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On the dynamics of a cancer tumor growth model with multiphase structure

Abstract

In this paper, we study a phase-space analysis of a mathematical model of tumor growth with an immune response. Mathematical analysis of the model equations with multipoint initial condition, regarding to dissipativity, boundedness of solutions, invariance of non-negativity, nature of equilibria, local and global stability will be investigated. We study some features of behavior of one three-dimensional tumor growth model with dynamics described in terms of densities of three cells populations: tumor cells, healthy host cells and effector immune cells. We find the upper and lower bounds for the effector immune cells population, with $t \to \infty$. Further, we derive 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 equilibrium point; the healthy equilibrium point; the “death” equilibrium point are examined. Biological implications of our results are considered.

Keywords: Cancer tumour model, Mathematical modelling, Immune system, Positively invariant domain, Stability, Attraction sets

1. Introduction

Beginning with this article we intend to attempt to investigate the problems of Mathematical and Biological approaches to modelings of 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. This 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 – 10]. 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, the development of powerful cancer immunotherapies requires first an understanding of the mechanisms governing the dynamics of tumor growth. One of main reasons for a 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 ordinary differential equations and dynamical systems theory. In this paper we examine the dynamics of one cancer growth model proposed in [5] but possess mutiphase structure, i.e. we consider the dynamical system

\[
\begin{align*}
\dot{T} &= r_1 T (1 - k_1^{-1} T) - a_{12} NT - a_{13} TI, \\
\dot{N} &= r_2 N (1 - k_2^{-1} N) - a_{21} NT, \\
\dot{I} &= \frac{r_3 I}{k_3 + T} - a_{31} IT - d_3 I,
\end{align*}
\]

(1.1)

with multipoint initial condition

\[
\begin{align*}
T(t_0) &= T_0 + \sum_{k=1}^{m} \alpha_{1k} T(t_k), \\
N(t_0) &= N_0 + \sum_{k=1}^{m} \alpha_{2k} N(t_k), \\
I(t_0) &= I_0 + \sum_{k=1}^{m} \alpha_{3k} I(t_k),
\end{align*}
\]

(1.2)

where \(T = T(t), N = N(t), I = I(t)\) denote the density of tumor cells, healthy host cells and the effector immune cells, respectively at the moment \(t\), \(\alpha_{jk}\) are real numbers and \(m\) is a natural number. 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.

One of main aim is derivation of sufficient conditions under which the possible biologically feasible dynamics is local and global stable and a convergence 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. Note that the local and global stability properties of (1.1) with 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 attraction in which it starts.

By scaling $x_1 = Tk_1^{-1}$, $x_2 = NK_2^{-1}$, $x_3 = Ik_3^{-1}$, $\hat{t} = r_1 t$ in (1.1) - (1.2) and omitting the tilde notation we obtain the multipoint initial value problem (IVP)

\[
\begin{align*}
\dot{x}_1 &= x_1 (1 - x_1) - a_{12} x_1 x_2 - a_{13} x_1 x_3, \\
\dot{x}_2 &= r_2 x_2 (1 - x_2) - a_{21} x_1 x_2, \\
\dot{x}_3 &= \frac{r_3 x_1 x_3}{x_1 + k_3} - a_{31} x_1 x_3 - d_3 x_3, \quad t \in [0, T),
\end{align*}
\]

(1.3)

\[
\begin{align*}
x_1 (t_0) &= x_{10} + \sum_{k=1}^{m} \alpha_{1k} x_1 (t_k), \\
x_2 (t_0) &= x_{20} + \sum_{k=1}^{m} \alpha_{2k} x_2 (t_k), \\
x_3 (t_0) &= x_{30} + \sum_{k=1}^{m} \alpha_{3k} x_3 (t_k), \\
& \quad t_0 \in [0, T), \quad t_k \in (0, T),
\end{align*}
\]

(1.4)

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

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

(1.5)

Note that, for $\alpha_{j1} = \alpha_{j2} = ... \alpha_{jm} = 0$ the problem (1.3) - (1.4) turns to be the classical IVP

\[
\begin{align*}
\dot{x}_1 &= x_1 (1 - x_1) - a_{12} x_1 x_2 - a_{13} x_1 x_3, \\
\dot{x}_2 &= r_2 x_2 (1 - x_2) - a_{21} x_1 x_2, \\
\dot{x}_3 &= \frac{r_3 x_1 x_3}{x_1 + k_3} - a_{31} x_1 x_3 - d_3 x_3, \quad t \in [0, T],
\end{align*}
\]

(1.6)

\[
\begin{align*}
x_1 (t_0) &= x_{10}, \\
x_2 (t_0) &= x_{20}, \\
x_3 (t_0) &= x_{30}, \quad t_0 \in [0, T).
\end{align*}
\]

2. Notations and background.

Consider the multipoint IVP for nonlinear equation

\[
\frac{du}{dt} = f(u), \quad t \in [0, T],
\]

(2.1)

\[
u (t_0) = u_0 + \sum_{k=1}^{m} \alpha_k u (t_k), \quad t_0 \in [0, T), \quad t_k \in (0, T),
\]
in a Banach space $E$, where $\alpha_k$ are complex numbers and $m$ is a natural number and $u = u(t)$ is a $E$ valued function. Note that, for $\alpha_1 = \alpha_2 = ... \alpha_m = 0$ the problem (2.1) become to be the following local Cauchy problem

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

(2.2)

We can generalized classical Picard existence theorem for nonlocal nonlinear problem (2.1), i.e. by reasoning as a classical case we obtain

**Theorem 2.1.** Let $X$ be a Banach space. Suppose that $f : X \to X$ satisfies local Lipschitz condition on a closed ball $\bar{B}_r(v_0) \subset X$, where $r > 0$, i.e.

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

for each $u, v \in \bar{B}_r(v_0)$, where

$$v_0 = u_0 + \sum_{k=1}^{m} \alpha_k u(t_k)$$

and there exists $\delta > 0$ such that

$$t_k \in O_\delta(t_0) = \{ t \in \mathbb{R} : |t - t_0| < \delta \}.$$

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 $\delta \leq \frac{r}{M}$.  

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

$$u = v_0 + \int_{t_0}^{t} f(u(s)) \, ds.$$

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

$$Y = C([-\eta, \eta]; \bar{B}_r(v_0)).$$

Let

$$Qu = v_0 + \int_{t_0}^{t} f(u(s)) \, ds.$$

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

$$\|Qu - v_0\|_X \leq \left\| \int_{t_0}^{t} f(u(s)) \, ds \right\|_X \leq M \eta < r.$$
Hence, $Qu \in Y$ so that $Q : Y \to Y$. Moreover, for all $u, v \in Y$ we have

$$
\|Qu - Qv\|_X \leq \left\| \int_{t_0}^{t} [f(u(s)) - f(v(s))] \, ds \right\|_X \leq L_f \eta \|u - v\|_X ,
$$

where $L_f$ is a Lipschitz constant for $f$ on $\bar{B}_r(v_0)$. Hence, if we choose

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

then $Q$ is a contraction on $Y$ and it has a unique fixed point. Since $\eta$ depends only on the Lipschitz constant of $f$ and on the distance $r$ of the initial data from the boundary of $\bar{B}_r(v_0)$, repeated application of this result gives a unique local solution defined for $|t - t_0| < \frac{\eta}{M}$.

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

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

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

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

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

**Proof.** The key point of proof is to show that the constant $\delta$ of Theorem 2.1 can be made independent of the $v_0$. It is not hard to see that the independence of $v_0$ comes through the constant $M$ in them $\frac{r}{M}$ 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.

**3. Boundedness, invariance of non-negativity, and dissipativity**

In this section, we shall show that the model equations are bounded with negative divergence, positively (non-negatively) invariant with respect to a region in $R^3_+$ and dissipative. As we are interested in biologically relevant solutions of the system, the next two results show that the positive octant is invariant and that all trajectories in this octant are recurrent. Let

$$
B = \{ x = (x_1, x_2, x_3) \in R^3_+: 0 \leq x_i \leq K_i, \; i = 1, 2, 3 \} .
$$
Theorem 3.1. Assume
\[ d_3 > 1 + r_2, \quad r_i > 0, \quad k_i > 0, \quad a_{ij} > 0, \quad r_3 < k_3 a_{31}. \] (3.1)

Then:
1. \( B \) is positively invariant with respect to (1.2) – (1.3);
2. all solutions of problem (1.2) – (1.3) with initial values \( x_{i0} > 0 \) are uniformly bounded and are attracted into the region \( B \);
3. the system (1.2) is with negative divergence;
4. the system (1.2) is dissipative.

Proof. (1); Consider the first equation of the system (1.2):
\[ \dot{x}_1 = x_1 (1 - x_1) - a_{12} x_1 x_2 - a_{13} x_1 x_3. \]

By condition (3.1) we get
\[ \dot{x}_1 < x_1 (1 - x_1). \]

It is clear that
\[ x_1 (1 - x_1) = 0, \quad \frac{d}{dx_1} [x_1 (1 - x_1)] = 1 - 2x_1 < 0 \]
for \( x_1 = 1 \). Thus
\[ x_1 (t) \leq \max \left\{ 1, \ x_{10} - \sum_{k=1}^{m} \alpha_{1k} x_1 (t_k) \right\}, \]
\[ \dot{x}_1 < 0 \text{ for } x_1 > 1. \]

Hence,
\[ \limsup_{t \to \infty} x_1 (t) \leq K_1 = 1. \] (3.2)

For
\[ \dot{x}_2 = r_2 x_2 (1 - x_2) - a_{21} x_1 x_2, \]
a similar analysis gives
\[ x_2 (t) \leq \max \left\{ K_2, \ x_{20} - \sum_{k=1}^{m} \alpha_{2k} x_2 (t_k) \right\}, \]
\[ \limsup_{t \to \infty} x_2 (t) \leq K_2. \] (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

\[ x_3(t) \leq \max \left\{ K_3, \ x_{30} - \sum_{k=1}^{m} a_{1k} x_3(t_k) \right\}, \]

\[ \limsup_{t \to \infty} x_3(t) \leq K_3. \] (3.4)

Hence, from (3.2) – (3.4) we obtain (1) and (2) assumptions.

Now, let us show (3)-(4). Since

\[
\begin{align*}
\frac{\partial f_1}{\partial x_1} + \frac{\partial f_2}{\partial x_2} + \frac{\partial f_3}{\partial x_3} &= 1 - 2x_1 - a_{12} x_2 + r_2 - 2r_1 x_2 - a_{21} x_1 + \\
r_3 x_1 - a_{31} x_1 - d_3 &= (1 + r_2 - d_3) - (2 + a_{21}) x_1 - \\
(2r_1 + a_{12}) x_2 + \left[ \frac{r_3}{x_1 + k_3} - a_{31} \right] x_1.
\end{align*}
\] (3.5)

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 (1.2) is with negative divergence and is dissipative.

### 4.1 The equilibria, existence and local stability

The equilibria of system (1.2) are obtained by solving the system of isocline equations

\[ x_1 (1 - x_1) - a_{12} x_1 x_2 - a_{13} x_1 x_3 = 0, \]

\[ r_2 x_2 (1 - x_2) - a_{21} x_1 x_2 = 0, \] (4.1)

\[ \frac{r_3 x_1 x_3}{x_1 + k_3} - a_{31} x_1 x_3 - d_3 x_3 = 0. \]

Since we are interested in biologically relevant solutions of (4.1) we find sufficient conditions under which this system have positive solutions.

**Condition 4.1.** Assume:

1. \( r_3 > d_3 + a_{31} k_3; \)
2. \( (r_3 - a_{31} k_3 - d_3)^2 \geq 4d_3 k_3 a_{31}. \)
Lemma 4.1. Let the Condition 4.1 hold. Then the system (1.2) have the following equilibria points

\[ E_0(0,0,0), E_1(1,0,0), E_2(0,1,0), E \left( \frac{r_2}{a_{21}}, 0, \frac{a_{21} - r_2}{a_{13}a_{21}} \right), \]

\[ E_{ij}(x_{1i}, x_{2j}, x_{3ij}), \quad i = 1, 2, \quad j = 0, 1, 2, \quad \text{(4.2)} \]

where the points \( E_{ij}(\bar{x}_1, \bar{x}_2, \bar{x}_3) \) will be defined below.

Proof. The possible equilibria are of the form

\[ E_0(0,0,0), E_1(1,0,0), E_2(0,1,0), E_3 \left( \frac{r_2}{a_{21}}, 0, \frac{a_{21} - r_2}{a_{13}a_{21}} \right), E_{ij}(\bar{x}_1, \bar{x}_2, \bar{x}_3). \]

It is clear to see that the points \( E_0, E_1 \) and \( E_2 \) are equilibria points. It remain to find the points \( E_{ij} = E_{ij}(\bar{x}_1, \bar{x}_2, \bar{x}_3) \).

From the third equation of (4.1) for \( x_3 \neq 0 \) we have

\[ \frac{r_3 x_1}{x_1 + k_3} - a_{31} x_1 - d_3 = 0, \]

i.e. we have the following square algebraic equation

\[ a_{31} x_1^2 + (a_{31} k_3 + d_3 - r_3) x_1 + d_3 k_3 = 0. \quad \text{(4.3)} \]

By solving the equation (4.3) we get

\[ x_1 = \frac{-(a_{31} k_3 + d_3 - r_3) \pm \sqrt{D}}{2a_{31}}, \]

where

\[ D = (a_{31} k_3 + d_3 - r_3)^2 - 4d_3 k_3 a_{31} \geq 0. \]

Hence,

\[ x_{11} = \frac{-(a_{31} k_3 + d_3 - r_3) + \sqrt{D}}{2a_{31}}, \quad x_{12} = \frac{-(a_{31} k_3 + d_3 - r_3) - \sqrt{D}}{2a_{31}}. \quad \text{(4.4)} \]

From first and second equation of (4.1) we have

\[ (1) \quad x_1 = \frac{r_2}{a_{21}}, \quad x_2 = 0, \quad x_3 = \frac{a_{21} - r_2}{a_{13}a_{21}}, \]

i.e. the point \( E \left( \frac{r_2}{a_{21}}, 0, \frac{a_{21} - r_2}{a_{13}a_{21}} \right) \) is a equilibria point; By taking (4.4) in the second equation of (4.1) we get

\[ (2) \quad x_1 > 0, \quad x_2 = \frac{r_2 - a_{21} x_1}{r_2}, \quad x_2 \neq 0; \]
For the case of (2) we get

\[ x_{21} = \frac{r_2 - a_{21}x_{11}}{r_2}, \quad x_{22} = \frac{r_2 - a_{21}x_{12}}{r_2}, \]  

(4.5)

Moreover, by taking (4.5) in the first equation of (4.1) we obtain

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

(4.6)

Thus we obtain that the points (4.2) are equilibria points the Jacobian matrix due to liberalization of the system (1.2), where \( x_{1i}, x_{2j}, x_{3ij}, i, j = 1, 2 \) are defined by (4.4) – (4.6).

**Remark 4.1.** For \( a_{21} > r_2 \) the system (1.2) have the biologically feasible equilibria points

\[ E_0 (0, 0, 0), E_1 (1, 0, 0), E_2 (0, 1, 0), E_3 \left( \frac{r_2}{a_{21}}, 0, \frac{a_{21} - r_2}{a_{13}a_{21}} \right). \]

Indeed, our system (1.2) describe the biological possess we have to consider this system in positive domain. So, all roots of (4.1) must be positive. For case of (2) \( x_{11} > 0 \) and \( x_{12} < 0 \) when \( r_3 > d_3 + a_{31}k_3 \); for \( r_3 < d_3 + a_{31}k_3 \) both roots \( x_{11}, x_{12} \) are negative; the root \( x_3 \) is positive if \( x_1 < 1 \), i.e.

\[ r_3 - \left( a_{31}k_3 + d_3 \right) + \sqrt{D} < 2a_{31}. \]  

(4.7)

The roots \( x_{21}, x_{22} \) are positive when

\[ r_3 \geq d_3 + a_{31}k_3 + D. \]  

(4.8)

Moreover, \( x_{3ij}, i, j = 1, 2 \) positive when

\[ a_{12} < 1, \quad a_{12}a_{21} < r_2 \quad \text{or} \quad a_{12} > 1, \quad a_{12}a_{21} > r_2. \]  

(4.9)

Hence, if Condition 4.1 and (4.7)-(4.9) are satisfied, then the equilibria points (4.2) belong to positive domain

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

**Remark 4.2.** There exist 3 type dead case: (1) for equilibrium \( E_0 (0, 0, 0) \) three type cell population are zero; (2) for point \( E_1 (1, 0, 0) \) tumor cells survive but normal and immune cells population are zero; (3) for point \( E (a, 0, b) \) normal cells are zero but tumor and immune cells population are survived; (4) \( E_2 (0, 1, 0) \)-tumor-free and immune free case; in this category, normal cells survive but tumor and immune cells population are zero; (5) The equilibrium points \( E_{ij} (x_{1i}, x_{2j}, x_{3ij}), i = 1, 2, j = 0, 1, 2 \) correspond the cases when tumor, normal and immune population are survived. We now discuss the (local) linearized stability of system (1.2) – (1.3) restricted to a neighborhood of the equilibrium points (4.2).
The Jacobian matrix due to the liberalization of \((1.2)\) about an arbitrary equilibrium point \(E(x_1, x_2, x_3)\) is given by

\[
A_{E(x_1, x_2, x_3)} = \begin{bmatrix}
1 - 2x_1 - a_{12}x_2 - a_{13}x_3 & -a_{12}x_1 & -a_{13}x_1 \\
a_{21}x_2 & r_2 - 2r_2x_2 - a_{21}x_1 & 0 \\
\frac{k_1r_1x_1}{(x_1 + k_1)} & a_{31}x_3 & 0 - a_{31}x_1 - d_3
\end{bmatrix}.
\]

The linearized matrices for equilibria points \(E_0(0, 0, 0), E_1(1, 0, 0), E_2(0, 1, 0)\) will be correspondingly as:

\[
A_0 = \begin{bmatrix}
1 & 0 & 0 \\
0 & r_2 & 0 \\
0 & 0 & -d_3
\end{bmatrix},
A_1 = \begin{bmatrix}
-1 & -a_{12} & 0 \\
0 & r_2 - a_{21} & 0 \\
0 & 0 & \frac{r_3a}{1+k_3} - a_{31} - d_3
\end{bmatrix},
A_2 = \begin{bmatrix}
1 - a_{12} & 0 & 0 \\
-a_{21} & -r_2 & 0 \\
0 & 0 & -d_3
\end{bmatrix}.
\]

Then we have the linearized matrices for equilibria points \(E_3(a, 0, b)\):

\[
A_3 = A_{E(a, 0, b)} = \begin{bmatrix}
-a & -a_{12}a & -a_{13}a \\
0 & r_2 - a_{21}a & 0 \\
\left(\frac{k_1r_1a}{(a+k_1)} - a_{31}\right)b & 0 & \frac{r_3a}{a+k_3} - a_{31}a - d_3
\end{bmatrix},
\]

where

\[
a = \frac{r_2}{a_{21}}, \quad b = \frac{a_{21} - r_2}{a_{13}a_{21}}.
\]

In a similar way, we find that the linearized matrices \(A_{ij}\) for equilibria points \(E_{ij}\) is the following

\[
A_{ij} = A_{E(x_{1i}, x_{2j}, x_{3k})} = \begin{bmatrix}
1 - 2x_{1i} - a_{12}x_{2j} - a_{13}x_{3j} & -a_{12}x_{1i} & -a_{13}x_{1i} \\
a_{21}x_{2j} & r_2 - 2r_2x_{2j} - a_{21}x_{1i} & 0 \\
\frac{k_1r_1x_{1i}}{(x_{1i} + k_1)} & a_{31}x_{3j} & 0 - a_{31}x_{1i} - d_3
\end{bmatrix}.
\]

5. **Local stability analysis of points** \(E_0(0, 0, 0)\) and \(E_1(0, 1, 0)\)

In this section we show the following result:

**Theorem 5.1.** (1) The point \(E_0\) is an unstable point for the linearized system of \((1.2)\); (2) The point \(E_1\) is locally asymptotically stable point for the linearized system of \((1.2)\) when \(a_{21} > r_2, a_{31} + d_3 > \frac{r_3}{1+k_3}\) and is an unstable point when \(a_{21} < r_2\) and \(a_{31} + d_3 < \frac{r_3}{1+k_3}\); (3) The point \(E_2\) is locally asymptotically stable point for linearized system of \((1.2)\) when \(a_{12} > 1\) and is an unstable point when \(a_{12} < 1\).
Proof. Indeed, the eigenvalues of $A_{E_0(0,0,0)}$ are $1, r_2, -d_3$; eigenvalues of $A_1(1,0,0)$ are

$$-1, r_2 - a_{21}, \frac{r_3}{1 + k_3} - a_{31} - d_3;$$

and eigenvalues of $E_2(0,1,0)$ are

$$1 - a_{12}, -r_2, -d_3.$$ 

Since $1, r_2 > 0$, then by [5, Theorem 8.12] $E_0$ is unstable point. Due to negativity of $-1, r_2 - a_{21}, \frac{r_3}{1 + k_3} - a_{31} - d_3$ and $1 - a_{12}, -r_2, -d_3$ by [5, Theorem 8.12] we get that $E_1$ and $E_2$ are locally asymptotically stable points.

Now, consider the Jacobian matrices $A_{ij} = [b_{km}], k, m = 1, 2, 3$ to the linearized system of (1.2) on points $E_{ij}$ defined by (4.10). Let

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

$$b_{21}(ij) = -a_{21}x_{2i}, b_{22} = b_{22}(ij) = r_2 - 2r_2x_{2j} - a_{21}x_{1i},$$

$$b_{13} = b_{13}(ij) = -a_{13}x_{1i}, b_{31} = b_{31}(ij) =$$

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

Here we prove the following results:

**Theorem 5.2.** Assume the following conditions are satisfied:

1. $(a_{31}k_3 + d_3 - r_3)^2 \geq 4d_3a_{31};$
2. $\frac{x_{1i}x_{2j}}{k_1} < a_{31}x_{1i} + d_3$ and $2x_{1i} + a_{12}x_{2j} + a_{13}x_{3ij} + a_{31}x_{1i} > 1;$
3. $b_{11}b_{33} - b_{13}b_{31} > 0.$

Then the points $E_{ij}(x_{1i}, x_{2j}, x_{3ij})$ are locally asymptotically stable points to the linearized system of (1.2).

**Proof.** Eigenvalue of $A_{ij}$ are find as roots of the equations

$$|A_{ij} - \lambda| = \left| \begin{array}{ccc} b_{11}(ij) - \lambda & b_{12}(ij) & b_{13}(ij) \\ b_{21}(ij) & b_{22}(ij) - \lambda & 0 \\ b_{31}(ij) & 0 & b_{33}(ij) - \lambda \end{array} \right| = 0,$$

i.e.,

$$|A_{ij} - \lambda| = (b_{11} - \lambda)(b_{22} - \lambda)(b_{33} - \lambda) - b_{13}b_{31}(b_{22} - \lambda) -$$

$$b_{21}b_{13}(b_{33} - \lambda) = 0. \quad (5.1)$$

From (4.10) we get that if $\lambda = \lambda_1 = b_{33}$, then the equation (5.1) reduced to

$$(b_{22} - \lambda) [(b_{11} - \lambda)(b_{33} - \lambda) - b_{13}b_{31}] = 0,$$

i.e.,

$$\lambda^2 - (b_{11} + b_{33})\lambda + b_{11}b_{33} - b_{13}b_{31} = 0. \quad (5.2)$$
By solving (5.2) we obtain

\[
\lambda_2 = \frac{(b_{11} + b_{33}) + \sqrt{(b_{11} - b_{33})^2 + 4b_{13}b_{31}}}{2},
\]

\[
\lambda_3 = \frac{(b_{11} + b_{33}) - \sqrt{(b_{11} - b_{33})^2 + 4b_{13}b_{31}}}{2};
\]

Since \(b_{\mu\nu} = b_{\mu\nu}(ij)\), then eigenvalues \((\lambda_1, \lambda_2, \lambda_3)\) will depend on \(i, j\), i.e., the sets \((\lambda_1(ij), \lambda_2(ij), \lambda_3(ij))\) are eigenvalues of matrices \(A_{ij}\), respectively. Hence, by assumption (2) roots \(\lambda_2, \lambda_3\) of (5.2) are real and

\[
\lambda_1 = b_{33}(ij) = \frac{r_3x_{1i}}{x_{1i} + k_3} - a_{31}x_{1i} - d_3 < 0,
\]

\[
b_{11} + b_{33} = 1 - 2x_{1i} - a_{12}x_{2j} - a_{13}x_{3ij} + \frac{r_3x_{1i}}{x_{1i} + k_3} - a_{31}x_{1i} - d_3 < 0. \tag{5.4}
\]

Then from assumption (3) and from (5.2) - (5.4) we get that \(\lambda_k < 0, k = 1, 2, 3\) when

\[
(b_{11} - b_{33})^2 \geq -4b_{13}b_{31}.
\]

But \(\lambda_1\) is a negative number and \(\lambda_2, \lambda_3\) are complex numbers with negative real part, when

\[
(b_{11} - b_{33})^2 < -4b_{13}b_{31}.
\]

That is, under assumption (1)-(3) the points \(E_{ij}\) are locally asymptotically stable points of (1.2).

**Remark 5.1.** In view of assumptions (2), if

\[
\left[ a_{31} - \frac{k_3r_3}{(x_{1i} + k_1)^2} \right] x_{1i}x_{3ij} \geq 0,
\]

then condition (3) holds.

**Remark 5.2.** It is clear to see that the assumptions

\[
(b_{11} - b_{33})^2 \geq -4b_{13}b_{31}, \quad (b_{11} - b_{33})^2 < -4b_{13}b_{31}
\]

are satisfied under condition on coefficients of (1.2). One can fined this condition according its.

**Theorem 5.3.** Assume the following conditions are satisfied:

1. \((a_{31}k_3 + d_3 - r_3)^2 \geq 4d_3a_{31};\)
2. \(a_{31}x_{1i} + d_3 < \frac{r_3x_{1i}}{x_{1i} + k_3}\) and \(2x_{1i} + a_{12}x_{2j} + a_{13}x_{3ij} < 1;\)
3. \(b_{11}b_{33} - b_{13}b_{31} > 0.\)

Then the points \(E_{ij}(x_{1i}, x_{2j}, x_{3ij})\) are locally unstable points for the linearized system of (1.2).
Proof. Indeed, by assumption (2) roots $\lambda_2, \lambda_3$ of (4.8) are real and

$$\lambda_1 = b_{33} (ij) = \frac{r_3 x_{ij}}{x_{1i} + k_3} - a_{31} x_{1i} - d_3 > 0 \quad (5.5)$$

$$b_{11} + b_{33} = 1 - 2x_{1i} - a_{12} x_{2j} - a_{13} x_{3ij} + \frac{r_3 x_{ij}}{x_{1i} + k_3} - a_{31} x_{1i} - d_3 > 0.$$  

From assumption (3), from (5.5) and (5.2)–(5.3) we get that if $(b_{11} - b_{33})^2 \geq -4b_{13}b_{31}$, then $\lambda_k > 0$, $k = 1, 2, 3$. But if $(b_{11} - b_{33})^2 < -4b_{13}b_{31}$, then $\lambda_1$ is a positive number and $\lambda_2, \lambda_3$ are complex numbers with positive real part, i.e., under this assumptions the points $E_{ij} (x_{1i}, x_{2j}, x_{3ij})$ are locally unstable points of the system (1.2).

**Theorem 5.4.** Assume the following conditions are satisfied:

1. $(a_{31} k_3 + a_3 - r_3)^2 \geq 4d_3 a_{31};$
2. $b_{13} b_{33} - b_{13} b_{31} < 0.$

Then the points $E_{ij} (x_{1i}, x_{2j}, x_{3ij})$ are saddle points for the linearized system of (1.2).

Proof. Indeed, by assumption (2) eigenvalues $\lambda_2, \lambda_3$ are real and of opposite sign, i.e. $E_{ij} (x_{1i}, x_{2j}, x_{3ij})$ are saddle points of the system (1.2).

**Theorem 5.5.** Let (4.2) holds $b_{11} = b_{33} = 0$ and $b_{13} b_{22} b_{31} < 0$. Then $Tr A_{ij} = \lambda_1 + \lambda_2 + \lambda_3 = 0$ and $Det A_{ij} > 0$, i.e. the points $E (x_{1i}, x_{2j}, x_{3ij})$ are centers to linearized system of (1.2).

Proof. For $b_{11} + b_{33} = 0$ from (5.2) – (5.4) we get that eigenvalues $\lambda_2, \lambda_3$ are $\mp \psi, \omega \in \mathbb{R}$ when $(b_{11} - b_{33})^2 \geq -4b_{13}b_{31}$ and $\lambda_2, \lambda_3$ are $\mp i \psi$ when $(b_{11} - b_{33})^2 < -4b_{13}b_{31}$. Hence, for $b_{11} = b_{33} = 0$ we obtain

$$Tr A_{ij} = \lambda_1 + \lambda_2 + \lambda_3 = 0.$$  

Moreover,

$$Det A_{ij} = -b_{13} b_{22} b_{31} > 0,$$

i.e. we obtain the assertion.

**Remark 5.3.** For $b_{11} b_{33} - b_{13} b_{31} = 0$ we obtain

$$\lambda_2 = 0, \lambda_3 = \frac{(b_{11} + b_{33})}{2}.$$  

Now, consider the equilibria points $E_3 (a, 0, b).$

**Condition 5.6.** Assume:

1. $(a_{31} k_3 + a_3 - r_3)^2 \geq 4d_3 a_{31};$
2. $\frac{a_{21} r_3}{r_2 + a_{21} k_3} < a_{31} + \frac{a_{21} d_3}{r_2} + 1;$
3. $a_{31} + 1 > \frac{r_3}{k_3}, a = \frac{r_2}{a_{21}}, b = \frac{a_{21} - r_2}{a_{31} a_{21}}, a_{21} > \frac{r_2}{a};$
4. $c_{13} c_{33} - c_{13} c_{31} > 0.$

**Theorem 5.6.** Assume the Condition 5.6 hold. Then the point $E_3 (a, 0, b)$ is a locally asymptotically stable point for linearized system of (1.2).
Proof. Eigenvale of matrices $A_3$ are find as roots of the equations

$$|A_3 - \lambda| = \begin{vmatrix} c_{11} - \lambda & c_{12} & c_{13} \\ 0 & c_{22} - \lambda & 0 \\ c_{31} & 0 & c_{33} - \lambda \end{vmatrix} = 0,$$

i.e.,

$$|A_3 - \lambda| = (c_{11} - \lambda) (c_{22} - \lambda) (c_{33} - \lambda) - c_{13} c_{31} (c_{22} - \lambda) = (c_{22} - \lambda) [\lambda^2 - (c_{11} + c_{33}) \lambda + c_{11} c_{33} - c_{13} c_{31}] = 0,$$

where

$$c_{11} = -a, c_{12} = -a_{12} a, c_{13} = -a_{13} a, c_{22} = r_2 - a_{21} a,$$

$$c_{31} = \left( \frac{k_1 r_3}{(a + k_1)^2} - a_{31} \right) b, c_{33} = \frac{r_3 a}{a + k_3} - a_{31} a - d_3.$$

From (5.6) we get that $\lambda = \lambda_1 = c_{22}$ is one of eigenvale of $A_3$ and rest eigenvales are the root of the equation

$$[\lambda^2 - (c_{11} + c_{33}) \lambda + c_{11} c_{33} - c_{13} c_{31}] = 0. \quad (5.7)$$

By solving (5.7) we obtain

$$\lambda_2 = \frac{(c_{11} + c_{33}) + \sqrt{(c_{11} - c_{33})^2 + 4 c_{13} c_{31}}}{2}, \quad (5.8)$$

$$\lambda_3 = \frac{(c_{11} + c_{33}) - \sqrt{(c_{11} - c_{33})^2 + 4 c_{13} c_{31}}}{2};$$

The set $(\lambda_1, \lambda_2, \lambda_3)$ are eigenvales of matrices $A_3$, respectively. Hence, by assumption (3) and (2) we get

$$\lambda_1 = r_2 - a_{21} a < 0, \quad c_{11} + c_{33} = -a + \frac{r_3 a}{a + k_3} - a_{31} a - d_3 < 0. \quad (5.9)$$

Then from (5.6) - (5.9) we get that $\lambda_k < 0, \ k = 1, 2, 3$ when

$$(c_{11} - c_{33})^2 \geq -4 c_{13} c_{31}. \quad (5.10)$$

But $\lambda_1$ is negative and $\lambda_2, \lambda_3$ are complex numbers with negative real part when

$$(c_{11} - c_{33})^2 < -4 c_{13} c_{31}. \quad (5.11)$$

That is, under assumption (1)-(3) the point $E_3 (a, 0, b)$ is a locally asymptotically stable point of the system (1.2).

Theorem 5.7. Assume the the following conditions are satisfied:

1. $(a_{31} k_3 + d_3 - r_3)^2 \geq 4 d_3 a_{31},$
2. $\frac{a_{21} r_3}{r_2 + a_{21} k_3} > a_{31} + \frac{a_{21} a_{33}}{r_2} + 1, \ a_{21} < \frac{r_2}{a}.$
Then the point \( E_3(a, 0, b) \) is a locally unstable point for (1.2)

**Proof.** Indeed, by assumption (2) roots \( \lambda_2, \lambda_3 \) of (4.16) are real and

\[
\lambda_1 = c_{22} = r_2 - a_{21}a > 0,
\]

\[
c_{11} + c_{33} = -a + \frac{r_3a}{a + k_3} - a_{31}a - d_3 > 0.
\]

(5.12)

Then from assumption (3) and from (5.7), (5.8), (4.12) we get that \( \lambda_k < 0 \), \( k = 1, 2, 3 \) when \( (c_{11} - c_{33})^2 > -4c_{13}c_{31} \). But if \( (c_{11} - c_{33})^2 < -4c_{13}c_{31} \), then \( \lambda_1 < 0 \) and \( \lambda_2, \lambda_3 \) are complex numbers with negative real part. That is, under assumption (1)-(3) the points \( E(a, 0, b) \) are locally unstable points for (1.2).

**Theorem 5.8.** Let the assumption (4.2) hold and \( b_{11}b_{33} - b_{13}b_{31} > 0 \). Then, the dimensions of the stable manifold \( W^+ \) and unstable manifold \( W^- \) are given, respectively, by

\[
\dim W^+ (E_{ij}(x_1i, x_2j, x_{3ij})) = 2, \quad \dim (W^- E_{ij}(x_1i, x_2j, x_{3ij})) = 2.
\]

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

\[
A_{ij}x = \lambda x,
\]

i.e. consider the system of homogenous linear equation

\[
(b_{11} - \lambda) x_1 + b_{12}x_2 + b_{13}x_3 = 0,
\]

\[
b_{21}x_1 + (b_{22} - \lambda) x_2 = 0,
\]

\[
b_{31}x_1 + (b_{33} - \lambda) x_3 = 0,
\]

(5.13)

where

\[
b_{\mu\nu} = b_{\mu\nu} (ij), \mu, \nu = 1, 2, 3, i = 1, 2, \quad j = 0, 1, 2.
\]

By solving of (5.13) we obtain that the subspaces

\[
B (x_1i, x_2j, x_{3ij}) = \left\{ x = \begin{pmatrix} 0, & -\frac{b_{21}}{b_{22} - \lambda}, & -\frac{b_{31}}{b_{33} - \lambda} \end{pmatrix} a \in \mathbb{R}^3 \right\}
\]

(5.14)

are eigenspaces of matrices \( A_{ij} \), where \( a \) is arbitrary number from \( \mathbb{R} \).

Let the assumption (2) of Theorem 5.2 are hold, then we get that

\[
B (x_1i, x_2j, x_{3ij}) = W^+ (E_{ij}(x_1i, x_2j, x_{3ij}));
\]

if the assumption (2) of Theorem 5.3 are hold, then we have

\[
B (x_1i, x_2j, x_{3ij}) = W^- (E_{ij}(x_1i, x_2j, x_{3ij})).
\]

In view of (5.14) we obtain the assertion.

In a similar way we obtain
Theorem 5.9. Let the assumption (4.2) hold and \( b_{11}b_{33} - b_{13}b_{31} \leq 0 \). Then, the dimensions of the hyperbolic saddle manifold \( W^0 \) are given and

\[
\text{Dim } W^0 (E_{ij} (x_{1i}, x_{2j}, x_{3ij})) = 2.
\]

Definition 5.1. A set \( A \subset S \) is called a strong 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. The \( B \) is a strong attractor set with respect to \( R^3_+ \).

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

6. Global stability of equilibria points

In this section, we derive the sufficient conditions for the global stability to system (1.2) on the domain \( B \subset R^3_+ \) defined by (3.0). Consider the equilibria point \( E(\bar{x}_1, \bar{x}_2, \bar{x}_3) \).

Theorem 6.1. Assume the following conditions are satisfied:

1. \( \bar{x} = (\bar{x}_1, \bar{x}_2, \bar{x}_3) \in B \) is a local asymptotic stable point of linearized system (1.2);
2. \( a_{13}d_3 > r_3 \);
3. \((a_{31}k_3 + d_3 - r_3)^2 \geq 4d_3a_{31} \).

Then the equilibria solution \( \bar{x} = (\bar{x}_1, \bar{x}_2, \bar{x}_3) \) is global stable in the sense of Lyapunov.

Proof. Consider the candidate of Lyapunov function \( V(x) \) defined by

\[
V(x) = \sum_{i,j=1}^{3} d_{ij} (x_i - \bar{x}_i)(x_j - \bar{x}_j), \quad d_{ij} \in \mathbb{R} \text{ and } a_{ij} = a_{ji}.
\]  

(6.1)

It is clear that

\[
V(x) = (x - \bar{x})^T A(x - \bar{x}) =
\]

\[
[x_1 - \bar{x}_1, x_2 - \bar{x}_2, x_3 - \bar{x}_3] \begin{bmatrix}
  d_{11} & d_{12} & d_{13} \\
  d_{21} & d_{22} & d_{23} \\
  d_{31} & d_{32} & d_{33}
\end{bmatrix}
\begin{bmatrix}
  x_1 - \bar{x}_1 \\
  x_2 - \bar{x}_2 \\
  x_3 - \bar{x}_3
\end{bmatrix} =
\]

\[
\sum_{k=1}^{3} d_{kk} (x_k - \bar{x}_k)^2 + \sum_{i,j=1}^{3} 2d_{ij} (x_i - \bar{x}_i)(x_j - \bar{x}_j),
\]

(6.2)

where

\[
d_{ij} = d_{ji}, \quad d_{ij} \in \mathbb{R}, \quad x \in R^3.
\]
It is known that the quadratic forma defined by (5.1) is positive defined, when

\[d_{11} > 0, \; d_{11}d_{22} - d_{12}^2 > 0, \; \text{Det} \; A = d_{11}d_{22}d_{33} + 2d_{12}d_{13}d_{23} -
\]
\[(d_{13}^2d_{22} + d_{11}d_{23}^2 + d_{12}d_{33}) = d_{33}(d_{11}d_{22} - d_{12}^2) + 2d_{12}d_{13}d_{23} -
\]
\[(d_{13}^2d_{22} + d_{11}d_{23}^2) > 0.\]

Hence, if we assume \(d_{11} > 0, \; d_{33} > 0, \; d_{11}d_{22} - d_{12}^2 > 0\) and \(d_{13}^2d_{22} + d_{11}d_{23}^2 < 2d_{12}d_{13}d_{23}\) then \(V(x) > 0\).

Moreover, the orbital derivative of \(V(x)\) with respect to system (1.2) is given by

\[L_t V = \dot{V}(x) = \sum_{k=1}^{3} \frac{\partial V}{\partial x_k} \frac{dx_k}{dt} = \sum_{k,j=1}^{3} 2d_{kj} (x_j - \bar{x}_j) \frac{dx_k}{dt} =
\]
\[-[(2d_{11} + 2d_{21}a_{12})x_1^2 + (2d_{12} + 2d_{22}r_2)x_2^2 + 2d_{13}a_{13}x_3^2] -
\]
\[2d_{11} [a_{12}x_1x_2 + a_{13}x_1x_3] - 2d_{12} [x_1x_2 + a_{13}x_2x_3] - 2d_{13} [x_1x_3 + a_{12}x_2x_3] -
\]
\[[(2d_{12}r_2 + 2d_{22}a_{21})x_1x_2 + 2d_{33}r_2x_2x_3 + 2d_{33}a_{21}x_1x_3] + \]
\[2d_{11} (1 + \bar{x}_1) + 2d_{12}\bar{x}_2 + 2d_{13}\bar{x}_3 + 2d_{12}r_2 + 2a_{21} (d_{12}\bar{x}_1 + d_{22}\bar{x}_2 + d_{23}\bar{x}_3)] x_1 +
\]
\[2d_{11}a_{12}\bar{x}_1 + 2d_{12}a_{12}\bar{x}_2 + 2d_{12}a_{12}\bar{x}_2 + 2d_{12}r_2\bar{x}_1 + 2d_{22}r_2 (1 + \bar{x}_2) + 2d_{33}r_2\bar{x}_3] x_2 +
\]
\[2d_{11}a_{13}\bar{x}_1 + 2d_{12}a_{13}\bar{x}_2 + 2d_{13} + 2d_{13}a_{13}\bar{x}_3] x_3 -
\]
\[2r_2 [d_{12}\bar{x}_1 + d_{22}\bar{x}_2 + d_{33}\bar{x}_3] + 2d_{12}r_2 (x_1 + \bar{x}_1x_2) +
\]
\[-2 [d_{11}x_1 + d_{12}\bar{x}_2 + d_{13}\bar{x}_3 + r_2 (d_{12}\bar{x}_1 + d_{22}\bar{x}_2 + d_{32}\bar{x}_3)] +
\]
\[2 (d_{31} (x_1 - \bar{x}_1) + d_{32} (x_2 - \bar{x}_2) + d_{33} (x_3 - \bar{x}_3))] \left[ \frac{r_3 x_1}{x_1 + k_3} - a_{13}x_1 - d_3 \right].\]

Since for \(x \in \Omega_K\),

\[-2d_{11} [a_{12}x_1x_2 + a_{13}x_1x_3] \leq 0,\]

in view of inequalities

\[2ab \leq a^2 + b^2, \; x_1^2 + x_2^2 \leq ||x||^2, \; x_2^2 + x_3^2 \leq ||x||^2\] (6.4)

(6.3) holds if

\[\frac{r_3 x_1}{x_1 + k_3} - a_{13}x_1 - d_3 \leq 0,\] (6.5)

\[-[(2d_{11} + 2d_{21}a_{12})x_1^2 + (2d_{12} + 2d_{22}r_2)x_2^2 + 2d_{13}a_{13}x_3^2] +
\]
\[d_{12} (x_1^2 + x_2^2) + d_{12} a_{13} (x_2^2 + x_3^2) + d_{13} (x_1^2 + x_3^2) + d_{13} a_{13} (x_2^2 + x_3^2) +
\]
\[\frac{r_3 x_1}{x_1 + k_3} - a_{13}x_1 - d_3 \leq 0.\]
\[(d_{12}| r_2 + |d_{22}| a_{21}) (x_1^2 + x_2^2) + |d_{33}| r_2 (x_2^2 + x_3^2) + |d_{33}| a_{21} (x_1^2 + x_3^2) \leq \]
\[- [(2d_{11} + 2d_{12}a_{12}) x_1^2 + (2d_{12} + 2d_{22}r_2) x_2^2 + 2d_{13}a_{13}x_3^2] + \eta |x|^2 < 0, \quad (6.6)\]

\[\eta_1 x_1 + \eta_2 x_2 + \eta_3 x_3 < 0, \quad d_{11}\bar{x}_1 + d_{12}\bar{x}_2 + d_{13}\bar{x}_3 < 0, \quad (6.7)\]

where

\[\eta = \max \left\{ (|d_{12}| r_2 + |d_{22}| a_{21}), \quad |d_{33}|, \quad d_{33}r_2 \right\}, \]

\[\eta_1 = 2d_{11} (1 + \bar{x}_1) + 2d_{12}\bar{x}_2 + 2d_{13}\bar{x}_3 + 2d_{12}r_2 + \]

\[2a_{21} (d_{12}\bar{x}_1 + d_{22}\bar{x}_2 + d_{23}\bar{x}_3), \quad (6.8)\]

\[\eta_2 = 2d_{11}\bar{x}_1 + 2d_{12}\bar{x}_2 + 2d_{12}a_{12}\bar{x}_2 + 2d_{12}r_2\bar{x}_1 + \]

\[2d_{22}r_2 (1 + \bar{x}_2) + 2d_{33}r_2\bar{x}_3, \]

\[\eta_3 = 2d_{11}a_{13}\bar{x}_1 + 2d_{12}a_{13}\bar{x}_2 + 2d_{13} + 2d_{13}a_{13}\bar{x}_3. \]

By assumption (2), (6.5) holds for all \(x \in \Omega_K\). The inequality (6.5) satisfied for all \(x \in \Omega_K\), when

\[\eta < \min \left\{ (2d_{11} + 2 |d_{12}| a_{12}), \quad (2 |d_{12}| + 2 |d_{22}| r_2), \quad 2 |d_{13}| a_{13} \right\}. \quad (6.9)\]

So, we obtain that \(\dot{V}(x) < 0\), when

\[x \in \Omega_0 = \{x \in \Omega_K, \quad \eta_1 x_1 + \eta_2 x_2 + \eta_3 x_3 < 0\}. \]

Hence, \(V(x)\) is a Lyapunov function on the domain \(D_V\) and the solution \(\bar{x} = (\bar{x}_1, \bar{x}_2, \bar{x}_3)\) of system (1.2) satisfying (6.7) is global stable in the sense of Lyapunov.

**7. Attraction sets for biologically feasible equilibria points**

In this section we will derive global stability of equilibria points

\[E_1 (1, 0, 0), \quad E_2 (0, 1, 0), \quad E_3 (a, 0, b)\]

and we will find their attraction sets, where

\[a = \frac{r_2}{a_{21}}, \quad b = \frac{a_{21} - r_2}{a_{13}a_{21}}. \]

Let

\[\Omega_K = \{x \in \mathbb{R}^3, \quad 0 \leq x_i \leq K_i, \quad i = 1, 2, 3\}\]

and

\[B_r (\bar{x}) = \{x \in \mathbb{R}^3, \quad ||x - \bar{x}||_{\mathbb{R}^3} < r^2\}. \]

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Theorem 7.1. Assume the following assumptions are satisfied:
(1) $r_2 - a_{21} < 0$, $r_2 + 1 \leq a_{12}$;
(2) $a_{13} > 1$, $r_3 < k_3a_{31}$;
(3) $d^2 + \frac{1}{4} \geq 3d + \frac{a_{12}^2}{c_{22}}$, where
$$c_{22} = r_2 + a_{21} - 1, \quad d = \frac{a_{12}^2 + c_{22}}{2c_{22}(a_{21} - r_2)};$$
(4) $\mu = a_{12} + \frac{a_{12}}{c_{22}} + \frac{a_{12}}{c_{22}r_2} > 0$ and $\frac{d}{c_{13}} < \min\{1, \mu\}$.

Then the system (1.2) is globally stable at the equilibrium point $E_1 (1, 0, 0)$ and the attraction set of the point $E_1 (1, 0, 0)$ belongs to the set $\Omega_C \subset \Omega_K \cap \Omega_1$, where
$$\Omega_1 = \{x \in \Omega_K: 2x_1 + a_{13}x_3 < v x_2\}, \quad \Omega_C = \{x \in R^3: V_1 (x) \leq C\},$$
here the positive constant $C$ is defined below and $\nu = \left(a_{12} + \frac{a_{12}}{c_{22}} + \frac{a_{12}}{c_{22}r_2}\right)$.

Proof. Let $A_1$ be the linearized matrix with respect to the equilibrium point $E_1 (1, 0, 0)$, i.e.
$$A_1 = \begin{bmatrix} -1 & -a_{12} & 0 \\ 0 & r_2 - a_{21} & 0 \\ 0 & 0 & c_{13} \end{bmatrix},$$
where
$$c_{13} = \frac{r_3}{1 + k_3} - a_{31} - d_3 < 0.$$

By assumption (2), $c_{13} < 0$. We consider the Lyapunov equation
$$P_1 A_1 + A_1^T P_1 = -I, \quad (7.1)$$
where
$$P_1 = \begin{bmatrix} b_{11} & b_{12} & b_{13} \\ b_{21} & b_{22} & b_{23} \\ b_{31} & b_{32} & b_{33} \end{bmatrix}.$$

The equation (7.1) is reduced to the following linear system of algebraic equations,
$$2b_{11} = -1,$$
$$-a_{12}b_{11} + (r_2 - a_{21} - 1)b_{12} = 0,$$
$$-(c_{13} + 1)b_{13} = 0,$$
$$-a_{12}b_{11} + (r_2 - a_{21} - 1)b_{21} = 0,$$
$$-a_{12}(b_{12} + b_{21}) + 2(r_2 - a_{21})b_{22} = -1,$$
$$-a_{21}b_{13} + (r_2 - a_{21} - c_{13})b_{23} = 0. \quad (7.2)$$
\[(c_{13} - 1) b_{31} = 0,
-a_{12} b_{31} + (r_2 - a_{21} - c_{13}) b_{32} = 0,
-2c_{13} b_{33} = -1\]

By solving (7.2) we obtain

\[b_{11} = \frac{1}{2},
 b_{12} = b_{21} = \frac{1}{2} a_{12} c_{22},
 b_{13} = 0,\]

\[b_{22} = \frac{a_{12}^2 + c_{22}}{2(a_{21} - r_2) c_{22}},
 b_{23} = 0, b_{31} = 0, b_{32} = 0, b_{33} = \frac{1}{2c_{13}},\]

\[P_1 = \begin{bmatrix}
\frac{1}{2} & b_{12} & 0 \\
b_{12} & b_{22} & 0 \\
0 & 0 & -\frac{1}{2c_{13}}
\end{bmatrix}.\]

Moreover,

\[|P_1 - \lambda I| = \left(\lambda - \frac{1}{2c_{13}}\right) \left[\lambda^2 - \left(b_{22} + \frac{1}{2}\right) \lambda + \left(b_{22} + b_{12}^2\right)\right] = 0. \quad (7.3)\]

From the assumption (2) we deduced \(b_{22} > 0\). By assumption (3) we have

\[\left(b_{22} + \frac{1}{2}\right)^2 - 4 \left(b_{22} + b_{12}^2\right) \geq 0.\]

So, (7.3) have positive roots, i.e. the matrix \(P_1\) is positive defined. Hence, the quadratic function

\[V_1(x) = X^T P_1 X = \frac{1}{2} (x_1 - 1)^2 + \frac{a_{12}}{c_{22}} (x_1 - 1) x_2 + b_{22} x_2^2 + \frac{1}{2c_{13}} x_3^2\]

is a positive defined Lyapunov function candidate in certain neighborhood of \(E_1(1,0,0)\). We need now, to determine a domain \(\Omega_1\) about the point \(E_1\), where \(\dot{V}_1(x)\) is negative 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

\[\dot{V}_1(x) = \sum_{k=1}^{3} \frac{\partial V_1}{\partial x_k} \frac{dx_k}{dt} = \left[(x_1 - 1) + \frac{a_{12}}{c_{22}} x_2\right] \left[(1 - x_1) - a_{12} x_2 - a_{13} x_3\right] + \left[\frac{a_{12}}{c_{22}} (x_1 - 1) + b_{22} x_2\right] x_2 \left[r_2 (1 - x_2) - a_{12} x_1\right] - \frac{1}{c_{13}} x_3 \left[\frac{r_3 x_1}{x_1 + k_3} - a_{31} x_1 - d_3\right] = \]

\[20\]
in view of inequalities

\[-(1 - x_1)^2 - a_{12}(1 - x_1)x_2 + a_{13}(1 - x_1)x_3 - \frac{a_{12}}{c_{22}}(1 - x_1)x_2 + \]

\[-\frac{a_{12}^2}{c_{22}}x_2^2 + \frac{a_{12}}{c_{22}}a_{13}x_2x_3 + \frac{a_{12}}{c_{22}}r_2(1 - x_1)x_2(1 - x_2) - \frac{a_{12}^2}{c_{22}}x_1(x_1 - 1)x_2 + \]

\[b_{22}r_2x_2^2(1 - x_2) - b_{22}a_{12}x_1x_2^2 + \frac{1}{c_{13}}x_3^2\left[\frac{r_3x_1}{x_1 + k_3} - a_{31}x_1 - d_3\right] = \]

\[-x_1^2 + \left(b_{22}r_2 - \frac{a_{12}^2}{c_{22}} - \frac{a_{12}}{c_{22}}r_2\right)x_2^2 - \frac{d_3}{c_{13}}x_3^2 + \left(a_{12} + \frac{a_{12}}{c_{22}} + \frac{a_{12}^2}{c_{22}}\right)x_1x_2 - \]

\[\frac{a_{12}}{c_{22}}r_2x_1x_2 + \frac{a_{12}}{c_{22}}a_{13}x_2x_3 - \frac{a_{12}}{c_{22}}r_2x_1x_2 - \frac{a_{12}^2}{c_{22}}x_1^2x_2 - \quad (7.4)\]

\[b_{22}r_2x_2^3 - b_{22}a_{12}a_{13}x_1x_2^2 + \frac{1}{c_{13}}x_3^2\left(\frac{r_3x_1}{x_1 + k_3} - a_{31}x_1\right) + \]

\[2x_1 - \left(a_{12} + \frac{a_{12}}{c_{22}} + \frac{a_{12}^2}{c_{22}}r_2\right)x_2 + a_{13}x_3 - 1 < 0.\]

Since for \(x \in \Omega_K\),

\[-\frac{a_{12}}{c_{22}}x_1x_2 \leq 0, \quad -1 < 0,\]

in view of inequalities

\[2ab \leq a^2 + b^2, \quad x_1^2 + x_2^2 \leq \|x\|^2, \quad x_2^2 + x_3^2 \leq \|x\|^2 \quad (7.5)\]

the inequality (7.4) holds if

\[-\left[x_1^2 + \left(\frac{a_{12}^2}{c_{22}} + \frac{a_{12}}{c_{22}}r_2 - b_{22}r_2\right)x_2^2 + \frac{d_3}{c_{13}}x_3^2\right] + \]

\[\frac{1}{2}\left(a_{12} + \frac{a_{12}}{c_{22}}r_2 + \frac{a_{12}^2}{c_{22}}\right)|x|^2 + \frac{a_{12}}{2c_{22}}a_{13}|x|^2 < 0, \quad (7.6)\]

\[2x_1 + a_{13}x_3 < \left(a_{12} + \frac{a_{12}}{c_{22}} + \frac{a_{12}^2}{c_{22}}r_2\right)x_2 + 1, \]

\[\frac{r_3x_1}{x_1 + k_3} - a_{31}x_1 < 0.\]

In view of the assumption (1) we get that the solution set of third inequality of (7.6) is \(\Omega_K\). By assumption (4), it is not hard to see that the first inequality (6.6) is satisfied for all \(x \in \Omega_K\). The solution set of second inequality in (7.6) is
the set $\Omega_1$. Hence, $\dot{V}_1$ is negative defined on the domain. Hence, $\dot{V}_1$ is negative defined on the domain

$$
\Omega_1 = \{ x \in B_r(\bar{x}), 2x_1 + a_{13}x_3 < \nu x_2 \} = B_r(\bar{x}) \cap \Omega_a,
$$

where

$$
\bar{x} = (1, 0, 0), \ r \leq \sqrt{K_1^2 + K_2^2 + K_3^2}, \ \nu = a_{12} + \frac{a_{12}}{c_{22}} + \frac{a_{12}}{c_{22}}r_2,
$$

$$
\Omega_a = \{ x \in \Omega_K, 2x_1 + a_{13}x_3 < \nu x_2 \},
$$
i.e., the system (1.2) is global stable at $E_1 (1, 0, 0)$. Let now find the set $\Omega_C \subset B_r(\bar{x})$, where

$$
\nu = a_{12} + \frac{a_{12}}{c_{22}} + \frac{a_{12}}{c_{22}}r_2,
$$

$$
\Omega_C = \{ x \in \Omega_K, 2x_1 + a_{13}x_3 < \nu x_2 \},
$$
i.e., the system (1.2) is global stable at $E_1 (1, 0, 0)$. Let now find the set $\Omega_C \subset B_r(\bar{x})$, when

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

$\lambda_{\min}(P_1)$ denotes a minimum eigenvalue of $P_1$, i.e.

$$
\lambda_{\min}(P_1) = \min \left\{ \frac{1}{2c_{13}}, \frac{(b_{22} + \frac{1}{2}) \pm \sqrt{b_{22}^2 + \frac{1}{4} - 3b_{22} - 4b_{12}^2}}{2} \right\}
$$

and

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

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

$$
0 \leq x_i \leq K_i, 2x_1 + a_{13}x_3 < \nu x_2.
$$

So,

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

where

$$
\tilde{r} = [\nu^2 \min \{ 4, a_{13}^2 \} + 1] K_2^2.
$$

Then we obtain that

$$
C < \min_{|x|=r_1} V_1(x) = \lambda_{\min}(P_1) \tilde{r}^2,
$$
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 7.2.** Assume the following assumptions are satisfied:

1. $r_3 < k_3 a_{31}$;
2. $c_{11} = a_{12} - 1 > 0$;
3. $\frac{a_{21}}{c_{13}} (d + 1)^2 + d^2 \geq \frac{a_{21}}{r_2 c_{11}} (d + 1)$;
Then the system (1.2) is global stable at equilibria point $E_1 (0, 1, 0)$ and the attraction set of the point $E_2 (0, 1, 0)$ belongs to the set $\Omega_C \subset \Omega_K \cap \Omega_2$, where

$$\Omega_2 = \{ x \in \Omega_K: \left(2b_{11} + \frac{a_{12}}{r_2} + 2b_{12}\right)x_1 + 2b_{12}\left(1 + a_{12}\right)x_2 + 2b_{12}a_{13}x_3 \leq 0\}.$$ 

$$\Omega_C = \{ x \in \mathbb{R}^3: V_2(x) \leq C \}.$$

Here $V_2(x)$ and the constant $C$ is defined in bellow.

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

$$A_2 = \begin{bmatrix} 1 - a_{12} & 0 & 0 \\ -a_{21} & -r_2 & 0 \\ 0 & 0 & -d_3 \end{bmatrix}.$$ 

Consider the Lyapunov equation

$$P_2 A_2 + A_2^T P_2 = -I, \quad (7.7)$$

where

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

The equation (7.7) is reduced to the following linear system of algebraic equation

$$2c_{11}b_{11} - 2a_{21}(b_{12} + b_{21}) = -1, \quad -\left(c_{11} + r_2\right)b_{12} - a_{21}b_{22} = 0, \quad -\left(c_{11} + d_3\right)b_{13} - a_{21}b_{23} = 0,$$

$$-\left(c_{11} + r_2\right)b_{21} - a_{21}b_{22} = 0, \quad -2r_2b_{22} = -1, \quad -\left(d_3 + r_2\right)b_{23} = 0,$$

$$-\left(c_{11} + d_3\right)b_{31} - a_{21}b_{32} = 0, \quad -\left(r_2 + d_3\right)b_{32} = 0, \quad -2d_3b_{33} = -1. \quad (7.8)$$

By solving (7.8) we obtain

$$b_{13} = 0, \quad b_{12} = b_{21} = \frac{-a_{21}}{2r_2(c_{11} + r_2)}, \quad b_{11} = \frac{a_{21}}{c_{11}} \left[\frac{a_{21}}{r_2(c_{11} + r_2)} + 1\right],$$

$$b_{22} = \frac{1}{2r_2}, \quad b_{23} = b_{32} = 0, \quad b_{33} = \frac{1}{2d_3}, \quad b_{31} = 0,$$

$$23$$
i.e.

\[
P_2 = \begin{bmatrix}
  b_{11} & b_{12} & 0 \\
  b_{12} & \frac{1}{r_2} & 0 \\
  0 & 0 & \frac{1}{d_3}
\end{bmatrix}.
\]

Moreover,

\[
|P_2 - \lambda I| = \left(\frac{1}{2d_3} - \lambda\right) \left[\lambda^2 - \left(b_{11} + \frac{1}{2r_2}\right) \lambda + \left(b_{11} \frac{1}{2r_2} - b_{12}^2\right)\right] = 0. \tag{7.9}
\]

In view of the assumption (1) it is clear to see that \(b_{11} > 0\). By assumption (3),

\[
\left(b_{11} + \frac{1}{2r_2}\right)^2 - 4 \left(\frac{b_{11}}{2r_2} - b_{12}^2\right) \geq 0.
\]

So, (7.9) have positive roots, i.e. the matrix \(P_2\) is positive defined for all \(x\). Hence, the quadratic function

\[
V_2(x) = \dot{X}^TP_2X = b_{11}x_1^2 + b_{12}x_1(x_2 - 1) + \frac{1}{2r_2} \left(x_2 - 1\right)^2 + \frac{1}{2d_3}x_3^2
\]

is a positive defined Lyapunov function candidate in certain neighborhood of \(E_2(0, 1, 0)\). 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 \(x_k \geq 0, k = 1, 2, 3\), we will find the solution set of the following inequality

\[
\dot{V}_2(x) = \sum_{k=1}^{3} \frac{\partial V_2}{\partial x_k} \frac{dx_k}{dt} =
\]

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

\[
\left[2b_{12}x_1 + \frac{1}{r_2}(x_2 - 1)\right]x_2\left[r_2(1 - x_2) - a_{12}x_1\right] +
\]

\[
\frac{1}{d_3}x_3^2\left[\frac{r_3x_1}{x_1 + k_3} - a_{31}x_1 - d_3\right] = -\left(2b_{11}x_1^2 + a_{12}x_2^2 + d_3x_3^2\right) - 2b_{12}a_{12}\left(x_1^2 + x_2^2\right) -
\]

\[
2b_{11}\left(a_{12}x_1x_2 + a_{13}x_1x_3\right) - 2b_{12}\left(x_1x_2 + a_{13}x_2x_3\right) - x_2\left(x_2 - 1\right)^2 -
\]

\[
a_{12}r_2x_1x_2 + \left(2b_{11} + \frac{a_{12}}{r_2} + 2b_{12}\right)x_1 + 2b_{12}(1 + a_{12})x_2 +
\]

\[
2b_{12}a_{13}x_3 + 2b_{12}r_2\left(x_1x_2 - x_1x_2^2\right) + \frac{1}{d_3}x_3^2\left[\frac{r_3x_1}{x_1 + k_3} - a_{31}x_1\right] < 0. \tag{7.10}
\]

It is clear to see that for all \(x \in \Omega_K\)

\[
-2b_{11}\left(a_{12}x_1x_2 + a_{13}x_1x_3\right) < 0, -\frac{a_{12}}{r_2}x_1x_2, -2b_{12}r_2x_1x_2^2 < 0. \tag{7.11}
\]

Moreover, in view of (7.5) and (7.11) the inequality (7.10) holds if
\[-(2b_{11}x_1^2 + a_{12}x_2^2 + d_3x_3^2) + 2b_{12} \left( r_2 - \left( a_{12} + \frac{1}{2}(1 + a_{13}) \right) \right) \|x\|^2 < 0,\]

\[
\left( 2b_{11} + \frac{a_{12}}{r_2} + 2b_{12} \right) x_1 + 2b_{12} (1 + a_{12}) x_2 + 2b_{12}a_{13}x_3 \leq x_2 (x_2 - 1)^2, \quad (7.12)
\]

\[
\frac{r_3x_1}{x_1 + k_3} - a_{31}x_1 < 0.
\]

In view of assumption (1) the solution set of third inequality of (6.13) is \(\Omega_K\). By assumption (4), it is not hard to see that the first inequality (7.12) is satisfied for all \(x \in \Omega_K\). The solution set of second inequality in (7.12) is the set \(\Omega_2\). Hence, \(\dot{V}_2\) is negative defined on the domain

\[
\Omega_0 = B_r(\bar{x}) \cap \Omega_2, \quad r \leq K_1^2 + K_2^2 + K_3^2,
\]

i.e., the sytem (1.2) is global stabile at \(E_1(0,1,0)\). We will find \(C > 0\) such that \(\Omega_C \subset B_r(\bar{x}) \cap \Omega_2\), i.e.

\[
\Omega_C \subset B_r(\bar{x}) \cap \Omega_2.
\]

It is clear to see that \(\Omega_C \subset B_r(\bar{x})\), when

\[
C < \min_{|x-\bar{x}|=r} V_2(x) = \lambda_{\text{min}}(P_2) r^2, \quad \bar{x} = (0,1,0),
\]

here \(\lambda_{\text{min}}(P_2)\) denotes a minimum eigne value of \(P_2\), i.e.

\[
\lambda_{\text{min}}(P_2) = \min \left\{ \frac{1}{2d_3}, \left( \frac{b_{22} + \frac{1}{r_2}}{2} \right) \pm \sqrt{\frac{b_{22}^2}{4r_2^2} + \frac{b_{12}^2}{4r_2^4} - \frac{b_{11}}{r_2^2}} \right\}.
\]

Moreover, for some \(C > 0\) the inclusion \(\Omega_C \subset \Omega_2\) means the existence of \(C > 0\) so that \(x \in \Omega_C\) implies \(x \in \Omega_2\), i.e.

\[
x \in \Omega_K, \quad \left( 2b_{11} + \frac{a_{12}}{r_2} + 2b_{12} \right) x_1 + 2b_{12} (1 + a_{12}) x_2 + 2b_{12}a_{13}x_3 \leq 0. \quad (7.13)
\]

(7.13) implies

\[
\left( 2b_{11} + \frac{a_{12}}{r_2} \right) x_1 \leq -2b_{12} [(1 + a_{12}) x_2 + a_{13}x_3],
\]

So,

\[
x \in B_{\bar{\rho}}(\bar{x}) = \left\{ x \in \mathbb{R}^3, \ |x-\bar{x}| < \bar{\rho} \right\},
\]

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where

\[ \eta_1 = \frac{-2b_{12} (1 + a_{12})}{2b_{11} + \frac{a_{12} r_2}{r_2}}, \quad \eta_2 = \frac{-2b_{12} a_{13}}{2b_{11} + \frac{a_{12} r_2}{r_2}}, \quad \bar{r} = \left[ 2 \left( 1 + \eta_1^2 \right) K_2^2 + 2 \left( 1 + \eta_2^2 \right) K_3^2 \right]^{\frac{1}{2}}. \]

Then we obtain that

\[ C < \min_{|x|=r_0} V_2(x) = \lambda_{\min}(P_2) \bar{r}^2, \]

i.e.

\[ C < \lambda_{\min}(P_2) \bar{r}^2 \text{ for } r_0 = \min \{ r, \bar{r} \}. \]

**Remark 7.1.** It is clear to see that if \( a_{21} \geq \frac{a_{12} r_2}{r_2} \), then the assumption (3) is satisfied. Moreover, if \( a_{12} + \frac{1}{2} (1 + a_{13}) > r_2 \), then the assumption (4) holds.

Let \( A_3 \) be the linearized matrix with respect to equilibria point \( E_3(a, 0, b) \) defined by (4.11), i.e.,

\[ A_3 = \begin{bmatrix} -a & d_{12} & d_{13} \\ 0 & d_{22} & 0 \\ d_{31} & 0 & d_{33} \end{bmatrix}, \]

where

\[ d_{12} = -a_{12}a, \quad d_{13} = -a_{13}a, \quad d_{22} = r_2 - a_{21}a, \quad a = \frac{r_2}{a_{21}}, \quad d_{31} = \frac{k_1 r_3}{(a + k_1)^2} - a_{31}b, \quad d_{33} = \frac{r_3 a}{a + k_3} - a_{31}a - d_3, \quad b = \frac{a_{21} - r_2}{a_{13}a_{21}}. \]

By reasoning as the above we obtain

**Theorem 7.3.** Assume the Condition 5.6 hold and:

(1) \( a_{31} > \frac{k_1 r_3}{(a + k_1)^2}, a_{31} + d_3 > \frac{r_3 a}{(a + k_3)^2}; \)

(2) \[ \frac{a_{31} - \frac{k_1 r_3}{(a + k_1)^2}}{d_3 + a_{31} - \frac{r_3 a}{(a + k_3)^2}} > \frac{1}{a \left( a_{12} + a_{13} \right)}. \]

Then the system (1.2) is globally stable at equilibria point \( E_3(a, 0, b) \) and the attractor set of the point \( E_3(a, 0, b) \) belongs to the set \( \Omega_C \subset \Omega_K \cap \Omega_3 \), where

\[ \Omega_3 = \{ x = (x_1, x_2, x_3) \in \Omega_K : \alpha x_1 + \alpha_2 x_2 + \alpha_3 x_3 \geq 0, \alpha x_1 + \beta_2 x_2 + \beta_3 x_3 \geq 0 \}, \quad (7.14) \]

\[ \Omega_C = \{ x \in \mathbb{R}^3 : V_3(x) \leq C \} , \]

here \( V_3(x) \) and the constant \( C \) is defined in bellow and

\[ \alpha = \frac{d_{12}}{(\mu a + d_{12} d_{31})}, \quad \alpha_2 = \frac{2(1 + d_{12} b_{12})}{d_{12} + 2d_{22}}, \quad \alpha_3 = \frac{2(d_{12} + d_{13})}{d_{22} + d_{33}} b_{12}, \]

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\[ \beta_2 = \frac{2(d_{12} + d_{13})}{d_{22} + d_{33}} b_{12}, \quad \beta_3 = \frac{1}{d_{33}} (1 + 2d_{13} b_{12}). \]

**Proof.** Consider the Lyapunov equation

\[ P_3 A_3 + A_3^T P_3 = -I, \tag{7.15} \]

where

\[ P_3 = \begin{bmatrix} b_{11} & b_{12} & b_{13} \\
 b_{21} & b_{22} & b_{23} \\
 b_{31} & b_{32} & b_{33} \end{bmatrix}, \quad b_{ij} = b_{ji}. \]

By solving algebraic equation in \( b_{ij} \) according to (7.15) we obtain

\[ b_{12} = b_{13} = \frac{d_{12}}{2(\mu a + d_{12} d_{31})}, \quad b_{11} = - \frac{\mu b_{12}}{d_{12}}, \quad b_{22} = - \frac{(1 + d_{12} b_{12})}{d_{12} + 2d_{22}}, \]

\[ b_{23} = - \frac{d_{12} + d_{13}}{d_{22} + d_{33}} b_{12}, \quad b_{33} = - \frac{1}{2d_{33}} (1 + 2d_{13} b_{12}), \tag{7.16} \]

\[ \mu = d_{22} - a - \frac{(d_{12} + d_{13}) d_{31}}{d_{22} + d_{33}}. \]

Then by using the assumptions (1) and (2) we get that that \( P_3 \) have positive eigen values, i.e. the quadratic function

\[ V_3(x) = X^T P_3 X = - \frac{\mu}{d_{12}} x_1^2 - \frac{(1 + d_{12} b_{12})}{d_{12} + 2d_{22}} x_2^2 - \frac{1}{2d_{33}} (1 + 2d_{13} b_{12}) x_3^2 - \]

\[ - \frac{d_{12}}{(\mu a + d_{12} d_{31})} (x_1 x_2 + x_1 x_3) - \frac{2(d_{12} + d_{13})}{d_{22} + d_{33}} b_{12} x_2 x_3. \]

is a positive defined Lyapunov function candidate in neighborhood of \( E_3(a, 0, b) \).

By assuming \( x_k \geq 0, k = 1, 2, 3 \), we find that

\[ \dot{V}_3(x) = \sum_{k=1}^{3} \frac{\partial V_3}{\partial x_k} \frac{dx_k}{dt} = \tag{7.17} \]

\[ - \left[ \frac{2\mu}{d_{12}} x_1 + \frac{d_{12}}{(\mu a + d_{12} d_{31})} (x_2 + x_3) \right] x_1 [(1 - x_1) - a_{12} x_2 - a_{13} x_3] - \]

\[ (\alpha x_1 + \alpha_2 x_2 + \alpha_3 x_3) [r_2 (1 - x_2) - a_{12} x_1] - \]

\[ (\alpha x_1 + \beta_2 x_2 + \beta_2 x_2) \left[ \frac{r_3 x_1}{x_1 + k_3} - a_{31} x_1 - d_3 \right] = \]

\[ \frac{2\mu}{d_{12}} [-x_1^2 (1 - x_1) + a_{12} x_1 x_2 + a_{13} x_1 x_3] - \alpha (x_1 x_2 + x_1 x_3) (1 - x_1) + \]

\[ \alpha \left( a_{12} (x_2^2 + x_2 x_3) + a_{13} (x_3^2 + x_2 x_3) \right) - \frac{2(1 + d_{12} b_{12}) r_2}{d_{12} + 2d_{22}} x_2 (1 - x_2) + \]

\[ \frac{2\mu}{d_{12}} [-x_1^2 (1 - x_1) + a_{12} x_1 x_2 + a_{13} x_1 x_3] - \alpha (x_1 x_2 + x_1 x_3) (1 - x_1) + \]

\[ \alpha \left( a_{12} (x_2^2 + x_2 x_3) + a_{13} (x_3^2 + x_2 x_3) \right) - \frac{2(1 + d_{12} b_{12}) r_2}{d_{12} + 2d_{22}} x_2 (1 - x_2) + \]
\[
\begin{align*}
2 (1 + d_{12} b_{12}) a_{12} \frac{d_{12}}{d_{12} + 2d_{22}} x_1 x_2 - \alpha r_2 x_1 (1 - x_2) + \frac{d_{12} r_2 a_{12}}{(\mu a + d_{12} d_{31})} x_1^2 + \\
- \frac{2 (d_{12} + d_{13}) r_2}{d_{22} + d_{33}} b_{12} x_3 (1 - x_2) + \frac{2 (d_{12} + d_{13}) a_{12}}{d_{22} + d_{33}} b_{12} x_1 x_3 - \\
(\alpha x_1 + \beta_2 x_2 + \beta_3 x_3) \left[ \frac{r_3 x_1}{x_1 + k_3} - a_{31} x_1 - d_3 \right].
\end{align*}
\]

By assumption (1), (2), \(\mu > 0\), \(d_{12} < 0\), \(d_{13} < 0\). So, for \(x \in \Omega_K\) we have
\[
\frac{2 \mu}{d_{12}} x_1^3 \leq 0, \quad \frac{d_{12}}{(\mu a + d_{12} d_{31})} (x_1 x_2 + x_1 x_3) x_1 \leq 0.
\]

In view of (7.14) the estimate (7.17) holds if the following inequality is satisfied

\[
\begin{align*}
\frac{2 \mu}{d_{12}} [-x_1^2 + a_{12} x_1 x_2 + a_{13} x_1 x_3] - & \frac{d_{12}}{(\mu a + d_{12} d_{31})} (x_1 x_2 + x_1 x_3) + \\
& \frac{d_{12}}{(\mu a + d_{12} d_{31})} \left[ a_{12} (x_2^2 + x_2 x_3) + a_{13} (x_3^2 + x_2 x_3) \right] + \frac{2 (1 + d_{12} b_{12}) r_2}{d_{12} + 2d_{22}} x_2^2 + \\
& \left[ \frac{2 (1 + d_{12} b_{12}) a_{12}}{d_{12} + 2d_{22}} + \frac{d_{12} r_2}{(\mu a + d_{12} d_{31})} \right] x_1 x_2 + \frac{d_{12} r_2 a_{12}}{(\mu a + d_{12} d_{31})} x_1^2 + \\
& \frac{2 (d_{12} + d_{13}) r_2}{d_{22} + d_{33}} b_{12} x_2 x_3 + \frac{2 (d_{12} + d_{13}) a_{12}}{d_{22} + d_{33}} b_{12} x_1 x_3 < 0. \quad (7.18)
\end{align*}
\]

By Condition 5.6 and by assumptions (1), (2) the inequality (7.18) is satisfied for \(x \in \Omega_K\). So, (7.17) holds if the inequalities (7.14) and (7.18) are satisfied for \(x \in \Omega_K\). Hence, \(V_3\) is negative defined on the domain
\[
\Omega_0 = B_r(\bar{x}) \cap \Omega_3, \ r \leq K_1^2 + K_2^2 + K_3^2,
\]
i.e., the system (1.2) is global stable at the point \(E_3(a, 1, b)\). We will find \(C > 0\) such that \(\Omega_C \subset B_r(\bar{x}) \cap \Omega_3\), i.e.
\[
\Omega_C \subset B_r(\bar{x}) \cap \Omega_3.
\]

It is clear to see that \(\Omega_C \subset B_r(\bar{x})\), when
\[
C < \min_{|x - \bar{x}|=r} V_2(x) = \lambda_{\min}(P_2) r^2, \ \bar{x} = (a, 0, b),
\]
here \(\lambda_{\min}(P_3)\) denotes a minimum eigen value of \(P_3\).

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. (7.17) holds.

So,
\[
x \in B_r(\bar{x}) = \left\{ x \in \mathbb{R}^3, \ |x - \bar{x}| < r \right\},
\]

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where
\[ \mu_2 = \min \left\{ -\frac{\alpha_2}{\alpha}, -\frac{\beta_2}{\alpha} \right\}, \quad \mu_3 = \left\{ -\frac{\alpha_3}{\alpha}, -\frac{\beta_3}{\alpha} \right\}, \]
\[ \bar{r} = \left[ 2 \left( 1 + \mu_2^2 \right) K_2^2 + 2 \left( 1 + \mu_3^2 \right) K_3^2 \right]^{\frac{1}{2}}. \]

Then we obtain that
\[ C < \min_{|x|=r_0} V_3(x) = \lambda_{\min}(P_3) \bar{r}^2, \]
i.e.
\[ C < \lambda_{\min}(P_3) \bar{r}^2 \text{ for } r_0 = \min \{ r, \bar{r} \}. \]

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