The local and global dynamics of a cancer tumor growth and chemotherapy treatment model

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Abstract

In this paper, we studied phase-space analysis of a certain mathematical model of tumor growth with an immune responses and chemotherapy therapy. Mathematical modelling of this process is viewed as a potentially powerful tool in the development of improved treatment regimens. Mathematical analysis of the model equations with multipoint initial condition, regarding nature of equilibria, local and global stability have been investigated. We studied some features of behavior of one of 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. The addition of a drug term to the system can move the solution trajectory into a desirable basin of attraction. We show that the solutions of the model with a time-varying drug term approach can be evaluated more fruitful way and down to earth style from the point of practical importance than the solutions of the system without drug treatment, in the condition of stimulated immune processes, only.

Keywords: Mathematical modeling of timor dynamics, Immune system, Stability of dynamical systems, Drug treatment, Multiphase attractors

1. Introduction

Beginning with this article, we intend to attempt to investigate the problems of mathematical and biological approaches to the modeling of cancer growth dynamics processes and operations, enlisting a new parameter as chemotherapeutic agent to the system, consisted of host, tumor and immune cells. The mathematical processing of the model is based on nonlinear property of cancer growth, when it concerns the foundation of the model’s logistic part. This approach appears very convenient in description of unexpected dynamics in the processes of growth in response to changing reactions of the system to different concentrations of immune cells and drug application at the different stages of cancer.
growth development [1 − 13]. 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 − 7]. Of course, for the development of a powerful mathematical model on cancer immunotherapy, it is required first of all, an understanding of the mechanisms governing the dynamics of tumor growth. One of the main reasons for creation of non-spatial dynamical models of a multiphase 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 ordinary differential equations and dynamical systems theory. In this paper, we examine the dynamics of a cancer growth model with drug interaction proposed in [5], taking account the system as a multiphase structure, i.e. in dynamics:

\[
\dot{T} = r_1 T (1 - k_1^{-1} T) - a_{12} N T - a_{13} T I - g_1 (u) T, \\
\dot{N} = r_2 N (1 - k_2^{-1} N) - a_{21} N T - g_2 (u) N, \\
\dot{I} = s + \frac{r_3 I T}{k_3 + T} - a_{31} I T - d_3 I - g_3 (u) I, \\
\dot{u} + d_2 u (t) = v (t)
\]

with multipoint initial condition

\[
T (t_0) = T_0 + \sum_{j=1}^{m} \alpha_{1j} T (t_j) , \quad N (t_0) = N_0 + \sum_{j=1}^{m} \alpha_{2j} N (t_j) ,
\]

\[
I (t_0) = I_0 + \sum_{j=1}^{m} \alpha_{3j} I (t_j) , \quad t_0 \in [0, \delta) , \quad t_j \in (0, \delta) , \quad t_j > t_0 , \quad u (t_0) = u_0,
\]

where \( T = T (t) , \quad N = N (t) , \quad I = I (t) \) denote the densities of tumor cells, healthy host cells and the effector immune cells respectively, at the moment \( t \), \( k_i > 0 , \alpha_{ij} \) are real numbers, \( m \) is a natural number such that

\[
T (t_0) > 0 , \quad N (t_0) > 0 , \quad I (t_0) > 0
\]

and

\[
g_i (u) \geq 0 , \quad g_i (0) = 0 , \quad \lim_{u \to \infty} g_i (u) = a_i > 0 , \quad i = 1, 2, 3. \quad (1.3)
\]

For

\[
g_i (u) = a_i (1 - e^{-\nu_i u}) , \quad \nu_i > 0 , \quad i = 1, 2, 3 \quad (1.4)
\]

we generalize the case that has been derived in [5].
The source of the immune cells is considered to be outside of the system so it is reasonable to assume a constant influx rate \( s \), furthermore, in the absence of any tumor, the cells will die off at a per capita rate \( d_3 \), resulting in a long-term population size of \( s/d_3 \) cells, \( u(t) \) denotes the amount of drug at the tumor site at time \( t \), this is determined by the dose given \( v(t) \), and a per capita decay rate of the drug once it is injected, here it is assumed that the drug kills all types of cells, but that the kill rate differs for each type of cell, with the response curve in all cases given by

\[
g(u) = (g_1(u), g_2(u), g_3(u))
\]

For case of (1.4), \( g(u) \) is the fractional cell kill for a given amount of drug \( u \), at the tumor site, this decay rate incorporates all pathways of elimination of the drug, by \( a_1 \), \( a_2 \) and \( a_3 \) denoted the three different response coefficients, here

\[
a = (a_1, a_2, a_3), \quad \nu = (\nu_1, \nu_2, \nu_3)
\]

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 \( d_3 \), here we suppose that the constant influx of the activated effector cells into the tumor microenvironment is zero. We suppose that the constant influx \( s \) of the activated effector cells into the tumor microenvironment is zero.

Therein, note that, the nonlinear dynamic systems and references studied e.g. in [14 – 15]. One of main aims is derivation of sufficient conditions under which the possible biologically feasible dynamics is local and globally stable, and 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 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 condition of the patient are compared at various times \( t_0, t_1, ..., t_m \) and correlated. Note that the local and global stability properties of (1.1) with the classical initial condition were studied in [8] and [9], respectively. We prove that
all orbits are bounded and must converge to one of several possible equilibrium points. Therefore, the long-term behavior of an orbit is classified according to the basin of multipoint attraction in which it starts. By scaling $x_1 = T_k^{-1}$, $x_2 = Nk^{-1}$, $x_3 = Ik^{-1}$, $t = rt$ in (1.1) – (1.2) and omitting the tilde notation we obtain the multipoint initial value problem (IVP)

$$
\dot{x}_1 = x_1 (1 - x_1) - a_{12} x_1 x_2 - a_{13} x_1 x_3 - g_1 (u) x_1, \\
\dot{x}_2 = r_2 x_2 (1 - x_2) - a_{21} x_1 x_2 - g_2 (u) x_2, \\
\dot{x}_3 = \frac{r_3 x_1 x_3}{x_1 + k_3} - a_{31} x_1 x_3 - d_3 x_3 - g_3 (u) x_3, \quad t \in [0, T),
$$

(1.5)

where $u + d_2 u (t) = v (t)$, $u (t_0) = u_0$,

$$
x_1 (t_0) = x_{10} + \sum_{j=1}^{m} \alpha_{1j} x_1 (t_j), \quad x_2 (t_0) = x_{20} + \sum_{j=1}^{m} \alpha_{2j} x_2 (t_j),
\\
x_3 (t_0) = x_{30} + \sum_{j=1}^{m} \alpha_{3j} x_3 (t_j), \quad t_0 \in [0, \delta), \quad t_j \in (0, T), \quad t_j > t_0,
$$

(1.6)

where $\alpha_{ij}$ are real numbers and $m$ is a natural number such that

$$
x_{j0} + \sum_{k=1}^{m} \alpha_{jk} x_j (t_k) \geq 0, \quad j = 1, 2, 3.
$$

(1.7)

By solving the problem

$$
\dot{u} (t) + d_2 u (t) = v (t), \quad u (t_0) = u_0
$$

(1.8)

we get

$$
u (t) = e^{t_0} u_0 + \int_{t_0}^{t} e^{- (t - \tau)} v (\tau) d\tau, \quad t \in (0, T],
$$

(1.9)

i.e. the system (1.5) is equivalent to the following

$$
\dot{x}_1 = x_1 (1 - x_1) - a_{12} x_1 x_2 - a_{13} x_1 x_3 - g_1 (v) x_1, \\
\dot{x}_2 = r_2 x_2 (1 - x_2) - a_{21} x_1 x_2 - g_2 (v) x_2, \\
\dot{x}_3 = \frac{r_3 x_1 x_3}{x_1 + k_3} - a_{31} x_1 x_3 - d_3 x_3 - g_3 (v) x_3, \quad t \in [0, T),
$$

(1.10)

where $g_i (v) = f_i (u)$, here $u$ is defined by (1.9). Note that, for $\alpha_{j1} = \alpha_{j2} = \ldots \alpha_{jm} = 0$ the problem (1.5) – (1.6) turns to be the Cauchy problem

$$
\dot{x}_1 = x_1 (1 - x_1) - a_{12} x_1 x_2 - a_{13} x_1 x_3 - g_1 (u) x_1,
$$
\[
\begin{align*}
\dot{x}_2 &= r_2 x_2 (1 - x_2) - a_{21} x_1 x_2 - g_2(u) x_2, \\
\dot{x}_3 &= \frac{r_3 x_2 x_3}{x_1 + k_3} - a_{31} x_1 x_3 - d_3 x_3 - g_3(u) x_3, \\
\dot{u} + d_2 u(t) &= v(t), \quad t \in [0, T], \\
x_1(t_0) &= x_{10}, \quad x_2(t_0) = x_{20}, \quad x_3(t_0) = x_{30}, \quad u(t_0) = u_0, \quad t_0 \in [0, T).
\end{align*}
\]

2. Notations and background.

Consider the multipoint IVP for nonlinear equation
\[
\frac{du}{dt} = f(u), \quad t \in [0, T],
\]
\[
u(t_0) = u_0 + \sum_{k=1}^{m} \alpha_k u(t_k), \quad t_0 \in [0, T), \quad t_k \in (0, T), \quad t_k > t_0
\]
in a Banach space \(X\), where \(\alpha_k\) are complex numbers, \(m\) is a natural number and \(u = u(t)\) is a \(X\)-valued function. Note that, for \(\alpha_1 = \alpha_2 = \ldots = \alpha_m = 0\) the problem (2.1) becomes the following local Cauchy problem
\[
\frac{du}{dt} = f(u), \quad u(t_0) = u_0, \quad t \in [0, T), \quad t_0 \in [0, T).
\]

For \(u_0 \in X\) let \(\bar{B}_r(u_0)\) denotes a closed ball in \(X\) with radius \(r\) centered at \(u_0\), i.e.,
\[
\bar{B}_r(u_0) = \{ u \in X : \| u - u_0 \|_X \leq r \}.
\]
From [19] we have

**Theorem 2.1.** Let \(X\) be a Banach space. Suppose \(f : X \to X\) satisfies local Lipschitz condition on \(\bar{B}_r(v_0) \subset X\), i.e.
\[
\| f(u) - f(v) \|_X \leq L \| u - v \|_X
\]
for each \(u, v \in \bar{B}_r(v_0)\) and there exists \(\delta > 0\) such that
\[
t_k \in O_\delta(t_0) = \{ t \in \mathbb{R} : |t - t_0| < \delta \},
\]
where
\[
v_0 = u_0 + \sum_{k=1}^{m} \alpha_k u(t_k).
\]
Moreover, let
\[
M = \sup_{u \in \bar{B}_r(v_0)} \| f(u) \|_X < \infty.
\]
Then, problem (2.1) has a unique continuously differentiable local solution \(u(t)\), for \(t \in O_\delta(t_0)\), where \(\delta \leq \frac{r}{M}.\)
Theorem 2.2. Let $X$ be a Banach space. Suppose that $f : X \to X$ satisfies global Lipschitz condition, i.e.

$$\|f(u) - f(v)\|_X \leq L \|u - v\|_X$$

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

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

Then problem (2.1) has a unique continuously differentiable local solution $u(t)$, for $|t - t_0| < \delta$, where $\delta \leq \frac{\gamma}{M}$.

Let $X$ be a Banach space. $x \in X$ is called a critical point (or equilibria point) for the equation (2.1) if $f(x) = 0$.

We denote the solution of the problem (2.1) by $\phi(t, u_0) = \phi(t, u(t_0), u(t_1), ..., u(t_m))$.

Definition 2.1. Let $u_0 \in X$. A critical point $x \in X$ of the equation (2.1) is called a positive multiphase attractor if there exists a neighborhood $O_x \subset X$ of $x$ such that the relation

$$u_0 = u(t_0) - \sum_{k=1}^{m} \alpha_k u(t_k) \subset O_x \text{ for } t_0 \in [0, T), t_k \in (0, T), t_k > t_0$$

implies $\lim_{t \to \infty} u(t) = x$.

Definition 2.2. Assume $x \in X$ is a multiphase attractor of (2.1). A set of $u_0 \in X$ with a property that for solution $\phi(t, u_0)$ of (2.1) we have $\lim_{t \to \infty} u(t) = x$, is called a domain of multiphase attractor (domain of multiphase asymptotic stability, or multiphase basin) of $x$.

3. The equilibria points, existence and local stability

The equilibria points of the system (1.3) are obtained by solving the system of isocline equations

$$x_1 (1 - x_1) - a_{12} x_1 x_2 - a_{13} x_1 x_3 - g_1(v) x_1 = 0,$$

$$r_2 x_2 (1 - x_2) - a_{21} x_1 x_2 - g_2(v) x_2 = 0,$$

$$\frac{r_3 x_1 x_3}{x_1 + k_3} - a_{31} x_1 x_3 - d_3 x_3 - g_3(v) x_3 = 0.$$

Since we are interested in biologically relevant solutions of (3.1), we find sufficient conditions under which this system have positive solutions.

It is clear to see that the points $E_0(0,0,0)$, $E_1(\gamma,0,0)$, $E_2(0,\delta,0)$ are equilibria points for the system of (1.11), where

$$\gamma = 1 - g_1(v), \ \delta = 1 - \frac{g_2(v)}{r_2}.$$
Remark 3.1. It is clear that the points $E_0(0, 0, 0)$, $E_1(\gamma, 0, 0)$, $E_2(0, \delta, 0)$ are biologically feasible equilibria points for the system (1.10).

Let
\[ R_i^3 = \{ x \in R^3: x_i > 0, i = 1, 2, 3 \}. \]

Remark 3.2. (1) consider the equilibrium points $E_0(0, 0, 0)$; for $E_0$ three type cell populations are zero; (2) for points $E_1(\gamma, 0, 0)$ tumor cells have survived but normal and immune cells are zero, this case can be called as "dead" case; (3) $E_2(0, \delta, 0)$—tumor-free and immune free case; in this category, normal cells have survived but tumor and immune cells are zero.

We now will derive that the linearized matrices of the system (1.11) for equilibria points $E_0(0, 0, 0)$, $E_1(\gamma, 0, 0)$, $E_2(0, \delta, 0)$ are following:

\[
A_0 = \begin{bmatrix}
\gamma & 0 & 0 \\
0 & d_{22} & 0 \\
0 & 0 & c_{33}
\end{bmatrix}, \quad A_1 = \begin{bmatrix}
d_{11} & -a_{12}\gamma & -a_{13}\gamma \\
0 & d_{22} & 0 \\
0 & 0 & d_{33}
\end{bmatrix}, \quad A_2 = \begin{bmatrix}
c_{11} & 0 & 0 \\
-a_{21}\delta & c_{22} & 0 \\
0 & 0 & c_{33}
\end{bmatrix},
\]

where
\[
d_{11} = 1 - 2\gamma - g_1(v), \quad d_{22} = r_2 - a_{21}\gamma - g_2(v),
\]
\[
d_{33} = \left(\frac{r_3}{\gamma + k_3} - a_{31}\right)\gamma - d_3 - g_3(v), \quad c_{11} = 1 - a_{12}\delta - g_1(v),
\]
\[
c_{22} = r_2(1 - 2\delta) - a_{21}\delta - g_2(v), \quad c_{33} = -d_3 - g_3(v).
\]

4. local stability analysis of equilibria points

In this section we show the following result:

Theorem 4.1. (1) $E_0(0, 0, 0)$ is a locally asymptotically stable point if $g_1(v) > 1, g_2(v) > r_2$ and $E_0$ is an unstable point if $g_1(v) < 1, g_2(v) < r_2$; (2) $E_1(\gamma, 0, 0)$ is a locally asymptotically stable point for the linearized system of (1.11) when $d_{ii} < 0$ for $i = 1, 2, 3$, it is an unstable point when $d_{ii} > 0$; (3) $E_2(0, \delta, 0)$ is a locally asymptotically stable point for linearized system of (1.11) when $c_{ii} < 0$ for $i = 1, 2$, it is an unstable point if $c_{ii} > 0$, where $\gamma, \delta$ were defined by (3.2) and $d_{ii}, c_{ii}, i = 1, 2, 3$ defined by (3.4).

Proof. Indeed, the eigenvalues of the matrix $A_0$ are $\gamma, d_{22}, c_{33}$; eigenvalues of the matrix $A_1$ are $d_{ii}$ and eigenvalues of the matrix $A_2$ are $c_{ii}$. Hence, by [5, Theorem 8.12] we obtain the assertions.

Theorem 4.2. Let $g_1(v) > 1$ and $g_2(v) > r_2$. Then, the dimension of the stable manifold $W_0^+$ and unstable manifold $W_0^-$ are given, respectively, by
\[
\text{Dim } W_0^+(E_0(0, 0, 0)) = 1, \quad \text{Dim } (W_0^-E_0(0, 0, 0)) = 1.
\]

Proof. Let we solve the following matrix equation
\[
A_0x = \lambda x,
\]
i.e. consider the system of homogenous linear equation

\[(1 - g_1 (v) - \lambda) x_1 = 0, \quad (r_2 - g_2 v - \lambda) x_2 = 0, \quad -(d_3 + g_3 (v) + \lambda) x_3 = 0.\]

By solving of (4.2) we get that eigenspaces corresponding to eigenvalues \(\lambda_1 = \gamma, \lambda_2 = d_{22}, \lambda_3 = \theta\) are respectively, the following:

\[
B_{01} = \{ x \in \mathbb{R}^3 : x = (a, 0, 0) \},
\]

\[
B_{02} = \{ x \in \mathbb{R}^3 : x = (0, a, 0) \},
\]

\[
B_{03} = \{ x \in \mathbb{R}^3 : x = (a, b, 0) \}
\]

where \(a\) is any real number, i.e. we obtain (4.1).

In a similar way we obtain

**Theorem 4.3.** Let \(g_1 (v) < 1\) and \(g_2 (v) < r_2\). Then, the dimension of the hyperbolic saddle manifold \(W^0\) is given by

\[
\dim W^0 (E_0 (0, 0, 0)) = 1.
\]

**Theorem 4.4.** Let \(d_{ii} < 0, \ i = 1, 2, 3.\) Then, the dimension of the stable manifold \(W^+_1\) and unstable manifold \(W^-_1\) are given, respectively, by

\[
\dim W^+_0 (E_1 (\gamma, 0, 0)) = 1, \quad \dim W^-_0 (E_0 (\gamma, 0, 0)) = 1. \quad (4.3)
\]

**Proof.** Let we solve the the following matrix equation

\[
A_1 x = \lambda x,
\]

i.e. consider the system of homogenous linear equation

\[(d_{11} - \lambda) x_1 - a_{12} \gamma x_2 = 0, \quad (d_{22} - \lambda) x_2 = 0, \quad (d_{33} - \lambda) x_3 = 0.\]

By solving of (4.4) we get that eigenspaces corresponding to eigenvalues \(\lambda_1 = d_{11}, \lambda_2 = d_{22}, \lambda_3 = d_{33}\) are respectively, the following:

\[
B_{11} = \{ x \in \mathbb{R}^3 : x = (a, 0, 0) \},
\]

\[
B_{12} = \{ x \in \mathbb{R}^3 : x = (b, a, 0) \},
\]

\[
B_{13} = \{ x \in \mathbb{R}^3 : x = (0, b, 0) \}
\]

where \(a\) is any real number and

\[
b = \frac{(1 - 2 \gamma - r_2 + g_2 (v))}{a_{12} \gamma},
\]

i.e. we obtain (4.3).

In a similar way we obtain

**Theorem 4.5.** Let \(d_{ii} > 0.\) Then, the dimension of the hyperbolic saddle manifold \(W^0_1\) is given by

\[
\dim W^0_1 (E_1 (\gamma, 0, 0)) = 1.
\]
Theorem 4.6. Let $c_{ii} < 0$, $i = 1, 2, 3$. Then, the dimension of the stable manifold $W^+_2$ and unstable manifold $W^-_2$ are given, respectively, by

$$
\dim W^+_2 (E_1 (0, \delta, 0)) = 1, \quad \dim W^-_2 (E_2 (0, \delta, 0)) = 1. \tag{4.5}
$$

Proof. Let we solve the following matrix equation

$$A_2 x = \lambda x, \tag{4.6}$$

i.e. consider the system of homogenous linear equation

$$(c_{11} - \lambda) x_1 = 0, \quad -a_{21} \delta x_1 + (c_{22} - \lambda) x_2 = 0, \quad (c_{33} - \lambda) x_3 = 0,$$

where $c_{ii}$ were defined by (3.4). By solving of (4.6) we get that eigenspaces corresponding to eigenvalues $\lambda_1 = c_{11}, \lambda_2 = c_{22}, \lambda_3 = c_{33}$ are respectively, the following:

$$B_{21} = \{ x \in \mathbb{R}^3 : x = (a, 0, 0) \},$$

$$B_{22} = \{ x \in \mathbb{R}^3 : x = (0, a, 0) \}, \quad B_{23} = \{ x \in \mathbb{R}^3 : x = (0, 0, a) \},$$

where $a$ is any real number. i.e. we obtain (4.5).

In a similar way we obtain

Theorem 4.7. Let $c_{ii} > 0$. Then, the dimension of the hyperbolic saddle manifold $W^0_2$ is given by

$$\dim W^0_2 (E_2 (0, \delta, 0)) = 1.$$

Definition 4.1. A set $A \subset S$ is called a strong multipoint attractor with respect to $S$ if

$$\limsup_{t \to \infty} \rho (u (t), A) = 0,$$

where $u (t)$ is an orbit such that $u (t_0) - \sum_{k=1}^{m} \alpha_k u (t_k) \in S$ and $\rho$ is the Euclidean distance function.

Lemma 5.1. $B$ is a strong multipoint attractor with respect to $\mathbb{R}^3$.

Proof. The proof is done using standard comparison as in Theorem 3.1.

5. Global stability of equilibria points

In this section, we will derive global stability condition of equilibria points $E_0 (0, 0, 0), E_1 (\gamma, 0, 0), E_2 (0, \delta, 0)$.

Let

$$R^3_+ = \{ x = (x_1, x_2, x_3) \in \mathbb{R}^n : x_k \geq 0 \}, \quad \Omega_K = \{ x \in \mathbb{R}^3 : 0 \leq x_i \leq K_i, \ i = 1, 2, 3 \}$$

and

$$B_r (\bar{x}) = \{ x \in \mathbb{R}^3, \ ||x - \bar{x}||_{\mathbb{R}^3} < r^2 \}.$$
**Theorem 5.0.** Assume: (1) \(g_1(v) > 1\) and \(g_2(v) > r_2\); (2) \(a_{31} k_3 > r_3\). Then the system (1.11) is global asymptotically stable at equilibria point \(E_0(0, 0, 0)\).

**Proof.** Let \(A_0\) be the linearized matrix with respect to equilibria point \(E_0(0, 0, 0)\), i.e.

\[
A_0 = \begin{bmatrix}
1 - g_1(v) & 0 & 0 \\
0 & r_2 - g_2(v) & 0 \\
0 & 0 & -d_3 - g_3(v)
\end{bmatrix}.
\]

We consider the Lyapunov equation

\[
B_0 A_0 + A_0^T B_0 = -I, \quad B_0 = \begin{bmatrix}
b_{11} & b_{12} & b_{13} \\
b_{21} & b_{22} & b_{23} \\
b_{31} & b_{32} & b_{33}
\end{bmatrix}.
\]

The equation above is reduced to a linear system of algebraic equation with respect to \(b_{ij}\). By solving this algebraic equation we get

\[
b_{11} = \frac{1}{2(g_1(v) - 1)}, \quad b_{22} = \frac{1}{2(g_2(v) - r_2)}, \quad b_{33} = \frac{1}{2(g_3(v) + d_3)},
\]

i.e.,

\[
B_0 = \begin{bmatrix}
b_{11} & 0 & 0 \\
0 & b_{22} & 0 \\
0 & 0 & b_{33}
\end{bmatrix}.
\]

Hence,

\[
P_0(\lambda) = |B_0 - \lambda I| = (b_{11} - \lambda) (b_{22} - \lambda) (b_{33} - \lambda) = 0. \tag{5.0}
\]

By assumption, eigenvalues \(\lambda_1 = b_{11}, \lambda_2 = b_{22}, \lambda_3 = b_{33}\) of the matrix \(B_0\) are positive. So, the quadratic function

\[
V_0(x) = X^T B_0 X = b_{11} x_1^2 + b_{22} x_2^2 + b_{33} x_3^2 \tag{5.10}
\]

is a positive defined Lyapunov function candidate in the certain neighborhood of \(E_0(0, 0, 0)\). By [12, Corollary 8.2] we need now to determine a domain \(\Omega_0\) about the point \(E_1\), where \(V_0(x)\) is negatively defined and a constant \(C\) such that \(\Omega_C\) is a subset of \(\Omega_0\). By assuming \(x_k \geq 0, k = 1, 2, 3\), we will find the solution set of the following inequality

\[
\dot{V}_0(x) = \sum_{k=1}^{3} \frac{\partial V_0}{\partial x_k} \frac{dx_k}{dt} = 2b_{11} (1 - g_1(v)) x_1^2 + 2b_{22} (r_2 - g_2(v)) x_2^2 - 2b_{33} (d_3 + g_3(v)) x_3^2 - 2b_{11} g_1(v) x_1^2 - 2b_{22} x_2^3 - 2b_{11} g_1(v) x_1^2 -
\]

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\[ 2b_{11}x_1^2 (a_{12}x_2 + a_{13}x_3) - 2b_{22}g_2(v)x_2^2 - \\
2b_{22}a_{21}x_2^2x_1 + 2b_{33}x_3^2 \left[ \frac{r_3x_1}{x_1 + k_3} - a_{31}x_1 \right] < 0 \]  \(5.1\)

For \(x \in R_+^3\) we have

\[-2b_{11}x_1^3 - 2b_{22}x_2^3 - 2b_{11}x_1^2(a_{12}x_2 + a_{13}x_3) - 2b_{22}a_{21}x_2^2x_1 \leq 0.\]

Hence, in view of inequalities

\[ 2ab \leq a^2 + b^2, \quad x_1^2 + x_2^2 \leq \|x\|^2, \quad x_2^2 + x_3^2 \leq \|x\|^2 \]  \(5.2\)

for \(x \in R_+^3\) we obtain that the inequality \(5.1\) holds if

\[ 2b_{11} (1 - g_1(v))x_1^2 + 2b_{22} (r_2 - g_2(v))x_2^2 - 2b_{33} (d_3 + g_3(v))x_3^2 \leq 0, \]

\[ \frac{r_3}{x_1 + k_3} - a_{31} < 0. \]  \(5.3\)

By assumption (1) the first inequality of \(5.3\) are satisfied for all \(x \in R^3\) and the second inequality holds by assumption (2). So, \(V_0(x) < 0\) for \(x \in R_+^3\), i.e. the point \(E_0\) is global asymptotically stable at equilibria point.

**Theorem 5.1.** Assume: (1) \(d_{11} < 0, d_{22} < 0, d_{33} < 0\); (2); \(- (d_{22} + d_{33}) < a_{21}\gamma, \)

\[ \gamma < -2(d_{11} + d_{22}), \quad -2d_{22}a_{12}^2\gamma < a_{21} [a_{12}^2\gamma + d_{11} (d_{11} + d_{22})], \]

\[ (3) \quad \frac{b_{12}^2}{2} \geq \frac{2b_{12}^2}{b_{11}}, \quad \frac{b_{33}^2}{2} \geq \frac{2b_{13}^2}{b_{11}}, \quad \frac{b_{33}^2}{2} \geq \frac{2b_{33}^2}{b_{22}}; \]

\[ (4) \quad r_2 > g_2(v), \quad (a_{12} + \gamma d_{22})a_{12}\gamma < d_{11} (d_{11} + d_{12}). \]

Then the system \((1.10)\) is global asymptotically stable at equilibria point \(E_1(\gamma, 0, 0)\).

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

\[ A_1 = \begin{bmatrix} d_{11} & -a_{12}\gamma & -a_{13}\gamma \\ 0 & d_{22} & 0 \\ 0 & 0 & d_{33} \end{bmatrix}, \]

where \(d_{11}\) was defined by \((3.4)\).

By assumption (1), \(d_{ii} < 0\). We consider the Lyapunov equation

\[ B_1A_1 + A_1^TB_1 = -I, \]  \(5.4\)

where

\[ B_1 = \begin{bmatrix} b_{11} & b_{12} & b_{13} \\ b_{21} & b_{22} & b_{23} \\ b_{31} & b_{32} & b_{33} \end{bmatrix}. \]
The equation (5.4) is reduced the linear system of algebraic equation with respect to $b_{ij}$, by solving which we obtain

$$b_{11} = -\frac{1}{2d_{11}}, \quad b_{12} = b_{21} = -\frac{a_{12} \gamma}{2d_{11} (d_{11} + d_{22})}, \quad b_{13} = b_{31} = -\frac{a_{13} \gamma}{2d_{11} (d_{11} + d_{22})}, \quad b_{22} = \frac{1}{2d_{22}} (2a_{12} b_{12} \gamma - 1),$$

$$b_{23} = \frac{(a_{13} b_{12} + a_{12} b_{13}) \gamma}{d_{22} + d_{33}}, \quad b_{33} = -\frac{1}{2d_{33}} (2a_{13} \gamma b_{13} - 1). \quad (5.5)$$

Consider now, the quadratic function

$$V_1(x) = X^T B_1 X = b_{11} (x_1 - \gamma)^2 + b_{22} x_2^2 + b_{13} x_3 + 2b_{12} (x_1 - \gamma) x_2 + 2b_{13} (x_1 - \gamma) x_3 + 2b_{23} x_2 x_3.$$  

It is clear to see that

$$V_1(x) = b_{11} (x_1 - \gamma)^2 + 2b_{12} (x_1 - \gamma) x_2 + b_{22} x_2^2 + 2b_{13} x_1 x_3 + b_{33} x_3^2 + 2b_{23} x_2 x_3 = \frac{b_{11}}{2} (x_1 - \gamma + \frac{2b_{12}}{b_{11}} x_2)^2 + \left[\frac{b_{22}}{2} - \frac{2b_{12}^2}{b_{11}^2}\right] x_2^2 + \frac{b_{11}}{2} (x_1 - \gamma + \frac{2b_{13}}{b_{11}} x_3)^2 + \left[\frac{b_{33}}{2} - \frac{2b_{13}^2}{b_{11}^2}\right] x_3^2 + \frac{b_{22}}{2} (x_2 + \frac{2b_{23}}{b_{22}} x_3)^2 + \left[\frac{b_{33}}{2} - \frac{2b_{23}^2}{b_{22}^2}\right] x_3^2 \geq 0, \quad (5.6)$$

i.e. $V_1(x)$ is a positive defined Lyapunov function candidate in neighborhood of $E_1 \subset \Omega_K$ when the assumption (3) hold. By [12, Corollary 8.2] we need now to determine a domain $\Omega_1$ about the point $E_1$, where $\dot{V}_1(x)$ is negatively defined and a constant $C$ such that $\Omega_C$ is a subset of $\Omega_1$. By assuming $x_k \geq 0$, $k = 1, 2, 3$, we will find the solution set of the following inequality

$$\dot{V}_1(x) = \sum_{k=1}^{3} \frac{\partial V_1}{\partial x_k} \frac{dx_k}{dt} = (5.7)$$

$$2 [b_{11} (x_1 - \gamma) + b_{12} x_2 + b_{13} x_3] x_1 [(1 - x_1) - a_{12} x_2 - a_{13} x_3 - g_1 (v)] + 2 [b_{12} (x_1 - \gamma) + b_{22} x_2 + b_{23} x_3] x_2 [r_2 (1 - x_2) - a_{21} x_1 - g_2 (v)] + 2 [b_{23} x_2 + b_{13} (x_1 - \gamma) + b_{33} x_3] x_3 \left[\frac{r_3 x_3}{x_1 + k_3} - a_{31} x_1 - d_3 - g_3 (v)\right] < 0.$$

By assumption (1) $b_{11}, b_{22}, b_{33} > 0, b_{12}, b_{13} < 0, b_{23} > 0$. So, by assumption (2), some coefficients of terms $x_1 x_2, x_1 x_3, x_1 x_2^2, x_1^2 x_2, x_1 x_2 x_3$ are negative. Hence, the estimate (5.7) holds if

$$\eta_{11} x_1^2 + \eta_{22} x_2^2 + \eta_{33} x_3^2 + 2b_{11} \gamma [a_{12} x_1 x_2 + a_{13} x_1 x_3] < 0, \quad (5.8)$$

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\[
\alpha_1 x_1 + \alpha_2 x_2 + \alpha_3 x_3 < 0,
\]
where,
\[
\eta_{11} = 2b_{11} [1 + \gamma - g_1 (v)], \quad \eta_{22} = 2b_{12} \gamma + 2r_2 b_{22} - 2b_{22}g_2 (v),
\]
\[
\eta_{33} = -2d_3, \quad \alpha_1 = 2b_{11} \gamma [g_1 (v) - 1], \quad \alpha_2 = 2b_{12} \gamma [g_2 (v) - r_2],
\]
\[
\alpha_3 = 2b_{13} [g_3 (v) + d_3].
\]
By assumption (4) and in view of (5), \(\eta_{ii} > 0\) for \(i = 1, 2, 3\). Moreover, by applying (5.2) we get that (5.8) hold if
\[
\mu_1 (x_1 - \gamma)^2 + \eta_2 x_2^2 + \alpha_3 x_3^2 < \mu_1 \gamma^2,
\]
\[
(\alpha_1 + 2\mu_1) x_1 + \alpha_2 x_2 + \alpha_3 x_3 \leq 0,
\]
where
\[
\mu_1 = \eta_{11} + b_{11} \gamma a_{12}, \quad \mu_2 = \eta_{22} + b_{12} \gamma a_{13}.
\]
Hence, \(\dot{V}_1\) is negative defined on the domain \(\Omega_1 = B_r (\bar{x}) \cap \Omega_\gamma\), if
\[
(x_1 - \gamma)^2 + x_2^2 + x_3^2 < r^2,
\]
\[
(\alpha_1 + 2\mu_1) x_1 + \alpha_2 x_2 + \alpha_3 x_3 \leq 0,
\]
where
\[
\bar{x} = (\gamma, 0, 0), \quad r = \left( \frac{\mu_0}{\mu_1 \gamma^2} \right)^{\frac{1}{2}}, \quad \mu_0 = \max \{\mu_1, \eta_2, \alpha_3\},
\]
\[
r \leq \sqrt{K_1^2 + K_2^2 + K_3^2}, \quad \Omega_\gamma = \{x \in \mathbb{R}_+^3, \ (\alpha_1 + 2\mu_1) x_1 + \alpha_2 x_2 + \alpha_3 x_3 \leq 0\}.
\]
(5.11)
i.e., the system (1.11) is global asymptotically stable at \(E_1 (\gamma, 0, 0)\).

**Remark 5.1.** In view of (5.5), the assumption (3) can be realized as the condition on the coefficients of the system (1.11).

Let \(c_i\) be the numbers defined by (3.4). Now, we consider the equilibria point \(E_2 (0, \delta, 0)\) and prove the following result

**Theorem 5.2.** Assume (1) \(c_{11} < 0, \ \delta = 1 - \frac{g_1 (v)}{g_2 (v)} > 0, \ c_{22} < 0\) (2) \(g_1 (v) < 1; (3)
\[
g_1 (v) + g_2 (v) + r_2 > r_2 (\delta - 1), \ g_1 (v) - 1 > \delta (a_{12} + 1).
\]

Then the system (1.11) is global asymptotically stable at equilibria point \(E_2 (0, \delta, 0)\).

**Proof.** Let \(A_2\) be the linearized matrix with respect to equilibria point \(E_2 (0, \delta, 0)\), i.e.
\[
A_2 = \begin{bmatrix}
c_{11} & 0 & 0 \\
-c_{21} \delta & c_{22} & 0 \\
0 & 0 & c_{33}
\end{bmatrix}
\]

Consider the Lyapunov equation
\[
B_2 A_2 + A_2^T B_2 = -I,
\]
(5.12)
where

\[ B_2 = \begin{bmatrix} b_{11} & b_{12} & b_{13} \\ b_{21} & b_{22} & b_{23} \\ b_{31} & b_{32} & b_{33} \end{bmatrix}. \]

The equation (5.12) is reduced to the linear system of algebraic equation in \( b_{ij} \) and by solving this system we get

\[ b_{13} = 0, \quad b_{22} = -\frac{1}{2c_{22}}, \quad b_{12} = -\frac{a_{21}\delta}{2c_{22}(c_{11} + c_{22})}, \]

\[ b_{11} = -\frac{1}{c_{11}} \left[ \frac{a_{21}^2\delta^2}{2c_{22}(c_{11} + c_{22})} + \frac{1}{2} \right], \quad b_{23} = b_{32} = 0, \]

\[ b_{33} = -\frac{1}{2d_{33}}, \quad b_{13} = b_{31} = 0, \]

\[ B_2 = \begin{bmatrix} b_{11} & b_{12} & 0 \\ b_{12} & b_{22} & 0 \\ 0 & 0 & b_{33} \end{bmatrix}. \quad (5.12) \]

Moreover,

\[ P_2(\lambda) = (b_{33} - \lambda)[\lambda^2 - (b_{11} + b_{22})\lambda - (b_{12}^2 - b_{11}b_{22})] = 0. \quad (5.13) \]

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

\[ b_{11} > 0, \quad b_{22} > 0, \quad b_{33} > 0, \quad b_{12} < 0. \]

By assumption (3),

\[ (b_{11} + b_{22})^2 + 4(b_{12}^2 - b_{11}b_{22}) = (b_{11} - b_{22})^2 + 4b_{12}^2 \geq 0. \]

So, (5.13) has positive roots, i.e. the matrix \( B_2 \) is positive defined for all \( x \). Hence, the quadratic function

\[ V_2(x) = X^TP_2X = b_{11}x_1^2 + 2b_{12}x_1(x_2 - \delta) + 2b_{22}(x_2 - \delta)^2 + b_{33}x_3^2 \quad (5.12) \]

is a positive defined Lyapunov function candidate in certain neighborhood of \( E_2(0, \delta, 0) \). We need to determine a domain \( \Omega_2 \) about the point \( E_2 \), where \( \dot{V}_2(x) \) is negative defined and a constant \( C \) such that \( \Omega_C \) is a subset of \( \Omega_2 \). By assuming \( x \in \mathbb{R}^3_+ \) we will find the solution set of the following inequality,

\[ \dot{V}_2(x) = \sum_{k=1}^{3} \frac{\partial V_2}{\partial x_k} \frac{dx_k}{dt} = \\
[2b_{11}x_1 + 2b_{12}(x_2 - \delta)](1 - x_1) - a_{12}x_2 - a_{13}x_3 - g_1(v)x_1 + \\
[2b_{22}(x_2 - \delta) + 2b_{12}x_1][r_2(1 - x_2) - a_{21}x_1 - g_2(v)x_2] + \\
b_{33}x_3^2 \left[ \frac{r_3x_1}{x_1 + k_3} - a_{31}x_1 - d_3 - g_3(v) \right] < 0. \quad (5.14) \]
By assumptions, the coefficients of terms \( x_1^3, \ x_2^3, \ x_1x_2^2, \ x_1^2x_2, \ x_1x_2x_3 \) and some coefficients of \( x_1x_2, \ x_1x_3 \) are negative. So, by assumption (2) and by (6q_2) for \( x \in R_+^3, \) the inequality (6.14) holds if

\[
[2b_{11} (1 - g_1 (v)) - 2\delta b_{12}g_1 (v)] x_1^2 + 2\delta b_{22} [r_2 + g_2 (v)] x_2^2 -
\]

\[
b_{33} (d_3 + g_3 (v)) x_3^3 + [-2\delta b_{12}\gamma_{12} + 2\delta b_{22}\alpha_{21} - 2b_{12}g_1 (v)] x_1 x_2 +
\]

\[
2\delta b_{12}g_1 (v) x_1 + [2b_{22}g_2 (v) (\delta - r_2)] x_2 +
\]

\[-[b_{12}r_2 + 2b_{22}\alpha_{21}] x_1 x_2^2 + 2b_{12} [g_1 (v) - a_{21}] - 2b_{11}\alpha_{12} \] \( x_1^2 x_2 \) \( < \) 0.

By assumption (3)

\[-[b_{12}r_2 + 2b_{22}\alpha_{21}] < 0, \ \{2b_{12} [g_1 (v) - a_{21}] - 2b_{11}\alpha_{12}\} < 0. \]

Hence, in view of inequalities (6.2), the above inequality holds if

\[
\mu_0 \left[ x_1^2 + (x_2 - \delta)^2 + x_3^2 \right] < \mu_0\delta^2 - b_{12} (\delta a_{12} + g_1 (v)) + \delta b_{22}\alpha_{21},
\]

\[
2\delta b_{12}g_1 (v) x_1 + [2b_{22}g_2 (v) (\delta - r_2) + 2\mu_0\delta] x_2 \leq 0,
\]

(5.15)

where

\[
\mu_1 = [2b_{11} (1 - g_1 (v)) - 2\delta b_{12} g_1 (v)], \ \mu_2 = 2\delta b_{22} [r_2 + g_2 (v)],
\]

\[
\mu_3 = b_{33} (d_3 + g_3 (v)), \ \mu_0 = \max \{\mu_1, \mu_2, \mu_3\}.
\]

From (5, q_2) it is easy to see that \( \mu_k > 0. \) Hence, \( \hat{V}_2 \) is negative defined on the domain \( \Omega_2 = B_r (\bar{x}) \cap \Omega_\delta, \) where

\[
\bar{x} = (0, \delta, 0), \ r = \left( \frac{\eta}{\mu_0} \right)^{\frac{1}{2}}, \ r \leq \sqrt{K_1^2 + K_2^2 + K_3^2},
\]

\[
\eta = \mu_0\delta^2 - b_{12} (\delta a_{12} + g_1 (v)) + \delta b_{22}\alpha_{21} + \mu_2\delta^2,
\]

\[
\Omega_\delta = \{ x \in R_+^3, \ 2\delta b_{12}g_1 (v) x_1 + [2b_{22}g_2 (v) (\delta - r_2) + 2\mu_0\delta] x_2 \leq 0 \}.
\]

(5.q_3)

i.e., the system (1.11) is global asymptotically stable at \( E_1 (0, \delta, 0). \)

6. Basins of multiphase attraction sets

In this section we will derive momains of multipoint attraction sets, \( E_0 (0, 0, 0), \ E_1 (\gamma, 0, 0), \ E_2 (0, \delta, 0), \) where \( \gamma, \delta \) were defined by (3.2).

We show in this section the following results

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Theorem 6.0. Assume that all conditions of Theorem 5.0 are satisfied. Then the basin of multiphase attraction set of the point $E_0 (0,0,0)$ belongs to the set $\Omega_C \subset \Omega_K$, where the positive constant $C$ is defined in bellow.

**Proof.** Let us now find the set $\Omega_C \subset B_r (\bar{x})$, where

$$C < \min_{|x|=r} V_0 (x) = \lambda_{\min} (P_0) r^2,$$

here $P_0$ was defined by (6.0), $\lambda_{\min} (P_0)$ denotes a minimum eigenvalue of $P_0$, i.e.

$$\lambda_{\min} (P_1) = \min \{b_{11}, b_{22}, b_{33}\}$$

and

$$r \leq \sqrt{K_1^2 + K_2^2 + K_3^2}.$$

Moreover, for some $C > 0$ the inclusion $\Omega_C \subset \Omega_K$ means the existence of $C > 0$ so that $x \in \Omega_C$ implies $x \in \Omega_K$, i.e.

$$0 \leq x_i \leq K_i, K_i > \lambda_{\min} (P_1).$$

Theorem 6.1. Assume that all conditions of Theorem 6.1 are satisfied. Then the basin of multiphase attraction set of the point $E_1 (\gamma,0,0)$ belongs to the set $\Omega_C \subset \Omega_K \cap \Omega_\gamma \cap B_r (\bar{x})$, where $\Omega_\gamma$ was defined by (5.9), the positive constant $C$ and $r$ were defined in bellow.

**Proof.** Let us now find the set $\Omega_C \subset B_r (\bar{x})$, where

$$C < \min_{|x-\bar{x}|=r} V_1 (x) = \lambda_{\min} (P_1) \frac{\eta}{\mu_0}, \bar{x} = (\gamma,0,0), P_1 (\lambda) = |B_1 - \lambda|,$$

here $B_1$ is a matrix defined by (5.5), $\lambda_{\min} (P_1)$ denotes a minimum eigenvalue of $P_1$, $\eta, \mu_0$ were defined by (5.10) and (5.11). Moreover, for some $C > 0$ the inclusion $\Omega_C \subset \Omega_\gamma$ means the existence of $C > 0$ so that $x \in \Omega_C$ implies $x \in \Omega_\gamma$, i.e.

$$0 \leq x_i \leq K_i, x_1 \leq \frac{1}{\alpha_1 + 2\mu_1} [\alpha_2 x_2 + \alpha_3 x_3],$$

$\alpha_i, \mu_i$ were defined by (5.9).

So,

$$x \in B_r (\bar{x}) = \{x \in \mathbb{R}^3, |x-\bar{x}| < r_0 \},$$

where

$$r_0 = \min \left\{ \left( \frac{\mu_0}{\mu_1 \gamma^2} \right)^{-\frac{1}{2}}, \left[ 2\gamma^2 + (2\zeta_2^2 + 1) K_2^2 + \zeta_2^2 K_3^2 \right]^{-\frac{1}{2}} \right\},$$

$$\zeta_2 = \left| \frac{\alpha_2}{\alpha_1 + 2\mu_1} \right|, \zeta_3 = \left| \frac{\alpha_3}{\alpha_1 + 2\mu_1} \right|.$$

Then we obtain that

$$C < \min_{|x-\bar{x}|=r} V_1 (x) = \lambda_{\min} (P_1) \bar{r}^2,$$
i.e.\[ C < \lambda_{\min}(P_1) \bar{r}^2, \ r = \min \{ r_0, \ \bar{r} \}. \]

Then we obtain that\[ C < \min _{|x-\bar{x}|=\bar{r}} V_1(x) = \lambda_{\min}(P_1) \bar{r}^2, \]
i.e.\[ C < \lambda_{\min}(P_1) \bar{r}^2, \ r = \min \{ r_0, \ \bar{r} \}. \]

Now, we consider the equilibria point \( E_2(0, \delta, 0) \) and prove the following result

**Theorem 6.2.** Assume all conditions of Theorem 5.2 are satisfied. Then the basin of multiphase attraction set of \( E_2(0, \delta, 0) \) belongs to the set \( \Omega_C \subset \Omega_K \cap \Omega_3 \cap B_r(\bar{x}) \), where \( \Omega_3 \) was defined by (5.3) and
\[
\Omega_C = \{ x \in \mathbb{R}^3: V_2(x) \leq C \} , \ \bar{x} = (0, \delta, 0),
\]
here \( V_2(x) \) was defined by (6.2), the constants \( C \) and \( r \) are defined in bellow.

**Proof.** We will find \( C > 0 \) such that \( \Omega_C \subset \Omega_K \cap B_r(\bar{x}) \). It is clear to see that \( \Omega_C \subset B_r(\bar{x}) \), when
\[
C < \min _{|x-\bar{x}|=r} V_2(x) = \lambda_{\min}(P_2) r^2, \ \bar{x} = (0, \delta, 0),
\]
here \( \lambda_{\min}(P_2) \) denotes a minimum eigenvalue of \( P_2 \), i.e.
\[
\lambda_{\min}(P_2) = \min \left\{ \frac{1}{2d_3}, \left( \frac{b_{22} + \frac{1}{2r_2}}{r_2} \right) \pm \sqrt{\frac{b_{11}^2 + b_{12}^2 + \frac{1}{4r_2^2} - \frac{b_{14}}{r_2}}{2}} \right\}.
\]

Moreover, for some \( C > 0 \) the inclusion \( \Omega_C \subset \Omega_3 \) means the existence of \( C > 0 \) so that \( x \in \Omega_C \) implies \( x \in \Omega_3 \), i.e.
\[
x \in \Omega_K, x_2 \leq \beta x_1, \ \beta = -\frac{2\delta \mu_1 g_1(v)}{[2b_{12}g_2(v)(\delta - r_2) + 2\mu_0 \delta]}, \quad (6.1)
\]
So, \( x \in B_{\bar{r}}(\bar{x}) \), where \( \mu_i \) were defined by (5.15) and
\[
\bar{r} = \left[ K_1^2 + \beta^2 (K_1 - \delta)^2 + K_3^2 \right]^{1/2}.
\]
Then we obtain that\[ C < \min _{|x|=r_0} V_2(x) = \lambda_{\min}(P_2) r_0^2, \]
i.e.\[ C < \lambda_{\min}(P_2) r^2 \text{ for } r = \min \{ r_0, \ \bar{r} \}. \]

**Remark 6.1.** It is clear to see that if \( a_{21} \geq \frac{a_{12} - 1}{r_2^2} \), then the assumption (3) is satisfied. Moreover, if \( a_{12} + \frac{1}{2} (1 + a_{13}) > r_2 \), then the assumption (4) holds.
Remark 6.2. The assumptions (3) and $\mu_i > 0$ can be realized in terms of coefficients of (1.3) by using (5.20).

Conclusion. 1. Multipoint Initial Condition (MIC): The condition determining initial state of complex system consisted of tumor cells, Immune cells – natural killer and host cells densities at the beginning of observation; this condition is can be enriched with addition to the system drug concentration.

2. MIC is operated not only by changing the concentrations of the complex system parameters, but also taking into account the impact of the drug effects on the parameters, in order to direct the system to possible equilibrium points.

3. The possible equilibrium points can be selected and reached by the help by changing the situation in behalf of a new, more effective equilibrium point, one of multimodal attraction points, which multimodal attraction basin is consisted of. This operation drifts the complex system into situation, where Tumor Cells are trying to reach at least “Dormant State” that creates new chance to get more important condition as healthy attraction point, which can be estimated as globally stable condition.

   a) All these operations are traced beginning local lipschitz condition (Theorem 2.1) application to IVP, being developed to global lipschitz condition (Theorem 2.2). The conditions make it possible to figure out positive multiphase attractor and multiphase basin;

   b) By the help of Remarks (3.1) and (3.2.) the equilibrium points are described. These points relate to situation impeding tumor cell growth;

   c) Theorem (4.1) makes it possible to reach asymptotically stable point (point, the function in the included conditions continuously approaches the point) depending on relationships between kill rate of drug and rate of tumor cell proliferation. Rate of Immune cell killing by tumor cells is also considered for reaching the point. For reaching the target, condition of positivity in relationships between combinations of different rates (cii) were included;

   d) By the help of Theorems (4.1. – 4.7.), the main parametric conditions are proved and determined for strong multipoint attractor, corresponding to suppression of tumor growth, the possible healthy stable point in Multimodal attraction basin;

   e) The important condition as a strong impact on tumor growth is reached by proving theorems (5.0. – 5.2) as global stability of equilibria points and multiphase attraction sets;

   f) Theorems (6.0. – 6.2.) describe the condition determining Multiphase Attraction Set Basin, within which tumor cells are successfully suppressed;

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, with addition another one vector as a
drug, negatively or positively converging to the basins of attractions, depending on their importances for the complex system consisted of the four factors. 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 local 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.

It is reasonable to observe of patients, to get analysis (e.g. the status of blood cells shown above) at different times that determines the states patient at these times (maltipoint times) and its correlation. Moreover, to define the system to be in stable, healthy state if it is in the basin of multimodal attraction healthy point. Furthermore, it is reasonable that a mathematical model of such a system should include at least two stable multimodal attracting basin, one of which is considered “healthy” and another which is “diseased”. For if this were not the case, we would not observe both types of behavior. A system with only an multipoint attracting healthy state would never need to be treated, since it would naturally move back to this state despite any exogenous shock. On the other hand, a system with no multimodal attracting healthy state would never stay cured, and no remission from disease would ever be observed.

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