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On the Stability Analysis of the General Mathematical Modeling of Bacterial Infection

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Abstract

In this study, a mathematical model in form ODEs system examined the dynamics among populations of susceptible bacteria and resistant bacteria to antibiotic, antibiotic concentration and hosts immune system cells in an individual (or host), received antibiotic therapy in the case of a local bacterial infection, was proposed. For equilibrium points of this model, both local and global stability analysis have been also performed. In addition that, results of these analysis have been supported by numerical simulations.

Keywords: Mathematical model, Stability analysis, Numerical simulation, Immune system, Antibiotic.

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1. Introduction

Infections are shown as the main cause of diseases throughout human history and bacterial ones among these are more noticeable [1]. The first respond of host to such infections is through its immune system [2]. In this sense, the different host reactions to fight the same infection may be different due to hosts immune system response. If the host can not provide the respond required to destroy or limit the infection, then additional procedures can be needed. The most prevalent method for struggling bacterial infection is by way of antibiotic therapy. Howeover, the most important problem derived from this therapy is the development of the bacteria resistance ability against the used antibiotic. Resistance to antimicrobial agents is both the reasonable and expected result of the use of these agents to treat human infections [3]. In this respect, the dynamics among antibiotic therapy, immune cells and bacteria in case of bacterial infection in host are significant to find out the character of the infection.

Mathematical models used in analyzed of biological applications are significant tools used not only in researching the spread of infectious diseases of individuals in a population, but also in estimating the timing and expansion of infection and possible reinfection processes in an individual [4,5]. Discovering the early dynamics of acute infections and foreseeing the time of

occurrence and magnitude of the maximum load of the bacteria and the immune system cells can be vital in choice of the efficient interference schemes [6].
In this study, it has been formed a continuous time model considering immune system response of host against bacteria causing infection and the main functions of bacterial resistance occuring due to effect of antibiotic. In this context, the aim of proposed model is to get the specific circumstances connected on the bacteria growth under the pressure of immune cells and antibiotic.

2. Mathematical Model

It has constituted this study by considering within-host models. Many of existing mathematical models, which assume that resistance development as a consequence of antibiotic use is in the host, are investigate how antibiotic treatment methods can both cause and be focused to avoid the occurrence of antibiotic resistance [7,8]. In addition that, the influences of the hosts immune system response due to the bacterial infection are often either ignored or presumed at a constant rate. In here, it has been generated the mathematical model comprising the effects of cell-mediated immune response. Also, treatment forms containing antibiotic have implemented in most bacterial infections. The effects of antibiotic therapy by using Holling function is examined. In this sense, it has been investigated the changes in concentrations of the bacteria and immune cells in a host receiving antibiotic treatment to fight off infectious bacteria by mathematical modelling.
It has presumed that $S(t)$ and $R(t)$ symbolize the population sizes of susceptible and resistant bacteria to antibiotic at time t, respectively. In addition that, it has assumed that $B(t)$ and $A(t)$ denote the population sizes of immune cells and the antibiotic concentration at time t, respectively. By aforementioned assumptions, it has obtained the following system of four ODE:

$$\begin{aligned}
\frac{dS}{dt} &= \beta_S S\left(1-\frac{S+R}{T}\right) - \overline{\eta}SB - S\frac{E_{max}A}{E_{50}+A} - \mu SA - \sigma SR \\
\frac{dR}{dt} &= \beta_R R\left(1-\frac{S+R}{T}\right) - \overline{\eta}RB + \mu SA + \sigma SR \\
\frac{dB}{dt} &= \beta_B B\left(1-\frac{B}{\Lambda}\right) - \lambda B(S+R) \\
\frac{dA}{dt} &= -\alpha A
\end{aligned} \tag{1}$$

where $S \equiv S(t)$, $R \equiv R(t)$, $B \equiv B(t)$ and $A \equiv A(t)$ and the system (1) has to be finished with positive initial conditions $S(t_0) = S_0$, $R(t_0) = R_0$, $B(t_0) = B_0$ and $A(t_0) = A_0$. In addition, the expressions of these parameters are as follows: it is presumed that bacteria have a logistic growth rule and its the carrying capacity is T. The parameters β_S and β_R are the growth rate of susceptible and resistant bacteria, respectively. Specific mutations emerging resistance to chemical control often include an inherent fitness cost which may be outcomed through reduced reproductive capacity and/or competitive ability [6]. Therefore, it is

$$\beta_S > \beta_R \tag{2}$$

In the same mind in the bacteria growth, immune cells produce by logistic growth rule, and so, they are recruited to the site of infection at rate β_B and its carrying capacity is Λ [9,10]. Immune cells are lost through pathogen-induced apoptosis (at rate λ). In the presence of the pathogen, this is biological meaningful when proliferation of immune cells is considered. These interacts among bacteria, immune cells and antibiotic have depicted a generalised mathematical model of a local bacterial infection, such as wound infection or tuberculosis. The above scenario related to the parameters used in the model (1) has been graphically described in Fig.1.

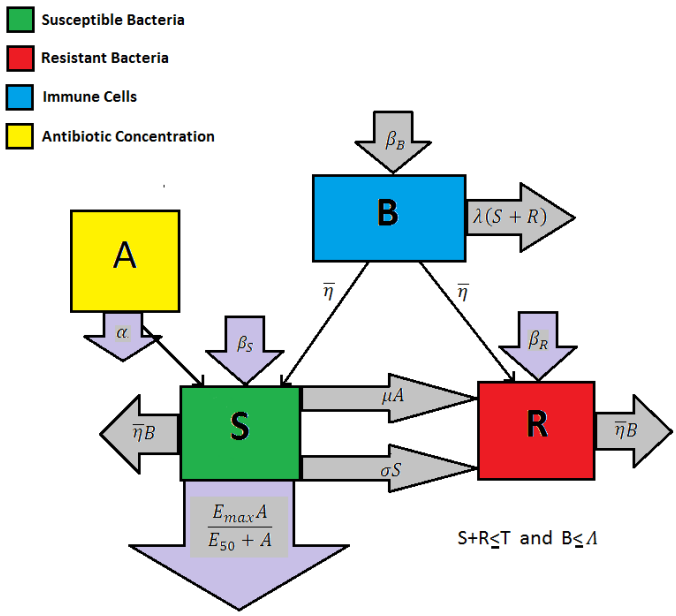

Fig.1. In the model (1), schematic representation of the main interactions involved in an infection treated by antibiotics with S (antibiotic-susceptible bacteria), R (antibiotic-resistant bacteria), B (immune cells, e.g. phagocytes or B cells), A (antibiotic concentration)

It is assumed that antibiotic has administered in dose α [11,12]. Through the administration of the antibiotic, a number of resistant bacteria to this antibiotic can emerge due to mutations of susceptible bacteria exposed to such antibiotic and this case is modelled by μSA where the mutation rate of susceptible bacteria due to exposure to antibiotic is μ. In addition that, the most common form of resistance acquisition to antibiotic is the conjugation including the transfer of genes between susceptible and resistant bacteria [13,14]. Since this transfer occurs between adjacent bacteria in a well mixed population [15,16], we have represented that this interaction through mass action kinetics with a conjugation rate, σ, being proportional to the levels of susceptible and resistant bacteria to antibiotic in the population [17,18].

Moreover, bacteria have per capita rates of death due to immune cells response of host, and so this rate in (1) is $\overline{\eta}$. In addition that, susceptible bacteria die due to the antibiotic effect. It has supposed that the effect of the antibiotic on susceptible bacteria is modelled by using a saturating response. This response is $\frac{E_{max}A}{E_{50}+A}$ where E_{max} and E_{50} are the maximum killing rate and the antibiotic concentration needed for half maximum effect, respectively [11,17,19,20]. For the parameters used in the model, it has satisfied

$$\beta_S, \beta_R, \beta_B, T, \Lambda, \mu, \overline{\eta}, E_{max}, E_{50}, \sigma, \lambda, \alpha > 0. \tag{3}$$

For the ease analyze of the model (1), it has changed the variables as folows

$$s = \frac{S}{T}, r = \frac{R}{T}, b = \frac{B}{\Lambda}, a = \frac{A}{\frac{\overline{\eta}\Lambda}{\mu}}. \tag{4}$$

By (4), the model (1) transforms to following system:

$$\begin{aligned} \frac{ds}{dt} &= \eta\left(k_1 s\big(1-(s+r)\big) - bs - \left(\frac{E_{max}}{E_{50}\mu+\eta a}+1\right)as - k_4 sr\right) \\ \frac{dr}{dt} &= \eta\big(k_2 r\big(1-(s+r)\big) - br + as + k_4 sr\big) \\ \frac{db}{dt} &= \beta_B b\big((1-b) - k_3(s+r)\big) \\ \frac{da}{dt} &= -\alpha a \end{aligned} \tag{5}$$

where

$$\begin{aligned} &\frac{\beta_S}{\overline{\eta}\Lambda} = k_1, \frac{\beta_R}{\overline{\eta}\Lambda} = k_2, \frac{\lambda T}{\beta_B} = k_3, \frac{\sigma T}{\overline{\eta}\Lambda} = k_4, \overline{\eta}\Lambda = \eta, \\ &k_1, k_2, k_3, k_4, \eta > 0 \end{aligned} \tag{6}$$

Moreover, it is obtained

$$k_1 > k_2 \tag{7}$$

by (2) and (6). The studied region as biological is given by the set

$$\Omega = \{(s, r, b, a) \in R^4 : 0 \le s, r, 0 \le s + r \le 1, 0 \le b \le 1, 0 \le a \le a(0)\}. \tag{8}$$

where $a(0)$ is positive initial condition of a.

Proposition 2.1. The region Ω definiting in (8) is positively invariant for the system (5).
Proof: From the first and second equations in the system (5), it is

$$\frac{ds}{dt} + \frac{dr}{dt} = (k_1 s + k_2 r)\eta\big(1-(s+r)\big) - b\eta(s+r) - as\frac{\eta E_{max}}{E_{50}\mu+\eta a} \tag{9}$$

Considering the region Ω, it has reached the following inequality;

$$\frac{d(s+r)}{dt} \leq k_1\eta(s+r)\big(1-(s+r)\big). \tag{10}$$

By the solution according to $(s+r)$ of inequality (10), it has followed that $0 \leq s+r \leq 1$ for all $t \geq 0$. In the same mind, we have

$$\frac{db}{dt} \leq \beta_B b(1-b) \tag{11}$$

from third equation in system (5). Therefore, it has obtained $0 \leq b \leq 1$ for all $t \geq 0$ by (11).

Furthermore, the solution of the last equations of system (5) is

$$a(t) = a(0)e^{-\alpha t} \tag{12}$$

with positive initial conditions, $a(0)$. From (12), it is obtained that $0 \leq a \leq a(0)$ for all $t \geq 0$. Let consider the vector field of the system (5) limited to the boundary of Ω. This field does not includes a point at the exterior of it. Thereby, the solutions starting there is in the region Ω for all $t \geq 0$ and these solutions have biological meaning.

3. Qualitative Analysis of System (5)

In here, the equilibrium points of system (5) is founded. Lastly, the analyze of both the local stability and global stability of these equilibrium points is done.

3.1. Equilibrium Points

We have accepted that the general terms of equilibria contained in Ω of the system (5) show as $E_j = \left(\overline{s}, \overline{r}, \overline{b}, \overline{a}\right)$ for $j = 1,2,\dots,6$.

Proposition 3.1. The system (5) always has the infection-free equilibrium points $E_0 = (0,0,0,0)$ and $E_1 = (0,0,1,0)$, and other points $E_2 = (0,1,0,0)$ and $E_3 = (1,0,0,0)$. If $k_3 < 1 < k_2$ or $k_2 < 1 < k_3$, then $E_4 = \left(0, \frac{(k_2-1)}{(k_2-k_3)}, \frac{k_2(1-k_3)}{(k_2-k_3)}, 0\right)$ exists. Likewise, when $k_3 < 1 < k_1$ or $k_1 < 1 < k_3$, then $E_5 = \left(\frac{(k_1-1)}{(k_1-k_3)}, 0, \frac{k_1(1-k_3)}{(k_1-k_3)}, 0\right)$ reveals in Ω. Moreover, if $k_2 < \frac{(1-k_3)(k_1-k_2)}{k_4} + 1 < min\left\{k_1, \frac{k_1-k_2}{k_4}+1\right\}$, then $E_6 = \left(\frac{1}{k_4} - \frac{k_2+\frac{k_3}{k_4}(k_1-k_2)}{k_1-k_2+k_4}, \frac{k_1+\frac{k_3}{k_4}(k_1-k_2)}{k_1-k_2+k_4} - \frac{1}{k_4}, 1 - k_3\frac{k_1-k_2}{k_1-k_2+k_4}, 0\right)$ exists as another equilibrium points.

Proof: The equilibrium points the system (5) in Ω are obtained by solving the following system:

$$\begin{aligned}
&\eta s\left(k_1\big(1-(s+r)\big)-b-\left(\frac{E_{max}}{E_{50}\mu+\eta a}+1\right)a-k_4 r\right)=0\\
&\eta r\left(k_2\big(1-(s+r)\big)-b+a\frac{s}{r}+k_4 s\right)=0\\
&\beta_B b\big((1-b)-k_3(s+r)\big)=0\\
&-\alpha a=0.
\end{aligned} \tag{13}$$

From the last equation of system (13), we have $\overline{a}=0$ for all of the equilibrium points. Therefore, (13) transforms to

$$\begin{aligned}
&s\big(k_1\big(1-(s+r)\big)-b-k_4 r\big)=0\\
&r\big(k_2\big(1-(s+r)\big)-b+k_4 s\big)=0\\
&b\big((1-b)-k_3(s+r)\big)=0.
\end{aligned} \tag{14}$$

By solving (14), it is obtained the equilibrium points following:

$$\begin{aligned}
&E^I=\left(\left(\frac{1}{-k_1+k_2-k_4}\right)k_2,-\left(\frac{1}{-k_1+k_2-k_4}\right)k_1,0,0\right),\\
&E_0=(0,0,0,0),E_1=(0,0,1,0),E_2=(0,1,0,0),E_3=(1,0,0,0),\\
&E_4=\left(0,\frac{k_2-1}{k_2-k_3},\frac{k_2(1-k_3)}{k_2-k_3},0\right),E_5=\left(\frac{k_1-1}{k_1-k_3},0,\frac{k_1(1-k_3)}{k_1-k_3},0\right),\\
&E_6=\left(\frac{1}{k_4}-\frac{k_2+\frac{k_3}{k_4}(k_1-k_2)}{k_1-k_2+k_4},\frac{k_1+\frac{k_3}{k_4}(k_1-k_2)}{k_1-k_2+k_4}-\frac{1}{k_4},1-k_3\frac{k_1-k_2}{(k_1-k_2+k_4)},0\right).
\end{aligned} \tag{15}$$

Altought the equilibrium points E_0,E_1,E_2 and E_3, on the orijin, b-axis, r-axis and s-axis respectively, always exist in Ω, the equilibrium point E^I in which signs of $\overline{s}$ and $\overline{r}$ are opposite due to (6), is not biological meaning. Thereby, E^I is not in Ω. If $0<\frac{(k_2-1)}{(k_2-k_3)}<1$ and $0<\frac{k_2(1-k_3)}{k_2-k_3}<1$, that is, $k_3<1<k_2$ or $k_2<1<k_3$, then an interior planar equilibrium E_4 occuring in the $r-b$ plane exists in Ω. In the same mind, when $0<\frac{k_1-1}{k_1-k_3}<1$ and $0<\frac{k_1(1-k_3)}{k_1-k_3}<1$, that is, $k_3<1<k_1$ or $k_1<1<k_3$, E_5 occurs in the $s-b$ plane in Ω. Moreover, if $0<1-\frac{k_3(k_1-k_2)}{k_1-k_2+k_4}<1$, $0<\frac{1}{k_4}-\frac{k_2+\frac{k_3}{k_4}(k_1-k_2)}{k_1-k_2+k_4}<1$ and $0<\frac{k_1+\frac{k_3}{k_4}(k_1-k_2)}{k_1-k_2+k_4}-\frac{1}{k_4}<1$, that is, $k_2<\frac{(1-k_3)(k_1-k_2)}{k_4}+1<min\left\{k_1,\frac{k_1-k_2}{k_4}+1\right\}$, then E_6, the interior equilibrium occuring in the $s-r-b$ plane, exists in Ω.

In table 1, proposition 3.1 is summarized.

Table 1. Biological meaning conditions for the equilibrium points founded in proposition 3.1.

The Equilibrium Point	**The Biological Existence Condition**
$E_0 = (0,0,0,0)$	Always exists
$E_1 = (0,0,1,0)$	Always exists
$E_2 = (0,1,0,0)$	Always exists
$E_3 = (1,0,0,0)$	Always exists
$E_4 = \left(0, \frac{(k_2-1)}{(k_2-k_3)}, \frac{k_2(1-k_3)}{(k_2-k_3)}, 0\right)$	$k_3 < 1 < k_2$ or $k_2 < 1 < k_3$
$E_5 = \left(\frac{(k_1-1)}{(k_1-k_3)}, 0, \frac{k_1(1-k_3)}{(k_1-k_3)}, 0\right)$	$k_3 < 1 < k_1$ or $k_1 < 1 < k_3$
$E_6 = \left(\frac{1}{k_4} - \frac{k_2 + \frac{k_3}{k_4}(k_1-k_2)}{k_1-k_2+k_4}, \frac{k_1 + \frac{k_3}{k_4}(k_1-k_2)}{k_1-k_2+k_4} - \frac{1}{k_4}, 1 - k_3\left(\frac{k_1-k_2}{k_1-k_2+k_4}\right), 0\right)$	$k_2 < \frac{(1-k_3)(k_1-k_2)}{k_4} + 1 < min\left\{k_1, \frac{k_1-k_2}{k_4} + 1\right\}$

3.2. The Analysis of Locally Asymtotically Stability of Equilibrium Points

Theorem 3.1. Let $\frac{dX}{dt} = F(X)$ as a nonlinear first-order autonomous system with its equilibrium point $\overline{X}$. In addition that, it is assumed that the Jacobian matrix of F evaluated at $\overline{X}$ is $J(\overline{X})$. If the characteristic equation of $J(\overline{X})$,

$$\lambda^n + a_1\lambda^{n-1} + a_2\lambda^{n-2} + \ldots + a_{n-1}\lambda + a_n = 0,$$

meets the Routh-Hurwitz criteria, that is, the determinants of all of the Hurwitz matrices are positive, then $\overline{X}$ is locally asimptotically stable. If the determinants of the some Hurwitz matrices are negative, then $\overline{X}$ is unstable point [21]. In this sense, the Routh-Hurwitz criteria for polynomial of degree $n = 2, 3, 4$ and 5 of the above characteristic equation are summarized as following :

$n = 2$: $a_1, a_2 > 0$,
$n = 3$: $a_1, a_3 > 0$ and $a_1 a_2 > a_3$,
$n = 4$: $a_1, a_3, a_4 > 0$ and $a_1 a_2 a_3 > {a_3}^2 + {a_1}^2 a_4$,
$n = 5$: $a_1, a_2, a_3, a_4, a_5 > 0, a_1 a_2 a_3 > {a_3}^2 + {a_1}^2 a_4$
and $(a_1 a_4 - a_5)(a_1 a_2 a_3 - {a_3}^2 - {a_1}^2 a_4) > a_5 (a_1 a_2 - a_3)^2 + a_1 {a_5}^2$.

Locally asimptotically stability (LAS) conditions of equilibrium points in the Table 1 have examined in the following proposition.

Proposition 3.2. For the equilibrium points in proposition 3.1, the followings are provided.

(i) E_0 and E_3 are always unstable points.
(ii) If $k_1 < 1$, then E_1 is LAS.
(iii) If $1 < k_3$, then E_2 is LAS.
(iv) Let $k_3 < 1 < k_2$ or $k_2 < 1 < k_3$. If $1 < \frac{(1-k_3)(k_1-k_2)}{k_4} + 1 < k_2$, then E_4 is LAS.
(v) Let $k_3 < 1 < k_1$ or $k_1 < 1 < k_3$. If $1 < k_1 < \frac{(1-k_3)(k_1-k_2)}{k_4} + 1$, then E_5 is LAS.
(vi) Let $k_2 < \frac{(1-k_3)(k_1-k_2)}{k_4} + 1 < min\left\{k_1, \frac{k_1-k_2}{k_4} + 1\right\}$. If $k_3 < 1$, then E_6 is LAS.

Proof: For the stability analysis, the functions of the right side of the system (5) are adjusted as the following:

$$\begin{aligned}
\varphi_1(s,r,b,a) &= \eta\left(k_1 s\big(1-(s+r)\big) - bs - \left(\frac{E_{max}}{E_{50}\mu+\eta a} + 1\right) as - k_4 sr\right) \\
\varphi_2(s,r,b,a) &= \eta\big(k_2 r\big(1-(s+r)\big) - br + as + k_4 sr\big) \\
\varphi_3(s,r,b,a) &= \beta_B b\big((1-b) - k_3(s+r)\big) \\
\varphi_4(s,r,b,a) &= -\alpha a
\end{aligned} \tag{16}$$

That jacobian matrix obtained from (16) is

$$J = \begin{pmatrix}
\eta\begin{pmatrix} k_1\big(1-(s+r)\big) - k_1 s - b \\ -k_4 r - \left(\frac{E_{max}}{E_{50}\mu+\eta a} + 1\right) a \end{pmatrix} & -\eta s(k_1 + k_4) & -\eta s & -\eta s\left(\frac{E_{max} E_{50}\mu}{(E_{50}\mu+\eta a)^2} + 1\right) \\
\eta(a + k_4 r - k_2 r) & \eta\begin{pmatrix} k_2\big(1-(s+r)\big) \\ -b + k_4 s - k_2 r \end{pmatrix} & -\eta r & \eta s \\
-k_3 b\beta_B & -k_3 b\beta_B & \beta_B\begin{pmatrix} 1-2b \\ -k_3(s+r) \end{pmatrix} & 0 \\
0 & 0 & 0 & -\alpha
\end{pmatrix} \tag{17}$$

Since $\overline{a} = 0$ in all equilibria of the system (5), the jacobian matrix showed in (17) can be rewritten as follows:

$$J=\begin{pmatrix} \eta\begin{pmatrix} k_1\big(1-(s+r)\big) \\ -k_1 s-b-k_4 r \end{pmatrix} & -\eta s(k_1+k_4) & -\eta s & -\eta s\left(\frac{E_{max}}{E_{50}\mu}+1\right) \\ \eta r(k_4-k_2) & \eta\begin{pmatrix} k_2\big(1-(s+r)\big) \\ -b+k_4 s-k_2 r \end{pmatrix} & -\eta r & \eta s \\ -k_3 b\beta_B & -k_3 b\beta_B & \beta_B\big(1-2b-k_3(s+r)\big) & 0 \\ 0 & 0 & 0 & -\alpha \end{pmatrix} \quad (18)$$

For ease of examination, we have assumed that the τ-th eigenvalue of the equilibrium point E_k is displayed as $\lambda_{k,\tau}$ for $\tau = 1,2,3,4$ and $k = 0,1,2,\dots,6$.

(i) For E_0, the jacobian matrix evaluated in (18) is $J(E_0)=\begin{pmatrix} \eta k_1 & 0 & 0 & 0 \\ 0 & \eta k_2 & 0 & 0 \\ 0 & 0 & \beta_B & 0 \\ 0 & 0 & 0 & -\alpha \end{pmatrix}$. Therefore, the eigenvalues are obtained as $\lambda_{0,1}=\eta k_1$, $\lambda_{0,2}=\eta k_2$, $\lambda_{0,3}=\beta_B$ and $\lambda_{0,4}=-\alpha$. From Theorem 3.1, E_0 is unstable point, since all of the eigenvalues have not lie in the left half of the complex plane due to (6).
In the same mind, the jacobian matrix for E_3 is $J(E_3)=\begin{pmatrix} -\eta k_1 & -\eta(k_1+k_4) & -\eta & -\eta\left(\frac{E_{max}}{E_{50}\mu}+1\right) \\ 0 & \eta k_4 & 0 & \eta \\ 0 & 0 & \beta_B(1-k_3) & 0 \\ 0 & 0 & 0 & -\alpha \end{pmatrix}$, and so, the eigenvalues are $\lambda_{3,1}=-\eta k_1$, $\lambda_{3,2}=\eta k_4$, $\lambda_{3,3}=\beta_B(1-k_3)$ ve $\lambda_{3,4}=-\alpha$. All of these is not negative due to (6). From Theorem 3.1, it can be seen that E_3 is unstable point.

(ii) Jacobian matrix evaluated at the equilibrium point E_1 is $J(E_1)=\begin{pmatrix} \eta(k_1-1) & 0 & 0 & 0 \\ 0 & \eta(k_2-1) & 0 & 0 \\ -k_3\beta_B & -k_3\beta_B & -\beta_B & 0 \\ 0 & 0 & 0 & -\alpha \end{pmatrix}$. Therefore, eigenvalues are $\lambda_{1,1}=\eta(k_1-1)$, $\lambda_{1,2}=\eta(k_2-1)$, $\lambda_{1,3}=-\beta_B$ and $\lambda_{1,4}=-\alpha$. By (6), $\lambda_{1,3}$ and $\lambda_{1,4}$ are negative. If $k_1<1$ (already $k_1>k_2$ in (7)), then $\lambda_{1,1}$ and $\lambda_{1,2}$ are negative from (6). Considering Theorem 3.1, if $k_1<1$, then E_1 is LAS.

(iii) Jacobian matrix in (18) for E_2 is $J(E_2)=\begin{pmatrix} -\eta k_4 & 0 & 0 & 0 \\ \eta(k_4-k_2) & -\eta k_2 & -\eta & 0 \\ 0 & 0 & \beta_B(1-k_3) & 0 \\ 0 & 0 & 0 & -\alpha \end{pmatrix}$.
So, the eigenvalues are founded as $\lambda_{2,1}=-\eta k_4$, $\lambda_{2,2}=-\eta k_2$, $\lambda_{2,3}=\beta_B(1-k_3)$ and $\lambda_{2,4}=-\alpha$. Due to (6), $\lambda_{2,1},\lambda_{2,2}$ and $\lambda_{2,4}$ are negative. Moreover, when $1<k_3$, $\lambda_{2,3}<0$ (already $\beta_B>0$ in (3) and $\eta>0$ in (6)). By Theorem 3.1, if $1<k_3$, then E_2 is LAS.

(iv) Let

$$k_3<1<k_2 \text{ or } k_2<1<k_3. \quad (19)$$

In this case, E_4 is in Ω. Evaluating E_4 in J, we have

$$J(E_4)=\begin{pmatrix} \eta\frac{(1-k_3)(k_1-k_2)-k_4(k_2-1)}{(k_2-k_3)} & 0 & 0 & 0 \\ -\eta\frac{(k_2-k_4)(k_2-1)}{(k_2-k_3)} & -\eta\frac{k_2(k_2-1)}{(k_2-k_3)} & -\eta\frac{(k_2-1)}{(k_2-k_3)} & 0 \\ -\beta_B\frac{k_3k_2(1-k_3)}{(k_2-k_3)} & -\beta_B\frac{k_3k_2(1-k_3)}{(k_2-k_3)} & -\beta_B\frac{k_2(1-k_3)}{(k_2-k_3)} & 0 \\ 0 & 0 & 0 & -\alpha \end{pmatrix}. \quad (20)$$

That two eigenvalues obtained from (20) are $\lambda_{4,1}=\eta\left(\frac{(1-k_3)(k_1-k_2)-k_4(k_2-1)}{(k_2-k_3)}\right)$ and $\lambda_{4,2}=-\alpha$. If

$$\frac{(1-k_3)(k_1-k_2)-k_4(k_2-1)}{(k_2-k_3)}<0, \quad (21)$$

then $\lambda_{4,1}$ is negative. Also, $\lambda_{4,2}$ is negative by (3). The other eigenvalues are founded from the following matrix;

$$J^{B(E_4)}=\begin{pmatrix} -\eta\frac{k_2(k_2-1)}{(k_2-k_3)} & -\eta\frac{(k_2-1)}{(k_2-k_3)} \\ -\beta_B\frac{k_3k_2(1-k_3)}{(k_2-k_3)} & -\beta_B\frac{k_2(1-k_3)}{(k_2-k_3)} \end{pmatrix} \quad (22)$$

where $J^{B(E_4)}$ is the block matrix of $J(E_4)$. Hence, characteristic equation of (22) is

$$\lambda^2+\lambda\left(\eta(k_2-1)+\beta_B(1-k_3)\right)\frac{k_2}{(k_2-k_3)}+\eta(k_2-1)\beta_B(1-k_3)\frac{k_2}{(k_2-k_3)}=0. \quad (23)$$

from (19), let

$$k_2>1>k_3. \quad (24)$$

In case of (24), all of the roots of polynomial in (23) are negative or have negative real parts by Theorem 3.1 ($n=2$), that is, $Re\{\lambda_{4,3},\lambda_{4,4}\}<0$. Thus, if (21) and (24) are held, that is, $1<\frac{(1-k_3)(k_1-k_2)}{k_4}+1<k_2$, then all of the eigenvalues evaluated at E_4 are negative or have negative reel parts. In this respect, it is LAS.

(v) In analogy to (iv), if $1<k_1<\frac{(1-k_3)(k_1-k_2)}{k_4}+1$, then E_5 is LAS.

(vi) Lastly, when

$$k_2<\frac{(1-k_3)(k_1-k_2)}{k_4}+1<min\left\{k_1,\frac{k_1-k_2}{k_4}+1\right\}. \quad (25)$$

E_6 is revealed in Ω. That eigenvalues of jacobian matrix evaluated at E_6 are $\lambda_{6,1}=-\alpha,\lambda_{6,2},\lambda_{6,3}$ and $\lambda_{6,4}$. The $\lambda_{6,1}$ is negative due to (3). Also, $\lambda_{6,2}$, $\lambda_{6,3}$ and $\lambda_{6,4}$ are founded from following block matrix;

$$J^{B(E_6)} = \begin{pmatrix} -\eta k_1 \overline{s} & -\eta \overline{s}(k_1 + k_4) & -\eta \overline{s} \\ \overline{r}\eta(k_4 - k_2) & -\eta k_2 \overline{r} & -\eta \overline{r} \\ -k_3 \overline{b}\beta_B & -k_3 \overline{b}\beta_B & -\overline{b}\beta_B \end{pmatrix} \tag{26}$$

where

$$E_6 = \left(\overline{s}, \overline{r}, \overline{b}, \overline{a}\right) = \left(\frac{1}{k_4} - \frac{k_2 + \frac{k_3}{k_4}(k_1 - k_2)}{k_1 - k_2 + k_4}, \frac{k_1 + \frac{k_3}{k_4}(k_1 - k_2)}{k_1 - k_2 + k_4} - \frac{1}{k_4}, 1 - \frac{k_3(k_1 - k_2)}{k_1 - k_2 + k_4}, 0\right), \tag{27}$$

$\overline{s}, \overline{r}, \overline{b} > 0$.

Characteristic equation of (26) is obtained as follows:

$$\lambda^3 + P_1\lambda^2 + P_2\lambda + P_3 = 0 \tag{28}$$

where

$$\begin{aligned} P_1 &= \left(\eta(k_1\overline{s} + k_2\overline{r}) + \overline{b}\beta_B\right) \\ P_2 &= \eta\left(\eta\overline{sr}k_4(k_1 - k_2 + k_4) + \overline{b}\beta_B\left((k_1\overline{s} + k_2\overline{r}) - k_3(\overline{s} + \overline{r})\right)\right) \\ P_3 &= \beta_B\overline{b}\eta^2\overline{sr}a_4(k_1 - k_2 + k_4) \end{aligned} \tag{29}$$

In (29),

$$P_1 > 0 \tag{30}$$

due to (3), (6) and (27) and

$$P_3 > 0 \tag{31}$$

due to (3), (6), (7) and (27). In addition that, it is

$$P_1P_2 - P_3 = \begin{pmatrix} \eta(k_1\overline{s} + k_2\overline{r}) + \\ \overline{b}\beta_B \end{pmatrix}\left[\begin{matrix} (k_1 - k_2 + k_4)k_4\overline{r}\eta\overline{s} + \\ \left((k_1\overline{s} + k_2\overline{r}) - k_3(\overline{s} + \overline{r})\right)\overline{b}\beta_B \end{matrix}\right] - (k_1 - k_2 + k_4)k_4\eta\eta\overline{sr}\overline{b}\beta_B,$$

and so,

$$P_1P_2 - P_3 = \eta(k_1\overline{s} + k_2\overline{r})\left[\begin{matrix} (k_1 - k_2 + k_4)k_4\overline{r}\eta\overline{s} + \\ \left((k_1\overline{s} + k_2\overline{r}) - k_3(\overline{s} + \overline{r})\right)\overline{b}\beta_B \end{matrix}\right] + \begin{pmatrix} (k_1\overline{s} + k_2\overline{r}) - \\ k_3(\overline{s} + \overline{r}) \end{pmatrix}\overline{b}\beta_B\overline{b}\beta_B\eta \tag{32}$$

By (27), the expression $(k_1\overline{s} + k_2\overline{r}) - k_3(\overline{s} + \overline{r})$ in (32) can be writing as

$$= k_1\left(-\frac{k_2}{k_1 - k_2 + k_4} + \frac{1}{k_4}\overline{b}\right) + k_2\left(\frac{k_1}{k_1 - k_2 + k_4} - \frac{1}{k_4}\overline{b}\right) - k_3\frac{k_1 - k_2}{k_1 - k_2 + k_4}$$

$$= (k_1 - k_2)\left(\frac{1}{k_4}\overline{b} - k_3\frac{1}{k_1-k_2+k_4}\right) = \frac{k_1-k_2}{k_4}\left(\left(1 - \frac{(k_1-k_2)k_3}{k_1-k_2+k_4}\right) - \frac{k_3k_4}{k_1-k_2+k_4}\right).$$

and so,

$$(k_1\overline{s} + k_2\overline{r}) - k_3(\overline{s} + \overline{r}) = \frac{k_1-k_2}{k_4}(1 - k_3) \tag{33}$$

(already $k_1 > k_2$ due to (7)). If

$$k_3 < 1, \tag{34}$$

then $(k_1\overline{s} + k_2\overline{r}) - k_3(\overline{s} + \overline{r}) > 0$, that is,

$$P_1P_2 - P_3 > 0 \tag{35}$$

By considering (30), (31) and (35), if (25) and (34) are satisfied, then it is

$$Re\{\lambda_{6,2}, \lambda_{6,3}, \lambda_{6,4}\} < 0 \tag{36}$$

from Theorem 3.1 ($n = 3$). In this respect, we have that E_6 is LAS.

In table 2, proposition 3.2 are summarized.

Table 2. The LAS conditions of the equilibria of system (5).

Equilibrium Points	**LAS Conditions**
$E_1 = (0,0,1,0)$	$k_1, k_2 < 1$
$E_2 = (0,1,0,0)$	$1 < k_3$
$E_4 = \left(0, \frac{(k_2-1)}{(k_2-k_3)}, \frac{k_2(1-k_3)}{(k_2-k_3)}, 0\right)$	$1 < \frac{(1-k_3)(k_1-k_2)}{k_4} + 1 < k_2 (< k_1)$
$E_5 = \left(\frac{(k_1-1)}{(k_1-k_3)}, 0, \frac{k_1(1-k_3)}{(k_1-k_3)}, 0\right)$	$1 < k_1 < \frac{(1-k_3)(k_1-k_2)}{k_4} + 1$
$E_6 = \left(\frac{1}{k_4} - \frac{k_2 + \frac{k_3}{k_4}(k_1-k_2)}{k_1-k_2+k_4}, \frac{k_1 + \frac{k_3}{k_4}(k_1-k_2)}{k_1-k_2+k_4}, -\frac{1}{k_4}, 1 - k_3\left(\frac{k_1-k_2}{k_1-k_2+k_4}\right), 0\right)$	$k_3 < 1$ and $k_2 < \frac{(1-k_3)(k_1-k_2)}{k_4} + 1 < min\left\{k_1, \frac{k_1-k_2}{k_4} + 1\right\}$

3.3. The Analysis of Globally Asymptotically Stability of Equilibrium Points

In here, it has been focused on globally asymtotically stability (GAS) of equilibrium points in Table 2. Let

$$k_1 < 1 < k_3 \tag{37}$$

(already $k_2 < k_1$ in (7)). When inequality (37) is satisfied, it is clear that the equilibrium points $E_1 = (0,0,1,0)$ and $E_2 = (0,1,0,0)$ are LAS in the same sub-region of Ω. Description of this case is shown in Fig.2. For the variables $s = a = 0$ and the parameters $\beta_B = \eta = 1$, $k_3 = 2$ $k_2 = \frac{1}{3} < k_1 = 1/2$ in the system (5), Fig.2 is plotted via the program pplane.jar. In here, the points $(0,1)$ and $(1,0)$ in plane represent the equilibrium points E_1 and E_2 respectively. Therefore, they are LAS.

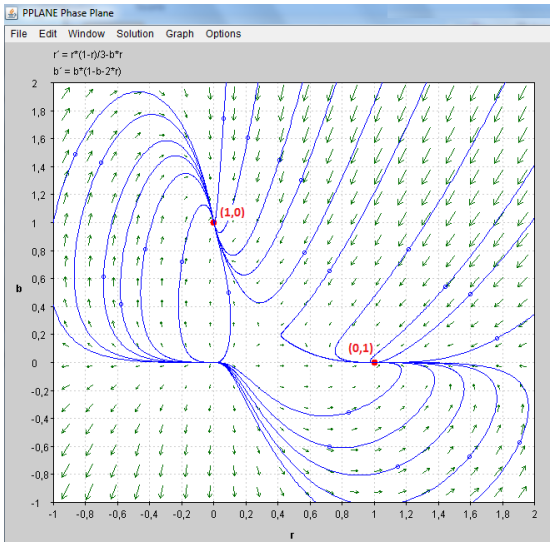

Fig.2. In case of $s = a = 0$, $\beta_B = \eta = 1$, $k_3 = 2$ $k_2 = \frac{1}{3} < k_1 = 1/2$ in system (5), The LAS of the equilibrium points E_1 and E_2.

Except for this inequality is held, there is no same sub-region of Ω where at least two of the equilibrium points E_1, E_2, E_4, E_5 and E_6 are LAS. In this section, it has been assumed that inequality (37) is not provided because of this reason.

Proposition 3.3. Let us denote by Γ_i the LAS region of the equilibrium point E_i in Ω for $i = 1,2,4,5,6$. Then $\Gamma_i \cap \Gamma_j = \emptyset$ for $i \neq j$ and $j = 1,2,4,5,6$.

Proof: This situation is evidently in Table 2.

Proposition 3.4. It is assumed that E_1 is LAS. In this case, it is GAS. Similarly, if E_2 is LAS, then it is GAS.

Proof: In the system (5), each variable in absence of the others has logistic form. Therefore, the GAS analysis of the equilibrium points E_1 and E_2 can be examined in a similar manner to each other.
For E_1, it is investigated as the following. Let us consider the region $\Omega_1 = \{b \in R: 0 \leq b \leq 1\}$ given by

$$\frac{db}{dt} = \beta_B b(1-b), \tag{38}$$

where $\beta_B > 0$ is the intrinsic growth rate of immune cells and $\overline{b} = 1$ is the carrying capacity of immune cells. There are two equilibria $\overline{b} = 0,1$. If (38) is solved by separation of itsvariables, then it is obtained that $b(t) = \frac{b(0)}{b(0)+(1-b(0))e^{-\beta_B t}}$. It can be seen $\lim_{t\to\infty} b(t) = 1$. Thus, $\overline{b} = 1$ (namely, E_1) is GAS.
Proposition 3.5. It is assumed that E_4 is LAS. Then it is GAS. Similarly, if E_5 is LAS, then it is GAS.
Proof: Since E_4 and E_5 are present in R^2, we have benefited from Bendixon-Dulac criteria for analysis of GAS.

Firstly, let us examine the E_4 in the region $\Omega_2 = \{(r,b) \in R^2: 0 < r < 1, 0 < b < 1\}$. Moreover, let $H(r,b) = \frac{1}{rb}$. It is obviously $H(r,b) > 0$ and functions $F_1(r,b)$ and $F_2(r,b)$ obtained from system (5) are denote as

$$\begin{aligned} F_1(r,b) &= \eta r(k_2(1-r) - b) \\ F_2(r,b) &= \beta_B b\big((1-b) - k_3 r\big). \end{aligned} \tag{39}$$

Considering $H(r,b)$, divergence obtained from these functions in (39) is founded as

$$\Delta(r,b) = \frac{\partial}{\partial r}(F_1 H) + \frac{\partial}{\partial b}(F_2 H) = \frac{\partial}{\partial r}\Big(\eta r(k_2(1-r) - b)\frac{1}{rb}\Big) + \frac{\partial}{\partial b}\Big(\beta_B b\big((1-b) - k_3 r\big)\frac{1}{rb}\Big) = \frac{\partial}{\partial r}\Big(\eta\frac{(k_2(1-r)-b)}{b}\Big) + \frac{\partial}{\partial b}\Big(\beta_B\frac{((1-b)-k_3 r)}{r}\Big),$$

and so,

$$\Delta(r,b) = -\Big(\eta\frac{k_2}{b} + \beta_B\frac{1}{r}\Big). \tag{40}$$

From (3), (6) and (8), the $\Delta(r,b)$ in (40) is negative. In this respect, by the Bendixon-Dulac criteria, there is not periodic orbit in the $r-b$ plane. Because E_4 is LAS in the above plane (namely Ω_2 and so, Ω), it is GAS. In the same way, it can be seen that E_5 is GAS.
Definition 3.1. (LaSalle's extension of the direct method of Lyapunov)**:** The system is of the form

$$\frac{dx_i}{dt} = \dot{x}_i = x_i F_i(x_1, x_2, \ldots, x_n), \quad i = 1,2,\ldots,n \tag{41}$$

where x_i is the density of the $i-th$ species in the community at time t. Each F_i is a continuous function from R_+^n, the nonnegative cone in R^n, to R and is sufficiently smooth to

guarantee that initial value problems associated with (41) have unique solutions in the population orthant, R_+^n.
Thus, the positive steady-state x^* of (41) is a globally asymptotically stable, if $F(x) > 0$ for all $x \in (0, x^*)$ and $F(x) < 0$ for all $x \in (x^*, \infty)$ [22].

Let us consider as $F_i(x_1, x_2, \ldots, x_n) = q_i + \sum_{k=1}^{n} w_{ik} x_k, \quad i = 1,2, \ldots, n.$

here $q_i, -w_{ii}$ are positive constants and $w_{ik}, i \neq k$ are constants with any sign. If we define w_{ik} and $q = (q_1, q_2, \ldots, q_n)$, then it can be shown that $x^* = -W^{-1}q^t$ is a steady-state of system. Let us suppose that $x^* \in R_+^n$ is positive and $C = diag(c_1, c_2, \ldots, c_n)$. Function $V(x) = \sum_{i=1}^{n} c_i \left(x_i - x_i^* - x_i^* ln \frac{x_i}{x_i^*} \right)$ can be used as a Lyapunov function. Clearly, $V(x)$ satisfied the conditions $V(x^*) = 0$, $V(x) > 0$ for all $x \in R_+^n$, $x \neq x^*$, $V(x) \to \infty$ as $x \to \infty$ and $x \to 0$. We have

$$\dot{V}(x) = \sum_{i=1}^{n} c_i (x_i - x_i^*) \left(q_i + \sum_{k=1}^{n} w_{ik} x_k \right) = \sum_{i=1}^{n} c_i (x_i - x_i^*) \left(\sum_{k=1}^{n} w_{ik} (x_k - x_k^*) \right)$$
$$= \frac{1}{2} (x - x^*)^t (CW + W^t C)(x - x^*).$$

From LaSalle's extension of the direct method of Lyapunov, we have the following

Theorem 3.2. The steady-state x^* of (41) is GAS, if there exists a positive diagonal matrix C such that $CW + W^t C$ is a negative semidefinite and the function

$$\dot{V}(x) = \frac{1}{2} (x - x^*)^t (CW + W^t C)(x - x^*)$$

does not vanish identically along a nontrivial solution [21,22].

Proposition 3.6. Let E_6 is LAS. If $0 < 4(k_1 + k_4)(k_2 - k_4) < k_1 k_2$, $4k_3 < k_2$, then it is GAS.

Proof: When the last equation of system (5) are separated, their solutions approach to $\overline{a} = 0$. Replacing this value in the first three equations of system (5), we have attained that the asymptotically equivalent system in the region

$$\Omega_3 = \{(s, r, b) \in R^3 : 0 < s < 1, 0 < r < 1, 0 < s + r < 1, 0 < b < 1\}. \qquad (42)$$

given by

$$\begin{aligned}\frac{ds}{dt} &= s(k_1\eta - k_1\eta s - (k_1 + k_4)\eta r - \eta b)\\ \frac{dr}{dt} &= r(k_2\eta - (k_2\eta - k_4\eta)s - k_2\eta r - \eta b)\\ \frac{db}{dt} &= b(\beta_B - k_3\beta_B s - k_3\beta_B r - \beta_B b).\end{aligned} \tag{43}$$

By Definition 3.1, we have presumed that the Lyapunov function of system (43) definited in the region (42) is

$$V(x) = \sum_{i=1}^{3} c_i \left(x_i - x_i^* - x_i^* ln\frac{x_i}{x_i^*}\right) \tag{44}$$

where each x_i^* for $i = 1,2,3$ are component at equilibrium point. Derivative of $V(x)$ in (44) is

$$\dot{V}(x) = \sum_{i=1}^{3} c_i(x_i - x_i^*)\,(q_i + \sum_{k=1}^{3} w_{ik}x_k), \tag{45}$$

By Theorem 3.2, (45) can be writing as following

$$\dot{V}(x) = \frac{1}{2}(x - x^*)^t(CW + W^tC)(x - x^*) \tag{46}$$

where

$$\begin{aligned} x = \begin{pmatrix} s \\ r \\ b \end{pmatrix}, x^* = \begin{pmatrix} \overline{s} \\ \overline{r} \\ \overline{b} \end{pmatrix}, q = \begin{pmatrix} k_1\eta & k_2\eta & \beta_B \end{pmatrix}, C = \begin{pmatrix} c_1 & 0 & 0 \\ 0 & c_2 & 0 \\ 0 & 0 & c_3 \end{pmatrix} \\ W = \begin{pmatrix} w_{11} & w_{12} & w_{13} \\ w_{21} & w_{22} & w_{23} \\ w_{31} & w_{32} & w_{33} \end{pmatrix} = -\begin{pmatrix} k_1\eta & \eta(k_1 + k_4) & \eta \\ \eta(k_2 - k_4) & k_2\eta & \eta \\ k_3\beta_B & k_3\beta_B & \beta_B \end{pmatrix}, \end{aligned} \tag{47}$$

In addition that, $q_{1i}, -w_{ii}$ for $i, k = 1,2,3$ are positive constants, w_{ik} for $i \neq k$ are constants with any sign and C is a positive diagonal matrix and $\overline{s}$, $\overline{r}$ and $\overline{b}$ are in (23). Moreover, $\begin{pmatrix} \overline{s} \\ \overline{r} \\ \overline{b} \end{pmatrix} = x^* = -W^{-1}q^t$ such that $detW \neq 0$.

By (47), it is obtained that

$$CW + W^tC = -\begin{pmatrix} 2c_1k_1\eta & (c_1+c_2)\eta(k_1+k_4) & (c_1\eta + c_3k_3\beta_B) \\ \eta\big(c_2(k_2-k_4)+c_1(k_1+k_4)\big) & 2c_2k_2\eta & (c_2\eta + c_3k_3\beta_B) \\ (c_1\eta + c_3k_3\beta_B) & (c_2\eta + c_3k_3\beta_B) & 2c_3\beta_B \end{pmatrix}. \quad (48)$$

If

$$k_2 > k_4, \quad (49)$$

then the matrix $CW + W^tC$ in (48) is negative-definite.

Moreover, the function $\dot{V}(x)$ in (46) is

$$\begin{aligned} \dot{V}(x) = {} & c_1w_{11}(x_1 - {x_1}^*)^2 + (c_1w_{12} + c_2w_{21})(x_1 - {x_1}^*)(x_2 - {x_2}^*) \\ & + c_2w_{22}(x_2 - {x_2}^*)^2 + (c_1w_{13} + c_3w_{31})(x_1 - {x_1}^*)(x_3 - {x_3}^*) \\ & + (c_2w_{23} + c_3w_{32})(x_2 - {x_2}^*)(x_3 - {x_3}^*) + c_3w_{33}(x_3 - {x_3}^*)^2. \end{aligned} \quad (50)$$

(50) can be more clearly written as following

$$\begin{aligned} \dot{V}(x) = {} & \left[\tfrac{1}{2}c_1w_{11}(x_1 - {x_1}^*)^2 + (c_1w_{12} + c_2w_{21})(x_1 - {x_1}^*)(x_2 - {x_2}^*) + \tfrac{1}{2}c_2w_{22}(x_2 - {x_2}^*)^2\right] \\ & + \left[\tfrac{1}{2}c_2w_{22}(x_2 - {x_2}^*)^2 + (c_2w_{23} + c_3w_{32})(x_2 - {x_2}^*)(x_3 - {x_3}^*) + \tfrac{1}{2}c_3w_{33}(x_3 - {x_3}^*)^2\right] \\ & + \left[\tfrac{1}{2}c_1w_{11}(x_1 - {x_1}^*)^2 + (c_1w_{13} + c_3w_{31})(x_1 - {x_1}^*)(x_3 - {x_3}^*) + \tfrac{1}{2}c_3w_{33}(x_3 - {x_3}^*)^2\right]. \end{aligned} \quad (51)$$

In this sense, (51) does not vanish identically along a nontrivial solution, if the following conditions are met;

$$\begin{aligned} \Delta_1 &= (c_1w_{12} + c_2w_{21})^2 - c_1c_2w_{11}w_{22} < 0 \\ \Delta_2 &= (c_2w_{23} + c_3w_{32})^2 - c_2c_3w_{22}w_{33} < 0 \\ \Delta_3 &= (c_1w_{13} + c_3w_{31})^2 - c_1c_3w_{11}w_{33} < 0 \end{aligned} \quad (52)$$

where Δ_1, Δ_2 and Δ_3 are the discriminant during each of the statement (51). If the elements of a positive diagonal matrix C are selected, for example, as follows

$$\begin{aligned} & c_2 = \frac{w_{11}w_{22} - 2w_{12}w_{21}}{2{w_{21}}^2}c_1, c_3 = \frac{w_{22}w_{33} - 2w_{23}w_{32}}{2{w_{32}}^2}c_2, \\ & c_1 = \frac{w_{11}w_{33} - 2w_{31}w_{13}}{2{w_{13}}^2}c_3, c_3 > 0, \end{aligned} \quad (53)$$

then it can be seen that inequalities in (52) have provided. From (52) and (53), we have

$$\begin{aligned} \Delta_1 &= 4w_{12}w_{21} - w_{11}w_{22} < 0 \\ \Delta_2 &= 4w_{23}w_{32} - w_{22}w_{33} < 0 \\ \Delta_3 &= 4w_{31}w_{13} - w_{11}w_{33} < 0. \end{aligned} \tag{54}$$

After the elements of the W matrix in (47) have written its places in (54), we have the following conditions:

$$4(k_1 + k_4)(k_2 - k_4) < k_1k_2, 4k_3 < k_2. \tag{55}$$

Therefore, if inequalities (55) is satisfied, the function $\dot{V}(x)$ does not vanish identically along a nontrivial solution. By (49) and (55), if

$$0 < 4(k_1 + k_4)(k_2 - k_4) < k_1k_2, 4k_3 < k_2, \tag{56}$$

then E_6 is GAS.

In the following discussion, we have demonstrated some of the contributions our mathematical modelling to the study of complex problems in host-microbe interactions.

4. Numerical study

In our numerical study, the datas of different species of bacteria including Staphylococcus aureus, Mycobacterium tuberculosis, Acinetobacter baumannii and E. coli in host have used. In this sense, each bacterial species has been evaluated separately in the model. By this study, dynamics of interactions among size of the bacteria population, concentration of the antibiotic and immune cells in host have examined. The parameter values used for numerical studies are given in the following Table 3.

Table 3. Interpretation and considered values of the parameters used in (1). Data are deduced from the literature (references).

Parameter	Description	Unit	Value [1]	Reference [1]	Value [2]	Reference [2]	Value [3]	Reference [3]	Value [4]	Reference [4]
β_S	Growth rate of susceptible bacteria	$days^{-1}$	24	[23]	0.8	[1]	1.2	[24]	0.6	[25]
β_R	Growth rate of resistant bacteria	$days^{-1}$	21.6	[26]	0.5	[1]	0.9	Hypothesis	0.4	Hypothesis
β_B	Growth rate of immune cells	$days^{-1}$	3	[26]	0.6	[27]	0.6	[27]	0.6	[27]
$\overline{\eta}$	Rate of bacteria destroyed by immune cells	$cells^{-1}$ $days^{-1}$	$2.4\ 10^{-4}$	[28]	10^{-6}	Hypothesis	10^{-6}	Hypothesis	10^{-6}	Hypothesis
Λ	Carrying capacity of immune cells	cells	$1.8\ 10^{5}$	[28]	$1.8\ 10^{5}$	[28]	10^{6}	[16]	10^{6}	[16]
T	Carrying capacity of bacteria	cells	10^{9}	[23]	10^{9}	[29]	10^{8}	[30]	10^{7}	[31]
α	Elimination rate of antibiotic under distinct doses days	$days^{-1}$	3.6	[23]	3.6	[23]	3.6	[23]	3.6	[23]
μ	Mutation rate of susceptible bacteria due antibiotic	$days^{-1}$	$9.8\ 10^{-5}$	[30]	$5.1\ 10^{-9}$	[32]	$9\ 10^{-6}$	Hypothesis	$9.3\ 10^{-6}$	[33]
λ	Bacterial induced death of immune cells	$cells^{-1}$ $days^{-1}$	$6\ 10^{-6}$	[28]	$6\ 10^{-6}$	[28]	$6\ 10^{-6}$	[28]	$6\ 10^{-6}$	[28]
σ	Conjugation rate constant	$days^{-1}$	10^{-5}	[26]	10^{-7}	Hypothesis	10^{-7}	Hypothesis	10^{-4}	Hypothesis
E_{max}	Maximum killing rate of susceptible bacteria	$days^{-1}$	36	[23]	36	[23]	36	[23]	36	[23]
E_{50}	Antibiotic concentration for half maximum effect on susceptible bacteria	μg/ml	0.25	[23]	0.25	[23]	0.25	[23]	0.25	[23]

To some specific diseases causing of Staphylococcus aureus, Mycobacterium tuberculosis, Acinetobacter baumannii and E. coli, respectively, values of parameters used in the system (2) is obtained from the literature. Antibiotic used is Ciprofloxacin. In addition that, it has showed
by [1], values and references for Staphylococcus aureus,
by [2], values and references for Mycobacterium tuberculosis,
by [3], values and references for Acinetobacter baumannii and
by [4], values and references for E. coli.

Taking into consideration values of the parameters in Table 3, qualitative analysis of the system (5) are supported by numerical simulations. Moreover, it has obtained the following figures in compliance with the results founded in Table 2.

The antibiotic concentration for equilibria of the system (5) is eliminated completely from the body after a while. This circumstance is biological meaning with respect to the antibiotic excreted from body, and it can be seen in Table 2 and in these figures obtained from different positive initial conditions.

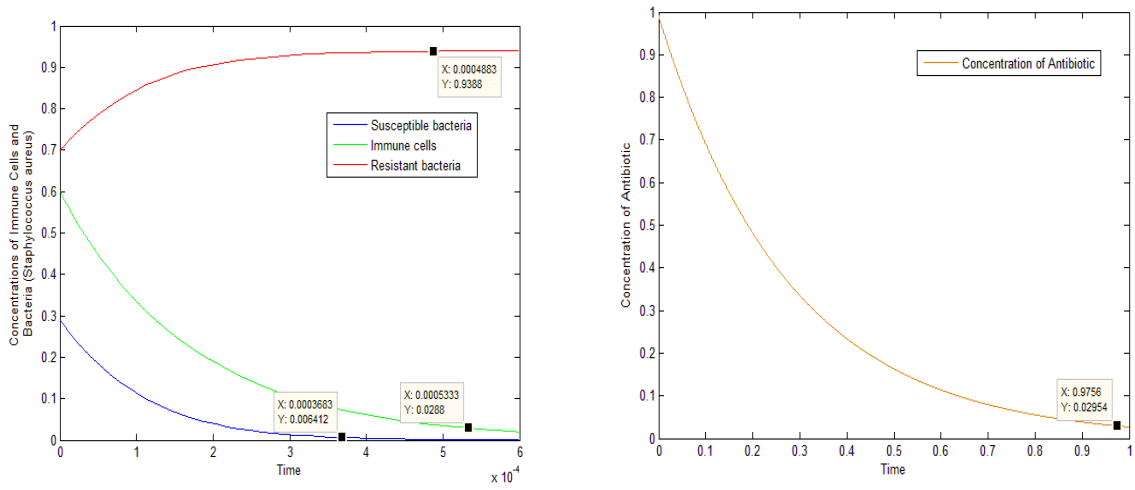

Fig.3. In case of $1 < k_3 = 2000$, Temporal course of bacteria population, immune cells and antibiotic by using the parameter values given in Table 3 for the Staphylococcus aureus.

In the Fig.3, it is founded the results relating to stability of $E_2(0,1,0,0)$ for Staphylococcus aureus. Also, it has observed that other variables except for resistant bacteria have eliminated completely from the body after a while. In here antibiotic concentration has excreted in one day. Within about one week, the resistant bacteria reaches a positive equilibrium point, that is, its carrying capacity, and susceptible bacteria and immune cells are removed completely from the body. In this sense, immune cells do not respond resistant bacteria to antibiotic.

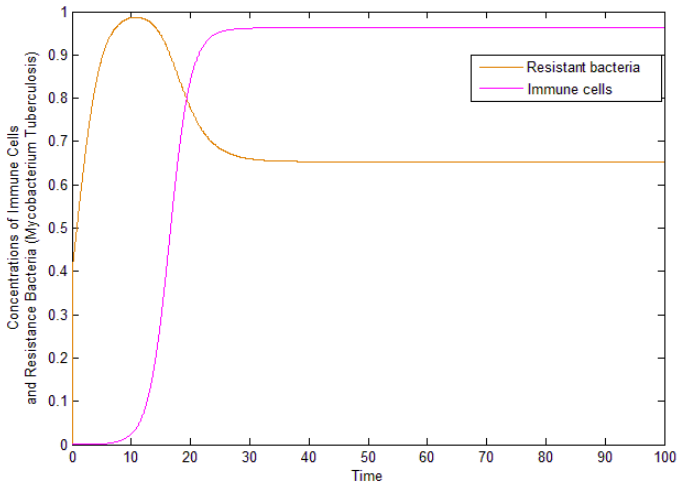

Fig.4. In case of $1 < \frac{(1-k_3)(k_1-k_2)}{k_4} + 1 = 1.02829 < k_2 = 2.7778$, Temporal course of bacteria population by using the parameter values given in Table 3 for the Mycobacterium tuberculosis.

Stability of the equilibrium point $E_4 = (0,0.6534,0.9627,0)$ for Mycobacterium tuberculosis is observed in the Fig.4. Also, while the susceptible bacteria is eleminated, resistant bacteria to antibiotic and immune cells are persist in host. In this Figure, it is seen that the

concentration of the antibiotic and susceptible bacteria have excreted from the body within one day and resistant bacteria and immune cells reach to their positive equilibrium values within 25 days.

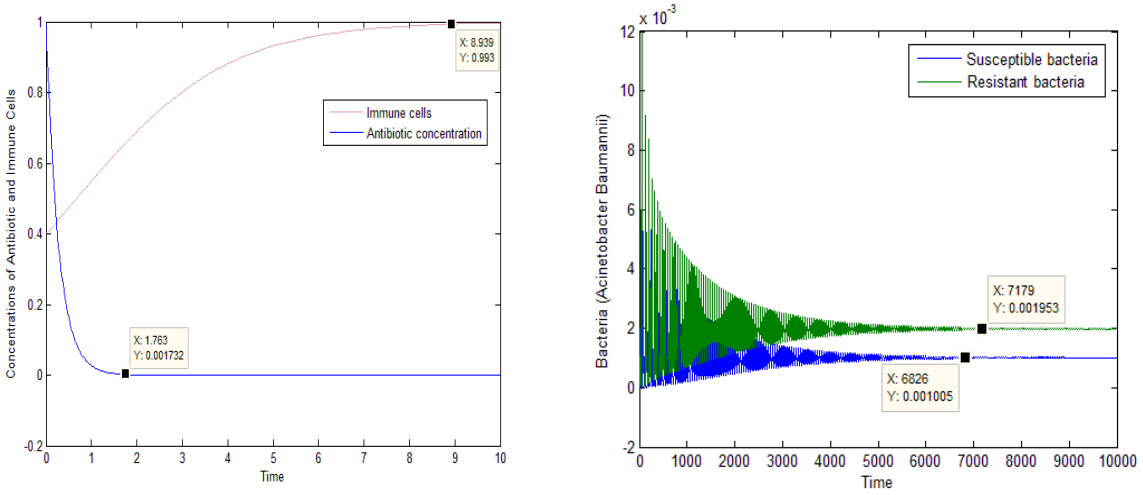

Fig.5. In case of $k_3 = 0.57 < 1$ and $k_2 = 0.9 < \frac{(1-k_3)(k_1-k_2)}{k_4} + 1 = 1{,}00129 < min\left\{k_1 = 1.2, \frac{k_1-k_2}{k_4} + 1 = 1.003\right\}$, Temporal course of bacteria population, immune cells and antibiotics by using the parameter values given in Table 3 for the Acinetobacter baumannii.

In the Fig.5, it has used that the datas obtained for Acinetobacter baumannii and we have observed that stability of $E_6 = (0.001009870389, 0.00198115653, 0.998295114656, 0)$ which the sub-populations of susceptible and resistant bacteria to antibiotic and immune cells persist. In this respect, the antibiotic concentration excreted within 2 days and immune cells reaches a positive equilibria within ten days. Therefore, susceptible and resistant bacteria to antibiotic reach to their a very small positive equilibrium values after a long time under the specific level of immune system cells.

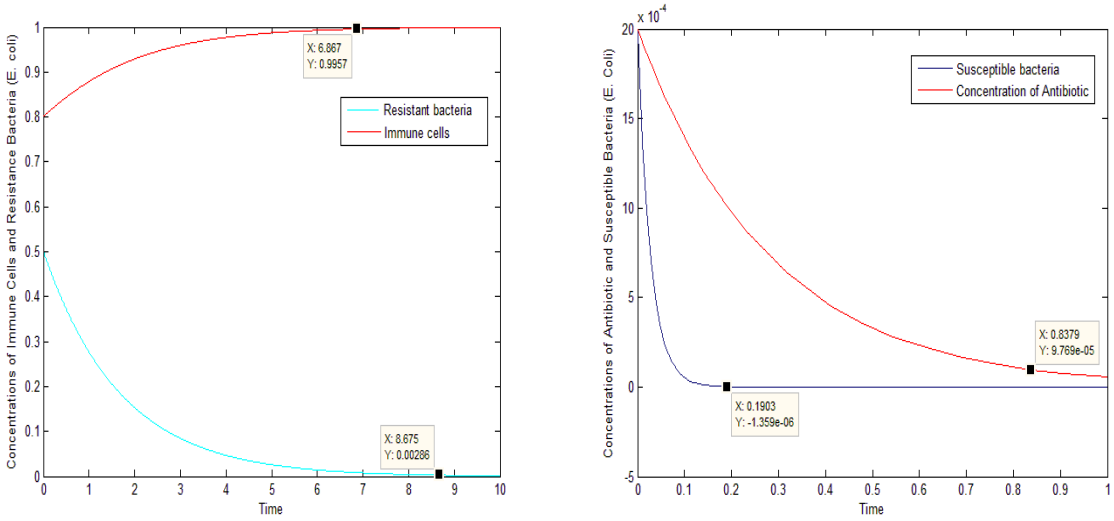

Fig.6. In case of $k_1 = 0.6 < 1$, Temporal course of bacteria population, immune cells and antibiotics by using the parameter values given in Table 3 for the E. coli.

Finally, the results relating to stability of $E_1 = (0,0,1,0)$ have shown in the Fig.6. by using the datas for E. coli. In this sense, antibiotic concentration and susceptible bacteria have eleminated within 24 hours. In 7-10 days, the resistant bacteria has disappeared and the immune cells has reached to it's carrying capacity.

In this study, the effects of antibiotics and immune system cells in case of bacterial infection have been assessed in certain intervals of time.

5. Results and Discussions

In this study, the values k_1, k_2, k_3 and k_4 have stated the conditions identifying the changes in the population sizes of the infectious bacteria, hosts immune cells and antibiotic. With regards to the biological meaning of the parameters describing these statements, the parameter k_1 can be comment as the number of bacteria generated by the fraction of susceptible bacteria surviving under pressure of immune cells independently from both the effect of antibiotic and the conjugation including the transfer of genes between susceptible and resistant bacteria. Analogously, k_2 represents the bacteria generated by resistant bacteria surviving under pressure of immune cells. The parameter $\frac{1}{k_3}$ can be expressed as the number of cells generated by the fraction of immune cells surviving under pressure of bacteria. Moreover, taking into consideration $\frac{k_1}{k_4+1} = \frac{\beta_S}{\sigma T+\overline{\eta}\Lambda}$ in (6), the parameter $\frac{k_1}{k_4+1}$ can be comment as the number of bacteria generated by the fraction of susceptible bacteria surviving under both the pressure of immune cells and the conjugation including the transfer of genes between susceptible and resistant bacteria independently from the effect of antibiotic. Hence, the biological existence and stability conditions of the equilibria of system (5) obtained from Table 2 have independent from the effect of antibiotic.

Let us held not the inequality (37). In case of $\frac{1}{k_3} < 1$, the state expressed only the existence of resistant bacteria independently from the status of all other variables is revealed. When $1 <$

$\frac{1}{k_3}$, the status of the other equilibrium point is taken into account. In this sense, the effect of the immune response of the host is very important in terms of the development of the infection.

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