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THE FOUR-DIMENSIONAL KIRSCHNER-PANETTA TYPE CANCER MODEL: HOW TO OBTAIN TUMOR ERADICATION?

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Abstract. In this paper we examine ultimate dynamics of the four-dimensional model describing interactions between tumor cells, effector immune cells, interleukin -2 and transforming growth factor-beta. This model was elaborated by Arciero et al. and is obtained from the Kirschner-Panetta type model by introducing two various treatments. We provide ultimate upper bounds for all variables of this model and two lower bounds and, besides, study when dynamics of this model possesses a global attracting set. The nonexistence conditions of compact invariant sets are derived. We obtain bounds for treatment parameters $s_{1,2}$ under which all trajectories in the positive orthant tend to the tumor-free equilibrium point. Conditions imposed on $s_{1,2}$ under which the tumor population persists are presented as well. Finally, we compare tumor eradication/ persistence bounds and discuss our results.

1. **Introduction.** The Kirschner-Panetta equations [2] have a great influence on the modelling tumor dynamics under immunotherapy. These equations describe dynamics of interactions between tumor cells, effector immune cells and interleukin-2 (IL-2). One of the promising generalizations of this model is obtained by incorporating in these equations yet another differential equation characterizing the dynamics of the suppressor cytokine, transforming growth factor-β (TGF-β), [1]. It is well-known [16] that TGF-β may display both inhibitory activity and stimulating activity on the growth of most of cells depending on type of cells, their differentiation and activation state. The production of TGF-β by tumor cells greatly challenges the immune system through the promotion of angiogenesis, enhancing tumor growth and metastasis. Tumors can evade immune surveillance by secreting various immunosuppressive factors including (interleukin-10) IL-10 and TGF-β, [8, 17]. It was indicated in [17] that activation of the immunosuppressed immune system by cytokine IL-2 therapy is a possible strategy to limit the malignant immuno-modulatory activities of TGF-β. This type of therapy may be applied alone or in combination

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with other immunotherapeutic approaches and is used in the clinical practice, [16]. This possible approach to cancer treatment is formalized in this paper by introducing into the model from [1] two treatment parameters $s_{1,2}$. Parameters $s_{1,2}$ are included in the equations for the same cells populations as in the Kirschner-Panetta (KP)- model. We recall that s_1 is the treatment term that represents an external source of IL-2 injected into the system; s_2 is the treatment term that represents an external source of effector cells such as LAK (lymphocytes activated killer cells) or TIL (tumor-infiltrating lymphocytes). Following to [1] we consider that $s_{1,2}$ are constants. So we come to the following model in the non-dimensional form

$$\begin{aligned} \dot{x} &= rx(1-\frac{x}{k}) - \frac{awx}{1+x} + \frac{p_2 xz}{1+z}, \\ \dot{y} &= -y + \frac{p_3 xw}{(g_4+x)(1+\alpha z)} + s_2, \\ \dot{z} &= -z + \frac{p_4 x^2}{x^2+\tau^2}, \\ \dot{w} &= \frac{cx}{1+\gamma z} - \mu_1 w + \frac{wy}{1+y}(p_1 - \frac{q_1 z}{q_2+z}) + s_1. \end{aligned} \qquad (1)$$

In equation (1) $x(t)$ describes the number of tumor cells at the moment t; $y(t)$ describes the concentration of effector molecules at the moment t; $z(t)$ describes TGF-β's immuno-suppressive and growth stimulatory effects in the single tumor-site compartment; $w(t)$ describes the number of immune cells at the moment t.

All parameters are supposed to be positive excepting $s_{1,2}$ which are nonnegative. In the first equation r is the cancer growth rate; a is the cancer clearance term. The proliferation of tumor cells due to the response to TGF-β is denoted by p_2 and is modeled by Michaelis-Menten kinetics. In the second equation p_3 is the rate of IL-2 production in the presence of effector cells; g_4 is half-saturation constant; α is a measure of inhibition. In the third equation p_4 is maximal rate of TGF-β production; τ is the critical tumor cells population at which angiogenesis switch occurs. In the fourth equation c is known as the antigenicity of the tumor which measures the ability of the immune system to recognize tumor cells; γ is inhibitory parameter; μ_1 is the death rate of immune cells; p_1 is the proliferation rate of immune cells; q_1 is the rate of anti-proliferative effect of TGF-β; q_2 is half-saturation constant. More details concerning these parameters are contained in [1].

We notice that if we put $z = 0, p_4 = 0$ in (1) we get the KP-model which was created for studying the immune response to tumors under special types of immunotherapy.

Dynamics of the KP-model has been studied in [1, 2, 3, 14] and some others. In particular, ultimate upper and lower bounds for state variables of the KP- model have been derived in different cases. The main result of [14] consists in global asymptotic tumor clearance conditions obtained under various assumptions imposed on the ratio between the proliferation rate of the immune cells and their mortality rate. To the best of the authors' knowledge, up to now there have not been published any results concerning rigorous dynamical analysis of (1). We notice that the system (1) introduced for the case $s_1 = s_2 = 0$ was explored in [1] only by means of numerical simulations of its dynamics.

In this paper we consider the tumor growth system pertained to the broad class of life sciences models which possess the following characteristic feature: there is a tumor-free equilibrium point, which is the most preferable state of the system.

From the biological point of view some deviations from this equilibrium point can be dangerous and cause fatal outcomes.

Therefore, the control goal is to return the system to the indicated equilibrium point and keep it in a sufficiently small neighborhood of this state. It can be done by different treatment injections.

This article establishes the existence conditions for the positively invariant polytope that has a biological meaning. Further, two types of conditions are found: the first one is the tumor persistence (impossibility to achieve the control goal), another one is the tumor eradication (possibility of global asymptotical stabilization at the tumor-free equilibrium point).

The goal and the novelty of this work consists in studies of ultimate dynamics (1) in case of applied treatments $s_i, i = 1, 2$. Namely, we find upper and lower ultimate bounds for all variables of the system (1) and establish conditions under which (1) is dissipative in the Levinson sense; 2) we propose the nonexistence conditions of compact invariant sets in the positive orthant; 3) we deduce the global asymptotic tumor eradication conditions; 4) we describe the tumor persistence conditions.

In other words, the three most important results for understanding of any dynamical system's behavior are actually proved: the existence conditions of the global system's attractor; the coincidence of this attractor with the tumor-free equilibrium point; the presence of a local attractor of the system that does not contain the tumor-free equilibrium point, but attracts almost all ("perturbed") trajectories of the system.

Our approach is based on the localization method of compact invariant sets in which the first order extremum conditions are utilized, see [4, 5, 6]. We also mention that earlier this method has been successfully utilized in studies of various cancer tumor growth models, see e.g. [7, 9, 10, 11, 12, 13, 14, 15] and references therein.

The remainder of the paper is organized as follows. In Section 2 we briefly present useful results. In Section 3 under some condition we obtain formulae for a polytope containing all compact invariant sets. This polytope provides us ultimate upper and lower bounds for all variables of the system (1), see Theorem 3.4. In Section 4 under the same condition as in Theorem 3.4 we show in Theorem 4.1 that this polytope contains the attracting set of the system (1). In Section 5 we present the nonexistence conditions of compact invariant sets in $\mathbf{R}^4_{+,0} \cap \{x > 0\}$, see Theorem 5.1. Further, in Section 6 using results of Theorems 3.4; 4.1; 5.1 we derive conditions of global asymptotic stability with respect to the tumor-free equilibrium point (TFEP), see Theorem 6.1. In the latter theorem we provide bounds for treatments parameters $s_i, i = 1, 2$, for which the global asymptotic tumor eradication process may be observed. In Section 7 we describe the persistence tumor conditions which are compared with tumor eradication bounds of Theorem 7.1 in Section 8. Section 9 contains the concluding remarks.

In what follows, we examine dynamics of (1) in the positive orthant

$$\mathbf{R}^4_+ = \{(w, x, y, z)^T \in \mathbf{R}^4, w; x; y; z > 0\};$$

let $\mathbf{R}^4_{+,0}$ be the closure of $\mathbf{R}^4_+$.

2. **Some useful results.**

We consider a nonlinear system

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

where v is a C^1-differentiable vector field; $x \in \mathbf{R}^n$ is the state vector. Let $h(x)$ be a C^1-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 $\{x \in \mathbf{R}^n \mid L_v h(x) = 0\}$, where $L_v h(x)$ is a Lie derivative of $h(x)$ with respect to v.

Assume that we are interested in the localization of all compact invariant sets contained in the set U. Further, we define

$$S(h;U) := S(h) \cap U = \{x \in U \mid L_v h(x) = 0\};$$
$$h_{\inf}(U) := \inf\{h(x) \mid x \in S(h;U)\};$$
$$h_{\sup}(U) := \sup\{h(x) \mid x \in S(h;U)\}.$$

Assertion 1 [5, 6] *For any $h(x) \in C^1(\mathbf{R}^n)$ all compact invariant sets of the system (2) located in U are contained in the localization set $K(h;U)$ defined by the formula*

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

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

Assertion 2. *Let U be a positively invariant set; $\dot{h}(x)|_H < 0$, where*

$$H = \{x \in U \mid h_{\sup}(U) < h(x)\}.$$

Then for any $\tau^0 > 0$ the extended localization set

$$\hat{K}(h;U;\tau^0) := \{x \in U \mid h(x) \le h_{\sup}(U) + \tau^0\} \tag{3}$$

is positively invariant.

Assertion 3. *Let U be a positively invariant set; $\tau^0 > 0$. If for any $\tau^1 \ge 0$ exists $c > 0$: $\dot{h}|_{H_1} \le -c$, where*

$$H_1 = \{x \in U \mid h_{\sup}(U) + \tau^0 \le h(x) \le h_{\sup}(U) + \tau^0 + \tau^1\},$$

then every trajectory of the system (2) goes into the set $\hat{K}(h;U;\tau^0)$ in finite time.

3. **Formulae for a polytope containing all compact invariant sets.** Here we find localization sets for the system (1). Let f be a vector field of this system.

Lemma 3.1. *All compact invariant sets in $\mathbf{R}^4_{+,0}$ are located in the set*

$$K_1 = K(x, \mathbf{R}^4_{+,0}) = \left\{0 \le x \le x_{\max} := \frac{k(p_2 + r)}{r}\right\} \cap \mathbf{R}^4_{+,0}. \tag{4}$$

Proof. We apply the function $h_1 = x$ and get that

$$S(h_1) = \left\{r(1 - \frac{x}{k}) - \frac{aw}{1+x} + \frac{p_2 z}{1+z} = 0\right\} \cup \{x = 0\}$$

and $h_{1,\inf}(\mathbf{R}^4_{+,0}) = 0$. On the set $S(h_1) \cap \mathbf{R}^4_{+,0} \cap \{x > 0\}$ the inequality

$$r\left(1 - \frac{x}{k}\right) + p_2 \frac{z}{1+z} = \frac{aw}{1+x} \ge 0$$

holds. Using the last inequality to calculate the supremum we obtain

$$h_{1,\sup}(\mathbf{R}^4_{+,0}) = \frac{k(p_2 + r)}{r}.$$

□

Let $\eta = \min(g_4; 1) a p_3^{-1}$.

Lemma 3.2. *All compact invariant sets in $\mathbf{R}^4_{+,0}$ are located in the set*

$$K_2 = \left\{y_{\min} := s_2 \le y \le y_{\max} := \frac{(1 + r + p_2)^2 k}{4 r \eta} + s_2\right\} \cap \mathbf{R}^4_{+,0}. \tag{5}$$

Proof. We apply the function $h_2 = x + \eta y$ and compute

$$\begin{aligned} L_f h_2 &= xw(\tfrac{p_3\eta}{(g_4+x)(1+\alpha z)} - \tfrac{a}{1+x}) - \eta y + rx - \tfrac{rx^2}{k} + \tfrac{p_2 xz}{1+z} + \eta s_2 \\ &= xw(\tfrac{p_3\eta}{(g_4+x)(1+\alpha z)} - \tfrac{a}{1+x}) + x - h_2 + rx - \tfrac{rx^2}{k} + \tfrac{p_2 xz}{1+z} + \eta s_2. \end{aligned}$$

In $\mathbf{R}^4_{+,0}$ we get the inequality

$$L_f h_2 \leq x - h_2 + rx - \frac{rx^2}{k} + p_2 x + \eta s_2$$

because $\frac{z}{1+z} \leq 1$ and η was chosen earlier such that

$$\frac{p_3\eta}{(g_4+x)(1+\alpha z)} - \frac{a}{1+x} \leq 0.$$

After calculating the supremum we obtain that

$$h_2|_{S(h_2,\mathbf{R}^4_{+,0})} \leq h_{2,\sup}(\mathbf{R}^4_{+,0}) = \sup_{x\geq 0}((1+r+p_2)x - \frac{r}{k}x^2) + \eta s_2 = \frac{(1+r+p_2)^2 k}{4r} + \eta s_2.$$

Now let us use the function $h_3 = y$ and compute

$$h_{3,\inf}(K_*) = s_2; \quad h_{3,\sup}(K_*) \leq \sup_{K_*} y \leq \frac{(1+r+p_2)^2 k}{4r\eta} + s_2.$$

Therefore,

$$K(h_3, K_*) \subset \{s_2 \leq y \leq \frac{(1+r+p_2)^2 k}{4r\eta} + s_2\} \cap K_* = K_2$$

and we come to the desirable conclusion. □

Lemma 3.3. *All compact invariant sets in* $\mathbf{R}^4_{+,0}$ *are located in the set*

$$K_3 = K(z, \mathbf{R}^4_{+,0}) = \{0 \leq z \leq z_{\max} := p_4\} \cap \mathbf{R}^4_{+,0}. \tag{6}$$

Proof. We apply the function $h_4 = z$ and get that

$$S(h_4) = \{z = \frac{p_4 x^2}{x^2 + \tau^2}\}, \quad h_{4,\sup}(\mathbf{R}^4_{+,0}) = p_4$$

which leads to the desirable conclusion. □

Let $M = K_1 \cap K_2 \cap K_3$.

Theorem 3.4. *If*

$$\mu_1 > \mu_1^{pol} = \mu_1^{pol}(s_2) := p_1 \frac{y_{\max}}{1 + y_{\max}}, \quad y_{\max} := \frac{(1+r+p_2)^2 k}{4r\eta} + s_2 \tag{7}$$

then all compact invariant sets are located in the polytope

$$\Pi = \{0 \leq x \leq x_{\max}; y_{\min} \leq y \leq y_{\max}; 0 \leq z \leq z_{\max}; w_{\min} \leq w \leq w_{\max}\},$$

where

$$w_{\min} = \frac{s_1}{\mu_1 + \frac{q_1 p_4}{q_2 + p_4} \cdot \frac{y_{\max}}{1+y_{\max}} - p_1 \frac{s_2}{1+s_2}}, \quad w_{\max} = \frac{c x_{\max} + s_1}{\mu_1 - \mu_1^{pol}(s_2)}.$$

Proof. We apply the function $h_5 = w$ and transform equation $L_f h_5 = 0$ in the equality

$$w(\mu_1 + \frac{y}{1+y}(\frac{q_1 z}{z+q_2} - p_1)) = \frac{cx}{1+\gamma z} + s_1.$$

Therefore,

$$h_5|_{S(h_5,M)}(\mu_1 - p_1\frac{y_{\max}}{1+y_{\max}}) \le cx_{\max} + s_1; \quad h_{5,\sup}(M) \le w_{\max}$$

and

$$s_1 \le h_5|_{S(h_5,M)}(\mu_1 + \frac{y}{1+y}\cdot\frac{q_1 z}{q_2+z} - p_1\frac{y}{1+y}) \le$$
$$\le h_5|_{S(h_5,M)}(\mu_1 + \frac{y_{\max}}{1+y_{\max}}\cdot\frac{q_1 z_{\max}}{q_2+z_{\max}} - p_1\frac{y_{\min}}{1+y_{\min}});$$
$$h_5|_{S(h_5,M)} \ge h_{5,\inf}(M) \ge w_{\min},$$

because

$$\mu_1 + \frac{y_{\max}}{1+y_{\max}}\cdot\frac{q_1 z_{\max}}{q_2+z_{\max}} - p_1\frac{y_{\min}}{1+y_{\min}} > p_1\frac{y_{\max}}{1+y_{\max}} - p_1\frac{y_{\min}}{1+y_{\min}} \ge 0,$$

and all compact invariant sets are located in the set $\{w_{\min} \le w \le w_{\max}\} \cap M = \Pi$.

Corollary 1. *If*

$$\mu_1 > \mu_1^M = \mu_1^M(s_2) := -\frac{q_1 p_4}{q_2+p_4}\cdot\frac{y_{\max}}{1+y_{\max}} + p_1\frac{s_2}{1+s_2} \tag{8}$$

then all compact invariant sets are located in the set

$$M_1 := \{w_{\min} \le w\} \cap M =$$
$$= \{0 \le x \le x_{\max}; y_{\min} \le y \le y_{\max}; 0 \le z \le z_{\max}; w_{\min} \le w\}.$$

□

4. **On the dissipativity in the sense of Levinson.** Below we shall establish conditions under which the system (1) is dissipative in the sense of Levinson. Here we recall that the system (2) is called dissipative in the sense of Levinson if there exists $r > 0$ such that for any $x \in \mathbf{R}^n$ we have that

$$\lim_{t\to\infty} \sup |\varphi(x,t)| < r;$$

here $|\varphi(x,t)|$ is the Euclidean norm of the solution $\varphi(x,t)$ of the system (2) starting in time $t = 0$ at the point $x \in \mathbf{R}^n$.

In this case there exists a bounded set which attracts any trajectory in $\mathbf{R}^n$.

Theorem 4.1. *If condition (7) is fulfilled then the system (1) is dissipative in sense of Levinson in* $\mathbf{R}^4_{+,0}$

Proof. Firstly, we note that extended localization sets

$$\hat{K}_1 = \{h_1 = x \le \hat{x}_{\max} := x_{\max} + \tau_1\} \cap \mathbf{R}^4_{+,0};$$
$$\hat{K}_2 = \left\{h_2 = x + \eta y \le \hat{h}_{2,\sup}(\mathbf{R}^4_{+,0}) := h_{2,\sup}(\mathbf{R}^4_{+,0}) + \tau_2\right\} \cap \mathbf{R}^4_{+,0};$$
$$\hat{K}_3 = \{h_4 = z \le \hat{z}_{\max} := z_{\max} + \tau_3\} \cap \mathbf{R}^4_{+,0},$$

where $\tau_i > 0$, $i = 1, 2, 3$, have the form of the set (3) and, by Assertions 2,3 (see remark below), are positively invariant and every trajectory goes into these sets in finite time. Therefore, the intersection of these sets $\hat{M} = \hat{K}_1 \cap \hat{K}_2 \cap \hat{K}_3$ is a positively invariant set and every trajectory goes into this set in finite time.

Next, if condition (7) is fulfilled then for some sufficiently small $\tau_2 > 0$ we get

$$\mu_1 > p_1 \frac{\hat{y}_{\max}}{1+\hat{y}_{\max}}, \quad \hat{y}_{\max} = y_{\max} + \frac{\tau_2}{\eta}.$$

We fix such value of τ_2 and find the localization set

$$K := \{w \le h_{5,\sup}(\hat{M}) \le \overline{w}_{\max}\} \cap \hat{M}, \quad \overline{w}_{\max} = \frac{c\hat{x}_{\max} + s_1}{\mu_1 - p_1 \frac{\hat{y}_{\max}}{1+\hat{y}_{\max}}}$$

(see the proof of Theorem 3.4). By Assertions 2,3 (see remark below), the bounded set

$$\hat{K}_4 := \{h_5 = w \le \hat{w}_{\max} := \overline{w}_{\max} + \tau_4\} \cap \hat{M}, \quad \tau_4 > 0,$$

is a positively invariant set and every trajectory goes into this set in finite time. As a result, the polytope $\hat{M}$ contains the attracting set of the system (1). □

Remark 1. The conditions of Assertions 2,3 are fulfilled for localizing functions h_1; h_2; h_4; h_5, because the next estimations for their derivatives are correct:

in the set $\{h_1 \ge \hat{x}_{\max}\} \cap \mathbf{R}^4_{+,0}$ the localizing function $h_1 = x$ is equal to $\hat{x}_{\max} + \Delta_1 > 0$, where $\Delta_1 \ge 0$, and therefore,

$$\begin{aligned} \dot{h}_1 &= (\hat{x}_{\max} + \Delta_1)\left\{r - \tfrac{r}{k}(x_{\max} + \tau_1 + \Delta_1) - \tfrac{aw}{1+x} + \tfrac{p_2 z}{1+z}\right\} \\ &\le -(x_{\max} + \tau_1 + \Delta_1)\tfrac{r}{k}(\tau_1 + \Delta_1) \le -(x_{\max} + \tau_1)\tfrac{r}{k}\tau_1 < 0; \end{aligned}$$

in the set $\{h_2 \ge \hat{h}_{2,\sup}(\mathbf{R}^4_{+,0})\} \cap \mathbf{R}^4_{+,0}$ the localizing function $h_2 = x + \eta y$ is equal to $\hat{h}_{2,\sup}(\mathbf{R}^4_{+,0}) + \Delta_2$, where $\Delta_2 \ge 0$, and therefore,

$$\dot{h}_2 \le -\tau_2 - \Delta_2 \le -\tau_2 < 0;$$

in the set $\{h_4 \ge \hat{z}_{\max}\} \cap \mathbf{R}^4_{+,0}$ the localizing function $h_4 = z$ is equal to $\hat{z}_{\max} + \Delta_3$, where $\Delta_3 \ge 0$, and therefore,

$$\dot{h}_4 \le -\tau_3 - \Delta_3 \le -\tau_3 < 0;$$

in the set $\{h_5 \ge \hat{w}_{\max}\} \cap \hat{M}$ the localizing function $h_5 = w$ is equal to $\hat{w}_{\max} + \Delta_4 > 0$, where $\Delta_4 \ge 0$, and therefore,

$$\dot{h}_5 \le c\hat{x}_{\max} + s_1 + (\overline{w}_{\max} + \tau_4 + \Delta_4)(-\mu_1 + p_1 \frac{\hat{y}_{\max}}{1+\hat{y}_{\max}}) = (\tau_4 + \Delta_4)(-\mu_1 + p_1 \frac{\hat{y}_{\max}}{1+\hat{y}_{\max}})$$

$$\le -\tau_4(\mu_1 - p_1 \frac{\hat{y}_{\max}}{1+\hat{y}_{\max}}) < 0.$$

5. **The nonexistence conditions of compact invariant sets in $\mathbf{R}^4_{+,0} \cap \{x > 0\}$.** Under condition (8) all compact invariant sets lying in the set $\mathbf{R}^4_{+,0} \cap \{x > 0\}$ are contained in the set $O_1 := M_1 \cap \{x > 0\}$ (see Corollary 1). Below we apply localizing function $h_1 = x$ and show that its derivative is negative in the set O_1 if some inequality holds. Therefore, in the case (8) this inequality is a nonexistence condition of compact invariant sets in the set $\mathbf{R}^4_{+,0} \cap \{x > 0\}$. This condition may hold both in case of the existence of the TFEP and its nonexistence. It means the nonexistence of bounded tumor persistence dynamics, for example, the tumor dormancy. As a corollary, we describe the property of the nonexistence of periodic orbits and tumor persistence equilibrium points (TPEPs) in some range of model and treatment parameters.

Let us denote

$$C_1 := \mu_1 - \frac{p_1 s_2}{s_2 + 1} + \frac{q_1 y_{\max} p_4}{(y_{\max} + 1)(q_2 + p_4)}; \quad C_2 := r + \frac{r}{k} + \frac{p_2 p_4}{1 + p_4}.$$

Theorem 5.1. *Suppose that (8) and*

$$s_1 > s_1^{att} = s_1^{att}(s_2) := \frac{w_0}{a} C_1, \tag{9}$$

where

$$w_0 = \begin{cases} r + \frac{p_2 p_4}{1+p_4}, & \text{if} \quad r(1-\frac{1}{k}) + \frac{p_2 p_4}{1+p_4} \le 0, \\ \frac{kC_2^2}{4r}, & \text{if} \quad r(1-\frac{1}{k}) + \frac{p_2 p_4}{1+p_4} > 0, \end{cases}$$

hold. Then there are no compact invariant sets in the set $\mathbf{R}^4_{+,0} \cap \{x > 0\}$.

Proof. Let us apply the function $h_1 = x$ and find that $L_f h_1|_{O_1} < 0$ in the set O_1 if

$$r(1 - \frac{x}{k}) - \frac{aw}{1+x} + \frac{p_2 z}{1+z} < 0,$$

i.e.

$$aw_{\min} > \max_{x \in [0; x_{\max}]} (1+x)\Big(r - \frac{rx}{k} + \frac{p_2 z_{\max}}{1+z_{\max}}\Big) = w_0.$$

In order to find w_0 we consider

$$\hat{\eta}(x) = (1+x)\Big(r - \frac{rx}{k} + \frac{p_2 p_4}{1+p_4}\Big)$$

and get

$$\hat{\eta}(0) = r + \frac{p_2 p_4}{1+p_4} > 0; \quad \hat{\eta}(x_{\max}) < 0; \quad \hat{\eta}'(0) = r(1-\frac{1}{k}) + \frac{p_2 p_4}{1+p_4};$$

$$\hat{\eta}'(x_*) = 0 \text{ if } x_* = \frac{k}{2} - \frac{1}{2} + \frac{kp_2 p_4}{2r(1+p_4)}; \quad \hat{\eta}(x_*) = \frac{k}{4r} C_2^2.$$

Therefore if $\hat{\eta}'(0) \le 0$ then $w_0 = \hat{\eta}(0)$ and if $\hat{\eta}'(0) > 0$ then $w_0 = \hat{\eta}(x_*)$. □

6. **Global asymptotic stability respecting the TFEP.** If

$$\mu_1 > \mu_1^{TFEP} = \mu_1^{TFEP}(s_2) := p_1 \frac{s_2}{1+s_2} \tag{10}$$

the system (1) has the TFEP

$$E_1 = (0, s_2, 0, w_1)^T,$$

where

$$w_1 = \frac{s_1(1+s_2)}{\mu_1 + \mu_1 s_2 - p_1 s_2} = \frac{s_1}{\mu_1 - p_1 \frac{s_2}{1+s_2}}.$$

The TFEP is asymptotically stable if $r < aw_1$ i.e.

$$s_1 > s_1^{st} = s_1^{st}(s_2) := \frac{r}{a}(\mu_1 - \frac{p_1 s_2}{1+s_2}). \tag{11}$$

Theorem 6.1. *If conditions (7); (9) and (11) hold then the TFEP attracts all trajectories in* $\mathbf{R}^4_{+,0}$.

Proof. If conditions of this theorem are fulfilled then all trajectories of the system (1) go into bounded positively invariant set $\hat{K}_4$; the TFEP exists and is asymptotically stable. Therefore, in order to prove Theorem 6.1 it is sufficient to show that the TFEP is the unique compact invariant set of the system.

The system (1) has no compact invariant sets in $\mathbf{R}^4_{+,0} \cap \{x > 0\}$ (see Theorem 5.1). The TFEP is the only compact invariant set of the system in the invariant plane $\{x = 0\}$. Indeed, let us consider the system restricted on this plane

$$\begin{aligned} \dot{y} &= -y + s_2, \\ \dot{z} &= -z, \\ \dot{w} &= -\mu_1 w + \frac{wy}{1+y}(p_1 - \frac{q_1 z}{q_2 + z}) + s_1. \end{aligned} \tag{12}$$

Next, applying localizing functions x; y; w we obtain localization sets for compact invariant set of the system (12)

$$K(y, \mathbf{R}^3) = Y := \{y = s_2\}; \quad K(z, \mathbf{R}^3) = Z := \{z = 0\};$$
$$K(w, Y \cap Z) = \{(s_2, 0, w_1)\}.$$

□

Now let us prove that the system (1) has no compact invariant set C for which $C \cap \mathbf{R}^4_{+,0} \cap \{x > 0\} \neq \emptyset$ and $C \cap \{x = 0\} \neq \emptyset$. Indeed, otherwise $C \cap \{x = 0\} = E_1$ and there exists a point $P \in C \cap \mathbf{R}^4_{+,0} \cap \{x > 0\}$. In this case the α–limit set of the trajectory starting at the point P is a nonempty compact invariant set D and $E_1 \notin D$ because otherwise the point E_1 is not stable. Therefore, the nonempty compact invariant set D is a subset of $\mathbf{R}^4_{+,0} \cap \{x > 0\}$ and the statement of the theorem follows from this contradiction with Theorem 5.1.

7. Tumor persistence conditions.

Theorem 7.1. *Suppose that condition (7) holds and $\omega_{\max} < r/a$ i.e.*

$$s_1 < s_1^{per} = s_1^{per}(s_2) := \frac{r}{a}(\mu_1 - p_1 \frac{y_{\max}}{1 + y_{\max}}) - ck(\frac{p_2}{r} + 1). \tag{13}$$

Then in $\mathbf{R}^3_{+,0} \cap \{x > 0\}$ each trajectory goes into the bounded positively invariant set

$$P := \hat{K}_4 \cap \{x \geq x_+ - \tau_5\}$$

where sufficiently small $\tau_5 > 0$;

$$x_+ := \frac{k-1}{2} + \sqrt{\frac{(k-1)^2}{4} + k - \frac{ak}{r} w_{\max}}$$

in finite time.

Proof. In the set $\mathbf{R}^3_{+,0} \cap \{x > 0\}$ each trajectory goes into bounded positively invariant set $\hat{K}_4 \cap \{x > 0\}$ in finite time (see the proof of Theorem 4.1). In the set $\hat{K}_4 \cap \{x > 0\}$ we have that

$$\dot{x} \geq x(r - \frac{r}{k}x - \frac{a\hat{w}_{\max}}{1+x}) = -\frac{rx}{k(1+x)}Q(x), \quad Q(x) = x^2 + x(1-k) + \frac{ak}{r}\hat{w}_{\max} - k.$$

We note that $\hat{w}_{\max} \to w_{\max}$ under $\tau_1, \tau_2, \tau_4 \to 0$. Therefore, if the condition (13) holds there exist sufficiently small τ_1, τ_2, τ_4 for which $\hat{w}_{\max} < \frac{r}{a}$. Hence, then for any $\tau_5 > 0$, $\tau_5 << \min\{x_+; 1\}$, the inequality $Q(x) < 0$ is fulfilled in

$$\{0 < x \leq x_+ - \tau_5\} \cap \hat{K}_4.$$

For any $x_1 \in (0; x_+ - \tau_5)$ the derivative $\dot{x}$ is separated from zero in compact set $\{x_1 \leq x \leq x_+ - \tau_5\} \cap \hat{K}_4$ and we come to the statement of the theorem. □

8. **Comparison of bounds.** Now we describe how some features of ultimate dynamics depend on values s_1 and s_1 under condition that all other parameters are fixed. We recall the formulas

$$\begin{aligned} \mu_1^{TFEP}(s_2) &= p_1 \frac{s_2}{1+s_2} \quad \text{(see (10))}; \\ \mu_1^{M}(s_2) &= -\frac{q_1 p_4}{q_2+p_4} \cdot \frac{y_{\max}}{1+y_{\max}} + p_1 \frac{s_2}{1+s_2} \quad \text{(see (8))}; \\ \mu_1^{pol}(s_2) &= p_1 \frac{y_{\max}}{1+y_{\max}} \quad \text{(see (7))}. \end{aligned}$$

It is easy to see that if $s_2 > 0$ then the double inequality

$$\mu_1^{M}(s_2) < \mu_1^{TFEP}(s_2) < \mu_1^{pol}(s_2)$$

is fulfilled. We notice that the value s_2 determines the existence of:

(i) the localization set $\hat{M}_1$ for compact invariant sets of (1) under condition $\mu_1^{M}(s_2) < \mu_1$;

(ii) TFEP, with $\mu_1^{TFEP}(s_2) < \mu_1$;

(iii) bounded localization set Π for compact invariant sets of the system and global attractor, with $\mu_1^{pol}(s_2) < \mu_1$.

Let us consider the case when our system has the TFEP, i.e. $\mu_1 > \mu_1^{TFEP}(s_2)$. In this case the value s_1 determines the behavior of system trajectories relating to the TFEP. Indeed, we have introduced above functions

$$\begin{aligned} s_1^{per}(s_2) &= \frac{r}{a}(\mu_1 - p_1 \frac{y_{\max}}{1+y_{\max}}) - ck(\frac{p_2}{r}+1) = \\ &= \frac{r}{a}(\mu_1 - \mu_1^{pol}(s_2)) - ck(\frac{p_2}{r}+1) \quad \text{(see (13))}; \end{aligned}$$

$$s_1^{st}(s_2) = \frac{r}{a}(\mu_1 - \frac{s_2}{1+s_2}) = \frac{r}{a}(\mu_1 - \mu_1^{TFEP}(s_2)) \quad \text{(see (11))};$$

$$s_1^{att}(s_2) = \frac{w_0}{a}(\mu_1 - \frac{p_1 s_2}{s_2+1} + \frac{q_1 y_{\max} p_4}{(y_{\max}+1)(q_2+p_4)}) = \frac{w_0}{a}(\mu_1 - \mu_1^{M}(s_2)) \quad \text{(see (9))}.$$

It is easy to see that

$$s_1^{per}(s_2) < s_1^{st}(s_2) < s_1^{att}(s_2), \; s_2 > 0.$$

If $s_1 < s_1^{st}(s_2)$ holds then the TFEP is not stable and under additional conditions

$$s_1 < s_1^{per}(s_2); \quad \mu_1^{pol}(s_2) < \mu_1$$

we have the tumor persistence.

If $s_1 > s_1^{st}(s_2)$ holds then the TFEP is asymptotically stable and under additional conditions

$$s_1 > s_1^{att}(s_2); \quad \mu_1^{pol}(s_2) < \mu_1$$

all trajectories in $\mathbf{R}_+^4$ tend to the TFEP.

9. **Concluding remarks.** The main contribution of the present paper lies in the rigorous dynamical analysis of the four-dimensional system (1) and in obtaining global tumor clearance conditions via the localization method of compact invariant sets. We have studied various aspects of the ultimate dynamics of (1) describing interactions of cancer cells, TGF-β and immune cells under two types of the treatment. This research includes the following parts.

1. Under condition (7) we have found all upper bounds for variables of the state vector of the system (1). Moreover, in this case it was shown that (1) has

the property of the dissipativity in the sense of Levinson, because there exists the positively invariant polytope.

2. Further, we provide conditions (8) and (9) under which there are no compact invariant sets in the set $\mathbf{R}^4_{+,0} \cap \{x > 0\}$. As a result, there is no conditions for tumor dormancy. In particular, the system (1) has neither TPEPs nor periodic orbits.

3. We find conditions (7); (9) and (11) under which the TFEP attracts all trajectories in $\mathbf{R}^4_{+,0}$. The biological sense of this behavior consists in asymptotic eradication of tumor cells which means that after a while the tumor cells population will be under control.

4. Tumor eradication and tumor persistence bounds are compared in Section 8. One can point to the following essential difference of dynamics of (1) in cases $s_{1,2} = 0$, [1], and in case $s_{1,2} > 0$ under varying antigenicity c. Namely, it was noticed in [1] that there are many negative scenarios including uncontrolled tumor growth and damped oscillations around the TPEP, which corresponds to tumor dormancy. In our work, because of the proper assignment of treatment parameters $s_{1,2}$ satisfying Theorem 6.1 for given model parameters $a, k, r, \mu_1, g_4, p_1, p_2, p_3, p_4$ one may achieve tumor eradication regardless the value of c, where $c > 0$. However, the tumor persistence bound s_1^{per} depends on parameter c.

All assertions are formulated in terms of simple algebraic inequalities imposed on parameters of the model and treatments. These inequalities are stable for sufficiently small perturbations caused by imprecise knowledge of parameters' values which is convenient in applications.

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REFERENCES

[1] J. C. Arciero, T. L. Jackson and D. E. Kirschner A mathematical model of tumor-immune evasion and siRNA treatment, *Discrete Contin. Dynamic. Syst. Ser. B*, **4** (2004), 39–58.

[2] D. Kirschner and J. Panetta, Modelling immunotherapy of the tumor-immune interaction, *J. Math. Biol.*, **37** (1998), 235–252.

[3] D. Kirschner and A. V. Tsygvintsev, On the global dynamics of a model for tumor immunotherapy, *Math. Biosci. Engin.*, **6** (2009), 573–583.

[4] A. P. Krishchenko, Estimations of domains with cycles, *Comput. & Math. Appl.*, **34** (1997), 325–332.

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

[6] A. P. Krishchenko and K. E. Starkov, Localization of compact invariant sets of the Lorenz system, *Phys. Lett. A*, **353** (2006), 383–388.

[7] A. P. Krishchenko and K. E. Starkov, On the global dynamics of a chronic myelogenous leukemia model, *Commun. Nonlin. Sci. Numer. Simul.*, **33** (2016), 174–183.

[8] F. Salazar-Onfray, Interleukin-10: A cytokine used by tumors to escape immunosurveillance, *Medical Oncology*, **16** (1999), 86–94.

[9] K. E. Starkov, On dynamic tumor eradication conditions under combined chemical/anti-angiogenic therapies, *Phys. Lett. A*, **382** (2018), 387–393.

[10] K. E. Starkov and S. Bunimovich-Mendrazitsky, Dynamical properties and tumor clearance conditions for a nine-dimensional model of bladder cancer immunotherapy, *Math. Biosci. Eng.*, **13** (2016), 1059–1075.

[11] K. E. Starkov and D. Gamboa, Localization of compact invariant sets and global stability in analysis of one tumor growth model, *Mathematical Methods in the Applied Sciences*, **37** (2014), 2854–2863.

[12] K. E. Starkov and L. Jimenez Beristain, Dynamic analysis of the melanoma model: from cancer persistence to its eradication, *Internat. J. Bifur. Chaos Appl. Sci. Engrg.*, **27** (2017), 1750151, 11pp.

[13] K. E. Starkov and A. P. Krishchenko, On the global dynamics of one cancer tumor growth model, *Commun. Nonlin. Sci. Numer. Simul.*, **19** (2014), 1486–1495.

[14] K. E. Starkov and A. P. Krishchenko, Ultimate dynamics of the Kirschner–Panetta model: Tumor eradication and related problems, *Phys. Lett. A*, **381** (2017), 3409–3416.

[15] K. E. Starkov and A. Pogromsky, Global dynamics of the Owen–Sherratt model describing the tumor-macrophage interactions, *Internat. J. Bifur. Chaos Appl. Sci. Engrg.*, **23** (2013), 1350020, 9pp.

[16] K. E. de Visser and W. M. Kast, Effects of TGF-ß on the immune system: Implications for cancer immunotherapy, *Journal of Immunotherapy*, **20** (1997), 165–177.

[17] S. Wojtowicz-Praga, Reversal of tumor-induced immunosuppression: A new approach to cancer therapy, *Journal of Immunotherapy*, **20** (1997), 165–177.

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