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Abstract

We present a phase-space analysis of a mathematical model of tumor growth with an immune responses. We consider mathematical analysis of the model equations with multipoint initial condition regarding to dissipativity, boundedness of solutions, invariance of non-negativity, local and global stability and the basins of attractions. We derive some features of behavior of the three-dimensional tumor growth models with dynamics described in terms of densities of three cells populations: tumor cells, healthy host cells and effector immune cells. We found sufficient conditions, under which trajectories from the positive domain of feasible multipoint initial conditions tend to one of equilibrium points. Here, cases of the small tumor mass equilibria-the healthy equilibrium point, the "death" equilibria have been examined. Biological implications of our results are discussed.

Beginning with this article we intend to investigate the problems of mathematical and biological approaches to model the cancer growth dynamics processes and operations. It is important to take into account "the nonlinear property of cancer growth processes" in construction of mathematical logistic models. The nonlinearity approach appears very convenient to display unexpected dynamics in cancer growth processes expressed in different reactions of the dynamics to different concentrations of immune cells at different stages of cancer growth developments $[1-21]$. Taking into account all the complex processes, nonlinear mathematical models can be estimated capable of compensation and minimization the inconsistencies between different mathematical models related to cancer growth-anticancer factor affections. The elaboration of mathematical non-spatial models of the cancer tumor growth in the broad framework of tumor immune interactions studies is one of intensively developing areas in the modern mathematical biology, see works $[1-9]$. Of course, the development of powerful cancer immunotherapies requires an understanding of the mechanisms governing the dynamics of tumor growth. One of main reasons for creation of non-spatial dynamical models of this nature is related to the fact that they are described by a system of ordinary differential equations, which can be efficiently investigated by powerful methods of qualitative theory of dynamical systems theory. Mathematical models for tumour growth have been extensively studied in the literature to understand the mechanism of the disease and predict its future behavior. Interactions of tumour cells with other cells of the body, i.e. healthy host cells and immune system cells are the main components of these models and these interactions may yield different outcomes. Some important phenomena of the tumour progression such as tumour dormancy, creeping through, and escaping from immune surveillance have been investigated by using these models. Kuznetsov et al. [1] proposed a model of second order ordinary differential equations (ODEs), which includes the effector immune cell and the tumour cell populations. They demonstrated that even with two cell populations, these models can provide rich dynamics depending on the system parameters and explained some important aspects of the stages of cancer progression. Three equation mathematical models of tumor growth with an immune responses were studied e.g. in [4, 5, 7, 9, 10] . For instance, Kirschner and Panetta [4] examined the tumour cell growth in the presence of the effector immune cells and the cytokine IL-2 which has an essential role in the activation and stimulation of the immune system. de Pillis and Radunskaya [5] included a normal tissue cell population in this model, performed phase space analysis and investigated the effect of chemotherapy treatment by using optimal control theory. In [9], interactions between cancer cells, effector cells, and cytokines (such as IL-2, TGF-β, IFN-γ) studied. In [7] interactions between cancer cells, effector cells, and normal tissue cells are investigated. In [6], a four-dimensional model is discussed which can undergo Hopf bifurcations leading to periodic orbits, a possible route to the development of chaotic attractors (for general review see e.g. [1, 3]). In [10] global behavior of the tumour growth population dynamics was investigated. The local stability, the chaotic behavior properties and some features of global behavior tumour growth model of (1.1) with the classical initial condition were studied in [12] and [11], respectively. The complex oscillations were studied in [16]. Moreover, the model has been also used to define optimal control problems (see e.g. [16 − 18]). Note that nonlinear dynamic systems studied e.g. in [22 − 24]. In contrast to mentioned works, here mathematical analysis of multipoint IVP for (1.1), local and global stability and the multiphase basins of attractions have been investigated. We prove that all orbits are bounded and must converge to one of several possible equilibria. Therefore, the long-term behavior of an orbit is classified according to the basin of multipoint attraction in which it starts. Here, we examine the dynamics of one cancer growth model proposed in [5], but possessing multiphase structure, i.e. we consider the following multipoint initial value problem (IVP) for dynamical system

$$\dot{T} = r_1 T \left(1 - k_1^{-1} T\right) - a_{12} NT - a_{13} IT,$$

$$\dot{N} = r_2 N \left(1 - k_2^{-1} N\right) - a_{21} NT, \ \dot{I} = \frac{r_3 IT}{k_3 + T} - a_{31} IT - d_3 I, \tag{1.1}$$

$$T(t_0) = T_0 + \sum_{k=1}^{m} \alpha_{1k} T(t_k), \ N(t_0) = N_0 + \sum_{k=1}^{m} \alpha_{2k} N(t_k), \tag{1.0}$$

$$I(t_0) = I_0 + \sum_{k=1}^{m} \alpha_{3k} I(t_k), \ t_0 \in [0, \ \eta), \ t_k \in O_\delta(t_0),$$

where $T = T(t),\ N = N(t),\ I = I(t)$ denote the densities of tumor cells, healthy host cells and the effector immune cells, respectively at the moment t,

α_{jk} are real numbers, m is a natural number and

$$O_\delta(t_0) = \{t \in \mathbb{R} : |t - t_0| < \delta\} \text{ for a } \delta > 0. \tag{1.2}$$

The assumption (1.0) is given on coefficients α_{ij} and $t_0, t_1, t_2, ...t_m$; here, (T_0, N_0, I_0) indicate the given pre-healing vector (or pre-healing vector state) such that T_0 is small enough but N_0, I_0 are big enough. The condition (1.2) links the values of vector function $V(t) = (T(t), N(t), I(t))$ at various points $t_0, t_1, ..., t_m$ to each other by healing vector (T_0, N_0, I_0); so, we called (1.2) a multipoint IVP. The first term of the first equation corresponds to the logistic growth of tumor cells in the absence of any effect from other cells populations with the growth rate of r_1 and maximum carrying capacity k_1. The competition between host cells and tumor cells $T(t)$ which results in the loss of the tumor cells population is given by the term $a_{12}NT$. Next, the parameter a_{13} refers to the tumor cell killing rate by the immune cells $I(t)$. In the second equation, the healthy tissue cells also grow logistically with the growth rate of r_2 and maximum carrying capacity k_2. We assume that the cancer cells proliferate faster than the healthy cells which gives $r_1 > r_2$. The tumor cells also inactivate the healthy cells at the rate of a_{21}. The third equation of the model describes the change in the immune cells population with time t. The first term of the third equation illustrates the stimulation of the immune system by the tumor cells with tumor specific antigens. The rate of recognition of the tumor cells by the immune system depends on the antigenicity of the tumor cells. The model of the recognition process is given by the rational function which depends on the number of tumor cells with positive constants r_3 and k_3. The immune cells are inactivated by the tumor cells at the rate of a_{31} as well as they die naturally at the rate d_3. We suppose that the constant influx s of the activated effector cells into the tumor microenvironment is zero. One of main aims is derivation of sufficient conditions under which the possible biologically feasible dynamics is local and globally stable, and a converges to one of equilibria. Since these equilibrium points have a biological sense, we notice that understanding limit properties of dynamics of cells populations based on solving problems (1.1) – (1.2) may be of an essential interest for the prediction of health conditions of a patient without a treatment, when the data (e.g. the status of blood cells shown above) that determines the conditions of the patient are compared at various times $t_0, t_1, ..., t_m$ and correlated.

By scaling $x_1 = Tk_1^{-1}$, $x_2 = Nk_2^{-1}$, $x_3 = Ik_3^{-1}$, $\tilde{t} = r_1 t$ in (1.1) and omitting the tilde notation we get the multipoint IVP for the following dynamical system

$$\begin{aligned} \dot{x}_1 &= x_1(1 - x_1) - a_{12}x_1x_2 - a_{13}x_1x_3, \\ \dot{x}_2 &= r_2x_2(1 - x_2) - a_{21}x_1x_2, \\ \dot{x}_3 &= \frac{r_3x_1x_3}{x_1 + k_3} - a_{31}x_1x_3 - d_3x_3, \ t \in [0, \ T), \end{aligned} \tag{1.3}$$

$$x_1(t_0) = x_{10} + \sum_{k=1}^{m} \alpha_{1k}x_1(t_k), \ x_2(t_0) = x_{20} + \sum_{k=1}^{m} \alpha_{2k}x_2(t_k), \tag{1.4}$$

$$x_3\left(t_0\right)=x_{30}+\sum_{k=1}^{m}\alpha_{3k}x_3\left(t_k\right),\ t_0\in[0,\ T),\ t_k\in O_\delta\left(t_0\right).$$

We are interested in biologically relevant solutions of the system (1.3) – (1.4).

Note that, for $\alpha_{j1}=\alpha_{j2}=...\alpha_{jm}=0$ the problem (1.3) – (1.4) becomes the classical IVP for the dynamical system (1.3).

Remark 1.1. Consider for example, the multipoint IVP for ordinary equation

$$\frac{dx}{dt}=\frac{2x}{1+t},\ x\left(0\right)=x_0+\alpha_1x\left(t_1\right)+\alpha_2x\left(t_2\right),\ t_1,t_2\in O_\delta\left(0\right), \tag{1.5}$$

where x_0 is a given positive number, t_1,t_2 are points in $O_\delta\left(0\right)$, α_1 and α_2 are real numbers such that

$$x\left(0\right)-\alpha_1x\left(t_1\right)-\alpha_2x\left(t_2\right)\geq 0.$$

Then it is clear to see that there exists a solution of (1.5) expressed as

$$x\left(t\right)=\left[1-\alpha_1\left(1+t_1\right)^2-\alpha_2\left(1+t_2\right)^2\right]^{-1}x_0\left(1+t\right)^2,$$

where

$$\alpha_1\left(1+t_1\right)^2+\alpha_2\left(1+t_2\right)^2\leq 1. \tag{1.6}$$

The assumption (1.6) given on t_1,t_2 and coefficients α_1, α_2.

2. Notations and background.

Consider the multipoint IVP for nonlinear equation

$$\frac{du}{dt}=f\left(u\right),\ t\in[0,T], \tag{2.1}$$

$$u\left(t_0\right)=u_0+\sum_{k=1}^{m}\alpha_ku\left(t_k\right),\ t_0\in[0,\ T),\ t_k\in O_\delta\left(t_0\right),$$

in a Banach space X, where α_k are complex numbers, m is a natural number and $u=u\left(t\right)$ is a $X-$valued function.

Note that, for $\alpha_1=\alpha_2=...\alpha_m=0$ the problem (2.1) becomes the following local Cauchy problem

$$\frac{du}{dt}=f\left(u\right),\ u\left(t_0\right)=u_0,\ t\in[0,T],\ t_0\in[0,\ T). \tag{2.2}$$

For $u_0\in X$ let $\bar{B}_r\left(u_0\right)$ denotes a closed ball in X with radius r centered at u_0, i.e.,

$$\bar{B}_r\left(u_0\right)=\left\{u\in X:\left\|u-u_0\right\|_X\leq r\right\}.$$

We can generalized the classical Picard existence theorem for the multipoint IVP (2.1).

By reasoning as in [24, p.218,223)] we obtain

Theorem 2.1. Let X be a Banach space. Suppose $f : X \to X$ satisfies local Lipschitz condition on $\bar{B}_r(\upsilon_0) \subset X$, i.e.

$$\|f(u) - f(\upsilon)\|_X \leq L_f \|u - \upsilon\|_X$$

for each u, $\upsilon \in \bar{B}_r(\upsilon_0)$ and $t_k \in O_\delta(t_0)$ for some $\delta > 0$, where

$$\upsilon_0 = u_0 + \sum_{k=1}^{m} \alpha_k u(t_k).$$

Moreover, let

$$M = \sup_{u \in \bar{B}_r(\upsilon_0)} \|f(u)\|_X < \infty.$$

Then, problem (2.1) has a unique continuously differentiable local solution $u(t)$ for $t \in O_\delta(t_0)$, where $\delta \leq \frac{r}{M}$.

Proof. We rewrite the initial value problem (2.1) as an integral equation

$$u = \upsilon_0 + \int_{t_0}^{t} f(u(s))\, ds.$$

For $0 < \eta < \frac{r}{M}$ we define the space

$$Y = C\left([-\eta, \eta]; \bar{B}_r(\upsilon_0)\right).$$

Let

$$Qu = \upsilon_0 + \int_{t_0}^{t} f(u(s))\, ds.$$

First, note that if $u \in Y$ then

$$\|Qu - \upsilon_0\|_X \leq \left\| \int_{t_0}^{t} f(u(s))\, ds \right\|_X \leq M\eta < r.$$

Hence, $Qu \in Y$ so that $Q : Y \to Y$. Moreover, for all u, $\upsilon \in Y$ we have

$$\|Qu - Q\upsilon\|_X \leq \left\| \int_{t_0}^{t} \left[f(u(s)) - f(\upsilon(s))\right] ds \right\|_X \leq$$

$$L_f \eta \|u - \upsilon\|_X, \tag{2.3}$$

where L_f is a Lipschitz constant for f on $\bar{B}_r(\upsilon_0)$. Hence, if we choose

$$\eta < \min\left\{\frac{r}{M}, \frac{1}{L_f}\right\} \tag{2.4}$$

then Q is a contraction on Y and it has a unique fixed point. Since η depends only on the Lipschitz constant of f and on the distance r of the initial data from the boundary of $\bar{B}_r(\upsilon_0)$. Then repeated application of this result gives a unique local solution defined for $|t-t_0| < \frac{r}{M}$.

Theorem 2.2. Let X be a Banach space. Suppose that $f : X \to X$ satisfies global Lipschitz condition, i.e.

$$\|f(u) - f(\upsilon)\|_X \leq L_f \|u - \upsilon\|_X$$

for each u, $\upsilon \in X$. Moreover, let

$$M = \sup_{u \in X} \|f(u)\|_X < \infty.$$

Then problem (2.1) has a unique continuously differentiable global solution $u(t)$.

Proof. The key point of proof is to show that the constant δ of Theorem 2.1 can be made independent of the υ_0. It is not hard to see that the independence of υ_0 comes through the constant M in therm $\frac{r}{M}$ in (2.4). Since in the current case the Lipschitz condition holds globally, one can choose r arbitrary large. Therefore, for any finite M, we can choose r large enough and by using (2.3), (2.4), we obtain the assertion.

Let X be a Banach space. $w \in X$ is called a critical point (or equilibria point) for (2.1) if $f(w) = 0$. We denote the solution of the problem (2.1) by

$$\phi(t, \upsilon_0) = \phi(t, u(t_0), u(t_1), ..., u(t_m)).$$

Definition 2.1. Let $u_0 \in X$, $u(t) = \phi(t, \upsilon_0)$ be a solution of (1.13) and $w \in X$ be a critical point of (2.1). If there exists a neighbourhood $O(w) \subset X$ of w such that $\lim_{t \to \infty} \phi(t, \upsilon_0) = w$ for $u_0 + \sum_{k=1}^{m} \alpha_k u(t_k) \subset O(w)$, $t_0 \in [0,\ T)$, $t_k \in O_\delta(t_0)$ and a $\delta > 0$, then w is called a positive multiphase attractor.

Definition 2.2. Assume $w \in X$ is a multiphase attractor point of (2.1) and $u(t) = \phi(t, u_0)$ is a solution of (2.1). A set $\Omega = \left\{ \upsilon \colon\ \upsilon = u_0 + \sum_{k=1}^{m} \alpha_k u(t_k) \right\} \subset X$ is called a domain of multiphase basin (multiphase attractor or domain of multiphase asymptotic stability) of w if $\lim_{t \to \infty} \phi(t, u_0) = w$ for $\upsilon \in \Omega$.

3. Boundedness and dissipativity

In this section, we shall show that the model are bounded with negative divergence, positively invariant with respect to a region in R^3_+ and dissipative. As we are interested in biologically relevant solutions of the system, the next results show that the positive octant is invariant and that the upper limits of trajectories depend on the parameters of multipoint initial conditions.

Let

$$B_{\alpha,m} = \left\{ x = (x_1, x_2, x_3) \in \mathbb{R}^3_+ \colon\ 0 \leq x_i \leq K_i(\alpha, m) \right\},\ i = 1,\ 2,\ 3, \tag{3.0}$$

where

$$K_i = K_i(\alpha, m) = \max\left\{1,\ x_{i0} + \sum_{k=1}^{m} \alpha_{ik} x_1(t_k)\right\},\ t_k \in O_\delta(t_0).$$

Consider the problem $(1.3) - (1.4)$ with $t_0 = 0$.

Theorem 3.1. Assume

$$d_3 > 1 + r_2,\ r_i > 0,\ k_i > 0,\ a_{ij} > 0,\ r_3 < k_3 a_{31}. \tag{3.1}$$

Then:(1) $B_{\alpha,m}$ is positively invariant with respect to $(1.3) - (1.4)$; (2) all solutions of $(1.3) - (1.4)$ are uniformly bounded and are attracted into the region $B_{\alpha,m}$; (3) the system (1.3) is with the negative divergence; (4) the system (1.3) is dissipative.

Proof. By Theorem 2.1 there exists a unique solution of multipoint problem $(1.3) - (1.4)$.(1) Consider the first equation of the system (1.3):

$$\dot{x}_1 = x_1(1 - x_1) - a_{12} x_1 x_2 - a_{13} x_1 x_3.$$

By condition $a_{ij} > 0$ we get $\dot{x}_1 < x_1(1 - x_1)$.

It is clear that

$$x_1(1 - x_1) = 0,\ \frac{d}{dx_1}[x_1(1 - x_1)] = 1 - 2x_1 < 0$$

for $x_1 = 1$. Thus

$$x_1(t) \le \max\left\{1,\ x_{10} + \sum_{k=1}^{m} \alpha_{1k} x_1(t_k)\right\},\ \dot{x}_1 < 0 \text{ for } x_1 > 1.$$

Hence,

$$\limsup_{t\to\infty} x_1(t) \le 1. \tag{3.2}$$

For

$$\dot{x}_2 = r_2 x_2(1 - x_2) - a_{21} x_1 x_2,$$

a similar analysis gives

$$x_2(t) \le \max\left\{1,\ x_{20} + \sum_{k=1}^{m} \alpha_{2k} x_2(t_k)\right\},$$

$$\limsup_{t\to\infty} x_2(t) \le 1. \tag{3.3}$$

Now consider

$$\dot{x}_3 = \frac{r_3 x_1 x_3}{x_1 + k_3} - a_{31} x_1 x_3 - d_3 x_3.$$

From (3.1) we have

$$\dot{x}_3 < \frac{r_3 x_1 x_3}{x_1 + k_3} - a_{31} x_1 x_3 = x_1 x_3 \left(\frac{r_3}{x_1 + k_3} - a_{31} \right) < 0.$$

Then by reasoning as the case of x_1 we deduced

$$x_3(t) \leq \max \left\{ 1,\ x_{30} + \sum_{k=1}^{m} \alpha_{1k} x_3(t_k) \right\},$$

$$\limsup_{t \to \infty} x_3(t) \leq 1. \tag{3.4}$$

Hence, from (3.2) – (3.4) we obtain (1) and (2) assertions. Now, let us show (3)-(4). Since

$$\frac{\partial f_1}{\partial x_1} + \frac{\partial f_2}{\partial x_2} + \frac{\partial f_3}{\partial x_3} = 1 - 2x_1 - a_{12} x_2 - a_{13} x_3 + r_2 - 2r_2 x_2 - a_{21} x_1 +$$
$$\frac{r_3 x_1}{x_1 + k_3} - a_{31} x_1 - d_3 = (1 + r_2 - d_3) - (2 + a_{21}) x_1 - \tag{3.5}$$
$$(2r_2 + a_{12}) x_2 + \left[\frac{r_3}{x_1 + k_3} - a_{31} \right] x_1 - a_{13} x_3,$$

where $f_1,\ f_2,\ f_3$ denote the right sides of the system (1.3).

By condition (3.1) from (3.5), we obtain

$$\frac{\partial f_1}{\partial x_1} + \frac{\partial f_2}{\partial x_2} + \frac{\partial f_3}{\partial x_3} < 0 \text{ for } x \in B,$$

i.e. the system (1.3) is dissipative.

4. The Lyapunov stability of equilibria points

In this section, we will derive the stability properties of equilibria points of the system (1.3).

Remark 4.1. It is clear that the points $E_0(0,0,0)$, $E_1(1,0,0)$, $E_2(0,1,0)$ are biologically feasible equilibria points for the system (1.3). Moreover, if $a_{21} > r_2$ and

$$r_3 > d_3 + a_{31} k_3 + \sqrt{D},\ \ (2 + k_3) a_{31} + d_3 > r_3 + \sqrt{D},$$
$$x_{1i} + a_{12} x_{2j} < 1,\ D = b_1^2 - 4 d_3 k_3 a_{31} \geq 0,$$

then the system (1.3) have the biologically feasible equilibria points

$$E_3(a_{\pm}, 0, b_{\mp}),\ E_4(\bar{x}_1, \bar{x}_2, 0),\ E_{ij}(x_{1i}, x_{2j}, x_{3ij})$$

(see e.g. [12]), where

$$a_{\pm} = \frac{b_1 \pm \sqrt{D}}{2a_{31}},\ b_{\mp} = \frac{2a_{31} - b_1 \mp \sqrt{D}}{2a_{13} a_{31}}, \tag{4.0}$$

$$\bar{x}_1 = \frac{a_{12}a_{21} - r_2}{r_2\left(a_{12} - 1\right)},\ \bar{x}_2 = \frac{a_{12}\left(r_2 - a_{21}\right)}{r_2\left(a_{12} - 1\right)a_{12}},$$

$$b_1 = r_3 - d_3 - a_{31}k_3,\ x_{2i} = \frac{r_2 - a_{21}x_{1i}}{r_2},\ x_2 \neq 0,\ i = 1,\ 2,$$

$$x_{3ij} = \frac{1 - x_{1i} - a_{12}x_{2j}}{a_{13}},\ i,\ j = 1, 2.$$

$$R_+^3 = \left\{x \in R^3\colon\ x_i > 0,\ i = 1, 2, 3\right\}.$$

Remark 4.0. (1) In the point $E_0\left(0,0,0\right)$, three type cell populations are zero; (2) at the point $E_1\left(1,0,0\right)$, tumor cells have survived but normal and immune cells are zero, this case can be called as "dead" case; (3) the point $E_2\left(0,1,0\right)$ −tumor-free and immune free case. At this points, normal cells have survived but tumor and immune cells are zero; (4) at the points $E_3\left(a_\pm, 0, b_\mp\right)$, normal cells are zero, but tumor and immune cells have been struggling; (5) at $A_4 = E_4\left(\bar{x}_1, \bar{x}_2, 0\right)$, tumor and normal cells populations have survived but immune cells populations are zero. This case also called a "diseased" case. (6) the points $E_{ij}\left(x_{1i}, x_{2j}, x_{3ij}\right)$, $i = 1,\ 2,\ j = 0,\ 1,\ 2$ correspond to the coexisting cases, i.e., when tumor, normal and immune populations have survived.

By virtue of [8] we obtaın: the linearized system (1.3) has the followıng fixed points: $E_1\left(0,0,0\right)$ which means none of the cell. The eigenvalues of the Jacobian matrix at this point are $\lambda_1 = 1$, $\lambda_2 = r_2$, and $\lambda_3 = -d_3$. Since all the parameters are positive, the equilibrium has two unstable and one stable eigenvalue. Therefore, we have a saddle at this point and populations exists; around at $E_2\left(0,1,0\right)$ the system is in healthy stage. The eigenvalues of the Jacobian matrix at the tumour-free equilibrium point are $\lambda_1 = -r_2$, $\lambda_2 = -d_3$ and $\lambda_3 = 1 - a_{12}$. Stability of this point depends on the value of a_{12}. If $a_{12} > 1$ this point is stable and unstable for $a_{12} < 1$; at $E_3\left(1,0,0\right)$, the tumour population is in the maximum limit in that compartment. The eigenvalues of the Jacobian matrix at this point are obtained as:

$$\lambda_1 = -1,\ \lambda_2 = r_2 - a_{21},\ \lambda_3 = \left(r_3 - d_3 - a_{31} - a_{31}k_3 - d_3k_3\right)\left(1 + k_3\right)^{-1}.$$

By choose the parameters in expression of λ_2 and λ_3 we can obtain stability and unstability of the point E_3; the point $E_4\left(\bar{x}_1, \bar{x}_2, 0\right)$ for $\bar{x}_1 = \frac{r_2(a_{12}-1)}{a_{12}a_{21}-r_2}$, $\bar{x}_2 = \frac{a_{12}-r_2}{a_{12}a_{21}-r_2}$ and $a_{12}a_{21} \neq r_2$.This point is a biologically feasible equilibria if $a_{12} \geq 1$ and yields the real eigenvalues with different signs; the point $E_5\left(\eta_1, \eta_2, \eta_3\right)$, where $\eta_1,\ \eta_2 > 0$, $\eta_3 = \varphi - \psi a_{12}$ for positive parameters φ and ψ; In order to have a biologically relevant point we assume $\varphi \geq \psi a_{12}$.This point has one real unstable eigenvalue and two complex eigenvalues with positive real parts; $E_6\left(y_1, 0, y_3\right)$: assuming y_1 and y_3 are positive. This point has one unstable real and two complex eigenvalues with stable real parts with the selected parameter sets; consider the point $E_7\left(z_1, 0, z_3\right)$, where $z_3 < 0$. Since this equilibrium has a negative value for z_3, it is biologically irrelevant; The eighth and last equilibrium point for the system (1.3) is $E_8\left(x_1, x_2, x_3\right)$ with nonpositive value for x_2. Since this point biologically irrelevant we do not consider to this point.

Let

$$R^3_+ = \left\{x \in R^3\colon\ x_i \geq 0,\ i = 1,2,3\right\},\ B_r(\bar{x}) = \left\{x \in R^3,\ \|x - \bar{x}\|_{R^3} < r\right\}.$$

In this section we show the following results:

Theorem 4.1. Assume (1) $r_2 - a_{21} < 0$, $\frac{r_3}{k_3} - a_{31} < 0$;(2) $c_{13} = \frac{r_3}{1+k_3} - a_{31} - d_3 < 0$, $a_{12} > a_{13}$. Then the system (1.3) is asymptotically stable at the equilibria point $E_1(1,0,0)$ in the Lyapunov sense. If $a_{21} > r_2$ or $c_{13} > 0$, then the system (1.3) is unstable at $E_1(1,0,0)$.

Proof. Let A_1 be the linearized matrix with respect to equilibria point $E_1(1,0,0)$, i.e.

$$A_1 = \begin{bmatrix} -1 & -a_{12} & -a_{13} \\ 0 & r_2 - a_{21} & 0 \\ 0 & 0 & c_{13} \end{bmatrix}.$$

By assumption (2), $c_{13} < 0$. We consider the Lyapunov equation

$$P_1 A_1 + A_1^T P_1 = -I,\ P_1 = \begin{bmatrix} b_{11} & b_{12} & b_{13} \\ b_{21} & b_{22} & b_{23} \\ b_{31} & b_{32} & b_{33} \end{bmatrix}. \tag{4.1}$$

By solving (4.1) with respect to b_{ij}, we obtain

$$b_{11} = \frac{1}{2},\ b_{12} = b_{21} = \frac{a_{12}}{2(a_{21} - r_2 + 1)},\ b_{13} = b_{31} = \frac{a_{13}}{2(1 - c_{13})},$$

$$b_{22} = \frac{1 - a_{12}b_{12}}{2(a_{21} - r_2)},\ b_{23} = b_{32} = \frac{a_{13}b_{12} + a_{12}b_{13}}{(r_2 - a_{21} + c_{13})}, \tag{4.2}$$

$$b_{33} = \frac{2a_{13}b_{13} - 1}{2c_{13}},\ P_1 = \begin{bmatrix} b_{11} & b_{12} & b_{13} \\ b_{12} & b_{22} & b_{23} \\ b_{13} & b_{23} & b_{33} \end{bmatrix}.$$

From (4.2) and assumptions (1)-(3) we have

$$b_{12} > 0,\ b_{13} > 0,\ b_{23} < 0 \text{ if } r_2 + a_{31} + d_3 > a_{21} + \frac{r_3}{1+k_3},\ b_{23} > 0 \tag{4.3}$$

$$\text{if }\ a_{21} > r_2 + a_{31} + d_3 - \frac{r_3}{1+k_3},\quad b_{11} > 0,\ b_{22} > 0,\ b_{33} > 0.$$

The eigenvalues of the matrix A_1 can be founds as the roots of characteristic equation

$$|P_1 - \lambda I| = \lambda^3 - \left(b_{22} + b_{33} - \frac{1}{2}\right)\lambda^2 -$$

$$\left[b_{13}^2 + b_{12}^2 - \frac{1}{2}(b_{22} + b_{33}) + b_{12}^2 - b_{22}b_{23}\right]\lambda + b_{12}^2 b_{33} - b_{13}^2 b_{22}^2 - 2b_{12}b_{13}b_{23} = 0.$$

Hence, the eigenvalues of A_1 are positive if the quadratic function

$$V_1(x) = X^T P_1 X = b_{11}x_1^2 + b_{22}x_2^2 + b_{33}x_3^2 + 2b_{12}x_1x_2 +$$

$$2b_{13}x_1x_3 + 2b_{23}x_2x_3.$$

is positive defined. It is clear to see that

$$V_1(x) = \frac{1}{2}b_{11}\left[\left(x_1 + 4\frac{b_{12}}{b_{11}}x_2\right)^2 + \left(\frac{b_{22}}{b_{11}} - 4\left(\frac{b_{12}}{b_{11}}\right)^2\right)x_2^2\right] +$$

$$\frac{1}{2}b_{11}\left[\left(x_1 + 2\frac{b_{12}}{b_{11}}x_3\right)^2 + \left(\frac{b_{33}}{b_{11}} - 4\left(\frac{b_{13}}{b_{11}}\right)^2\right)x_3^2\right] +$$

$$\frac{1}{2}b_{22}\left[\left(x_2 + 2\frac{b_{23}}{b_{22}}x_3\right)^2 + \left(\frac{b_{33}}{b_{22}} - 4\left(\frac{b_{23}}{b_{22}}\right)^2\right)x_3^2\right] > 0$$

when

$$4b_{12}^2 \leq b_{11}b_{22},\ 4b_{13}^2 \leq b_{11}b_{33},\ 4b_{23}^2 \leq b_{22}b_{33}, \tag{4.4}$$

i.e. the matrix A_1 is positive defined. Hence, the quadratic function

$$V_1(x_1 - 1, x_2, x_3) = b_{11}(x_1 - 1)^2 + b_{22}x_2^2 + b_{33}x_3^2 +$$

$$2b_{12}(x_1 - 1)x_2 + 2b_{13}(x_1 - 1)x_3 + 2b_{23}x_2x_3$$

is a positive defined Lyapunov function candidate (see e.g. [22, 23, 25, 26]). By [12, Corollary 8.2] we need now to determine a domain Ω_1 on which $\dot{V}_1(x)$ is negatively defined. By assuming $x_k \geq 0$, $k = 1, 2, 3$, we will find the solution set of the following inequality

$$\dot{V}_1(x_1 - 1, x_2, x_3) = \sum_{k=1}^{3} \frac{\partial V_1}{\partial x_k}\frac{dx_k}{dt} = \tag{4.5}$$

$$-2(b_{11}x_1 + b_{22}r_2x_2) - 2[b_{12}a_{13} + b_{23}a_{21} + b_{13}a_{12}]x_1x_2x_3 -$$

$$2\{[(b_{11}a_{12} + b_{12}(a_{21}+1))]x_1 + [b_{22}a_{21} + b_{12}a_{12} + b_{12}r_2]x_2\}x_1x_2 -$$

$$2[b_{11}a_{13} + b_{13}]x_1^2x_3 - 2\left[b_{11}x_1^3 + b_{22}r_2x_2^3 + b_{13}a_{13}x_1x_3^2 + b_{23}r_2x_2^2x_3\right] -$$

$$2b_{11}x_1^2 + b_{13}x_1x_3 + 2(b_{11}a_{12} + b_{12}a_{21} + r_2 + 1)x_1x_2 +$$

$$2r_2\left[(b_{22} + b_{12})x_2^2 + b_{23}x_2x_3\right] +$$

$$2[b_{13}(x_1 - 1) + b_{23}x_2 + b_{33}x_3]\left[\left(\frac{r_3}{x_1 + k_3} - a_{31}\right)x_1 - d_3\right]x_3 \leq 0.$$

By assumptions (1)-(3), the inequality (4.5) holds if

$$-2\{[(b_{11}(a_{12} + a_{13}) + b_{12}(a_{21}+1)) + b_{13}]x_1 +$$

$$b_{12}r_2x_2 + b_{23}a_{21}x_3\} x_1x_2- \tag{4.6}$$

$$[(b_{11}x_1 + (b_{11}a_{13} + b_{13}) x_3)] x_1^2 - [(b_{22}a_{21}x_1 + b_{22}r_2x_2 + b_{23}r_2x_3)] x_2^2-$$

$$2 [(b_{11}a_{13} + b_{13}) x_1 + b_{13}a_{13}x_3] x_1x_3 + 2 \left[b_{11} (x_1 - 1)^2 - b_{11}\right] + 2 (b_{22} + b_{12}) x_2^2-$$

$$2b_{23}r_2 [1 - x_2] x_2x_3 + 2 [(b_{11}a_{12} + b_{12}a_{21} + r_2 + 1) - (b_{22}a_{21} + b_{12}a_{12}) x_2] x_1x_2-$$

$$b_{22}r_2x_2 + 2 [b_{11}a_{13} - (b_{12}a_{13} + b_{13}a_{12}) x_2] x_1x_3+$$

$$2 [b_{13} (x_1 - 1) + b_{23}x_2 + b_{33}x_3] \left[\left(\frac{r_3}{x_1 + k_3} - a_{31}\right) x_1 - d_3\right] x_3 \le 0,$$

when

$$[\ (b_{11} (a_{12} + a_{13}) + b_{12} (a_{21} + 1)) + b_{13}] x_1 + \ b_{12}r_2x_2 + b_{23}a_{21}x_3 \ge 0,$$

$$(b_{11}x_1 + (b_{11}a_{13} + b_{13}) x_3) \ge 0,\ b_{22}a_{21}x_1 + b_{22}r_2x_2 + b_{23}r_2x_3 \ge 0, \tag{4.7}$$

$$(b_{11}a_{13} + b_{13}) x_1 + b_{13}a_{13}x_3 \ge 0,\ b_{11} (x_1 - 1)^2 + (b_{22} + b_{12}) x_2^2 \le b_{11},\ x_2 \ge 1,$$

$$(b_{11}a_{12} + b_{12}a_{21} + r_2 + 1)-(b_{22}a_{21} + b_{12}a_{12}) x_2 \le 0,\ b_{11}a_{13}-(b_{12}a_{13} + b_{13}a_{12}) x_2 \le 0\ ,$$

$$b_{13}x_1 + b_{23}x_2 + b_{33}x_3 \ge b_{13}.$$

If $a_{21} > r_2$ or $c_{13} > 0$, then one of eigenvalue of the matrix A_1 is positive, i.e. the system (1.3) is unstabile at $E_1 (1, 0, 0)$.

Remarke 4.1. Hence, $\dot{V}_1 (x)$ is negative defined on the following domain

$$\Omega_1 = \left\{x \in \mathbb{R}_+^3,\ \ b_{11} (x_1 - 1)^2 + (b_{22} + b_{12}) x_2^2 \le b_{11},\right. \tag{4.8}$$

$$\left. x_2 \ge \eta_2,\ \ \alpha_1x_1 + \alpha_2x_2 + \alpha_3x_3 \ge \eta_0\right\},$$

where

$$\eta_2 = \max\left\{1, \frac{b_{11}a_{12} + b_{12}a_{21} + r_2 + 1}{b_{22}a_{21} + b_{12}a_{12}}, \frac{b_{11}a_{13}}{b_{12}a_{13} + b_{13}a_{12}}\right\},$$

$$\eta_0 = b_{13},\ \alpha_1 = \ \min \{[b_{11} (a_{12} + a_{13}) + b_{12} (a_{21} + 1) + b_{13}],\ b_{22}a_{21},\ b_{13}\ \},$$

$$\alpha_2 = \ \min \{b_{12}r_2,\ b_{22}r_2, b_{23}\} = b_{23},\ \alpha_3 = \min \{b_{23}a_{21},\ b_{23}r_2,\ b_{33}\}.$$

Hence, the system (1.3) is asymptotically stabile at $E_1 (1, 0, 0)$ in the Lyapunov sense.

Now, we consider the equilibria point $E_2 (0, 1, 0)$ and prove the following result:

Theorem 4.2. Assume: (1) $c_{11} = 1-a_{12} < 0$, (2) $a_{21}^2 > r_2 (r_2 - c_{11})$. Then the system (1.3) is asymptotically stable at the equilibria point $E_1 (0, 1, 0)$ in the sense of Lyapunov.

Proof. Let A_2 be the linearized matrix with respect to equilibria point $E_2(0,1,0)$, i.e.

$$A_2 = \begin{bmatrix} c_{11} & 0 & 0 \\ -a_{21} & -r_2 & 0 \\ 0 & 0 & -d_3 \end{bmatrix}.$$

Consider the Lyapunov equation

$$P_2 A_2 + A_2^T P_2 = -I, \tag{4.9}$$

where

$$P_2 = \begin{bmatrix} b_{11} & b_{12} & b_{13} \\ b_{21} & b_{22} & b_{23} \\ b_{31} & b_{32} & b_{33} \end{bmatrix}.$$

By solving the equation (4.9) in b_{ij} we get

$$b_{13} = 0,\, b_{22} = \frac{1}{2r_2},\; b_{12} = b_{21} = -\frac{a_{21}}{2r_2\left(r_2 - c_{11}\right)},$$

$$b_{11} = -\frac{1}{c_{11}}\left[\frac{a_{21}^2 b_{22}}{\left(r_2 - c_{11}\right)} - \frac{1}{2}\right],\; b_{23} = b_{32} = 0, \tag{4.10}$$

$$b_{33} = \frac{1}{2d_3},\; b_{13} = b_{31} = 0,\, B_2 = \begin{bmatrix} b_{11} & b_{12} & 0 \\ b_{12} & b_{22} & 0 \\ 0 & 0 & b_{33} \end{bmatrix}.$$

In view of the assumption (1) and (2) it is clear to see that

$$b_{11} > 0,\; b_{22} > 0,\; b_{33} > 0,\; b_{12} < 0. \tag{4.11}$$

The eigenvalues of A_2 can be founds as the roots of characteristic equation

$$P_2(\lambda) = \left(b_{33} - \lambda\right)\left[\lambda^2 - \left(b_{11} + b_{22}\right)\lambda - \left(b_{12}^2 - b_{11}b_{22}\right)\right] = 0.$$

Hence, the roots of the above equation are positive if the quadratic function

$$V_2\left(x_1, x_2 - 1, x_3\right) = b_{11}x_1^2 + b_{22}\left(x_2 - 1\right)^2 + b_{33}x_3^2 + 2b_{12}x_1\left(x_2 - 1\right)$$

is positive defined. The same as the above theorem it is clear to see that

$$V_2\left(x_1, x_2 - 1, x_3\right) \le 0 \tag{4.13}$$

if

$$b_{11}x_1 + \left(b_{11}a_{12} + b_{12}r_2\right)x_2 + b_{12}a_{13}x_3 \le 0,$$
$$\left(b_{11}a_{12} + b_{12}\right)x_1 + b_{22}a_{21}x_2 \ge 0,\; b_{12}x_1 + b_{22}r_2x_2 \ge 0,$$
$$b_{11}a_{13}x_1 + b_{12}a_{13}x_2 \ge 0,\; b_{12}x_1 + b_{22}x_2 \ge 0.$$

Remark 4.2. Hence, the inequality (4.13) holds in the following domain

$$\Omega_2 = \big\{x \in \mathbb{R}_+^3,\;\; b_{11}x_1 + \left(b_{11}a_{12} + b_{12}r_2\right)x_2 + b_{12}a_{13}x_3 \le 0,$$

$$(b_{11}a_{12}+b_{12})\,x_1+b_{22}a_{21}x_2\geq 0,\quad x_1\leq\gamma x_2\},$$

where

$$\gamma=\min\left\{\frac{b_{22}r_2}{-b_{12}},\ \frac{-b_{12}a_{13}}{b_{11}a_{13}},\ \frac{b_{22}}{-b_{12}}\right\}.$$

If

$$b_{11}a_{12}+b_{12}\geq 0,\ b_{11}\,(a_{12}+\gamma)+b_{12}r_2\leq 0, \tag{4.14}$$

then we deduced that

$$b_{11}x_1+(b_{11}a_{12}+b_{12}r_2)\,x_2+b_{12}a_{13}x_3\leq 0$$

for all $x\in\mathbb{R}^3_+$, i.e. the system (1.3) is global asymptotically stabile at the point $E_2\,(0,1,0)$.

Result 4.2. The system (1.3) is globally asymptotically stabile at $E_1\,(0,1,0)$ if assumptıons (1), (2) and the following holds:

$$-\frac{a_{12}}{c_{11}}\left[\frac{a_{21}^2}{r_2\,(r_2-c_{11})}-1\right]\geq\frac{a_{21}}{r_2\,(r_2-c_{11})}, \tag{4.15}$$

$$-\frac{(a_{12}+\gamma)}{c_{11}}\left[\frac{a_{21}^2}{r_2\,(r_2-c_{11})}-1\right]\leq\frac{a_{21}}{(r_2-c_{11})}.$$

Indeed, the inequalities (4.14) are valid if the assumption (4.15) holds.Thus, (4.13) is satisfies for all $x\in\mathbb{R}^3_+$

Let A_3 be the linearized matrices with respect to equilibria points $E_3\,(a_\pm,0,b_\mp)$, i.e.,

$$A_3=\begin{bmatrix} d_{11} & d_{12} & d_{13}\\ 0 & d_{22} & 0\\ d_{31} & 0 & d_{33}\end{bmatrix},$$

where

$$a_\pm=\frac{b_1\pm\sqrt{D}}{2a_{31}},\ b_1=r_3-d_3-a_{31}k_3,\ D=b_1^2-4d_3k_3a_{31}\geq 0,$$

$$d_{11}=1-2a_\pm-a_{13}b_\mp,\ d_{12}=-a_{12}a_\pm,\ d_{13}=-a_{13}a_\pm, \tag{4.16}$$

$$d_{22}=r_2-a_{21}a_\pm,\ d_{31}=\left(\frac{k_1r_3}{(a_\pm+k_3)^2}-a_{31}\right)b_\mp,$$

$$d_{33}=\frac{r_3a_\pm}{a_\pm+k_3}-a_{31}a_\pm-d_3.$$

Let

$$\beta=\frac{d_{13}-d_{12}}{d_{11}+d_{22}},\ \rho=\frac{d_{11}+d_{33}}{d_{11}+d_{22}},\ \varkappa=\frac{(d_{22}+d_{33})\,d_{12}+d\beta}{d_{31}d_{12}-d\rho},$$

$$d=(d_{11}+d_{22})\,(d_{22}+d_{33})-d_{31}a_{13}.$$

Let $a_{\pm}$, $b_{\mp}$ and D are the numbers defined by (4.0). Now, we prove the following result:

Theorem 4.3. Assume

$$a_{21}a_{\pm} > r_2,\ a_{\pm} + a_{31}a_{\pm} + d_3 > \frac{r_3 a_{\pm}}{a_{\pm} + k_3},\ \ (2 + k_3)\, a_{31} + d_3 > r_3 + \sqrt{D}.$$

Moreover, suppose

$$a_{13} > a_{12},\ a_{31} > \frac{k_1 r_3}{(a_{\pm} + k_1)^2},\ d_{31}d_{12} > d\rho.$$

Then system (1.3) is asymptotically stabile at equilibria points $E_3\,(a_{\pm}, 0, b_{\mp})$ in the sense of Lyapunov.

Proof. Consider the Lyapunov equation

$$B_3A_3 + A_3^T B_3 = -I, \tag{4.17}$$

where

$$B_3 = \begin{bmatrix} b_{11} & b_{12} & b_{13} \\ b_{21} & b_{22} & b_{23} \\ b_{31} & b_{32} & b_{33} \end{bmatrix},\ b_{ij} = b_{ji}.$$

By solving (4.17) according in b_{ij} we obtain

$$b_{11} = -\frac{1}{d_{11} + 2\varkappa d_{31}},\ b_{13} = -\frac{\varkappa}{d_{11} + 2\alpha d_{31}}, \tag{4.18}$$

$$b_{12} = -\frac{1}{(d_{11} + d_{12})\,(d_{11} + 2\varkappa d_{31})}\left[\varkappa\,(d_{11} + d_{33}) + d_{13} - d_{12}\right],\ b_{22} =$$

$$-\frac{1}{2d_{22}}\,(1 + 2d_{12}b_{12})\,,\ b_{23} = -\frac{(d_{13} + d_{12})\, b_{12}}{d_{22} + d_{33}},\ b_{33} = -\frac{1}{2d_{33}}\,(1 + 2d_{13}b_{13})\,.$$

Consider the quadratic function

$$V_3\,(x_1 - a_{\pm}, 0, x_3 - b_{\mp}) = b_{11}\,(x_1 - a_{\pm})^2 + b_{22}x_2^2 + \tag{4.19}$$

$$b_{33}\,(x_3 - b_{\mp})^2 - +2b_{12}\,(x_1 - a_{\pm})\, x_2 + 2b_{13}x_1\,(x_3 - b_{\mp}) + 2b_{23}x_2\,(x_3 - b_{\mp}) =$$

$$\frac{1}{2}b_{11}\left[x_1 - a_{\pm} + \frac{2b_{12}}{b_{11}}x_2\right]^2 + \left(b_{22} - \left(\frac{b_{12}}{b_{11}}\right)^2\right)x_2^2 +$$

$$\frac{1}{2}b_{11}\left[x_1 - a_{\pm} + \frac{2b_{13}}{b_{11}}x_3\right]^2 + \left(b_{22} - \frac{2b_{12}^2}{b_{11}}\right)x_2^2 + \left(b_{33} - \frac{2b_{13}^2}{b_{11}}\right)x_3^2 +$$

$$\frac{1}{2}b_{22}\left[x_2 + \frac{2b_{13}}{b_{11}}\,(x_3 - b_{\mp})\right]^2 + \left(b_{33} - \frac{2b_{13}^2}{b_{22}}\right)(x_3 - b_{\mp})^2 > 0,$$

when

$$b_{22} \geq \frac{2b_{12}^2}{b_{11}},\ 2b_{33} - \frac{2b_{13}^2}{b_{22}}. \tag{4.20}$$

By assumptions we get

$$d > 0,\ \beta > 0,\ \ \rho > 0,\ \ \varkappa > 0,\ \ b_{11} > 0,\ b_{12} > 0,\ \ b_{13} > 0,$$

$$b_{23} < 0,\ \ b_{22} > 0,\ \ b_{33} > 0. \tag{4.21}$$

Hence, $V_3(x)$ is a positive defined Lyapunov function candidate. Then, we have only to show the following inequality

$$\dot{V}_3\left(x_1 - a_{\pm}, 0, x_3 - b_{\mp}\right) = \sum_{k=1}^{3} \frac{\partial V_3}{\partial x_k}\frac{dx_k}{dt} =$$

$$\begin{gathered}
-2\left[b_{11}a_{\pm} + b_{13}b_{\mp} + 2a_{\pm}\left(b_{11} + b_{11}a_{\pm} + b_{13}b_{\mp}\right)\right]x_1 + \\
2\left[r_2\left(b_{12}a_{\pm} + b_{23}b_{\mp}\right) - 2b_{\pm}r_2\left(b_{12}a_{\pm} + b_{23}b_{\mp} + b_{22}\right)\right]x_2 + \\
2\left(b_{11} + b_{11}a_{\pm} + b_{13}b_{\mp}\right)\left(x_1 - a_{\pm}\right)^2 + \qquad (4.22) \\
2r_2\left(b_{12}a_{\pm} + b_{23}b_{\mp} + b_{22}\right)\left(x_2 - a_{\pm}\right)^2 - 2r_2\left(b_{12}a_{\pm} + b_{23}b_{\mp} + b_{22}\right) - 2b_{11}x_1^3 + \\
2\left[\left(b_{11}a_{\pm} + b_{13}b_{\mp}\right)a_{13} + b_{13} - b_{13}x_1\right]x_1x_3 - -\left(b_{11}a_{13}x_1 + b_{23}a_{21}x_3\right)x_1x_2 - \\
2\left\{\left[\left(b_{11}a_{12}a_{\pm} + b_{12} + b_{13}a_{12}b_{\mp} + a_{21}b_{12}a_{\pm} + a_{21}b_{23}b_{\mp}\right)\right] - \right. \\
2\left[\left(b_{11}x_1 + b_{12}x_2 + b_{13}x_3\right)a_{12} + \left(b_{12}x_1 + b_{22}x_2\right)a_{21}\right] - \\
\left. 2\left[\left(b_{12} + a_{12}b_{11} + a_{21}b_{22}\right)x_1\right]\right\}x_1x_2 - 2r_2\left[b_{12}x_1 + b_{22}x_2 + b_{23}x_3\right]x_2^2 - \\
2\left[a_{21}b_{23}x_2 + a_{13}b_{13}x_3\right]x_1x_3 - 2\left(b_{11}a_{13}x_1 + b_{23}a_{21}x_3\right)x_1x_2 + 2Q(x) \leq 0,
\end{gathered}$$

where

$$Q(x) = \left[b_{13}\left(x_1 - a_{\pm}\right) + b_{23}x_2 + b_{33}\left(x_3 - b_{\mp}\right)\right]\left[\frac{r_3x_1}{x_1 + k_3} - a_{31}x_1 - d_3\right].$$

By condition, the estimate (4.22) holds for all $x \in \mathbb{R}_+^3$, if

$$\begin{gathered}
\left[b_{11}a_{\pm} + b_{13}b_{\mp} - 2a_{\pm}\left(b_{11} + b_{11}a_{\pm} + b_{13}b_{\mp}\right)\right]x_1 + \\
\left[r_2\left(b_{12}a_{\pm} + b_{23}b_{\mp}\right) - 2a_{\pm}r_2\left(b_{12}a_{\pm} + b_{23}b_{\mp} + b_{22}\right)\right]x_2 \geq 0, \\
\left(b_{11} + b_{11}a_{\pm} + b_{13}b_{\mp}\right)\left(x_1 - a_{\pm}\right)^2 + r_2\left(b_{12}a_{\pm} + b_{23}b_{\mp} + b_{22}\right)\left(x_2 - a_{\pm}\right)^2 \leq \\
r_2\left(b_{12}a_{\pm} + b_{23}b_{\mp} + b_{22}\right) + b_{11}x_1^3, \\
\left(b_{11}a_{\pm} + b_{13}b_{\mp}\right)a_{13} + b_{13} - \left(b_{13} + a_{13}b_{11}\right)x_1 \leq 0, \\
\left(b_{11}a_{12}a_{\pm} + b_{12} + b_{13}a_{12}b_{\mp} + a_{21}b_{12}a_{\pm} + a_{21}b_{23}b_{\mp}\right) - \\
\left[\left(b_{11}x_1 + b_{12}x_2 + b_{13}x_3\right)a_{12} + \left(b_{12}x_1 + b_{22}x_2\right)a_{21}\right] -
\end{gathered}$$

$$(b_{12}+a_{12}b_{11}+a_{21}b_{22})\,x_1\leq 0,\ b_{12}x_1+b_{22}x_2+b_{23}x_3\geq 0,$$

$$a_{21}b_{23}x_2+a_{13}b_{13}x_3\geq 0,\ b_{11}a_{13}x_1+b_{23}a_{21}x_3\geq 0,\ b_{13}x_1+b_{23}x_2+b_{33}x_3\geq 0.$$

Thus (1.3) is asymptotically stabile at points $E_3\,(a_\pm,0,b_\mp)$.

Remark 4.3. Hence, $\dot{V}_3$ is negative defined on the following domain

$$\Omega_3=\left\{x\in\mathbb{R}^3_+\colon \alpha_1x_1+\alpha_2x_2+\alpha_3x_3\geq\gamma_0,\ x_1\geq\gamma_1,\ x_2\leq\gamma_2x_3,\ x_3\leq\gamma_3x_1,\right.$$

$$(b_{11}+b_{11}a_\pm+b_{13}b_\mp)\,(x_1-a_\pm)^2+r_2\,(b_{12}a_\pm+b_{23}b_\mp+b_{22})\,x_2^2\leq \qquad (4.23)$$

$$\left.r_2\,(b_{12}a_\pm+b_{23}b_\mp+b_{22})+b_{11}x_1^3\right\},$$

where

$$\alpha_1=\min\left\{[b_{11}a_\pm+b_{13}b_\mp-2a_\pm\,(b_{11}+b_{11}a_\pm+b_{13}b_\mp)]\,,\right.$$

$$\left.b_{11}a_{12}+b_{12}a_{21},\ b_{12},\ \ b_{13}\right\},$$

$$\alpha_2=\ \min\left\{\,r_2\,(b_{12}a_\pm+b_{23}b_\mp)-2a_\pm r_2\,(b_{12}a_\pm+b_{23}b_\mp+b_{22})\,,\right.$$

$$\left.b_{12}a_{12}+b_{22}a_{21},\ b_{22},\ b_{23}\ \right\},\ \alpha_3=\min\left\{b_{13}a_{12},\ b_{23},\ b_{33}\right\}=b_{23},$$

$$\gamma_0=(b_{11}a_{12}a_\pm+b_{12}+b_{13}a_{12}b_\mp+a_{21}b_{12}a_\pm+a_{21}b_{23}b_\mp)\,,$$

$$\gamma_1=\frac{(b_{11}a_\pm+b_{13}b_\mp)\,a_{13}+b_{13}}{(b_{13}+a_{13}b_{11})},\ \gamma_2=\frac{a_{13}b_{13}x_3}{-a_{21}b_{23}},\ \gamma_3=\frac{b_{11}a_{13}}{-b_{23}a_{21}}.$$

Let A_4 be the linearized matrices with respect to equilibria points $E_4\,(\bar{x}_1,\bar{x}_2,0)$, i.e.,

$$A_4=\begin{bmatrix} d_{11} & d_{12} & d_{13}\\ d_{21} & d_{22} & 0\\ 0 & 0 & d_{33}\end{bmatrix},$$

where

$$\bar{x}_1=\frac{r_2\,(a_{12}-1)}{a_{12}a_{21}-r_2},\ \bar{x}_2=\frac{a_{12}-r_2}{a_{12}a_{21}-r_2},$$

$$d_{11}=1-2\bar{x}_1-a_{12}\bar{x}_2,\ d_{12}=-a_{12}\bar{x}_1,\ d_{13}=-a_{13}\bar{x}_1, \qquad (4.24)$$

$$d_{21}=-a_{21}\bar{x}_2,\ d_{22}=r_2\,(1-2\bar{x}_2)-a_{21}\bar{x}_1,\ d_{33}=\frac{r_3\bar{x}_1}{\bar{x}_1+k_3}-a_{31}\bar{x}_1-d_3.$$

Now, we prove the following result:

Condition 4.4. Let $a_{12}\geq 1$, $a_{12}\geq r_2$, $a_{12}a_{21}>r_2$, $d_{33}<0$ and

$$Re\left\{(d_{11}+d_{22})+\sqrt{(d_{11}+d_{22})^2-4\,(d_{12}a_{21}\bar{x}_2+d_{11}d_{22})}\right\}<0.$$

Theorem 4.4. Assume the Condıtıon 4.4 is satisfied. Then system (1.3) is asymptotically stable at the equilibria point $E_4\,(\bar{x}_1,\bar{x}_2,0)$ in the Lyapunov sense.

Proof. Consider the Lyapunov equation

$$B_4A_4 + A_4^T B_4 = -I, \tag{4.25}$$

where

$$B_4 = \begin{bmatrix} b_{11} & b_{12} & b_{13} \\ b_{21} & b_{22} & b_{23} \\ b_{31} & b_{32} & b_{33} \end{bmatrix},\ b_{ij} = b_{ji}.$$

By solving the equation (4.25) with respect to b_{ij}, we obtain

$$b_{11} = \frac{D_1}{D},\ b_{12} = b_{21} = \frac{D_2}{D},\ b_{22} = \frac{D_3}{D},\ b_{13} = \frac{-d_{13}\left[b_{11}\left(d_{22}+d_{33}\right) - b_{12}d_{21}\right]}{d},$$

$$b_{23} = \frac{-d_{13}\left[b_{12}\left(d_{11}+d_{33}\right) - d_{12}b_{11}\right]}{d},\ d = \left(d_{11}+d_{33}\right)\left(d_{22}+d_{33}\right) - d_{12}d_{21},$$

$$b_{33} = -\frac{1}{d_{33}}\left[\frac{1}{2} + d_{13}b_{13}\right], \tag{4.26}$$

where

$$D = \begin{vmatrix} d_{11} & d_{21} & 0 \\ d_{12} & d_{11}+d_{22} & d_{21} \\ 0 & d_{12} & d_{22} \end{vmatrix} = \left(d_{11}+d_{22}\right)\left(d_{11}d_{22} - d_{12}d_{21}\right),$$

$$D_1 = \begin{vmatrix} -\frac{1}{2} & d_{21} & 0 \\ 0 & d_{11}+d_{22} & d_{21} \\ -\frac{1}{2} & d_{12} & d_{22} \end{vmatrix} = \frac{1}{2}\left[d_{22}\left(d_{11}+d_{22}\right) + d_{21}\left(d_{21}-d_{12}\right)\right],$$

$$D_2 = \begin{vmatrix} d_{11} & -\frac{1}{2} & 0 \\ d_{12} & 0 & d_{21} \\ 0 & -\frac{1}{2} & d_{22} \end{vmatrix} = -\frac{1}{2}\left[d_{12}d_{22} + d_{11}d_{21}\right],\ D_3 = \begin{vmatrix} d_{11} & d_{21} & -\frac{1}{2} \\ d_{12} & d_{11}+d_{22} & 0 \\ 0 & d_{12} & -\frac{1}{2} \end{vmatrix} =$$

$$\frac{1}{2}\left[d_{11}\left(d_{11}+d_{22}\right) + d_{12}^2 - d_{12}d_{21}\right].$$

Remark 4.6. $D > 0$, $d > 0$ when

$$a_{12} \geq 1,\ a_{12} \geq r_2,\ a_{12}a_{21} > r_2,\ a_{13} > a_{21},\ a_{21} < 2,\ a_{12}\left(2 - a_{21}\right) > r_2,$$

$$r_3 \leq 1 + \frac{k_3}{\bar{x}_1},\ d_{33} < 0. \tag{4.27}$$

If (4.27) holds, then by using (4.24) we dedused that $b_{11} > 0$ if $a_{12}a_{21}+r_2 < 2a_{12}$, $a_{12} > 1$, $a_{12}r_2\left(a_{12}-1\right) > a_{21}\left(a_{12}-r_2\right)$ and $2a_{12}\left(a_{12}+2r_2\right) > a_{12}a_{21}r_2 + 3r^2$ or $a_{12}a_{21} + r_2 > 2a_{12}$, $a_{12}r_2\left(a_{12}-1\right) < a_{21}\left(a_{12}-r_2\right)$, $2a_{12}\left(a_{12}+2r_2\right) < a_{12}a_{21}r_2 + 3r^2$; $b_{12} < 0$, when $a_{12}a_{21} + r_2 < 2a_{12}$, $a_{12}^2 + a_{12}r_2 > 1 + 2r_2$, $b_{12} > 0$ if $a_{12}a_{21} + r_2 > 2a_{12}$, $a_{12}^2 + a_{12}r_2 < 1 + 2r_2$; $b_{22} > 0$, if $a_{21} < 2$, $a_{12}\left(2 - a_{21}\right) > r_2$, $a_{12}a_{21} + r_2 < a_{12}\left(a_{21}+r_2\right) < r_2\left(a_{21} + a_{12}^2\right)$; $b_{22} > 0$, when $a_{12}^2 + 4a_{12}r_2 > a_{12}a_{21} + 2r_2$ and $a_{12}\left(a_{12}-1\right) > a_{21}\left(a_{12}-r_2\right)$; $b_{13} < 0$ if $b_{11} > 0$ and $b_{12} < 0$; $b_{23} > 0$, when $b_{11} > 0$ and $b_{12} < 0$; $b_{33} > 0$ if $d_{33} < 0$.

Consider the quadratic function

$$V_4(x) = X^T B_4 X = b_{11}x_1^2 + b_{22}x_2^2 + b_{33}x_3^2 + 2b_{12}x_1x_2 +$$

$$2b_{13}x_1x_3 + 2b_{23}x_2x_3.$$

It is clear to see that

$$V_4(x_1 - \bar{x}_1, x_2 - \bar{x}_2, x_3) = b_{11}(x_1 - \bar{x}_1)^2 + 2b_{12}(x_1 - \bar{x}_1)(x_2 - \bar{x}_2) +$$

$$2b_{13}(x_1 - x_2 - \bar{x}_2)x_3 + b_{22}(x_2 - \bar{x}_2)^2 + 2b_{23}(x_2 - \bar{x}_2)x_3 + b_{33}x_3^2 =$$

$$\frac{1}{2}b_{11}\left[x_1 - \bar{x}_1 + \frac{2b_{12}}{b_{11}}(x_2 - \bar{x}_2)\right]^2 + \left[b_{22} - \left(\frac{b_{12}}{b_{11}}\right)^2\right](x_2 - \bar{x}_2)^2 + \tag{4.28}$$

$$\frac{1}{2}b_{11}\left[x_1 - \bar{x}_1 + \frac{2b_{13}}{b_{11}}x_3\right]^2 + \left(b_{22} - \frac{2b_{12}^2}{b_{11}}\right)(x_2 - \bar{x}_2)^2 +$$

$$\left(b_{33} - \frac{b_{13}^2}{b_{11}}\right)x_3^2 + \frac{1}{2}b_{22}\left[x_2 - \bar{x}_2 + \frac{2b_{13}}{b_{11}}x_3\right]^2 + \left(b_{33} - \frac{2b_{13}^2}{b_{22}}\right)x_3 > 0,$$

when

$$2b_{12}^2 \le\ b_{11}b_{22},\ 2b_{13}^2 \le\ b_{22}b_{33}. \tag{4.29}$$

Hence, $V_4(x)$ is a positive defined Lyapunov function candidate in neighborhood of $E_4(\bar{x}_1, \bar{x}_2, 0) \subset \mathbb{R}_+^3$. We have to show the following inequality:

$$\mathring{V}_4(x_1 - \bar{x}_1, x_2 - \bar{x}_2, x_3) = 2\left[a_{13}(b_{11}\bar{x}_1 + b_{12}\bar{x}_2)x_3 - (b_{11}\bar{x}_1 + b_{12}\bar{x}_2)\right]x_1 +$$

$$2\left[b_{12}x_1 - r_2(b_{12}\bar{x}_1 + b_{22}\bar{x}_2)\right]x_2 +$$

$$2(b_{11}\bar{x}_1 + b_{12}\bar{x}_2)(x_1 - \bar{x}_1)^2 + 2r_2(b_{12}\bar{x}_1 + b_{22}\bar{x}_2)(x_2 - \bar{x}_2)^2 -$$

$$2(b_{11}\bar{x}_1 + b_{12}\bar{x}_2)\bar{x}_1^2 - 2r_2(b_{12}\bar{x}_1 + b_{22}\bar{x}_2)\bar{x}_2^2 - 2b_{22}r_2x_2^3 -$$

$$2\left[b_{11}x_1 + (b_{12} + a_{12}b_{11} + a_{21}b_{22})x_2 + b_{13}x_3\right]x_1^2 +$$

$$2\left[b_{13} - (a_{12}b_{13} + a_{13}b_{12})x_2 - a_{13}b_{11}x_1\right]x_1x_3 +$$

$$\left[a_{21}(b_{12}\bar{x}_1 + b_{22}\bar{x}_2 + b_{12}r_2) - (a_{12}b_{12} + a_{21}b_{22})x_2\right]x_1x_2 + \tag{4.30}$$

$$2r_2b_{23}(1 - x_2)x_2x_3 + \left[a_{12}(b_{11}\bar{x}_1 + b_{12}\bar{x}_2) - b_{12}x_2\right]x_1x_2 -$$

$$2\left[a_{21}b_{23}x_2 + a_{13}b_{13}x_3\right]x_1x_3 + 2Q(x) \le 0,$$

where

$$Q(x) = \left[b_{13}(x_1 - \bar{x}_1) + b_{23}(x_2 - \bar{x}_2) + b_{33}x_3\right]\left[\frac{r_3x_1}{x_1 + k_3} - a_{31}x_1 - d_3\right].$$

The inequality (4.30) holds on the following set

$$\Omega_4 = \left\{ x \in \mathbb{R}^3_+ \colon\ x_1 \leq \frac{r_2 \left(b_{12}\bar{x}_1 + b_{22}\bar{x}_2\right)}{b_{12}}, \right.$$

$$\left(b_{11}\bar{x}_1 + b_{12}\bar{x}_2\right)\left(x_1 - \bar{x}_1\right)^2 + r_2\left(b_{12}\bar{x}_1 + b_{22}\bar{x}_2\right)\left(x_2 - \bar{x}_2\right)^2 \leq$$

$$\left(b_{11}\bar{x}_1 + b_{12}\bar{x}_2\right)\bar{x}_1^2 + r_2\left(b_{12}\bar{x}_1 + b_{22}\bar{x}_2\right)\bar{x}_2^2 + b_{22}r_2x_2^3, \tag{4.31}$$

$$b_{11}x_1 + \left(b_{12} + a_{12}b_{11} + a_{21}b_{22}\right)x_2 + b_{13}x_3 \geq 0,$$

$$\left(a_{12}b_{13} + a_{13}b_{12}\right)x_2 + a_{13}b_{11}x_1 \geq b_{13},$$

$$x_2 \geq \gamma_2,\ x_3 \leq \frac{\left(b_{11}\bar{x}_1 + b_{12}\bar{x}_2\right)}{a_{13}\left(b_{11}\bar{x}_1 + b_{12}\bar{x}_2\right)},$$

$$\left. x_3 \leq \frac{a_{21}b_{23}}{-b_{13}a_{13}}x_2,\ \ b_{13}\left(x_1 - \bar{x}_1\right) + b_{23}\left(x_2 - \bar{x}_2\right) + b_{33}x_3 \geq 0 \right\},$$

where

$$\gamma_2 = \max\left\{ \frac{a_{21}\left(b_{12}\bar{x}_1 + b_{22}\bar{x}_2 + b_{12}r_2\right)}{\left(a_{12}b_{12} + a_{21}b_{22}\right)},\ 1,\ \ \frac{a_{12}\left(b_{11}\bar{x}_1 + b_{12}\bar{x}_2\right)}{b_{12}} \right\}.$$

Now, we consider the equilibria points E_{ij}. Let A_{ij} be the linearized matrix with respect to equilibria point E_{ij} and b_{ij} were defined by (4.26).

Let

$$b_{11} = b_{11}\left(i,j\right) = 1 - 2x_{1i} - a_{12}x_{2j} - a_{13}x_{3ij},\ b_{21} =$$

$$b_{21}\left(i,j\right) = -a_{21}x_2,\ b_{22} = b_{22}\left(i,j\right) = r_2 - 2r_2x_{2j} - a_{21}x_{1i},$$

$$b_{13} = b_{13}\left(i,j\right) = -a_{13}x_{1i},\ b_{31} = b_{31}\left(i,j\right) = \tag{4.32}$$

$$\frac{k_1r_3x_{3ij}}{\left(x_{1i} + k_1\right)^2} - a_{31}x_{3ij}, b_{33} = b_{33}\left(i,j\right) = \frac{r_3x_{1i}}{x_{1i} + k_3} - a_{31}x_{1i} - d_3.$$

Now, we show the following:

Condition 4.5. Assume: (1) $r_2 < d_3$, $\left(a_{31}k_3 + d_3 - r_3\right)^2 \geq 4d_3a_{31}$; (2) $a_{31} + d_3 + 2x_{1i} + a_{12}x_{2j} + a_{13}x_{3ij} + a_{31}x_{1i} > 1$,

$$\frac{r_3x_{1i}}{x_{1i} + k_3} < a_{31}x_{1i} + d_3,\ b_{11}b_{33} - b_{13}b_{31} > 0.$$

Theorem 4.5. Assume the Condition 4.5 is satisfied. Moreover, suppose

$$b_{22} + b_{33} > 0,\ \ -\left(b_{11} + b_{33}\right)\left(b_{22} + b_{33}\right) < b_{12}b_{21},$$

$$4p_{12}^2\ \leq p_{11}p_{22},\ 4p_{13}^2\ \leq p_{11}p_{33},\ 4p_{23}^2\ \leq p_{22}p_{33}\ .$$

Then the system (1.3) is asymptotically stable at equilibria points E_{ij} in the Lyapunov sense.

Proof. Let A_{ij} be the linearized matrix with respect to equilibria point A_{ij}, i.e,

$$A_{ij} = A_{E(x_{1i},x_{2j},x_{3ij})} =$$

$$\begin{bmatrix} 1-2x_{1i}-a_{12}x_{2j}-a_{13}x_{3ij} & -a_{12}x_{1i} & -a_{13}x_{1i} \\ -a_{21}x_{2j} & r_2-2r_2x_{2j}-a_{21}x_{1i} & 0 \\ \frac{k_3r_3x_{3ij}}{(x_{1i}+k_3)^2}-a_{31}x_{3ij} & 0 & \frac{r_3x_{1i}}{x_{1i}+k_3}-a_{31}x_{1i}-d_3 \end{bmatrix}.$$

Consider the following Lyapunov equation

$$P_{ij}A_{ij} + A_{ij}^T P_{ij} = -I, \tag{4.33}$$

where

$$P_{ij} = \begin{bmatrix} p_{11} & p_{12} & p_{13} \\ p_{21} & p_{22} & p_{23} \\ p_{31} & p_{32} & p_{33} \end{bmatrix}, \ p_{mk} = p_{mk}\left(i,j\right), \ p_{mk} = p_{km}.$$

By solving algebraic equation (4.33) in p_{mk} we obtain:

$$p_{12} = \frac{b_3b_{12} + b_2\left(b_{22}+b_{33}\right)}{D}, \ p_{13} = -\frac{b_3b_{13}}{D}, \ p_{33} = \frac{b_2b_{13}}{D},$$

$$p_{22} = -\frac{1}{2b_{22}}\left(1+2b_{12}p_{12}\right), \ p_{11} = \frac{-\left(1+2b_{21}p_{12}+2b_{31}p_{13}\right)}{2b_{11}},$$

$$p_{23} = -\frac{1}{b_{21}}\left[b_{31}p_{33} - \left(b_{11}+b_{33}\right)p_{13}\right], \tag{4.34}$$

where,

$$b_2 = b_{12} + \frac{\left(b_{22}+b_{33}\right)\left(b_{11}+b_{33}\right)}{b_{21}}, \ b_3 = -\frac{\left(b_{22}+b_{33}\right)b_{31}}{b_{21}},$$

$$D = \begin{vmatrix} b_{13} & b_{12} & b_{22}+b_{33} \\ 0 & 2b_{13} & 2b_{33} \\ b_{13} & b_2 & b_3 \end{vmatrix}.$$

By using the assumptions (1), (2) and by (4.20), (4.34) we get that

$$b_2 > 0, \ b_3 < 0, \ p_{12} < 0, \ p_{11} > 0, \ p_{22} > 0, \ p_{13} > 0, \ p_{33} > 0, \ p_{23} < 0. \tag{4.35}$$

So, by (4.32) we get $D < 0$. Consider now, the quadratic function

$$V_{ij}\left(x\right) = X^T P_{ij} X = p_{11}x_1^2 + p_{22}x_2^2 + p_{33}x_3^2 + 2p_{12}x_1x_2 + 2p_{13}x_1x_3 + 2p_{23}x_2x_3.$$

It is clear to see that

$$V_{ij}\left(x\right) = \frac{p_{11}}{2}\left(x_1 + \frac{p_{12}}{p_{11}}x_2\right)^2 + \frac{p_{11}}{2}\left(x_1 + \frac{p_{13}}{p_{11}}x_3\right)^2 +$$

$$\frac{p_{22}}{2}\left(x_2 + \frac{p_{23}}{p_{22}}x_3\right)^2 + \left(\frac{p_{22}}{2} - \frac{2p_{12}^2}{p_{11}}\right)x_2^2 + \left[\frac{p_{33}}{2} - \frac{2p_{13}^2}{p_{11}}\right]x_3^2 +$$

$$\left[\frac{p_{22}}{2} - \frac{2p_{23}^2}{p_{22}}\right] x_3^2 \geq 0,$$

i.e. $V_{ij}(x)$ is a positive defined Lyapunov function candidate when the assumption (3) holds. By assuming $x_k \geq 0$, $k = 1, 2, 3$, we have to show that

$$\dot{V}_{ij}(x_1 - x_{1i}, x_2 - x_{2j}, x_3 - x_{3ij}) = \sum_{k=1}^{3} \frac{\partial V_{ij}}{\partial x_k} \frac{dx_k}{dt} = \tag{4.36}$$

$$\{[(a_{13} + 2x_{1i}) Q_1 + (a_{21} + r_2 + 2x_{2j}) Q_2] x_1 - -r_2\} x_2 + 2Q_1 [a_{13}x_3 - 1] x_1 +$$
$$2\left[Q_1 (x_1 - x_{1i})^2 + Q_2 r_2 (x_2 - x_{2j})^2 - Q_1 x_{1i}^2 - Q_1 x_{2j}^2 - p_{22} r_2 x_2^3\right] -$$
$$2[-p_{11}(x_1 + a_{12}x_2 + a_{13}x_3) + p_{12}x_2] x_1^2 -$$
$$2[(p_{23}a_{21} + p_{13}a_{13}) x_1 + p_{12}a_{13}x_2 + p_{13}a_{13}x_3] x_1 x_3 - 2[p_{12}(a_{12} + r_2) x_2 + p_{13}a_{12}x_3 +$$
$$(p_{22}a_{21}x_2 + p_{12}a_{21}x_1)\} x_1 x_2 + 2p_{23} r_2 (1 - x_2) x_2 x_3 +$$
$$2[p_{13}(x_1 - x_{1i}) + p_{23}(x_2 - x_{2j}) + p_{33}(x_3 - x_{3ij})] \left[\frac{r_3}{x_1 + k_3} - a_{31}\right] x_1 x_3 < 0.$$

where

$$Q_1 = Q_1(i,j) = p_{11}x_{1i} + p_{13}x_{3ij}, \; Q_2 = \; Q_2(i,j) = p_{12}x_{1i} + p_{22}x_{2j} + p_{23}x_{3ij}.$$

The inequality (4.36) holds if

$$\begin{gathered}
[(a_{13} + 2x_{1i}) Q_1 + (a_{21} + r_2 + 2x_{2j}) Q_2] x_1 - -r_2 \leq 0, \; a_{13}x_3 - 1 \leq 0, \\
Q_1 (x_1 - x_{1i})^2 + Q_2 r_2 (x_2 - x_{2j})^2 \leq Q_1 x_{1i}^2 + Q_1 x_{2j}^2 + p_{22} r_2 x_2^3, \\
p_{11}(x_1 + a_{12}x_2 + a_{13}x_3) + p_{12}x_2 \geq 0, \\
(p_{23}a_{21} + p_{13}a_{13}) x_1 + p_{12}a_{13}x_2 + p_{13}a_{13}x_3 \geq 0, \\
p_{12}a_{21}x_1 + [p_{12}(a_{12} + r_2) + p_{22}a_{21}] x_2 + p_{13}a_{12}x_3 \geq 0, \;\; x_2 \geq 1, \\
(p_{13}(x_1 - x_{1i}) + p_{23}(x_2 - x_{2j}) + p_{33}x_3 (x_3 - x_{3ij})) \geq 0.
\end{gathered} \tag{4.37}$$

Hence, $\dot{V}_{ij}$ is negative defined on

$$\begin{gathered}
\Omega_{ij} = \left\{x \in \mathbb{R}_+^3 : \; x_1 \leq \gamma_1, \; x_3 \leq \frac{1}{a_{13}}, \; x_2 \geq 1,\right. \\
Q_1 (x_1 - x_{1i})^2 + Q_2 r_2 (x_2 - x_{2j})^2 \leq Q_1 x_{1i}^2 + Q_1 x_{2j}^2 + p_{22} r_2, \\
\left. \alpha_1 x_1 + \alpha_2 x_2 + \alpha_3 x_3 \geq 0\right\},
\end{gathered} \tag{4.38}$$

where

$$\begin{aligned}
\gamma_1 &= \frac{r_2}{(a_{13} + 2x_{1i}) Q_1 + (a_{21} + r_2 + 2x_{2j}) Q_2}, \\
\alpha_1 &= \min\{p_{11}, \; p_{23}a_{21} + p_{13}a_{13}, \; p_{12}a_{21}, \, p_{13}\}, \\
\alpha_2 &= \min\{p_{11}a_{12} + p_{12}, \, p_{12}a_{13}, \, p_{12}(a_{12} + r_2) + p_{22}a_{21}, \, p_{23}\}, \\
\alpha_3 &= \min\{p_{11}a_{13}, \; p_{13}a_{13}, \; p_{13}a_{12}, \, p_{33}\}.
\end{aligned}$$

i.e., the system (1.3) is asymptotically stabile at points E_{ij}.

5. Basins of multiphase attractions

In this section, we will derive the domains of multipoint attraction sets of the problem $(1.3)-(1.4)$ at the the following attractor points

$$E_1\left(1,0,0\right), \; E_2\left(0,1,0\right), \; E_3\left(a_{\pm},0,b_{\mp}\right), \;\; E_4\left(\bar{x}_1,\bar{x}_2,0\right), \; E_{ij}\left(x_{1i},x_{2j},x_{3ij}\right),$$

where $a_{\pm}$, $b_{\mp}$, $\bar{x}_1, \bar{x}$, x_{1i}, x_{2j}, x_{3ij} were defined by (4.16) and (4.24).

Lyapunov's method can be used to find the region of attraction or an estimate of it. We show in this section the following results:

Theorem 5.1. Assume that the all conditions of Theorem 4.1 are satisfied. Then the basin of multiphase attraction set of $(1.3)-(1.4)$ at $\bar{x} = (1,0,0)$ belongs to the set $\Omega_C \subset \Omega_1$, where Ω_1 was defined by (4.8) and

$$\Omega_C = \left\{x \in R^3_+ \colon \; V_1\left(x\right) \leq C \;\right\},$$

here a positive constant C is defined in bellow.

Proof. We are interested in the largest set Ω_C that we can determine the largest value for the constant C such that $\Omega_C \subset D\left(V_1\right)$, where

$$D\left(V_1\right) = \left\{x \in R^3, \; V_1\left(x\right) \geq 0, \; \dot{V}_1\left(x\right) < 0\right\}.$$

Let us now, find the set $\Omega_C \subset B_r\left(\bar{x}\right)$, where

$$C < \min_{|x-\bar{x}|=r} V_1\left(x\right) = \lambda_{\min}\left(P_1\right) r^2,$$

here P_1 was defined by (4.1), $\lambda_{\min}\left(P_1\right)$ denotes a minimum eigenvalue of the corresponding matrix A_1.

Moreover, for some $C > 0$ the inclusion $\Omega_C \subset \Omega_1$ means the existence of $C > 0$ such that $x \in \Omega_C$ implies $x \in \Omega_1$, where

$$\Omega_1 = \left\{x \in \mathbb{R}^3_+, \, x_j = x_{j_0} + \sum_{k=1}^{m} \alpha_{jk} x_j\left(t_k\right) \geq 0, \; j=1,2,3, \;\; x_2 \geq \eta_2, \right.$$
$$\left[\left(b_{11}\left(a_{12}+a_{13}\right) + b_{12}\left(a_{21}+1\right)\right) + b_{13}\right] x_1 + b_{12} r_2 x_2 + b_{23} a_{21} x_3 \geq 0,$$
$$b_{22} a_{21} x_1 + b_{22} r_2 x_2 + b_{23} r_2 x_3 \geq 0, \tag{5.1}$$
$$\left. b_{11}\left(x_1-1\right)^2 + \left(b_{22}+b_{12}\right) x_2^2 \leq b_{11}, \, b_{13} x_1 + b_{23} x_2 + b_{33} x_3 \geq b_{13} \right\},$$

where

$$\eta_2 = \max\left\{1, \frac{b_{11}a_{12} + b_{12}a_{21} + r_2 + 1}{b_{22}a_{21} + b_{12}a_{12}}, \frac{b_{11}a_{13}}{b_{12}a_{13} + b_{13}a_{12}}\right\},$$

$$x_{j_0} = x_j\left(t_0\right), \; t_k \in O_\delta\left(t_0\right),$$

here $O_\delta\left(t_0\right)$ was defined by (1.2). Since $b_{23} < 0$, we get from (5.1) that

$$x_3 \leq \beta_1 x_1 + \beta_2 x_2, \; b_{13} x_1 + b_{33} x_3 \geq b_{13},$$

$$b_{11}(x_1-1)^2+(b_{22}+b_{12})x_2^2+x_3^2\le b_{11}+(\beta_1x_1+\beta_2x_2)^2,$$

where

$$\beta_1=-\frac{1}{b_{23}a_{21}}\left[\left((b_{11}(a_{12}+a_{13})+b_{12}(a_{21}+1)\right)+b_{13})\right],\ \beta_2=-\frac{b_{12}r_2}{b_{23}a_{21}}.$$

Hence,

$$\Omega_{10}=\left\{x\in\mathbb{R}_+^3,\ b_{11}(x_1-1)^2+(b_{22}+b_{12})x_2^2+x_3^2\le\right.$$
$$\left.b_{11}+(\beta_1+\beta_2\eta_2)^2,\ x_1\ge 1\right\}\subset\Omega_1.$$

So, it is not hard to see that

$$B_{\tilde{r}}(\bar{x})=\left\{x\in R^3,\ |x-\bar{x}|<\tilde{r}\right\}\subset\Omega_1,$$

where

$$\tilde{r}=\eta_0^{\frac{1}{2}}\left[b_{11}+(\beta_1+\beta_2\eta_2)^2\right]^{\frac{1}{2}},\ \eta_0=\max\{b_{11},\ b_{22}+b_{12},1\}.$$

Then we obtain

$$C<\min_{|x|=r_1}V_1(x)=\lambda_{\min}(P_1)\tilde{r}^2,$$

i.e.

$$C<\lambda_{\min}(P_1)r_0^2,\ r_0=\min\{r,\ \tilde{r}\}.$$

Now, we consider the equilibria point $E_2(0,1,0)$ and prove the following result

Theorem 5.2. Assume that the all conditions of Theorem 4.2 and (4.15) are satisfied.Then the basin of multiphase attraction set of $(1.3)-(1.4)$ at $E_2(0,1,0)$ is whole $\mathbb{R}_+^3$.

Proof. Indeed, by Theorem 4.2 the system (1.3) is global stable at $E_2(0,1,0)$. Thus, the basin of multiphase attraction set coincides with $\mathbb{R}_+^3$.

Theorem 5.3. Assume that the all conditions of Theorem 4.3 are satisfied. Then the basin of multiphase attraction set of $(1.3)-(1.4)$ at $E_3(a_\pm,0,b_\mp)$ belongs to the set $\Omega_C\subset\Omega_3$, where Ω_3 was defined by (4.23), here $V_3(x)$ was defined by (4.15).

Proof. We will find $C>0$ such that $\Omega_C\subset B_r(E_3)\cap\Omega_3$. It is clear to see that $\Omega_C\subset B_r(E_3)$ for

$$C<\min_{|x-\bar{x}|=r}V_3(x)=\lambda_{\min}(P_3)r^2,\ \bar{x}=(a_\pm,0,b_\mp),$$

here $\lambda_{\min}(P_3)$ denotes a minimum eignevalue of A_3. Let Ω_3 is a domain defined by (4.23), i.e.

$$\Omega_3=\left\{x\in\mathbb{R}_+^3:\ x_j=x_{j_0}+\sum_{k=1}^{m}\alpha_{jk}x_j(t_k)\ge 0,\ j=1,2,3,\right.$$

$$\alpha_1x_1+\alpha_2x_2+\alpha_3x_3\ge\gamma_0,\ x_1\ge\gamma_1,\ x_2\le\gamma_2x_3,\ x_3\le\gamma_3x_1,$$

$$(b_{11}+b_{11}a_{\pm}+b_{13}b_{\mp})(x_1-a_{\pm})^2+r_2(b_{12}a_{\pm}+b_{23}b_{\mp}+b_{22})x_2^2\leq$$
$$r_2(b_{12}a_{\pm}+b_{23}b_{\mp}+b_{22})+b_{11}x_1^3,\},$$

where

$$\alpha_1=\min\{\ [b_{11}a_{\pm}+b_{13}b_{\mp}-2a_{\pm}(b_{11}+b_{11}a_{\pm}+b_{13}b_{\mp})],$$
$$b_{11}a_{12}+b_{12}a_{21},\ b_{12},\ b_{13}\},$$
$$\alpha_2=\ \min\{\ r_2(b_{12}a_{\pm}+b_{23}b_{\mp})-2a_{\pm}r_2(b_{12}a_{\pm}+b_{23}b_{\mp}+b_{22}),$$
$$b_{12}a_{12}+b_{22}a_{21},\ b_{22},\ b_{23}\},\ \alpha_3=\min\{b_{13}a_{12},\ b_{23},\ b_{33}\}=b_{23},$$
$$\gamma_0=(b_{11}a_{12}a_{\pm}+b_{12}+b_{13}a_{12}b_{\mp}+a_{21}b_{12}a_{\pm}+a_{21}b_{23}b_{\mp}),$$
$$\gamma_1=\frac{(b_{11}a_{\pm}+b_{13}b_{\mp})a_{13}+b_{13}}{(b_{13}+a_{13}b_{11})},\ \gamma_2=\frac{a_{13}b_{13}x_3}{-a_{21}b_{23}},\ \gamma_3=\frac{b_{11}a_{13}}{-b_{23}a_{21}}.$$

It is clear that $\alpha_2,\alpha_3\leq 0$ and $\alpha_1>0$. Hence, $\alpha_1x_1-\gamma_0>0$. Moreover, since

$$\alpha_1x_1+\alpha_2x_2+\alpha_3x_3\geq\gamma_0,\ x_1\geq\gamma_1,\ x_2\leq\gamma_2x_3,\ x_3\leq\gamma_3x_1,$$

we get

$$0\leq x_3\leq\beta_1\gamma_1-\beta_2,$$

where

$$\beta_1=\frac{\alpha_1}{-(\alpha_2\gamma_2+\alpha_3)},\ \beta_2=\frac{\gamma_0}{-(\alpha_2\gamma_2+\alpha_3)}.$$

Thus,

$$\Omega_{30}=\Big\{x\in\mathbb{R}_+^3:\ x_j=x_{j_0}+\sum_{k=1}^{m}\alpha_{jk}x_j(t_k)\geq 0,\ j=1,2,3, \tag{5.3}$$
$$(b_{11}+b_{11}a_{\pm}+b_{13}b_{\mp})(x_1-a_{\pm})^2+r_2(b_{12}a_{\pm}+b_{23}b_{\mp}+b_{22})x_2^2+x_3^2\leq$$
$$r_2(b_{12}a_{\pm}+b_{23}b_{\mp}+b_{22})+b_{11}\gamma_1^3+(\beta_1\gamma_1-\beta_2)^2\Big\}.$$

From (4.23) it is not hard to see that

$$B_{\bar r}(\bar x)=\big\{x\in R_+^3,\ |x-\bar x|<\bar r\big\}\subset\Omega_3 \text{ for } \bar x=(0,a_{\pm},b_{\mp}),$$

where

$$(\bar r)^2=\frac{1}{\eta}\Big[r_2(b_{12}a_{\pm}+b_{23}b_{\mp}+b_{22})+b_{11}\gamma_1^3+(\beta_1\gamma_1-\beta_2)^2\Big],$$

$$\eta=\max\{(b_{11}+b_{11}a_{\pm}+b_{13}b_{\mp}),\ r_2(b_{12}a_{\pm}+b_{23}b_{\mp}+b_{22}),1\}.$$

Then we obtain that

$$C<\min_{|x-\bar x|=\bar r}V_3(x)=\lambda_{\min}(P_3)\bar r^2,$$

i.e.

$$C<\lambda_{\min}(P_3)\bar r^2 \text{ for } r_0=\min\{r,\ \bar r\}.$$

Consider the point $E_4(\bar{x}_1, \bar{x}_2, 0)$. By reasoning as the above we prove the following result:

Theorem 5.4. Assume that the all conditions of Theorem 4.4 are satisfied. Then the basin of multiphase attraction sets of $(1.3)-(1.4)$ at $E_4(\bar{x}_1, \bar{x}_2, 0)$ belongs to the set Ω_4, where Ω_4 was defined by (4.31).

Proof. We will find $C > 0$ such that $\Omega_C \subset B_r(E_4) \subset \Omega_4$. It is clear to see that $\Omega_C \subset B_r(\bar{x})$ for

$$C < \min_{|x-\bar{x}|=r} V_4(x) = \lambda_{\min}(P_4) r^2, \ \bar{x} = (\bar{x}_1, \bar{x}_2, 0),$$

here $\lambda_{\min}(P_4)$ denotes a minimum eignevalue of A_4. From (4.31) we get

$$\Omega_{40} = \{ x \in \mathbb{R}^3_+ \colon x_j = x_{j_0} + \sum_{k=1}^{m} \alpha_{jk} x_j(t_k) \geq 0, \ j = 1, 2, 3, \tag{5.4}$$

$$x_1 \leq \gamma_1, \ x_2 \geq \gamma_2, \ x_3 \leq \gamma_3,$$

$$(b_{11}\bar{x}_1 + b_{12}\bar{x}_2)(x_1 - \bar{x}_1)^2 + r_2(b_{12}\bar{x}_1 + b_{22}\bar{x}_2)(x_2 - \bar{x}_2)^2 \leq$$

$$(b_{11}\bar{x}_1 + b_{12}\bar{x}_2)\bar{x}_1^2 + r_2(b_{12}\bar{x}_1 + b_{22}\bar{x}_2)\bar{x}_2^2 + b_{22}r_2x_2^3, \ x_3 \leq \frac{a_{21}b_{23}}{-b_{13}a_{13}}x_2,$$

$$\alpha_1 x_1 + \alpha_2 x_2 + \alpha_3 x_3 \geq b_{13}\} \subset \Omega_4,$$

where

$$\gamma_1 = \frac{b_{12} - r_2(b_{12}\bar{x}_1 + b_{22}\bar{x}_2)}{b_{12}}, \ \gamma_3 = \frac{(b_{11}\bar{x}_1 + b_{12}\bar{x}_2)}{a_{13}(b_{11}\bar{x}_1 + b_{12}\bar{x}_2)},$$

$$\gamma_2 = \max\left\{\frac{a_{21}(b_{12}\bar{x}_1 + b_{22}\bar{x}_2 + b_{12}r_2)}{(a_{12}b_{12} + a_{21}b_{22})}, 1, \frac{a_{12}(b_{11}\bar{x}_1 + b_{12}\bar{x}_2)}{b_{12}}\right\},$$

$$\alpha_1 = \min\{b_{11}, \ b_{13}\}, \ \alpha_3 = \min\{b_{13}, \ b_{23}\},$$

$$\alpha_2 = \min\{(b_{12} + a_{12}b_{11} + a_{21}b_{22}), \ a_{12}b_{12} + a_{21}b_{22}, \ b_{23}\}.$$

From (5.4) It is not hard to see that $\gamma_1 \leq \frac{\alpha_2\gamma_2}{-b_{13}}$ and

$$B_r(\bar{x}) = \left\{x \in R^3_+, \ |x - \bar{x}| < \bar{r}\right\} \subset \Omega_{40} \text{ for } \bar{x} = (\bar{x}_1, \bar{x}_2, 0),$$

where

$$(\bar{r})^2 = \frac{1}{\eta}\left[(b_{11}\bar{x}_1 + b_{12}\bar{x}_2)\bar{x}_1^2 + r_2(b_{12}\bar{x}_1 + b_{22}\bar{x}_2)\bar{x}_2^2 + b_{22}r_2\gamma_2^3 + d^2\right],$$

$$\eta = \max\{b_{11}\bar{x}_1 + b_{12}\bar{x}_2, \ r_2(b_{12}\bar{x}_1 + b_{22}\bar{x}_2), 1\}, \ d = \min\left\{\frac{\alpha_2\gamma_2}{-b_{13}} - \gamma_1, \ \gamma_3\right\}.$$

Then we obtain that

$$C < \min_{|x-\bar{x}|=\bar{r}} V_4(x) = \lambda_{\min}(P_4)\bar{r}^2,$$

i.e.

$$C < \lambda_{\min}(P_4)\bar{r}^2 \text{ for } r_0 = \min\{r, \ \bar{r}\}.$$

Consider the points E_{ij}.

Theorem 5.5. Assume that the all conditions of Theorem 4.5 are satisfied. Then the basin of multiphase attraction sets of $(1.3)-(1.4)$ at points E_{ij} belong to Ω_{ij}, where Ω_{ij} was defined by (4.38).

Proof. We will find $C>0$ such that $\Omega_C \subset B_r(E_{ij}) \subset \Omega_{ij}$. It is clear to see that $\Omega_C \subset B_r(\bar{x})$ for

$$C < \min_{|x-\bar{x}|=r} V_5(x) = \lambda_{\min}(P_5)\, r^2,$$

here $\lambda_{\min}(P_5)$ denotes a minimum eignevalue of A_5. Assume $a_{13}>1$.Then from (4.38) it is not hard to see that

$$B_r(E_{ij}) \subset \Omega_{ij0} = \Bigg\{ x \in \mathbb{R}_+^3 \colon\ x_j = x_{j_0} + \sum_{k=1}^{m} \alpha_{jk} x_j(t_k) \geq 0,\ j=1,2,3, \tag{5.5}$$

$$x_1 \leq \gamma_1,\ x_2 \geq 1,\ x_3 \leq \frac{1}{a_{13}},$$

$$Q_1(x_1 - x_{1i})^2 + Q_2 r_2 (x_2 - x_{2j})^2 + (x_3 - x_{3ij})^2 \leq Q_1 x_{1i}^2 + Q_1 x_{2j}^2 +$$

$$\left(\frac{1}{a_{13}} - x_{3ij}\right)^2 + p_{22} r_2 + d^2,\ -\ [\alpha_1 x_1 + \alpha_2 x_2] \leq \alpha_3 x_3 \Bigg\},$$

where

$$\alpha_1 = \min\{p_{11},\ p_{23}a_{21} + p_{13}a_{13},\ p_{12}a_{21},\ p_{13}\},$$

$$\alpha_2 = \min\{p_{11}a_{12} + p_{12},\ p_{12}a_{13},\ p_{12}(a_{12}+r_2) + p_{22}a_{21},\ p_{23}\},$$

$$\alpha_3 = \min\{p_{11}a_{13},\ p_{13}a_{13},\ p_{13}a_{12},\ p_{33}\},\ d = \frac{-p_{12}}{\alpha_3}(1+\gamma_1),$$

$$a = \max\{a_{21},\ a_{12}r_2\}$$

$$\gamma_1 = \frac{r_2}{(a_{13} + 2x_{1i})Q_1 + (a_{21} + r_2 + 2x_{2j})Q_2},$$

$$(\bar{r})^2 = \frac{1}{\eta}\left[Q_1 x_{1i}^2 + Q_1 x_{2j}^2 + \left(\frac{1}{a_{13}} - x_{3ij}\right)^2 + p_{22}r_2 + d^2\right],$$

$$\eta = \max\{Q_1,\ Q_2,\ 1\}.$$

Then we obtain that

$$C < \min_{|x-\bar{x}|=\bar{r}} V_5(x) = \lambda_{\min}(P_5)\, \bar{r}^2,$$

i.e.

$$C < \lambda_{\min}(P_5)\, \bar{r}^2 \text{ for } r_0 = \min\{r,\ \bar{r}\}.$$

Conclusion. Taking into account different and effective features of mathematical modelling and its possibilities to figure out a problem in dynamics on the basis of its logic properties, it was surely pointed out the characteristics of a mathematical model to use in description of needed processes of a given dynamic system with identified problems. In this paper, a three dimensional model was devoted to mathematical description and regulation possibilities of uncontrolled tumor processes by organism as a complex system. The dynamics of interactions of the dimensions corresponded to tumor cells, immune cells and healthy – "host" – cells were given as forces of vectors, negatively or positively converging to basins of attractions, depending on their importance for the complex system. In order to make the model subjected to control, there was included multiphase IVP, describing the system's important parameters to operate with it in the farther processes of stages of development. The model was undergone different changes to determine its limits of survival: it was determined the conditions of boundedness the system can be restricted, invariance in non- negativity, which means the model keeps its properties of reactions to changing in proper way, being subjected to different analysis, and the circumstances the system can be forced to be dissipated in. The system was exposed to changing pressures to estimate its convenience to biologically important properties as points of equilibria and Lyapunov stability conditions. The next step in exploring of the model were very complex and logistic approaches to its properties for verification of the conditions, providing the global equilibria points and multimodal attraction sets, having biologically strong value in regulation of the processes towards the positive effects of feasible medical external implementation at the convenient stages, determined by multimodal attraction basins.

Biological implications. Here we study a multiphase host-tumor model that enhances the type of effector immune cells that can fight a tumor, and stimulates effector immune cells to proliferate. Interactions between cancer tumor cells, healthy host cells and the effector immune cells can explain long-term tumor relapse. Here, the sufficient conditions is derived that under which the possible biologically feasible dynamics is stable in the Lyapunov sense, and a converges to one of equilibrium points. Since these equilibrium points have a biological sense, we notice that understanding limit properties of dynamics of cells populations based on solving the problem (1.3) – (1.4) may be of an essential interest for the prediction of health conditions of a patient without a treatment, when the data (e.g. the status of blood cells shown above) that determines the condition of the patient are compared at various times $t_0, t_1, ..., t_m$ and correlated. In the section 3, we find the positively invariant domain $B_{\alpha,m}$ that depend on multipoint IVP condition parameters α_k, t_k and m. Moreover, the boundedness of orbits of the system (1.3) – (1.4) is derived. As a result, the future evolution of cells populations involved in this model is completely predictable in the following sense: by knowing the specific linear connection between the tumor, guest and immune cells at the t_0, t_1,...t_m time phase densities, populations has an accurate and predictable estimate of its change. In the section 4, lyapunov stability of the system (1.3) at the corresponding equilibria points are studied. We show that the system (1.3) is global stable at the "free tumor " equilibria point $E_2(0,1,0)$. In the section 5, the basins of multiphase attractors of the system $(1.3)-(1.4)$ are constructed dependent on multipoint parameters of IVP.

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