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Global stability and tumor clearance conditions for a cancer chemotherapy system

Paul A. Valle[a,*], Konstantin E. Starkov[a], Luis N. Coria[b]

[a] Instituto Politécnico Nacional, CITEDI-IPN, Av. del IPN No. 1310, Mesa de Otay, Tijuana 22510, B.C., México
[b] Instituto Tecnológico de Tijuana, Blvd. Limón Padilla s/n, Mesa de Otay, Tijuana 22454, B.C., México

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ABSTRACT

In this paper we study the global dynamics of a cancer chemotherapy system presented by de Pillis et al. (2007). This mathematical model describes the interaction between tumor cells, effector-immune cells, circulating lymphocytes and chemotherapy treatment. By applying the localization method of compact invariant sets, we find lower and upper bounds for these three cells populations. Further, we define a bounded domain in $\mathbf{R}^4_{+,0}$ where all compact invariant sets of the system are located and provide conditions under which this domain is positively invariant. We apply LaSalle's invariance principle and one result concerning two-dimensional competitive systems in order to derive sufficient conditions for tumor clearance and global asymptotic stability of the tumor-free equilibrium point. These conditions are computed by using bounds of the localization domain and they are given in terms of the chemotherapy treatment. Finally, we perform numerical simulations in order to illustrate our results.

1. Introduction

Cancer is a general term used to define a group of more than 100 diseases, which can affect almost any part of the body and is characterized by the uncontrolled growth of abnormal cells that have lost the ability to regulate their lifespan. This phenomenon allows them to grow beyond their usual boundaries and invade surrounding tissues and organs, creating new cancer sources better known as malignant tumors. The process in which tumor cells spread throughout the body is called metastasis and it is the main death reason of cancer patients [1].

According to the World Health Organization [2] and GLOBOCAN [3], cancer was responsible for 8.2 million deaths worldwide in 2012. Lung, liver, stomach, colorectal and breast cancers cause the most number of deaths each year. It is predicted the continuing growth of cancer cases from 14 million in 2012 to 22 million in the following two decades.

In order to understand the complex dynamics of cancer, mathematical modeling has been used as a tool by biologists and mathematicians in the past years. Mathematical models must be designed in biological congruence with experimental data and clinical results and provide proper interactions between tumor cells and immune cells populations. Further, these models must give some insights concerning the short and long-term treatment effects of immunotherapy or/and chemotherapy. One may consult in [4–13] and many others.

* Corresponding author. Tel.: +52 6646231344.
E-mail addresses: pvallet1200@alumno.ipn.mx, pvalle@citedi.mx (P.A. Valle), kstarkov@ipn.mx (K.E. Starkov), luis.coria@gmail.com (L.N. Coria).

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The *Localization of Compact Invariant Sets* (LCIS) is a method used to analyze global dynamics of mathematical models defined by ordinary differential equations. This method was proposed by Krishchenko in [14], see also [15]. Recently, this method has been combined with Lyapunov stability theory and LaSalle's invariance principle in order to study biological systems that describe cancer tumor growth, see [16–23].

The LCIS method is used to find a domain where all compact invariant sets of a dynamical system are located. Bounds of this domain are given in terms of parameters of the system and may provide important information about the dynamics of biological systems that describe evolution of malignant tumors such as: tumor burden, efficiency of the immune system to fight cancer cells and efficacy of the treatments applied to a patient.

The main contribution of our work is to study several features about the ultimate global dynamics of the cancer chemotherapy model presented in Section 2 and the tumor clearance problem. We do not pretend to examine medical aspects of the long period application of chemotherapy treatment on the immune system and patient's health entirely. Namely, we find lower and upper bounds for all cells populations, prove the dissipativity property in the sense of Levinson in the nonnegative orthant, i.e. the existence of a bounded positively invariant domain, and derive sufficient conditions for tumor clearance and global asymptotic stability of the tumor-free equilibrium point. Our analysis is based on the LCIS method, LaSalle's invariance principle and one result concerning two-dimensional competitive systems, [27].

The paper is organized as follows. In Section 2 the cancer chemotherapy system is described and values and units of parameters are given. In Section 3 we present the theory corresponding to LCIS method. In Section 4 a domain is computed in which all compact invariant sets of the cancer chemotherapy system are located. In Section 5 we prove the existence of a bounded positively invariant domain. In Section 6 sufficient conditions for tumor clearance and global asymptotic stability of the tumor-free equilibrium point are derived. In Section 7 we perform numerical simulations to illustrate the mathematical results. In Section 8 a brief discussion about our results is presented. Finally, Section 9 contains conclusions of our work.

2. The cancer chemotherapy model

In our work the global dynamics of a cancer chemotherapy system presented by de Pillis et al. in [13] is studied. This mathematical model describes chemotherapy effects in tumor cells and the immune system by the following ordinary differential equations:

$$\dot{T} = aT - abT^2 - c_1NT - K_TMT, \tag{1}$$

$$\dot{N} = \alpha_1 + g\frac{T}{s+T}N - \mu N - pNT - K_NMN, \tag{2}$$

$$\dot{C} = \alpha_2 - \beta C - K_CMC, \tag{3}$$

$$\dot{M} = -\gamma M + V_M(t), \tag{4}$$

where $T(t)$ is the tumor cells population, $N(t)$ is the effector immune cells population, $C(t)$ is the circulating lymphocytes population and $M(t)$ is the chemotherapy drug concentration. According to de Pillis et al. the dynamics of each equation is as follows. In Eq. (1) tumor cells are assumed to grow logistically with an intrinsic rate a and carrying capacity of b^{-1} in the absence of effector cells and chemotherapy. A fraction of tumor cells are killed by the interaction with effector immune cells and the chemotherapy treatment, as it is shown by the third and fourth term. In Eq. (2) effector immune cells are assumed to have a constant source rate α_1 and recruited by tumor cells through a Michaelis–Menten term with a saturation given by g. The third term represents natural death of effector immune cells with rate μ. Additionally effector cells are inactivated by cancer cells and killed by chemotherapy, as it is defined by the fourth and fifth term. In Eq. (3) circulating lymphocytes have a constant source rate α_2 with a natural death rate β. The third term represents elimination of circulating lymphocytes by chemotherapy. The dynamics of the chemotherapy drug concentration is presented in Eq. (4) with a decay rate of γ and an outside source term that can be taken as a time function $V_M(t)$ or a constant input V_M. One can see that chemotherapy affects all three cell populations at different rates given by K_T, K_N and K_C. The description of parameters and its estimation are given in [13] and we show them in Table 1.

The dynamics of the system (1)–(4) is located in the nonnegative orthant:

$$\mathbf{R}^4_{+,0} = \{T \geq 0, N \geq 0, C \geq 0, M \geq 0\}.$$

3. Mathematical preliminaries and notations

The LCIS method is used to determine a domain on the state space where all compact invariant sets are located. As examples of compact invariant sets, one may recall equilibrium points, periodic orbits, homoclinic and heteroclinic orbits, invariant tori and chaotic attractors. The relevance of this analysis is due to the fact that it is useful to study the long-time dynamics of the system. Let us consider an autonomous nonlinear system of the form:

$$\dot{x} = f(x), \tag{5}$$