of this paper is as follows. In section 2, we present the model and discuss the model's assumptions. Section 3 deals with the application of potimal control to the model, beginning with the description of the objective functional. In section 4, we present the Forward Backward Sweep Method to solve the optimality system and we discuss numerical simulations, starting with simulating immunotherapy alone, chemotherapy alone and combinations of these.

2 Model Formulation

In this section, we use an existing immunology model, taken from [1] which describes the dynamic evolution of three populations of immune cells in the presence of tumor and under the combined immunotherapy and chemotherapy treatment. This model involves the following cell populations :

- T, tumor cell population (Units: Number of Cells).
- N, total of natural killer cell (NK) population. These cells are part of the innate immune system and therefore exist even when no tumor cells are present (See, [2]) (Units: Number of Cells per Liter).
- L, total of cytotoxic T lymphocytes (CD8+T) cell population. These cells are active tumor specific cells that are part of the specific immune response. These cells are only present in a large number when tumor cells are present (See, [2],[3]) (Units: Number of Cells per Liter).
- C, number of circulating lymphocytes. This number can be used as a measure of the patient health (See, [12],[11],[10]) (Units: Number of Cells per Liter).
- M, chemotherapy drug concentration in the bloodstream (Units: Milligrams per Liter).
- I, immunotherapy drug: tumor infiltrating lymphocyte (Tils), interleukins (IL-2) concentration in the bloodstream (Units: International Units (IUs) per Liter).

Before going into the model description, it is important to note that, as it is recalled in [1], *there is no universal agreement as to the underlying dynamics or the precise cascades of events that take place in the immune response process. The model recalled and described below is however based on published statements and conjectures as well as reasonable assumptions:*

Tumor Equation(T): The tumor cell population grows logistically, $aT(1-bT)$, in the absence of an immune response, as justified in [13][14]. Death of tumor cells due to natural killer cells takes the form $-cNT$, whereas death due to CD8+T is given by $-DT$ (See, for example, [14],[15],[16]). The presence of tumor cells also stimulates the Natural Killer cells, $g\frac{T^2}{h+T^2}N$, and CD8+T cells, $j\frac{D^2T^2}{K+D^2T^2}L$, (See, for example, [20],[21]).

Natural Killer Cell Equation(N): the source of the NK cell population, eC , is represented as a fraction of the circulating lymphocyte population, a simplification meant to represent the complex cascade of biological events that leads to NK cell stimulation (see, eg, [20]). It's also assumed that a fraction of natural killer cells die when they have interaction with a tumor cell, this gives us the term $-pNT$, (See, [19]).

Tumor Specific T Cell (CD8+T) Equation(L): It's assumed that this population have a linear natural death rate, $-mL$, as well as a quadratic death rate, $-uNL^2$ (see, e.g., [23][24]). The CD8+T cells may also die through interaction with the tumor and this is represented by a mass action term $-qLT$, (See, [19]). Interactions of the tumor with the larger lymphocyte populations, N and C, stimulate CD8+T production, these stimulatory terms are represented by the two positive mass action terms, r_1NT , r_2CT . (See, e.g[22])

Circulating Lymphocyte Equation(C): It's assumed that these cells have a constant source term and a linear death rate.

The Effects of chemotherapy Medicine: Once injected, medicine is assumed to have a linear decay rate. The medicine interacts with each of the four cell populations, T, N, L and C through a term of the form $K_X(1 - e^{-M})X$ (X being T, Nor L), (See,[18]), For each cell population, this term represents cell death due to the medicine. also it's assumed that the fraction of cells killed by chemotherapy depends on the amount of drug present in the system.

The Effects of immunotherapy Medicine (IL-2): Although naturally produced, the cytokine IL-2 is often used to treat cancer(See for example[47]). This model assumes a linear de-

cay rate, additionally, when a CD8+T cells is stimulated by IL-2 it will secrete more IL-2 as represented by $\frac{P_I LI}{g_I + I}$, (See, [3]). The model is governed by the following system of ordinary differential equations :

$$\frac{dT}{dt} = aT(1 - bT) - cNT - DT - K_T(1 - e^{-M})T \tag{1}$$

$$\frac{dN}{dt} = eC - fN + g\frac{T^2}{h + T^2}N - pNT - K_N(1 - e^{-M})N \tag{2}$$

$$\frac{dL}{dt} = -mL + j\frac{D^2 T^2}{K + D^2 T^2}L - qLT + (r_1 N + r_2 C)T - uNL^2 - K_L(1 - e^{-M})L + \frac{P_I LI}{g_I + I} + v_L \tag{3}$$

$$\frac{dC}{dt} = \alpha - \beta C - K_C(1 - e^{-M})C \tag{4}$$

$$\frac{dM}{dt} = -\gamma M + v_M(t) \tag{5}$$

$$\frac{dI}{dt} = -\mu_I I + v_I(t) \tag{6}$$

Where $D = d\frac{(L/T)^i}{s+(L/T)^i}$ and $T(0) = T_0, N(0) = N_0, L(0) = L_0, C(0) = C_0, M(0) = M_0, I(0) = I_0$.

In Table 1, we have provided a summary of equation term descriptions, and in Table 2 we have a list of parameter values taken from experimental results of the patient 9 in [1].

3 The control problem

In this section we consider v_L (TIL treatment), v_M (chemotherapy treatment), v_I (IL-2 treatment) as controls, our aim is to find the best strategy of treatment for fighting cancer. There are various optimal therapy strategies for cancer treatment, it depends on the control objective and the formulation of problem, such as:

- Formulation based on minimizing the drug during the treatment period which also results with the less toxicity effect to the healthy tissues.
- optimal therapy aim at minimizing the drug toxicity and maximizing T-helper

cells(CD4+T), which role is sending signals to other types of immune cells, including CD8+T killer cells, this last destroy and kill the infection or virus.

- Formulation focuses on the health level by allowing a less faster decrease of the tumor size.
- Formulation based on improving the health indicator at price of a gradually longer treatment duration.

In this work we are interested in determining an optimal control, in order to minimize the tumor size and the side effects of the therapy on finite time interval $[0, t_f]$. Limited treatment window $[0, t_f]$ is necessary because the tumor can mutate and develop a resistance to the treatment after some finite time.

The objective functional to be minimized is:

$$J(v_L, v_M, v_I) = \int_0^{t_f} T(t) + A' v_M^2(t) + B' v_I^2(t) + C' v_L^2(t) dt \quad A', B', C' \geq 0 \tag{7}$$

which is quadratic in the three controls and where A' , B' and C' are weight factors.

$$J(V^*) = \min \{J(V) : V \in U\}$$

The main objective is to decrease the number of tumor cells T; More precisely we seek an optimal control $\vec{V}^*(t)$ which minimize the functional subject such that

Where $\vec{V}^*(t) = \begin{pmatrix} v_L^*(t) \\ v_M^*(t) \\ v_I^*(t) \end{pmatrix}$ and U is the control set defined by :

$$U = \left\{ v_L(t), v_M(t), v_I(t) \text{ admissible, } 0 \leq v_L(t) \leq L', 0 \leq v_M(t) \leq M', 0 \leq v_I(t) \leq I', \forall t \in [0, t_f] \right\}$$

There are three constraints associated with this model in which the total drug administered of chemotherapy, IL-2 and Tils are limited by a constant L' , M' , I' , which represents the maximal tolerated dose of immunotherapy and chemotherapy suitable for our patient case(See[1]): $L' = 10^9$ cells is the maximum boost of Tils, $I' = 5 \times 10^6$ cells is the maximum

boost of IL-2, $M' = 5$ mg is the maximum concentration of chemotherapy drug.

Theorem 3.1 Consider the control problem with system equations (1)-(6) and objective functional(7). There exists $V^* \in U$ such that

$$J(V^*) = \min \{J(V) : V \in U\}$$

3.1 Characterization of the Optimal Control

The optimal control is characterized by using Pontryagin's Maximum Principle(See, [25]).

Theorem 3.2 Given an optimal control triple, $V^* = (v_L^*(t), v_M^*(t), v_I^*(t))$, and solutions of the corresponding state system, there exist adjoint variables λ_i for $i=1,2,\dots,6$, satisfying the following equations:

$$\begin{aligned} \frac{d\lambda_1}{dt} &= -1 - \lambda_1 \left(a - 2abT - cN - D + \frac{ds(L/T)^l}{(s+(L/T)^l)^2} - K_T(1 - e^{-M}) \right) - \lambda_2 \left(\frac{2gNTb}{(h+T^2)^2} - pN \right) - \\ &\lambda_3 \left(\frac{-2DTdlsjLk(L/T)^l}{(k+D^2T^2)^2(s+(L/T)^l)^2} + \frac{2D^2TjLk}{(k+D^2T^2)^2} - qL + r_1N + r_2C \right) \\ \frac{d\lambda_2}{dt} &= \lambda_1 cT - \lambda_2 \left(-f + \frac{gT^2}{h+T^2} - pT - K_N(1 - e^{-M}) \right) - \lambda_3 (r_1T - \mu L^2) \\ \frac{d\lambda_3}{dt} &= \lambda_1 \left(\frac{dsl(L/T)^{l-1}}{(s+(L/T)^l)^2} \right) - \lambda_3 \left(-m - qT - 2\mu NL - K_L(1 - e^{-M}) + \frac{P_I I}{g_I + I} + \frac{2jkDdsl(L/T)^l T^2}{(s+(L/T)^l)^2(k+D^2T^2)^2} + \frac{jD^2T^2}{k+D^2T^2} \right) \\ \frac{d\lambda_4}{dt} &= -\lambda_2 e - \lambda_3 r_2 T + \lambda_4 (\beta + K_C(1 - e^{-M})) \\ \frac{d\lambda_5}{dt} &= \lambda_1 K_T e^{-M} T + \lambda_2 K_N e^{-M} N + \lambda_3 K_L e^{-M} L + \lambda_4 K_C e^{-M} C \\ \frac{d\lambda_6}{dt} &= -\lambda_3 \left(\frac{P_I L g_I}{(g_I + I)^2} + \lambda_6 u_I \right) \end{aligned}$$

Where $\lambda_i(t_f) = 0$ for $i = 1, 2, \dots, 6$. Furthermore we have

$$v_L^*(t) = \min \left(\max(0, \frac{-\lambda_3}{2C'}, L') \right)$$

$$v_M^*(t) = \min \left(\max(0, \frac{-\lambda_5}{2A'}, M') \right)$$

$$v_I^*(t) = \min \left(\max(0, \frac{-\lambda_6}{2B'}), I' \right)$$

Proof

The Lagrangian for our problem is the integrand of the objective functional, coupled with the right hand sides of the state equations (1)-(6) through the adjoint variables, it's given by:

$$\begin{aligned} L = & T(t) + Av_M^2(t) + Bv_I^2(t) + Yv_L^2(t) \\ & +\lambda_1(aT(1 - bT) - cNT - DT - K_T(1 - e^{-M})T) \\ & +\lambda_2(eC - fN + \frac{gT^2N}{h+T^2} - pNT - K_N(1 - e^{-M})N) \\ & +\lambda_3(-mL + j\frac{D^2T^2}{K+D^2T^2}L - qLT + (r_1N + r_2C)T - uNL^2 - K_L(1 - e^{-M})L + \frac{P_I L I}{g_I + I} + v_L(t)) \\ & +\lambda_4(\alpha - \beta C - K_C(1 - e^{-M})C) \\ & +\lambda_5(-\gamma M + v_M(t)) \\ & +\lambda_6(\mu_I I + v_I(t)) \\ & -w_1(t)v_L(t) - w_2(t)(L' - v_L(t)) - w_3(t)v_M(t) - w_4(t)(M' - v_M(t)) - w_5(t)v_I(t) - w_6(t)(I' - v_I(t)) \end{aligned}$$

Where $\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6$ are the adjoint variables and $w_1, w_2, w_3, w_4, w_5, w_6$ are penalty multipliers which attach the control constraints and verify the conditions

$$\begin{aligned} w_1(t) \geq 0, w_3(t) \geq 0, w_5(t) \geq 0 \text{ and} \\ w_2(t)(L' - v_L(t)) = 0, \text{ and } w_1(t)v_L = 0, \text{ at } v_L^*(t) \\ w_4(t)(M' - v_M(t)) = 0, \text{ and } w_3(t)v_M = 0, \text{ at } v_M^*(t) \\ w_6(t)(I' - v_I(t)) = 0, \text{ and } w_5(t)v_I = 0, \text{ at } v_I^*(t) \end{aligned}$$

we differentiate the Lagrangian with respect to states, T, N, L, C, M and I, respectively, and the adjoint system can be written as

$$\begin{aligned} \frac{d\lambda_1}{dt} = & -1 - \lambda_1 \left(a - 2abT - cN - D + \frac{ds(L/T)^l}{(s+(L/T)^l)^2} - K_T(1 - e^{-M}) \right) - \lambda_2 \left(\frac{2gNT}{(h+T^2)^2} - pN \right) - \\ & \lambda_3 \left(\frac{-2DTdsjLk(L/T)^l}{(k+D^2T^2)^2(s+(L/T)^l)^2} + \frac{2D^2TjLk}{(k+D^2T^2)^2} - qL + r_1N + r_2C \right) \\ \frac{d\lambda_2}{dt} = & \lambda_1 cT - \lambda_2 \left(-f + \frac{gT^2}{h+T^2} - pT - K_N(1 - e^{-M}) \right) - \lambda_3 (r_1T - \mu L^2) \\ \frac{d\lambda_3}{dt} = & \lambda_1 \left(\frac{dsl(L/T)^{l-1}}{(s+(L/T)^l)^2} \right) - \lambda_3 \left(-m - qT - 2\mu NL - K_L(1 - e^{-M}) + \frac{P_I I}{g_I + I} + \frac{2jkDdsl(L/T)^l T^2}{(s+(L/T)^l)^2(k+D^2T^2)^2} + \frac{jD^2T^2}{k+D^2T^2} \right) \end{aligned}$$

$$\begin{aligned}\frac{d\lambda_4}{dt} &= -\lambda_2 e - \lambda_3 r_2 T + \lambda_4 (\beta + K_C (1 - e^{-M})) \\ \frac{d\lambda_5}{dt} &= \lambda_1 K_T e^{-M} T + \lambda_2 K_N e^{-M} N + \lambda_3 K_L e^{-M} L + \lambda_4 K_C e^{-M} C \\ \frac{d\lambda_6}{dt} &= -\lambda_3 \left(\frac{P_I L g_I}{(g_I + I)^2} + \lambda_6 u_I \right)\end{aligned}$$

Where the transversality conditions $\lambda_i(t_f) = 0$ for $i = 1, 2, \dots, 6$.

To characterize v_L^* , v_M^* , v_I^* , we analyze the necessary optimality condition

$$\frac{\partial L}{\partial v_L} = 0, \text{ at } v_L^*$$

$$\frac{\partial L}{\partial v_M} = 0, \text{ at } v_M^*$$

$$\frac{\partial L}{\partial v_I} = 0, \text{ at } v_I^*$$

we differentiate the Lagrangian with respect to v_L , v_M , v_I , then we obtain

$$\frac{\partial L}{\partial v_L} = 2C' v_L + \lambda_3 - W_1 + W_2$$

$$\frac{\partial L}{\partial v_M} = 2A' v_M + \lambda_5 - W_3 + W_4$$

$$\frac{\partial L}{\partial v_I} = 2B' v_I + \lambda_6 - W_5 + W_6$$

Where

$$\begin{cases} w_2(t)(L' - v_L^*(t)) = 0 & \text{and } w_1(t)v_L^* = 0 \\ w_4(t)(M' - v_M^*(t)) = 0 & \text{and } w_3(t)v_M^* = 0 \\ w_6(t)(I' - v_I^*(t)) = 0 & \text{and } w_5(t)v_I^* = 0 \end{cases}$$

$$v_L = \begin{cases} 0 & \text{if } \frac{-\lambda_3}{2C'} \leq 0 \\ \frac{-\lambda_3}{2C'} & \text{if } 0 < \frac{-\lambda_3}{2C'} < L' \\ L' & \text{if } \frac{-\lambda_3}{2C'} \geq L' \end{cases}$$

$$v_M = \begin{cases} 0 & \text{if } \frac{-\lambda_5}{2A'} \leq 0 \\ \frac{-\lambda_5}{2A'} & \text{if } 0 < \frac{-\lambda_5}{2A'} < M' \\ M' & \text{if } \frac{-\lambda_5}{2A'} \geq M' \end{cases}$$

$$v_I = \begin{cases} 0 & \text{if } \frac{-\lambda_6}{2B'} \leq 0 \\ \frac{-\lambda_6}{2B'} & \text{if } 0 < \frac{-\lambda_6}{2B'} < I' \\ I' & \text{if } \frac{-\lambda_6}{2B'} \geq I' \end{cases}$$

Combining these three cases, the optimal controls are characterized by:

$$v_L^*(t) = \min \left(\max(0, \frac{-\lambda_3}{2C'}), L' \right)$$

$$v_M^*(t) = \min \left(\max(0, \frac{-\lambda_5}{2A'}), M' \right)$$

$$v_I^*(t) = \min \left(\max(0, \frac{-\lambda_6}{2B'}), I' \right)$$

4 Numerical simulations

4.1 Method and Algorithm

For notational simplicity, we express the problem as finding (X, Λ, V) ,

$$\text{where } X = \begin{pmatrix} T \\ N \\ L \\ C \\ M \\ I \end{pmatrix}, \Lambda = \begin{pmatrix} \lambda_1 \\ \lambda_2 \\ \lambda_3 \\ \lambda_4 \\ \lambda_5 \\ \lambda_6 \end{pmatrix}$$

and $V^* = \begin{pmatrix} v_L^* \\ v_M^* \\ v_I^* \end{pmatrix}$

$$\begin{cases} \dot{X} = f(X, V) \in \mathbb{R}^6, & X(0) = X_0, & (4.1) \\ \dot{\Lambda} = g(\Lambda, X) \in \mathbb{R}^6, & \Lambda(t_f) = 0, & (4.2) \\ V = h(X, \Lambda) & & (4.3) \end{cases}$$

our problem can be written as:

$$\begin{cases} \dot{X} = f(X, h(X, \lambda)) = f_1(X, \lambda) \\ \dot{\Lambda} = g(\Lambda, X) \end{cases}$$

Letting $\dot{Y} = \begin{pmatrix} \dot{X} \\ \dot{\Lambda} \end{pmatrix} = \begin{pmatrix} f_1(X, \lambda) \\ g(\Lambda, X) \end{pmatrix} = g_1(X, \Lambda) = g_1(Y) \in \mathbb{R}^{12}$

$$\begin{cases} \dot{Y} = g_1(Y) \\ X(0) = X_0, \\ \Lambda(t_f) = 0, \end{cases} \text{ which is two-point boundary value problem (TBVP)}$$

This process requires The Forward Backward Sweep Method

The Forward Backward Sweep Method first solves the state equation (4.1) with a Runge-Kutta routine, then solves the costate equation (4.2) backwards in time with the Runge-Kutta solver, and then updates the control. This provokes a new approximation of the state, costate, and control. The method continues by using these new updates and calculating new values approximations for (X, λ, V) .

The algorithm describing the approximation method for obtaining the optimal control is the following

Algorithm:

Step 1. Make an initial guess for V over the interval. we choose $V_0 = \begin{pmatrix} L'/2 \\ M'/2 \\ I'/2 \end{pmatrix}$

Step 2. Using the initial condition $X(t_0) = X_0$ and the stored values for V, solve X forward in time according to its differential equation in the optimality system.

Step 3. Using the transversality condition $\Lambda(t_f) = 0$ and the stored values for V and X, solve Λ backward in time according to its differential equation in the optimality system.

Step 4. Update the control by entering the new X and Λ values into the characterization of V.

Step 5. Check convergence. if values of the variables in this interaction and the last iteration are negligibly small, output the current values as solutions. If values are not small, return to Step 2.

The method terminates when there is enough agreement between the states, costates, and controls of two passes through the approximation loop.

For Steps 2 and 3, we use a Runge-Kutta 4 routine, many types of convergence tests exist for Step 5, it is sufficient to require $\|V_{i+1} - V_i\|$ to be small, where V_{i+1} is the vector of estimated values of the control during the current iteration, and V_i is the vector of estimated values from the previous iteration. Both these vectors are of length $n+1$, which is the number of time steps. We require the percentage error to be negligibly small ,i.e.,

$$\|V_{i+1} - V_i\| \leq \epsilon$$

Where ϵ is the accepted tolerance.

4.2 Numerical Experiments

In this section, we test the behavior of the model using parameters taken from experimental results of patient(patient 9 in[1]) from Rosenberg's study on metastatic melanoma. First we present a tumor burden which can be controlled by the immune system and case which this last is not able alone to kill the tumor. We also present a case for which either chemotherapy alone or immunotherapy alone can control the tumor, and case for which a combination therapy is essential

to the survival of the patient.

4.2.1 Immune system response to Tumor:

For this first case we examine an initial tumor burden of 10^5 cells which is controlled easily by the immune system over 130 days(see Figure 1), but a tumor burden of 10^6 cells grows to a dangerous level(see Figure 2).

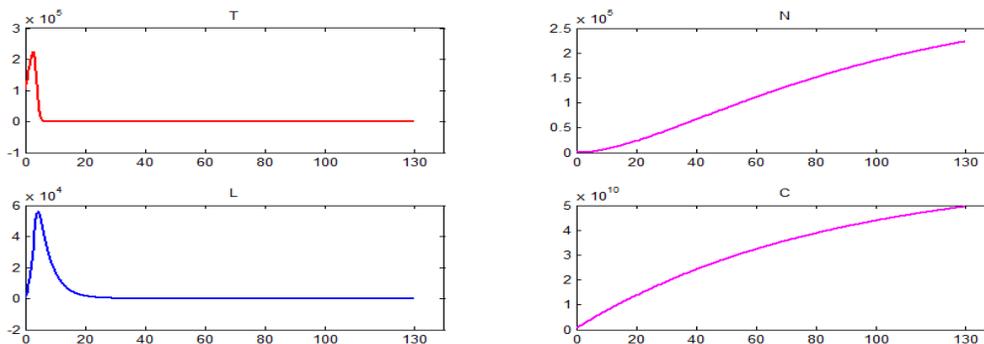


Figure 1: Initial conditions: 10^5 Tumor cells, 10^3 NK cells, 10 CD8+T cells, 6×10^8 circulating lymphocytes.

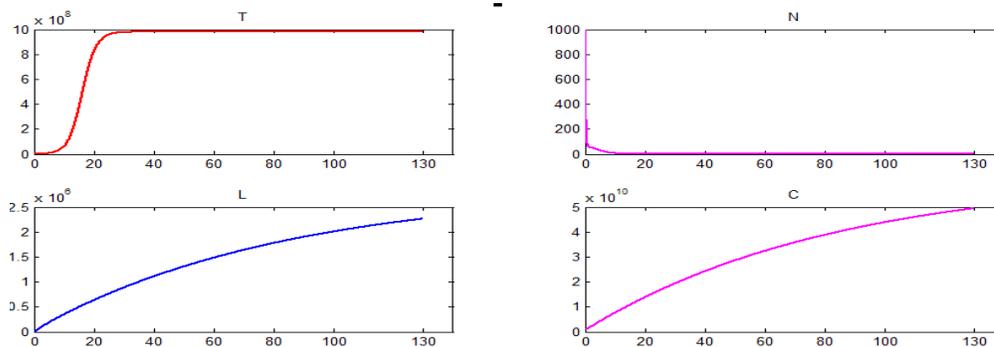


Figure 2: Initial conditions: 10^6 Tumor cells, 10^3 NK cells, 10 CD8+T cells, 6×10^8 circulating lymphocytes.

The innate immune is able to kill a tumor of size 10^5 cells (see figure 1), a size which in many cases is still considered to be below the threshold of clinical detectability in a human, although it's unable to kill a tumor size 10^6 cells (see figure 2) which grows to a dangerous level in the absence of treatment interventions. The body can't fight the virus alone. Parameters for these simulations are provided in Table 2.

4.2.2 Chemotherapy alone:

This experiment represents a situation in which the cancer is large enough considered potentially detectable and the immune system alone is unable to kill the tumor which imposes a treatment interventions. We examine pure chemotherapy for a tumor burden of 2×10^7 cells for 60 days then for 130 days.

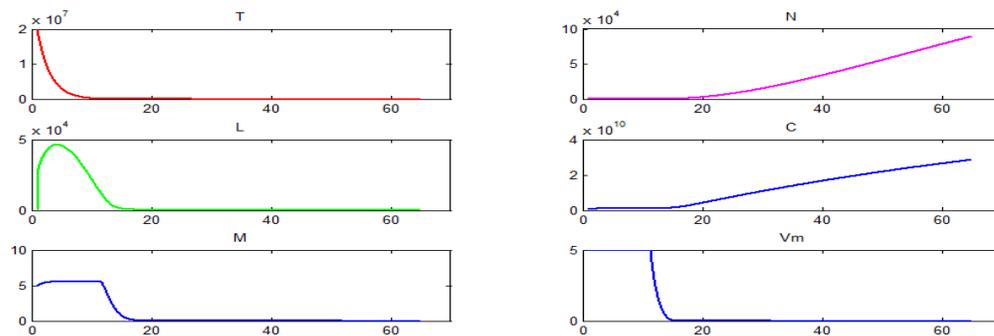


Figure 3: Initial conditions: 2×10^7 Tumor cells, 10^3 NK cells, 10 CD8+T cells, 6×10^8 circulating lymphocytes, V_M is the chemotherapy optimal control.

The chemotherapy treatment interventions given during the initial 20 days from 60 days of treatment is sufficient to eliminate a tumor of size 2×10^7 (Figure 3). Whene we ran the simulation for 130 days, the tumor decreases but survives

despite either chemotherapy treatments (Figure 4). The chemotherapy effectiveness may limited to short time of treatment. Parameters for these simulations are provided in Table 2.

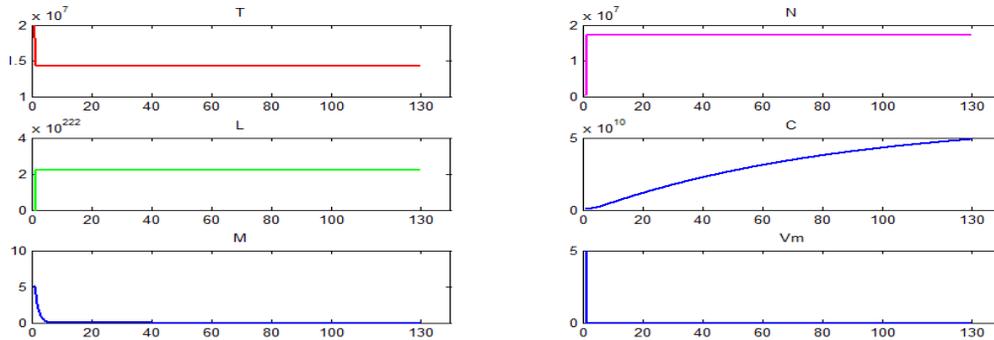


Figure 4: Initial conditions: 2×10^7 Tumor cells, 10^3 NK cells, 10 CD8+T cells, 6×10^8 circulating lymphocytes, V_M is the optimal control.

4.2.3 Immunotherapy alone:

In addition to pure chemotherapy treatments, we examine the effectiveness of pure immunother-

apy treatments with TIL and IL-2 injections for initial tumor size of 10^6 cells, then for tumor burden of 10^7 cells.

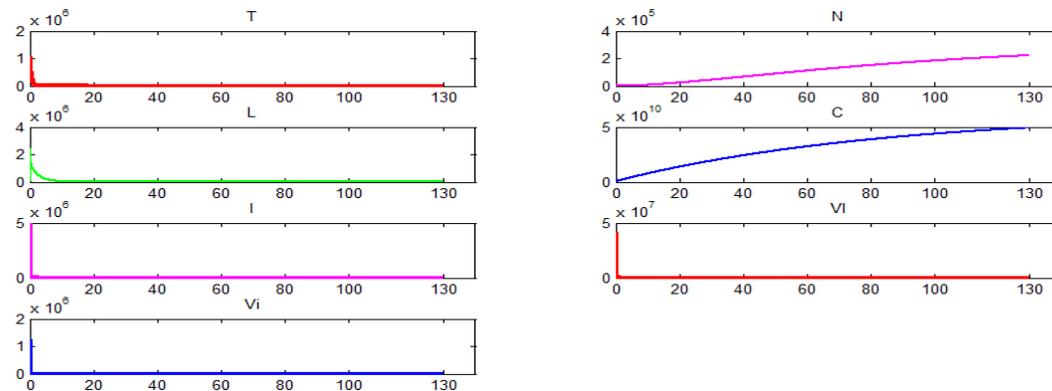


Figure 5: Initial conditions: 10^3 NK cells, 10 CD8+T cells, 6×10^8 circulating lymphocytes, 10^9 Tils, 5×10^6 IL-2. V_I (IL-2 therapy) and V_L (TIL therapy) are the optimal controls and are so small in value that it is barely visible in the graph.

The immunotherapy treatment interventions is sufficient to eliminate a tumor of size 10^6 (Figure 5). For tumor challenge of 10^7 cells, the tumor decreases and survives despite either

immunotherapy intervention (Figure 6). The immunotherapy effectiveness may limited to smaller tumor sizes. Parameters for these simulations are provided in Table 2.

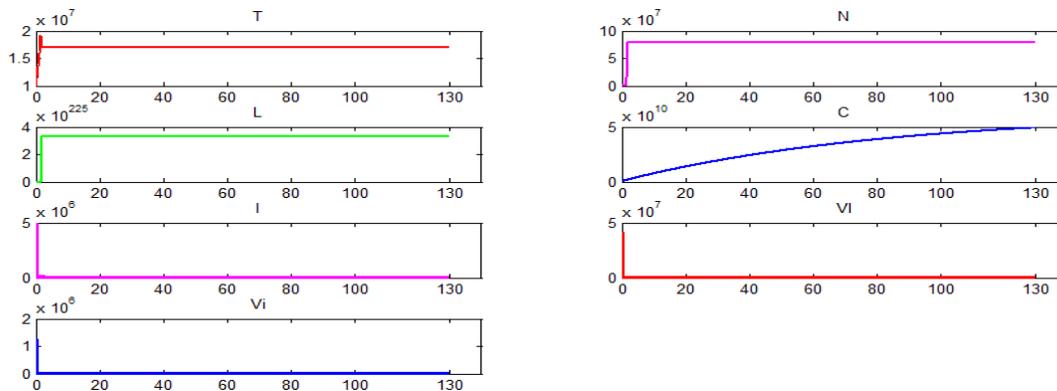


Figure 6: Initial conditions: 10^3 NK cells, 10 CD8+T cells, 6×10^8 circulating lymphocytes, 10^9 Tils, 5×10^6 IL-2, V_I and V_L are the optimal controls and are so small in value that it is barely visible in the graph.

4.2.4 Combination therapy:

We have presented cases for which chemotherapy alone or immunotherapy alone can kill a tumor, also we have presented situations in which these treatments in isolation are not sufficient to eliminate the cancer. Now we combine the separately unsuccessful therapies to examine the ef-

fectiveness of mixed therapy. We measure the patient's immunological health by the number of circulating lymphocytes in the body and do not allow the circulating lymphocytes to drop below a threshold where risk of infection may be too high. In our experiments, we chose that threshold to be the order of 10^8 cells (see,e.g.,[2]), we ran the simulation for 130 days.

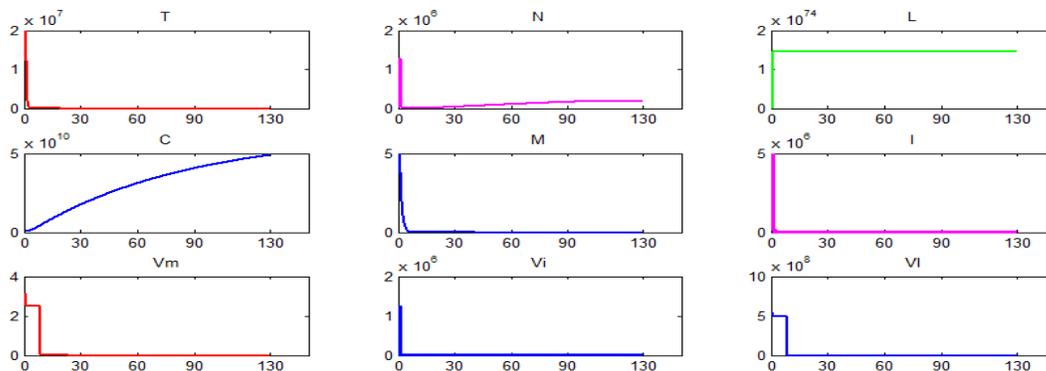


Figure 7: Initial conditions: 2×10^7 tumor cells, 10^3 NK cells, 10 CD8+T cells, 6×10^8 circulating lymphocytes, 10^9 Tils, 5×10^6 IL-2, V_M, V_I and V_L are the optimal controls. Parameters for these simulations are provided in Table 2.

The combination treatment with Til injections, IL-2 injections, and chemotherapy is now able to eliminate a tumor of 2×10^7 cells since the first week of treatment. The chemotherapy V_M and TIL therapy V_L dominate the treatment for the first 10 days of treatment, IL-2 therapy V_I

is so small in value it may be considered practically zero. All initial conditions and parameter values remain the same as in these previous experiments.

5 Conclusion

In this work we have used an existing model of cancer growth, immune response, and treatment that includes activated anticancer-cell transfer (TIL injections), and activation-protein injections (IL-2 injections) in combination with chemotherapy. Our development of combination immunotherapy-chemotherapy protocols demonstrates the following results:

The immune system can control small tumor, al-

though is not sufficient in treating the tumor with high size. Chemotherapy alone administered for short time is effective in killing the tumor. Immunotherapy alone effectiveness may limited to smaller tumor sizes, as is shown in figure 5-6. We use the cases for which chemotherapy alone or immunotherapy alone are not sufficient to kill the tumor, to show that the combination treatment (chemotherapy-immunotherapy) is now capable to eliminate tumor cells.

Eq	Term	Description
$\frac{dT}{dt}$	$aT(1-bT)$	Logistic tumor growth
	$-cNT$	NK-induced tumor death
	$-DT$	CD8+T cell-induced tumor death
	$-K_T(1 - e^{-M})T$	Chemotherapy-induced tumor death
$\frac{dN}{dt}$	eC	Production of NK cells from circulating lymphocytes
	$-fN$	Natural Killer breakdown
	$-pNT$	Natural killer death by exhaustion of tumor-killing
	$g \frac{T^2}{h+T^2} N$	The NK cell recruitment
	$-K_N(1 - e^{-M})N$	Chemotherapy-induced NK death
$\frac{dL}{dt}$	$-mL$	CD8+T cell breakdown
	$-qLT$	CD8+T cell death by exhaustion of tumor-killing resources
	$r_1 NT$	CD8+T cell stimulation by NK-lysed tumor cell debris
	$r_2 CT$	Interactions of the tumor with C cells , stimulate CD8+T production
	$\frac{P_I LI}{g_I + I}$	Stimulatory effect of IL-2((the cytokine interleukin-2)) on CD8+T cells
	$-K_L(1 - e^{-M})L$	Chemotherapy-induced CD8+T death
	$-\mu NL^2$	a quadratic death rate of CD8+T cell
	$j \frac{D^2 T^2}{k+D^2 T^2} L$	The CD8+T cell recruitment
$v_L(t)$	External Tils(tumor infiltrating lymphocyte) controllable	
$\frac{dC}{dt}$	α	a constant source rate
	$-\beta C$	Lymphocyte breakdown
	$-K_C(1 - e^{-M})C$	Chemotherapy-induced Lymphocyte death
$\frac{dM}{dt}$	$-\gamma M$	breakdown of chemotherapy medicine
	$v_M(t)$	External chemotherapy controllable
$\frac{dI}{dt}$	$-\mu_I I$	IL-2 breakdown
	$v_I(t)$	External IL-2 controllable

Table 1: The functional forms for each cell-interaction.

Parameter values

Estimated Value	Description	Source
$a = 4.31 \times 10^{-1}$	Tumor growth rate.	[26]
$b = 1.02 \times 10^{-9}$	1/b is tumor carrying capacity.	[26]
$c = 6.41 \times 10^{-11}$	Fractional (non)-ligand-transduced tumor cell kill by NK cells.	[26][27]
$d = 2.34$	Saturation level of fractional tumor cell kill by CD8+T cells. Primed with ligand-transduced cells, challenged with ligand-transduced cells.	[27]
$e = 2.08 \times 10^{-7}$	Fraction of circulating lymphocytes that become NK cells.	[28]
$l = 2.09$	Exponent of fractional tumor cell kill by CD8+T cells. Primed with ligand-transduced cells, challenged with ligand-transduced cells.	[27]
$f = 4.12 \times 10^{-2}$	Death rate of NK cells.	[28]
$g = 1.25 \times 10^{-2}$	Maximum NK cell recruitment rate by ligand-transduced tumor cells.	[26],[27]
$h = 2.02 \times 10^7$	Steepness coefficient of the NK cell recruitment curve.	[28]
$j = 2.49 \times 10^{-2}$	Maximum CD8+T cell recruitment rate. Primed with ligand-transduced cells, challenged with ligand-transduced cells.	[26],[27]
$k = 3.66 \times 10^7$	Steepness coefficient of the CD8+T cell recruitment curve.	[26],[27]
$m = 2.04 \times 10^{-1}$	Death rate of CD8+T cells.	[29]
$q = 1.42 \times 10^{-6}$	CD8+T cell inactivation rate by Tumor cells.	[28]
$p = 3.42 \times 10^{-6}$	NK cell inactivation rate by Tumor cells.	[26]
$s = 8.39 \times 10^{-2}$	Steepness coefficient of the Tumor-(CD8+T cell) lysis term D. Primed with ligand-transduced cells, challenged with ligand-transduced cells.	[27]
$r_1 = 1.10 \times 10^{-7}$	Rate at which CD8+T cells are stimulated to be produced as a result of tumor cells killed by NK cells.	[29][30]
$r_2 = 6.50 \times 10^{-11}$	Rate at which CD8+T cells are stimulated to be produced as a result of tumor cells interacting with circulating lymphocytes.	[1]
$u = 3.00 \times 10^{-10}$	Regulatory function by NK-cells of CD8+T-cells.	[1]
$K_T = 9.00 \times 10^{-1}$	Fractional tumor cell kill by chemotherapy.	[31]
$K_N = K_L = K_C = 6 \times 10^{-1}$	Fractional immune cell kill by chemotherapy.	[31]
$\alpha = 7.50 \times 10^8$	Constant source of circulating lymphocytes.	[34,35]
$\beta = 1.20 \times 10^{-2}$	Natural death and differentiation of circulating lymphocytes.	[34,35]
$\gamma = 9.00 \times 10^{-1}$	Rate of chemotherapy drug decay.	[33]
$p_I = 1.25 \times 10^{-1}$	Maximum CD8+T-cell recruitment rate by IL-2.	[3]
$g_I = 2.00 \times 10^7$	Steepness of CD8+T-cell recruitment curve by IL-2.	[3]
$\mu_I = 1.00 \times 10^1$	Rate of IL-2 drug decay.	[3]

Table 2: Estimated parameter values.

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