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Mathematical Model Of Tumor Therapy Using Biochemotherapy

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ABSTRACT

In this paper, we analyzed and simulated a mathematical model of therapy tumor using biochemotherapy in the form of a system ordinary differential equations (ODEs). This model describes tumor growth on a cell population in presence treatment. We analyzed the system ODE dynamics by determining equilibrium point, stability and bifurcation point. The system analysis are useful to understanding the parameter that play important role in system ODEs and also to help guide development of the best startegy of tumor therapy. Numerical simulation of variation therapy tumor using human set parameters are presented. We obtain therapy tumor with biochemotherapy has more benefit effective, since this treatment given little drug so that more safety and fewer negative side effect to patient.

Key words: bifurcation point, biochemotherapy, equilibrium point, ordinary diferential equations (ODEs), stability.

Introduction

Tumor begins a single cell mutates in such a way that lead to uncontrolled growth. A tumor cell can mutate in two important ways: the growth suppressing signals telling cells not divide are turned off or the signals telling cells to begin dividing are left on continuously. (W.W. Gibbs, 2003)Thus, tumor cells are always dividing and depleting large amounts of nutrients necessary for part of the body to function. If tumor mass grows large enough, it can cause illness and eventually death in their host.

There are many possible approaches to treating tumor, one popular approach is biochemotherapy. Biochemotherapy is treatment cancer using immunotherapy (biologic therapy or biotherapy) in conjunction with chemotherapy. The goal of biochemotherapy is to kill tumor cells at a higher rate than normal cells by administration of one or more drug and enhancing the effectiveness the immune system (L.G. de Pillis, 2006; J. Moore, 2007). The drug chemotherapy is typically administered intravenously. High doses of drug chemotherapy can also damage other tissue in the body (J.F. Holland and I.E. Frei, 1973). Therefore, combination of chemotherapy and immunotherapy uses many medical to treatment tumor.

This paper based on previous work (L.G. de Pillis, 2006) and experiment (J.A. Spratt, 1993) where a system of coupled ordinary differential equations (ODEs) has been proposed to generalized logistic tumor growth model and three systems immune as well as a combined immunotherapy and chemotherapy. In Section 2, we present the set of incorporated assumptions into generalized tumor growth model and the system of ODEs that describe the mathematical model. In Section 3, we presented parameters value to run simulation of the model from previous works (L.G. de Pillis, 2006; J. A. Spratt, et al., 1993). Section 4 discusses an analysis of the non dimensionalization model, finding equilibrium points, and stability analysis. In Section 5, we presented numerical simulation based on parameters from (L.G. de Pillis, 2006; J. A. Spratt, et al., 1993). In Section 6, we summarized our conclusions.

Mathematical Model:

Modeling tumor therapy requires a model of the untreated tumor growth. In this section, we formulated the following tumor behavior in the absence of medical intervention based (L.G. de Pillis, 2006; J. A. Spratt, et al., 1993):

- There was clinical evidence that tumor mass may become no longer detectable, then it was reappeared and grew to lethal size.
- Tumor grew uncontrolled, since accelerated growth rates.
Immune cells given detrimental effect on tumor cells.
Encounters immune cells and tumor cells caused inactivation of cytotoxic immune cells.
Global stimulatory effect of tumor cells on the immune response.
The presence of tumor cells on body responded by both nonspecific and specific immune.

In addition to determine improved combination therapy treatment protocols, we also include formulation of the mathematical model that represents both tumor cells and immune system response to medical intervention:

System response to chemotherapy such as direct cytotoxic effect on tumor and immune cell populations.
System response to chemotherapy such as IL-2 and tumor infiltrating lymphocytes (TIL) injections.

Model Assumptions:

The model is a system of ordinary differential equations (ODEs) whose state variables are populations of tumor cells, specific and nonspecific immune cells, and concentrations of therapeutic interventions. The ODEs model is based on that originally developed by de Pillis (L.G. de Pillis, 2006), and we improve the model by change growth tumor term based on previous work (J.A. Spratt, \textit{et al.}, 1993). For sake the completeness, we outline the assumptions of the mathematical model as follows:

- Tumor grows generalized logistically in the absence of an immune response. This is one accepted growth model for tumor and is also based on fitting of the data in (J.A. Spratt, \textit{et al.}, 1993).
- Both NK and CD8$^+$T cells are capable of killing tumor cells as well as respond to tumor cells by expanding and increasing metabolic activity (A. Diefenbach, \textit{et al.}, 2001; Osada, T., \textit{et al.}, 2004).
- There are always NK cells in the body, even when no tumor cells are present, since they are part of the innate immune response. While CD8$^+$T cells are only present in large numbers when tumor cells are present (L.G. de Pillis, 2006).
- NK and CD8$^+$T cells eventually become inactive after some number of encounters with tumor cells (L.G. de Pillis, 2006).

We add the following additional assumptions in our model formulation are used in the development of therapeutic terms:

- Circulating lymphocyte levels can be used as a measure of patient health (Mustafa, M.M., 1998; Melichar, B., \textit{et al.}, 2001; Glas, R., 2000).
- Chemotherapy kills a fraction of the tumor population according to the amount of drug in the system. The fraction killed reaches a saturation point, since only tumor cells in certain stages of development can be killed by chemotherapy (R. Pazdur, 2001).
- A fraction of NK cells, CD8$^+$T cells, and circulating lymphocytes are also killed by chemotherapy, according to a similar fractional kill curve (Gardner, S.N., 2000).
- NK cells regulate the production and elimination of activated CD8$^+$ T-cells (L.G. de Pillis, 2006).

Model Formulations:

Our mathematical model describes the kinetics of population tumor cells and three types of immune cells (NK cells, CD8$^+$T cells, circulating lymphocytes), as well as two drug concentrations in the bloodstream. We outline a series of coupled ordinary differential equations based on schematic diagram in Figure 1 and model developed by (L.G. de Pillis, 2006; J.A. Spratt, \textit{et al.}, 1993). The populations are denoted by:

- $T(t)$, tumor cell population at time $t$
- $N(t)$, total NK cell effectiveness at time $t$
- $L(t)$, total CD8$^+$T cell effectiveness at time $t$
- $C(t)$, number of circulating lymphocytes (or white blood cells) at time $t$
- $M(t)$, chemotherapy drug concentration in the bloodstream at time $t$
- $I(t)$, immunotherapy drug concentration in the bloodstream at time $t$

The equation governing the population kinetics must take into account a net growth term for growth and death ($G$), the fractional cell kill ($F$), per cell recruitment ($R$), cell inactivation ($I$) and external intervention with medicine ($H$). We attempt to use simplest expressions for each term that still accurately reflect experimental data and recognize population interactions.

\[
\frac{dT}{dt} = G(T) - F_N(T, N) - F_L(T, L) - F_{MT}(T, M)
\]

\[
\frac{dN}{dt} = G(N) + R_N(T, N) - I_N(T, N) - F_{MN}(N, M)
\]
\[
\frac{dL}{dt} = G(L) + R_L(T, L) - I_L(T, L) + R_L(T, N) + R_L(T, C) - I_L(N, L) - F_{ML}(L, M) + F_{IL}(I, L) + H_L
\]
\[
\frac{dC}{dt} = G(C) - F_{MC}(C, M)
\]
\[
\frac{dM}{dt} = G(M) + H_M
\]
\[
\frac{dl}{dt} = G(I) + H_l
\]

The functional form that we choose for each cell interaction term are discussed more detail below.

**Tumor Cells Formulations:**

Tumor growth is assumed to be generalized logistic, based on data gathered from Spartt et al. (1993). Therefore
\[
G(T) = aT \left[ 1 - \left( \frac{T}{b} \right)^e \right], \quad \text{where } a \text{ represent tumor growth rate, } b \text{ is tumor carrying capacity and } e
\]
is parameter which characterizes the shape of the sigmoidal growth curve. We take our fractional cell kill term for \( N \) and \( L \) from (L.G. de Pillis, et al., 2006). The fractional cell kill terms represent negative interactions between two population. They can represent competition on space and nutrients as well as regulatory action and direct cell population interaction. The interaction between tumor and NK cells takes the form
\[
F_N(T, N) = cNT, \quad c \text{ represent fractional non ligand tranduced tumor cells kill by NK cells. While interaction tumor and CD8+T cells has the form } \frac{dL}{dt} = \frac{d}{s + \left( \frac{L}{T} \right)^{e}}, \text{this term represent inactived tumor by CD8+T cells. In order to simplify this term letting } D = d \frac{\left( \frac{L}{T} \right)^{e}}{s + \left( \frac{L}{T} \right)^{e}} \text{ and we have } F_L(T, L) = DT.
\]
Chemotherapy drug also kill tumor cells, in the mathematical term, we use reflects the dose response curve suggested by the literature (Gardner, S.N., 2000). We therefore let
\[
F_{MT}(T, M) = K_T \left( 1 - \exp(-M) \right)T, \quad K_T \text{ represent fractional immune cell kill by chemotherapy.}
\]

**NK Cells Formulations:**

In this model, growth and death term from NK cell is tied to the overall immune health levels as measured by population of circulating lymphocytes. This allows for the suppression of stem cells during chemotherapy, which lowers circulating lymphocytes counts and affects the production rate of NK cells (L.G. de Pillis, et al., 2006). Therefore, \( G(N) = eC - fN \), \( e \) represent fractional of circulating lymphocytes that become NK cells and \( f \) represent death rate of NK cells. The recruitment of NK cells form is \( R_N(T, N) = g \frac{T^2}{h + T^2} N \), \( g \)
represent maximum NK cell recruitment rate by tumor cells and \( h \) represent steepness coefficient of the NK cell recruitment curve. Inactivation of cytolityc potential occurs when NK cell has interacted with tumor cells several times and ceases to be effective. Therefore, \( I_N(T, N) = pNT \), the parameter \( p \) represent NK cell inactivation rate by tumor cells. Thus, interaction between NK cell and chemotherapy in term \( F_{MN}(N, M) = K_N \left( 1 - \exp(-M) \right)N, K_N \) represent fractional immune cell kill by chemotherapy.

**CD8+T Cells Formulations:**

Growth and death term 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, so \( G(L) = -mL \) where \( m \) represent death rate of CD8+T
cells. The CD8+T cell recruitment term has a form similar with NK cell recruitment, yet the tumor population is replaced with the interaction between tumor and tumor lysis by CD8+T cells.

Therefore, \( R_j(T, L) = \frac{j D^2 T^2}{k + D^2 T^2} L \), \( j \) represent maximum CD8+T cell recruit rate and \( k \) represent steepness coefficient of the CD8+T cell recruitment curve. CD8+T cells can also be recruited by the debris from tumor cells lysed by NK cells (A.Y.C. Huang, 1994). This recruitment term is dependent on some fraction of the number of cells killed. From this, we procure the term \( R_j(T, N) = r_j N T \). The immune system is also stimulated by the tumor cells to produce more CD8+T cells. This is also assumed to be a direct cells interaction term, and is written \( R_j(T, C) = r_2 C T \). Where \( r_1 \) and \( r_2 \) respectively represent rate at which CD8+T cells are stimulated to be produced as result of tumor cells killed by NK cells and interacting with circulating lymphocytes. Inactivation of cytolytic potential occurs when CD8+T cell has interacted with tumor cells several times and ceased to be effective. Therefore, we procure the term \( I_k(T, L) = q L T \), where \( q \) represent CD8+T cell inactivation rate by tumor cells. When there are very high level of activated CD8+T cells without responsiveness to cytokines present in the system caused regulation and suppression of CD8+T cell activity. From this, we procure the term \( I_k(N, L) = u N L^2 \), where \( u \) represent regulatory function by NK cells of CD8+T cells. In this model also presence immunotherapy, this drug is actually a naturally occurring in the human body. The presence this drug stimulates the production of CD8+T cells, so we let \( F_{IL}(I, L) = p_I \frac{LI}{g_I + I} \). This is the activation term developed in kirschner’s tumor-immune model (D. Kirschner and J.C. Panetta, 1998). Where \( p_I \) and \( g_I \) respectively represent maximum CD8+T cell recruitment rate by IL-2 and steepness of CD8+T cell recruitment curve by IL-2.

Thus, interaction between CD8+T cell and chemotherapy in term \( F_{MC}(L, M) = K_c (1 - \exp(-M) )L \), \( K_c \) represent fractional immune cell kill by chemotherapy. The TIL drug intervention term, \( H_L = v_L(t) \) for the CD8+T cell population represent immunotherapy where the immune cell levels are directly boosted.

Circulating Lymphocytes Formulations:

We assume that circulating lymphocyte are generated at a constant rate and that each cell has a natural lifespan. From this, we procure the term \( G(C) = \alpha - \beta C \), where \( \alpha \) represent constant source of circulating lymphocytes and \( \beta \) reflect natural death and differentiation of circulating lymphocytes. Thus, interaction between CD8+T cell and chemotherapy in term \( F_{MC}(C, M) = K_c (1 - \exp(-M) )C \), \( K_c \) represent fractional immune cell kill by chemotherapy.

Chemotherapy and Immunotherapy Formulations:

The chemotherapy drug has a natural lifespan, since we assume after injection, chemotherapy will be eliminated from the body over time at a rate proportional to its concentration, from this we procure it decay at some at some rate such that \( G(M) = -\gamma M \). Similarly, the immunotherapy drug has a natural lifespan and decay in the same way, \( G(I) = -\mu I \). Where \( \gamma \) and \( \mu \) respectively represent rate of chemotherapy and immunotherapy drug decay. In addition, drug intervention term are functions of time denoted, respectively by \( H_M = v_M(t) \) and \( H_I = v_I(t) \).

ODE Formulations:

The full system of equation built up from the specific terms for each cell growth and death as well as interaction terms, are listed below. The expression for \( D \) is one that appear in several locations, and so is listed separately below:

\[
\frac{dT}{dt} = aT \left( 1 - \left( \frac{T}{b} \right)^{\epsilon} \right) - cNT - DT - K_f (1 - \exp(-M))T
\]

(7)
\[
\frac{dN}{dt} = eC - fN + g \frac{T^2}{h + T^2} N - pNT - K_N \left(1 - \exp\left(-M\right)\right)N \\
\frac{dL}{dt} = -mL + j \frac{D^2T^2}{k + D^2T^2} L - qLT + (r_1N + r_2C)T - uNL^2 - K_L \left(1 - \exp\left(-M\right)\right)L \\
+ p_I \frac{LI}{g_I + I} + v_I(t) \\
\frac{dC}{dt} = \alpha - \beta C - K_C \left(1 - \exp\left(-M\right)\right)C \\
\frac{dM}{dt} = -\gamma M + v_M(t) \\
\frac{dl}{dt} = -\mu_I L + v_I(t) \\
\text{where } D = d \frac{(L/T)^l}{s + (L/T)^l}
\]  

(8)

(9)

(10)

(11)

(12)

(13)

Parameter Derivation:

System parameters are very sensitive into determine our system equations. In fact, the parameters sets can vary greatly from one individual to another, so multiple data sets can be used to obtain accurate parameter. 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 (L.G. de Pillis, 2006) and also several parameters were taken from Sparrt et al. work (J.A. Spratt, 1993). 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

<table>
<thead>
<tr>
<th>Patient</th>
<th>Units</th>
<th>Description</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a)</td>
<td>(4.31 \times 10^{-1})</td>
<td>Tumor growth rate</td>
<td>[6]</td>
</tr>
<tr>
<td>(b)</td>
<td>(0.98 \times 10^{1})</td>
<td>Tumor carrying capacity</td>
<td>[5]</td>
</tr>
<tr>
<td>(c)</td>
<td>(6.41 \times 10^{11})</td>
<td>Fractional (non) ligand transduced tumor cell kill by NK cells</td>
<td>[6, 16]</td>
</tr>
<tr>
<td>(d)</td>
<td>(2.34)</td>
<td>Saturation level of fractional tumor cell kill by CD8+ T Cells. Primed with ligand-transduced cells, challenged with ligand-transduced</td>
<td>[16]</td>
</tr>
<tr>
<td>(e)</td>
<td>(2.08 \times 10^{7})</td>
<td>Fraction of circulating lymphocytes that became NK cells</td>
<td>[17]</td>
</tr>
<tr>
<td>(l)</td>
<td>(2.09)</td>
<td>Exponent of fractional tumor cell kill by CD8+ T cells. Fractional tumor cell kill by chemotherapy</td>
<td>[16]</td>
</tr>
<tr>
<td>(f)</td>
<td>(4.12 \times 10^{7})</td>
<td>Date rate of NK cells</td>
<td>[6]</td>
</tr>
<tr>
<td>(g)</td>
<td>(1.25 \times 10^{2})</td>
<td>Maximum NK cells recruitment by ligand-transduced tumor cells</td>
<td>[17]</td>
</tr>
<tr>
<td>(h)</td>
<td>(2.02 \times 10^{1})</td>
<td>Steepness coefficient of the NK cell recruitment curve</td>
<td>[17]</td>
</tr>
<tr>
<td>(j)</td>
<td>(2.49 \times 10^{7})</td>
<td>Maximum CD8+ T cell recruitment rate. Primed with ligand-transduced cells</td>
<td>[6, 16]</td>
</tr>
<tr>
<td>(k)</td>
<td>(3.66 \times 10^{10})</td>
<td>Steepness coefficient of the CD8+ T cell recruitment curve</td>
<td>[6, 16]</td>
</tr>
<tr>
<td>(m)</td>
<td>(2.04 \times 10^{1})</td>
<td>Death rate of CD8+ T cells</td>
<td>[18]</td>
</tr>
<tr>
<td>(q)</td>
<td>(1.42 \times 10^{8})</td>
<td>CD8+ T cell inactivation rate by tumor cells</td>
<td>[17]</td>
</tr>
<tr>
<td>(p)</td>
<td>(3.42 \times 10^{6})</td>
<td>NK cell inactivation rate by tumor cells</td>
<td>[16]</td>
</tr>
<tr>
<td>(r)</td>
<td>(8.39 \times 10^{2})</td>
<td>Steepness coefficient of tumor – (CD8+ T cell) lysis term D. Primed with ligand-transduced cells, challenged with ligand-transduced.</td>
<td>[6]</td>
</tr>
<tr>
<td>(r_1)</td>
<td>(1.10 \times 10^{1})</td>
<td>Rate of which CD8+ T cells are stimulated</td>
<td>[18]</td>
</tr>
</tbody>
</table>
Non Dimensionalization And Analysis:

In order to examine the qualitative behavior of our system and uncover the dominating parameters, we simplify the relationship between variables by non dimensionalization. The purpose behind this process is to determine which parameter variations will have the greatest effect on our system, as well as to decrease the total number of parameters that can be altered. To allow for analysis, we now consider the system of Eqs. (7)-(13) in the absence of treatment. When chemotherapy and immunotherapy are eliminated, the model is reduced to a four population system of ordinary differential equations. We rescale all variables so that all cell populations are approximately equal to unity at their equilibrium values. We let the non dimensionalized state variables below:

\[ T = T_0 \tilde{T}, \quad N = N_0 \tilde{N}, \quad L = L_0 \tilde{L}, \quad C = C_0 \tilde{C} \]

\[ t = t_0 \tilde{t}, \quad D = D_0 \tilde{D} \]

Next we note that this non dimensionalization transforms Eqs. (7)-(13) in the absence of treatment into the following:

\[ \frac{d\tilde{T}}{dt} = t_0 a \tilde{T} \left( 1 - \left( \frac{T_0 \tilde{T}}{b} \right)^{\epsilon} \right) - t_0 c N_0 \tilde{N} \tilde{T} - t_0 D_0 \tilde{D} \tilde{T} \]

\[ \frac{d\tilde{N}}{dt} = \frac{t_0}{N_0} C_0 \tilde{C} - t_0 f N_0 \tilde{N} + t_0 g \left( \frac{\tilde{T}}{h + (\tilde{T})^2} \right) \tilde{N} - t_0 p N_0 \tilde{T} \]

\[ \frac{d\tilde{L}}{dt} = -t_0 m \tilde{L} + t_0 j \left( \frac{D_0 \tilde{D}}{k} \right) \tilde{L} - t_0 q L_0 \tilde{N} \tilde{T} + t_0 \left( r_1 N_0 \tilde{N} + r_2 C_0 \tilde{C} \right) \]

\[ \frac{d\tilde{C}}{dt} = \frac{t_0}{C_0} \tilde{C} - t_0 D_0 \tilde{D} \]

\[ \tilde{D} = \frac{\left( \frac{L_0 \tilde{L}}{D_0 \tilde{T}} \right)}{s + \left( \frac{L_0 \tilde{L}}{D_0 \tilde{T}} \right)} \]

We then simplify this new system by choosing \( T_0 \) and other new constants as follows:
and the corresponding parameters as follows:

\[ \begin{align*}
T_0 &= L_0 = b, \\
N_0 &= \frac{\alpha e}{a^2}, \\
C_0 &= \frac{\alpha}{a}, \\
t_0 &= \frac{1}{a}, \\
D_0 &= a
\end{align*} \]

Leaving the other parameters unchanged, and dropping the embellishment and star for notational clarity, the non dimensionalized system is given by:

\[ \begin{align*}
\frac{dT}{dt} &= T(1 - T^\epsilon - cNT - DT) \quad \text{(19)} \\
\frac{dN}{dt} &= C - fN + g \frac{T^2}{h + T^2} N - pNT \quad \text{(20)} \\
\frac{dL}{dt} &= -mL + j \frac{D^2T^2}{k + D^2T^2} L - qLT + (r_1N + r_2C)T - uNL^2 \quad \text{(21)} \\
\frac{dC}{dt} &= 1 - \beta C \\
D &= \frac{d}{s + \left( \frac{L}{T} \right)^{\gamma}} \\
\beta &= \frac{\beta}{a} \\
\end{align*} \]

This new non dimensionalized version of our model is useful for further qualitative analysis. Specifically we utilize it to determine equilibria and perform a bifurcation analysis.

**Determination of Equilibria:**

In order to examine the behavior of these cell population according to our model, we note first that Eq. (22) decouples from Eqs. (19)-(21), so that we reduce the system down to three equations by allowing the number of circulating lymphocytes in the body remain to constant at its equilibrium, \( C = \frac{1}{\beta} \). Since the differential equation for circulating lymphocytes is independent of the other cell populations, this is its only stable state. Thus, this leaves a system Eqs. (19)-(21), which we set simultaneously equal to zero to obtain their equilibria. By setting the derivative in Eq. (19) to zero, we obtain \( T = 0 \) and \( T = \left( 1 - cN - D \right)^\epsilon \). Similarly, requiring that Eq. (20) equal zero gives \( N = \frac{h + T^2}{\beta \left( fh + phT + (f - g)T^2 + T^3 \right)} \). Finally, we setting derivative Eq. (21) to zero and we procure:

\[ L = \frac{-\left( m - j \frac{D^2T^2}{k + D^2T^2} + qT \right) \pm \sqrt{\left( m - j \frac{D^2T^2}{k + D^2T^2} + qT \right)^2 + 4(\alpha N)(r_1N + r_2C)T}}{2(\alpha N)} \]

In the case where \( T = 0 \), we obtained \( N = \frac{1}{\beta f} \), \( L = 0 \) and \( L = -\frac{m\beta}{u} \). Since all parameter \( m, \beta, f \) are positive constant, so that \( L = 0 \) and \( L < 0 \). We only use \( L = 0 \), since this result acceptable behavior biology. While \( L < 0 \) not acceptable behavior biology. So that, we obtain the equilibrium our system is given by \( \left( T_0, N_0, L_0, C_0 \right) = \left( 0, \frac{1}{\beta f}, 0, \frac{1}{\beta} \right) \). This equilibrium shown that there aren’t CD8+T cells in the body, when no
tumor cells are present and there are always NK cells and circulating lymphocytes in the body, even when no tumor cells are present. This equilibrium represents the purpose treatment of tumors that is successful in killing tumors. In the case where $T \neq 0$, this equilibrium represents the failure treatment of tumors that lead to tumor growth and tumor endpoint $\epsilon$. This equilibrium point can be found numerically, yet in this paper we do not analyze this point.

**Stability Analysis:**

System of ordinary differential equations nondimensionalized (19)-(21) is nonlinear. In order to analyze the equilibrium stability, we require linearizing this system equations to find the eigenvalues of the Jacobian.

The general Jacobian matrix for our system nondimensionalized is:

$$J = \begin{bmatrix}
1 - T^2 - \xi^2 - cN - D + ds & \frac{T^i}{sT^i + L^i} & -cT \\
2gh\frac{TN}{(h + T^2)} & f + g\frac{T^2}{h + T^2} - pT & 0 \\
2j\frac{TL^2}{(h + D^2T^2)} - qL + r_1N + r_2C & rT - uL^2 & -m + j\frac{D^2T^2}{k + D^2T^2} - qT - 2uNL
\end{bmatrix}$$

At the equilibrium point $(T_E, N_E, L_E, C_E) = \left(0, \frac{1}{\beta f}, 0, \frac{1}{\beta} \right)$, the Jacobian matrix becomes

$$J = \begin{bmatrix}
1 - \frac{c}{\beta f} & 0 & 0 \\
-\frac{p}{\beta f} - f & 0 & 0 \\
\frac{r_1}{\beta f} + \frac{r_2}{\beta} & 0 & -m
\end{bmatrix}$$

The eigenvalues of the system linearized about this equilibrium point are therefore:

$$\lambda_1 = 1 - \frac{c}{\beta f}, \quad \lambda_2 = -f, \quad \lambda_3 = -m$$

Since $f, m$ are positive constants, therefore $\lambda_2$ and $\lambda_3$ are always negative. Thus, equilibrium point for system nondimensionalized is stable if and only if $\lambda_1 = 1 - \frac{c}{\beta f} < 0 \iff c > \beta f$. From this, we procure that the system is stable if $c > \beta f$. Inequality is not true for our parameter set in Table 1, this inequality is not true so that this equilibrium point is an unstable. This inequality indicates that the necessary criteria for stable equilibrium point is that the tumor growth rate ($a$) is low, the death rate of NK cells ($f$) is lower, the fractional tumor cell kill by NK cells ($c$) is larger, and the production of NK cells ($\frac{ae}{a^3}$) is larger.

From this, we procure that parameter $c$ have important role for change stability of the system. We obtain bifurcation point for our system is $c \approx 0.6 \times 10^6$. In Figure 1 shows two simulations. The blue line illustrates the case in which $c$ smaller than the bifurcation point, so that our equilibrium point is unstable where a small perturbation from equilibrium point will cause the system to move away from that point. In this case, one tumor cell can grows to larger tumor mass greater than $2 \times 10^9$ cells in 250 days. However, as illustrated by green line, if $c$ is larger than the bifurcation point value, the system becomes stable and a single tumor cell will die.
Numerical Simulation Results:

In this section, we simulated the behavior of our model using set parameter in Table 1. Firstly, we simulated the model with the set of parameter representing patient 9 to determine initial value for next simulation which extra therapy. This process is very important to determining whether or not the immune system in body alone can kill a tumor. In Figure 2A show that the innate immune responses able strong to control the tumor, This simulation with intial value set to $10^6$ tumor cells, $10^5$ NK cells, $10^2$ CD8+T cells, and $6 \times 10^8$ circulating lymphocytes. However, when initial value change to $10^6$ tumor cells, $10^3$ NK cells, $10^2$ CD8+T cells, and $6 \times 10^8$ circulating lymphocytes. The immune system unable to control the tumor, $10^6$ tumor cells grows to a dangerous level in the absence of therapy intervention as pictured in Figure 2B.

![Simulation for illustration system behavior with parameter c.](image1)

**Fig. 1:** Simulation for illustration system behavior with parameter $c$.

**Fig. 2:** Simulation for the immune system response to tumor with set parameter patient 9 in Table 1. A: The healthy immune system effectively kills tumor cells. B: The depleted immune system fails to kill tumor cells when left untreated.
Simulation for Tumor Therapy with Parameter Patient 9:

In this subsection, we simulated these model for variation therapy tumor to obtain the effective therapy. In this simulation we denoted as an initially value with $10^7$ tumor cells, $10^3$ NK cells, 10 CD8+T cells, and $6 \times 10^8$ circulating lymphocytes.

Fig. 3: Simulation for immunotherapy. A: $10^9$ TILs are administered from day 7 through 8, IL-2 is administered in 6 pulses at strength $5 \times 10^6$ from day 8 to day 12. B: $10^9$ TILs are administered from day 7 through 8, IL-2 is administered in 6 pulses at strength $5 \times 10^7$ from day 8 to day 12. C: $10^{10}$ TILs are administered from day 7 through 8, IL-2 is administered in 6 pulses at strength $5 \times 10^6$ from day 8 to day 12.
Fig. 4: Simulation for chemotherapy. A: nine doses of chemotherapy drug at strength 5 per dose on a 5 days cycle. B: nine doses of chemotherapy drug at strength 10 per dose on a 5 days cycle.

Fig. 5: Simulation for biochemotherapy. $10^6$ TILs are administered from day 7 through 8, IL-2 is administered in 4 pulses at strength $5 \times 10^6$ from day 8 to day 12, and four doses of chemotherapy drug at strength 1 per dose on a 5 days cycle.

Simulation for Tumor Therapy with Parameter Patient 10:

In order to examine whether these treatment simulations vary from patient to patient, we change set parameter patient 9 to patient 10 as in Table 1. In this simulation we denoted as an initially value with $10^6$ tumor cells, $10^3$ NK cells, 10 CD8+T cells, and $6 \times 10^8$ circulating lymphocytes.
**Fig. 6:** Simulation for immunotherapy with parameter patient 10. $10^8$ TILs are administered from day 7 through 8, IL-2 is administered in 3 pulses at strength $5 \times 10^6$ from day 8 through 13, 20 through 25, and 80 through 90.

**Fig. 7:** Simulation for chemotherapy with parameter patient 10. A: nine doses of chemotherapy drug at strength 5 per doses on a 5 days cycle. B: nine doses of chemotherapy drug at strength 10 per doses on a 5 days cycle.
Fig. 8: Simulation for biochemotherapy with parameter patient 10. 10^9 TILs are administered from day 7 through 8, IL-2 is administered in 2 pulses at strength 5 x 10^6 from day 8 through 13, and 20 through 25, as well as four doses of chemotherapy drug at strength 4 per doses on a 5 days cycle.

Conclusions:

We have improved previous mathematical model (L.G. de Pillis, 2006) that govern tumor growth with generalized logistic model in present treatment. Our mathematical model is system of ordinary differential equations that describe the effect of tumor infiltrating lymphocytes (TIL), interleukin-2 (IL-2) and chemotherapy drug on dynamics of tumor cells. Our simulation shown that the treatment plays important role to remission or even to kill the tumor cells completely. This model used to investigate most effectiveness of therapy tumor.

In order to investigate of system equations, we have to examine behavior of our system then manage the dominating parameter that appear in our system. We use non dimensionalization to simplify the relationship between variable. From this non dimensionalized, we procure the new system equations in the absence treatment. This system equations used to determine equilibrium point and analysis their stability. We obtain two equilibrium point from this system equations is a tumor-free equilibrium \( (T = 0) \) which shown to be unstable and high-tumor equilibrium \( (T \neq 0) \) which shown to be stable for our set parameter. Tumor-free equilibrium point is given by \( (T^*_E, N^*_E, L^*_E, C^*_E) = \left(0, \frac{1}{\beta f}, 0, \frac{1}{\beta} \right) \). This equilibrium represent effective treatment tumor that is success kill tumor. Other hand, for high-tumor equilibrium point represent the failure treatment tumor that is tumor grow lead to point \( T = (1 - cN - D)^{\frac{1}{c}} \). From analysis tumor-free equilibrium we procure the parameter fractional tumor cell kill by NK cells (c) most dominate in the system equations. This parameter can change the stability system equation. We obtain bifurcation point for this parameter is given by \( c \approx 0.6 \times 10^6 \). Our simulation shown that if value \( c \) smaller than the bifurcation point, the system equations to be unstaible where a small perturbation from tumor-free equilibrium point will cause the system to move away from this point. If value \( c \) larger than the bifurcation point the system equations to be stable.

Results of numerical simulation from our mathematical model have been showed in Figure 2 through to Figure 8. This simulation to find the best strategy of therapy in controlling the tumor growth to dangerous level. For simulation parameter patient 9 we obtain that simulation of immunotherapy can kill tumor cells at high dose immunotherapy drug (TIL and IL-2). External dose from TIL and IL-2 caused the immune system can be boosted, TIL can activated specific immune cells while IL-2 increased the production of immune cells. For simulation of chemotherapy shown that this treatment can kills tumor cells at high dose too. Both of immunotherapy and chemotherapy at high dose have more negative side effect. External high dose beside kills tumor cells, it also damage other tissue in the body. Therefore, there are must simulation therapy for clear this problem. This simulation is biochemotherapy, this simulation therapy use low dose immunotherapy in conjuction with chemotherapy and using lower periode. This treatment has beneficial in which patient get little drug and periode, so more safety and fewer side effect to patient. Similarly simulation for parameter patient 9, simulation in parameter patient 10 obtained same result. Where biochemotherapy more effectiveness than immunotherapy and chemotherapy alone. The result of this simulation are essential and will gave the benefit for clinicians to
predict the result through the mathematical modeling before they do real experiment on human object. The benefit are will minimize the dangerous effect and the cost of experiment as well as many varies will guide the clinicians.

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References


