AMCA

Memorias del Congreso Nacional de Control Automático
ISSN: 2594-2492

Analysis and Estimation of Chaotic Tumor Evolution under Immunotherapy Treatment

Itzel Sanchez-Robles * **Paul A. Valle-Trujillo** *
Ramon Ramirez-Villalobos *

* *Tecnológico Nacional de México - Instituto Tecnológico de Tijuana, Blvd. Alberto Limón Padilla s/n, Mesa de Otay, 22454, Tijuana, B.C. México (e-mail: {itzel.sanchez18, paul.valle, ramon.ramirez}@tectijuana.edu.mx).*

Abstract: This paper is focused on the study of the global dynamics of a chaotic-cancer system. This mathematical model describes the dynamics of cancer cells and its interaction with healthy cells and effector-immune cells, the system considers the influx of effector cells by adding an immunotherapy treatment parameter. By applying the Localization of Compact Invariant Sets method we derive lower and upper bounds with conditions written in terms of the immunotherapy treatment parameter. Furthermore, due to the difficulty to measure the population of effector-immune cells in lab environments, a nonlinear observer is designed to estimate the concentration of these cells. We design the observer by considering the measurements of cancer cells and healthy host cells, as well as the upper bounds computed with the LCIS method. Finally, numerical simulations are performed to illustrate and support the analytical results.

Keywords: Cancer, Chaos, Global stability, Immunotherapy, Localizing domain, Mathematical model, Observer design.

1. INTRODUCTION

Cancer is the name given to a set of diseases related to an uncontrolled process in the division of cells. The normal process of cell regeneration occurs when the cells grow and divide to form new cells. In the particular case of cancer, the regeneration process is uncontrolled, that is, old and damaged cells survive instead of being replaced and new cells are formed when they are not required. These new cells can divide uncontrollably and form masses, which are called tumors (National Cancer Institute , 2015).

Immunotherapy is a type of biological therapy that helps to boost the immune system to fight cancer. In this treatment, substances produced by the body are used to stop or delay the growth of cancer cells. In addition, it prevents the spread of cancer to other parts of the body and helps the immune system to destroy cancer cells (National Cancer Institute , 2018). However, as consequence of an interaction between biological factors such as cell proliferation, apoptosis and mutation; and microenvironmental factors like angiogenesis and inflammation; immunotherapy has a low success rate. Moreover, some clinical studies have shown that individualized immunotherapy treatment protocols have a better success rate with fewer side effects. Nevertheless, these studies are very expensive and can only be applied individually Valle et al. (2018). In order to understand the behavior of cancer and how it interacts with the immunotherapy treatment, not only is necessary to perform clinical trials, this could also be known through Biomathematics. The aim of this science is to apply analysis and theoretical mathematical techniques to understand, in both short- and long-term, the behavior of complex biological systems. Thereby, it is possible to identify properties not obvious to the experimenter Hoppensteadt (1995). In this context, mathematical models of first-order ordinary differential equations (ODEs) are useful to estimate the complex dynamics between tumor growth, immune response and the effect produced by the application of a treatment such as immunotherapy.

In last decades, diverse mathematical models have been presented with this purpose; for example, the authors in Kirschner and Panetta (1998) applied mathematical modeling in order to explain the dynamics between tumor cells and immune-effector cells under an adoptive cellular immunotherapy. This study helps to explain tumor oscillations depending on immune response, and also in long-term tumor recovery. In addition, the effects of cellular immunotherapy are explored. In another study, a dynamical model of cancer growth is developed by Itik and Banks (2010), which includes the interactions between tumor cells, healthy tissue cells, and activated immune system cell. In C. Latellier et al. (2013), authors analyze the model constructed by Pillis and Radunskaya (2003), this model contains three types of cells populations, host,

immune and tumor cells. The main purpose of this study is to show how an unconventional analysis can suggest new trends to understand the interactions between some tumor cells and their environment. In recent years, studies have been reported on the analysis of global dynamics of the model formulated by Pillis and Radunskaya (2003). For example, in Starkov and Krishchenko (2014) the global behavior of the three-dimensional model is analyzed. In this study sufficient conditions were found where all trajectories, within the positive octant, go to an equilibrium point; the latter could be the equilibrium point of the small tumor mass, the healthy equilibrium point or the equilibrium point representing death.

The motivation of this paper lies on analyzing and estimating the global dynamics of the three-dimensional chaotic cancer model presented by Itik and Banks (2010). We apply the LCIS method in order to compute all upper bounds for the three cells populations described by the system. These bounds allows us to design an observer to estimate the concentration of the effector-immune cells population. This concentration is important in the sense that an elevated value of effector cells could be harmful for any patient. Hence, by measuring cancer cells and healthy host cells we are able to estimate a total value for the effector cells population when it is boosted by the immunotherapy treatment. With this information, we can control the total amount of treatment that is administered at any given time. Thus, we avoid critical values that could be harmful in real-life scenarios.

The remainder of this paper proceeds as follows. Section 2 presents the mathematical preliminaries concerning the LCIS method. In Section 3 we introduced the nonlinear chaotic-cancer model. In Section 4 we stablish the bounds of a localizing domain containing all compact invariant sets of the chaotic-cancer model, while sufficient conditions for the elimination of cancer is also discussed. In Section 5, the observer design to estimate the immune cells is introduced. Numerical simulations illustrate the analytical results in Section 6. Finally, concluding remarks are presented in Section 7.

2. MATHEMATICAL PRELIMINARIES

Consider an autonomous nonlinear system of the form

$$\dot{x} = f(x), \tag{1}$$

where $f(x)$ is $\mathcal{C}^\infty$–differentiable vector function and $x \in \mathbb{R}^n$ is the state vector. Let $h(x) : \mathbb{R}^n \to \mathbb{R}$ be a $\mathcal{C}^\infty$–differentiable function. The function $h(x)$ is called localizing function and it is assumed that $h(x)$ is not the first integral of $f(x)$. By $S(h)$ we denote the set $\{x \in \mathbb{R}^n : L_f h(x) = 0\}$, where $L_f h(x)$ represents the Lie derivative with respect to the vector field $f(x)$ corresponding to the system (1). Now, let us define

$$h_{\inf} = \inf\{h(x) : x \in S(h)\},$$

and

$$h_{\sup} = \sup\{h(x) : x \in S(h)\},$$

then, the General Theorem concerning the localization of all compact invariant sets of a dynamical system is established as follows

Theorem 1. (General Theorem, see Krishchenko (2005)). Each compact invariant set Γ of system (1) is contained in the localizing domain

$$K(h) = \{h_{\inf} \leq h(x) \leq h_{\sup}\}.$$

Localizing functions are selected by an heuristic process; this means that one may need to analyze several functions in order to find a proper set that will allow fulfilling Theorem 1. If it is considered the location of all compact invariant sets inside the domain $U \subset \mathbb{R}^n$, we have the set $K(h) \cap U$, with $K(h)$ defined in Theorem 1. It is evident that if all compact invariant sets are located in the sets Q_1 and Q_2, with $Q_1, Q_2 \subset \mathbb{R}^n$, then they are located in the set $Q_1 \cap Q_2$ as well. Furthermore, a refinement of the localizing domain is realized with the help of the Iterative Theorem stated as follows

Theorem 2. (Iterative Theorem, in Krishchenko (2005)). Let $h_m(x)$, $m = 0, 1, 2, \ldots$, be a sequence of $\mathcal{C}^\infty$–differentiable functions. Sets

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

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 (1) and

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

3. MATHEMATICAL MODEL OF CANCER EVOLUTION

Modelling cancer evolution by first-order ODEs allows us to understand the dynamics of tumors in diverse scenarios that will be difficult to study *in situ* with real-life patients. In this paper, we analyze the mathematical model presented by Itik and Banks (2010) under the immunotherapy treatment as strategy to control tumor growth. The mathematical model describes the dynamics betwen healthy cells, cancer cells and immune effector cells by the following equations:

$$\dot{x} = x(1 - x) - a_{12}xy - a_{13}xz, \tag{2}$$

$$\dot{y} = r_2 y(1 - y) - a_{21}xy, \tag{3}$$

$$\dot{z} = \frac{r_3 xz}{x + k_3} - a_{31}xz - d_3 z + s_1, \tag{4}$$

where $x(t)$ represents the rate of change in the cancer cells population, $y(t)$ healthy host cells, $z(t)$ the effector cells population and s_1 is the adoptive cellular immunotherapy treatment. Further, it should be noticed that dynamics of the system (2)–(4) is located in the non-negative octant, given by

$$\mathbb{R}^3_{+,0} = \{0 \leq x(t) \leq 1, \quad 0 \leq y(t) \leq 1, \quad z(t) \geq 0\}.$$

Description of all parameters is shown below in Table 1. All values were proposed by Itik and Banks (2010) in order to demonstrate the existence of a chaotic attractor in the tumor evolution described by Eqs. (2)–(4).

Table 1. Description and values of parameters

Parameter	Description	Value
a_{12}	Fractional tumor cells killed by healthy cells	1
a_{13}	Fractional tumor cells killed by effector cells	2.5
r_2	Healthy host cells growth rate	0.6
a_{21}	Fractional healthy cells killed by tumor cells	1.5
r_3	Maximum effector cells recruitment rate by tumor cells	4.5
k_3	Steepness coefficient of the effector cells recruitment	1
a_{31}	Fractional effector cells inactivated by tumor cells	0.2
d_3	Death rate of effector cells	0.5
s_1	Immunotherapy treatment parameter	—

In Fig. 1 is illustrated the chaotic attractor of (2)–(4), which is located in the non-negative octant $\mathbb{R}^3_{+,0}$. As one can see, all parameters are nondimensionalized and positive, furher, the maximum carrying capacity for both tumor and healthy cells populations has been normalized to 1.

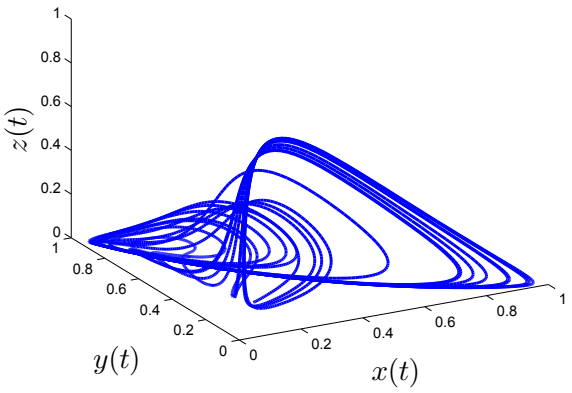

Fig. 1. Dynamics of the chaotic-cancer system.

4. LOCALIZATION OF COMPACT INVARIANT SETS

In this section we applied the LCIS method to define the localizing domain for the cancer evolution system (2)–(4). Boundaries are given by inequalities in terms of the system parameters.

Theorem 3. All compact invariant sets of the chaotic-cancer system (2)–(4) are located inside the localizing domain

$$K_{xyz} = K_x \cap K_y \cap K_z,$$

where

$$K_x = \{0 \leq x(t) \leq x_{\text{sup}} = 1 - a_{13} z_{\text{inf}}\},$$
$$K_y = \{0 \leq y(t) \leq y_{\text{sup}} = 1\},$$
$$K_z = \left\{ z_{\text{inf}} = \frac{s_1}{d_3} \leq z(t) \leq z_{\text{sup}} \right\}.$$

with z_{sup} is defined as follows

$$z_{\text{sup}} := \frac{(1-4s_1)(1+k_3)}{4(r_3 - d_3 - d_3 k_3)} + x_{\max}.$$

Proof. First, let us take a linear localizing function to compute the upper bound of the tumor population

$$h_1 = x,$$

now, let us compute its Lie derivative as follows

$$L_f h_1 = x(1-x) - a_{12}xy - a_{13}xz,$$

then, we get the set $S(h_1) = \{L_f h_1 = 0\}$ as

$$S(h_1) = \{x = 1 - a_{12}y - a_{13}z\} \cup \{x = 0\},$$

and we formulate the next

$$h_1|_{S(h_1)} = 1 - a_{12}y - a_{13}z,$$

from which we are able to conclude that non–divergent solutions to Equation (2) will be located inside the set

$$K(h_1) = \{0 \leq x(t) \leq x_{\max} = 1\}.$$

Now, to compute the maximum value of the healthy cells population we exploit the next localizing function

$$h_2 = y,$$

and compute the Lie derivative as shown below

$$L_f h_2 = r_2 y(1-y) - a_{21}xy,$$

therefore we get the set $S(h_2) = \{L_f h_2 = 0\}$

$$S(h_2) = \left\{ y = \frac{r_2 - a_{21}x}{r_2} \right\} \cup \{y = 0\},$$

and we formulate the next

$$h_2|_{S(h_2)} = 1 - \frac{a_{21}}{r_2}x,$$

from which we are able to conclude that non–divergent solutions to Equation (3) will be located inside the set

$$K_y = \{0 \leq y(t) \leq y_{\text{sup}} = 1\}.$$

Now, let us take the next localizing function

$$h_3 = z,$$

and compute the Lie derivative as follows

$$L_f h_3 = \frac{r_3 xz}{x + k_3} - a_{31}xz - d_3 z + s_1,$$

hence we get the set $S(h_3) = \{L_f h_3 = 0\}$

$$S(h_3) = \left\{ d_3 z = s_1 + \frac{r_3 - a_{31}(x+k_3)}{x+k_3} xz \right\},$$

and by assuming a set of solutions that fulfills the next

$$r_3 - a_{31}(x + k_3) \geq 0, \tag{5}$$

we are able to conclude that the lower bound for all solutions to Equation (4) is given by

$$K(h_3) = \left\{ z(t) \geq z_{\text{inf}} = \frac{s_1}{d_3} \right\},$$

therefore, by applying the Iterative Theorem we can establish an upper bound for the cancer cells population as indicated below, we take again the set $S(h_1)$

$$S(h_1) \cap K(h_3) \subset \{x \leq 1 - a_{12}y - a_{13}z_{\inf}\},$$

hence, the upper bound for the cancer cells population considering the immune response with immunotherapy is given by the set

$$K_x = \{0 \leq x(t) \leq x_{\sup} = 1 - a_{13}z_{\inf}\}. \tag{6}$$

Finally, let us compute the upper bound for the effector cells population, let us exploit the localizing function

$$h_4 = z - x,$$

and its Lie derivative is computed below

$$\begin{aligned} L_f h_4 = &\frac{r_3 xz}{x + k_3} - a_{31}xz - d_3 z + s_1 - x \\ &+x^2 + a_{12}xy + a_{13}xz, \end{aligned}$$

and by grouping terms and considering the next condition

$$a_{13} > a_{31}, \tag{7}$$

we can write set $S(h_4) = \{L_f h_4 = 0\}$ as follows

$$\begin{aligned} S(h_4) = \Bigg\{ &\left(\frac{(r_3 - d_3)x - d_3 k_3}{x + k_3} \right) z = \frac{1}{4} - s_1 \\ &- \left(x - \frac{1}{2} \right)^2 - a_{12}xy \\ &-(a_{13} - a_{31})xz \Bigg\}, \end{aligned}$$

therefore, by considering that $z = h_4 + x$ we get

$$\begin{aligned} S(h_4) = \Bigg\{ &h_4 + x = \frac{x + k_3}{(r_3 - d_3)x - d_3 k_3} \\ &\cdot \left[\frac{1}{4} - s_1 - \left(x - \frac{1}{2} \right)^2 - a_{12}xy \right. \\ &\left. -(a_{13} - a_{31})xz \right] \Bigg\}, \end{aligned}$$

which implies the following

$$\begin{aligned} S(h_4) = \Bigg\{ &h_4 = \frac{x + k_3}{(r_3 - d_3)x - d_3 k_3} \\ &\left[\frac{1}{4} - s_1 - \left(x - \frac{1}{2} \right)^2 - a_{12}xy \right. \\ &\left. - (a_{13} - a_{31})\, xz \right] - x \Bigg\}, \end{aligned}$$

hence, by applying the Iterative Theorem, we obtain the next subset

$$S(h_4) \cap K(h_1) \subset \left\{ h_4 \leq \frac{(1 - 4s_1)(1 + k_3)}{4(r_3 - d_3 - d_3 k_3)} \right\},$$

thus, if the next conditions hold

$$r_3 > d_3(1 + k_3), \tag{8}$$

$$s_1 < \frac{1}{4}, \tag{9}$$

we establish the next result

$$K(h_4) = \left\{ z - x \leq \frac{(1 - 4s_1)(1 + k_3)}{4(r_3 - d_3 - d_3 k_3)} \right\},$$

from which, by applying once more the Iterative Theorem, we are able to conclude that nondivergent solutions to Equation (4) will be located inside the set

$$K_z = \left\{ z_{\inf} = \frac{s_1}{d_3} \leq z(t) \leq z_{\sup} \right\}, \tag{10}$$

with

$$z_{\sup} := \frac{(1 - 4s_1)(1 + k_3)}{4(r_3 - d_3 - d_3 k_3)} + x_{\max}, \tag{11}$$

the existence of the boundary $z_{\sup}$ also depends on conditions (7)–(9). Thus, Theorem 3 is proved. ■

5. OBSERVER DESIGN

Since, the measurement on immune cells require a complex experiments in the lab environment Rokhforoz et al. (2017). In this section, we design a nonlinear observer to estimate the immune cells .

Consider a nonlinear dynamic system of the next form

$$\dot{w} = Aw + f(w, u), \tag{12}$$

$$y = Cw, \tag{13}$$

where $w \in \mathbb{R}^n$ is the state vector, $u \in \mathbb{R}^m$ is the vector input and $y \in \mathbb{R}^p$ is the output measurable vector; A and C are matrices of corresponding dimensions. In addition, the pair (A, C) is observable.

Now, consider an observer of the following form

$$\dot{\widehat{w}} = A\widehat{w} + f(\widehat{w}, u) + L(y - C\widehat{w}), \tag{14}$$

where $\widehat{w} \in \mathbb{R}^n$ represents the estimate of state vector x. The observer gain matrix L has corresponding dimensions.

The nonlinear term $f(w, u)$ in (12) is said to be locally Lipschitz in a domain $\mathcal{D}$ and uniformly bounded in u, i.e., satisfies the following condition

$$\|f(w, u) - f(\widehat{w}, u)\| \leq \gamma \|w - \widehat{w}\|, \quad w \in \mathcal{D}, \tag{15}$$

where the smallest $\gamma > 0$ in (15) is known as the Lipschitz constant, see Marquez (2003). This constant is defined as follows

$$\gamma = \limsup \left\| \frac{\partial f(w, u)}{\partial w} \right\|, \quad \forall w \in \mathcal{D}.$$

For the observer design consider the following Theorem, proposed by Panomchoeng and Rajamani (2010),

Theorem 4. For the class of system and observer forms described in (12)–(13) and (14), if and observer gain matrix L can be chosen such that

$$\begin{bmatrix} (A - LC)^T P + P(A - LC) + \varepsilon\gamma^2 I_n & P \\ P & -\varepsilon I_n \end{bmatrix} < 0, \tag{16}$$

for some positive definite symmetric matrix P, then this choice of L leads to asymptotically state estimates by the observer (14) for system (12).

Now, for the observer design, system (2)–(4) represented in terms of the state-space vector $w = [x, y, z]^T$ can be specified as nonlinear system (12)–(13) with

$$\begin{aligned} A = \begin{bmatrix} 1 & 0 & 0 \\ 0 & r_2 & 0 \\ 0 & 0 & -d_3 \end{bmatrix}, \quad C = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \end{bmatrix}, \\ f(w, u) = \begin{bmatrix} -x^2 - a_{12}xy - a_{13}xz \\ r_2 y^2 - a_{21}xy \\ \dfrac{r_3 xz}{x + k_3} - a_{31}xz + s_1 \end{bmatrix}. \end{aligned} \tag{17}$$

In this case, the inmunotherapy treatment parameter s_1 represents the input of (2)–(4).

Finally, by applying Theorem 4 to system (2)–(4) and the observer (14) specified with (17), it is derived an asymptotically state estimations by the proposed observer.

6. RESULTS

Firstly, in order to illustrate our results concerning to LCIS analysis, in Fig. 2 we present the numerical simulation of the tumor cells population, healthy host cells population and effector-immune cells population under the immunotherapy treatment. The values of parameters considered for simulation purposes are provided in Table 1 and the initial conditions were selected as $x(0) = y(0) = z(0) = 0.1$.

Fig. 2 shows the evolution of (2)–(4) considering the immunotherapy treatment parameter $s_1 = 1/7$, this value satisfies inequality (9). It can be seen that the population of tumor cells $x(t)$, healthy cells $y(t)$ and effector-immune cells $z(t)$ remain inside of the localizing domain K_{xyz}, given in Theorem 3, i.e., the corresponding solution will not go beyond this limits. It is important to highlight that $x(t)$ converges to a tumor-free state. In addition, healthy cells $y(t)$ converges to y_{sup}. The latter was of course to be expected, because in the absence of tumor cells, the amount of healthy cells increases to their maximum carrying capacity and the density of effector-immune cells will be governed only by the value of immunotherapy treatment parameter s_1.

Finally, results concerning to estimation of effector-immune cells are presented as follows. For the observer design, the cancer cells and healthy host cells populations were considered as the only available measurement. Thus, the pair (A, C) subject to (17) is observable. The observer gain matrix L is selected as

$$L = \begin{bmatrix} 2.5 & 0 \\ 0 & 1.5 \\ 0 & 0 \end{bmatrix}.$$

The Lipschtz constant was calculated by considering (15). In this case, we assume that $f(w, u)$, defined in (17), is Lipschitzian on the localizing domain K_{xyz}. Thereby, as result, we obtain

$$\gamma(K_{xyz}) \leq \max_{w \in K_{xyz}} \left|\left| \frac{\partial f(w,u)}{\partial w} \right|\right| \leq 2.7482.$$

Now, considering $\varepsilon = \gamma(K_{xyz})^{-2}$, there exists a positive definite and symmetric matrix P given by

$$P = \begin{bmatrix} 0.3746 & 0 & 0 \\ 0 & 0.3991 & 0 \\ 0 & 0 & 0.4305 \end{bmatrix}$$

such that, the LMI defined in (16) is fulfilled.

The estimation of effector-immune cells population is shown in Fig. 3. The initial conditions for system (2)–(4) and the proposed were set as

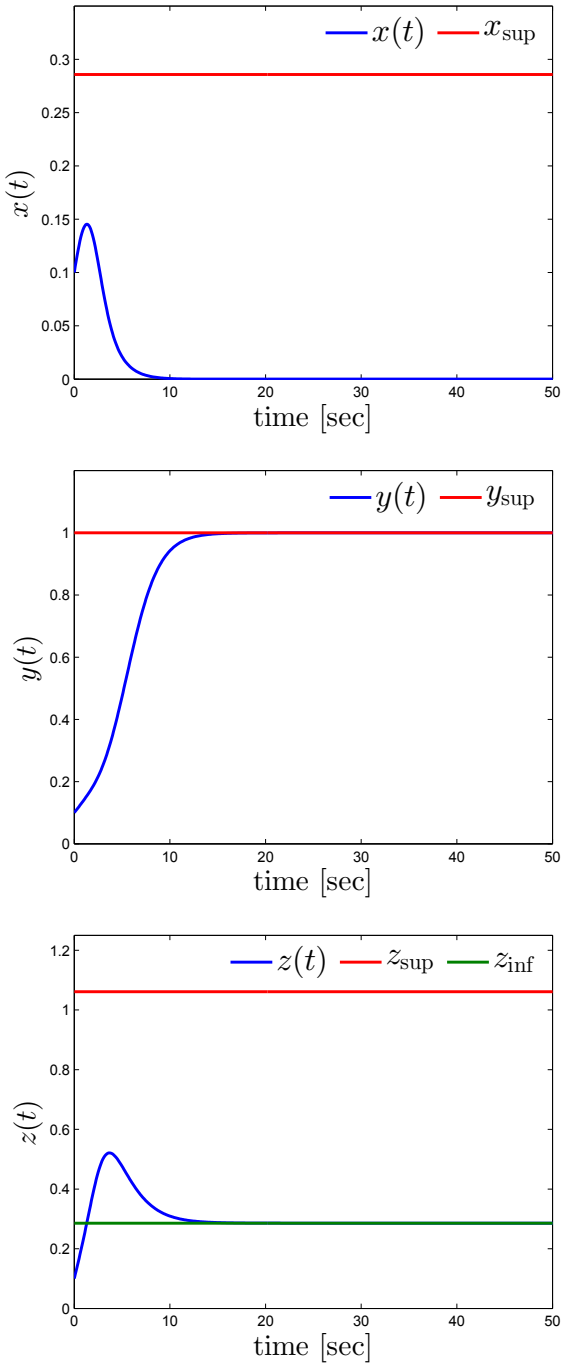

Fig. 2. System response under immunotherapy treatment s_1.

$$w(0) = [x(0), y(0), z(0)]^T = 0.1 \in \mathbb{R}^3,$$
$$\widehat{w}(0) = [\widehat{x}(0), \widehat{y}(0), \widehat{z}(0)]^T = 0.4 \in \mathbb{R}^3,$$

respectively.

As one can observer from Fig. 3, the estimation value of the effector-immune cells population (red dashed line) converges to the real values (blue solid line).

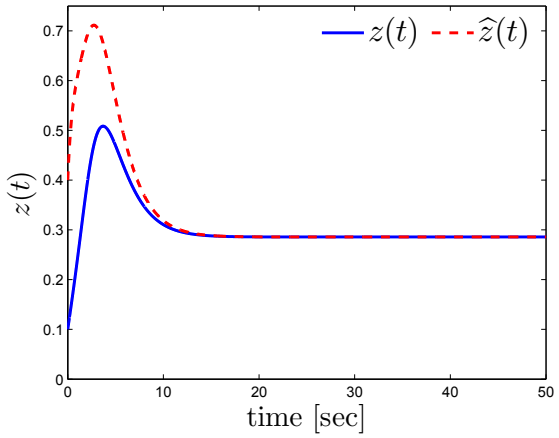

Fig. 3. Estimated and real values of effector-immune cells under immunotherapy treatment s_1.

7. CONCLUSIONS

An analysis of the global dynamic of the chaotic-cancer system by means of the LCIS method was considered in this paper, in order to establish the lower and upper bounds for a cancer-chaotic mathematical model under an immunotherapy treatment. The LCIS method and Iterative Theorem allows us to determine all bounds for the chaotic-cancer system. In addition, a nonlinear observer is designed to estimate the immune cells. In the observer design is considered only the measurements of cancer cells and healthy host cells, and the upper bounds defined by the LCIS analysis. Numerical simulations support the analytical results. Further research direction is toward to establish conditions for the elimination of cancer through an immunotherapy treatment by means of stability theories.

Real-life applicability of our results remains as an open question, the observer we implemented in this work was designed by assuming that we could measure the concentration of both cancer and normal cell in order to estimate the effector cells. Nonetheless, in a real-life scenario, cancer cells can only be observed in clinical studies when they reach a certain size which is usually given by 1 cm^3 or 1 g. Effector cells, could be estimated by blood test, the concentration of effector cells in the blood is expected to rise if the body is fighting a disease, normal cells in the other hand could be very difficult to measure or even estimate. Therefore, for a real-life application of our results we need to compute design an observer the could estimate most of the variables by measuring the easiest and whose value can be obtained in regular not costly clinical studies.

ACKNOWLEDGEMENTS

This work was supported by TecNM project number 5268.19-P titled as “Biomatemáticas modelizado y análisis para comprender fenómenos del mundo real” and TecNM project number 6006.19-P titled as “Observadores robustos para la solución de problemas en ingeniería”.

REFERENCES

F. Hoppensteadt Getting Started in Mathematical Biology. *NOTICES OF THE AMS*, 42(9), 969–947, 1995.

M. Itik and S.P. Banks Chaos in a three-dimensional cancer model. *International Journal of Bifurcation and Chaos*, 20(1), 71–79, 20103

D. Kirschner and J. C. Panetta Modeling immunotherapy of the tumor–immune interaction. *Journal of Mathematical*, 37(3), 235–252, 1998.

A.P. Krishchenko Localization of invariant compact sets of dynamical systems *Journal of Differential Equations*, 41(12), 1669–1676, 2005.

C. Latellier and F. Denis and L.A. Aguirre What Can be Learned from a Chaotic Cancer Model? *Journal of Theoretical Biology*, 322, 7–16, 2013.

H. J. Marquez *Nonlinear Control Systems: Analysis and Design* John Wiley & sons, 2013.

National Cancer Institute Immunotherapy to Treat Cancer https://www.cancer.gov/about-cancer/treatment/types/immunotherapy

National Cancer Institute What Is Cancer? https://www.cancer.gov/about-cancer/understanding/what-is-cancer

G. Panomchoeng and R. Rajamani Observer Design for Lipschitz Nonlinear Systems Using Riccati Equations *Proceeding of the 2010 American Control Conference ACC*, 6060–6065, 2010.

L. G. Pillis and A. Radunskaya The Dynamics of an Optimally Controlled Tumor Model: A Case Study *Mathematical and Computer Modelling*, 37(11), 1221–1244, 2003.

P. Rokhforoz and A.A. Jamshidi and N. Namazi Adaptive robust control of cancer chemotherapy with extended Kalman filter observer *Informatics in Medicine Unlocked*, 8, 1–7, 2017.

K.E. Starkov and A.P. Krishchenko On the Global Dynamics of One Cancer Tumor Growth Model *Communications in Nonlinear Science Numerical Simulation*, 19(5), 1486–1495, 2014.

P.A. Valle and L.N. Coria and D. Gamboa and C. Plata Bounding the Dynamics of a Chaotic-Cancer Mathematical Model *Mathematical Problems in Engineering*, ID 9787015, 14 pages, 2018.

