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Mathematical Model of Cancer Treatments Using Immunotherapy, Chemotherapy and Biochemotherapy

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Abstract. In this paper, mathematical model of cancer treatments have been presented and analyzed using coupled ordinary differential equations (ODEs). This model describes cancer growth on a cell population level with combination immunotherapy and chemotherapy treatments are often called biochemotherapy. This model also describes the effect of tumor infiltrating lymphocytes (TIL), interleukin-2 (IL-2) and interferon alpha (INF-α) on dynamics of tumor cells under the influence of immunotherapy, chemotherapy and biochemotherapy. Through this mathematical model, numerical simulations of immunotherapy, chemotherapy and biochemotherapy for some cases such as variation of tumor size and variation of parameter among patient 9 and patient 10 were presented. Our result shown that for parameter set patient 9 and patient 10, the biochemotherapy more effective than the immunotherapy and chemotherapy.

Mathematics Subject Classification: 35F25, 37N25, 92C50

Keywords: ordinary differential equations, immunotherapy, chemotherapy, biochemotherapy, tumor infiltrating lymphocytes (TIL), interleukin-2 (IL-2), interferon alpha (INF-α)

1. Introduction

Cancer is the uncontrolled growth of abnormal cells in the body [1, 14]. These three malignant properties of cancer differentiate malignant tumors from benign tumors, which do not grow uncontrollably, directly invade locally, or

metastasize to regional lymph nodes or distant body sites like brain, bone, liver, or other organs [1].

The Cancer Research Institute reports that in 1995, an estimated 1.252.000 cases were diagnosed, with 547.000 deaths in the United States alone. With new techniques for detection and treatment of cancer, the relative survival rate has now risen to 54 percent [4]. Cancer causes 1 in 8 deaths worldwide and is rapidly becoming a global pandemic. According to the International Agency for Research on Cancer, there were 12.7 million new cancer cases in 2008. If rates don't change, the global cancer burden is expected to nearly double to 21.4 million cases and 13.5 million deaths by 2030 [17]. It is significant to explore new treatment techniques, in order to reduce the rate of mortality due to cancer in the future. The most common cancer therapy have developed to fight cancer is chemotherapy and radiotherapy. The basic idea behind chemotherapy is to kill cancerous cells faster than healthy cells, while radiotherapy is using the radiation to kill cancerous cells.

This paper is based on recent works [14, 5] where a system of coupled ordinary differential equations has been proposed to model growth of cell population levels in presence of tumor cells and as well as a combined immunotheraphy and chemotheraphy are often called biochemotherapy. In section 2, modified model is discussed. Next section, we presented parameters value for run simulation of the model from previous works [14, 5, 10]. Finally, section 4 presented numerical result and the last section we summarized and discussed our conclusion.

1.1. Immunotherapy

Immunotherapy is also called as *biologic therapy* or *biotherapy*. Immunotherapies are quickly becoming an important component in the multi-pronged approaches being developed to treat certain forms of 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 [5]. There are known three main categories of immunotherapy: immune response modifiers (cytokines), monoclonal antibodies and vaccines [18]. Cytokines are chemical made by immune system cells. They have an important role in regulating the growth and activity of other immune system cells and blood cells. The most commons cytokines are interleukins-2 (IL-2) and interferon alpha (INF-α). Interleukins-2 is the only drug approved in the United States. It is also approved in many other countries. But IL-2 isn't just a drug. IL-2 is a natural part of your immune system, a messenger protein called a cytokine which activates parts of your immune system. IL-2 does not kill tumor cells directly like classical chemotherapy. Instead, IL-2 activates and stimulates the growth of immune cells, most importantly T-Cells, but also Natural Killer Cells (NK Cells), both of which are capable of destroying cancer cells directly [8].

Interferon alpha (INF-α) has a similar response rate to many IL-2 regimens, including high dose IL-2, however responses are much less likely to be either complete or lasting with one major proponent characterizing response duration of

more than two years as rare [8]. In addition, when one of the randomized trials with the best results was reanalyzed excluding the responders that didn't change the results [19], suggesting its benefits are unrelated to the transient responses, so that unlike high dose IL-2, response does not translate to long-term benefit. We don't find no real evidence that INF-α creates long term survivals. Benefit from INF-α is most likely due to a modest slowing of tumor growth in many patients. It has direct effects on the proliferation rate of cancer cells, and also has anti-angiogenic effects which could account for this kind of benefit.

1.2. Chemotherapy

Chemotherapy is the administration of one or more drugs aimed to kill tumor cells in which growth rate are faster than normal cells. Chemotherapy drugs can be divided into two categories. They are cell cycle specific and cell cycle nonspecific. Cell cycle specific drugs can only kill cells in certain phases of the cell cycle, while non-specific drugs can kill cells in any phase of cell division [16]. The distinction between specific and non-specific chemotherapy drugs is important in considering how a tumor population responds to the drug. Most commonly, chemotherapy acts by killing cells that divide rapidly, one of the main properties of most cancer cells. This means that it also harms cells that divide rapidly under normal circumstances is cells in the bone marrow, digestive tract and hair follicles. This results in the most common side effects of chemotherapy is myelosuppression, mucositis, and alopecia [3].

1.3. Biochemotherapy

The use of immunotherapy in conjunction with chemotherapy is known as biochemotherapy [11]. This treatment maybe use several kinds of drugs to kill cancer, these are administered at differing times on a set schedule. In essence, biochemotherapy is a treatment regimen that combines chemotherapy drugs with two active biological agents, IL-2 and INF-α. Interferon can be combined with other drugs during the treatment so that model interaction of immunotherapy and chemotherapy created more effective treatments.

2. Mathematical Model

This mathematical model is based on the de Pillis's model [5] and Isaeva and Osiopov's model [10]. de Pillis's model describes effect interlukin2 (IL-2), tumor infiltrating lymphocytes (TIL), and chemotherapy on tumor-immune interaction while Isaeva and Osiopov's model describes effect IL-2, INF-α and chemotherapy on tumor-immune interaction. In order to investigate how the effect of IL-2, INF-α and TIL in the presence of treatment components such as immunotherapy and chemotherapy, we modified the model has been developed by de Pillis with involve the presence of INF-α. For the sake of completeness, we outline the assumptions of the original model [5] here:

- Tumor grows logistically in the absence of an immune response.

- Both NK and CD8+ T-cells are capable of killing tumor cells.
- Both NK and CD8+ T-cells respond to tumor cells by expanding and increasing cytolytic activity.
- There are always present NK cells in the body, even when no tumor cells are present.
- As part of the specific immune respone, active tumor-specific CD8+ T-cells are only present in large numbers when tumor cells are present.
- NK and CD8+ T-cells eventually become inactive after some number of encounters with tumor cells.
- Tumor cells inactivation due to there are present INF-α.

We added assumptions are used in the development of therapeutic terms:

- Circulating lymphocyte levels can be used as a measure of patient health.
- The fraction of the tumor population killed by chemotherapy depends on the amount of drug in the system. The fraction killed has a maximum less than one, since only tumor cells in certain stages of development can be killed by chemotherapy.
- A fraction of NK cells, CD8+ T-cells, and circulating lymphocytes are also killed by chemotherapy, according to a similar fractional kill curve.
- NK and T cells are components of the process of stimulation and elimination of activated effector cells, a model simplification meant to reflect the self-regulatory nature of the immune system.

There are four populations and three drug concentration in this model. They are tumor cells population $T(t)$, natural killer cells $N(t)$, CD8+T cells $L(t)$, circulating lymphocytes cell $C(t)$, concentration of IL-2 $I(t)$, concentration of INF-α $I_\alpha(t)$, and concentration of chemotherapy drug $M(t)$. The model modified expressed in the following coupled ordinary differential equations below:

$$\frac{dT}{dt} = aT(1-bT) - cNT - DT - K_T(1-e^{-M})T - c'TL \tag{1}$$

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

$$\frac{dL}{dt} = -mL + j\frac{D^2T^2}{k+D^2T^2}L - qLT + (r_1N + r_2C)T - uNL^2 - K_L(1-e^{-M})L + \frac{piLI}{gi} + v_L(t) \tag{3}$$

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

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

$$\frac{dI}{dt} = -\mu iL - j'LI - k'TI + v_I(t) \tag{6}$$

$$\frac{dI_\alpha}{dt} = V_\alpha(t) - gI_\alpha \tag{7}$$

where $D = d\dfrac{(L/T)^l}{s+(L/T)^l}$ (8)

$$c' = c_{CTL}\left(2 - e^{-\frac{I_\alpha}{I_{\alpha 0}}}\right) \quad (9)$$

The system of coupled ordinary differential equations (1)-(9) is as follow. Eventually, the system consists the terms governing the population kinetics must take into account a net growth term for each population, term of the fractional cell kill, term of per cell recruitment, term of cell inactivation and term of external intervention with medication. We discussed more detail in Section 2.1 to Section 2.5.

2.1 Growth and Death Terms

Term $aT(1-bT)$ represents that tumor growth is assumed to be logistic, based on data gathered from immunodeficient mice [6]. Term $eC - fN$ represents the growth of NK cells. Cell growth for CD8+ T cells consists only of natural death rates, since no CD8+ T Cells are assumed to be present in the absence of tumor cells CD8+ T cells decrease express term 1, $-mL$ in equation (3). Term $\alpha - \beta C$ in equation (4) represents that circulating lymphocytes are generated a constant rate and that each cell has a natural lifespan. We assume that chemotherapy drug will decays exponentially in the body at constant rate. This gives us the term, $-\gamma M$ in equation (5). Similarly, the immunotherapy drug, Interleukin-2 (IL-2) and interferon INF-α, decays exponentially, $-\mu iL - j'LI - k'TI$ in equation (6) and $-gI_\alpha$ in equation (7). Term, $-jLI$, represents the consumption rate of IL-2 [10]. It was found that inhibition of IL-2 results from an accumulation of immune-suppressing substances, prostaglandins. Their number is proportional to the tumor population. Prostaglandins suppress of the production of IL-2 and can directly destroy it molecules [10]. While term, $-kTI$, express the IL-2 destruction rate by prostaglandins [10].

2.2 Fractional Cell Kill

The fractional cell kill terms for N and L are taken from de Pillis [5] while fractional cell kill terms for I_α and L are taken from Isaeva [10]. These fractional cell kill terms represent negative interactions between two populations. The interaction between tumor and NK cells takes the form $-cNT$ in equation (1). Tumor inactivation by CD8+ T-cells has the form $d\dfrac{(L/T)^l}{s+(L/T)^l}T$, let

$D = d\dfrac{(L/T)^l}{s+(L/T)^l}$. Thus, we have DT in equation (2). To describe the effect of chemotherapy, to our model added a chemotherapy drug kill terms to each of the cell populations. Chemotherapeutic drugs are only effective during certain phases of the cell division cycle, so we use a saturation term $I-e^{-M}$ for the fractional cell kill. The chemotherapy drug kill term is represented by $K_i\left(1-e^{-M}\right)i$ for i = *T, N, L, C*. In addition, our model includes an activated CD8+ T-cells boost from the immunotherapy drug, IL-2. The presence of IL-2 stimulates the production of CD8+ T-cells, and represented by $\dfrac{p_i LI}{g_i}$, modification from [12].

2.3 Recruitment

The recruitment term of NK cell has form $g\dfrac{T^2}{h+T^2}N$ in equation (2). There are three factor caused by presence the CD8+ T-cells. The first impact is interaction CD8+ T-ceels and tumor represented by $j\dfrac{D^2T^2}{k+D^2T^2}L$ in equation (3). The second impact is caused by the debris from tumor cells lysed by NK cells. This recruitment term is represented by r_1NT in equation (3). The last impact is the presence of tumor cells to produce mores CD8+ T-cells. Recognition of the presence of the tumor is proportional to the average number of encounter between circulating lymphocytes and tumor. Hence, the term of recruitment is represented by r_2CT in equation (3).

2.4 Inactivation Terms

The interaction between INF-α, CD8+ T-cells and tumor takes the form $c' = c_{CTL}\left(2-e^{-I_\alpha/I_{\alpha 0}}\right)$, where c_{CTL} is a rate of tumor cells inactivation by CTL. This agrees with the fact that INF-enhances immune-mediated anti-tumor responses by increasing expression of MHC molecules on tumor cells, thus enhancing their recognition by CTL [20]. There are three inactivation term for NK cell and CD8+ T-cells in this model. The first and second terms are $-pNT$ in equation (2) and $-qLT$ in equation (3). These terms represent inactivation of NK cell and CD8+ T-cells after interact with tumor cell several times and ceases to be effective. The third inactivation term, $-uNL^2$ in equation (3), describes the NK cell regulation of CD8+ T cells, which occurs when there are very high levels of activated CD8+ T-cells without responsiveness to cytokines present in the system.

2.5. Drug Intervention Terms

In this model, there are treatment drugs such as IL-2, TIL and INF-α in immunotherapy, chemotherapy and biochemotherapy. The injection of IL-2, TIL, INF-α and chemotherapy drug to the body are represented by $v_I = v_I(t)$, $v_L = v_L(t)$, $v_\alpha = v_\alpha(t)$ and $v_M = v_M(t)$, respectively. All of these terms are function of time that describes amount of drug and injection time to the patient.

3. Parameter Derivation

To complete the simulation and analysis, it necessary to obtain accurate parameters. System parameters are very sensitive to the choice of parameters. In fact, the parameter sets vary not only for specific cancer type but also from one individual to another. In our simulation, we only consider and focus to two patient, patient 9 and patient 10. Most of parameters in this work obtained from Pillis's work [5] and also several parameters (c_{CTL}, *j, k*) were taken from Isaeva and Osipov's work [10]. Table 1 describes all parameters to run simulation our model for two patients such as patient 9 and patient 10.

Table 1: Parameter values used for numerical simulation

Patient 9	Patient10	Units	Description	Source
$a = 4.31 \times 10^{-1}$	$a = 4.31 \times 10^{-1}$	day^{-1}	*Tumor growth rate*	[6]
$b = 1.02 \times 10^{-9}$	$b = 1.02 \times 10^{-9}$	$cell^{-1}$	*1/b is tumor carrying capacity*	[6]
$c = 6.41 \times 10^{-11}$	$c = 6.41 \times 10^{-11}$	$day^{-1} \cdot cell^{-1}$	*Fractional (non) ligand transduced tumor cell kill by NK cells*	[6], [7]
$d = 2.34$	$d = 1.88$	day^{-1}	*Saturation level of fractional tumor cell kill by CD8+ T Cells. Primed with ligand-transduced cells, challenged with ligand-transduced*	[7]
$e = 2.08 \times 10^{-7}$	$e = 2.08 \times 10^{-7}$	day^{-1}	*Fraction of circulating lymphocytes that became NK cells*	[13]
$l = 2.09$	$l = 1.81$	dimensionless	*Exponent of fractional tumor cell kill by CD8+ T cells. Fractional tumor cell kill by chemotherapy*	[7]
$f = 4.12 \times 10^{-2}$	$f = 4.12 \times 10^{-2}$	day^{-1}	*Date rate of NK cells*	[6]
$g = 1.25 \times 10^{-2}$	$g = 1.25 \times 10^{-2}$	day^{-1}	*Maximum NK cells recruitment by ligand-transduced tumor cells*	[13]
$h = 2.02 \times 10^{7}$	$h = 2.02 \times 10^{7}$	$cell^{2}$	*Steepness coefficient of the NK cell recruitment curve*	[13]
$j = 2.49 \times 10^{-2}$	$j = 2.49 \times 10^{-2}$	day^{-1}	*Maximum CD8+ T cell recruitment rate. Primed with ligand-transduced cells*	[6], [7]
$k = 3.66 \times 10^{7}$	$k = 5.66 \times 10^{7}$	$cell^{2}$	*Steepness coefficient of the CD8+ T cell recruitment curve*	[6], [7]
$m = 2.04 \times 10^{-1}$	$m = 9.12$	day^{-1}	*Death rate of CD8+ T cells*	[21]
$q = 1.42 \times 10^{-6}$	$q = 1.42 \times 10^{-6}$	$day^{-1} \cdot cell^{-1}$	*CD8+ T cell inactivation rate by tumor cells*	[13]
$p = 3.42 \times 10^{-6}$	$p = 3.59 \times 10^{-6}$	$day^{-1} \cdot cell^{-1}$	*NK cell inactivation rate by tumor cells*	[7]

$s = 8.39 \times 10^{-2}$	$s = 5.12 \times 10^{-1}$	dimensionless	*Steepness coefficient of tumor – (CD8+ T cell) lysis term D. Primed with ligand-transduced cells, challenged with ligand-transduced.*	[6]
$r_1 = 1.10 \times 10^{-7}$	$r_1 = 1.10 \times 10^{-7}$	$day^{-1} \cdot cell^{-1}$	*Rate of which CD8+ T cells are stimulated to be produced as a result a tumor cells killed by NK cells*	[21]
$r_2 = 6.50 \times 10^{-11}$	$r_2 = 6.50 \times 10^{-11}$	$cell^{-1} \cdot day^{-1}$	*Rate of which CD8+ T cells are stimulated to be produced as a result a tumor cells interaction with circulating lymphocytes*	-
$u = 3.00 \times 10^{-10}$	$u = 3.00 \times 10^{-10}$	$cell^{-2} \cdot day^{-1}$	*Regulatory function by NK cells of CD8+ T cells*	-
$\alpha = 7.50 \times 10^{8}$	$\alpha = 5.00 \times 10^{8}$	cell · day–1	*Constant source of circulating lymphocytes*	[9]
$\beta = 1.20 \times 10^{-2}$	$\beta = 8.00 \times 10^{-3}$	day^{-1}	*Natural death and differentiation of circulating lymphocytes*	[9]
$\gamma = 9.00 \times 10^{-1}$	$\gamma = 9.00 \times 10^{-1}$	day^{-1}	*Rate of chemotherapy drug decay*	[2]
$p_i = 1.25 \times 10^{-1}$	$p_i = 1.25 \times 10^{-1}$	day^{-1}	*Maximum CD8+ T cell recruitment curve by IL-2*	[12]
$g_i = 2.00 \times 10^{2}$	$g_i = 2.00 \times 10^{2}$	$cells^{2}$	*Constant*	-
$\mu_i = 1.00 \times 10^{1}$	$\mu_i = 1.00 \times 10^{1}$	day^{-1}	*Rate of IL-2 drug decay*	[12]
$c_{CTL} = 4.4 \times 10^{-9}$		$cell^{-1}day^{-1}$	*Rate of tumor cells inactivation by CD8+ T cells*	[10]
$g' = 1.7$		day^{-1}	*Decay rate of therapeutic INF-*α	[10]
$j' = 3.3 \times 10^{-9}$		$cell^{-1}day^{-1}$	*Rate consumption IL-2 by CD8+ T cells*	[10]
$k' = 1.8 \times 10^{-8}$		$cell^{-1}day^{-1}$	*Inactivation of IL-2 molecules by prostaglandins*	[10]
$I\alpha_0$		Units	*Initial Interferon*	[10]

4. Analysis and Numerical Simulation

In this section, we simulated the model using set of parameters in Table 1. Firstly, we simulated model tumor growth without treatment. This simulation represents immune system respone to tumor size 1×10^{6} tumor cells. The first simulation we denoted as an initially immune system with 1×10^{5} natural killer cells, 1×10^{2} CD8+ T-cells, and 6×10^{10} circulating lymphocytes. As shown in Figure 1A, the innate immune system is sufficiently strong to control tumor cells. However, when simulation with initial condition set to 1×10^{3} natural killer cells, 10 CD8+ T-cells, and 6×10^{8} circulating lymphocytes, are shown in Figure 1B. This result represents that the immune system is weakened. Next, we simulated a variety of cancer treatment that is immunotherapy, chemotherapy, and biochemotherapy for patient 9 and patient 10.

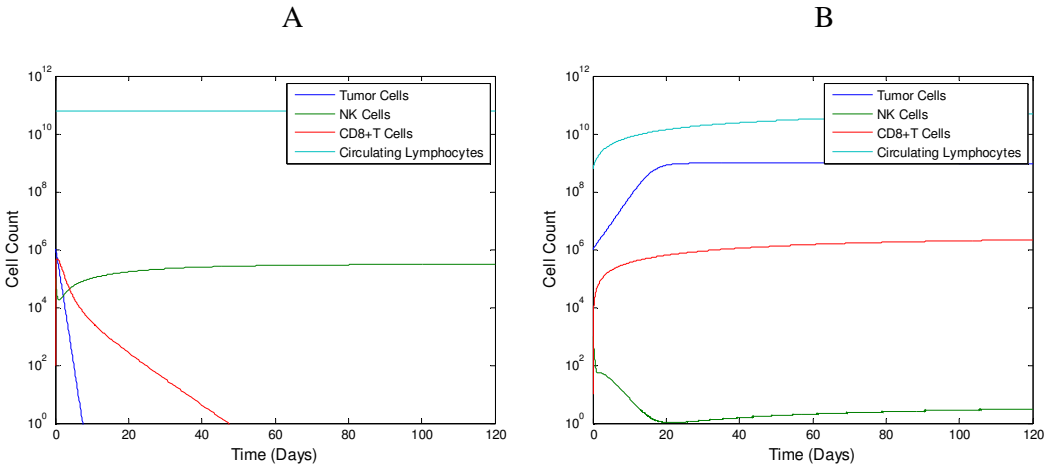

Figure 1. Simulations of the immune system respone to tumor. A: The healthy immune system effectively kills tumor cells. Initial Conditions: 1×10^{6} tumor cells, 1×10^{5} natural killer cells, 1×10^{2} CD8+ T-cells, and 6×10^{10} circulating lymphocytes. B: The depleted immune system fails to kill tumor cells when left untreated. Initial Conditions: 1×10^{6} tumor cells, 1×10^{3} natural killer cells, 10 CD8+ T-cells, and 6×10^{8} circulating lymphocytes.

4.1. Treatment for Patient 9

In this subsection, we simulated immunotherapy, chemotherapy, and biochemotherapy for parameter patient 9. This simulation we denoted as an initially immune system with 1×10^{5} natural killer cells, 1×10^{2} CD8+ T-cells, and 6×10^{10} circulating lymphocytes. Firstly, we simulated model tumor growth with immunotherpy treatment. In this simulation, we injected IL-2, INF-α and TIL. IL-2 is administered in 6 pulses at strength 5×10^{6} on day 8 to day 12, 10^{9} TILs are administered on day 6 to 7, and $I_{\alpha}(t)$ = 5 MU administered for four days in a 10 day cycle. As shown in Figure 2A, immunotherapy is sufficiently strong to control 1×10^{6} tumor cells. However, when tumor size increased to 7×10^{6} cells, this treatment is not effective at treating the tumor of size 7×10^{6} cells, is shown in Figure 2B. Secondly, we simulated model tumor growth with chemotherapy treatment. This treament with nine one-day chemotherapy doses of strength $v_{M}(t)$ = 5 every 10 days. This treatment is sufficiently strong to control 1×10^{6} tumor cells but not able to eliminate 7×10^{6} tumor cells, are shown in Figure 3A and Figure 3B. The last is simulation of biochemotherpy treatment. In this simulation, we injected immunotherapy and chemotherapy together. As shown in Figure 4, this result shown that biochemotherapy able to eliminate the tumor cells until size 1×10^{7}.

4.2.Treatment for Patient 10

In this subsection, we examined these treatment simulations different with parameters of patient 9, so we changed patient specific parameters extracted from

Rosenberg's study and run similar simulations with the parameters for patient 10 [7]. These parameters are given in Table 1. This simulation we denoted as an initially immune system with 1×10^{5} natural killer cells, 1×10^{2} CD8+ T-cells, and 6×10^{10} circulating lymphocytes. The result of numerical simulations is shown in Figure 5. Result of simulation treatment immunotherapy and chemotherapy for patient 10 shown in Figure 5A and Figure 5B. This treatment is not effective at treating the tumor of size 1×10^{6} cells. This size tumor could be eliminated by biochemotherapy, as is shown in Figure 5C. Instead, biochemotherapy could be kill tumor cells until size 1×10^{7}. This simulation result is shown in Figure 5D.

A B

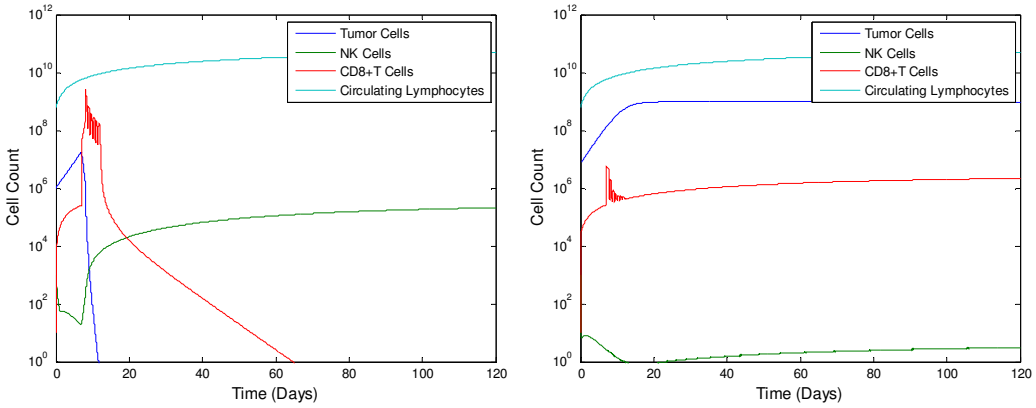

Figure 2. Simulations of immunotherapy for patient 9 with initial conditions: 1×10^{3} natural killer cells, 10 CD8+ T-cells, and 6×10^{8} circulating lymphocytes. 10^{9} TILs are administered from day 7 through 8. IL-2 is administered in 6 pulses at strength 5×10^{6} from day 8 to day 12. INF-α is administered in 4 pulses at strength 5 from day 1 to day 34. A: 1×10^{6} tumor cells. B: 7×10^{6} tumor cells.

A **B**

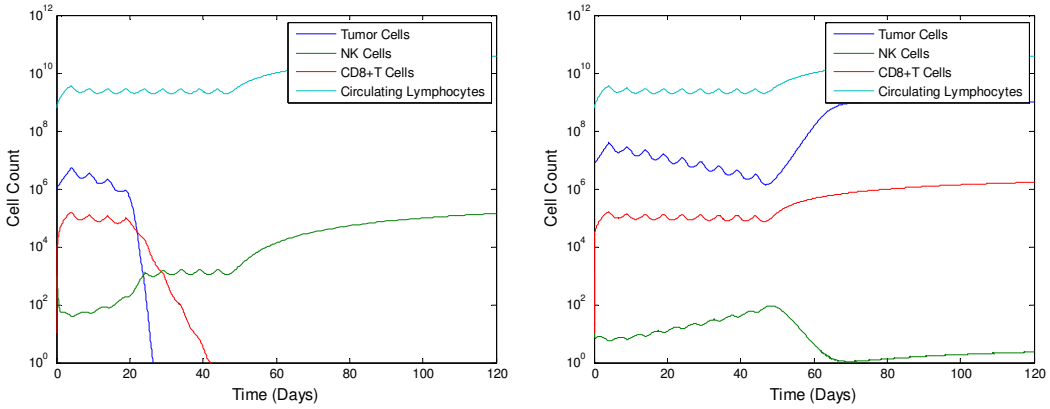

Figure 3. Simulations of chemotherapy for patient 9 with initial conditions: 1×10^{3} natural killer cells, 10 CD8+ T-cells, and 6×10^{8} circulating lymphocytes. Drug administration patternis nine doses, strength $v_M(t)$ = 5.1 day per dose on a 5 day cycle. A: 1×10^{6} tumor cells. B: 7×10^{6} tumor cells.

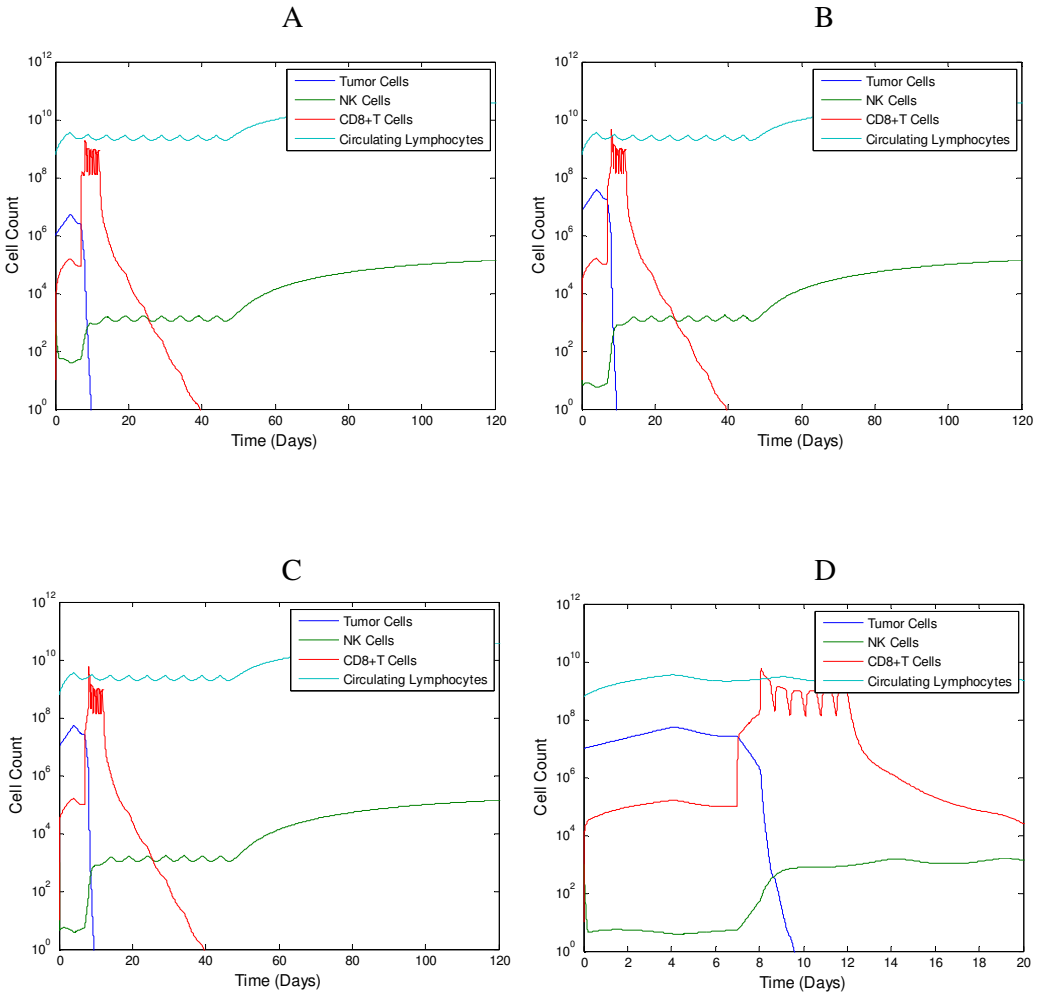

Figure 4. Simulations of biochemotherapy for patient 9 with initial conditions: 1×10^{3} natural killer cells, 10 CD8+ T-cells, and 6×10^{8} circulating lymphocytes. 10^{9} TILs are administered from day 7 through 8. IL-2 is administered in 6 pulses at strength 5×10^{6} from day 8 to day 12. INF-α is administered in 4 pulses at strength 5 from day 1 to day 34. Drug administration patternis nine doses, strength $v_M(t)$ = 5.1 day per dose on a 5 day cycle. A: 1×10^{6} tumor cells. B: 7×10^{6} tumor cells. C: 1×10^{7} tumor cells. D: more detail from figure C.

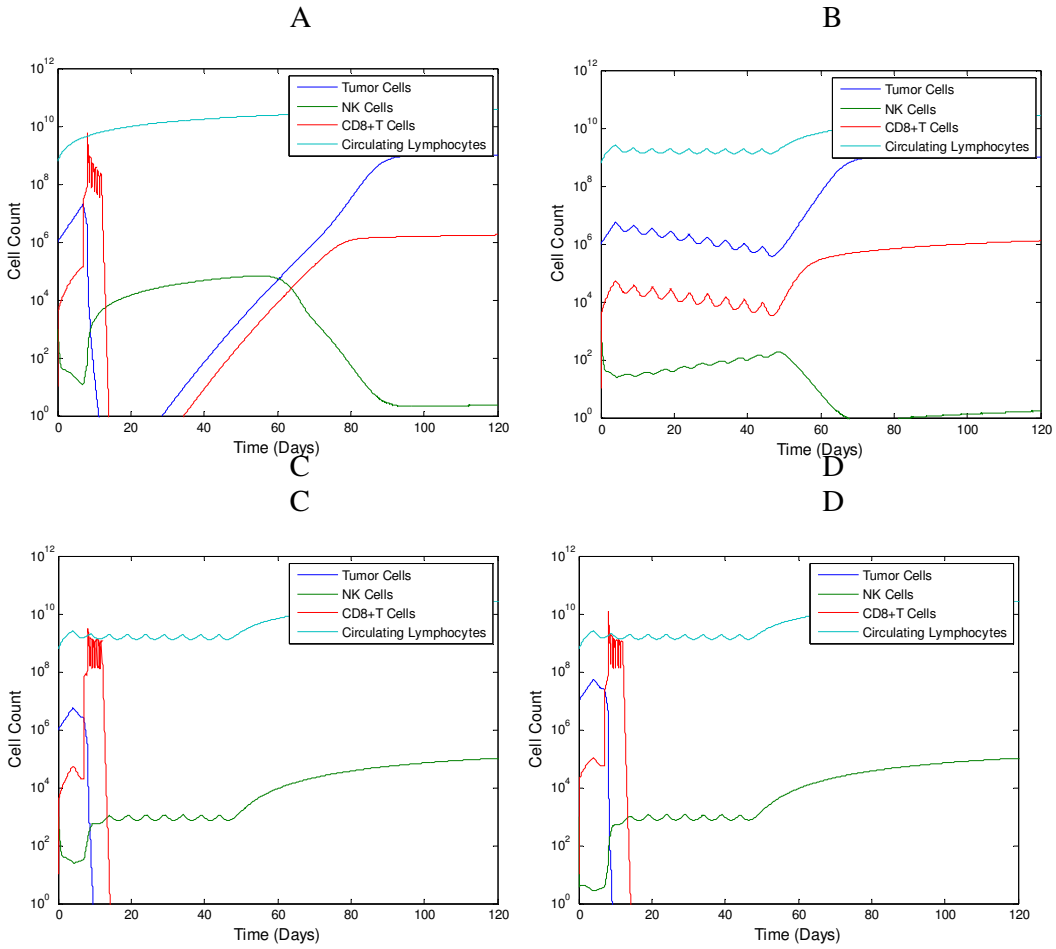

Figure 5. Simulations of biochemotherapy for patient 10 with initial conditions: 1×10^3 natural killer cells, 10 CD8+ T-cells, and 6×10^8 circulating lymphocytes. 10^9 TILs are administered from day 7 through 8. IL-2 is administered in 6 pulses at strength 5×10^6 from day 8 to day 12. INF-α is administered in 4 pulses at strength 5 from day 1 to day 34. Drug administration patternis nine doses, strength $v_M(t)$ = 5.1 day per dose on a 5 day cycle. A: immunotherapy with 1×10^6 tumor cells. B: chemotherapy with 1×10^6 tumor cells. C: bichemotherapy with 1×10^6 tumor cells. D: bichemotherapy with 1×10^7 tumor cells.

5. Discussion and Conclusion

We applied a model developed by de Pillis's *et al*. [5] in the form of a system coupled ordinary differential equation. Then we extended this model to include the presence of INF-α. The model used to investigate effect of TIL, IL-2, and INF-α on dynamics of tumor cells under the influence of immunotherapy,

chemotherapy and biochemotherapy. Our simulation shown that the treatments play important role to remission or even to kill the tumor cells completely.

In the first our simulation, we examine an initial size of tumor cells is 1×10^6. This simulation shows a that the immune system has not become activated to kill the tumor cells. For this tumor, immune system strength is very important in determining whether or not the immune system alone can kill a tumor. The first simulation specifies what we will denote as an initially immune system with 1×10^5 natural killer cells, 1×10^2 CD8+ T-cells, and 6×10^{10} circulating lymphocytes [5]. As seen in Figure 1A, the innate immune response is sufficiently strong to control the tumor. However, when the immune system is weakened, a tumor of the same size grows to a dangerous level in the absence of treatment interventions. Simulated results for this weakened immune case, with initial conditions set to 1×10^3 natural killer cells, 10 CD8+ T-cells, and 6×10^8 circulating lymphocytes, are shown in Figure 1B.

For the case patient 9, our simulation shows that immunotherapy and chemotherapy able to kill 1×10^6 tumor cells, are pictured in Figure 2A and Figure 3A. From this simulation we known that immunotherapy more quickly to kill tumor cells than chemotherapy. However, both of these treatment is not effective when the tumor size increased to 7×10^6 cells, are pictured in Figure 2B and Figure 3B. Next, simulation of biochemotherapy are shown in Figure 4. Based from this figure, this treatment is successfully killing the tumor cells 1×10^6 until 1×10^7. Our result shown that biochemotherapy is more effective treatment than immunotherapy and chemotherapy.

Similiar with the case patient 9, our simulation for patient 10 shown that biochemotherapy able to kill tumor cells 1×10^6 until 1×10^7, are shown in Figure 5C and Figure 5D. But immunotherapy and chemotherapy is unable to kill tumor cells 1×10^6. As shown in Figure 5A, immunotherapy cause reduction the tumor cells until clean completely on day 10 and then relapsed on day 30 to level dangerous, instead chemotherapy is unable to kill this tumor size, as shown in Figure 5B.

This work is still necessary to investigation on how the effect of drug injection for another cells or how the effect another cytokines such as IL-4, IL-10 and IL-12 in future.

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