Bounding the long-time dynamics of a tumor immune-evasion model

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Abstract. In this document, we present results concerning the boundary for a localizing domain that contains all compact invariant sets for a tumor immune-evasion model. This model consists of a system of four nonlinear ordinary differential equations which describes the dynamics between tumor cells, immune effectors cells, the immuno-stimulatory cytokine Interleukin 2 and the suppressive cytokine TGF-β. The boundary for the final localizing set is expressed with some algebraic inequalities depending on the model parameters. This domain is important in the study of mathematical models which describes the dynamics of certain diseases because it provides important information about its long-time behavior, i.e. the location of equilibrium points, chaotic attractors, limit cycles, periodic orbits, homoclinic orbits and heteroclinic orbits. Our results are obtained by using two methods, one called *Localization of compact invariant sets*, which is based on first order extremum conditions, and the *Iterative theorem*. Finally, numerical simulations of dynamics of tumor growth are fulfilled in order to illustrate the localizing bounds.

Keywords: Boundary, Localization, Compact invariant sets, Iterative theorem, Cancer, Immune system.

1 Introduction

The design of mathematical models for biological systems began with the interaction of mathematics and biology; these models started to play a major role in the field of medicine by helping to better understand the evolution and spread of certain diseases, specially those whose study has generated an extremely complex problem to physicians through the years, e.g. : HIV-AIDS [1], [2], [3], hepatitis C [4], [5], H1N1 influenza [6], [7], tuberculosis [8], and some others. Furthermore, it should be noted that in practice it is necessary to develop *in vivo* experiments in order to determine the effect of different treatments. Therefore, numerical simulations of the models can help to diminish the amount of these experiments [9]. For this reason, a group of diseases of particular interest is cancer.

Cancer is a group of over 100 diseases characterized by uncontrolled proliferation of abnormal cells. These cells spread through the body and interfere with vital functions by invading tissues and organs, this process is called metastases and can lead to death of the individual [10]. Despite the fact that overall mortality rates have declined in recent years, it remains as a major cause of illness and death worldwide in both men and women [11]. Although, over time there have been developed different types of treatments for this disease, only surgery, radiotherapy and chemotherapy have been accepted by medical society as conventional treatments. Nevertheless, the human body's immune system has proven to have the potential to fight cancer [12]. Therefore, its interaction with the immune system has been of particular interest in the scientific community and it is well documented: [13], [14], [15], [16], [17], among others. Some mathematical models also describe the effect of certain treatments, such as chemotherapy and biotherapy, with the aim to provide physicians a tool that allows them to plan more scientifically the schedules for therapies [15], [18], [19].

Simultaneously with mathematical modeling, some methods for analyzing dynamic systems have been adapted in order to study mathematical models of biological systems. Such models require a different approach from those used to analyze other types of systems such as: physical, chemical, electronic, artificial, and others. This is because the state variables of biological systems describe the interaction of large populations such as: cells, proteins, antibodies, viruses, bacteria, swarms, and some others. Moreover, mathematical models of biological systems are much more complex and their evolution over time is slow, in the case of tumor growth this evolution may take several years [20].

Two methods of particular interest which have been used to study the global dynamics of biological systems, see [21], [22], [23], are the so called *Localization of compact invariant sets*, which is based on first order extremum conditions, and *Iterative theorem*. These methods allow us to define a domain in the state space in which all compact invariant sets of a dynamical system are located. This domain is important in the study of biological systems because it provides important information about the location of equilibrium points, chaotic attractors, limit cycles and periodic, homoclinic and heteroclinic orbits. Moreover, since the localization domain depends on system parameters, in some cases, it is possible to propose conditions to reduce its bounds to such degree that the only possible dynamic will be an equilibrium point. This equilibrium point can be interpreted as healthy state for an individual affected by a disease such as cancer.

Therefore, since the analysis of biological systems play an important role in oncology, in this paper we study the dynamics of a tumor immune-evasion mathematical model, which describes the dynamics among four populations: effector cells ($\dot{x}$), cancer cells ($\dot{y}$), cytokine interleukin 2 ($\dot{z}$) and cytokine TGF-β_1 ($\dot{w}$):

$$\begin{aligned}
\dot{x} &= \frac{cy}{1+\gamma w} - \mu_1 x + \left(\frac{xz}{g_1+z}\right)\left(p_1 - \frac{q_1 w}{q_2+w}\right); \\
\dot{y} &= ry\left(1-\frac{y}{b}\right) - \frac{axy}{g_2+y} + \frac{p_2 wy}{g_3+w}; \\
\dot{z} &= \frac{p_3 xy}{(g_4+y)(1+\alpha w)} - \mu_2 z; \\
\dot{w} &= \frac{p_4 y^2}{\tau_c^2+y^2} - \mu_3 w.
\end{aligned} \tag{1}$$

This tumor immune-evasion model, according to [24], can help doctors to better understand the evolution of a malignant tumor, its mechanisms of immune evasion and its interaction with effector cells. The main feature of this model is that it takes into consideration the secretion from the tumor of the cytokine Transforming growth factor - β_1 (TGF-β_1) which at: counter immuno-stimulating properties of IL-2, preventing tumor detection by the immune system, reducing the expression of antigens on cancer cells and inhibit activation and expansion of cytotoxic T cells and B cells, *prevents the destruction of the malignant tumor*. In addition, cytokine TGF-β_1 possesses angiogenic properties, which benefits the development and metastasis of malignant tumors [25].

The main objective of this paper is to establish the existence and form a compact invariant domain in the space R^4_+ for the tumor immune-evasion model (1). The importance of this domain lies in the fact that at being a compact invariant set any trajectory that enters into this domain will remain in it for all future time i.e. trajectories will not diverge exponentially. Biologically, this implies that concentrations of cytokines and cells described by system (1) will not increase uncontrollably, which would affect negatively the patient health.

The paper is organized as follows: section 2 presents mathematical preliminaries concerning the method for the localization of compact invariant sets, section 3 shows our localization results obtained by means of linear and nonlinear localizing functions, in section 4 we present numerical simulations in order to illustrate our final localizing domain, in section 5 we give a description about the biological implication of our results, section 6 presents the conclusions and finally the reader can see the references used in the development of this document.

2 Localization of compact invariant sets

By *Localization of compact invariant sets* we mean the calculation of the domain on the state space where all compact invariant sets are located. These compact invariant sets are presented under certain conditions in any specific mathematical model. The relevance of this analysis is because it is useful to study the long-term dynamics of the system. The general localization method of compact invariant sets of a nonlinear system was described in [26], [27]. In this section we present useful results. Let us consider a nonlinear system with the form:

$$\dot{x} = f(x); \tag{2}$$

where f is a continuous vectorial function for a $C^\infty-$differentiable vector field; $x \in \mathbf{R}^n$ is the state vector. Let $h(x)$ be a C^∞ such that h is not the first integral of (2). By $h|_B$ we denote the restriction of h on a set $B \subset \mathbf{R}^n$. The function h used in this statement is called localizing. By $S(h)$ we denote the set $\{x \in \mathbf{R}^n \mid L_f h(x) = 0\}$, where $L_f h(x)$ represents the Lie derivative of (2) and is given by: $L_f h(x) = \dfrac{\partial h}{\partial x} f(x)$. Let us define $h_{\inf} := \inf\{h(x) \mid x \in S(h)\}$; $h_{\sup} := \sup\{h(x) \mid x \in S(h)\}$.

2.1 General theorem

The general theorem concerning the localization of all compact invariant sets of a dynamical system establishes the following:

Theorem 2.1. *Each compact invariant set Γ of (2) is contained in the localization set $K(h) = \{h_{\inf} \leq h(x) \leq h_{\sup}\}$.*

If we consider the location of all compact invariant sets inside the domain $U \subset \mathbf{R}^n$ we have the localization set $K(h) \cap U$, with $K(h)$ defined in **Theorem 2.1**. It is evident that if all compact invariant sets are located in the sets Q_1 and Q_2, with $Q_1; Q_2 \subset \mathbf{R}^n$, then they are located in the set $Q_1 \cap Q_2$ as well.

2.2 Non existence condition

Suppose that we are interested in the localization of all compact invariant sets located in some subset Q of the state space $\mathbf{R}^n$. We formulate

Proposition 2.1. *If $Q \cap S(h) = \emptyset$ then the system (2) has no compact invariant sets located in Q.*

2.3 Iterative theorem

A refinement of the localization set $K(h)$ is realized with help of the iteration theorem stated as follows.

Theorem 2.2 *Let $h_m(x), m = 0, 1, 2, \ldots$ be a sequence of infinitely differentiable functions. Sets*

$$K_0 = K(h_0), \quad K_m = K_{m-1} \cap K_{m-1,m}, \quad m > 0,$$

with

$$\begin{aligned} K_{m-1,m} &= \{x : h_{m,inf} \leq h_m(x) \leq h_{m,sup}\}, \\ h_{m,sup} &= \sup_{S(h_m) \cap K_{m-1}} h_m(x), \\ h_{m,inf} &= \inf_{S(h_m) \cap K_{m-1}} h_m(x), \end{aligned}$$

contain any compact invariant set of the system (2) and

$$K_0 \supseteq K_1 \supseteq \cdots \supseteq K_m \supseteq \ldots .$$

3 Main localization results

In this section we present results for linear and nonlinear localizing functions. The intersections of these regions make the localization of all compact invariant sets for the tumor immune-evasion model shown above. Since variables x, y, z and w in model (1) represent concentrations with biological sense, we examine compact invariant sets only inside the positive domain:

$$R_+^4 = \{x > 0, y > 0, z > 0, w > 0\} ;$$

which is also consider a compact invariant set. In addition all parameters of this model are supposed to be positive. Also, for the simplicity of notations we consider the following: $S(h) = S(h) \cap R_+^4$ and therefore $K(h) = K(h) \cap \mathbf{R}_+^4$.

3.1 Localization by means of linear functions

In order to obtain a localizing set that provides *the supreme value for the secretion of the cytokine TGF-*β_1 by the tumor, we propose the following localizing function $h_1 = w$; from which by calculating its Lie derivative and performing the corresponding operations we can obtain the next set

$$S(h_1) = \left\{ \mu_3 w = p_4 \left(1 - \frac{\tau_c^2}{\tau_c^2 + y^2} \right) \right\} ;$$

now, we can define the following

Theorem 3.1: *The supreme value for the concentration of the cytokine TGF-*β_1 *is given by* w_{max} *in the localizing set:*

$$K(h_{11}) = \left\{ w_{min} = 0 \leq w \leq \frac{p_4}{\mu_3} = w_{max} \right\} . \tag{3}$$

Now, we propose the localizing function $h_2 = y$ in order to establish a *supreme value for the concentration of cancer cells,* from which by calculating its the Lie derivative and applying the iterative theorem with the localizing set (3) we can obtain the next

$$S(h_1) \cap K(h_{11}) \subset \left\{ h_{2|_{S(h_1)}} \leq b \left(1 + \frac{p_2 p_4}{(\mu_3 g_3 + p_4) r} \right) \right\} ;$$

then, according to calculations performed we can have the following

Theorem 3.2: *The maximum concentration of cancer cells is given by the value* y_{max} *on the localizing set:*

$$K(h_{21}) = \left\{ y_{min} = 0 \leq y \leq b \left(1 + \frac{p_2 p_4}{(\mu_3 g_3 + p_4) r} \right) = y_{max} \right\} . \tag{4}$$

Now, in order to obtain a *supreme value for the dynamics of the state variable corresponding to the effector cells*, we take the localizing function $h_3 = x$; from which by calculating its Lie derivative and applying the iterative theorem with the sets (3) and (4) we can obtain the set

$$S(h_3) \cap K(h_{11}) \cap K(h_{21}) \subset \left\{ x \leq \frac{c y_{max}}{\mu_1 - p_1} \right\};$$

and if the next condition is fulfilled

$$\mu_1 > p_1; \tag{5}$$

we can define the next

Theorem 3.3: *If condition (5) is fulfilled, then the maximum concentration of effector cells at the tumor site is given by the value x_{max} in the next localizing set:*

$$K(h_{31}) = \left\{ x_{min} = 0 \leq x \leq \frac{c y_{max}}{\mu_1 - p_1} = x_{max} \right\}. \tag{6}$$

Now, trying to obtain the *supreme value for the cytokine IL-2 concentration at the tumor site* we take the localizing function $h_4 = z$; from which by calculating its Lie derivative, applying the iterative theorem by using the sets (3), (4) and (6), and if condition (5) is fulfilled we can obtain the following

$$S(h_4) \cap K(h_{11}) \cap K(h_{21}) \cap K(h_{31}) \subset \left\{ z \leq \frac{1}{\mu_2} \frac{p_3 (x_{max})}{1 + \alpha (w_{min})} \left(1 - \frac{g_4}{g_4 + y_{max}} \right) \right\};$$

then, we can get the next

Theorem 3.4: *If condition (5) is fulfilled, then the maximum concentration of IL-2 at the site of the tumor is given by the value z_{max} in the next localizing set:*

$$K(h_{41}) = \left\{ z_{min} = 0 \leq z \leq \frac{p_3 x_{max} y_{max}}{\mu_2 (g_4 + y_{max})} = z_{max} \right\}. \tag{7}$$

3.2 Localization by means of nonlinear functions

Nonlinear localizing functions are used to reduce the domain conformed by the intersection of the sets obtained by linear functions. The relevance in reducing this domain remains in the fact that it would be easier to find the different dynamics of a system by numerical simulations. In addition, the decrease of the bounds allows us to better understand the system dynamics in the long term. Below we show results obtained with the nonlinear localizing function $h_5 = xy$; from which by calculating its Lie derivative and by using the localizing sets (3), (4) in order to apply the iterative theorem we can get the following

$$S(h_5) \cap K(h_{11}) \cap K(h_{21}) \subset \left\{ xy \leq \frac{b}{r} \left(c y_{max} - \beta_1 x^2 + \beta_2 x \right) \right\};$$

where
$$\beta_1 := \frac{a}{g_2 + y_{max}} \quad \text{and} \quad \beta_2 := \frac{p_2 p_4}{\mu_3 g_3 + p_4} + p_1 + r - \mu_1;$$

then, according to the sign of β_2 we can define the following:

Theorem 3.5: *If* $\beta_2 > 0$; *then the localizing set is given by*

$$K(h_{51}) = \left\{ xy \leq \frac{b}{r}\left(\frac{\beta_2^2}{4\beta_1} + c y_{max}\right)\right\}. \tag{8}$$

Theorem 3.6: *If* $\beta_2 \leq 0$; *then the localizing set is given by*

$$K(h_{52}) = \left\{ xy \leq \frac{b c y_{max}}{r}\right\}. \tag{9}$$

4 Numerical simulations

The final compact localizing set in which all compact invariant sets of (1) are located is given by the intersections of the following sets:

$$K(h_{11}) \cap K(h_{21}) \cap K(h_{31}) \cap K(h_{41}) \cap K(h_{51}).$$

Now, since all localizing sets depend on system parameters we use specific values in order to get our results. The periodic orbit and the boundaries illustrated in Figure 1 were obtained by using the following values in system parameters: $\mu_1 = 0.03$; $p_1 = 0.01$; $g_1 = 2 \times 10^7$; $c = 0.005$; $q_1 = 0.1121$; $q_2 = 2 \times 10^6$; $\gamma = 10$; $r = 0.18$; $b = 1 \times 10^9$; $a = 1$; $g_2 = 1 \times 10^5$; $p_2 = 0.27$; $g_3 = 2 \times 10^7$; $p_3 = 5$; $g_4 = 1 \times 10^3$; $\mu_2 = 10$; $\alpha = 1 \times 10^{-3}$; $\mu_3 = 10$; $\tau_c = 1 \times 10^6$; $p_4 = 0.1204$.

Figure 1.(a) shows the localizing domain concerning the variables x (Effector cells), y (Cancer cells) and z (Cytokine IL-2) and Figure 1.(b) shows the localizing domain concerning the variables x (Effector cells), y (Cancer cells) and w (Cytokine TGF-β_1).

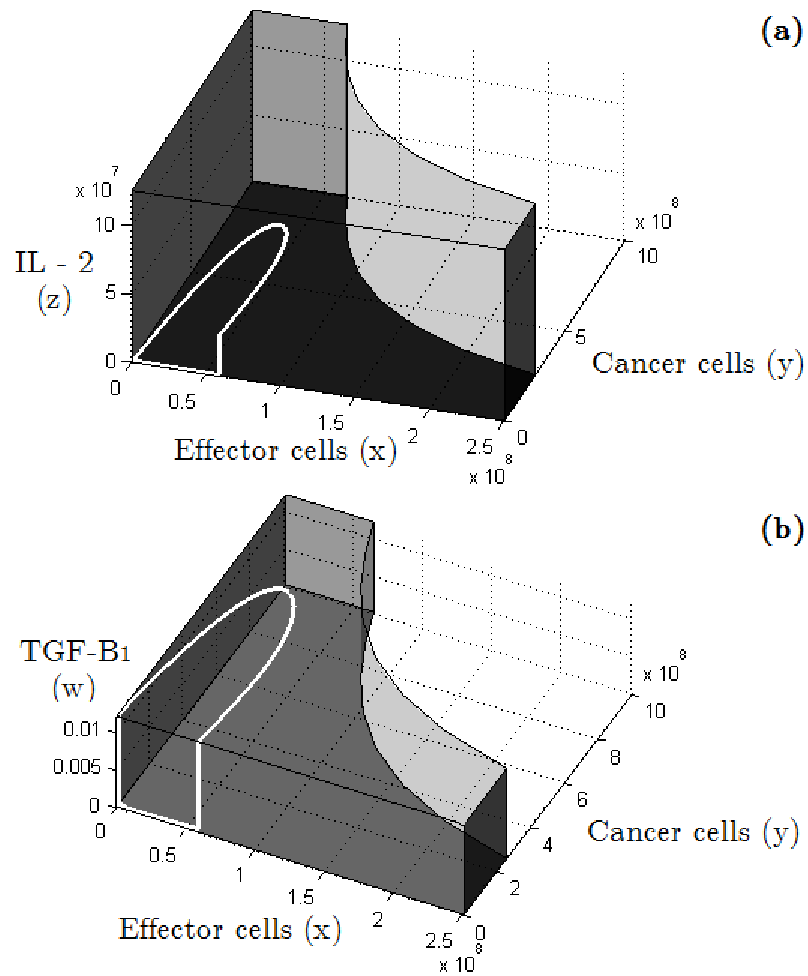

Fig. 1. Localizing domain for the tumor immune-evasion model (1):(a) Dynamics of the state variables x, y y z. (b) Dynamics of the state variables x, y y w.

5 Biological implications

The dynamical properties in long-time behavior of a specific system become observable if we can find their bounds. The existence of the localizing sets $K(h_{31})$ and $K(h_{41})$ (which represent effector cells and IL-2 concentration respectively) depends on the condition (5) $(\mu_1 > p_1)$. This condition means that the mortality rate of effector cells is greater than its proliferation rate. Although this condition implies deterioration in the health of the patient, it is important to analyze it. We have found in the literature that the condition $\mu_1 > p_1$ may occur in a patient due to the following scenarios:

– **Tumor defense mechanisms.** These mechanisms affect the lifetime of immune cells and are generated by the genetic instability of cancer cells [28], [25], some of which may contribute to fulfill the condition (5) are:

1. Some tumors have levels of antigens too low to be detected by the immune system which can induce apoptosis in T cells due to the lack of warning signals to alert the immune system. This phenomenon can lead to immune tolerance to cancer cells.
2. Production by the tumor of immune inhibitory substances such as TGF-β_1. This protein performs several functions within the cell including the process of apoptosis.
3. Induction in proliferation of suppressor T cells by the malignant tumor.

– **Treatments such as chemotherapy and radiotherapy.** These play an important role in immune system deficiency because they affect the patient ability to generate T cells, which decreases the number of white blood cells and weakens the immune system. Furthermore, this contributes to make the patient more susceptible to acquire various types of infections [29], [30], [31], [32] y [33].

6 Conclusions

Our approach can be compared with the results obtained by Kirschner and Tsygvintsev (2009) in [34], where the authors use quasi-Lyapunov functions in order to establish some bounds for a cancer immunotherapy mathematical model. Nevertheless, in [35] Starkov and Coria (2012) use the Localization of compact invariant sets method and the Iterative theorem in order to establish a compact domain where all compact invariant sets of the cancer immunotherapy model are located; also they give some conditions for a tumor free equilibrium point, it is important to say that this conditions depend only on the system parameters. The advantages of using localizing functions instead of quasi-Lyapunov functions remain in the fact that these functions do not have the same limitations, e.g. localizing functions does not have to be positive definite and its derivative does not have to be negative definite, in order to get useful information the Lie derivative of the localizing function needs to have a definite sign, with which we are able to define a supreme or an infinite value for the bounds according with **Theorem 2.1**. Additionally, we can obtain an improvement of the bounds if it is possible to use the **Theorem 2.2**.

The tumor immune evasion system (1) is an extension of the cancer immunotherapy model presented by Kirschner and Tsygvintsev and we were able to establish a compact domain for all compact invariant sets of (1) by applying linear and nonlinear localizing functions which intersection makes. Nevertheless, since system (1) does not have any treatment parameters, i.e. the cellular immunotherapy and the external administration of IL-2 from the cancer immunotherapy system, it is not possible to give conditions for a tumor free equilibrium point; also the boundaries given in section 3 are not as manipulable as the ones presented in [35].

Now, we present some general conclusions about our results:

– We were able to define supreme values for each of the state variables of the biological system under study, these values are given by the localizing sets: $K\left(h_{i1}\right)$

and $K(h_{5j})$; $i = 1,2,3,4$; $j = 1,2$; which define the compact domain in the state space where all compact invariant sets of the system (1) are located.
- The existence of the localizing sets concerning the supreme values of effector cells ($K(h_{31})$) and IL-2 ($K(h_{41})$) concentrations depends on the condition (5): $\mu_1 > p_1$, see discussion in the previous section.
- Localizing sets $K(h_{51})$ and $K(h_{52})$ (obtained through the nonlinear localizing function h_5), allows to reduce the localizing region in the xy plane. Additionally, the function h_5 provides a general overview of the interaction between effector cells and cancer cells i.e. as the concentration of effector cells increases the upper bound for cancer cells concentration decreases and viceversa. Therefore, it became obvious that in order to completely eradicate the malignant tumor it is necessary to maintain a sufficient amount of effector cells in the tumor site.
- The existence of the sets: $K(h_{11})$, $K(h_{21})$, $K(h_{51})$ and $K(h_{52})$ does not depend on any condition that may have conflict with the biological sense of the system parameters.

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