Proceedings of the International Conference on Industrial Engineering and Operations Management
Paris, France, July 26-27, 2018

Numerical Analysis for Identifying Mathematical Model of Tumor Therapy

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Abstract

In this paper, a numerical analysis of mathematical model, in the form of a system of ordinary differential equations (ODEs) was carried out. The mathematical model describes the effect of tumor infiltrating lymphocytes (TIL) and interleukin-2 (IL-2) on the dynamics of tumor cells. It characterizes the ordinary differential equations system dynamics by determining stability properties. The system characteristic is useful to gain a broad understanding of the specific system dynamics and to help guide the development of tumor therapy.

Keywords:
Ordinary differential equations, tumor infiltrating lymphocytes, interleukin-2, stability properties.

1. Introduction

A tumor is an abnormal growth of body tissue. It begins to form when a single cell mutates in such a way that lead to uncontrolled growth (Chang et al., 2003). Tumors can be cancerous (malignant) or noncancerous (benign). In

general, tumors occur when cells divide excessively in the body. Typically, cell division is strictly controlled. New cells are created to replace older ones or to perform new function. Cells those are damaged or no longer to make room for healthy replacements (Moscow and Cowan, 2007). Problems with the immune system can lead to tumor. Tobacco cause more death from cancer than any other environmental substance (Moscow and Cowan, 2007). The Cancer Research Institute reports that in 1995, an estimated 1.252 million cases were diagnosed, with 547 000 deaths in the United States alone. The relative survival rate had been increasing to 54 % with new techniques for detection and treatment of cancer (Chang et al., 2003). According to the International Agency for Research on Cancer, about 715 000 new cancer cases and 542 000 cancer deaths occurred in Africa (Rebbeck, 2011). These numbers were projected to nearly double (1.28 million new cancer cases and 970 000 cancer deaths) by 2030 simply due to the aging and growth of the population, with the potential to be even higher because of the adoption of behavior and lifestyles associated with economic development, such as smoking, unhealthy diet and physical inactivity (Rebbeck, 2011).

In order to model the effect of any therapy on tumor growth alone, one should first model kinetics of growth of an untreated tumor. Most often the growth of untreated tumor is well described by the Gompertz function (Chignola et al., 2000; Miller et al., 2001; Isaeva and Osipov, 2009) and Logistic function (de Pillis and Radunskaya, 2001; de Pillis et al., 2006), yet for some tumor the more general Bertalanffy-Richards (Generalized Logistic) model is required to describe data adequately (Spratt et al., 1993; Kartono and Subiyanto, 2012; Mamat et al., 2012; Mamat et al., 2013; Subiyanto et al., 2013).

In this paper, it presents numerical analysis of mathematical model of tumor therapy. The model is a system of ordinary differential equations whose state variables are populations of tumor cells, specific and nonspecific immune cells, and concentrations of therapeutic interventions. The goal of this paper is to search the parameter whose alter the stability of the equilibrium point.

2. Mathematical Model

In this section, a mathematical model in the absence of therapy will be considered. The model described interaction between tumor cells and immune cells without any treatment. The mathematical model is a system of ordinary differential equations (ODEs) whose state variables are populations of tumor cells based on previous work (Kartono and Subiyanto, 2012; Mamat et al., 2012; Mamat et al., 2013; Subiyanto et al., 2013). The couple 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:

$$\frac{dT}{dt} = aT\left(1-\left(\frac{T}{b}\right)^{\varepsilon}\right) - cNT - DT \tag{1}$$

$$\frac{dN}{dt} = eC - fN + g\frac{T^2}{h+T^2}N - pNT \tag{2}$$

$$\frac{dL}{dt} = -mL + j\frac{D^2T^2}{k+D^2T^2}L - qLT + \left(r_1N + r_2C\right)T - \mu NL^2 \tag{3}$$

$$\frac{dC}{dt} = \alpha - \beta C \tag{4}$$

$$D = d\frac{\left(L/T\right)^l}{s+\left(L/T\right)^l} \tag{5}$$

where:

$T(t)$, 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*

Table 1: Parameters of the mathematical model in the equation 1-5

Parameter	Units	Description	Source
$a = 4.31 \times 10^{-1}$	day^{-1}	*Tumor growth rate*	(Diefenbach et al., 2006)
$b = 1.02 \times 10^{-9}$	$cell^{-1}$	*1/b is tumor carrying capacity*	(Diefenbach et al., 2006)
$c = 6.41 \times 10^{-11}$	$day^{-1} \cdot cell^{-1}$	*Fractional (non) ligand transduced tumor cell kill by NK cells*	(Diefenbach et al., 2006), (Dudley et al., 2002)
$d = 2.34$	day^{-1}	*Saturation level of fractional tumor cell kill by CD8+ T Cells. Primed with ligand-transduced cells, challenged with ligand-transduced*	(Dudley et al., 2002)
$e = 2.08 \times 10^{-7}$	day^{-1}	*Fraction of circulating lymphocytes that became NK cells*	(Kuznetsov et al., 1994)
$l = 2.09$	dimensionless	*Exponent of fractional tumor cell kill by CD8+ T cells. Fractional tumor cell kill by chemotherapy*	(Dudley et al., 2002)
$f = 4.12 \times 10^{-2}$	day^{-1}	*Date rate of NK cells*	(Diefenbach et al., 2006)
$g = 1.25 \times 10^{-2}$	day^{-1}	*Maximum NK cells recruitment by ligand-transduced tumor cells*	(Kuznetsov et al., 1994)
$h = 2.02 \times 10^{7}$	$cell^{2}$	*Steepness coefficient of the NK cell recruitment curve*	(Kuznetsov et al., 1994)
$j = 2.49 \times 10^{-2}$	day^{-1}	*Maximum CD8+ T cell recruitment rate. Primed with ligand-transduced cells*	(Diefenbach et al., 2006), (Dudley et al., 2002)
$k = 3.66 \times 10^{7}$	$cell^{2}$	*Steepness coefficient of the CD8+ T cell recruitment curve*	(Diefenbach et al., 2006), (Dudley et al., 2002)
$m = 2.04 \times 10^{-1}$	day^{-1}	*Death rate of CD8+ T cells*	(Yates and Callard, 2002)
$q = 1.42 \times 10^{-6}$	$day^{-1} \cdot cell^{-1}$	*CD8+ T cell inactivation rate by tumor cells*	(Kuznetsov et al., 1994)
$p = 3.42 \times 10^{-6}$	$day^{-1} \cdot cell^{-1}$	*NK cell inactivation rate by tumor cells*	(Dudley et al., 2002)
$s = 8.39 \times 10^{-2}$	dimensionless	*Steepness coefficient of tumor – (CD8+ T cell) lysis term D. Primed with ligand-transduced cells, challenged with ligand-transduced.*	(Diefenbach et al., 2006)
$r_1 = 1.10 \times 10^{-7}$	$day^{-1} \cdot cell^{-1}$	*Rate of which CD8+ T cells are stimulated to be produced as a result a tumor cells killed by NK cells*	(Yates and Callard, 2002)
$r_2 = 6.50 \times 10^{-11}$	$cell^{-1} \cdot day^{-1}$	*Rate of which CD8+ T cells are stimulated to be produced as a result a tumor cells interaction with circulating lymphocytes*	-
$u = 3.00 \times 10^{-10}$	$cell^{-2} \cdot day^{-1}$	*Regulatory function by NK cells of CD8+ T cells*	-
$\alpha = 7.50 \times 10^{8}$	cell · day−1	*Constant source of circulating lymphocytes*	(Hauser, 2001)
$\beta = 1.20 \times 10^{-2}$	day^{-1}	*Natural death and differentiation of circulating lymphocytes*	(Hauser, 2001)

3. Result and Discussion

In order to perform the numerical analysis of the mathematical model, 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 tumor type but also from one individual to another. Table 1 describes all parameters to perform the numerical analysis of the mathematical model. Based on the value of the all parameters in Table 1, the system of ordinary differential equations in section 2 was obtained equilibrium points at $T = 0$, $N = 1/\beta f$, $L = 0$ and $C = 1/\beta$ when the "tumor-free" equilibrium and possibly several non-zero tumor equilibria. The system of ordinary differential equations 1 through 5 is nonlinear. Linearize these system equations to find the eigenvalues of its Jacobian is required, in order to analysis the equilibrium stability. So that, it necessary to set equations 1 through 3 to new form as follows:

$$f_1 = T\left(1 - T^{\varepsilon}\right) - cNT - \left(\frac{dL^l T}{sT^l + L}\right) \tag{6}$$

$$f_2 = C - fN + g\frac{T^2}{h + T^2}N - pNT \tag{7}$$

$$f_3 = -mL + j\frac{\left(\frac{dL^l T}{sT^l + L}\right)^2 T^2}{k + \left(\frac{dL^l T}{sT^l + L}\right)^2 T^2}L - qLT + \left(r_1 N + r_2 C\right)T - \mu NL^2 \tag{8}$$

At equilibrium points at $T = 0$, $N = 1/\beta f$, $L = 0$ and $C = 1/\beta$ the system of ordinary differential equations 6 through 8 was obtained the Jacobian matrix as follows:

$$J = \begin{pmatrix} 1 - \frac{c}{\beta f} & 0 & 0 \\ -\frac{p}{\beta f} & -f & 0 \\ \frac{r_1}{\beta f} + \frac{r_2}{\beta} & 0 & -m \end{pmatrix} \tag{9}$$

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

$$\left(1 - \frac{c}{\beta f} - \lambda\right)(-f - \lambda)(-m - \lambda) = 0$$

Hence, will be gotten:

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

Since f, m is positive constants, therefore λ_2 and λ_3 is always negative. Thus, equilibrium point for the system equation is stable if and only if $\lambda_1 = 1 - \frac{c}{\beta f} < 0 \Leftrightarrow c > \beta f$. From this, we procure system dimensional is stable if and only if $\frac{c\alpha e}{a^3} > \frac{\beta}{a}\frac{f}{a} \Leftrightarrow c > \frac{\beta f a}{\alpha e}$. Unfortunately 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 are 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 $\left(e\frac{\alpha}{\beta}\right)$ is larger. Based on this result, we procure that parameter c have important role for change stability of the system. We obtain bifurcation point for our system is $c \approx 0.6x10^6$. 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 grow to larger tumor mass greater than $2x10^9$ 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.

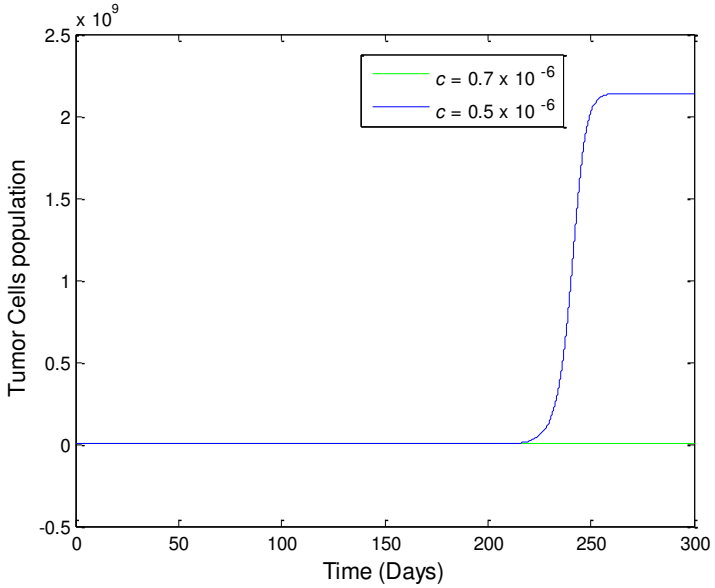

Figure 1. Simulation illustration system behavior for parameter c

4. Conclusion

The bifurcation point in this model has been analyzed. Through this analysis we search the parameter whose alter the stability of the equilibrium point. We procure that parameter c (the fractional tumor cell kill by NK) cells have important role for change stability of the system. We obtain bifurcation point for our system is $c \approx 0.6x10^6$. In this case which parameter c smaller than the bifurcation point, thereby equilibrium point is unstable where a small perturbation from equilibrium point will cause the system to move away from that point. The immune system cannot handle a single tumor cell and consequently tumor continued to grow and become aggressive. However, if parameter c is larger than the bifurcation point value, the system becomes stable and a single tumor cell will die.

Acknowledgements

Acknowledgments are conveyed to the Rector, Director of DRPMI, and the Dean of FPIK, Universitas Padjadjaran, who has granted an Internal Grant program of Universitas Padjadjaran, which is a means of enhancing research and publication activities for researchers at Universitas Padjadjaran.

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