ON THE GLOBAL DYNAMICS OF THE CANCER AIDS-RELATED MATHEMATICAL MODEL

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In this paper we examine some features of the global dynamics of the four-dimensional system created by Lou, Ruggeri and Ma in 2007 which describes the behavior of the AIDS-related cancer dynamic model in vivo. We give upper and lower ultimate bounds for concentrations of cell populations and the free HIV-1 involved in this model. We show for this dynamics that there is a positively invariant polytope and we find a few surfaces containing omega-limit sets for positive half trajectories in the positive orthant. Finally, we derive the main result of this work: sufficient conditions of ultimate cancer free behavior.

Keywords: cancer growth model, AIDS, compact invariant set, omega-limit set, localization, ultimate cancer free dynamics

Classification: 34C11, 34D23, 92D25, 93D20

1. INTRODUCTION

The Human Immunodeficiency Virus (HIV) is a serious threat worldwide in the last 30 years. It has claimed more than 25 million lives and its impact is more acute in societies with low income. This disease is characterized by deteriorating of the immune system avoiding a good response to an infection and a disease. When the level of the immune system defense decreases respecting to the normal level the patient enters to a state of immunodeficiency called Acquired Immune Deficiency Syndrome (AIDS). A HIV-infected individual is vulnerable to the threat of cancer cells, bacteria or viruses that may represent infections or a certain cancer. During more than 20 years efforts of many researchers have been aimed for a creation of various mathematical models describing interactions of the immune system and HIV. A brief list is [1, 2, 10]. Nowadays a number of publications is devoted to studies of dynamics of deterministic cancer tumor growth models in case when the immune system of a patient is attacked by HIV, see, for example, [7, 8, 9, 19, 20].

Mainly, due to the complexity of models analysis fulfilled in these papers concerns local stability of equilibrium points. In addition, we mention that global stability conditions with respect to the infection-free equilibrium point are obtained in articles [7, 20] for some three-dimensional models. Appearance of chaos and the existence of periodic

orbits are studied numerically for some ranges of parameters via the Hopf bifurcation analysis in these publications as well.

In our paper we examine the four-dimensional model constructed in [9] in which two ways of a transmission of HIV-1 *in vivo* are considered: the virus-cell transmission and the cell-cell translation. This model has the form

$$
\begin{aligned}
\dot{x}_1 &= r_1 x_1 \left(1 - \frac{x_1 + x_2 + x_3}{m}\right) - k_1 x_1 x_2; \\
\dot{x}_2 &= s + r_2 x_2 \left(1 - \frac{x_1 + x_2 + x_3}{m}\right) - \mu_T x_2 - k_2 x_2 x_4 - k_3 x_2 x_3; \\
\dot{x}_3 &= k_2 x_2 x_4 + k_3 x_2 x_3 - \mu_I x_3; \\
\dot{x}_4 &= q\mu_I x_3 - \delta x_4.
\end{aligned}
\tag{1}
$$

Here $x \in \mathbf{R}^4_{+,0} := \{x_i \geq 0; \ i = 1, 2, 3, 4\}$ and variables $x_1/x_2/x_3/x_4$ describe concentrations of cancer cells/ healthy CD4+ T-cells/ infected CD4+ T-cells/ free virus HIV-1 respectively. For the reader's convenience let us remind some basic information relating to this system taken from [9]. According with the literature, [6], the number of healthy cells that convert to cancer cells is very small compared with the uncontrolled proliferation of cancer cells. We suppose that the AIDS-related cancer is appeared by a single clone mechanism. We use the following notations: parameter r_1 represents its uncontrolled proliferation law; parameter k_1 is the immune system's killing rate of cancer cells; s is the source rate of generation of new CD4+ T-cells from precursors in the bone marrow and thymus; r_2 is the intrinsic growth rate of healthy cells; μ_T represents the natural death rate of a CD4+ T-cells in unifected individuals since healthy T-cells have a finite life span. If a T-cell encounters the antigen for which it is specific, it may be stimulated to grow with the growth rate r_2. Further, we use m for carrying capacity of the whole T-cells population in the body; the term $k_2 x_2 x_4$ is exploited for modeling the rate at which free virus infects CD4+ T-cells. A simple mass-action type of term is used with rate k_2. Similarly, for the parameter k_3 describing the rate at which infected CD4+ T-cells infect a healthy T-cell by the cell-to-cell route. Active viral replication is assumed to lead to lysis at rate μ_I for infected cells; q is the total number of infection virus particles produced by one infected cell during its lifetime; δ represents the killing effect to HIV-1 by the whole immune system.

Our interest to this model is due to the fact that complex dynamics of various types has been observed in [9]; namely, authors of [8] have shown numerically that a chaotic attractor or periodic orbits may exist for some ranges of parameters. The *goal* of this work is to continue studies of dynamics of this model in the biologically feasible domain $\mathbf{R}^4_{+,0} := \{x_i \geq 0; i = 1, \ldots, 4\}$ with help of the solution of the localization problem of compact invariant sets, see [3, 4, 5]. Here a localization means a description of the location of all compact invariant sets of the polynomial or rational/polynomial system of ordinary differential equations by means of algebraic inequalities and equations depending on parameters of this system. Finding a localization domain, i. e. a domain which contains all compact invariant sets is of a substantial interest because of the potential application of computer-based methods for its search narrowed in the localization domain. This information may be efficiently used in studies of some qualitative features of a long-time behavior of the system, for example, nonchaoticity, or the nonexistence

of periodic orbits, see e. g. [12].

The existence problem of a bounded positively invariant domain (BPID) in $\mathbf{R}^4_{+,0}$ for cancer tumor models of population dynamics is a problem which is examined in a number of papers, see [13, 14, 15, 16, 17, 18] with references therein. Interest to this problem stems from the fact that the ultimate upper and lower bounds for the trajectories in the positive orthant have biological meaning, characterizing the final state of the patient's health and effectiveness of applied immunotherapy and drug treatment. Further, bounds for a BPID are computed as functions of the model parameters. If some of these parameters can be manipulated by biologists the latter have chance to adjust the global dynamics through the process of changing the parameters allowed for manipulations.

Recently, the localization analysis of compact invariant sets has been efficiently applied in studies of global dynamics of some cancer tumor growth models and their interactions with the immune system of a patient, see [13, 14, 15, 16, 17, 18]. In most of these works sufficient conditions of global asymptotic clearance of the tumor cells population have been obtained.

Our paper is organized as follows. Namely,

1) in Section 2 we provide necessary information about the localization method applied in this work and remind some known results on dynamics of the system 1;

2) in Section 3 we obtain ultimate upper bounds for all four components of the state vector of (1);

3) by using results described in Section 3 we find in Section 4 two additional localization sets characterizing lower bounds for the healthy cells population;

4) in Section 5 we prove the existence of the bounded positively invariant domain (BPID) in the biologically feasible orthant $\mathbf{R}^4_{+,0}$, i. e. we prove that there are no escaping to infinity positive half trajectories in $\mathbf{R}^4_{+,0}$;

5) in Section 6 we give the formula for one quadratic surface containing $\omega-$ limit sets of positive half trajectories in $\mathbf{R}^4_{+,0}$;

6) further, in Section 7 we present our main result (Theorem 7.1) in which the global asymptotic cancer tumor clearance conditions are described;

    6a) the statement of Theorem 7.1 is presented in the form of conditions under which ω-limit sets of trajectories in $\mathbf{R}^4_{+,0}$ are located in the cancer free hyperplane $x_1 = 0$;

    6b) the proof of Theorem 7.1 is based on using results of Sections $3-5$;

7) concluding remarks are contained in Section 8; in Supplement we describe two additional quadratic surfaces containing $\omega-$ limit sets of positive half trajectories in $\mathbf{R}^4_{+,0}$.

2. MATHEMATICAL PRELIMINARIES, NOTATIONS AND SOME RELEVANT INFORMATION RESPECTING THE SYSTEM (1)

Briefly speaking, our approach is based on exploiting the localization method of all compact invariant sets, see [3, 4, 5]. Here the principal idea is to study extrema of some differentiable functions called localizing which are restricted on trajectories taken from compact invariant sets; this idea is realized with help of using the first order extremum conditions and in some cases the high order extremum conditions, see [12]. Then loci of compact invariant sets are described in terms of these extrema.

We consider 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. Our basic tool consists in using the following assertions, [3, 4, 5]. By $h|_U$ we denote the restriction of h on a set $U \subset \mathbf{R}^n$. By $S(h)$ we denote the set $\{x \in \mathbf{R}^n \mid L_F h(x) = 0\}$, where $L_F h(x)$ is a Lie derivative with respect to F. Suppose that we are interested in the localization of all compact invariant sets located in the set U. Let U be some domain in $\mathbf{R}^n$, $U \subseteq \mathbf{R}^n$. Further, we define $h_{\inf}(U) := \inf\{h(x) \mid x \in U \cap S(h)\}$, $h_{\sup}(U) := \sup\{h(x) \mid x \in U \cap S(h)\}$.

Proposition 2.1. 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 defined by the formula

$$K(U; h) := \{x \in U \mid h_{\inf}(U) \leq h(x) \leq h_{\sup}(U)\}$$

as well. 2. If $S(h) \cap U = \emptyset$ then (2) has no compact invariant sets in U.

The function h used in the solution of the localization problem of compact invariant sets is called a localizing function.

Proposition 2.2. Let $h_m(x), m = 1, 2, \ldots$ be a sequence of functions from $C^\infty(\mathbf{R}^n)$. Sets

$$K_1 = K(U; h_1), \quad K_m = K_{m-1} \cap K_{m-1,m}, \quad m > 1,$$

with

$$K_{m-1,m} = \{x : h_{m,\inf} \leq h_m(x) \leq h_{m,\sup}\},$$
$$h_{m,.\sup} = \sup_{S_{h_m} \cap K_{m-1}} h_m(x),$$
$$h_{m,\inf} = \inf_{S_{h_m} \cap K_{m-1}} h_m(x),$$

contain all compact invariant sets of the system (2) and $K_1 \supseteq K_2 \supseteq \cdots \supseteq K_m \supseteq \ldots$.

Below for the sake of simplicity of notations we shall write $S(h) := S(h) \cap \mathbf{R}^4_{+,0}$ and $K(h) := K(h) \cap \mathbf{R}^4_+$.

At last, we recall some information respecting equilibrium points obtained in [9].

The system (1) may contain four types of equilibrium points with respect to a location in $\mathbf{R}^4_{+,0}$:

1) healthy equilibrium point $E_0 = (0, x_{20}, 0, 0)^T$, with

$$x_{20} = \frac{m(r_2 - \mu_T) + \sqrt{m^2(r_2 - \mu_T)^2 + 4msr_2}}{2r_2}$$

2) HIV infected equilibrium point $E_H = (0, x_{2H}, x_{3H}, x_{4H})^T$

3) cancer equilibrium point $E_C = (x_{1C}, x_{2C}, 0, 0)^T$

4) interior cancer-HIV equilibrium point $E_* = (x_{1*}, x_{2*}, x_{3*}, x_{4*})^T$.

Authors of [9], found explicit formulae for equilibrium points $E_H; E_C; E_*$ and conditions of their existence were obtained too. Besides, local stability analysis was fulfilled for these equilibrium points as well. For example, it is proved in [9] that the healthy equilibrium point E_0 always exists and if the condition

$$\frac{r_1(m - x_{20})}{mk_1 x_{20}} < 1; \quad \frac{qk_2\mu_I x_{20}}{\delta(\mu_I - k_3 x_{20})} < 1 \tag{3}$$

holds then E_0 is locally asymptotically stable and HIV infected equilibrium point E_H does not exist.

Finally, we mention that it is easy to see that the domain $\mathbf{R}^4_{+,0}$ is positively invariant which means that each trajectory in $\mathbf{R}^4_{+,0}$ cannot escape from $\mathbf{R}^4_{+,0}$.

3. UPPER BOUNDS FOR CELLS POPULATIONS

1. Upper bound for cancer cells.

Lemma 3.1. All compact invariant sets are located in the set

$$K_1 = \{x_1 \leq m\}. \tag{4}$$

P r o o f. We apply the function $h_1 = x_1$. As a result,

$$L_f h_1 = r_1 x_1 \left(1 - \frac{x_1 + x_2 + x_3}{m}\right) - k_1 x_1 x_2;$$

and we have that

$$\frac{r_1}{m} h_1|_{S(h_1) \cap \{x_1 > 0\}} = r_1 - \left(\frac{x_2 + x_3}{m} + k_1 x_2\right)|_{S(h_1) \cap \{x_1 > 0\}} \leq r_1.$$

Thus,

$$h_1|_{S(h_1) \cap \{x_1 > 0\}} \leq m$$

and we come to the desirable assertion. □

2. Upper bounds for concentration of healthy cells cells (x_2) and infected cells (x_3).

Lemma 3.2. All compact invariant sets are contained in the set

$$K_j = \left\{ x_j \le x_{j\,\max} := \frac{m(\mu_I + r_2 - \mu_T)^2}{4\mu_I r_2} + \frac{s}{\mu_I}, j = 2,3 \right\}. \tag{5}$$

P r o o f. Let us exploit the localizing function $h_2 = x_2 + x_3$. We have that the set $S(h_2)$ is defined by

$$S(h_2) = \left\{ -\frac{r_2}{m}x_2^2 + r_2 x_2 - \mu_T x_2 - \mu_I x_3 - \frac{r_2}{m}x_1 x_2 - \frac{r_2}{m}x_2 x_3 + s = 0 \right\}.$$

Therefore

$$\begin{aligned}
h_2|_{S(h_2)} &\le -\frac{r_2}{\mu_I m}\left(x_2 - \frac{m(\mu_I + r_2 - \mu_T)}{2r_2} \right)^2 \Big|_{S(h_2)} + \frac{m(\mu_I + r_2 - \mu_T)^2}{4\mu_I r_2} + \frac{s}{\mu_I} \\
&\le \frac{m(\mu_I + r_2 - \mu_T)^2}{4\mu_I r_2} + \frac{s}{\mu_I}
\end{aligned}$$

and the result is proved. $\square$

3. Upper bound for free virus HIV-1.

Lemma 3.3. All compact invariant sets are contained in the set

$$K_4 = \left\{ x_4 \le \frac{q\mu_I}{\delta} x_{3\,\max} \right\}.$$

P r o o f. We apply the localizing function $h_3 = x_4$ and we obtain

$$S(h_3) = \left\{ x_4 = \frac{q\mu_I x_3}{\delta} \right\}.$$

Hence

$$S(h_3) \cap K_3 \subset \left\{ x_4 \le \frac{q\mu_I x_{3\,\max}}{\delta} \right\}$$

and the result is proved. $\square$

Summarizing our assertions we have

Theorem 3.4. All compact invariant sets are located in the polytope

$$\Pi := \cap_{j=1}^{4} K_j.$$

4. GETTING CLOSER TO COMPACT INVARIANT SETS

Now we show how we can get closer to compact invariant sets of the system (1). With this goal we find various bounds describing the ultimate location of the healthy cells population. Firstly, we demonstrate that the ultimate lower bound $x_{2\,\min}$ for the healthy cells population is always positive for positive s. More precisely, we have

Proposition 4.1   All compact invariant sets are contained in the domain $K_5 = \{x_2 \geq x_{2\min}\}$, with

$$x_{2\min} := \frac{s\delta}{x_{2\max}(2r_2\delta + k_3\delta + k_2q\mu_I) + \delta\mu_T}. \tag{6}$$

P r o o f.   We introduce the localizing function $h_4 = x_2$. Then the set $S(h_4)$ is defined by

$$x_2\left\{ -r_2 + \frac{r_2}{m}(x_1 + x_2 + x_3) + \mu_T + k_2x_4 + k_3x_3 \right\} = s$$

and its intersection with Π is contained in the set D_1 defined by

$$x_2\left\{ \frac{r_2}{m}(x_{2\max} + x_{3\max}) + \mu_T + k_2x_{4\max} + k_3x_{3\max} \right\} \geq s.$$

Since

$$\inf_{S(h_4)\cap\Pi} h_4 \geq \min_{D_1} h_4$$

we come to the inequality

$$x_2 \geq \frac{sm}{r_2(x_{2\max} + x_{3\max}) + (\mu_T + k_2x_{4\max} + k_3x_{3\max})m}$$

which entails the desirable assertion.   □

Let us take into consideration real numbers

$$\nu_1 = \left\{ \begin{array}{l} 0, \text{ if } r_2 \leq r_1 \\ r_2 - r_1, \text{ if } r_2 > r_1 \end{array} \right\}; \quad \nu_2 = \left\{ \begin{array}{l} x_{2\min}, \text{ if } r_2 \leq r_1 + mk_1 \\ x_{2\max}, \text{ if } r_2 > r_1 + mk_1 \end{array} \right\}$$

$$\nu_3 = \left\{ \begin{array}{l} 0, \text{ if } r_2 \leq r_1 - mk_3 \\ x_{3\max}, \text{ if } r_2 > r_1 - mk_3 \end{array} \right\}; \quad \nu_3 = k_2x_{4\max}.$$

Next, we are in position to establish

Proposition 4.2.   All compact invariant sets in $\mathbf{R}^4_{+,0} \cap \{x_1 > 0\}$ are contained in the domain K_6 defined by the formula

$$K_6 = \left\{ \frac{x_2}{x_1} \geq \frac{s}{m}\left(\sum_{i=1}^4 v_i\right)^{-1} \right\}. \tag{7}$$

P r o o f.   Let us apply the function $h_5 = \frac{x_2}{x_1}$. We have that the set $S(h_5)$ is given by

$$\frac{s}{x_1} = \frac{x_2}{x_1}\left(\mu_T + r_1 - r_2 + x_1\frac{r_2 - r_1}{m} + x_2\left(-k_1 + \frac{r_2 - r_1}{m}\right) + x_3\left(k_3 + \frac{r_2 - r_1}{m}\right) + k_2x_4 \right) = 0.$$

Further, it is obvious that the set $S(h_5) \cap K_1 \cap \{x_1 > 0\}$ is contained in the set defined by the inequality

$$
\begin{aligned}
& \frac{x_2}{x_1}\left(\mu_T + r_1 - r_2 + x_1\frac{r_2 - r_1}{m}\right. \\
& \left. + x_2\left(-k_1 + \frac{r_2 - r_1}{m}\right) + x_3\left(k_3 + \frac{r_2 - r_1}{m}\right) + k_2 x_4\right) \\
\geq \quad & \frac{s}{m}.
\end{aligned}
\tag{8}
$$

Now using in the set $\Pi \cap K_5 \cap \{x_1 > 0\}$ upper or lower bounds for $x_j, j = 1, 2, 3, 4$, in the dependence on the sign of a corresponding coefficient in (8) we come to the localization set (7). So the proof is completed. $\qquad\square$

5. ON THE EXISTENCE OF BPID IN $\mathbf{R}^4_{+,0}$

In this section we prove the existence for a BPID in $\mathbf{R}^4_{+,0}$. We remind that this assertion means that there exists a bounded domain in $\mathbf{R}^4_{+,0}$ such that any positive half trajectory in $\mathbf{R}^4_{+,0}$ eventually enters this domain and remains there.

Theorem 5.1. Suppose that

$$
s \geq \frac{(mk_3 + r_2)\mu_I}{r_1 k_3}.
\tag{9}
$$

Then the polytope Π is a BPID in $\mathbf{R}^4_{+,0}$.

Proof.
    Case 1: $\mathbf{R}^4_{+,0} \cap \{x_1 > 0\}$.
    We propose the following Lyapunov candidate function

$$
h_6 = \gamma_1 x_1 - \ln x_1 + \gamma_2 x_2 + \gamma_3 x_3 + \gamma_4 x_4
$$

for $\mathbf{R}^4_{+,0} \cap \{x_1 > 0\}$ and with some positive coefficients $\gamma_i > 0$; $i = 1, 2, 3, 4$, to be defined. Then we obtain that

$$
\begin{aligned}
L_f h_6 \quad = \quad & -\frac{\gamma_1 r_1}{m}x_1^2 + \frac{\gamma_1 m + r_1}{m}x_1 - \frac{\gamma_2 r_2}{m}x_2^2 - x_1 x_2\left(\frac{\gamma_1 r_1 + \gamma_2 r_2}{m} + \gamma_1 k_1\right) \\
& + x_2\left(k_1 + \frac{r_1}{m} + \gamma_2 r_2 - \gamma_2 \mu_T\right) - \frac{\gamma_1 r_1}{m}x_1 x_3 + x_3\left(\frac{r_1}{m} - \gamma_3 \mu_I + \gamma_4 q\mu_I\right) \\
& + x_2 x_3\left(-\frac{\gamma_2 r_2}{m} - \gamma_2 k_3 + \gamma_3 k_3\right) + x_2 x_4 k_2(\gamma_3 - \gamma_2) - \gamma_4 \delta x_4 + \gamma_2 s - r_1.
\end{aligned}
\tag{10}
$$

Let us impose conditions that coefficients in (10) with respect to monomials $x_3; x_2 x_3; x_2 x_4$ satisfy the following inequalities

$$0 \; > \; \frac{r_1}{m} - \gamma_3 \mu_I + \gamma_4 q \mu_I; \tag{11}$$

$$0 \; \geq \; -\frac{\gamma_2 r_2}{m} - \gamma_2 k_3 + \gamma_3 k_3; \tag{12}$$

$$0 \; \geq \; \gamma_3 - \gamma_2; \tag{13}$$

$$A \; : \; = \; \frac{(k_1 m + r_1 + m \gamma_2 r_2 - m \gamma_2 \mu_T)^2}{4 m \gamma_2 r_2}$$

$$+ \frac{(m \gamma_1 + r_1)^2}{4 m \gamma_1 r_1} + \gamma_2 s - r_1 \tag{14}$$

$$> \; 0.$$

It is easy to see that the system of inequalities $(11) - (14)$ is solvable in positive real numbers respecting $\gamma_j, j = 1, 2, 3$. In order to prove this assertion, let us take any positive γ_4^*. Then we choose any γ_3^* such that

$$\gamma_3^* > \frac{1}{\mu_I} \left(\frac{r_1}{m} + \gamma_4^* q \mu_I \right)$$

and any γ_2^* such that

$$\gamma_2^* > \max \left\{ \gamma_3^*; \frac{r_1}{s} \right\}.$$

So the set of $\gamma_j^*, j = 1, 2, 3$, is a solution of system of inequalities $(11) - (14)$. Now we apply this choice of parameters in the formula for h_6.

Then

$$L_f h_6 \; = \; A - \frac{\gamma_1^* r_1}{m} \left(x_1 - \frac{\gamma_1^* m + r_1}{2 \gamma_1^* r_1} \right)^2 - x_1 x_2 \left(\frac{\gamma_1 r_1 + \gamma_2 r_2}{m} + \gamma_1 k_1 \right) \tag{15}$$

$$- \frac{\gamma_2^* r_2}{m} \left(x_2 - \frac{k_1 m + r_1 + m \gamma_2^* r_2 - m \gamma_2^* \mu_T}{2 \gamma_2^* r_2} \right)^2 - \frac{\gamma_1 r_1}{m} x_1 x_3$$

$$+ x_3 \left(\frac{r_1}{m} - \gamma_3 \mu_I + \gamma_4 q \mu_I \right)$$

$$+ x_2 x_3 \left(- \frac{\gamma_2 r_2}{m} - \gamma_2 k_3 + \gamma_3 k_3 \right) + x_2 x_4 k_2 (\gamma_3 - \gamma_2) - \gamma_4 \delta x_4.$$

So $L_f h_6$ may be written in the form $L_f h_6 = A - Q(x)$ for the quadratic polynomial Q given in (15) which is positive on $\mathbf{R}_+^4$.

Let us define the domain U in $\mathbf{R}_+^4$ by formula

$$U = \{ A < Q(x) \}. \tag{16}$$

We notice that its complement $C\{U\}$ in $\mathbf{R}_+^4$ is a bounded domain. Further, by construction $L_f h_6 \mid_U < 0$. The latter means that eventually all trajectories in $\mathbf{R}_{+,0}^4 \cap \{x_1 > 0\}$ enter into the domain $C\{U\}$ and remain there. Therefore for each point $x \in \mathbf{R}_+^4 \cap \{x_1 > 0\}$ its omega-limit set $\omega(x)$ is not empty and it is a compact invariant set, see Perko [11] in §3.2. Hence, $\omega(x) \subset \Pi$ which is the BPID.

Case 2: $\mathbf{R}^4_{+,0} \cap \{x_1 = 0\}$.

Let f_{red} be the vector field of the system (1) restricted on the invariant plane $x_1 = 0$. We propose the following Lyapunov candidate function

$$h_7 = x_2 + x_3 + \xi x_4.$$

Then we have:

$$
\begin{aligned}
L_{f_{red}} h_7 &= s + \frac{(r_2 - \mu_T)^2 m}{4r_2} - \frac{r_2}{m}\left(x_2 - \frac{(r_2 - \mu_T)m}{2r_2}\right)^2 - \frac{r_2}{m}x_1 x_2 - \frac{r_2}{m}x_2 x_3 \\
&\quad + x_3 \mu_I (q\xi - 1) - \xi \delta x_4.
\end{aligned}
$$

Now we define the domain U in $\mathbf{R}^4_+$ by formula (16), with

$$
\begin{aligned}
A &= s + \frac{(r_2 - \mu_T)^2 m}{4r_2}; \\
Q(x) &= \frac{r_2}{m}\left(x_2 - \frac{(r_2 - \mu_T)m}{2r_2}\right)^2 + \frac{r_2}{m}x_1 x_2 + \frac{r_2}{m}x_2 x_3 - x_3 \mu_I(q\xi - 1) + \xi \delta x_4, \\
0 &< \xi < \frac{1}{q}
\end{aligned}
$$

and after this we argue as in the first case. Then the proof is completed. $\qquad\square$

6. ONE QUADRATIC SURFACE CONTAINING $\omega-$ LIMIT SETS

In this Section we describe one quadratic surface containing $\omega-$ limit sets for positive half trajectories in $\mathbf{R}^4_+$.

Let us define a domain D_1 in $\mathbf{R}^4_+$ by the formula

$$D_1 = \left\{ \frac{r_1}{m}\left(x_1 - \frac{m}{2}\right)^2 + \frac{r_1 + k_1 m}{m}x_1 x_2 + x_4 \frac{r_1 \delta}{mq\mu_I} \geq \frac{r_1 m}{4} \right\}.$$

Here we establish the following result:

Theorem 6.1. Suppose that condition (9) is fulfilled and $s > 0$. Then for any point $x \in D_1$ we have that the set $\omega(x) \cap D_1$ is contained in the set $\partial D_1 \cup \{x_1 = 0\}$, with ∂D_1 defined by the formula

$$\partial D_1 = \left\{ \frac{r_1}{m}\left(x_1 - \frac{m}{2}\right)^2 + \frac{r_1 + k_1 m}{m}x_1 x_2 + x_4 \frac{r_1 \delta}{mq\mu_I} = \frac{r_1 m}{4} \right\}.$$

P r o o f. Let us exploit the function $h_8 = x_1 \exp(\xi x_4)$, ξ is a positive real number defined below. Now we compute that

$$\frac{L_f h_8}{\exp(\xi x_4)} = r_1 x_1 - \frac{r_1 x_1^2}{m} - \frac{r_1 x_1 x_2}{m} - \frac{r_1 x_1 x_3}{m} - k_1 x_1 x_2 + \xi x_1 (q\mu_I x_3 - \delta x_4).$$

Let us choose

$$\xi = \frac{r_1}{mq\mu_I}.$$

Then we have

$$\frac{L_f h_8}{\exp(\xi x_4)} = -\frac{r_1}{m}(x_1 - \frac{m}{2})^2 + \frac{mr_1}{4} - \frac{1 + k_1 m}{m}x_1 x_2 - \frac{r_1 \delta}{mq\mu_I}x_1 x_4.$$

Further, we notice that

$$L_f h_8 \mid_{D_1} \leq 0 \tag{17}$$

and we have equality in (17) on $\partial D_1 \cup \{x_1 = 0\}$.

Now reminding that for any point $x \in \mathbf{R}^4_{+,0}$ the set $\omega(x) \neq \varnothing$ we obtain with help of the LaSalle theorem the desirable conclusion. $\qquad \square$

Remark 6.1. The surface ∂D_1 in $\mathbf{R}^4_{+,0}$ is a reducible surface formed by a couple of planes: $x_1 = 0$ and

$$r_1 - \frac{r_1 x_1}{m} - \left(\frac{r_1}{m} + k_1\right)x_2 - \frac{r_1 \delta}{mq\mu_I}x_4 = 0. \tag{18}$$

This surface does not depend on parameters $s; k_3; r_2$ and μ_T characterizing dynamics of the healthy cells proliferation.

7. MAIN RESULT: CONDITIONS OF ULTIMATE CANCER FREE BEHAVIOR

In this section we describe the main result of this paper: sufficient conditions under which the $\omega-$limit set of any trajectory in $\mathbf{R}^4_{+,0} \cap \{x_2 > 0\}$ is contained in the plane $x_1 = 0$. Let $\mu_0 = \max\{\mu_T; \mu_I\}$.

We present

Theorem 7.1. Suppose that conditions (9) and

$$s > m(\mu_0 + r_2) \tag{19}$$

are fulfilled. Then we establish that the set $\omega(x)$ is contained in the set

$$\{x_1 = 0\} \cap K_2 \cap K_3 \cap K_4 \cap K_5 \tag{20}$$

for each trajectory in $\mathbf{R}^4_{+,0} \cap \{x_2 > 0\}$.

P r o o f. Let us apply the function $h_9 = x_1(x_2 + x_3)^{-\eta}$ with respect to $\mathbf{R}^4_{+,0} \cap \{x_2 > 0\}$. Here parameter η is chosen according to the inequality

$$0 < \eta < \frac{r_1}{r_2} \tag{21}$$

and will be specified below. Then we compute that

$$
\begin{aligned}
L_f h_9 &= h_9 \Big\{ r_1 - \frac{r_1}{m}(x_1 + x_2 + x_3) - k_1 x_2 \\
&\quad - \frac{\eta}{x_2 + x_3}\big(s + r_2 x_2\big(1 - \frac{x_1 + x_2 + x_3}{m}\big) - \mu_T x_2 - \mu_I x_3\big)\Big\} \\
&\leq h_9 \Big\{ r_1 - \frac{r_1}{m}x_1 - \big(\frac{r_1}{m} + k_1\big)x_2 - \frac{r_1}{m}x_3 - \frac{\eta s}{x_2 + x_3} \\
&\quad + \frac{\eta r_2 x_2}{x_2 + x_3}\frac{x_1 + x_2 + x_3}{m} + \frac{\eta(\mu_T x_2 + \mu_I x_3)}{x_2 + x_3}\Big\}.
\end{aligned}
\tag{22}
$$

Since

$$\frac{\eta r_2 x_2}{x_2 + x_3} \frac{x_1 + x_2 + x_3}{m} \leq \frac{\eta r_2}{m}(x_1 + x_2 + x_3)$$

and

$$-\frac{\eta s}{x_2 + x_3} - \frac{r_1 - \eta r_2}{m}(x_2 + x_3) \leq -2\sqrt{\frac{s(r_1 - \eta r_2)}{m}}\eta$$

we can continue the formula (22) as follows:

$$L_f h_9 \leq h_9 \left\{ r_1 + \eta \mu_0 - 2\sqrt{\frac{s(r_1 - \eta r_2)}{m}}\eta - \frac{r_1 - \eta r_2}{m}x_1 \right\}. \tag{23}$$

Then let us consider the equation

$$r_1 + \eta \mu_0 = 2\sqrt{\frac{s(r_1 - \eta r_2)}{m}}\eta \tag{24}$$

respecting η. Its roots are given by the formula

$$\eta_{\pm} = \frac{r_1(2s - m\mu_0) \pm 2r_1\sqrt{s^2 - sm(\mu_0 + r_2)}}{\mu_0^2 m + 4sr_2}. \tag{25}$$

It follows from (19) that these roots are real, distinct and $\eta_+ > 0; \eta_- < 0$. Besides, by direct routine computations omitted here we obtain that the inequality (21) holds for η_+. Now applying the localizing function h_9, with specified parameter $\eta = \eta_+$, we derive from (23) that

$$L_f h_9 \leq -\frac{r_1 - \eta_+ r_2}{m}h_9 x_1 \leq 0. \tag{26}$$

Further, since each positive half trajectory $\varphi(x, t), t > 0$, has a nonempty ω-limit set $\omega(x)$ which is a compact invariant set then it is located in domain $\Pi \cap K_5$. Therefore eventually each positive half trajectory enters in the domain $K_2 \cap K_3 \cap K_4 \cap K_5$. As a result, applying the LaSalle theorem we derive from the inequality (26) that $\omega(x) \subset \{x_1 = 0\} \cap K_2 \cap K_3 \cap K_4 \cap K_5$. The proof is completed. $\square$

This assertion may be referred to as the global asymptotic cancer clearance theorem. Now we give two remarks.

Remark 7.1. Comparing assertions of Theorems 6.1 and 7.1 we notice that for values of parameter s indicated in the formulation of Theorem 7.1 the part of the plane (18), with $x_1 > 0$, does not contain any $\omega-$ limit set and eventually any trajectory is attracted to the cancer free plane $x_1 = 0$.

Remark 7.2. We notice that in virtue of Proposition 3, see in [9], or its citation in Section 2 of this paper, the set

$$\Omega := \cup_{x \in \mathbf{R}_+^4} \omega(x)$$

contains the healthy equilibrium point E_0 provided (3) holds. Though the detailed dynamic analysis of the restriction of the system (1) on the plane $x_1 = 0$ is a sufficiently difficult task we may avoid it when we apply Theorem 7.1 because of the formula (20). Indeed, even if there are other $\omega-$limit sets aside from E_0 which are located in the plane $x_1 = 0$ these $\omega-$limit sets are contained in the three-dimensional polytope $K_2 \cap K_3 \cap K_4 \cap K_5$ as well. Therefore we can apply the ultimate upper bounds given in the formulae for K_3 or for K_4 with respect to infected cells/ the concentration of the free HIV-1 in order to estimate a risk level for the life of a patient.

8. CONCLUDING REMARKS

The main research interest of our paper is to demonstrate how the localization method of compact invariant sets works in the global analysis of the AIDS-related cancer dynamic model. The biological significance of compact invariant sets is related to the fact that they carry information about the long-time behavior of cells populations involved in the model.

1. In Sections 3 and 4 various bounds $(x_{j\,\max}, j = 1, \ldots, 4; x_{2\,\min})$ for ultimate concentrations of cancer/healthy/infected cell populations and the free HIV-1 are derived. Examining ultimate upper bounds we notice that they do not depend on parameters $r_1; k_j; \ j = 1, 2, 3$, but depend on all other parameters. The ultimate lower bound $x_{2\,\min}$ is a conservative bound for the healthy cells population; this bound does not depend on parameters $r_1; k_1$ but depend on all other parameters. We believe that it is of interest why the ultimate values of population dynamics of the model (1) do not depend on parameters $r_1; \ k_1$.

2. Further, these bounds are exploited in order to deduce in Theorem 5.1, see Section 5, the formula for the bounded positively invariant domain $K_{\mathrm{B}PID}$ which is given in a form of a polytope in $\mathbf{R}^4_{+,0}$. The polytope $K_{\mathrm{B}PID}$ consists of points whose dynamics in the positive time always satisfies bounds for $K_{\mathrm{B}PID}$. As a result, the future evolution of cell populations involved in the model (1) as well as of the concentration $x_4(t)$ of the free HIV-1 is completely predictable in the following sense: these concentrations have a predictable estimate of their changes both in short time intervals and long time intervals.

3. Besides, in Theorem 6.1 we find a formula for two planes containing ω- limit sets for trajectories taken from one unbounded domain which is explicitly described.

4. In Section 7, see Theorem 7.1, we derive that if the parameter s exceeds the value

$$\max \left\{ \frac{(mk_3 + r_2)\mu_I}{r_1 k_3}; m(\mu_0 + r_2) \right\} \tag{27}$$

then each positive half trajectory in $\mathbf{R}^4_{+,0} \cap \{x_2 > 0\}$ is attracted to the tumor free plane $x_1 = 0$. This property of trajectories means the global asymptotic clearance of the cancer cells population $x_1(t)$. Since we know about the ultimate value for this half trajectory that it is contained inside the set (20) ultimate upper bounds for concentrations of healthy cells /infected cells/ the free HIV-1 are explicitly indicated.

5. Further, the cancer clearance condition in Theorem 7.1 is expressed in the form of a simple algebraic inequality imposed on the source rate s. We point out that this

inequality is preserved under sufficiently small perturbations of model parameters entering into the formula (27); in this sense we can talk about the robustness property of the cancer clearance condition. On the authors' opinion, it is of interest to analyze why some of system parameters, namely $k_1; k_2; q; \delta$, do not enter into the value (27). The answer to this question may serve both for better understanding dynamical properties of the model obtained in [9] and the biological essence of the tumor clearance process.

9. SUPPLEMENT

It is of interest for future studies of the system (1) that one can find two additional quadratic surfaces which may contain $\omega-$ limit sets. Since these results are not used in our work we place them in the supplement. In order to present these assertions, we introduce two domains

$$D_2 = \left\{ \frac{r_2}{m}\left(x_2 - \frac{(r_2 - \mu_T)m}{2r_2}\right)^2 + \frac{r_2}{m}x_1x_2 + x_2x_4\left(\frac{r_2 + mk_3}{mq\mu_I}\delta + k_2\right) \geq s + \frac{(r_2 - \mu_T)^2 m}{4r_2} \right\};$$

$$
\begin{aligned}
D_3 \quad : \quad = \Bigg\{ & \frac{r_2 - m\xi r_2 + \xi m\mu_T}{m}\left(x_2 - \frac{(r_2 - \mu_I + \xi s)m}{2(r_2 - m\xi r_2 + \xi m\mu_T)}\right)^2 \\
& + \mu_I x_3 + \left(\frac{r_2}{m} + \xi(\mu_T - r_2)\right)x_2x_3 \\
& + \xi(x_2 + x_3)\left(\frac{r_2}{m}x_1x_2 + \frac{r_2}{m}x_2^2 + \frac{r_2}{m}x_2x_3 + \frac{\delta}{q}x_4\right) \\
\geq \quad & s + \frac{(r_2 - \mu_I + \xi s)^2 m}{4(r_2 - m\xi r_2 + \xi m\mu_T)} \Bigg\}
\end{aligned}
$$

for some positive parameter ξ described below.

Theorem 9.1. Suppose that condition (9) is fulfilled and $s > 0$. Then for any point $x \in D_2$ we have that the set $\omega(x) \cap D_2$ is contained in the set ∂D_2 defined by the formula

$$\frac{r_2}{m}\left(x_2 - \frac{(r_2 - \mu_T)m}{2r_2}\right)^2 + \frac{r_2}{m}x_1x_2 + x_2x_4\left(\frac{r_2 + mk_3}{mq\mu_I}\delta + k_2\right) = s + \frac{(r_2 - \mu_T)^2 m}{4r_2}.$$

P r o o f. Let us exploit the function $h_{10} = x_2 \exp(\xi x_4), \xi$ is a positive real number defined below. Now we compute that

$$
\begin{aligned}
\frac{L_f h_{10}}{\exp(\xi x_4)} \quad = \quad & s + (r_2 - \mu_T)x_2 - \frac{r_2}{m}x_2^2 + x_2x_3\left(\xi q\mu_I - \frac{r_2}{m} - k_3\right) \qquad (28) \\
& - \frac{r_2}{m}x_1x_2 - x_2x_4(\xi\delta + k_2).
\end{aligned}
$$

Let us put in the formula (28)

$$\xi = \frac{r_2 + mk_3}{mq\mu_I}. \qquad (29)$$

Then we derive from (28):

$$
\begin{aligned}
L_f h_{10} &= \exp\left(\frac{r_2 + mk_3}{mq\mu_I}x_4\right)\left\{s - \frac{r_2}{m}x_1x_2 - \frac{r_2}{m}(x_2 - \frac{(r_2 - \mu_T)m}{2r_2})^2 + \frac{(r_2 - \mu_T)^2 m}{4r_2}\right. \\
&\quad \left. -x_2x_4\left(\frac{r_2 + mk_3}{mq\mu_I}\delta + k_2\right)\right\}.
\end{aligned}
$$

Further, we notice that

$$
L_f h_{10} \mid_{D_2} \leq 0 \tag{30}
$$

and we have equality in (30) on ∂D_2.

Now reminding that for any point $x \in \mathbf{R}_{+,0}^4$ the set $\omega(x) \neq \varnothing$ we obtain with help of the LaSalle theorem the desirable conclusion. $\qquad\square$

Theorem 9.2. Suppose that condition (9) is fulfilled and $r_2 > \mu_T$. Then for any point $x \in D_3$ we have that the set $\omega(x) \cap D_3$ is contained in the set ∂D_3 defined by the formula

$$
\begin{aligned}
D_3 \quad : \quad &= \left\{\frac{r_2 - m\xi r_2 + \xi m\mu_T}{m}(x_2 - \frac{(r_2 - \mu_I + \xi s)m}{2(r_2 - m\xi r_2 + \xi m\mu_T)})^2\right. \\
&\quad +\mu_I x_3 + (\frac{r_2}{m} + \xi(\mu_T - r_2))x_2x_3 \\
&\quad +\xi(x_2 + x_3)(\frac{r_2}{m}x_1x_2 + \frac{r_2}{m}x_2^2 + \frac{r_2}{m}x_2x_3 + \frac{\delta}{q}x_4) \\
&= \quad s + \frac{(r_2 - \mu_I + \xi s)^2 m}{4(r_2 - m\xi r_2 + \xi m\mu_T)}\left.\right\}.
\end{aligned}
$$

P r o o f. Let us exploit the function $h_{11} = (x_2 + x_3)\exp(\xi(x_2 + x_3 + q^{-1}x_4)), \xi$ is a positive real number defined below. Now we compute that

$$
\begin{aligned}
\frac{L_f h_{11}}{\exp(\xi(x_2 + x_3 + q^{-1}x_4))} \\
= \quad &s + (r_2 - \mu_T)x_2 - \frac{r_2}{m}x_1x_2 - \frac{r_2}{m}x_2^2 - \frac{r_2}{m}x_2x_3 - \mu_I x_3 \\
&+\xi(x_2 + x_3)\left(s + (r_2 - \mu_T)x_2 - \frac{r_2}{m}x_1x_2 - \frac{r_2}{m}x_2^2 - \frac{r_2}{m}x_2x_3 - \frac{\delta}{q}x_4\right) \\
= \quad &s - (\frac{r_2}{m} - \xi r_2 + \xi\mu_T)x_2^2 + (r_2 - \mu_I + \xi s)x_2 - (\frac{r_2}{m} + \xi(\mu_T + \mu_I - r_2))x_2x_3 \\
&-\mu_I x_3 - \frac{r_2}{m}x_1x_2 \\
&-\xi(x_2 + x_3)(\frac{r_2}{m}x_1x_2 + \frac{r_2}{m}x_2^2 + \frac{r_2}{m}x_2x_3 + \frac{\delta}{q}x_4) \\
= \quad &-\frac{r_2 - m\xi r_2 + \xi m\mu_T}{m}(x_2 - \frac{(r_2 - \mu_I + \xi s)m}{2(r_2 - m\xi r_2 + \xi m\mu_T)})^2 + \frac{(r_2 - \mu_I + \xi s)^2 m}{4(r_2 - m\xi r_2 + \xi m\mu_T)} \\
&-\mu_I x_3 - (\frac{r_2}{m} + \xi(\mu_T - r_2))x_2x_3 \\
&-\xi(x_2 + x_3)(\frac{r_2}{m}x_1x_2 + \frac{r_2}{m}x_2^2 + \frac{r_2}{m}x_2x_3 + \frac{\delta}{q}x_4) + s.
\end{aligned}
$$

Let us choose ξ such that

$$0 < \xi < \frac{r_2}{m(r_2 - \mu_T)}.$$

Further, we notice that

$$L_f h_{11} \mid_{D_3} \leq 0 \tag{31}$$

and we have equality in (31) on ∂D_3.

Now reminding that for any point $x \in \mathbf{R}^4_{+,0}$ the set $\omega(x) \neq \varnothing$ we get with help of the LaSalle theorem the desirable conclusion. $\qquad\square$

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