A novel dynamic model describing the spread of virus

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Abstract

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Keywords: Mathematical modeling, Virus, Immune system, Stability of dynamical systems

1. Introduction

It is well-known that dynamic models are still playing important roles in describing the interactions among uninfected cells, free viruses, and immune responses (see, e.g., $[1-4]$. A three-dimensional dynamic model for viral infection is proposed by Nowak et al. (see, e.g, $[2-4]$). They are able to generalise numerical methods from the autonomous dynamical systems. More over, they characterise a Lyapunov function as a solution of a suitable linear first-order partial differential equation and approximate it using radial basis functions (see, e.g [17]). A mathematical model employs non-constant transmission rates which vary with environmental conditions and the epidemiological status and which reflect the impact of the on-going disease control measures (see, e.g [18]). Model developers have acknowledged the challenge of designing mathematical models of virus dynamics. Several models have been produced, resulting, sometimes, in different estimates. They have devised a deterministic compartmental (SEIR) model (see, e.g [19]). Mathematical epidemiology models can be used to combat epidemic outbreaks. It offers a new spatial approach (SBDiEM) for infectious

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dynamic publishing, prediction, and modeling. This model can be adjusted to identify past outbreaks and virus. Methodologies can have important implications for national health systems, international stakeholders, and policymakers (see, e.g [20]). In this study, they studied the transmission dynamics of virus on the one hand and a separate mathematical model described on the one hand or between animals in different regions. Also, Implementing the most appropriate campaigns by preventing the individual from moving from one region to another, encouraging them to participate in quarantine centers, using awareness campaigns aimed at being affected by viruses, security campaigns and health measures in the region (see, e.g [21]). They demonstrate how mathematical modeling can help estimate outbreak dynamics and provide decision guidelines for successful outbreak control. Their model can become a valuable tool to estimate the potential of vaccination and quantify the effect of relaxing political measures including total lock down, shelter in place, and travel restrictions for low-risk subgroups of the population or for the population as a whole (see, e.g [22]). We have created a mathematical model of virus transmission based on the SEIR model. Those identified by the World Health Organization (WHO), by mathematical modeling, can play an important role in providing evidence-based information to healthcare decision makers and policy makers. Modeling can help better understand a virus spreading in the population. We consider here, the following mathematical model concerning to the initial value problem for following nonlinear systems

$$
\begin{gathered}
\dot{T}\left(t\right) = a - \beta_1 V\left(t\right) T\left(t\right) - d_1 T\left(t\right), \\
\dot{I}\left(t\right) = qT\left(t\right) V\left(t\right) - \beta_2 E\left(t\right) I\left(t\right) - d_2 I\left(t\right), \qquad (1.1) \\
\dot{E}\left(t\right) = \beta_3 I\left(t\right) E\left(t\right) - d_3 E\left(t\right), \\
\dot{V}\left(t\right) = bI\left(t\right) - cV\left(t\right),
\end{gathered}
$$

$$
\begin{gathered}
T\left(t_0\right) = T_0,\ I\left(t_0\right) = I_0,\ E\left(t_0\right) = E_0, \qquad (1.2) \\
V\left(t_0\right) = V_0,\ t_0 \in \left[0,\ a\right),
\end{gathered}
$$

where $T = T\left(t\right)$, $I = I\left(t\right)$, $E\left(t\right)$ and $V\left(t\right)$ denote the concentration of uninfected cells, infected cells, effector immune cells and free viruses at time $t \in (0, m)$, respectively.

Uninfected cells are supplied at a rate a and uninfected hepatocytes (target cells, T) are infected by virus V at a rate β_1. They are d_i $(i = 1, 2, 3)$ that die naturally at the rate q is the rate constant characterizing infection of the infected cells. Effector cells mediate infection by eliminating productively infected cells at a rate β_2. Effector immune cells E are supplied to the presence of tumor cells stimulates the immune response. The effector immune cells are activated by the virus at the rate of β_3. The infected cells produce new viruses at the rate b during their life. The constant $c > 0$ is the rate at which the viruses are cleared (see, e.g., $[29 - 31]$.

2. Boundedness and dissipativity

In this section, we shall show that the model are bounded with negative divergence, positively invariant with respect to a region in $\mathbb{R}_+^4$ and dissipative. As we are interested in biologically relevant solutions of the system, the next results show that the positive octant is invariant and that the upper limits of trajectories depend on the parameters.

We put

$$T(t) = x_1(t),\ I(t) = x_2(t),\ E(t) = x_3(t),\ V(t) = x_4(t).$$

Then the problem (1.1) – (1.2) is reduced the following form:

$$\dot{x}_1(t) = a - \beta_1 x_4(t) x_1(t) - d_1 x_1(t), \tag{2.1}$$
$$\dot{x}_2(t) = q x_1(t) x_4(t) - \beta_2 x_3(t) x_2(t) - d_2 x_2(t),$$
$$\dot{x}_3(t) = \beta_3 x_2(t) x_3(t) - d_3 x_3(t),$$

$$\dot{x}_4(t) = b x_2(t) - c x_4(t),$$

$$x_1(t_0) = x_{10},\ x_2(t_0) = x_{20},\ x_3(t_0) = x_{30}, \tag{2.2}$$

$$x_4(t_0) = x_{40},\ t_0 \in [0,\ a).$$

Let

$$x = x(t) = (x_1, x_2, x_3, x_4),\ x_j = x_j(t),\ j = 1, 2, 3, 4, \tag{2.3}$$
$$f_1(x) = a - \beta_1 x_4(t) x_1(t) - d_1 x_1(t)$$
$$f_2(x) = q x_1(t) x_4(t) - \beta_2 x_3(t) x_2(t) - d_2 x_2(t)$$
$$f_3(x) = \beta_3 x_2(t) x_3(t) - d_3 x_3(t),\ f_4(x) = b x_2(t) - c x_4(t).$$

Here,

$$\mathbb{R}_+^4 = \left\{x = (x_1, x_2, x_3, x_4) \in \mathbb{R}^4,\ x_k > 0\right\},$$

$$\Omega = \left\{x \in \mathbb{R}_+^4 \colon\ \beta_3 x_2 - \beta_1 x_4 - \beta_2 x_3 \leq d_1 + d_2 + d_3 + c.\right.$$

Consider the problem (2.1) – (2.2) with $t_0 = 0$.

Theorem 2.1. Then the system (2.1) is with the negative divergence and is dissipative in the domain $\Omega \subset \mathbb{R}_+^4$.

Proof. Indeed, from (2.1) and (2.2) we have

$$\frac{\partial f_1}{\partial x_1} + \frac{\partial f_2}{\partial x_2} + \frac{\partial f_3}{\partial x_3} + \frac{\partial f_4}{\partial x_4} = -(\beta_1 x_4 + d_1) -$$

$$\beta_2 x_3(t) - d_2 + \beta_3 x_2(t) - d_3 - c.$$

Hence, by Condittion 2.1, the system (2.1) is dissipative on the domain Ω.

3. The local stability of equilibria points

In this section, we will derive the stability properties of equilibria points of the system (1.1). Let

$$\mathbb{R}_{+}^{4}=\left\{x\in\mathbb{R}^{4}\colon\ x_i\geq 0,\ i=1,2,3,4\right\},\ B_r\left(\bar{x}\right)=\left\{x\in\mathbb{R}^{4},\ \left\|x-\bar{x}\right\|_{\mathbb{R}^{3}}<r\right\}.$$

Condition 3.1. Let

$$\frac{bd_3}{c}\neq d_1,\ bd_3\neq d_1c,\ \frac{ba_{33}a_{24}+a_{32}a_{23}c+a_{33}a_{21}a_{14}b}{a_{21}a_{14}b+ba_{33}a_{24}-a_{32}a_{23}}<0,\ d_3>\beta_3\bar{x}_2. \tag{3.1}$$

Theorem 3.1. Assume that the Condition 3.1 is satisfied.There is a point $P=(x_1,x_2,x_3,x)$ that is a equilibria points of the system (1.1) in $\mathbb{R}_{+}^{4}$.

Proof. It is sufficient to find the solution of the following system of algebraic equation in x_1, x_2, x_3, x_4:

$$a-\left(\beta_1x_4-d_1\right)x_1=0,\ qx_1x_4-\beta_2x_3x_2-d_2x_2=0,$$
$$\beta_3x_2x_3-d_3x_3=0,\ bx_2-cx_4=0. \tag{3.2}$$

From first and second equations we have

$$\bar{x}_1=\frac{a}{\left(\beta_1x_4-d_1\right)},\ qx_1x_4-\beta_2x_3x_2-d_2x_2=0. \tag{3.3}$$

From third and fourth equations we get

$$\left(\beta_3x_2-d_3\right)x_3=0,\ x_4=\frac{b}{c}x_2. \tag{3.4}$$

If $x_3\neq 0$ we get that $\bar{x}_2=\frac{d_3}{\beta_3}$. By (3.4), then we dedused that $\bar{x}_4=\frac{bd_3}{c\beta_3}$. Hence, from (3.3) we have

$$\bar{x}_1=\frac{a}{\left(\frac{bd_3}{c}-d_1\right)},$$

$$\bar{x}_3=\frac{1}{\beta_2\bar{x}_2}\left[q\bar{x}_1\bar{x}_4-d_2\bar{x}_2\right]=\frac{abq}{\left(bd_3-d_1c\right)\beta_2}-\frac{d_2}{\beta_2}.$$

Thus we obtain that the system (1.1) have a unique equalibria point $P\left(\bar{x}_1,\bar{x}_2,\bar{x}_3,\bar{x}_4\right)$, where

$$\bar{x}_1=\frac{a}{\left(\frac{bd_3}{c}-d_1\right)},\ \bar{x}_2=\frac{d_3}{\beta_3},\ \bar{x}_3=\frac{abq}{\left(bd_3-d_1c\right)\beta_2}-\frac{d_2}{\beta_2},\ \bar{x}_4=\frac{bd_3}{c\beta_3}. \tag{3.5}$$

Remark 3.1. For the point to have biological meaning of stability point $P\left(\bar{x}_1,\bar{x}_2,\bar{x}_3,\bar{x}_4\right)$, it should be

$$d_1<\frac{bd_3}{c},\ bd_3-d_1c>0,\ \beta_2\bar{x}_3+d_2>0. \tag{3.6}$$

We show here, the following results

Theorem 3.2. Assume that the Condition 3.1 is satisfied. Suppose the estimate (3.6) holds. Then the point $P(\bar{x}_1, \bar{x}_2, \bar{x}_3, \bar{x}_4)$ is locally stable point for the system of (1.1).

Proof. Consider the linearized matrix of (1.1), i.e. the Jacobian matrix according to system (1.1) at point $P(\bar{x}_1, \bar{x}_2, \bar{x}_3, \bar{x}_4)$ is the following:

$$A = \frac{Df}{Dx} = \begin{bmatrix} \frac{\partial f_1}{\partial x_1} & \frac{\partial f_1}{\partial x_2} & \frac{\partial f_1}{\partial x_3} & \frac{\partial f_1}{\partial x_4} \\ \frac{\partial f_2}{\partial x_1} & \frac{\partial f_2}{\partial x_2} & \frac{\partial f_2}{\partial x_3} & \frac{\partial f_2}{\partial x_4} \\ \frac{\partial f_3}{\partial x_1} & \frac{\partial f_3}{\partial x_2} & \frac{\partial f_3}{\partial x_3} & \frac{\partial f_3}{\partial x_4} \\ \frac{\partial f_4}{\partial x_1} & \frac{\partial f_4}{\partial x_2} & \frac{\partial f_4}{\partial x_2} & \frac{\partial f_4}{\partial x_3} \end{bmatrix} = \begin{bmatrix} a_{11} & 0 & 0 & a_{14} \\ a_{21} & a_{22} & a_{23} & a_{24} \\ 0 & a_{32} & a_{33} & 0 \\ 0 & b & 0 & -c \end{bmatrix}, \tag{3.7}$$

where $\beta_3 x_2(t) x_3(t) - d_3 x_3(t)$

$$a_{11} = -(\beta_1 \bar{x}_4 + d_1),\ a_{14} = -\beta_1 \bar{x}_1,\ a_{21} = q\bar{x}_4,\ a_{22} = -(\beta_2 \bar{x}_3 + d_2),$$

$$a_{23} = -\beta_2 \bar{x}_2,\ a_{24} = q\bar{x}_1,\ a_{32} = \beta_3 \bar{x}_3,\ a_{32} = \beta_3 \bar{x}_3,\ a_{33} = \beta_3 \bar{x}_2 - d_3. \tag{3.8}$$

The eigenvalues of the matrix A can found as the solutions of the following equations

$$A - \lambda I = \begin{bmatrix} a_{11} - \lambda & 0 & 0 & a_{14} \\ a_{21} & a_{22} - \lambda & a_{23} & a_{24} \\ 0 & a_{32} & a_{33} - \lambda & 0 \\ 0 & b & 0 & -(c + \lambda) \end{bmatrix} =$$

$$[a_{11} - \lambda] \begin{bmatrix} a_{22} - \lambda & a_{23} & a_{24} \\ a_{32} & a_{33} - \lambda & 0 \\ b & 0 & -(c + \lambda) \end{bmatrix} -$$

$$a_{21}(i) \begin{bmatrix} 0 & 0 & a_{14} \\ a_{32} & a_{33} - \lambda & 0 \\ b & 0 & -(c + \lambda) \end{bmatrix} = \tag{3.9}$$

$$(a_{11} - \lambda)[-(c + \lambda)(a_{22} - \lambda)(a_{33} - \lambda) -$$

$$ba_{24}(a_{33} - \lambda) + a_{32}a_{23}(c + \lambda)] + a_{21}a_{14}b(a_{33} - \lambda) = 0.$$

Let we put

$$(c + \lambda)(a_{22} - \lambda)(a_{33} - \lambda) = 0.$$

i.e. $\lambda_1 = -c$, $\lambda_2 = a_{22}$ and $\lambda_3 = a_{33}$ are the eigenvalues of A. Then other solutions of A can be obtained by solving the equation

$$ba_{24}(a_{33} - \lambda) + a_{32}a_{23}(c + \lambda)] + a_{21}a_{14}b(a_{33} - \lambda) = \tag{3.10}$$

$$(a_{21}a_{14}b + ba_{33}a_{24} - a_{32}a_{23})\lambda = ba_{33}a_{24} + a_{32}a_{23}c + a_{33}a_{21}a_{14}b = 0$$

By solving the equation (3.10) we get the fourth eigenvalue of the matrix A

$$\lambda_4 = \frac{ba_{33}a_{24} + a_{32}a_{23}c + a_{33}a_{21}a_{14}b}{a_{21}a_{14}b + ba_{33}a_{24} - a_{32}a_{23}}.$$

For local stability of the system (1.1) it is sufficient to show that all eigenvalues of the matrix A are negative. Indeed, by (3.5) and (3.6), we have

$$\lambda_1 = -c < 0,\ \lambda_2 = a_{22} = -\left(\beta_2\bar{x}_3 + d_2\right) < 0, \tag{3.11}$$

$$\lambda_3 = a_{33} = \beta_3\bar{x}_2 - d_3 < 0,\ \lambda_4 = \frac{ba_{33}a_{24} + a_{32}a_{23}c + a_{33}a_{21}a_{14}b}{a_{21}a_{14}b + ba_{33}a_{24} - a_{32}a_{23}} < 0.$$

By assumption (3.6), and by (3.5) we see that,

$$\bar{x}_1 \geq 0,\ \bar{x}_2 \geq 0,\ \bar{x}_3 \geq 0,\ \bar{x}_4 \geq 0.$$

Hence by (3.11) we get

$$\lambda_1 < 0,\ \lambda_2 < 0,\ \lambda_3 < 0.$$

Moreover, it should be

$$\lambda_4 = \frac{b\beta_3 q\bar{x}_1\bar{x}_2 - c\beta_2\beta_3\bar{x}_2\bar{x}_3 - b\beta_1\beta_3 q\bar{x}_1\bar{x}_2 x_4}{-b\beta_1 q\bar{x}_1\bar{x}_4 + b\beta_3 q\bar{x}_1\bar{x}_2 + \beta_2\beta_3\bar{x}_2\bar{x}_3} < 0. \tag{3.12}$$

The estimate (3.12) satisfies if:

$$b\beta_3 q\bar{x}_1\bar{x}_2 - c\beta_2\beta_3\bar{x}_2\bar{x}_3 - b\beta_1\beta_3 q\bar{x}_1\bar{x}_2\bar{x}_4 < 0, \tag{3.13}$$
$$-b\beta_1 q\bar{x}_1\bar{x}_4 + b\beta_3 q\bar{x}_1\bar{x}_2 + \beta_2\beta_3\bar{x}_2\bar{x}_3 > 0..$$

or

$$b\beta_3 q\bar{x}_1\bar{x}_2 - c\beta_2\beta_3\bar{x}_2\bar{x}_3 - b\beta_1\beta_3 q\bar{x}_1\bar{x}_2\bar{x}_4 > 0, \tag{3.14}$$
$$-b\beta_1 q\bar{x}_1\bar{x}_4 + b\beta_3 q\bar{x}_1\bar{x}_2 + \beta_2\beta_3\bar{x}_2 x_3 < 0;$$

Since $x_k \geq 0$ the second inequality in (3.13) satisfied for all $x \in \mathbb{R}^4_+$, when

$$b\beta_3 q\bar{x}_1\bar{x}_2 - c\beta_2\beta_3\bar{x}_2\bar{x}_3 - b\beta_1\beta_3 q\bar{x}_1\bar{x}_2\bar{x}_4 < 0,$$

i.e. by (3.5) if

$$\frac{bqad_3c}{bd_3 - d_1c} < \frac{cd_3abq + b\beta_1 qad_3^2 b}{(bd_3 - d_1c)}.$$

By assumption (3.6), the above inequality is satisfied when

$$d_3c < cd_3 + \beta_1 d_3^2 b,$$

that it is clear that holds for all $x \in \mathbb{R}^4_+$. Since $b\beta_1 q\bar{x}_1\bar{x}_4 + b\beta_3 q\bar{x}_1\bar{x}_2 + \beta_2\beta_3\bar{x}_2\bar{x}_3 \geq 0$ for all $x \in \mathbb{R}^4_+$, the inequality (3.14) does not satisfied in $\mathbb{R}^4_+$. Hence we obtain that all eigenvalues of the matrix are negative under our assumptions.

In Figs. 1-3, We compare the viruses with the effector immune cells, the infected cells and uninfected cells. When the free viruses increase rapidly, the infected cells and uninfected cells decrease so quickly in Fig1 and Fig2. On the other hand, free virus does not increase rapidly when effector immunity in Fig3 decreases rapidly.

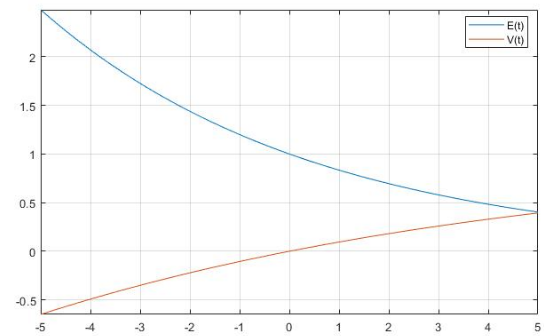

Figure 1: We compare effector immune cells(E(t)) and free viruses(V(t)). They are $E(0) > 0$ and $V(0) = 0$.

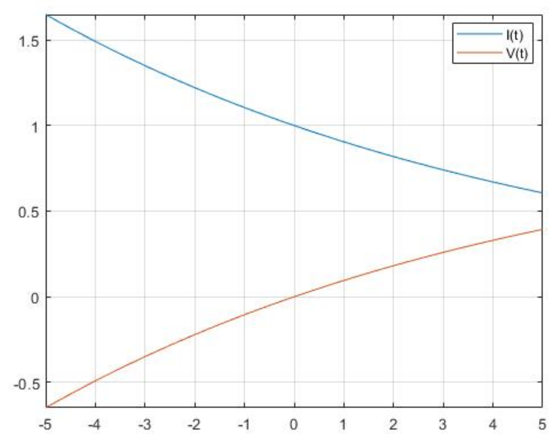

Figure 2: We compare infected cells(I(t)) and free viruses(V(t)). They are $I(0) > 0$ and $V(0) = 0$

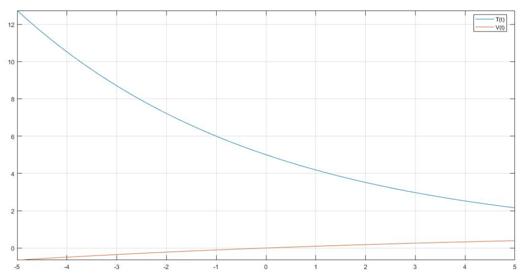

Figure 3: We compare uninfected cells (T(t)) and free viruses (V(t)). They are $T(0) > 0$ and $V(0) = 0$.

4. Lyapunov stability of equilibria points

Let $E(\bar{x})$ is a equilibria point, where $\bar{x} = (\bar{x}_1, \bar{x}_2, \bar{x}_3, \bar{x}_4) \in \mathbb{R}^4_+$ is defined by (3.5). In this section we show the following results: Let $A = A(\bar{x})$ be the linearized matrix with respect to equilibria $E(\bar{x})$ point defined by (3.7), i.e.

$$A = \begin{bmatrix} a_{11} & 0 & 0 & a_{14} \\ a_{21} & a_{22} & a_{23} & a_{24} \\ 0 & a_{32} & a_{33} & 0 \\ 0 & b & 0 & -c \end{bmatrix},$$

where a_{ij} are defined by (3.8). We consider the Lyapunov equation

$$BA + A^T B = -I, B = B(\bar{x}) = \begin{bmatrix} b_{11} & b_{12} & b_{13} & b_{14} \\ b_{21} & b_{22} & b_{23} & b_{24} \\ b_{31} & b_{32} & b_{33} & b_{34} \\ b_{41} & b_{42} & b_{43} & b_{44} \end{bmatrix}, b_{ij} = b_{ji}. \qquad (4.1)$$

It is clear that

$$BA = \begin{bmatrix} b_{11} & b_{12} & b_{13} & b_{14} \\ b_{21} & b_{22} & b_{23} & b_{24} \\ b_{31} & b_{32} & b_{33} & b_{34} \\ b_{41} & b_{42} & b_{43} & b_{44} \end{bmatrix} \begin{bmatrix} a_{11} & 0 & 0 & a_{14} \\ a_{21} & a_{22} & a_{23} & a_{24} \\ 0 & a_{32} & a_{33} & 0 \\ 0 & b & 0 & -c \end{bmatrix} =$$

$$\begin{bmatrix} -a_{11}b_{11} + a_{21}b_{12} & a_{22}b_{12} + a_{32}b_{13} + bb_{14} & a_{23}b_{12} + a_{33}b_{13} & a_{14}b_{11} + a_{24}b_{12} - cb_{14} \\ a_{11}b_{21} + a_{21}b_{22} - & a_{22}b_{22} + a_{32}b_{23} + bb_{24} & a_{23}b_{22} + a_{33}b_{23} & a_{14}b_{21} + a_{24}b_{22} - cb_{24} \\ a_{11}b_{31} + a_{21}b_{32} - & a_{22}b_{32} + a_{32}b_{33} + bb_{34} & a_{23}b_{32} + a_{33}b_{33} & a_{14}b_{31} + a_{24}b_{32} - cb_{34} \\ a_{11}b_{41} + a_{21}b_{42} - & a_{22}b_{42} + a_{32}b_{43} + bb_{44} & a_{23}b_{42} + a_{33}b_{43} & a_{14}b_{41} + a_{24}b_{42} - cb_{44} \end{bmatrix},$$

$$A^TB = \begin{bmatrix} -a_{11} & a_{21} & 0 & 0 \\ 0 & a_{22} & a_{32} & b \\ 0 & a_{23} & -a_{33} & 0 \\ a_{14} & a_{24} & 0 & -c \end{bmatrix} \begin{bmatrix} b_{11} & b_{12} & b_{13} & b_{14} \\ b_{21} & b_{22} & b_{23} & b_{24} \\ b_{31} & b_{32} & b_{33} & b_{34} \\ b_{41} & b_{42} & b_{43} & b_{44} \end{bmatrix} =$$

$$\begin{bmatrix} a_{11}b_{11} + a_{21}b_{21} & a_{11}b_{12} + a_{21}b_{22} & a_{11}b_{13} + a_{21}b_{23} & a_{11}b_{14} + a_{21}b_{24} \\ a_{22}b_{21} + a_{32}b_{31} + bb_{41} & a_{22}b_{22} + a_{32}b_{32} + bb_{42} & a_{22}b_{23} + a_{32}b_{33} + bb_{43} & a_{22}b_{24} + a_{32}b_{34} + bb_{44} \\ a_{23}b_{21} + a_{33}b_{31} & a_{23}b_{22} + a_{33}b_{32} & a_{23}b_{23} + a_{33}b_{33} & a_{23}b_{24} + a_{33}b_{34} \\ -a_{14}b_{11} + a_{24}b_{21} - cb_{41} & a_{14}b_{12} + a_{24}b_{22} - cb_{42} & a_{14}b_{13} + a_{24}b_{23} - cb_{43} & a_{14}b_{14} + a_{24}b_{24} - cb_{44} \end{bmatrix}.$$

(4.1) reduced to the following equation

$$BA + A^TB = \begin{bmatrix} g_{11} & g_{12} & g_{13} & g_{14} \\ g_{21} & g_{22} & g_{23} & g_{24} \\ g_{31} & g_{32} & g_{33} & g_{34} \\ g_{41} & g_{42} & g_{43} & g_{44} \end{bmatrix} = -I, \tag{4.2}$$

where

$$\begin{gathered} g_{11} = 2a_{11}b_{11} + 2a_{21}b_{12} = -1, \\ g_{12} = (a_{11} + a_{22})\, b_{12} + a_{32}b_{13} + bb_{14} + a_{21}b_{22} = 0, \\ g_{13} = a_{23}b_{12} + (a_{11} + a_{33})\, b_{13} + a_{21}b_{23} = 0, \\ g_{14} = a_{14}b_{11} + a_{24}b_{12} + (a_{11} - c)\, b_{14} + a_{21}b_{24} = 0, \\ g_{22} = 2a_{22}b_{22} + 2a_{32}b_{23} + 2bb_{24} = -1, \\ g_{23} = a_{23}b_{22} + (a_{22} + a_{33})\, b_{23} + a_{32}b_{33} + bb_{34} = 0, \\ g_{24} = a_{14}b_{12} + a_{24}b_{22} + (a_{22} - c)\, b_{24} + a_{23}b_{34} + bb_{44} = 0, \\ g_{33} = 2a_{23}b_{23} + 2a_{33}b_{33} = -1, \\ g_{34} = a_{14}b_{13} + a_{24}b_{23} + (a_{33} - c)\, b_{34} + a_{23}b_{24} = 0, \\ g_{44} = 2a_{14}b_{14} + 2a_{24}b_{24} - 2cb_{44} = -1. \end{gathered} \tag{4.3}$$

Main and associated determinants of the system (4.3) in $b_{11}, b_{12}, b_{13}, b_{14}, b_{22}, b_{23}, b_{24}, b_{33}, b_{34}, b_{44}$ is the following

$$\Delta = \begin{vmatrix} 2a_{11} & 2a_{21} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & a_{11} + a_{22} & a_{11} + a_{33} & a_{21} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & a_{23} & a_{11} + a_{33} & 0 & 0 & a_{21} & 0 & 0 & 0 & 0 \\ a_{14} & a_{24} & 0 & (a_{11} - c) & 0 & 0 & a_{21} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 2a_{22} & 2a_{32} & 2b & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & a_{23} & a_{22} + a_{33} & 0 & a_{32} & b & 0 \\ 0 & a_{14} & 0 & 0 & a_{24} & 0 & (a_{22} - c) & 0 & a_{23} & b \\ 0 & 0 & 0 & 0 & 0 & 2a_{23} & 0 & 2a_{33} & 0 & 0 \\ 0 & 0 & a_{14} & 0 & 0 & a_{24} & a_{23} & 0 & (a_{33} - c) & 0 \\ 0 & 0 & 0 & 2a_{14} & 0 & 0 & 2a_{24} & 0 & 0 & -2cb \end{vmatrix},.$$

$$\Delta_1 = \begin{vmatrix} -1 & 2a_{21} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & a_{11}+a_{22} & a_{11}+a_{33} & a_{21} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & a_{23} & a_{11}+a_{33} & 0 & 0 & a_{21} & 0 & 0 & 0 & 0 \\ -0 & a_{24} & 0 & (a_{11}-c) & 0 & 0 & a_{21} & 0 & 0 & 0 \\ -1 & 0 & 0 & 0 & 2a_{22} & 2a_{32} & 2b & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & a_{23} & a_{22}+a_{33} & 0 & a_{32} & b & 0 \\ 0 & a_{14} & 0 & 0 & a_{24} & 0 & (a_{22}-c) & 0 & a_{23} & b \\ -1 & 0 & 0 & 0 & 0 & 2a_{23} & 0 & 2a_{33} & 0 & 0 \\ 0 & 0 & a_{14} & 0 & 0 & a_{24} & a_{23} & 0 & (a_{33}-c) & 0 \\ -1 & 0 & 0 & 2a_{14} & 0 & 0 & 2a_{24} & 0 & 0 & -2cb \end{vmatrix},$$

$$\Delta_2 = \begin{vmatrix} 2a_{11} & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & a_{11}+a_{33} & a_{21} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & a_{11}+a_{33} & 0 & 0 & a_{21} & 0 & 0 & 0 & 0 \\ a_{14} & 0 & 0 & (a_{11}-c) & 0 & 0 & a_{21} & 0 & 0 & 0 \\ 0 & -1 & 0 & 0 & 2a_{22} & 2a_{32} & 2b & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & a_{23} & a_{22}+a_{33} & 0 & a_{32} & b & 0 \\ 0 & 0 & 0 & 0 & a_{24} & 0 & (a_{22}-c) & 0 & a_{23} & b \\ 0 & -1 & 0 & 0 & 0 & 2a_{23} & 0 & 2a_{33} & 0 & 0 \\ 0 & 0 & a_{14} & 0 & 0 & a_{24} & a_{23} & 0 & (a_{33}-c) & 0 \\ 0 & -1 & 0 & 2a_{14} & 0 & 0 & 2a_{24} & 0 & 0 & -2cb \end{vmatrix},$$

...

$$\Delta_{10} = \begin{vmatrix} 2a_{11} & 2a_{21} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 \\ 0 & a_{11}+a_{22} & a_{11}+a_{33} & a_{21} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & a_{23} & a_{11}+a_{33} & 0 & 0 & a_{21} & 0 & 0 & 0 & 0 \\ a_{14} & a_{24} & 0 & (a_{11}-c) & 0 & 0 & a_{21} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 2a_{22} & 2a_{32} & 2b & 0 & 0 & -1 \\ 0 & 0 & 0 & 0 & a_{23} & a_{22}+a_{33} & 0 & a_{32} & b & 0 \\ 0 & a_{14} & 0 & 0 & a_{24} & 0 & (a_{22}-c) & 0 & a_{23} & 0 \\ 0 & 0 & 0 & 0 & 0 & 2a_{23} & 0 & 2a_{33} & 0 & -1 \\ 0 & 0 & a_{14} & 0 & 0 & a_{24} & a_{23} & 0 & (a_{33}-c) & 0 \\ 0 & 0 & 0 & 2a_{14} & 0 & 0 & 2a_{24} & 0 & 0 & -1 \end{vmatrix}..$$

We assume that $\Delta \neq 0$. Then by by solving (4.3) with respect to b_{ij} by Kramer method, we obtain

$$b_{11} = \frac{\Delta_1}{\Delta},\ b_{12} = b_{21} = \frac{\Delta_2}{\Delta},\ ..., b_{44} = \frac{\Delta_n}{\Delta}. \tag{4.4}$$

Theorem 4.1. Assume the Condition 3.1 holds, $\Delta \neq 0$. Suppose a_{ij} such that $b_{ii} > 0$, $i = 1, 2, 3, 4$, $b_{ij} \geq 0$ for $i, j = 1, 2, 3, 4$, when $i \neq j$. Then the system (2.1) is asymptotically stable at the equilibria point $E(\bar{x})$ in the sense of Lyapunov.

Proof. By assumptions the function $P_A(x)$ associated with tha matrix A defined by

$$P_B(x) = x^T B x = \sum_{i,j=1}^{4} b_{ij} x_i x_j$$

is positive defined in $\mathbb{R}^4$. Hence, all eigenvalues $\lambda_1, \lambda_2, \lambda_3, \lambda_4$ of the the matrix $B = B(\bar{x})$ is positive in $\mathbb{R}^4$, i.e. $P_B(x)$ is a positive defined Lyapunov function candidate (see e.g. [22, 23]). By [12, Corollary 8.2]. We need now to determine a domain Ω on which $\dot{P}_B(x)$ is negatively defined. By assuming $x_k \geq 0$, $k = 1, 2, 3, 4$ we will find the solution set of the following inequality

$$f_1(x) = a - \beta_1 x_4(t) x_1(t) - d_1 x_1(t)$$

$$f_2(x) = q x_1(t) x_4(t) - \beta_2 x_3(t) x_2(t) - d_2 x_2(t)$$

$$f_3(x) = \beta_3 x_2(t) x_3(t) - d_3 x_3(t), \ f_4(x) = b x_2(t) - c x_4(t).$$

$$\dot{P}_B(x) = \sum_{j=1}^{4} \frac{\partial \dot{P}_B}{\partial x_j} f_j(x) =$$

$$2(b_{11}x_1 + b_{12}x_2 + b_{13}x_3 + b_{14}x_4)(a - \beta_1 x_4 x_1 - d_1 x_1) +$$

$$\begin{gathered} 2(b_{21}x_1 + b_{22}x_2 + b_{23}x_3 + b_{24}x_4)(q x_1 x_4 - \beta_2 x_3 x_2 - d_2 x_2) + \\ 2(b_{31}x_1 + b_{32}x_2 + b_{33}x_3 + b_{34}x_4)(\beta_3 x_2 x_3 - d_3 x_3) + \\ 2(b_{31}x_1 + b_{32}x_2 + b_{33}x_3 + b_{34}x_4)(b x_2 - c x_4) \leq 0. \end{gathered} \tag{4.5}$$

Hence, the system (2.1) is asymptotically stabile at $E(\bar{x})$ in the Lyapunov sense when,

$$a - \beta_1 x_4 x_1 - d_1 x_1 \leq 0, \ q x_1 x_4 - \beta_2 x_3 x_2 - d_2 x_2 \leq 0,$$

$$\beta_3 x_2 x_3 - d_3 x_3 \leq 0, \ \ b x_2 - c x_4,$$

i.e. the system (2.1) is asymptotically stabile at $E(\bar{x})$ in the Lyapunov sense in the following domain

$$\begin{gathered} \Omega_1 = \left\{ x \in \mathbb{R}_+^4 : \ (\beta_1 x_4 + d_1) x_1 \geq a, \ (\beta_2 x_3 + d_2) x_2 \geq \ q x_1 x_4, \right. \\ \left. \beta_3 x_2 \leq d_3 \right\}, \ x_4 \geq \frac{b}{c} x_2. \end{gathered} \tag{4.6}$$

Theorem 4.2. Assume the Condition 3.1 holds, $\Delta \neq 0$. Suppose a_{ij} such that $b_{ii} > 0$, $i = 1, 2, 3, 4$ and $b_{ij} \leq 0$ for $i, j = 1, 2, 3, 4$ when $i \neq j$.

Then the system (2.1) is asymptotically stable at the equilibria point $E(\bar{x})$ in the sense of Lyapunov.

Proof.

$$P_B(x) = x^T B x = \sum_{i,j=1}^{4} b_{ij} x_i x_j =$$

$$\frac{1}{4} b_{11} \left(x_1 + \frac{4b_{12}}{b_{11}} x_2 \right)^2 + \left[\frac{1}{3} b_{22} - \frac{4b_{12}^2}{b_{11}} \right] x_2^2 + \frac{1}{4} b_{11} \left(x_1 + \frac{b_{13}}{b_{11}} x_3 \right)^2 +$$

$$\left[\frac{1}{3} b_{33} - \frac{4b_{13}^2}{b_{11}} \right] x_3^2 + b_{11} \left(x_1 + \frac{b_{14}}{b_{11}} x_4 \right)^2 + \left[\frac{1}{3} b_{44} - \frac{4b_{14}^2}{b_{11}} \right] x_4^2 +$$

$$\frac{1}{3} b_{22} \left(x_2 + 3\frac{b_{23}}{b_{22}} x_3 \right)^2 + \left[\frac{1}{3} b_{33} - \frac{9b_{23}^2}{b_{22}} \right] x_3^2 + \frac{1}{3} b_{22} \left(x_2 + \frac{3b_{24}}{b_{22}} x_4 \right)^2 +$$

$$\left[\frac{1}{3} b_{44} - \frac{9b_{24}^2}{b_{22}} \right] x_4^2 + \frac{1}{3} b_{33} \left(x_3 + \frac{3b_{34}}{b_{33}} x_4 \right)^2 + \left[\frac{1}{3} b_{44} - \frac{9b_{34}^2}{b_{33}} \right] x_4^2 \geq 0,$$

when

$$\frac{1}{3} b_{22} \geq \frac{4b_{12}^2}{b_{11}},\ \frac{1}{3} b_{33} \geq \frac{4b_{13}^2}{b_{11}},\ \frac{1}{3} b_{44} \geq \frac{4b_{14}^2}{b_{11}},\ \frac{1}{3} b_{33} \geq \frac{9b_{23}^2}{b_{22}},$$

$$\frac{1}{3} b_{44} \geq \frac{9b_{24}^2}{b_{22}},\ \frac{1}{3} b_{44} \geq \frac{9b_{34}^2}{b_{33}}.$$

Then by resoaning as in Theorem 4.1. we obatain the conclusion.

Remark 4.2. Assume the Condition 3.1 holds, $\Delta \neq 0$. Suppose a_{ij} such that $b_{ii} > 0$, $i = 1, 2, 3, 4$, $b_{ij} \geq 0$ for $i, j = 1, 2$ and $b_{ij} \leq 0$ for $i, j = 3, 4$ when $i \neq j$ or

$b_{ij} \leq 0$ for $i, j = 1, 2$ and $b_{ij} \geq 0$ for $i, j = 3, 4$ when $i \neq j$. Then a similar way as in Theorem 4.1 we get that Then the system (2.1) is asymptotically stable at the equilibria point $E(\bar{x})$ in the sense of Lyapunov.

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