



Stability Analysis of the FDE Mathematical Model Examining the Effects of the Specific Immune System Cells and the Multiple Antibiotic Concentration against Infection

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Abstract

In this study, the infection process in infectious individual is mathematically modeled by using a system of fractional order differential equations with multiple-orders. Qualitative analysis of the model was done. To mathematically examine the effects of *Pseudomonas Aeruginosa* and *Mycobacterium tuberculosis* and their treatment methods, the results of the proposed model are compared with numerical simulations with the help of datas obtained from the literature.

Keywords: Fractional-Order Differential Equation, Infection model, Qualitative Analysis, Numerical Simulation.

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1. Introduction

In the process of forming and examining of mathematical models, the ordinary differential equations (ODE), the fractional-order differential equations (FDE) and the difference equations etc. are encountered in the literature. Especially, numerous literature on the application of fractional-order differential equations in nonlinear dynamics has recently been developed [1].

In the process of modeling real-life situations, the created models by using fractional-order differential and integration minimize the ignored errors that are caused by parameters, since the more general form of the concepts of integer-order differential and integration are



concepts of the fractional-order differential and integration. For this reason, the models formed by fractional-order differential equations are more realistic and feasible[2-11].

Fractional-order differential theory is based on the notes of Leibnitz in 1695. However, the earliest systematic studies on this subject were made by Liouville, Riemann and Holmgren in the 19th century [12]. At first this topic has been useful only in mathematics, but it has recently gained importance in other disciplines. FDE and its system are frequently used in the variety applications such as fluid mechanics, economics, viscoelasticity, biology, thermodynamics, physics and engineering [13-21]. Particularly, biology is a very rich resource for such models [22].

Considering the change of its size of a certain specy in population, the proposed models in the literature base on the mathematical growth models such as Malthus [23,24], Pearl-Verhulst Logistic [25,26], Gompertz [27-30] and Kemostat [31]. In addition that, there are interactive population models such as Lotka-Volterra prey-predator [32-34], Kolmogorov [35,35] and Epidemic [37] etc.

In this study, a mathematical model considering time-dependent changes of immune system cells, pathogen and drug concentrations in an infected individual receiving multiple drug treatment, is proposed. This model is in the form of fractional-order differential equations system. In this respect, the proposed model is mathematically different from the ones proposed in [38-41], since the different parameters under various scenarios have been added to the model in here.

2. Formation of Model

In this section, the infection model is introduced by giving the definitions of the used variables and parameters. In this sense, time-dependent changes of immune system cells and populations of susceptible bacteria to antibiotic and resistant bacteria to antibiotic in an individual receiving multiple antibiotic treatment in case of an infection have been investigated through mathematical modeling.

There are two types of immune system cells. These are *effector cells*, namely the first response or non-specific response of the immune system, and *memory cells*, namely the second response or specific response of immune system cells. When a sudden infection occurs in the host, first the effector cells and then the memory cells respond to the pathogen until the pathogen completely disappeared [42,43]. The effect of the memory cells of the immune system is investigated in the proposed model.

It has assumed that $B(t)$, $S(t)$, $R(t)$ and $A_i(t)$ for $i = 1, 2, \dots, n$ symbolize the population size of specific immune system cells, the population size of susceptible bacteria to antibiotic, the population size of resistant bacteria to antibiotic and concentrations of antibiotics at time t , respectively. If the orders of the derivative in the system are accepted as α_j for $j = 1, 2, \dots, n + 3$, respectively, then D^{α_j} expresses fractional derivatives in the sense of Caputo from the α_j -th order. By aforementioned assumptions, the nonlinear and autonomous FDEs system with multiple orders composed of $(n + 3)$ equations is

$$\begin{aligned}
 D^{\alpha_1} B &= v(S + R)B - \omega_B B \\
 D^{\alpha_2} S &= \beta_S S \left(1 - \frac{S+R}{\Lambda}\right) - \omega_S S - S \sum_{i=1}^n \varepsilon_i A_i - S \sum_{i=1}^n d_i A_i - \gamma BS \\
 D^{\alpha_3} R &= \beta_R R \left(1 - \frac{S+R}{\Lambda}\right) - \omega_R R + S \sum_{i=1}^n \varepsilon_i A_i - \gamma BR \\
 D^{\alpha_{i+3}} A_i &= \delta_i - \mu_i A_i, i = 1, 2, \dots, n
 \end{aligned} \tag{1}$$

for $t \geq 0$. The α_j for $j = 1, 2, \dots, n + 3$ can be any real or complex vector. In this study, it is taken into account that these derivatives are nonnegative real numbers, and so, $\alpha_j \in (0, 1]$. According to $B \equiv B(t)$, $S \equiv S(t)$, $R \equiv R(t)$, $A_1 \equiv A_1(t), \dots, A_n \equiv A_n(t)$, the initial conditions at the time $t = t_0$ are $B(t_0) = B_0$, $S(t_0) = S_0$, $R(t_0) = R_0$, $A_1(t_0) = A_{10}, \dots, A_n(t_0) = A_{n0}$. For the parameters used in the system (2.1), it is

$$\beta_S, \beta_R, \omega_S, \omega_R, \gamma, \Lambda, v, d_i, \varepsilon_i, \delta_i, \mu_i \in \mathbb{R}^+ \tag{2}$$

for $i = 1, 2, \dots, n$.

The definitions of the parameters in (2) are given below. Because it is assumed that the bacteria have grown in accordance with the logistic rules, the parameters β_S and β_R are the growth rates of susceptible and resistant bacteria to multiple antibiotic, respectively, and the parameter Λ indicates the carrying capacity of bacteria. Also, it is

$$\beta_S > \beta_R \tag{3}$$

due to fitness cost [41]. Immune system cells multiply at rate of v by the current bacterial load [44,45]. Susceptible bacteria, resistant bacteria and immune system cells have the natural death rates ω_S , ω_R and ω_B , respectively. In addition that, the susceptible and resistant bacteria have death rates due to immune system cells and this rates is γ [46]. During the administration of the i -th antibiotic, some resistant bacteria emerge due to mutations of susceptible bacteria exposed to this antibiotic. ε_i for $i = 1, 2, \dots, n$ is the mutation rate of susceptible bacteria exposed to the i -th antibiotic. Because susceptible bacteria are also killed by the action of antibiotics, d_i for $i = 1, 2, \dots, n$ is the death rate of susceptible bacteria exposed to the i -th antibiotic [38]. Lastly, the i -th antibiotic concentration is supplied at a constant rate δ_i , and is taken up at a constant per capita rate μ_i [39].

Thus, the model (1) under the above scenarios is the mathematical form of a general bacterial infection and the relationships among the variables used in this model have showed schematically in Fig.1.

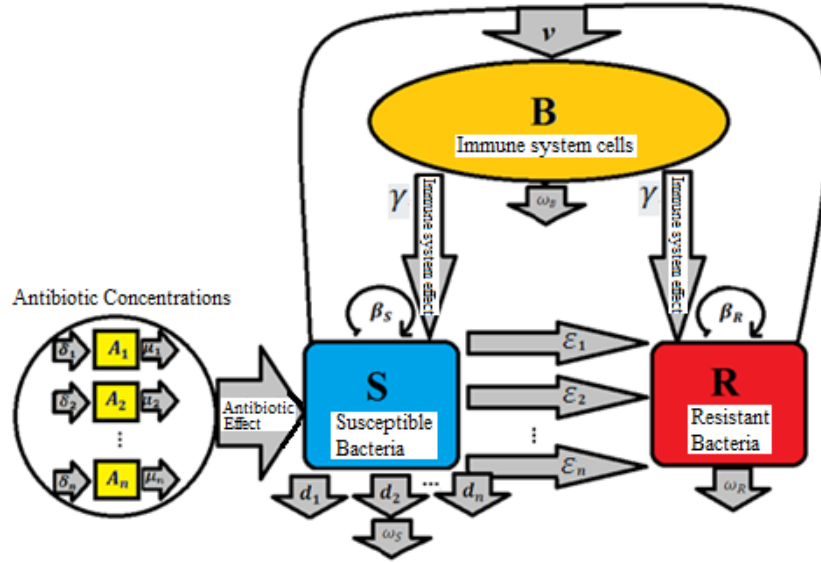


Fig.1. Schematic representation of the interaction among bacteria, immune system cells and antibiotic concentrations according to the parameters used in (1).

Definition 2.1. Let $i = 1, 2, 3, \dots, n + 3$. Model in (1) can be rewriting in the matrix form as following

$$\begin{aligned} D^\alpha X(t) &= f(X(t)) = UX(t) + x_2(t)N_2X(t) + x_3(t)N_3X(t) + P \\ X(0) &= X_0 \end{aligned} \quad (4)$$

where it is shown by $\alpha = [\alpha_1, \alpha_2, \alpha_3, \dots, \alpha_{n+3}]^T$ the derivatives, by $X(t) = [x_1(t), x_2(t), x_3(t), x_4(t) \dots, x_{n+3}(t)]^T = [B(t), S(t), R(t), A_1(t) \dots, A_n(t)]^T \in \mathbb{R}^{n+3}$ the variables, by $f = [f_1, f_2, f_3, \dots, f_{n+3}]^T \in \mathbb{R}^{n+3}$, $f_i: [0, +\infty) \times \mathbb{R}^{n+3} \rightarrow \mathbb{R}$ the functions. Also, when it is considered as $D^\alpha = [D^{\alpha_1}, D^{\alpha_2}, D^{\alpha_3}, \dots, D^{\alpha_{n+3}}]^T$, D^{α_i} expresses a fractional derivative in the sense of Caputo from the α_i -th order. For $D^\alpha X(t) = [D^{\alpha_1}x_1(t), D^{\alpha_2}x_2(t), D^{\alpha_3}x_3(t), \dots, D^{\alpha_{n+3}}x_{n+3}(t)]^T$, (4) is defined as follows:

$$\begin{aligned}
 U &= \begin{pmatrix} -\omega_B & 0 & 0 & 0 & \dots & 0 \\ 0 & (\beta_S - \omega_S) & 0 & 0 & \dots & 0 \\ 0 & 0 & (\beta_R - \omega_R) & 0 & \dots & 0 \\ 0 & 0 & 0 & -\mu_1 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & \dots & -\mu_n \end{pmatrix}, \\
 P &= \begin{pmatrix} 0 \\ 0 \\ 0 \\ \delta_1 \\ \vdots \\ \delta_n \end{pmatrix}, N_2 = \begin{pmatrix} v & 0 & 0 & 0 & \dots & 0 \\ -\gamma & -\frac{\beta_S}{\Lambda} & -\frac{\beta_S}{\Lambda} & -(\varepsilon_1 + d_1) & \dots & -(\varepsilon_n + d_n) \\ 0 & 0 & -\frac{\beta_R}{\Lambda} & \varepsilon_1 & \dots & \varepsilon_n \\ 0 & 0 & 0 & 0 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & \dots & 0 \end{pmatrix}, \\
 N_3 &= \begin{pmatrix} v & 0 & 0 & 0 & \dots & 0 \\ 0 & 0 & 0 & 0 & \dots & 0 \\ -\gamma & -\frac{\beta_R}{\Lambda} & 0 & 0 & \dots & 0 \\ 0 & 0 & 0 & 0 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & \dots & 0 \end{pmatrix} \text{ and } X_0 = \begin{pmatrix} B(0) \\ S(0) \\ R(0) \\ A_1(0) \\ \vdots \\ A_n(0) \end{pmatrix} = \begin{pmatrix} x_1(0) \\ x_2(0) \\ x_3(0) \\ x_4(0) \\ \vdots \\ x_{n+3}(0) \end{pmatrix}. \tag{5}
 \end{aligned}$$

Definition 2.2. For $X(t) = (x_1(t) \ x_2(t) \ x_3(t) \ x_4(t) \ \dots \ x_{n+3}(t))^T$, let $C^*[0, T]$ be a set of continuous column vectors in the interval $[0, T]$. Norm of the vector $X(t) \in C^*[0, T]$ defined in (4) is shown by $\|X(t)\| = \sum_{i=1}^{n+3} \sup_t |x_i(t)|$.

Proposition 2.1. We have keep in mind Definition 2.1. In this sense, let us consider $X(t) = (x_1(t) \ x_2(t) \ x_3(t) \ x_4(t) \ \dots \ x_{n+3}(t))^T$ in $\mathbb{R}_+^{n+3} = \{X \in \mathbb{R}^{n+3} : X \geq 0\}$ and $D^\alpha f(x) \in C[a, b]$ for $f(X) \in C[a, b]$, $0 < \alpha \leq 1$. According to generalized mean value theorem, it is $f(x) = f(a) + \frac{1}{\Gamma(\alpha)} D^\alpha f(\xi)(x - a)^\alpha$ for $\forall x \in [a, b]$ and $0 \leq \xi \leq x$. Also,

- When $D^\alpha f(x) > 0$ for $\forall x \in [a, b]$, the function $f(x)$ increases for each $x \in [a, b]$.
- When $D^\alpha f(x) < 0$ for $\forall x \in [a, b]$, the function $f(x)$ decreases for each $x \in [a, b]$.

In addition to the above mentioned, the vector field is the points in \mathbb{R}_+^{n+3} , due to $D^\alpha x_1(t)|_{x_1=x_2=x_3=x_{i+3}=0} = 0$, $D^\alpha x_2(t)|_{x_1=x_2=x_3=x_{i+3}=0} = 0$, $D^\alpha x_3(t)|_{x_1=x_2=x_3=x_{i+3}=0} = 0$ and $D^\alpha x_{i+3}(t)|_{x_1=x_2=x_3=x_{i+3}=0} = \gamma_i$ for $i = 1, 2, \dots, n$.

Proposition 2.2. If $X(t) \in C^*[0, T]$, then the system (4) has a single solution [47].

Proof Let $D^\alpha X(t) = UX(t) + x_2(t)N_2X(t) + x_3(t)N_3X(t) + P$. In this case, it is $F(X(t)) \in C^*[0, T]$ for the vector $X(t) \in C^*[0, T]$. For the vectors $X(t), Y(t) \in C^*[0, T]$ such that $X(t) \neq Y(t)$, we have the follows:

$$\begin{aligned}
 &\|F(X(t)) - F(Y(t))\| \\
 &= \|(UX(t) + x_2(t)N_2X(t) + x_3(t)N_3X(t) + P) - (UY(t) + y_2(t)N_2Y(t) + y_3(t)N_3Y(t) + P)\| \\
 &= \|UX(t) + x_2(t)N_2X(t) + x_3(t)N_3X(t) - UY(t) - y_2(t)N_2Y(t) - y_3(t)N_3Y(t)\|
 \end{aligned}$$

$$\begin{aligned}
 &= \left\| \left[U(X(t) - Y(t)) + x_2(t)N_2X(t) + x_3N_3X(t) - y_2(t)N_2Y(t) - y_3N_3X(t) \right] \right. \\
 &\quad \left. - \left(\frac{x_2(t)N_2Y(t) - x_2(t)N_2Y(t)}{0} \right) - \left(\frac{x_3(t)N_3Y(t) - x_3(t)N_3Y(t)}{0} \right) \right\| \\
 &= \left\| U(X(t) - Y(t)) + x_2(t)N_2(X(t) - Y(t)) + x_3(t)N_3(X(t) - Y(t)) \right. \\
 &\quad \left. + (x_2(t) - y_2(t))N_2Y(t) + (x_3(t) - y_3(t))N_3Y(t) \right\| \\
 &\leq \left(\|U(X(t) - Y(t))\| + \|x_2(t)N_2(X(t) - Y(t))\| + \|x_3(t)N_3(X(t) - Y(t))\| \right) \\
 &\quad \left(+ \|(x_2(t) - y_2(t))N_2Y(t)\| + \|(x_3(t) - y_3(t))N_3Y(t)\| \right) \\
 &\leq \left(\|U\| \|X(t) - Y(t)\| + |x_2(t)| \|N_2\| \|X(t) - Y(t)\| + |x_3(t)| \|N_3\| \|X(t) - Y(t)\| \right) \\
 &\quad \left(+ \|N_2\| |(x_2(t) - y_2(t))| \|Y(t)\| + \|N_3\| |(x_3(t) - y_3(t))| \|Y(t)\| \right) \\
 &\leq \left((\|U\| + |x_2(t)| \|N_2\| + |x_3(t)| \|N_3\|) \|X(t) - Y(t)\| + \right. \\
 &\quad \left. \|N_2\| \frac{|(x_2(t) - y_2(t))|}{\leq \|X(t) - Y(t)\|} \|Y(t)\| + \|N_3\| \frac{|(x_3(t) - y_3(t))|}{\leq \|X(t) - Y(t)\|} \|Y(t)\| \right) \\
 &\leq \left(\|U\| + \|N_1\| \|Y(t)\| + \|N_2\| |x_2(t)| + \right. \\
 &\quad \left. \|N_2\| \|Y(t)\| + \|N_3\| |x_3(t)| + \|N_3\| \|Y(t)\| \right) \|X(t) - Y(t)\| \\
 &\leq \left(\|U\| + \|N_2\| \left(\frac{|x_2(t)|}{\leq \|X(t)\|} + \|Y(t)\| \right) + \|N_3\| \left(\frac{|x_3(t)|}{\leq \|X(t)\|} + \|Y(t)\| \right) \right) \|X(t) - Y(t)\| \\
 &\leq (\|U\| + (\|N_2\| + \|N_3\|)(\|X(t)\| + \|Y(t)\|)) \|X(t) - Y(t)\|
 \end{aligned}$$

and so,

$$\|F(X(t)) - F(Y(t))\| \leq L \|X(t) - Y(t)\| \tag{6}$$

where $L = \|U\| + (\|N_2\| + \|N_3\|)(E_1 + E_2) > 0$ such that $E_1, E_2 \in \mathbb{R}^+$ and $\|X(t)\| \leq E_1$, $\|Y(t)\| \leq E_2$ due to $X(t), Y(t) \in C^*[0, T]$. Hence, there is only one solution of (4).

3. Qualitative Analysis of Mathematical Model

In this section, the equilibrium points of the mathematical model expressed in (1) are found and stability analysis of these equilibrium points is made.

Definition 3.1. For the system (1), the threshold parameters S_S , R_R and S_R are defined as follows:

$$S_S = \frac{(\beta_S - \omega_S - \sum_{i=1}^n (\varepsilon_i + d_i) \frac{\delta_i}{\mu_i})}{\frac{\beta_S}{\Lambda}}, R_R = \frac{(\beta_R - \omega_R)}{\frac{\beta_R}{\Lambda}}, S_R = \frac{\sum_{i=1}^n \varepsilon_i \frac{\delta_i}{\mu_i}}{\frac{\beta_R}{\Lambda}}. \tag{7}$$

where $S_R > 0$ and $S_S, R_R < \Lambda$ due to (2).

Proposition 3.2. We have presumed that the general expression of the equilibrium points of the system (1) is $E(\bar{B}, \bar{S}, \bar{R}, \bar{A}_1, \bar{A}_2, \dots, \bar{A}_n)$. If the threshold parameters in Definition 3.1 are taken into account, then the following expressions are provided:

- The infection-free equilibrium point is $E_0\left(0, 0, 0, \frac{\delta_1}{\mu_1}, \frac{\delta_2}{\mu_2}, \dots, \frac{\delta_n}{\mu_n}\right)$, and this point always exists.
- If $R_R > 0$, then the equilibrium point $E_1\left(0, 0, R_R, \frac{\delta_1}{\mu_1}, \frac{\delta_2}{\mu_2}, \dots, \frac{\delta_n}{\mu_n}\right)$ exists.
- Let $S_S + S_R \neq R_R$. If $S_S > R_R$, then the equilibrium point $E_2\left(0, (S_S - R_R)\left(\frac{S_S}{S_S + S_R - R_R}\right), S_R\left(\frac{S_S}{S_S + S_R - R_R}\right), \frac{\delta_1}{\mu_1}, \frac{\delta_2}{\mu_2}, \dots, \frac{\delta_n}{\mu_n}\right)$ exists.
- If $R_R - \frac{\omega_B}{v} > 0$, then the equilibrium point $E_3\left(\frac{R_R - \frac{\omega_B}{v}}{\frac{\gamma}{\beta_R}}, 0, \frac{\omega_B}{v}, \frac{\delta_1}{\mu_1}, \frac{\delta_2}{\mu_2}, \dots, \frac{\delta_n}{\mu_n}\right)$ exists.
- Let $S_S > \max\left\{R_R, \frac{\omega_B}{v}\right\}$. In this case, the positive equilibrium point is $E_4\left(\frac{S_S - \frac{\omega_B}{v}}{\frac{\gamma}{\beta_S}}, \frac{\omega_B}{v}\left(\frac{S_S - R_R}{S_S + S_R - R_R}\right), \frac{S_R - \frac{\omega_B}{v}}{(S_S + S_R - R_R)}, \frac{\delta_1}{\mu_1}, \frac{\delta_2}{\mu_2}, \dots, \frac{\delta_n}{\mu_n}\right)$, and it exists.

Proof Let us remember that the equilibrium solution of (1) is denoted by $E(\bar{B}, \bar{S}, \bar{R}, \bar{A}_1, \bar{A}_2, \dots, \bar{A}_n)$. This solution is obtained from $D^{\alpha_1}B = D^{\alpha_2}S = D^{\alpha_3}R = D^{\alpha_{i+3}}A_i = 0$ for $i = 1, 2, \dots, n$. Therefore, we have

$$\begin{aligned} v(\bar{S} + \bar{R})\bar{B} - \omega_B\bar{B} &= 0 \\ \beta_S\bar{S}\left(1 - \frac{\bar{S} + \bar{R}}{\Lambda}\right) - \omega_S\bar{S} - \bar{S}\sum_{i=1}^n \varepsilon_i \bar{A}_i - \bar{S}\sum_{i=1}^n d_i \bar{A}_i - \gamma\bar{B}\bar{S} &= 0 \\ \beta_R\bar{R}\left(1 - \frac{\bar{S} + \bar{R}}{\Lambda}\right) - \omega_R\bar{R} + \bar{S}\sum_{i=1}^n \varepsilon_i \bar{A}_i - \gamma\bar{B}\bar{R} &= 0 \\ \delta_i - \mu_i\bar{A}_i &= 0, \quad i = 1, 2, \dots, n. \end{aligned} \tag{8}$$

Let us consider that the threshold parameters in Definition 3.1. The equilibrium value $\bar{A}_i = \frac{\delta_i}{\mu_i}$ is founded by the equation $\delta_i - \mu_i\bar{A}_i = 0$, which is the fourth equation of the system (8). If this value is rewritten in the second and third equations in (8), then it is founded that

$$\begin{aligned} v(\bar{S} + \bar{R})\bar{B} - \omega_B\bar{B} &= 0 \\ \bar{S}\left(S_S - (\bar{S} + \bar{R}) - \frac{\gamma\Lambda\bar{B}}{\beta_S}\right) &= 0 \\ \bar{R}R_R - \bar{R}(\bar{S} + \bar{R}) + \bar{S}S_R - \frac{\Lambda\gamma\bar{B}\bar{R}}{\beta_R} &= 0 \end{aligned} \tag{9}$$

By the first equation of (9), it is either

$$\bar{B} = 0 \text{ or } (\bar{S} + \bar{R}) = \frac{\omega_B}{v} \tag{10}$$

(i) Let $\bar{B} = 0$. In this case, (9) transforms to

$$\begin{aligned}\bar{S}(S_S - (\bar{S} + \bar{R})) &= 0 \\ \bar{R}R_R - \bar{R}(\bar{S} + \bar{R}) + \bar{S}S_R &= 0.\end{aligned}\tag{11}$$

From first equation in (11), it is founded either $\bar{S} = 0$ or $\bar{S} + \bar{R} = S_S$.

- a.** Let $\bar{S} = 0$. If this value is written in the second equation of (11), $\bar{R} = 0$ and $\bar{R} = R_R$ are obtained. Therefore, $E_0\left(0, 0, 0, \frac{\delta_1}{\mu_1}, \frac{\delta_2}{\mu_2}, \dots, \frac{\delta_n}{\mu_n}\right)$ and $E_1\left(0, 0, R_R, \frac{\delta_1}{\mu_1}, \frac{\delta_2}{\mu_2}, \dots, \frac{\delta_n}{\mu_n}\right)$ are the equilibrium points. The equilibrium point E_0 is biological meaningful due to (2). On the other hand, the equilibrium point E_1 is biological meaningful when $R_R > 0$.
- b.** Let $\bar{S} + \bar{R} = S_S$. Taking into consideration the threshold parameters in (7), if this value is substituted in the second equation of the system (11), then

$$\begin{aligned}\bar{S} + \bar{R} &= S_S \\ \bar{S}S_R + \bar{R}(R_R - S_S) &= 0\end{aligned}\tag{12}$$

is founded. From (12), we have $\bar{S} = \frac{S_S(S_S - R_R)}{S_S + S_R - R_R}$ and $\bar{R} = \frac{S_S S_R}{S_S + S_R - R_R}$ for $S_S + S_R - R_R \neq 0$. For $S_R > 0$ in (7), if $S_S > \max\{R_R, 0\}$, then the equilibrium point $E_2\left(0, \frac{S_S(S_S - R_R)}{S_S + S_R - R_R}, \frac{S_S S_R}{S_S + S_R - R_R}, \frac{\delta_1}{\mu_1}, \frac{\delta_2}{\mu_2}, \dots, \frac{\delta_n}{\mu_n}\right)$ is biological meaning.

(ii) Let

$$(\bar{S} + \bar{R}) = \frac{\omega_B}{v}.\tag{13}$$

In this respect, the system (9) transforms to

$$\begin{aligned}(\bar{S} + \bar{R}) &= \frac{\omega_B}{v} \\ \bar{S}\left(S_S - \frac{\omega_B}{v} - \frac{\gamma}{\beta_S} \bar{B}\right) &= 0 \\ \bar{R}\left(R_R - \frac{\omega_B}{v} - \frac{\gamma}{\beta_R} \bar{B}\right) + \bar{S}S_R &= 0\end{aligned}\tag{14}$$

From the second equation in the system (14), it is clear that either $\bar{S} = 0$ or $\bar{B} = \frac{S_S - \frac{\omega_B}{v}}{\frac{\gamma}{\beta_S}}$.

- a.** Let us assume $\bar{S} = 0$. In this sense, the values $\bar{R} = \frac{\omega_B}{v}$ and then $\bar{B} = \frac{R_R - \frac{\omega_B}{v}}{\frac{\gamma}{\beta_R}}$ are founded from (14), and so the equilibrium point is $E_3\left(\frac{R_R - \frac{\omega_B}{v}}{\frac{\gamma}{\beta_R}}, 0, \frac{\omega_B}{v}, \frac{\delta_1}{\mu_1}, \frac{\delta_2}{\mu_2}, \dots, \frac{\delta_n}{\mu_n}\right)$. If

$$R_R - \frac{\omega_B}{v} > 0,\tag{15}$$

then this point is biological meaningful due to (2).

- b. Let $\bar{B} = \frac{S_S - \frac{\omega_B}{v}}{\frac{\gamma}{\beta_S} \frac{1}{\lambda}}$. If this value is substituted in the second equation of (14), then

$$\begin{aligned} (\bar{S} + \bar{R}) &= \frac{\omega_B}{v} \\ \bar{S}S_R + \bar{R}(R_R - S_S) &= 0 \end{aligned} \tag{16}$$

is obtained. By solving the equations in (16) for $S_S + S_R - R_R \neq 0$, the equilibrium values as $\bar{S} = \frac{\omega_B}{v} \left(\frac{S_S - R_R}{S_S + S_R - R_R} \right)$ and $\bar{R} = \frac{S_R \frac{\omega_B}{v}}{(S_S + S_R - R_R)}$ are obtained. Thereby, If $S_S > \max \left\{ R_R, \frac{\omega_B}{v} \right\}$ then, the equilibrium point $E_4 \left(\frac{S_S - \frac{\omega_B}{v}}{\frac{\gamma}{\beta_S} \frac{1}{\lambda}}, \frac{\omega_B(S_S - R_R)}{S_S + S_R - R_R}, \frac{\omega_B S_R}{S_S + S_R - R_R}, \frac{\delta_1}{\mu_1}, \frac{\delta_2}{\mu_2}, \dots, \frac{\delta_n}{\mu_n} \right)$ is biological meaningful due to (2) and (7).

The following table can be given with respect to the biological existence conditions depended on the parameters of the equilibrium points.

Table 1. The biological meaningful condition for equilibrium points of (1).

Equilibrium Point	Biological Existence Condition
$E_0 \left(0, 0, 0, \frac{\delta_1}{\mu_1}, \frac{\delta_2}{\mu_2}, \dots, \frac{\delta_n}{\mu_n} \right)$	Always
$E_1 \left(0, 0, R_R, \frac{\delta_1}{\mu_1}, \frac{\delta_2}{\mu_2}, \dots, \frac{\delta_n}{\mu_n} \right)$	$0 < R_R$
$E_2 \left(0, \frac{S_S(S_S - R_R)}{S_S + S_R - R_R}, \frac{S_S S_R}{S_S + S_R - R_R}, \frac{\delta_1}{\mu_1}, \frac{\delta_2}{\mu_2}, \dots, \frac{\delta_n}{\mu_n} \right)$	$\max\{R_R, 0\} < S_S, S_S + S_R - R_R \neq 0$
$E_3 \left(\frac{R_R - \frac{\omega_B}{v}}{\frac{\gamma}{\beta_R} \frac{1}{\lambda}}, 0, \frac{\omega_B}{v}, \frac{\delta_1}{\mu_1}, \frac{\delta_2}{\mu_2}, \dots, \frac{\delta_n}{\mu_n} \right)$	$\frac{\omega_B}{v} < R_R$
$E_4 \left(\frac{S_S - \frac{\omega_B}{v}}{\frac{\gamma}{\beta_S} \frac{1}{\lambda}}, \frac{\omega_B(S_S - R_R)}{S_S + S_R - R_R}, \frac{\omega_B S_R}{S_S + S_R - R_R}, \frac{\delta_1}{\mu_1}, \frac{\delta_2}{\mu_2}, \dots, \frac{\delta_n}{\mu_n} \right)$	$\max \left\{ R_R, \frac{\omega_B}{v} \right\} < S_S, S_S + S_R - R_R \neq 0$

Definition 3.2. In the stability analysis of the equilibrium points of the system (1), we have assumed that

$$\alpha_1 = \alpha_2 = \dots = \alpha_{n+3} = \alpha \tag{17}$$

for the orders of derivatives in this system.

Proposition 3.3. Let us assume that Definition 3.2. is provided. The following expressions for the equilibrium points of the system (1) are proved.

- (i) If $S_S, R_R < 0$, then $E_0 \left(0, 0, 0, \frac{\delta_1}{\mu_1}, \frac{\delta_2}{\mu_2}, \dots, \frac{\delta_n}{\mu_n} \right)$ is locally asymptotically stable.
- (ii) Let $0 < R_R$. If $S_S < R_R < \frac{\omega_B}{v}$, then $E_1 \left(0, 0, R_R, \frac{\delta_1}{\mu_1}, \frac{\delta_2}{\mu_2}, \dots, \frac{\delta_n}{\mu_n} \right)$ is locally asymptotically stable.
- (iii) Let $\max\{R_R, 0\} < S_S$ and $S_S + S_R - R_R \neq 0$. If $S_S < \frac{\omega_B}{v}$, then $E_2 \left(0, \frac{S_S(S_S - R_R)}{S_S + S_R - R_R}, \frac{S_S S_R}{S_S + S_R - R_R}, \frac{\delta_1}{\mu_1}, \frac{\delta_2}{\mu_2}, \dots, \frac{\delta_n}{\mu_n} \right)$ is locally asymptotically stable.
- (iv) Let $\frac{\omega_B}{v} < R_R$. If $\frac{\beta_S}{\beta_R} \left(S_S - \frac{\omega_B}{v} \right) < \left(R_R - \frac{\omega_B}{v} \right)$, then $E_3 \left(\frac{R_R - \frac{\omega_B}{v}}{\frac{\gamma}{\beta_R}}, 0, \frac{\omega_B}{v}, \frac{\delta_1}{\mu_1}, \frac{\delta_2}{\mu_2}, \dots, \frac{\delta_n}{\mu_n} \right)$ is locally asymptotically stable.
- (v) Let $\max \left\{ R_R, \frac{\omega_B}{v} \right\} < S_S$ and $S_S + S_R - R_R \neq 0$. $E_4 \left(\frac{S_S - \frac{\omega_B}{v}}{\frac{\gamma}{\beta_S}}, \frac{\omega_B(S_S - R_R)}{S_S + S_R - R_R}, \frac{\omega_B S_R}{S_S + S_R - R_R}, \frac{\delta_1}{\mu_1}, \frac{\delta_2}{\mu_2}, \dots, \frac{\delta_n}{\mu_n} \right)$ is locally asymptotically stable, when $S_R < \frac{\omega_B}{v}$.

Proof The functions obtained from the system (1) for $i = 1, 2, \dots, n$ are as the followings

$$\begin{aligned}
 g_1(B, S, R, A_1, \dots, A_n) &= v(S + R)B - \omega_B B \\
 g_2(B, S, R, A_1, \dots, A_n) &= \beta_S S \left(1 - \frac{S+R}{\Lambda} \right) - \omega_S S - S \sum_{i=1}^n \varepsilon_i A_i - S \sum_{i=1}^n d_i A_i - \gamma B S \\
 g_3(B, S, R, A_1, \dots, A_n) &= \beta_R R \left(1 - \frac{S+R}{\Lambda} \right) - \omega_R R + S \sum_{i=1}^n \varepsilon_i A_i - \gamma B R \\
 g_4(B, S, R, A_1, \dots, A_n) &= \delta_i - \mu_i A_i \\
 &\vdots \\
 g_{i+3}(B, S, R, A_1, \dots, A_n) &= \delta_i - \mu_i A_i
 \end{aligned} \tag{18}$$

In this sense, the jacobian matrix of this system, which has the form $J =$

$$\begin{pmatrix}
 (g_1)_B & (g_1)_S & (g_1)_R & (g_1)_{A_1} & \dots & (g_1)_{A_n} \\
 (g_2)_B & (g_2)_S & (g_2)_R & (g_2)_{A_1} & \dots & (g_2)_{A_n} \\
 (g_3)_B & (g_3)_S & (g_3)_R & (g_3)_{A_1} & \dots & (g_3)_{A_n} \\
 (g_4)_B & (g_4)_S & (g_4)_R & (g_4)_{A_1} & \dots & (g_4)_{A_n} \\
 \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\
 (g_{n+3})_B & (g_{n+3})_S & (g_{n+3})_R & (g_{n+3})_{A_1} & \dots & (g_{n+3})_{A_n}
 \end{pmatrix}, \text{ is}$$

$$J = \begin{pmatrix} v(S+R) - \omega_B & vB & vB & 0 & \dots & 0 \\ -\gamma S & \left(\beta_S - \omega_S - 2\frac{S\beta_S}{\Lambda} - \frac{R\beta_S}{\Lambda} \right) & -\frac{S\beta_S}{\Lambda} & -S(\varepsilon_1 + d_1) & \dots & -S(\varepsilon_n + d_n) \\ -\gamma R & \left(-\frac{\beta_{RR}}{\Lambda} + \sum_{i=1}^n \varepsilon_i A_i \right) & \left(\beta_R - \omega_R - \frac{\beta_{RS}}{\Lambda} \right) & 0 & \dots & 0 \\ 0 & 0 & 0 & -\mu_1 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & \dots & -\mu_n \end{pmatrix} \quad (19)$$

Let us remember that the values $\bar{A}_i = \frac{\delta_i}{\mu_i}$ for $i = 1, 2, \dots, n$ in all of the equilibrium points was founded in Proposition 3.2. By substituting these values in the Jacobian matrix in (19), this matrix transforms to

$$J^* = \begin{pmatrix} v(\bar{S} + \bar{R}) - \omega_B & v\bar{B} & v\bar{B} & 0 & \dots & 0 \\ -\gamma\bar{S} & \frac{\beta_S}{\Lambda} \left(S_S - 2\bar{S} - \bar{R} - \frac{\gamma}{\beta_S} \bar{B} \right) & -\frac{\bar{S}\beta_S}{\Lambda} & -\bar{S}(\varepsilon_1 + d_1) & \dots & -\bar{S}(\varepsilon_n + d_n) \\ -\gamma\bar{R} & \frac{\beta_R}{\Lambda} (-\bar{R} + S_R) & \frac{\beta_R}{\Lambda} \left(R_R - \bar{S} - 2\bar{R} - \frac{\gamma}{\beta_R} \bar{B} \right) & 0 & \dots & 0 \\ 0 & 0 & 0 & -\mu_1 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & \dots & -\mu_n \end{pmatrix} \quad (20)$$

where \bar{B}, \bar{S} and \bar{R} are the components of the equilibrium points. From the matrix (20) evaluated at the equilibrium points showed in Table 3.1, it is assumed that the eigenvalues are denoted by λ_i for $i = 1, \dots, n + 3$. Also, it is clear that $\lambda_{i+3} = -\mu_i < 0$, which meant that the stability states of the equilibrium points with respect to Routh-Hurwitz criteria do not affect. Therefore, it should be examined the following block matrix

$$J^{*Block} = \begin{pmatrix} v(\bar{S} + \bar{R}) - \omega_B & v\bar{B} & v\bar{B} \\ -\gamma\bar{S} & \frac{\beta_S}{\Lambda} \left(S_S - 2\bar{S} - \bar{R} - \frac{\gamma}{\beta_S} \bar{B} \right) & -\frac{\beta_S}{\Lambda} \bar{S} \\ -\gamma\bar{R} & \frac{\beta_R}{\Lambda} (-\bar{R} + S_R) & \frac{\beta_R}{\Lambda} \left(R_R - \bar{S} - 2\bar{R} - \frac{\gamma}{\beta_R} \bar{B} \right) \end{pmatrix}. \quad (21)$$

(i) The matrix (21) evaluated at $E_0 \left(0, 0, 0, \frac{\delta_1}{\mu_1}, \frac{\delta_2}{\mu_2}, \dots, \frac{\delta_n}{\mu_n} \right)$ is

$$J_{E_0}^{*Block} = \begin{pmatrix} -\omega_B & 0 & 0 \\ 0 & \frac{\beta_S}{\Lambda} S_S & 0 \\ 0 & \frac{\beta_R}{\Lambda} S_R & \frac{\beta_R}{\Lambda} R_R \end{pmatrix} \quad (22)$$

In this sense, the eigenvalues are $\lambda_1 = -\omega_B$, $\lambda_2 = \frac{\beta_S}{\Lambda} S_S$ and $\lambda_3 = \frac{\beta_R}{\Lambda} R_R$. These eigenvalues are real number and $\lambda_1 < 0$ due to (2). If

$$S_S, R_R < 0, \quad (23)$$

then $\lambda_1, \lambda_2 < 0$. In this case, E_0 is locally asymptotically stable.

(ii) Let $0 < R_R$. The matrix (21) evaluated at the point $E_1 \left(0, 0, R_R, \frac{\delta_1}{\mu_1}, \frac{\delta_2}{\mu_2}, \dots, \frac{\delta_n}{\mu_n} \right)$ is

$$J_{E_1}^{*Block} = \begin{pmatrix} vR_R - \omega_B & 0 & 0 \\ 0 & \frac{\beta_S}{\Lambda} (S_S - R_R) & 0 \\ -\gamma R_R & \frac{\beta_R}{\Lambda} (-R_R + S_S) & -\frac{\beta_R}{\Lambda} R_R \end{pmatrix} \quad (24)$$

In this case, the eigenvalues obtained from (24) are $\lambda_1 = vR_R - \omega_B$, $\lambda_2 = \frac{\beta_S}{\Lambda} (S_S - R_R)$ and $\lambda_3 = -\frac{\beta_R}{\Lambda} R_R$. From (2) and (7), it is clear that these eigenvalues are real number. Moreover, if the biological existence condition of E_1 is taken into account, then it is seen $\lambda_3 < 0$. According to Routh-Hurwitz criteria, If

$$S_S < R_R < \frac{\omega_B}{v}, \quad (25)$$

then λ_1 and λ_2 are negative real number, which means that E_1 is locally asymptotically stable.

(iii) Let $S_S + S_R - R_R \neq 0$ and

$$\max\{R_R, 0\} < S_S. \quad (26)$$

By the matrix (21) for $E_2 \left(0, \frac{S_S(S_S - R_R)}{S_S + S_R - R_R}, \frac{S_S S_R}{S_S + S_R - R_R}, \frac{\delta_1}{\mu_1}, \frac{\delta_2}{\mu_2}, \dots, \frac{\delta_n}{\mu_n} \right)$, it is

$$J_{E_2}^{*Block} = \begin{pmatrix} vS_S - \omega_B & 0 & 0 \\ \frac{-\gamma S_S(S_S - R_R)}{S_S + S_R - R_R} & -\frac{\beta_S S_S(S_S - R_R)}{\Lambda S_S + S_R - R_R} & -\frac{\beta_S S_S(S_S - R_R)}{\Lambda S_S + S_R - R_R} \\ -\gamma \bar{R} & \frac{\beta_R S_R(S_S - R_R)}{\Lambda S_S + S_R - R_R} & \frac{\beta_R}{\Lambda} \left(R_R - S_S - \frac{S_S S_R}{S_S + S_R - R_R} \right) \end{pmatrix}. \quad (27)$$

One of the eigenvalues obtained from (27) is $\lambda_1 = vS_S - \omega_B$ and the others are founded by the following matrix

$$J_{E_2}^{**Block} = \begin{pmatrix} -\frac{\beta_S}{\Lambda} \left(\frac{S_S(S_S - R_R)}{S_S + S_R - R_R} \right) & -\frac{\beta_S}{\Lambda} \left(\frac{S_S(S_S - R_R)}{S_S + S_R - R_R} \right) \\ \frac{\beta_R}{\Lambda} S_R \left(\frac{S_S - R_R}{S_S + S_R - R_R} \right) & \frac{\beta_R}{\Lambda} \left(R_R - S_S - \frac{S_S S_R}{S_S + S_R - R_R} \right) \end{pmatrix}. \quad (28)$$

λ_1 is real number due to (2) and (7). Moreover, if

$$S_S < \frac{\omega_B}{v}, \quad (29)$$

then $\lambda_1 < 0$. To find the eigenvalues λ_2 and λ_3 , the characteristic equation obtained from (28) is

$$\lambda^2 - [TrJ_{E_2}^{**Block}]\lambda + [DetJ_{E_2}^{**Block}] = 0 \quad (30)$$

where

$$\begin{aligned} TrJ_{E_2}^{**Block} &= -\left(\frac{\beta_R}{\Lambda}\left((S_S - R_R) + \frac{S_S S_R}{(S_S + S_R - R_R)}\right) + \frac{\beta_S}{\Lambda}\left(\frac{S_S(S_S - R_R)}{S_S + S_R - R_R}\right)\right) \\ DetJ_{E_2}^{**Block} &= \frac{\beta_S \beta_R}{\Lambda \Lambda} S_S (S_S - R_R) \end{aligned} \quad (31)$$

Let us consider (26), namely the biological existence condition of E_2 . In this case, $TrJ_{E_2}^{**Block} < 0$ and $DetJ_{E_2}^{**Block} > 0$. Therefore, it can be seen that all of the coefficients of (30) are positive real number. According to Routh-Hurwitz criteria, if the inequality in (29) is met, then all eigenvalues calculated at this equilibrium point are either complex numbers having negative real part or negative real numbers. In this case, E_2 is locally asymptotically stable.

(iv) Let

$$\frac{\omega_B}{v} < R_R. \quad (32)$$

In this respect, $E_3\left(\frac{R_R - \frac{\omega_B}{v}}{\frac{\gamma}{\beta_R}}, 0, \frac{\omega_B}{v}, \frac{\delta_1}{\mu_1}, \frac{\delta_2}{\mu_2}, \dots, \frac{\delta_n}{\mu_n}\right)$ biologically exists. The Jacobian matrix (21) calculated at this point is

$$J_{E_3}^{*Block} = \begin{pmatrix} 0 & v \frac{R_R - \frac{\omega_B}{v}}{\frac{\beta_R}{\Lambda}} & v \frac{R_R - \frac{\omega_B}{v}}{\frac{\beta_R}{\Lambda}} \\ 0 & \frac{\beta_S}{\Lambda} \left(\left(S_S - \frac{\omega_B}{v} \right) - \frac{\beta_R}{\beta_S} \left(R_R - \frac{\omega_B}{v} \right) \right) & 0 \\ -\gamma \frac{\omega_B}{v} & \frac{\beta_R}{\Lambda} \left(S_R - \frac{\omega_B}{v} \right) & -\frac{\omega_B \beta_R}{v \Lambda} \end{pmatrix} \quad (33)$$

From (33), it is $\lambda_1 = \frac{\beta_S}{\Lambda} \left(\left(S_S - \frac{\omega_B}{v} \right) - \frac{\beta_R}{\beta_S} \left(R_R - \frac{\omega_B}{v} \right) \right)$ and the eigenvalues λ_2 and λ_3 are obtained from the characteristic equation given as

$$\lambda^2 + \frac{\omega_B \beta_R}{v \Lambda} \lambda + \omega_B \frac{\beta_R}{\Lambda} \left(R_R - \frac{\omega_B}{v} \right) = 0 \quad (34)$$

If

$$\frac{\beta_S}{\beta_R} \left(S_S - \frac{\omega_B}{v} \right) < \left(R_R - \frac{\omega_B}{v} \right), \quad (35)$$

then λ_1 is negative real number. That all coefficients in (34) are positive real number due to (2) and (32), which meant $Tr J_{E_3}^{Block} < 0$ and $Det J_{E_3}^{Block} > 0$. In this respect, the eigenvalues λ_2 and λ_3 are either negative real numbers or complex numbers having negative real parts. In accord with Routh-Hurwitz criteria, if the inequality in (34) is provided, then E_3 is locally asymptotically stable.

(v) Let $S_S + S_R - R_R \neq 0$ and

$$\max \left\{ R_R, \frac{\omega_B}{v} \right\} < S_S. \quad (36)$$

By calculating the Jacobian matrix in (21) at the point $E_4 \left(\frac{S_S - \frac{\omega_B}{v}}{\frac{\beta_S}{\Lambda}}, \frac{\omega_B}{v} \frac{(S_S - R_R)}{(S_S + S_R - R_R)}, \frac{\omega_B}{v} \frac{S_R}{(S_S + S_R - R_R)}, \frac{\delta_1}{\mu_1}, \frac{\delta_2}{\mu_2}, \dots, \frac{\delta_n}{\mu_n} \right)$, it is founded

$$J_{E_4}^{*Block} = \begin{pmatrix} 0 & v\bar{B} & v\bar{B} \\ -\gamma\bar{S} & -\bar{S} \frac{\beta_S}{\Lambda} & -\bar{S} \frac{\beta_S}{\Lambda} \\ -\gamma\bar{R} & \frac{\beta_R}{\Lambda} (S_R - \bar{R}) & \frac{\beta_R}{\Lambda} \left(-S_R \frac{\bar{S}}{\bar{R}} - \bar{B} \gamma \Lambda \left(\frac{\beta_S - \beta_R}{\beta_S \beta_R} \right) - \bar{R} \right) \end{pmatrix}, \quad (37)$$

where the values \bar{B} , \bar{S} and \bar{R} are in E_4 . The characteristic equation for the eigenvalues λ_1 , λ_2 and λ_3 obtained from the matrix (37) is

$$\lambda^3 + c_1 \lambda^2 + c_2 \lambda + c_3 = 0, \quad (38)$$

where

$$\begin{aligned} c_1 &= \frac{1}{\Lambda} \left(\beta_S \bar{S} + \beta_R \left(S_R \frac{\bar{S}}{\bar{R}} + \bar{B} \gamma \Lambda \left(\frac{\beta_S - \beta_R}{\beta_S \beta_R} \right) + \bar{R} \right) \right) \\ c_2 &= \left(\bar{B} v \gamma \frac{\omega_B}{v} + \frac{1}{\Lambda^2} \bar{S} \beta_R \beta_S \left(S_R + S_R \frac{\bar{S}}{\bar{R}} + \bar{B} \gamma \Lambda \left(\frac{\beta_S - \beta_R}{\beta_S \beta_R} \right) \right) \right) \\ c_3 &= \frac{\bar{S} \bar{B} v \gamma}{\Lambda} \beta_R \left(S_R + S_R \frac{\bar{S}}{\bar{R}} + \bar{B} \gamma \Lambda \left(\frac{\beta_S - \beta_R}{\beta_S \beta_R} \right) \right). \end{aligned} \quad (39)$$

Let us recall that if $c_1, c_3 > 0$ and $c_1 c_2 > c_3$ for the third-degree characteristic polynomial in (38) according to Routh-Hurwitz criteria, then the equilibrium point is locally asymptotically stable. It is

$$c_1, c_2, c_3 > 0 \quad (40)$$

due to (2) and (3). Also, we have

$$c_1 \cdot c_2 - c_3 = \frac{1}{\Lambda} \left((L_2 + \beta_R L_1) \left(\bar{B} v \gamma \frac{\omega_B}{v} + \frac{1}{\Lambda^2} \bar{S} \beta_R \beta_S L_1 \right) - \bar{S} \bar{B} v \gamma \beta_R L_1 \right) \quad (41)$$

and so,

$$c_1 \cdot c_2 - c_3 = \frac{1}{\Lambda} \left(\frac{1}{\Lambda^2} \bar{S} \beta_R^2 \beta_S L_1^2 + L_2 \bar{B} v \gamma \frac{\omega_B}{v} + \left[L_2 \frac{1}{\Lambda^2} \bar{S} \beta_S + \bar{B} \gamma v \underbrace{\left[\frac{\omega_B}{v} - \bar{S} \right]}_* \right] \beta_R L_1 \right) \quad (42)$$

where

$$\begin{aligned} L_1 &= \left(S_R + S_R \frac{\bar{S}}{\bar{R}} + \bar{B} \gamma \Lambda \left(\frac{\beta_S - \beta_R}{\beta_S \beta_R} \right) \right) \\ L_2 &= (\beta_S \bar{S} - \beta_R S_R + \beta_R \bar{R}). \end{aligned} \quad (43)$$

In this sense, it is

$$0 < L_1 \quad (44)$$

due to (3). On the other hand, we have the follows

$$\begin{aligned} L_2 &= (\beta_S \bar{S} - \beta_R S_R + \beta_R \bar{R}), \\ L_2 &= \left(\beta_S \frac{\omega_B}{v} \left(\frac{S_S - R_R}{S_S + S_R - R_R} \right) - \beta_R S_R + \beta_R \frac{\omega_B}{v} \frac{S_R}{(S_S + S_R - R_R)} \right), \\ L_2 &= \frac{1}{(S_S + S_R - R_R)} \left(\underbrace{\beta_S}_{> \beta_R \text{ due to (2.3)}} \frac{\omega_B}{v} (S_S - R_R) - \beta_R S_R \left(S_S - R_R + S_R - \frac{\omega_B}{v} \right) \right), \\ L_2 &> \frac{\beta_R}{(S_S + S_R - R_R)} \left(\frac{\omega_B}{v} (S_S - R_R) - S_R \left(S_S - R_R + S_R - \frac{\omega_B}{v} \right) \right), \\ L_2 &> \frac{\beta_R}{(S_S + S_R - R_R)} \left(\frac{\omega_B}{v} (S_S - R_R + S_R) - S_R (S_S - R_R + S_R) \right) = \beta_R \left(\frac{\omega_B}{v} - S_R \right), \\ L_2 &> \frac{\beta_R}{(S_S + S_R - R_R)} \left(\frac{\omega_B}{v} (S_S - R_R + S_R) - S_R (S_S - R_R + S_R) \right) = \beta_R \left(\frac{\omega_B}{v} - S_R \right), \end{aligned}$$

and so,

$$L_2 > \beta_R \left(\frac{\omega_B}{v} - S_R \right). \quad (45)$$

If

$$S_R < \frac{\omega_B}{v}, \tag{46}$$

then

$$0 < L_2. \tag{47}$$

For the expression * in (42),

$$* = \left[\frac{\omega_B}{v} - \bar{S} \right] = \frac{\omega_B}{v} - \frac{\omega_B}{v} \left(\frac{S_S - R_R}{S_S + S_R - R_R} \right) = \frac{\omega_B}{v} \left[1 - \left(\frac{S_S - R_R}{S_S + S_R - R_R} \right) \right] > 0 \tag{48}$$

<1 due to (3.30)

is provided. To sum up, if (46) is provided, then it is

$$c_1 \cdot c_2 - c_3 > 0, \tag{49}$$

in (42), due to (44), (46) and (48). Let us consider (46). E_4 is locally asymptotically stable, when (40) and (49) are met.

As a result of this proposition, the following table can be given.

Table 2. Conditions of stability and biological meaningful for equilibrium points of (1).

Equilibrium Point	Biological Existence Condition	Stability Condition
$E_0 \left(0, 0, 0, \frac{\delta_1}{\mu_1}, \frac{\delta_2}{\mu_2}, \dots, \frac{\delta_n}{\mu_n} \right)$	Always	$S_S, R_R < 0$
$E_1 \left(0, 0, R_R, \frac{\delta_1}{\mu_1}, \frac{\delta_2}{\mu_2}, \dots, \frac{\delta_n}{\mu_n} \right)$	$0 < R_R$	$S_S < R_R < \frac{\omega_B}{v}$
$E_2 \left(0, \frac{S_S(S_S - R_R)}{S_S + S_R - R_R}, \frac{S_S S_R}{S_S + S_R - R_R}, \frac{\delta_1}{\mu_1}, \frac{\delta_2}{\mu_2}, \dots, \frac{\delta_n}{\mu_n} \right)$	$\max\{R_R, 0\} < S_S,$ $S_S + S_R - R_R \neq 0$	$S_S < \frac{\omega_B}{v}$
$E_3 \left(\frac{R_R - \frac{\omega_B}{v}}{\frac{\gamma}{\beta_R} \lambda}, 0, \frac{\omega_B}{v}, \frac{\delta_1}{\mu_1}, \frac{\delta_2}{\mu_2}, \dots, \frac{\delta_n}{\mu_n} \right)$	$\frac{\omega_B}{v} < R_R$	$\frac{\beta_S}{\beta_R} \left(S_S - \frac{\omega_B}{v} \right) < \left(R_R - \frac{\omega_B}{v} \right)$
$E_4 \left(\frac{S_S - \frac{\omega_B}{v}}{\frac{\gamma}{\beta_S} \lambda}, \frac{\omega_B}{v} \frac{S_S - R_R}{S_S + S_R - R_R}, \frac{\omega_B}{v} \frac{S_R}{S_S + S_R - R_R}, \frac{\delta_1}{\mu_1}, \frac{\delta_2}{\mu_2}, \dots, \frac{\delta_n}{\mu_n} \right)$	$\max\left\{R_R, \frac{\omega_B}{v}\right\} < S_S,$ $S_S + S_R - R_R \neq 0$	$S_R < \frac{\omega_B}{v}$

4. Applications of the Proposed Model in (1)

In this section, the values obtained from the literature to the parameters used in the system (1) are given. The qualitative analysis of the proposed model was supported by numerical simulations. Two application have been done in this context.

4.1. Application for Pseudomonas Aeruginosa

The parameter values in the studies of Handel et al. [48] and Ternent et al. [40] are used. For an individual receiving Meropenem and Antivirulence drug in case of the infection caused by Pseudomonas Aeruginosa, they proposed a mathematical model in ODE form, based on the relationship among phagocyte (immune system cells), bacteria and drug concentrations.

Table 3. Parameter values used in system (1) for Pseudomonas Aeruginosa

Parameter	Definition	Value	Reference
β_S	The growth rate of susceptible Pseudomonas Aeruginosa	24 day ⁻¹	[48]
β_R	The growth rate of resistant Pseudomonas aeruginosa	21.6 day ⁻¹	[40]
Λ	The carrying capacity of Pseudomonas Aeruginosa	10 ⁹ bakteri	[48]
ν	The growth rate of immune system cells in the presence of Pseudomonas Aeruginosa	3 day ⁻¹	[40]
ω_S	The natural death rate of susceptible Pseudomonas Aeruginosa	0.7 day ⁻¹	[40]
ω_R	The natural death rate of resistant Pseudomonas Aeruginosa	0.7 day ⁻¹	[40]
ω_B	The natural death rate of immune system cells	1.512 day ⁻¹	[49]
γ	The death rate of Pseudomonas Aeruginosa due to immune system cells	2.4 * 10 ⁻⁴ day ⁻¹	[49]
ε_1	The mutation rate of Pseudomonas Aeruginosa due to Meropenem	10 ⁻⁶ mutxgen	[50,51]
ε_2	The mutation rate of Pseudomonas Aeruginosa due to anti-virulence drug	0 mutxgen	[40]
d_1	The death rate of Pseudomonas Aeruginosa due to Meropenem	8.47 day ⁻¹	[40]
d_2	The death rate of Pseudomonas Aeruginosa due to anti-virulence drug	2.93 day ⁻¹	[50,51]
δ_1	The daily dose of Meropenem	4 mg/kg/day	[40,50,51]
δ_2	The daily dose of anti-virulence drug	4 mg/kg/day	[40,50,51]
μ_1	The remove rate from the body of Meropenem	0.15 day ⁻¹	[50,51]
μ_2	The remove rate from the body of anti-virulence drug	0.15 day ⁻¹	[50,51]
α	The orders of the derivative in the system (1)	0.9	Hypothesis
(B_0, S_0, R_0, A_{i_0})	Initial conditions for $i = 1,2$	(1,6000,2,4,4)	[40,48]

When parameter values in Table 3. are used, the threshold parameters in Definition 3.1. are $S_S = -11695802777$, $R_R = 967592592$ and $S_R = 1234567901$. From Proposition 3.2., the equilibrium points existed biologically are $E_0(0,0,0,26.66,26.66)$,

$E_1(0,0,967592592,26.66,26.66)$ and $E_3(87083.33,0,0.504,26.66,26.66)$, respectively. $E_3(87083.33,0,0.504,26.66,26.66)$ is locally asymptotically stable, because it is $\frac{\beta_S}{\beta_R} \left(S_S - \frac{\omega_B}{v} \right) = -\frac{2923950694376}{225} < \left(R_R - \frac{\omega_B}{v} \right) = 967592591.496$ in the Proposition 3.3. The drug dose and duration of treatment for this infection is determined by type and severity of the infection and the patient's condition. In the study of Handel et al.[48], they have investigated in a treatment duration of approximately 10 days. In this sense, we have considered the same treatment duration for this study. Thus, we have obtained the following figures.

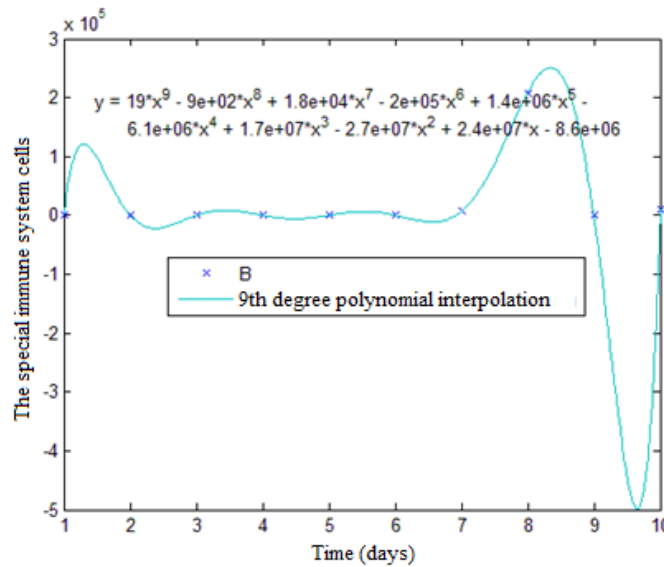


Fig.2. Time-dependent changes of the immune system cells during 10 days of the drug treatment according to Table 3.

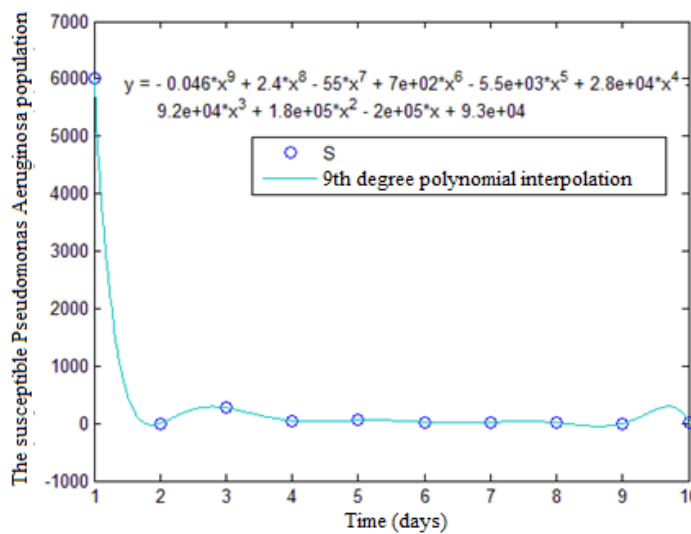


Fig.3. Time-dependent changes of the susceptible Pseudomonas Aeruginosa population during 10 days of drug treatment according to Table 3.

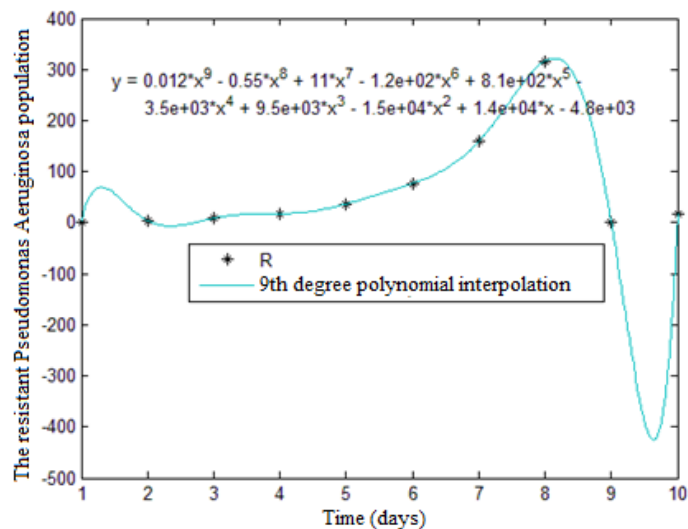


Fig.4. Time-dependent changes of the resistant Pseudomonas Aeruginosa population during 10 days of drug treatment according to Table 3.

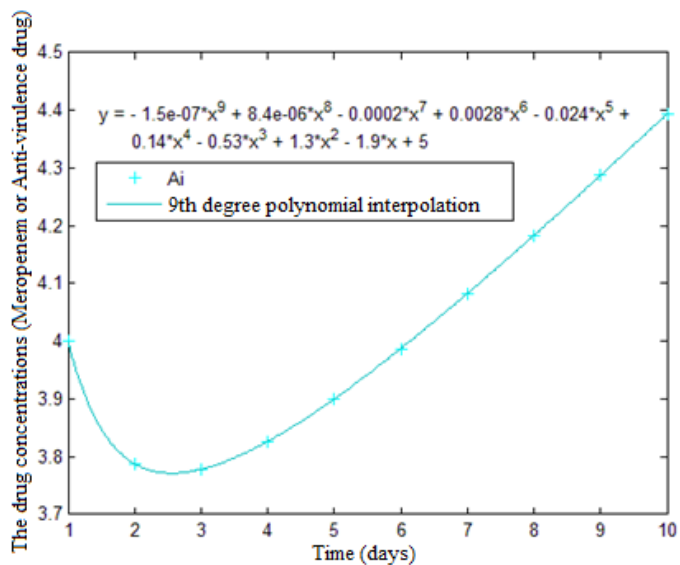


Fig.5. Time-dependent changes for the each drug concentrations (Meropenem or Anti-virulence drug) during 10 days of drug treatment according to Table 3.

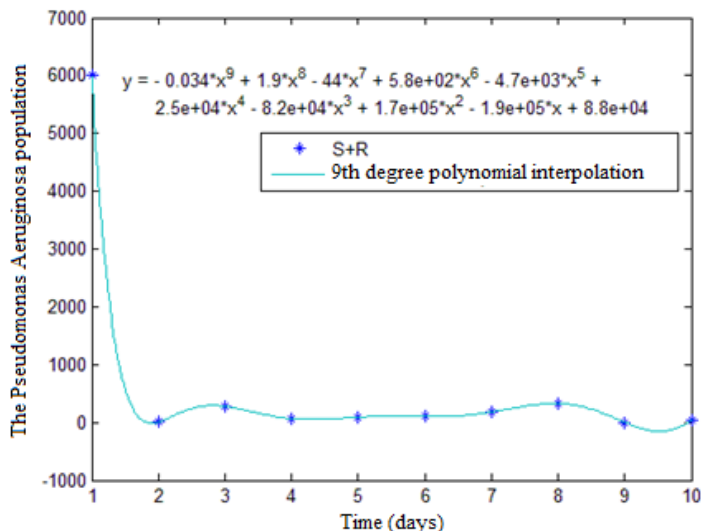


Fig.6. Time-dependent changes of the Pseudomonas Aeruginosa population during 10 days of drug treatment according to Table 3.

The daily ranges in quantities of the specific immune system cells, the susceptible Pseudomonas Aeruginosa population, the resistant Pseudomonas Aeruginosa population, the drug concentrations (Meropenem or Anti-virulence drug) and the Pseudomonas Aeruginosa population during the 10-day treatment period are shown respectively in Fig.2-6.

For ease of reviewing the daily values of the variables in these figures, the points on the graph were interpolated into polynomial at 9th degree (except for the initial conditions) to show the increase or decrease between consecutive days, due to it is a treatment method of 10 days.

Stability of the equilibrium points $E_3(87083.33,0,0.504,26.66,26.66)$ is seen in Fig. 7. Within 10 days of treatment, the antibiotic-resistant Pseudomonas aeruginosa population approaches 0.504 (quite small value) and the antibiotic-susceptible Pseudomonas aeruginosa population disappears. Also, it takes a long time that specific immune system cells approach to the value of 87083.33. As shown in Fig.7, this is due to the local stability and the parameters.

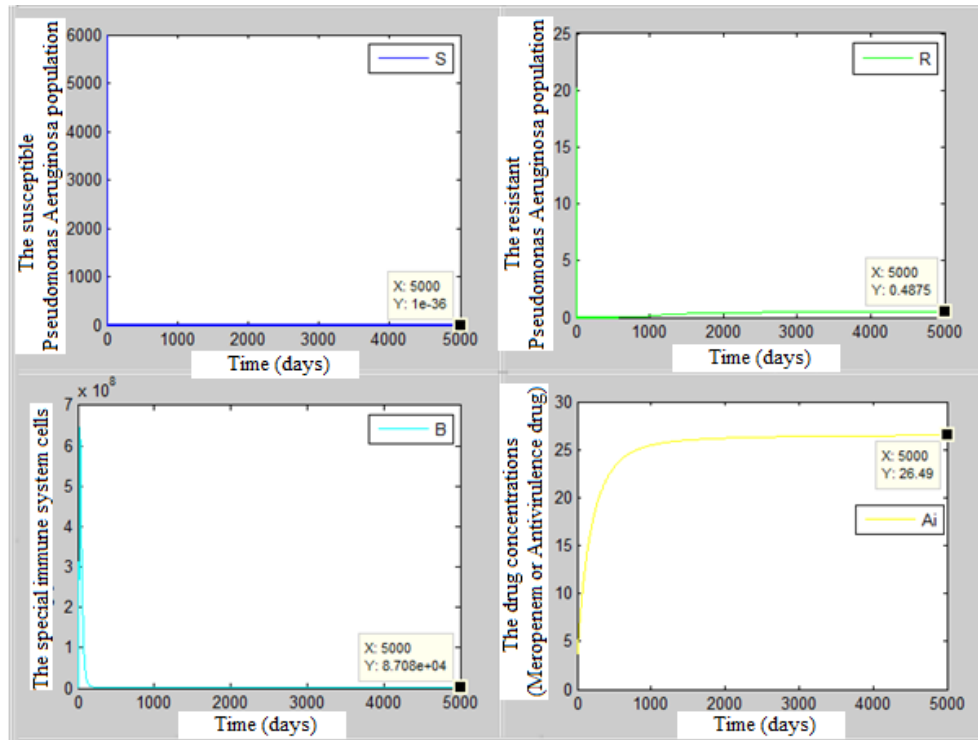


Fig.7. According to Table 3, Stability of the equilibrium point $E_3(87083.33,0,0.504,26.66,26.66)$.

4.2. Application for Mycobacterium Tuberculosis

The parameter values in the studies of Mondragón et al. [39] are used. For an individual receiving the antibiotics isoniazid (INH), rifampicin (RIF), streptomycin (SRT) and pyrazinamide (PZA) in case of the infection caused by Mycobacterium Tuberculosis, they proposed a mathematical model in ODE form, based on the relationship between bacteria and antibiotic concentrations. For this infection, the treatment time is about 6 months. In this sense, all of the antibiotics are used in the first two months and the antibiotics isoniazid and rifampicin are used in the remaining four months [52]. The parameter values used in the system (1) for numerical study are given in Table 4.

Table 4. Parameter values used in system (1) for Mycobacterium Tuberculosis

Parameter	Definition	Value	Reference
β_S	The growth rate of susceptible Mycobacterium Tuberculosis	0.8 day ⁻¹	[39]
β_R	The growth rate of resistant Mycobacterium Tuberculosis	0.4 day ⁻¹	[39]
Λ	The carrying capacity of Mycobacterium Tuberculosis	10 ⁹ bakteri	[53]
ν	The growth rate of immune system cells in the presence of Mycobacterium Tuberculosis	0.0002 day ⁻¹	Hypothesis
ω_S	The natural death rate of susceptible Mycobacterium Tuberculosis	0.312 day ⁻¹	[39]
ω_R	The natural death rate of resistant Mycobacterium Tuberculosis	0.312 day ⁻¹	[39]
ω_B	The natural death rate of immune system cells	0.35 day ⁻¹	[54]
γ	The death rate of Mycobacterium Tuberculosis due to immune system cells	2.4 * 10 ⁻⁴ day ⁻¹	[49]
ϵ_1	The mutation rate of Mycobacterium Tuberculosis due to isoniazid	10 ⁻⁶ mutxgen	[55]
ϵ_2	The mutation rate of Mycobacterium Tuberculosis due to rifampicin	10 ⁻⁸ mutxgen	[55]
ϵ_3	The mutation rate of Mycobacterium Tuberculosis due to streptomycin	0	[39]
ϵ_4	The mutation rate of Mycobacterium Tuberculosis due to pyrazinamide	0	[39]
d_1	The death rate of Mycobacterium Tuberculosis due to isoniazid	0.0039 day ⁻¹	[56]
d_2	The death rate of Mycobacterium Tuberculosis due to rifampicin	0.00375 day ⁻¹	[39]
d_3	The death rate of Mycobacterium Tuberculosis due to streptomycin	0.0025 day ⁻¹	[53]
d_4	The death rate of Mycobacterium Tuberculosis due to pyrazinamide	0.00001625 day ⁻¹	[53]
δ_1	The daily dose of isoniazid	5 mg/kg/day	[55]
δ_2	The daily dose of rifampicin	10 mg/kg/day	[55]
δ_3	The daily dose of streptomycin	15-25 mg/kg/ day	[55]
δ_4	The daily dose of pyrazinamide	20-35 mg/kg/ day	[55]
μ_1	The remove rate from the body of isoniazid	0.06 day ⁻¹	[57]
μ_2	The remove rate from the body of rifampicin	0.05 day ⁻¹	[57]
μ_3	The remove rate from the body of streptomycin	0.04 day ⁻¹	[57]
μ_4	The remove rate from the body of pyrazinamide	0.03 day ⁻¹	[57]
α	The orders of the derivative in the system (1)	0.9	Hypothesis
(B_0, S_0, R_0, A_{i0})	Initial conditions for $i = 1,2,3,4$	(1000, 6000, 20,0,0,0,0)	Hypothesis

Let us consider the parameter values in Table 4. and the treatment method mentioned above.

All antibiotics are used in the first two months of this treatment. In this sense, the threshold parameters are obtained as $S_S = -1919273333$, $R_R = 220000000$ and $S_R = 213333$. Considered in Table 1, the equilibrium points existing biologically are

$E_0(0,0,0,83,200,375,666)$, $E_1(0,0,220000000,83,200,375,666)$ and $E_3(0.5289575,0,1750,83,200,375,666)$. If the stability conditions of these equilibrium points with respect to Table 2. is considered, then it is obtained that E_0 is unstable due to $\frac{R_R}{220000000} > 0$, E_1 is unstable due to $\frac{\omega_B}{1750} < \frac{R_R}{220000000}$ and E_3 is locally asymptotically stable due to $\frac{\beta_S}{\beta_R} \left(S_S - \frac{\omega_B}{v} \right) < \left(R_R - \frac{\omega_B}{v} \right)$. During the first two months of treatment, some of the resistant bacteria population survives and the sensitive bacterial population disappears.

Isoniazid and rifampicin as antibiotic are used in the last four months of this treatment. Therefore, the threshold parameters are recalculated as $S_S = -733856666$, $R_R = 220000000$ and $S_R = 213333$. The equilibrium points existing biologically are $E_0(0,0,0,83,200,0,0)$, $E_1(0,0,220000000,83,200,0,0)$ and $E_3(0.5289575,0,1750,83,200,375,666)$. Similar to the calculation results in the first two months of treatment, the equilibrium point $E_3(0.5289575,0,1750,83,200,375,666)$ is locally asymptotically stable, since $\frac{\beta_S}{\beta_R} \left(S_S - \frac{\omega_B}{v} \right) < \left(R_R - \frac{\omega_B}{v} \right)$.

For six months of treatment, the special immune system cells, the susceptible Mycobacterium Tuberculosis population and the resistant Mycobacterium Tuberculosis population approach to the values 0.5289575, 0 and 1750, respectively.

These situations are evident in the following figures.

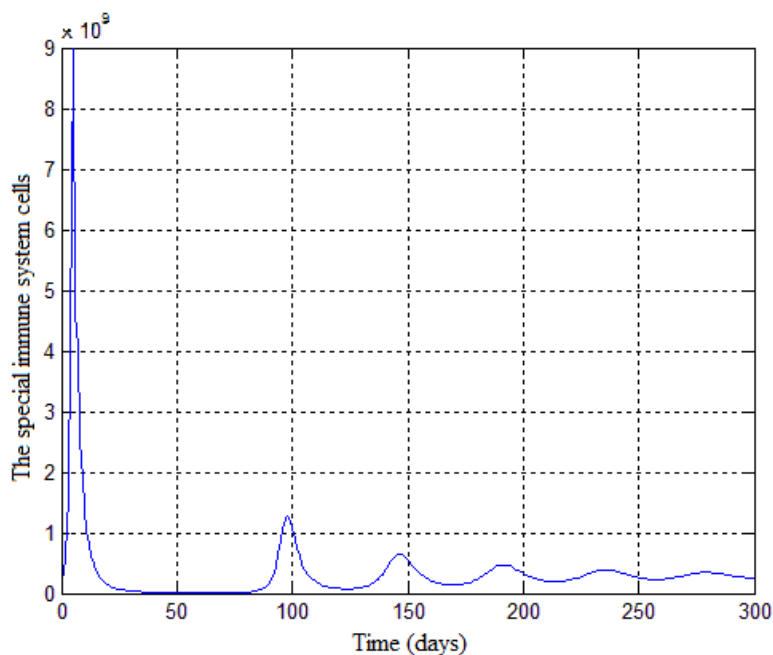


Fig.8. Time-dependent changes of the special immune system cells during 6 months of treatment according to Table 4.

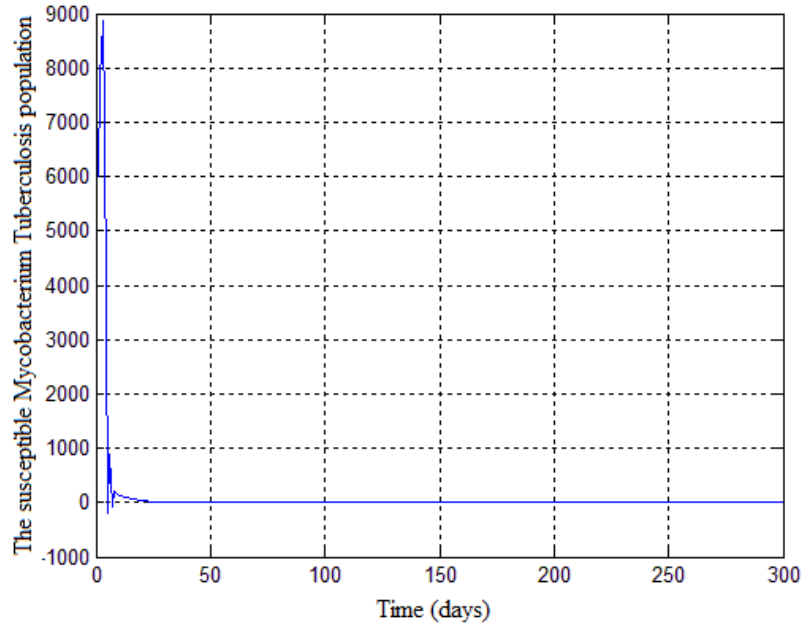


Fig.9 Time-dependent changes of the susceptible Mycobacterium Tuberculosis population during 6 months of treatment according to Table 4.

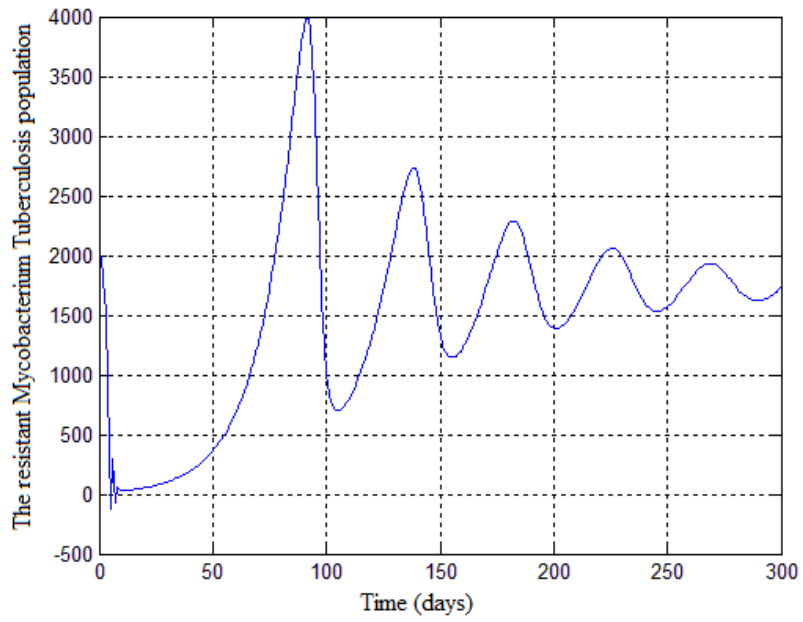


Fig.10. Time-dependent changes of the resistant Mycobacterium Tuberculosis population during 6 months of treatment according to Table 4.

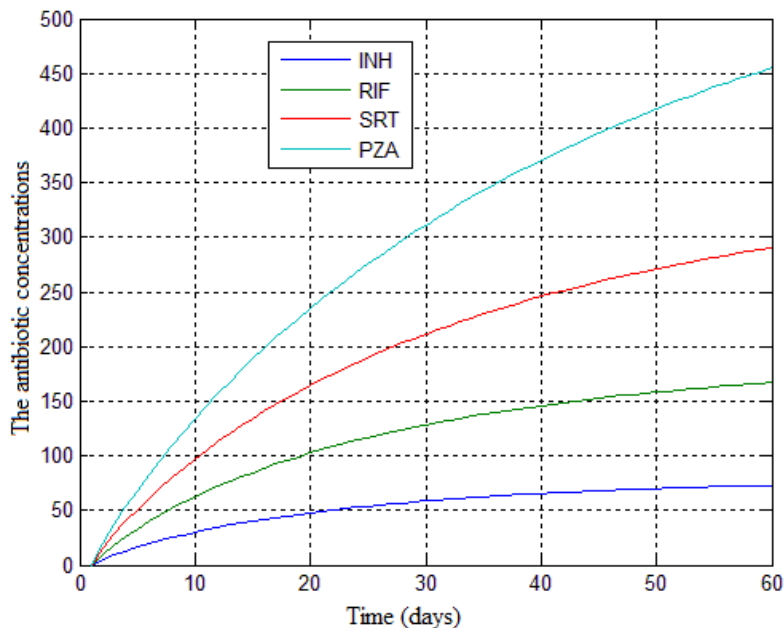


Fig.11. Time-dependent changes of the antibiotic concentrations during first 2 months of treatment according to Table 4.

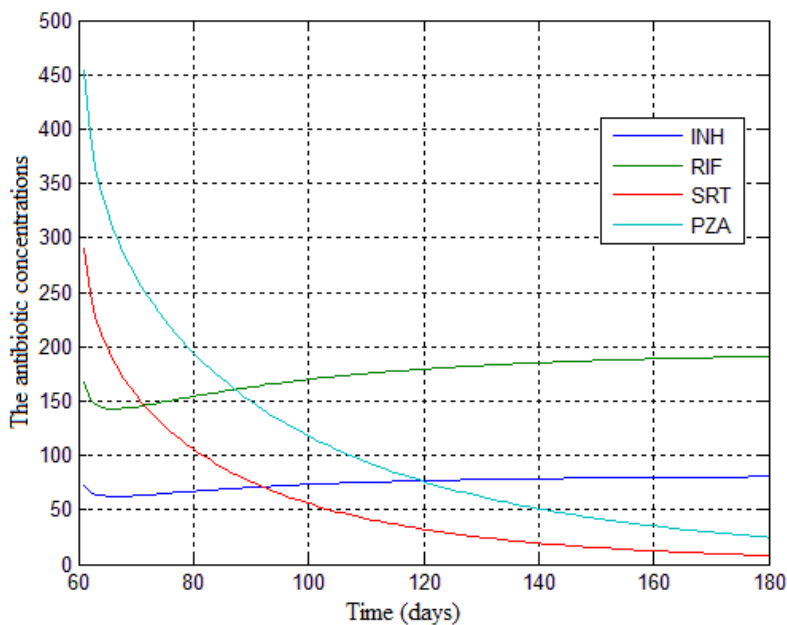


Fig.12. Time-dependent changes of the antibiotic concentrations during last 4 months of treatment according to Table 4.

5. Results and Discussions

As seen in the applications of the proposed model, while the susceptible bacteria population is disappeared and the resistant bacteria population is limited. Especially, the model is a useful model for explaining the recrudescence of a bacterial infection believed to have been destroyed when immune system of the individual is weakened. For example, the World

Health Organization explains that the rate of recurrence of Mycobacterium Tuberculosis is 5-10%. According to researches conducted in recent years, about 9.2 million people suffer from this infection every year in the world and about 1.6 million of them die due to this infection. This rate is increasing due to the causes such as long-term or close contact with the infectious people, excessive stress and weakening of the immune system etc. Therefore, the model proposed in this study can be considered as a very useful tool to estimate the timing and the magnitude of both infection and possible re-infection.

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