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Bounded immune response in immunotherapy described by the deterministic delay Kirschner–Panetta model

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ABSTRACT

We describe restrictions on the parameters of the delay Kirschner–Panetta model which has bounded immune system behavior.

1. Introduction

The famous Kirschner–Panetta system [1] and its generalizations have been the subject of numerous studies. In particular, there is now a substantial body of research on its stochastic and mean-field versions [2]. In some cases, the role of a delayed immune-response in the presence of stochastic processes was investigated [3]. The model, which explored the dynamics between tumor cells, immune effector cells and Interleukin-2 (IL-2), has illustrated under what circumstances tumor cells can be eradicated. However, the model has a limitation. The cost of elimination of tumor cells with any degree of antigenicity makes the immune system (effector cells) grow unbounded due to the administration of large amount of IL-2. In this paper, we investigate the delay Kirschner–Panetta equations [4] to obtain condition(s) on the system parameters, including the discrete time delay, to control the unboundedness of the effector cells and eradication of tumor cells.

The delay version of Kirschner–Panetta equations [4] consists of tumor cells modeled as a continuous variable as they are large and generally homogeneous; they are defined as $T(t)$. Immune cells (called effector cells) are also large in number and represent those cells that have been stimulated and are ready to respond to the foreign matter (known as antigen). They are defined as $E(t)$. Finally, effector molecules (cytokines, such as Interleukin-2) are represented as a concentration $C(t)$. These are self-stimulating, positive feedback proteins for effector cells that produce them. The equations that describe the interactions of these three state variables are given by:

$$\frac{dE(t)}{dt} = cT(t) - \mu_2 E(t) + \frac{p_1 E(t-\tau)C(t-\tau)}{g_1 + C(t-\tau)} + s_1 \tag{1}$$

$$\frac{dT(t)}{dt} = r_2 T(t)(1 - bT(t)) - \frac{aE(t)T(t)}{g_2 + T(t)} \tag{2}$$

$$\frac{dC(t)}{dt} = \frac{p_2 E(t)T(t)}{g_3 + T(t)} - \mu_3 C(t) + s_2. \tag{3}$$

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In Eq. (1), the first term represents stimulation by the tumor to generate effector immune cells. The parameter c is known as the antigenicity of the tumor. Since tumor cells begin as self, c represents how different the tumor cells are from self cells (i.e., how foreign). The second term in (1) represents natural death and the third is the proliferative enhancement effect of the cytokine IL-2 with delay $\tau > 0$, $s_1(t)$ represents the treatment terms of introducing LAK and TILs cells (for details see [1]). In Eq. (2), the first term is a logistic growth term for tumor growth, and the second is a clearance term by the immune effector cells. In the final equation, (3), IL-2 is produced by effector cells (in a Michaelis–Menten fashion) and decays via a known half-life (second term). s_2 represents the treatment due to Interleukin-2.

The solutions of the system (1)–(3) are defined by the following initial functions:

$$E(\theta) = \psi_1(\theta), \qquad C(\theta) = \psi_2(\theta), \qquad \psi_{1,2} \in \mathcal{C}([-\tau, 0], \mathbb{R}_+), \qquad T(0) \geq 0, \tag{4}$$

where $\mathbb{R}_+ = \{x \in \mathbb{R} \,|\, x \geq 0\}$.

2. Conditions for boundedness of the effector cells and IL-2

Let $I : (T, C) \in \mathbb{R}_+^2 \mapsto \mathbb{R}_+$ be the *quasi-Lyapunov function* [5]

$$I(T, C) = p_2 T + p_2(g_2 - g_3)\ln(T + g_3) + aC, \tag{5}$$

introduced in [6] for the non-delay version of the Kirschner–Panetta equations. We define the parameters

$$q = \frac{g_2}{4bg_3}, \qquad C^* = \frac{I(b^{-1}, \alpha + \beta q) - p_2(g_2 - g_3)\ln g_3}{a}, \tag{6}$$

where $\alpha = \frac{s_2}{\mu_3}$, $\beta = \frac{r_2 p_2}{a\mu_3}$.

Theorem 1. *Let $g_2 > g_3$ and $t \mapsto (E(t), T(t), C(t))$, $t \geq 0$ be the solution of the delay Kirschner–Panetta system (1)–(3) defined by the initial functions (4). Then*

$$\limsup_{t\to+\infty} C(t) \leq C^*. \tag{7}$$

If, in addition, we assume that the following condition is fulfilled

$$\mu_2 > \tilde{p}_1 \quad \text{where } \tilde{p}_1 = p_1 \frac{C^*}{g_1 + C^*}, \tag{8}$$

then E is a bounded function for $t \geq 0$ and satisfies

$$\limsup_{t\to+\infty} E(t) \leq \delta \quad \text{where } \delta = \frac{s_1 + \frac{c}{b}}{\mu_2 - \tilde{p}_1}. \tag{9}$$

Proof. We start by writing (1) in the following form:

$$\frac{dE(t)}{dt} = -\mu_2 E(t) + \phi(t)E(t - \tau) + s(t), \quad t \geq 0, \tag{10}$$

where $\phi(t) = (p_1 C(t - \tau))/(g_1 + C(t - \tau))$, $s(t) = s_1 + cT(t)$. Then s is a bounded positive function: $\forall\, t \geq 0$, $0 \leq s(t) \leq S$, $S = s_1 + c/b$, since T is bounded above by the carrying capacity b^{-1}. Let now $t \mapsto (E(t), T(t), C(t))$ be any solution of (1)–(3) defined for $t \geq 0$. After the derivation, one obtains

$$\forall\, t \geq 0 \quad \frac{d}{dt} I(T, C) = -a\mu_3 C(t) + as_2 + r_2 p_2 \frac{T(t)(1 - bT(t))(T(t) + g_2)}{T(t) + g_3}, \tag{11}$$

where we have used (2) and (3).

For $I_0 \in \mathbb{R}$, we introduce the domains $J = [0, b^{-1}]$, $D = J \times \mathbb{R}_+$ and consider the level line $\Delta_{I_0} = \{(T, C) \in D \,|\, I(T, C) = I_0\}$, which is a smooth curve in D. Solving the equation $I(T, C) = I_0$ with respect to C, one can represent Δ_{I_0} as a graph of the map $T \in J \mapsto C_{I_0}(T)$ where

$$C_{I_0}(T) = \frac{r}{a} - \frac{p_2 T}{a} - \frac{p_2(g_2 - g_3)}{a}\ln(T + g_3). \tag{12}$$

Let $L(T) = \frac{s_2}{\mu_3} + \frac{r_2 p_2}{a\mu_3}\frac{T(1-bT)(T+g_2)}{T+g_3}$. Then, as follows from the condition $g_2 > g_3$,

$$\frac{T(1 - bT)(T + g_2)}{T + g_3} \leq \sup_{T\in J} T(1 - bT) \sup_{T\in J}\left(\frac{T + g_2}{T + g_3}\right) = q, \tag{13}$$

and hence $\sup_{T\in J} L(T) \leq m$ where $m = \alpha + \beta q$. The curve $\Gamma \subset D$, defined as the graph of $T \in J \mapsto (T, L(T))$, is the restriction to D of the zero set of the Lie derivative of I given by (11). Thus, Γ splits D into two sets D_1, D_2 such that $D = D_1 \cup D_2 \cup \Gamma$ with D_1 and D_2 located respectively below and above Γ. The sign of the Lie derivative (11), restricted to D_1, is positive and

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