ESAIM: PROCEEDINGS AND SURVEYS, September 2014, Vol. 45, p. 285-289
J.-S. Dhersin, Editor

EVOLUTIONARY PARADIGM IN CANCER IMMUNOLOGY *

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Abstract. The dynamical system theory in combination with experimental medical data can serve to improve our understanding of how the immune system works and fights the cancer. Some recent mathematical models (see [1]) try to explain the complex interaction between tumor cells, immune-effector cells and both immunosuppressive and immunostimulating cytokines. In this paper the Kirschner-Panetta system [6] is considered. The objective of the study is to broaden, through evolutionary dynamics, our understanding of the efficiency of adoptive immunotherapy and also shed the light on the phenomena of spontaneous tumor remission.

Résumé. La théorie des systèmes dynamiques non linéaires en combinaison avec des données médicales expérimentales peut contribuer à notre compréhension comment le système immunitaire fonctionne et interagi avec le cancer. Les divers modèles mathématiques [1] décrivent l'interaction complexe entre les populations de cellules tumorales, de cellules immunitaires effectrices et des cytokines. Dans ce travail le système de Kirschner-Panetta [6] est analysé. L'objectif de ce travail est d'étudier, à travers de la dynamique évolutionnaire, l'efficacité de limmunotherapie adoptive et clarifier le phénomène de la régression spontanée.

Introduction

During past years, many mathematical models have been developed describing important aspects of non linear interaction of cancer and human immune system. The idea to use the qualitative theory of dynamical systems in mathematical biology reaches back to 1920's when Lotka and Volterra formulated a first simple mathematical model in population dynamics theory : the famous prey-predator system which was the beginning of the evolutionary approach in the mathematical biology. The evolutionary dynamics is described by interplay between several populations of cells and hormones and its basic aspects can be captured already by considering only three populations: the tumors cells, effectors cells and immunostimulating cytokines like IL-2. One of the key characteristics of immunity is the *antigenicity* i.e the recognition of non-self, or foreign antigens. The level of antigenicity of the tumor may be weak as the human immune system is trained to not kill self and usually tumor cells began as self, or non-foreign host cells. Taking into consideration the important immunosuppressive factors, like influence of TGF-β cytokine, can be done in two ways: either by adding one extra population of hormones to the global interaction scheme or by expressing the immunosuppressive mechanism by reducing the value of the antigenicity. In this paper we adopt the second approach and thus do not study explicitly the role of TGF-β and similar actors (see [2]) in the global dynamical picture. The present study does not take into account the phenomena of the memory of the immune system. That will be a subject of the future work.

* *This study was supported by the Indo French Centre for Applied Mathematics (IFCAM) (Grant No. MA/IFCAM/13/11).*

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1. Evolutionary Kirschner-Panetta model in the tumor-immune dynamics

The Kirschner-Panetta system describes the interaction of Tumor cells $T(t)$, tracked as a continuous variable as they are large and generally homogeneous; Effector cells $E(t)$ of immune system which are also large in number and represent those cells that have been activated and are ready to respond to the antigens; Effector molecules of Interleukin-2 represented as a concentration $C(t)$. These are self-stimulating proteins for effector cells which produce them. The three non linear ordinary differential equations describing the interactions of the three populations E, T and C are given by:

$$\frac{dE}{dt} = cT - \mu_2 E + \frac{p_1 EC}{g_1 + C} + s_1 \tag{1a}$$

$$\frac{dT}{dt} = r_2 T(1 - bT) - \frac{aET}{g_2 + T} \tag{1b}$$

$$\frac{dC}{dt} = \frac{p_2 ET}{g_3 + T} - \mu_3 C + s_2 \tag{1c}$$

and where first introduced by Kirschner and Panetta in 1998 [6]. In equation (1a), the first term represents stimulation of immune system cells by the tumor to generate new effector cells. The parameter c is called the antigenicity of the tumor and represents how different the tumor cells are from self cells. The second term in (1a) represents natural death and the third is the proliferative enhancement effect of the cytokine IL-2 ; s_1 represents the treatment terms of protocol injections of enhanced LAK and TILs cells (for details see [6]). The idea for this type of treatment arose from clinical studies yielding mixed results [7–10]. In equation (1b), the first term is a logistic growth term for tumor, and the second is a clearance term by the immune effector cells. In the third equation (1c), 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 protocol injections of Interleukin-2. All numerical values of parameters in the above model are taken from the paper [6].

The next theorem from [3] establishes the possibility of complete tumor clearance by a suitable adoptive immunotherapy protocol.

Theorem 1.1 (The adoptive immunotherapy)**.** *Let $s_2 = 0$ and $c > c_{\text{crit}} = \frac{r_2\mu_2}{a}$. We assume that s_1 satisfies the inequality*

$$\frac{r_2\mu_2 g_2}{a} \leq s_1 \leq g_2 c \tag{2}$$

Then for arbitrary initial tumor size $T(0)$ and every solution $t \mapsto (E(t), T(t), C(t))$, $t \geq 0$ of the Kirschner-Panetta system (1a)-(1c) *the following statement holds*

$$\lim_{t \to +\infty} T(t) = 0 \tag{3}$$

The Fig. 1 illustrates the application of Theorem 1.1 for the antigenicity value $c = 0.02$ and other parameter values taken from the paper [6].

The next result demonstrates how the action of immune system alone can lead to the tumor clearance independently of the antigenicity level and without treatment i.e can be interpreted as a spontaneous regression.

Theorem 1.2 (Tumor clearance by immune system)**.** *We assume that*

$$p_1 > \mu_2, \quad s_1 = s_2 = 0 \tag{4}$$

and put

$$C_0 = \frac{\mu_2 g_1}{p_1 - \mu_2}, \quad L(E) = \frac{C_0 \mu_3 g_3}{p_2 E - C_0 \mu_3}, \quad E_0 = \frac{C_0 \mu_3}{p_2} \tag{5}$$

Let $t \mapsto (E(t), T(t), C(t)))$, $t \geq 0$ be the solution of the Kirschner-Panetta system (1a)-(1c) *satisfying the initial condition*

$$E(0) > E_0, \quad 0 < T(0) < b^{-1}, \quad T(0) > L(E(0)), \quad C(0) > C_0 \tag{6}$$

Then there exists $t_0 > 0$ such that

$$T(t_0) < L(E(0)) \tag{7}$$

Proof. From the equation (1a), which takes the form

$$\frac{dE}{dt} = cT - \mu_2 E + \frac{p_1 EC}{g_1 + C}\,, \tag{8}$$

it is seen that $\frac{dE}{dt} > 0$ ($\frac{dE}{dt} < 0$) if $C > C_0$ ($C < C_0$) where C_0 is defined by (5). From the third equation (1c)

$$\frac{dC}{dt} = \frac{p_2 ET}{g_3 + T} - \mu_3 C \tag{9}$$

one derives that $\frac{dC}{dt} > 0$ ($\frac{dC}{dt} < 0$) if and only if $C < F(E,T)$ ($C > F(E,T)$) where

$$F = \frac{p_2}{\mu_3}\frac{ET}{g_3 + T}, \quad (E,T) \in D = (0, +\infty) \times I \tag{10}$$

Introducing the surface $\Sigma = \{(E,T,C) \in \mathbb{R}^{+3} : C = F(E,T),\ (E,T) \in D\}$ one verifies that $\frac{dC}{dt} > 0$ if and only if the point (E,T,C) lies below Σ. The projection on the plane $E-T$ of the intersection $\Sigma \cap \{C = C_0\}$ is given by the curve $T = L(E)$, $E \in J = (E_0, +\infty)$ with L and E_0 given by (5). One checks that $\lim\limits_{E \to +\infty} L(E) = 0$.

Now, let $S(t) = (E(t), T(t), C(t))$, $t \in \mathbb{R}^+$ be the solution of (1a)-(1c) starting from the point $(E(0), T(0), C(0))$ and satisfying the condition (6). Then, one has simultaneously $\frac{dE}{dt} > 0$ and $C(t) > C_0$ until the projection $S_{PT}(t)$ of $S(t)$ on the plane $T - E$ is above the curve $\Omega = \{(E,T) \in \mathbb{R}^{+2} : T = L(E),\ E \in J\}$. Thus, $E(t)$ is increasing function of time until $S_{PT}(t)$ meets Ω for some $t = t_0 > 0$ (see Fig. 2), which is equivalent to (7). As follows from the equation (1b), the inequality $\frac{dT}{dt} < 0$ holds if and only if

$$E > \frac{r_2}{a}(1 - bT)(g_2 + T) \tag{11}$$

Hence, starting from the moment the number of effector cells E is sufficiently high, $T(t)$ starts to decrease until it reaches the value $T(0)$. End of the proof. □

Remark 1.3. As follows from Theorem 1.2 , the concentrations of effector cells and IL-2 are growing functions of time inside the interval $0 \leq t \leq t_0$. If $L(T(0)) < 1$, then the inequality (7), in biological terms, can be viewed as complete tumor clearance since one has less than 1 tumor cell left for $t = t_0$.

The Fig. 3 illustrates the application of Theorem 1.2 in the zero antigenicity case $c = 0$ (aggressive immunosuppressive tumors) without treatment. The other parameter values are taken from the paper [6]. It demonstrates in particular that the tumor can be cleared by immune system alone, even if its initial load $T(0)$ is near the carrying capacity b^{-1}, under the condition that the immune system defense is strong enough initially i.e the values of $E(0)$ and $C(0)$ satisfy the conditions (6).

Acknowledgement: The author is grateful to anonymous referee for their useful remarks and suggestions.

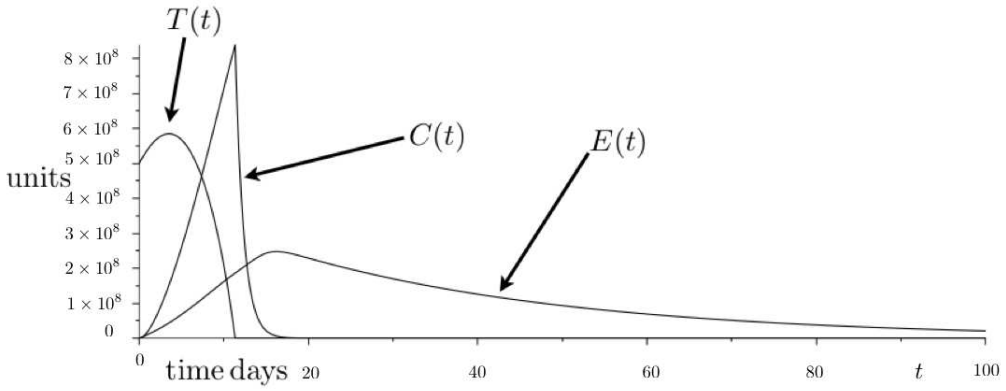

FIGURE 1. Clearance of tumor by adoptive immunotherapy with parameter values $\mu_2 = 0.03$, $p_1 = 0.1245$, $r_2 = 0.18$, $\mu_3 = 10$, $p_2 = 5$, $g_1 = 2 \times 10^7$, $g_2 = 1 \times 10^5$, $b = 1 \times 10^{-9}$, $a = 1$ and $c = 0.02$, $c_{\text{crit}} = 0.0054$, $s_1 = 550$, $s_2 = 0$. The initial conditions are chosen as follows : $E(0) = C(0) = 1$, $T(0) = 10^9/2$ (half of carrying capacity). The time of complete clearance t_c ($T(t_c) < 1$) is approx. 12 days.

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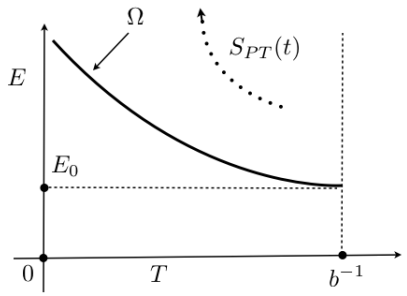

FIGURE 2. The graph Ω of $T = L(E)$ and projection S_{PT}.

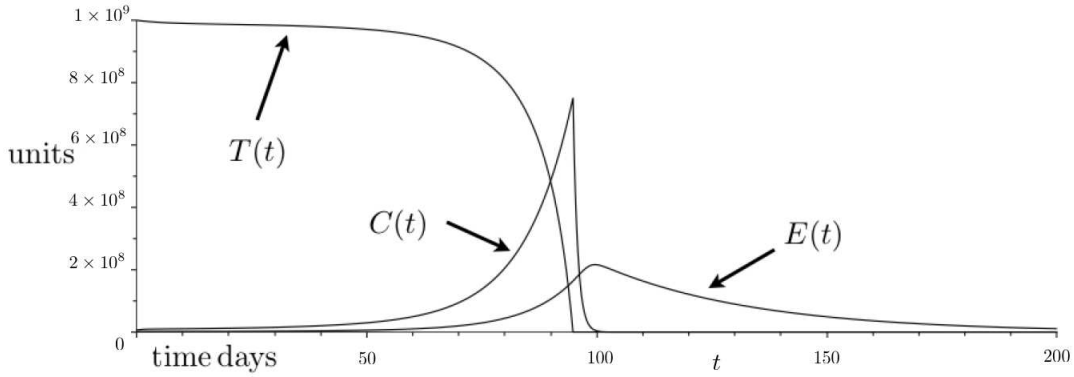

FIGURE 3. Clearance of tumor by immune system alone. The zero antigenicity case ($c = 0$) with no treatment ($s_1 = s_2 = 0$). Parameter values are: $\mu_2 = 0.03$, $p_1 = 0.1245$, $r_2 = 0.18$, $\mu_3 = 10$, $p_2 = 5$, $g_1 = 2 \times 10^7$, $g_2 = 1 \times 10^5$, $b = 1 \times 10^{-9}$, $a = 1$, $C_0 = 6349206.349$, $E_0 = 1269841.270$. The initial conditions are chosen as follows : $E(0) = 1969891 > E_0$, $C(0) = 6359207 > 0$, $T(0) = 10^9$ (the carrying capacity), $L(E(0)) = 1813.93$. The time of complete clearence t_c ($T(t_c) < 1$) is approx. 100 days.