Bounding the domain containing all compact invariant sets of a AIDS model related cancer

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Abstract. The suffering of two diseases like AIDS and cancer is a deadly danger to the life of any person. In this paper we analyzed a model which describes the dynamics between the immune system of four nonlinear differential equations where each state represents cell populations: cancer cells, healthy cells T-CD4+, infected cells T-CD4+ and HIV-1 free virus. The final localization domain is obtained by the method of Localization of Compact Invariant Sets, which consist in first order extreme conditions, and the iterative theorem. We proposed some linear and rationals localizing functions which intersections enclosed all compact invariant sets of the system under study. Finally, numerical simulations are presented in order to show the localization results.

Keywords: Cancer, HIV/AIDS, compact invariant sets, biological system.

1 Introduction

The mathematical models have been used years ago to analyze some physical models like biological models. Have been modeling different biological systems to observe its behavior, since models that represents a predator-prey system [1], viral infection [2], different types of cancer as brain tumours [3], bladder cancer [4], diabetes [5], hematologic disorders (leukemia) [6] and models that help in disease with some parameters of control through some treatment, for example in tumor immunotherapy [7]; or models showing the immune system response against some disease. Through this type of model has been observed the dynamic between the Human Immunodeficiency Virus (HIV) and the immune response [8], [9]. According to the number of deaths, some of these diseases represent a serious threat, being the main heart disease, cancer, respiratory diseases, among others [10]. The HIV/AIDS is one of the main causes of death in the world due it generate a serious deterioration of the immune system. When the count of cells T-CD4+ reaches a low amount, the body goes to the next level of infection is AIDS, which is the final stage of HIV where the body can contract various infections and diseases, including cancer. Cancer is characterized by show uncontrolled growth of abnormal cells leading to a tumor, which is one cause of death in AIDS patients.

Given the impact of these diseases on society, in this paper we analyze a mathematical model wich describes an interation of HIV/AIDS and immune system by the method called Localization of Compact Invariant Sets. This model has been of interest to some researchers, e.g. in [11], where authors analyze the system varying parameters. The results of these analyze is show a deep similarity the clinical observations from different types of cancer in patients infected with HIV-1. However, to our knowledge there are no reported for the system 1. Our analysis is important because it allow to know the region where are located different dynamics in the system.

The following model was developed by Lou *et al*. [12] based on the model of Perelson *et al.* [13], that describes the dynamics between immune system cells and the HIV virus. This system considered two routes of spread for HIV *in vivo*, besides entering a cell as a free infected particle, can be also be passed during cell-cell contact. Additionally to these two variables, immune system and HIV, in the next system are considered cancer cells in their analysis. About cancer, these cells proliferate on different way as normal cells. Finally the immune system can recognize between cancer cell and normal cells to play its role, protect. The model is represented by the following differential equations

$$
\begin{aligned}
\frac{dC(t)}{dt} &= r_1 C(t)\left(1-\frac{C(t)+T(t)+I(t)}{m}\right)-k_1C(t)T(t); \\
\frac{dT(t)}{dt} &= s + r_2T(t)\left(1-\frac{C(t)+T(t)+I(t)}{m}\right)-\mu_T T(t) \\
&\quad -k_2T(t)V(t)-k_3T(t)I(t); \\
\frac{dI(t)}{dt} &= k_2T(t)V(t)+k_3T(t)I(t)-\mu_I I(t); \\
\frac{dV(t)}{dt} &= q\mu_I I(t)-\delta V(t);
\end{aligned}
\tag{1}
$$

where $C(t)$ represents the concentration of cancer cells, $T(t)$ is the concentration healthy cells, $I(t)$ is the concentration infected cells and $V(t)$ is the concentration of virus HIV-1 free.

According to the literature, the number of healthy cells that become to cancerous cells is very small compared with the uncontrolled proliferation of cancer cells [14]. With respect to T cells, if they encounter some specific antigens can stimulate its growth. However, even when these cells are stimulated or highly proliferated, the total number of T cells in the body remains bounded. The term $k_2T(t)V(t)$ in (1) represents the rate at which the free virus infects T-CD4+ cells. Given to the biological characteristics of the system, parameters and states are positive. For the development of this analysis, nomenclature of each state was replaced by x_1, x_2, x_3, y x_4, respectively. The document is organized as follows: in the next section is shown some mathematical notations and concepts for the analysis of localization of compact invariant sets. After that, we propose some localizing functions and show in numerical simulations. Finally, we present the conclusion of this research.

2 Some mathematical preliminaries and notations

The localization method is used to define the region of the state space where are located all compact invariant sets, this analysis is useful for understanding the dynamics of the system. In order to find a localization we used a general method described in [15], [16] y [17]. The useful results from these papers are described below

Considering the following nonlinear system as:

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

where f is a C^{∞} -differentiable vector field-, here $x \in \mathbf{R}^n$ is the -state space vector-. Let $h(x)$ be a C^{∞} -differentiable function such that h is not the first integral of (2)-. By $h|_B$ we denote the restriction of h on a set $B \subset \mathbf{R}^n$. By $S(h)$ we denote the set $\{x \in \mathbf{R}^n \mid L_f h(x) = 0\}$ where $L_f h$ of (2) is given by $L_f h(x) = \frac{\partial h}{\partial x} f(x)$. Now we define $h_{\inf} = \inf\{h(x)|x \in S(h)\}$ and $h_{\sup} = \sup\{h(x)|x \in S(h)\}$ that will be used in this analysis.

Theorem 1. Each compact invariant set Γ of (2) is contained in the localization set:

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

The function h applied here is called localizing. It is evident that if all compact invariant sets are located in 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.

The iterative theorem is described as shown below:

Theorem 2. Let $h_m(x), m = 0, 1, 2, \dots$ be a sequence of functions C^{∞} ($\mathbf{R}^n$). The sets:

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

with

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

contain all compact invariant sets of the system (2) and

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

Due the biological and mathematical sense of each state that compose the system (1), the compact invariant sets will be present in R^4_+, and any localization outside of this region will not be useful for this analysis. In addition, system parameters are positive. Also, for the sake of simplicity of notations $K(h) = K(h) \cap \mathbb{R}^4_+$ and $S(h) = S(h) \cap \mathbb{R}^4_+$.

3 Localizations analysis of the AIDS model related cancer

In order to find the localization domain, we proposed different localizing functions among linear and rational. From our expertise of the localization analysis some special functions can be applied but no better results are found; especially with quadratic and high order functions, we obtain trivial results respecting of our previous calculations. The goal of proposing these functions is to implement the method developed by Dr. Krishchenko and Dr. Starkov, according to the analysis developed shows an advantage over other methods because the proposal does not restrict the use of functions and iterative method improves the bounds.

3.1 Localization results by linear functions

In this section we present different linear functions delimiting the domain of each of state variables.

1. We proposed the following function

$$h_1 = x_1; \tag{3}$$

and its $L_f h_1$ and from this is determinate $S(h_1)$,

$$S(h_1) \subset \left\{ \frac{r_1}{m} h_1|_{S(h_1)} = r_1 - \frac{x_2 + x_3}{m} - k_1 x_2 \right\}.$$

Then we obtained $h_1|_{S(h_1)}$ and we get $S(h_1) \subset \left\{ h_1|_{S(h_1)} \leq m \right\}$.
Therefore, all compact invariant sets are contained in

$$K(h_1) = \{x_1 \leq m\}.$$

2. The second function that we proposed is

$$h_2 = x_2;$$

by determining $L_f h_2$ is obtained $S(h_2)$:

$$S(h_2) = \left\{ (\mu_T - r_2)\, x_2 = -r_2 x_2 \left(\frac{x_1 + x_2 + x_3}{m} \right) - k_2 x_2 x_4 - k_3 x_2 x_3 + s \right\};$$

solving with respect to x_2 to get $h_2|_{S(h_2)}$ and simplifying the expression, we have

$$S(h_2) \subset \left\{ h_2|_{S(h_2)} \leq \frac{s}{\mu_T - r_2} \right\}.$$

Then we can state that if $\mu_T - r_2 > 0$, all compact invariant sets are located in

$$K_1(h_2) = \left\{ x_2 \leq \frac{s}{\mu_T - r_2} \right\}.$$

3. Developing the product situated on the right-expression $S(h_2)$ we have

$$S(h_2) = \left\{ \begin{array}{c} (\mu_T - r_2)\, x_2 = -m^{-1}(r_2 x_2^2 + r_2 x_1 x_2 + r_2 x_2 x_3) \\ -x_2(k_2 x_4 - k_3 x_3) + s \end{array} \right\};$$

and we rewrite respect to x_2

$$S(h_2) \subset \left\{ h_2|_{S(h_2)} \leq \frac{\sqrt{4r_2 sm + (\mu_T - r_2)^2 m^2} - (\mu_T - r_2)m}{2r_2} \right\}.$$

From the later formulae, all compact invariant sets are in the set

$$K_2(h_2) = \left\{ x_2 \leq \frac{\sqrt{4r_2 sm + (\mu_T - r_2)^2 m^2} - (\mu_T - r_2)m}{2r_2} \right\}.$$

4. In order to find a bound of x_3 we proposed the following function

$$h_3 = x_2 + x_3; \tag{4}$$

Calculating the Lie derivative and is obtained $S(h_3)$

$$S(h_3) = \left\{ -\frac{1}{m} r_2 x_2^2 + r_2 x_2 - \mu_T x_2 - \mu_I x_3 - \frac{1}{m} r_2 x_1 x_2 - \frac{1}{m} r_2 x_2 x_3 + s = 0 \right\};$$

solving respect x_3 of the expression to get $h_3|_{S(h_3)}$. Simplifying is rewritten as

$$S(h_3) \subset \left\{ \begin{array}{c} h_3|_{S(h_3)} \leq -\frac{r_2}{\mu_I m} \left(x_2 - \frac{m(\mu_I + r_2 - \mu_T)}{2r_2} \right)^2 \\ + \frac{m(\mu_I + r_2 - \mu_T)^2}{4\mu_I r_2} + \frac{s}{\mu_I} \end{array} \right\}.$$

Is necessary to calculate the $h_{3\,\sup}$ from $S(h_3)$ Then we can ensure that all compact invariant sets are located in the set

$$K(h_3) = \left\{ x_2 + x_3 \leq \frac{m(\mu_I + r_2 - \mu_T)^2}{4\mu_I r_2} + \frac{s}{\mu_I} \right\}. \tag{5}$$

5. Finally within a linear function is proposed $h_4 = x_4$.
Calculating its Lie derivative and obtaining

$$S(h_4) = \left\{ x_4 = \frac{q \mu_I x_3}{\delta} \right\}.$$

Applying the iterative theorem with (5) and using its limit for x_3, we have

$$S(h_4) \cap K(h_3) \subset \left\{ x_4 \leq \frac{q}{\delta} \left[\frac{m(\mu_I + r_2 - \mu_T)^2}{4r_2} + s \right] \right\};$$

then all compact invariant sets are located in

$$K(h_4) = \left\{ x_4 \leq \frac{q}{\delta} \left(\frac{(\mu_I + r_2 - \mu_T)^2 m}{4r_2} + s \right) \right\}. \tag{6}$$

3.2 Localization results by rational functions

After having proposed linear functions, we proposed some rational functions. With this kind of functions we expect a refinement of the localization region.

1. The first proposed rational function is

$$h_5 = \frac{x_4}{x_3}.$$

Calculating the $L_f h_5$ which is subsequently developed to obtain $h_5|_{S(h_5)}$

$$S(h_5) = h_5|_{S(h_5)} = \frac{1}{\delta - \mu_I}\left(q\mu_I - k_2 \frac{x_2 x_4^2}{x_3^2} - k_3 \frac{x_2 x_4}{x_3} \right), \quad \delta - \mu_I > 0;$$

we found that the supreme value is given by h_5

$$S(h_5) \subset \left\{ h_5|_{S(h_5)} \leq \frac{q\mu_I}{\delta - \mu_I} \right\}.$$

Then as a result we get that If $\delta - \mu_I > 0$, then all invariant compact sets are contained in

$$K(h_5) = \left\{ \frac{x_4}{x_3} \leq \frac{q\mu_I}{\delta - \mu_I} \right\}.$$

2. The next function is given by

$$h_6 = \frac{x_2}{x_1}. \tag{7}$$

Calculating the $L_f h_6$ and $S(h_6)$ is describe by

$$S(h_6) \subset \left\{ \begin{array}{c} \frac{1}{x_1}\left(s + r_2 x_2 \left(1 - \frac{x_1 + x_2 + x_3}{m} \right) - \mu_T x_2 - k_2 x_2 x_4 - k_3 x_2 x_3 \right) \\ - \frac{x_2}{x_1{}^2}\left(r_1 x_1 \left(1 - \frac{x_1 + x_2 + x_3}{m} \right) - k_1 x_1 x_2 \right) = 0 \end{array} \right\};$$

applying the iterative theorem with (6), considering the bound of x_4 is assigned to

$$\gamma := \frac{q}{\delta}\left(\frac{(\mu_I + r_2 - \mu_T)^2 m}{4 r_2} + s \right);$$

we get

$$S(h_6) \cap K(h_4) \subset \left\{ \begin{array}{c} \left(\frac{r_1}{m} + k_1 - \frac{r_2}{m} \right) x^2 + (r_2 - \mu_T - r_1 - k_2\gamma)\, x_2 \\ + \left(\frac{r_1}{m} - \frac{r_2}{m} \right) x_1 x_2 + \left(\frac{r_1}{m} - \frac{r_2}{m} - k_3 \right) x_2 x_3 + s = 0 \end{array} \right\}. \tag{8}$$

Whether it satisfies that

$$\frac{r_1}{m} + k_1 - \frac{r_2}{m} > 0; \tag{9}$$

the term of x_2 is

$$r_2 - \mu_T - r_1 - k_2\gamma < 0; \tag{10}$$

respecting $x_1 x_2$ is

$$\frac{r_1}{m} - \frac{r_2}{m} > 0; \tag{11}$$

and $x_2 x_3$

$$\frac{r_1}{m} - \frac{r_2}{m} - k_3 > 0; \tag{12}$$

then solving (8) in order to find a bound to x_2, we have

$$S(h_6) \cap K(h_4) \subset \left\{ x_2 \geq \frac{s}{r_1 + \mu_T + k_2\gamma - r_2},\ r_1 + \mu_T + k_2\gamma - r_2 > 0 \right\}.$$

After replacing the bound obtained for x_2 in function and using the iterative theorem (3), we have

$$S(h_6) \cap K(h_4) \cap K(h_1) \subset \left\{ h_6|_{S(h_6)} \geq \frac{s}{(r_1 + \mu_T + k_2\gamma - r_2)\, m} \right\}.$$

Therefore, if the inequalities (9), (10), (11) and (12) then all invariant compact sets are contained in the set

$$K(h_6) = \left\{ \frac{x_2}{x_1} \geq \frac{s}{(r_1 + \mu_T + k_2\gamma - r_2)\, m} \right\}.$$

3.3 Numerical simulations

Based on the functions obtained in the previous section, the Table 3.3 present some localizing functions valid according to certain parameters, in order to show with figures the results obtained. In order to perform the simulations we consider the following values on the parameters (13):

$$\begin{array}{lll} \delta = 3 & k_1 = 3.43 \times 10^{-4} & k_2 = 2.4 \times 10^{-5} \\ k_3 = 2.4 \times 10^{-5} & m = 1500 & \mu_T = 0.02 \\ \mu_I = 0.24 & q = 200 & r_1 = 0.5 \\ r_2 = 0.019 & s = 10 & \end{array} \tag{13}$$

Table 1. Localization result for the system (1).

Localization domain	Condition	Numerical values
$K(h_1) = \{x_1 \leq m\}$	*	$x_1 \leq 1500$
$K_2(h_2) = \left\{x_2 \leq \frac{\sqrt{4r_2 sm + (\mu_T - r_2)^2 m^2} - (\mu_T - r_2)m}{2r_2}\right\}$	$\mu_T > r_2$	$x_2 \leq 756.23$
$K(h_3) = \left\{x_2 + x_3 \leq \frac{m(\mu_I + r_2 + \mu_T)^2}{4\mu_I r_2} + \frac{s}{\mu_I}\right\}$	*	$x_2 + x_3 \leq 4730.8$
$K(h_4) = \left\{x_4 \leq \gamma := \frac{q}{\delta}\left(\frac{(\mu_I + r_2 - \mu_T)^2 m}{4r_2} + s\right)\right\}$	*	$x_4 \leq 75693$
$K(h_5) = \left\{\frac{x_4}{x_3} \leq \frac{q\mu_I}{\delta - \mu_I}\right\}$	$\delta > \mu_I$	$\frac{x_4}{x_3} \leq 17.391$
$K(h_6) = \left\{\frac{x_2}{x_1} \geq \frac{s}{(r_1 + \mu_T + k_2\gamma - r_2)m}\right\}$	$r_1 > r_2 > k_3$	$\frac{x_2}{x_1} \geq 2.3 \times 10^{-3}$

The analysis result of the localizing functions is given by the region bounded, for each state variable there is a supreme where is located all compact invariant sets of the system (1).

In the following Figure 1 shows the dynamics of the system along of the results of localization given by $K(h_1) \cap K_2(h_2) \cap K(h_3) \cap K(h_4) \cap K(h_5) \cap K(h_6)$.

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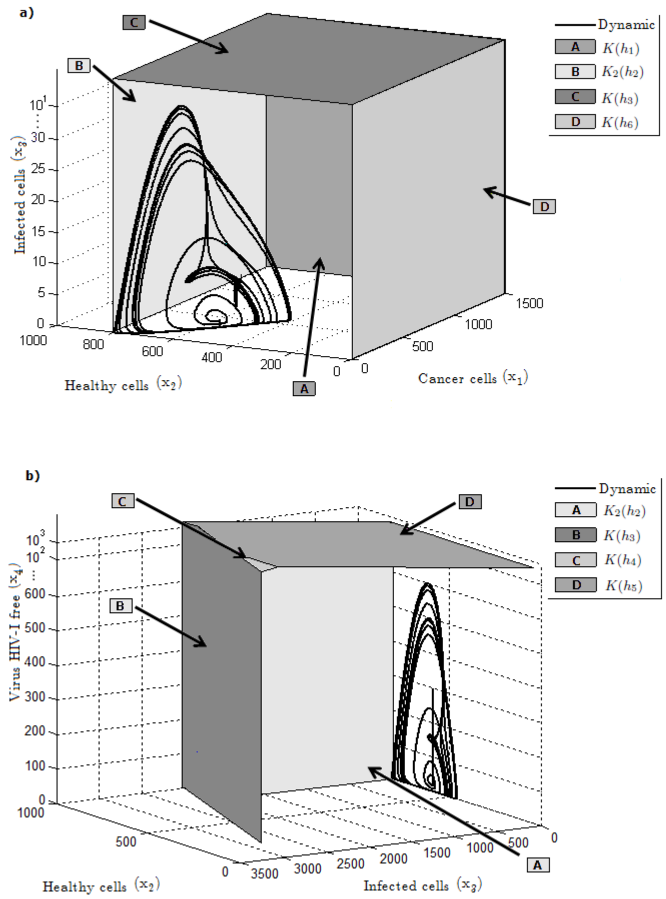

Fig. 1. Localization of compact invariant sets; a) x_1, x_2 and x_3; b) x_2, x_3 and x_4.

4 Conclusions

In the analysis of localization of compact invariant sets for the AIDS model related cancer we achieve a region in the domain $\mathbb{R}^4_+$ that encloses the dynamics system under the condition that the variables and parameters are positive. We used linear functions and subsequently we proposed rational functions to sharp the localization region. Numerical simulations allow to obtain a graphical interpretation of the including compact invariant sets and the localization behavior. The localization results give us information about how to manipulate the parameters, according to their biological characteristics can be manipulated in order to decrease the boundary of the system in-large. One of the parameter that can be modified, corresponds to the generation of T-CD4 + cells, represented by s. Note that according the medical implications described in the literature, the uncontrolled increase of this parameter can take the patient to a stable state to a critical state, causing autoimmune diseases.

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