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Dynamics in a tumor immune system with time delays

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ABSTRACT

In this paper, we study the dynamical behavior of a tumor–immune system (T–IS) interaction model with two discrete delays, namely the immune activation delay for effector cells (ECs) and activation delay for helper T cells (HTCs). By analyzing the characteristic equations, we establish the stability of two equilibria (tumor-free equilibrium and immune-control equilibrium) and the existence of Hopf bifurcations when two delays are used as the bifurcation parameter. Our results exhibit that both delays do not affect the stability of tumor-free equilibrium. However, they are able to destabilize the immune-control equilibrium and cause periodic solutions. We numerically illustrate how these two delays can change the stability region of the immune-control equilibrium and display the different impacts to the control of tumors. The numerical simulation results show that the immune activation delay for HTCs can induce heteroclinic cycles to connect the tumor-free equilibrium and immune-control equilibrium. Furthermore, we observe that the immune activation delay for HTCs can even stabilize the unstable immune-control equilibrium.

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1. Introduction

The dynamics of the antitumor immune response in vivo is very complicated and not well understood. The immune response begins when tumor cells are identified. There are two major branches of the adaptive immune response: humoral immunity, mediated by antibodies produced by B lymphocytes, and cell-mediated immunity, mediated by T lymphocytes, which act both independently and in concert to combat tumor progression. The activated immune-system cells, generally called effector cells (ECs) such as cytotoxic T lymphocytes (CTLs), macrophages, and natural killer cells (NKs) that are cytotoxic to the tumor cells (TCs), play an essential role in immune responses against tumors. Most CTLs also require cytokines from helper T cells (HTCs) in order to be activated efficiently. HTCs are stimulated through antigen presentation by macrophages or dendritic cells, which are found in all tissues in the body and circulate in the blood stream. Then HTCs secrete the cytokine interleukin-2 (IL-2 known as cytokines which are information signaling molecules) to stimulate proliferation of ECs to kill more and more TCs. Both the activation process of HTCs and ECs are not instantaneous but followed by a lag period.

Tumor–immune system (T–IS) interaction models have been around since the early 1990s and have evolved to capture much more complex aspects of the immune response as knowledge of the cellular and molecular dynamics of immunity has developed [26]. A good summary of early works of T–IS interaction dynamics can be found in [1]. A classical mathematical

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model of a cell mediated response to a growing tumor cell population was proposed and analyzed by Kuznetsov et al. [16] in 1994, which differs from most others because it takes into account the penetration of TCs by ECs as well as the inactivation of ECs. Kuznetsov–Taylor model [16] can be applied to describe two different mechanisms of the tumor: tumor dormancy and sneaking through. In 1998, Kirschner and Panetta [15] generalized Kuznetsov–Taylor model and illustrated the dynamics between TCs, ECs and IL-2. They firstly introduced adoptive cellular immunotherapy (ACI) into their models which can explain both short-term tumor oscillations in tumor sizes as well as long-term tumor relapse. Recently, Eftimie et al. [8] gave a detailed review of non-spatial models of interactions between a malignant tumor and the immune system. In order to investigate the helper role of $CD4^+$ T cells in the T–IS under the ACI treatments, Dong et al. [6] proposed a three dimensional system described by ordinary differential equations (ODEs). They gave the stability region of the interior equilibrium in the scaled two parameters plane and showed that HTCs play a crucial role in the long term periodic oscillation behaviors of T–IS interactions.

Time delays have been incorporated into biological models by numerous authors, such as virus-immune models [14,17,20], prey–predator models [12,23,24] and so on. For T–IS interaction models with time delays, we refer to [3,4,7,10,11,21,22,27,28] and references therein. In general, delay differential equations (DDEs) systems can exhibit much richer dynamics than ODEs systems have since a time delay could cause the loss of stability of equilibrium and arise periodic solutions through the Hopf bifurcation. The instabilities and oscillatory behavior caused by delays are all too common, however the delays could also have the opposite effect, namely that they could suppress oscillations and stabilize equilibria which would be unstable in the absence of delays. In particular, delays can induce stability in coupled identical limit cycle oscillators, leading to the phenomenon often referred to amplitude death or oscillator death, which was known earlier for nonidentical oscillators [2].

Because of both chemical transportation and cellular differentiation, the tumor induced recruitment of immune cells (such as ECs and HTCs) is not instantaneous but, instead, it exhibits some time lags. The effect of time delays in this process is taken into account to approximate missing dynamical components such as, exchanged chemical signals, maturation and activation of T-lymphocytes mediated by B-lymphocytes. Moreover, the immune system needs time to identify the tumor and to react properly [7]. To capture such a phenomenon, two delays namely the immune activation delay for ECs and activation delay for HTCs are incorporated into previous treatment model in [6]. Then we obtain the following system of DDEs:

$$\begin{cases} \frac{dT(t)}{dt} = aT(t)(1-bT(t)) - nE(t)T(t), \\ \frac{dE(t)}{dt} = s_1 + k_1T(t-t_1)E(t-t_1) - d_1E(t) + pE(t)H(t), \\ \frac{dH(t)}{dt} = s_2 + k_2T(t-t_2)H(t-t_2) - d_2H(t), \end{cases} \tag{1}$$

where $T(t)$, $E(t)$ and $H(t)$ represent the population of TCs, ECs and HTCs, respectively. The first equation describes the rate change of the TCs population. Here the logistic growth term $aT(1-bT)$ is chosen, where a is the maximal growth rate of the TCs population and b^{-1} is the carrying capacity of the biological environment for TCs. n represents the loss rate of TCs by ECs interaction. The second equation describes the rate change of the ECs population. s_1 represents the treatment of introducing lymphokine activated killer cells (LAK) and tumor infiltrating lymphocytes (TIL) into the region of tumor localization. k_1 is the ECs simulation rate by ECs-lysed TCs debris. ECs have a natural lifespan of an average $1/d_1$ days. p is the activation rate of ECs by HTCs. The third equation describes the rate change of the HTCs population. s_2 is the birth rate of HTCs produced in the bone marrow. k_2 is the HTCs stimulation rate by the presence of identified tumor antigens. HTCs have a natural lifespan of an average $1/d_2$ days. Two time delays t_1 and t_2 represent the time lags in the tumor stimulated proliferation of ECs and HTCs respectively.

We nondimensionalize the model (1) by taking the following scaling:

$$x = \frac{T}{T_0}, \quad y = \frac{E}{E_0}, \quad z = \frac{H}{H_0}, \quad \xi = nT_0t, \quad \alpha = \frac{a}{nT_0},$$
$$\beta = bT_0, \quad \sigma_1 = \frac{s_1}{nT_0H_0}, \quad \omega_1 = \frac{k_1}{n}, \quad \delta_1 = \frac{d_1}{nT_0}, \quad \rho = \frac{p}{n},$$
$$\sigma_2 = \frac{s_2}{nT_0H_0}, \quad \omega_2 = \frac{k_2}{n}, \quad \delta_2 = \frac{d_2}{nT_0}, \quad \tau_1 = nT_0t_1, \quad \tau_2 = nT_0t_2.$$

As suggested in [16], we choose the scaling $E_0 = T_0 = H_0 = 10^6$ cells to improve the performance of numerical simulations. Then, after the substitution of the scaling into (1) and replacing ξ by t, we obtain the following scaled model:

$$\begin{cases} \frac{dx(t)}{dt} = \alpha x(t)(1-\beta x(t)) - x(t)y(t), \\ \frac{dy(t)}{dt} = \sigma_1 + \omega_1 x(t-\tau_1)y(t-\tau_1) - \delta_1 y(t) + \rho y(t)z(t), \\ \frac{dz(t)}{dt} = \sigma_2 + \omega_2 x(t-\tau_2)z(t-\tau_2) - \delta_2 z(t). \end{cases} \tag{2}$$

We denote by C the Banach space of continuous functions $\varphi : [-\tau, 0] \to R^3$ equipped with the suitable sup-norm, where $\tau = \max\{\tau_1, \tau_2\}$. Further, let

$$C_+ = \{\varphi = (\varphi_1, \varphi_2, \varphi_3) \in C : \varphi_i(\theta) \geqslant 0 \quad \text{for all} \quad \theta \in [-\tau, 0],\ i = 1, 2, 3\}.$$

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