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Stability and bifurcations of equilibria in a delayed Kirschner–Panetta model

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ABSTRACT

In this paper, a delay differential equation model of immunotherapy for tumor-immune response is presented. The dynamics that interplays between the three model factors, namely, effector cells, tumor cells and interleukin-2 is studied and the quantitative analysis is performed. We estimate the length of delay to preserve the stability of an equilibrium state of biological significance. The impact of delay in the immunotherapy with interleukin-2, especially, at different antigenicity levels, is discussed, along with the scenarios under which the tumor remission can be prolonged.

1. Introduction

In his study with 283 patients, Rosenberg [1] provides a clear clinical evidence that the cytokine IL-2 therapy can cause the significant anti-tumor effects. The proposed mathematical model comprises a system of three ordinary differential equations, where $x(t)$, $y(t)$ and $z(t)$ denote the concentrations of the effector cells (which are basically the T-lymphocytes and their main role is very specific in terms of providing immunological support to infections), the tumor cells (rapidly proliferating cells, which are malignant) and the concentration of the IL-2 (IL-2 is the main cytokine which causes T-lymphocyte activation and it induces the growth of cells that can cause tumor regression) respectively. The corresponding differential equations are:

$$\begin{aligned} \frac{dx}{dt} &= cy + \frac{p_1 xz}{g_1 + z} - \mu_2 x \\ \frac{dy}{dt} &= r_2(1 - by)y - \frac{axy}{g_2 + y} \\ \frac{dz}{dt} &= \frac{p_2 xy}{g_3 + y} - \mu_3 z + kz(t - \tau) \end{aligned} \tag{1}$$

subject to the following initial conditions: $x(0) = \phi_1(0) > 0, y(0) = \phi_2(0) > 0, z(\theta) = \phi_3(\theta) \geq 0, \theta \in [-\tau, 0]$, $\phi_3(0) > 0$.

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The first equation represents the rate of change of effector cells. The effector cells grow at the rate of c due to presence of tumor and also have a Michaelis–Menten type of growth at rate p_1 due to stimulation by IL-2 and is indicative of the saturated effects of immune response, μ_2 is a natural death rate of effector cells. The parameter c measures the antigenicity of the tumor. The tumor growth is logistic in nature (a pattern widely accepted for the dynamics of tumors in general) at rate r_2 ($1/b$ is the carrying capacity) and the effect of the immune response on the tumor follows a Michaelis–Menten dynamics at rate a (stochastic intrinsic interaction between effector and tumor cells is neglected from a biophysical point of view). Finally IL-2 is augmented at a rate p_2 by the effector cells and the presence of tumor and also undergoes natural death at rate μ_3. The treatment term $kz(t-\tau)$ represents the external input of IL-2 into the system. g_1, g_2 and g_3 are half saturation constants. This will increase the IL-2 concentration. It is assumed that the external input (treatment term) of IL-2 into the system is dependent on time and the discrete time delay τ indicates the lag after a single dose of IL-2 is injected in a bolus of 600 000–700 000 IU/kg [1]. We want to look into the dynamics of treatment through Interleukin-2 by altering the value of τ.

The proposed model is the modified version of the Kirschner–Panetta (KP) model [2]. Similar studies on the modified version of KP model from the point of view of immunotherapies and delays have been done. A.d'Onofrio et al. studied stochastic simulation of a hybrid model obtained by modifying the KP model and considered the adoptive cellular immunotherapies as well as interleukin based therapies and their combinations. They concluded that the interleukin based therapies may not be effective for every patient [3]. Caravagna et al. also studied the delayed hybrid model (modified KP model) by introducing discrete time decay as well as distributive delay in the tumor induced recruitment term of the effector cells [4,5]. A proliferative enhancement effect of the cytokine IL-2 with delay has been studied by [6,7]. But, in this paper, the main factor which has been looked into here, is the effect of delay in the IL-2 input on the dynamics of the system in general and tumor burden in particular. Since, in reality, the treatment starts after the tumor has reached its stable steady state, it is realistic to assume that the effect of IL-2 starts after a certain time lag. The goal of this study is to clarify the effect of IL-2 therapy with varying immune threshold at low antigenicity of the tumors. Our approach is based on both analytical and numerical methods. The obtained results are in confirmation with the observation of the experiment done by Rosenberg [1] in 283 patients with metastatic melanoma or renal cell cancer. The main aim of this paper is to establish mathematically that IL-2 therapy alone can provide ample success for treatment of cancer like metastatic melanoma and renal cell cancer in this modified KP model.

2. Qualitative analysis of the model

We start by performing a linear stability analysis in the phase space. The steady states of biological significance of the system under consideration (1) are the following ones:

1. The axial equilibrium is given by $(0, 0, 0)$.
2. The x–y planar equilibrium is $\left(\frac{cy^*}{\mu_2}, y^*, 0\right)$, where,
$$y^* = -(ac - \mu_2 r_2 + r_2\mu_2 b g_2) + \sqrt{(ac - \mu_2 r_2 + r_2\mu_2 b g_2)^2 + 4br_2\mu_2(r_2\mu_2 g_2)}/(2br_2\mu_2).$$
3. The interior equilibrium is (x^*, y^*, z^*) where
$$x^* = \frac{r_2(1-by^*)(g_2+y^*)}{a}$$
$$z^* = \frac{p_2 r_2 y^*(1-by^*)(g_2+y^*)}{(g_3+y^*)(\mu_3-k)}.$$

The stability analysis around the origin $(0, 0, 0)$ and the point $((cy^*)/\mu_2, y^*, 0)$ is skipped as these equilibrium points are of the little relevance from our point of study and our study will be solely concentrated on the interior equilibrium point (x^*, y^*, z^*).

The variation matrix or the *Jacobian* around the interior equilibrium point is (see Appendix),

$$\begin{pmatrix} -cy^*/x^* & c & g_1p_1x^*/(g_1+z^*)^2 \\ -ay^*/(g_2+y^*) & -r_2by^* + ax^*y^*/(g_2+y^*)^2 & 0 \\ p_2y^*/(g_3+y^*) & p_2g_3x^*/(g_3+y^*)^2 & -\mu_3 + ke^{-\lambda\tau} \end{pmatrix}.$$

In the case of a positive delay, the characteristic equation for the linearized equation around the interior equilibrium point (x^*, y^*, z^*) is given by $\lambda^3 + a_0\lambda^2 + a_1\lambda + a_2 + e^{-\lambda\tau}(b_0\lambda^2 + b_1\lambda + b_2) = 0$, where,

$$a_0 = \frac{cy^*}{x^*} + r_2by^* + \mu_3 - \frac{ax^*y^*}{(g_2+y^*)^2}$$
$$a_1 = \mu_3\left(\frac{cy^*}{x^*} + r_2by^* - \frac{ax^*y^*}{(g_2+y^*)^2}\right) + \frac{acy^*}{(g_2+y^*)} + \frac{cy^*}{x^*}\left(r_2by^* - \frac{ax^*y^*}{(g_2+y^*)^2}\right) - \frac{g_1p_1p_2x^*y^*}{(g_3+y^*)(g_1+z^*)^2}$$