Physics Letters A ••• (••••) •••–•••

Contents lists available at ScienceDirect

Physics Letters A

www.elsevier.com/locate/pla

On dynamic tumor eradication conditions under combined chemical/anti-angiogenic therapies

Konstantin E. Starkov

Instituto Politecnico Nacional – CITEDI, Av. de IPN 1310, Nueva Tijuana, Tijuana 22435, B.C., Mexico

ARTICLE INFO

Article history:
Received 25 September 2017
Received in revised form 12 December 2017
Accepted 13 December 2017
Available online xxxx
Communicated by C.R. Doering

Keywords:
Ultimate dynamics
Tumor clearance
Chemotherapy
Antiangiogenic therapy

ABSTRACT

In this paper ultimate dynamics of the five-dimensional cancer tumor growth model at the angiogenesis phase is studied. This model elaborated by Pinho et al. in 2014 describes interactions between normal/cancer/endothelial cells under chemotherapy/anti-angiogenic agents in tumor growth process. The author derives ultimate upper bounds for normal/tumor/endothelial cells concentrations and ultimate upper and lower bounds for chemical/anti-angiogenic concentrations. Global asymptotic tumor clearance conditions are obtained for two versions: the use of only chemotherapy and the combined application of chemotherapy and anti-angiogenic therapy. These conditions are established as the attraction conditions to the maximum invariant set in the tumor free plane, and furthermore, the case is examined when this set consists only of tumor free equilibrium points.

1. Introduction

In recent fifteen years, a great effort has been made in the elaboration of mathematical non-spatial models for cancer tumor growth at the angiogenic stage in cases of no treatment and with treatment. It is well-known that tumor growth at the advanced stage, so called vascular stage, can be reasonably described by a system of ordinary differential equations, see e.g. [1,3,6,11,12,14,15,17,20,27]. Therefore this kind of models can be efficiently investigated by powerful methods of qualitative theory of ordinary differential equations and dynamical systems theory. Besides, it is worth to mention that issues of global dynamics of tumor growth have been explored in many articles including e.g. [7,16,18,19].

Angiogenesis is a transition process from avascular to vascular tumor. In this mechanism cancer cells induce substances that lead to an increase in the population of additional endothelial cells. This causes the proliferation of blood cells, i.e. neoformation of capillary blood vessels, which leads to additional oxygen and nutrients supplies for the tumor, [2].

In 2013 Pinho et al. have described the five-dimensional cancer tumor growth model at the angiogenesis phase for which chemotherapy and anti-angiogenic treatments are applied, [14]. This model has a noticeable impact on studies of dynamics of this phenomenon and can be written in the form:

$$\dot{x}_1 = a_1 x_1(1-x_1) - q_1 x_1 x_2 - p_1(x_3, w)\frac{x_1 y}{A_1 + x_1}, \tag{1}$$

$$\dot{x}_2 = a_2 x_2(1 - \frac{x_2}{1+\gamma x_3}) - q_2 x_1 x_2 - p_2(x_3, w)\frac{x_2 y}{A_2 + x_2},$$

$$\dot{x}_3 = \beta x_2 + a_3 x_3(1-x_3) - \frac{p_3 x_3 w}{A_3 + x_3},$$

$$\dot{y} = \delta - [\xi + \frac{d_1 x_1}{A_1 + x_1} + \frac{d_2 x_2}{A_2 + x_2}]y$$

$$\dot{w} = \phi - [\eta + \frac{d_3 x_3}{A_3 + x_3}]w,$$

with $p_i(x_3, w) = p_{i0} + p_{i1}x_3 + p_{i2}w, i = 1, 2$. Below it is used the notation for the nonnegative orthant $\mathbf{R}^5_{+,0} := \{x_1 \geq 0; x_2 \geq 0; x_3 \geq 0; y \geq 0; w \geq 0\}$ where equations (1) has a biological meaning.

In these equations the following notations are exploited: $x_1(t)/x_2(t)/x_3(t)$ are normalized concentrations of normal/cancer/endothelial cells populations correspondingly; $y(t)$ is a concentration of the chemotherapy agent; $w(t)$ is a concentration of the anti-angiogenic agent for $t \geq 0$. The model parameters in the normalized form can be described as follows: $a_i, i = 1, 2, 3$, are the proliferation rates of x_i; $q_i, i = 1, 2$, are two competition coefficients; $p_{i0}, i = 1, 2$, is the killing rate of chemotherapy on x_i in the absence of x_3 and w respectively; $p_{ij}, i, j = 1, 2$, is the rate of increased killing on x_i by cancer cells per concentration of x_3 $(j = 1)$ and w $(j = 2)$; p_3 is the killing rate of anti-angiogenic therapy on x_3; $A_i, i = 1, 2, 3$, is the Holling type 2 constant for $x_i, A_3 > 1$; β is the rate of creation cancer cells due to endothelial cells; γ is the proportion of endothelial cells responsible for the tumor angiogenesis; $d_i, i = 1, 2, 3$, is the rate at which an anti-angiogenic agent and cancer cells combine with x_i; δ and ϕ are the respective

E-mail addresses: kstarkov@ipn.mx, konstarkov@hotmail.com.

https://doi.org/10.1016/j.physleta.2017.12.025
0375-9601/

infusion rates of the chemotherapy agent and the anti-angiogenic agent; ξ and η are, respectively, the washout rates from the system of the chemotherapy agent and the anti-angiogenic agent.

In [14] various results on the system (1) dynamics have been obtained. Firstly, the property of dissipativity in the sense of Levinson has been described via the existence proof of an attracting polytope. Upper bounds for this polytope were presented, although the details of the derivation of the bound for x_3-population were not presented. Further, in case of no chemotherapy ($y \equiv 0; \delta = 0$) the persistence of the cancer cells population was established. Besides, in case of no anti-angiogenic therapy ($w \equiv 0; \phi = 0$) sufficient conditions of the cancer cells population persistence was shown. In addition, a local stability analysis of the tumor free-endothelial free equilibrium point ($x_2 = x_3 = 0$) has been provided.

The purpose of this work is to explore ultimate dynamics of the model (1) at large. The approach of this paper is based on: the localization method of compact invariant sets (LMCIS), [8,9]; one result for competitive systems, see e.g. in [4]; and the Dulac criterion for a two-dimensional asymptotically autonomous system, [26]. It is worth to recall that papers [10,21–25] are devoted to the global dynamic analysis of interactions between the tumor and the immune system, as well as finding the tumor eradication conditions; these works are based on the LMCIS.

The author's principal results and their novelty concern the derivation of a number of conditions under which all trajectories of (1) are attracted to the tumor-free plane. This property has the biological meaning of global asymptotic tumor clearance. In addition, it is noted that global asymptotic tumor clearance conditions for the model reveal that dynamic tumor growth can be controlled after some observational period. These conditions are stated in terms of inequalities imposed on the treatment parameters $\delta; \xi; \eta$ and ϕ. It is pointed out that in case when only chemotherapy treatment is applied in the model (1) the tumor eradication conditions (Theorem 1) can describe a positive scenario for the patient's health unlike the tumor persistence conditions found in [14]. Moreover, the combined application of chemotherapy and anti-angiogenic therapy is considered in Theorem 2 and global asymptotic tumor clearance conditions are obtained.

In order to deduce these conditions the derivation of ultimate densities for all variables involved in the model (1) is reviewed. In particular, the conservative bounds for concentrations of the chemotherapy agent and the anti-angiogenic agent are obtained.

This paper is organized as follows. Section 2 contains one basic assertion respecting the LMCIS. In Section 3, upper bounds were obtained for all concentrations of cell populations and both types of concentration of therapy using LMCIS. Further, positive lower bounds for ultimate concentration of both types of treatments are computed. The positivity of these lower bounds is essential in the proofs of main results (Theorems 1 and 2). Sections 4 and 5 contain preliminary remarks respecting dynamics on the tumor-free plane $x_2 = 0$/formulas for equilibrium points correspondingly. In Section 6 limit properties of trajectories are studied. Here in Proposition 2 the author provides conditions under which the ω-limit set of each trajectory is attracted to the set $x_1 x_2 = 0$ for the case when only chemotherapy is applied. In the case of chemotherapy alone, the conditions of attraction for each trajectory to the plane $x_2 = 0$ are established in Theorem 1. Theorem 2 gives conditions that guarantee the global asymptotic stability of the tumor-free equilibrium point for the case of using both types of therapy. It is worth to notice that the condition of Theorem 2 is fulfilled for parameters of Table 2, [14]. The latter theorem confirms results of numerical simulation presented in [14]. In Section 7 tumor eradication bounds are compared and discussed. In Section 8 conditions under which each trajectory in the tumor-free plane tends to one of the equilibrium points are presented. Concluding remarks are given in Section 9.

2. Some preliminaries and notations

For the reader's convenience the author reminds one helpful assertion. It is considered a nonlinear system

$$\dot{x} = F(x), \tag{2}$$

where $x \in \mathbf{R}^n$, $F(x) = (F_1(x), \ldots, F_n(x))^T$ is a differentiable vector field. Let $h(x) \in C^\infty(\mathbf{R}^n)$ be a function such that h is not the first integral of the system (2). The function h is used in the solution of the localization problem of compact invariant sets and is called a localizing function. Below $h|_U$ denotes the restriction of h on a set $U \subset \mathbf{R}^n$;

$$S(h) = \{x \in \mathbf{R}^n \mid L_F h(x) = 0\},$$

where $L_F h(x)$ is a Lie derivative with respect to F. It is proposed to get the localization of all compact invariant sets located in the set U. Further, it is used the following notation:

$$h_{\inf}(U) := \inf\{h(x) \mid x \in U \cap S(h)\};$$
$$h_{\sup}(U) := \sup\{h(x) \mid x \in U \cap S(h)\}.$$

Assertion. *[8,9]. For any $h(x) \in C^\infty(\mathbf{R}^n)$ all compact invariant sets of the system (2) located in U are contained in the set $K(U; h)$ defined by the formula*

$$\{x \in U \mid h_{\inf}(U) \le h(x) \le h_{\sup}(U)\}$$

as well.

3. Ultimate upper and lower bounds

In this section upper and lower bounds for the localization polytope containing all compact invariant sets are derived. Upper bounds give ultimate maximal values for all cells populations involved in the model. Lower bounds presented below serve as conservative measures of the chemotherapy agent/the anti-angiogenic agent concentrations.

Below the vector field of (1) is denoted by f. Firstly, the following lemma is presented:

Lemma 1. *All compact invariant sets are located in*

$$K_1 = \{0 \le x_1 \le x_{1\max} := 1\}; \tag{3}$$
$$K_2 = \{y_{\min} := \frac{\delta}{\xi + d_1 + d_2} \le y \le y_{\max} := \frac{\delta}{\xi}\};$$
$$K_3 = \{w_{\min} := \frac{\phi}{\eta + d_3} \le w \le w_{\max} := \frac{\phi}{\eta}\}.$$

Proof. Upper bounds in the formula (3) are easily derived by means of coordinate localizing functions $h_1 = x_1; h_2 = y; h_3 = w$. Now lower bounds for y and w will be denoted by $y_{\min}$ and $w_{\min}$. It follows from applying the function $h_2 = y$ that the set $S(h_2)$ is contained in the set defined by the inequality $\delta \le (\xi + d_1 + d_2)y$. So the last inequality yields the localization set $\{y_{\min} := \frac{\delta}{\xi + d_1 + d_2} \le y\}$. Similarly, by using the function $h_3 = w$ the localization set $\{w_{\min} := \frac{\phi}{\eta + d_3} \le w\}$ can be obtained. □

Bounds $x_{1\max}; y_{\max}; w_{\max}$ were got earlier in [14] and derived here in order to illustrate how the LMCIS works. Next, in order to obtain ultimate upper bounds for cells populations x_2 and x_3 the localizing function $h_4 = x_2 + cx_3$ is proposed to be exploited; here c is a positive parameter defined below. Then the formula

Please cite this article in press as: K.E. Starkov, On dynamic tumor eradication conditions under combined chemical/anti-angiogenic therapies, Phys. Lett. A (2018), https://doi.org/10.1016/j.physleta.2017.12.025