The Fractional-Order mathematical modeling of bacterial resistance against multiple antibiotics in case of local bacterial infection

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ABSTRACT

In this study, it is described the general forms of fractional-order differential equations and asymtotic stability of their system's equilibria. In addition that, the stability analysis of equilibrium points of the local bacterial infection model which is fractional-order differential equation system, is made. Results of this analysis are supported via numerical simulations drawn by datas obtained from literature for mycobacterium tuberculosis and the antibiotics isoniazid (INH), rifampicin (RIF), streptomycin (SRT) and pyrazinamide (PRZ) used against this bacterial infection.

Keywords: fractional-order differential equation system, mathematical model, stability analysis, equilibrium points, multiple antibiotics

Lokal Bakteriyel enfeksiyon durumunda çoklu antibiyotik tedavisine karşı bakteriyel direncin kesirsel mertebeden matematiksel modellemesi

ÖZ

Bu çalışmada kesirsel mertebeden diferansiyel denklemlerin genel biçimi ve bu denklemlerin sistemlerinin dengelerinin asimptotik kararlılıkları tanımlandı. Ayrıca kesirsel mertebeden diferansiyel denklem sistemi şeklinde ifade edilen lokal bir bakteriyel enfeksiyon modelinin denge noktalarının kararlılık analizi yapıldı. Bu analizin sonuçları mycobacterium tuberculosis bakterisi ve bu bakterinin neden olduğu enfeksiyona karşı kullanılan isoniazid (INH), rifampicin (RIF), streptomycin (SRT) ve pyrazinamide (PRZ) antibiyotikleri için literatürden elde edilen veriler kullanılarak çizilen nümerik simülasyonlar vasıtasıyla desteklendiler.

Anahtar Kelimeler: kesirsel mertebeden diferansiyel denklem sistemi, matematiksel model, kararlılık analizi, denge noktaları, çoklu antibiyotik tedavisi

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1. INTRODUCTION

Infections have been the major cause of disease through the human history [1]. There are especially bacterial infections among these. The most common procedure to combat bacterial infection is through antibiotic therapy. Howeover, the most important problem derived from this therapy is the development of the bacteria resistance ability against the used antibiotic [2]. The expression of resistance to antimicrobial agents is both the logical and inevitable consequence of using these agents to treat human infections [3,4].

Bacterial resistance to antibiotics is described as the ability of bacteria to resist the effects of antibiotics designed to eradicate or control them [5]. The introduction of every new class of antibiotic has been followed by the emergence of new strains of resistant bacteria to this class, usually showing up in the clinic a few years after the submission of the antibiotic [6-8]. Thereby, the development of new therapeutic strategies for bacterial infections is of utmost importance [9]. The most common method used to combat these infections still is through antibiotic treatment.

It has expressed that an antibiotic has bacteriostatic action when it's function is to stop the bacteria growth and bactericidal action when it's function is to eradicate the bacteria. But, this difference is not clear, as it depends on the drug concentration and the growth stage and the species of bacteria [10]. In this sense, multiple antibiotics is more convenient than single antibiotic.

Recently, mathematical models describing the dynamics of human infectious diseases have played an important role in the disease control in epidemiology [11]. Mathematical models are important tools used both in analyzing the spread of infectious diseases of individuals in a population [12,13], and in estimating the timing and enlargement of infection and possible reinfection processes in an individual [14,15]. While the former is generally used for planning, prevention and control strategies, the latter can be influence in the therapy and intervention programs for treating the individuals exposed to the specific pathogen. Understanding the early dynamics of acute infections and foreseeing the time of occurrence and magnitude of the maximum load of the bacteria can be critical in choosing effective intervention schemes [16].

Fractional-order differential equation have been the focus of many studies due to their frequent appearance in various applications in fluid mechanics, economic, viscoelasticity, biology, physics and engineering. Lately, a large amount of literature has been developed concerning the application of fractional differential equations in nonlinear dynamics [17].

2. ASYMTOTIC STABILITY OF THEIR EQUILIBRIUM POINTS IN THE FRACTIONAL-ORDER DIFFERENTIAL EQUATIONS SYSTEMS

Definition 2.1 The fractional integral of order $\beta \in R^+$ of the function $f(t), t > 0$ is described by

$$I^\beta f(t) = \int_0^t \frac{(t-s)^{\beta-1}}{\Gamma(\beta)} f(s) ds \qquad (1)$$

and the fractional derivative of order $\alpha \in (n-1, n]$ of $f(t), \ t > 0$ is defined by

$$D^\alpha f(t) = I^{n-\alpha} D^n f(t), \qquad D = \frac{d}{dt}. \qquad (2)$$

The following properties are some of the main properties of the fractional derivatives and integrals [15,18-21].

Let $\beta, \gamma \in R^+$ and $\alpha \in (0,1]$. Then

  i. $I_a^\beta: L^1 \to L^1$, and if $f(x) \in L^1$, then $I_a^\gamma I_a^\beta f(x) = I_a^{\gamma+\beta} f(x)$.

  ii. $\lim_{\beta \to n} I_a^\beta f(x) = I_a^n f(x)$ uniformly on $[a, b]$, $n = 1,2,3,\dots$ where $I_a^1 f(x) = \int_a^x f(s) ds$.

  iii. $\lim_{\beta \to 0} I_a^\beta f(x) = f(x)$ weakly.

  iv. If $f(x)$ is absolutely continuous on $[a, b]$, then $\lim_{\alpha \to 1} D^\alpha f(x) = \frac{df(x)}{dx}$.

  v.   If $f(x) = k \neq 0$, k is a constant, then $D^\alpha k = 0$.

We have the following lemma which can be easily proved [19].

Lemma 2.1 Let $\beta \in (0,1)$ if $f \in C[0,T]$, then $I^\beta f(t)|_{t=0} = 0$.
Let $\alpha \in (0,1]$ and consider the system [20,22-25].

$$\begin{aligned} D^\alpha y_1(t) &= f_1(y_1, y_2) \\ D^\alpha y_2(t) &= f_2(y_1, y_2) \end{aligned} \qquad (3)$$

with the initial values

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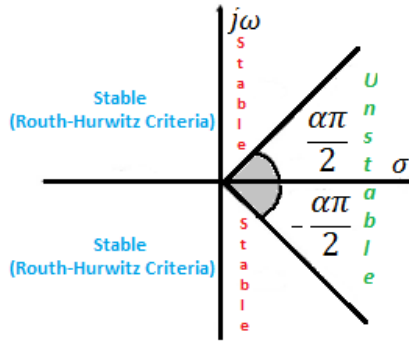$$y_1(0) = y_{o1} \text{ and } y_2(0) = y_{o2}. \tag{4}$$

Figure 1. Stability region of fractional-order system in (3)

To evaluate the equilibrium points, we have assumed $D^\alpha y_i(t) = 0 \Rightarrow f_i(y_1^{eq}, y_2^{eq}) = 0$ for $i = 1,2$. Therefore, we can get the equilibrium point (y_1^{eq}, y_2^{eq}) of system (3).

To evaluate the asymptotic stability of equilibrium points, the Jacobian matrix, $J = \begin{bmatrix} \frac{\partial f_1}{\partial y_1} & \frac{\partial f_1}{\partial y_2} \\ \frac{\partial f_2}{\partial y_1} & \frac{\partial f_2}{\partial y_2} \end{bmatrix}$, is used. If both the eigenvalues, λ_1 and λ_2, obtained from the equation $J_{(y_1,y_2)=(y_1^{eq},y_2^{eq})} = 0$ satisfies the conditions

$$\left(|arg(\lambda_1)| > \frac{\alpha\pi}{2}, \quad |arg(\lambda_2)| > \frac{\alpha\pi}{2}\right), \tag{5}$$

then, the equilibrium point (y_1^{eq}, y_2^{eq}) is locally asymptotically stable point for system (3). The stability region of the fractional-order system with α-order is observed in Figure 1 (in which σ, ω refer to the real and imaginary parts of the eigenvalues, respectively, and $j = \sqrt{-1}$). From this Figure, it is clearly seen that the stability region of the fractional-order case is greater than the stability region of the integer-order case.

Characteristic equation of $J_{(y_1,y_2)=(y_1^{eq},y_2^{eq})} = 0$ has the following generalized polynomial:

$$p(\lambda) = \lambda^2 + a_1\lambda + a_2 = 0. \tag{6}$$

When both the conditions (5) and the polynomial (6) are considered together, the conditions for locally asymptotically stability of the equilibrium point (y_1^{eq}, y_2^{eq}) are either Routh–Hurwitz conditions $(a_1, a_2 > 0)$ [2,26]

or:

$$a_1 < 0, 4a_2 > (a_1)^2,$$
$$\left| tan^{-1}\left(\frac{\sqrt{4a_2 - (a_1)^2}}{a_1}\right) \right| > \frac{\alpha\pi}{2}. \tag{7}$$

In this study, a continuous time model considering the main mechanisms of bacterial resistance occuring due to effect of antibiotic has been presented. In this context, the aim is to obtain the certain conditions dependent on the development of susceptible and resistant bacteria population under the pressure of antibiotic.

3. THE FRACTIONAL - ORDER MATHEMATICAL MODEL OF LOCAL BACTERIAL INFECTION

The proposed model in this study is fractional-order form of model suggested in [1]. In this respect, the population sizes of sensitive and resistant bacteria to multiple antibiotics at time t is denoted by $S(t)$ and $R(t)$, respectively. In addition that, the concentration of the i-th antibiotic, $i = 1,2,\dots,n$ is showed by $C_i(t)$. Therefore, it is obtained the following system of $(n + 2)$ fractional-order differential equation:

$$D^\alpha S(t) = S\left(\beta_s\left(1 - \frac{S+R}{K}\right) - [\sum_{i=1}^{n}(\overline{q_i} + \overline{\alpha_i}) C_i] - \mu_s\right)$$
$$D^\alpha R(t) = \beta_r R\left(1 - \frac{S+R}{K}\right) + S[\sum_{i=1}^{n} \overline{q_i} C_i] - \mu_r R \tag{8}$$
$$D^\alpha C_i(t) = \Lambda_i - \mu_i C_i, \qquad i = 1,2,\dots,n$$

where $\alpha \in (0,1]$. The parameters used in the model (8) are as follows: it is presumed that bacteria follow a logistic growth with carrying capacity K. The parameter β_S and β_r are the birth 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. Thus, it is

$$\beta_S > \beta_R \tag{9}$$

The sensitive and resistant bacteria to multiple antibiotics have per capita natural death rates μ_{B_1} and μ_{B_2}, respectively. During the administration of the i-th antibiotic, a number of resistant bacteria to it can be showed up due to mutations of exposed sensitive bacteria to such antibiotic, it is modeled this situation by the term $\overline{q_i} C_i S$ where $\overline{q_i}$ is the mutation rate of sensitive bacteria due to exposure to i-th antibiotic. Sensitive bacteria also die due to the action of the antibiotics, and it is assumed that this situation in model is by the term $\overline{\alpha_i} C_i S$, where $\overline{\alpha_i}$ is the death rate of sensitive bacteria due to exposure to i-th antibiotic. Finally, the i-th

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antibiotic concentration is supplied at a constant rate Λ_i, and is taken up at a constant per capita rate μ_i.

These interacts between bacteria and antibiotic have depicted a generalised model of a local bacterial infection, such as wound infection or tuberculosis.

3.1. Matrix form of model in (8)

Here, the fractional-order model (8) can be rewritten in the following matrix form

$$D^\alpha X(t) = AX(t) + S(t)B_1 X(t) + R(t)B_2 X(t)$$
$$+ C_1(t)B_3 X(t) + \ldots + C_n(t)B_{n+2}X(t) + H \quad (10)$$
$$X(0) = X_0$$

where $0 < \alpha \leq 1, t \in (0,1]$, and

$$X(t) = \begin{pmatrix} S(t) \\ R(t) \\ C_1(t) \\ C_2(t) \\ \ldots \\ C_n(t) \end{pmatrix} = \begin{pmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \\ x_4(t) \\ \ldots \\ x_{n+2}(t) \end{pmatrix}, X_0 = \begin{pmatrix} S(0) \\ R(0) \\ C_1(0) \\ C_2(0) \\ \ldots \\ C_n(0) \end{pmatrix}, A =$$

$$\begin{pmatrix} \beta_s - \mu_s & 0 & 0 & 0 & \ldots & 0 \\ 0 & \beta_r - \mu_r & 0 & \ldots & 0 & 0 \\ 0 & 0 & -\mu_1 & 0 & \ldots & 0 \\ 0 & 0 & 0 & -\mu_2 & 0 & 0 \\ \ldots & \ldots & 0 & 0 & \ldots & \ldots \\ 0 & 0 & 0 & 0 & 0 & -\mu_n \end{pmatrix}, H =$$

$$\begin{pmatrix} 0 \\ 0 \\ \Lambda_1 \\ \Lambda_2 \\ \ldots \\ \Lambda_n \end{pmatrix}, B_1 = \begin{pmatrix} -\frac{\beta_s}{K} & -\frac{\beta_s}{K} & 0 & 0 & \ldots & 0 \\ 0 & 0 & 0 & 0 & \ldots & 0 \\ 0 & 0 & 0 & 0 & \ldots & 0 \\ 0 & 0 & 0 & 0 & \ldots & 0 \\ \ldots & \ldots & \ldots & \ldots & \ldots & \ldots \\ 0 & 0 & 0 & 0 & \ldots & 0 \end{pmatrix}, B_2 =$$

$$\begin{pmatrix} 0 & 0 & 0 & 0 & \ldots & 0 \\ -\frac{\beta_r}{K} & -\frac{\beta_r}{K} & 0 & 0 & \ldots & 0 \\ 0 & 0 & 0 & 0 & \ldots & 0 \\ 0 & 0 & 0 & 0 & \ldots & 0 \\ \ldots & \ldots & \ldots & \ldots & \ldots & \ldots \\ 0 & 0 & 0 & 0 & \ldots & 0 \end{pmatrix}, B_3 =$$

$$\begin{pmatrix} -(\overline{q_1} + \overline{\alpha_1}) & 0 & 0 & 0 & \ldots & 0 \\ \overline{q_1} & 0 & 0 & 0 & \ldots & 0 \\ 0 & 0 & 0 & 0 & \ldots & 0 \\ 0 & 0 & 0 & 0 & \ldots & 0 \\ \ldots & \ldots & \ldots & \ldots & \ldots & \ldots \\ 0 & 0 & 0 & 0 & \ldots & 0 \end{pmatrix}, \ldots, B_{n+2} =$$

$$\begin{pmatrix} -(\overline{q_n} + \overline{\alpha_n}) & 0 & 0 & 0 & \ldots & 0 \\ \overline{q_n} & 0 & 0 & 0 & \ldots & 0 \\ 0 & 0 & 0 & 0 & \ldots & 0 \\ 0 & 0 & 0 & 0 & \ldots & 0 \\ \ldots & \ldots & \ldots & \ldots & \ldots & \ldots \\ 0 & 0 & 0 & 0 & \ldots & 0 \end{pmatrix}$$

$$(11)$$

Definition 3.1 For $X(t) = \left(S(t)\ R(t)\ C_1(t) \ldots C_n(t) \right)^{\mathrm{T}}$, let $C^*[0,T]$ be the set of continuous column vectors $X(t)$ on the interval $[0,T]$. The norm of $X(t) \in C^*[0,T]$ is given by $\|X(t)\| = \sum_{i=1}^n sup_t |x_i(t)|$ [27].

Proposition 3.1 System (8) has a unique solution if $X(t) \in C^*[0,T]$.

Proof Let
$F(X(t)) = AX(t) + S(t)B_1 X(t) + R(t)B_2 X(t) + C_1(t)B_3 X(t) + \ldots + C_n(t)B_{n+2}X(t) + H$, then $X(t) \in C^*[0,T]$ implies $F(X(t)) \in C^*[0,T]$. Furthermore, considering $X(t), Y(t) \in C^*[0,T]$ and $X(t) \neq Y(t)$; it has holded the following inequality:

$$\|F(X(t)) - F(Y(t))\|$$

$$= ||(AX(t) + x_1(t)B_1 X(t) + x_2(t)B_2 X(t) + \cdots$$
$$+ x_{n+2}(t)B_{n+2}X(t) + H) - (AY(t) + y_1(t)B_1 Y(t)$$
$$+ y_2(t)B_2 Y(t) + \ldots + y_{n+2}(t)B_{n+2}Y(t) + H)||$$

$$= ||AX(t) + x_1(t)B_1 X(t) + x_2(t)B_2 X(t) + \cdots$$
$$+ x_{n+2}(t)B_{n+2}X(t) - AY(t) - y_1(t)B_1 Y(t)$$
$$- y_2(t)B_2 Y(t) - \ldots - y_{n+2}(t)B_{n+2}Y(t)||$$

$$= ||A(X(t) - Y(t)) + x_1(t)B_1 X(t) + x_2(t)B_2 X(t)$$
$$+ \cdots + x_{n+2}(t)B_{n+2}X(t) - y_1(t)B_1 Y(t)$$
$$- y_2(t)B_2 Y(t) - \ldots - y_{n+2}(t)B_{n+2}Y(t)$$
$$- (x_1(t)B_1 Y(t) - x_1(t)B_1 Y(t))$$
$$- (x_2(t)B_2 Y(t) - x_2(t)B_2 Y(t)) - \ldots - (x_n(t)B_{n+2}Y(t)$$
$$- x_{n+2}(t)B_{n+2}Y(t))||$$

$$= ||A(X(t) - Y(t)) + x_1(t)B_1(X(t) - Y(t))$$
$$+ x_2(t)B_2(X(t) - Y(t)) + \ldots + x_{n+2}(t)B_{n+2}(X(t)$$
$$- Y(t)) + (x_1(t) - y_1(t))B_1 Y(t)$$
$$+ (x_2(t) - y_2(t))B_2 Y(t) + \ldots + (x_{n+2}(t)$$
$$- y_{n+2}(t))B_{n+2}Y(t)||$$

$$= \|A(X(t) - Y(t))\| + \|x_1(t)B_1(X(t) - Y(t))\|$$
$$+ \|x_2(t)B_2(X(t) - Y(t))\| + \ldots + \|x_{n+2}(t)B_{n+2}(X(t)$$
$$- Y(t))\| + \|(x_1(t) - y_1(t))B_1 Y(t)\|$$
$$+ \|(x_2(t) - y_2(t))B_2 Y(t)\| + \ldots + \|(x_{n+2}(t)$$
$$- y_{n+2}(t))B_{n+2}Y(t)\|$$

$$\leq \|A\|\|X(t) - Y(t)\| + \|B_1\|\|x_1(t)\|\|X(t) - Y(t)\|$$
$$+ \|B_2\|\|x_2(t)\|\|X(t)$$
$$- Y(t)\| + \ldots + \|B_{n+2}\|\|x_{n+2}(t)\|\|X(t) - Y(t)\|$$
$$+ \|(x_1(t) - y_1(t))\|\|B_1\|\|Y(t)\|$$
$$+ \|(x_2(t) - y_2(t))\|\|B_2\|\|Y(t)\| + \ldots + \|(x_{n+2}(t)$$
$$- y_{n+2}(t))\|\|B_{n+2}\|\|Y(t)\|$$

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$\leq (\|A\| + \|B_1\|\|x_1(t)\| + \|B_1\|\|Y(t)\| + \|B_2\|\|x_2(t)\|$
$+ \|B_2\|\|Y(t)\|+\ldots+\|B_{n+2}\|\|x_{n+2}(t)\|$
$+ \|B_{n+2}\|\|Y(t)\|)\|(X(t) - Y(t))\|$

$\leq (\|A\| + \|B_1\|(\|x_1(t)\| + \|Y(t)\|)$
$+ \|B_2\|(\|x_2(t)\| + \|Y(t)\|)+\ldots+\|B_{n+2}\|(\|x_{n+2}(t)\|$
$+ \|Y(t)\|))\|(X(t) - Y(t))\|$

and so, we have

$\|F(X(t)) - F(Y(t))\| \leq L\|(X(t) - Y(t))\|$

where $L = (\|A\| + \|B_1\| + \|B_2\|+\ldots+\|B_{n+2}\|)(M_1 + M_2) > 0$, and M_1 and M_2 are positive and satisfy $\|X(t)\| \leq M_1$, $\|Y(t)\| \leq M_2$ as a result of $X(t), Y(t) \in C^*[0,T]$. In this sense, the system (8) has a unique solution.

4. QUALITATIVE ANALYSIS OF MODEL IN (8)

The existence and stability of equilibria of the system (8) are characterized in here.

4.1. Equilibrium Points

That the general term of equilibria of the system (8) show as $(S^{eq}, R^{eq}, C_1^{eq}, C_2^{eq}, \ldots, C_n^{eq})$ have accepted.

Proposition 4.1 Let

$$S_0 = \frac{\beta_s - \left[\sum_{i=1}^{n}(\overline{q_i} + \overline{\alpha_i})\frac{\Lambda_i}{\mu_i}\right] - \mu_s}{\beta_s}, R_r = \frac{\beta_r - \mu_r}{\beta_r} \quad (12)$$

The system (8) always has the equilibrium points $E_0\left(0,0,\frac{\Lambda_1}{\mu_1},\frac{\Lambda_2}{\mu_2},\ldots,\frac{\Lambda_n}{\mu_n}\right)$ (namely, the infection-free equilibrium point. If $R_r > 0$, then $E_1\left(0, KR_r,\frac{\Lambda_1}{\mu_1},\frac{\Lambda_2}{\mu_2},\ldots,\frac{\Lambda_n}{\mu_n}\right)$ exists. Moreover, if $S_0 > 0$ and $S_0 > R_r$, then

$$E_2\left(\begin{array}{c} KS_0\left(\frac{\beta_r(S_0-R_r)}{\left[\sum_{i=1}^{n}\overline{q_i}\frac{\Lambda_i}{\mu_i}\right]+\beta_r(S_0-R_r)}\right), KS_0\frac{\left[\sum_{i=1}^{n}\overline{q_i}\frac{\Lambda_i}{\mu_i}\right]}{\left[\sum_{i=1}^{n}\overline{q_i}\frac{\Lambda_i}{\mu_i}\right]+\beta_r(S_0-R_r)} \\ \frac{\Lambda_1}{\mu_1},\frac{\Lambda_2}{\mu_2},\ldots,\frac{\Lambda_n}{\mu_n} \end{array}\right)$$

exists as another equilibrium points.

Proof For the fractional-order model in (8) to evaluate the equilibrium points, let $D^\alpha S = 0$, $D^\alpha R = 0$ and $D^\alpha C_i = 0$ for $i = 1,2,\ldots,n$. Then, we have following system

$$S\left(\beta_s\left(1 - \frac{S+R}{K}\right) - \left[\sum_{i=1}^{n}(\overline{q_i} + \overline{\alpha_i})C_i\right] - \mu_s\right) = 0$$

$$\beta_r R\left(1 - \frac{S+R}{K}\right) + S\left[\sum_{i=1}^{n}\overline{q_i}C_i\right] - \mu_r R = 0 \quad (13)$$

$$\Lambda_i - \mu_i C_i = 0, \qquad i = 1,2,\ldots,n$$

For all the equilibrium points, it is clear that $C_i^{eq} = \frac{\Lambda_i}{\mu_i}$ for $i = 1,2,\ldots,n$. Therefore, (13) transforms to

$$S\left(\beta_s\left(1 - \frac{S+R}{K}\right) - \left[\sum_{i=1}^{n}(\overline{q_i} + \overline{\alpha_i})\frac{\Lambda_i}{\mu_i}\right] - \mu_s\right) = 0$$

$$\beta_r R\left(1 - \frac{S+R}{K}\right) + S\left[\sum_{i=1}^{n}\overline{q_i}\frac{\Lambda_i}{\mu_i}\right] - \mu_r R = 0 \quad (14)$$

In (14), it is $S^{eq} = 0$ or $\beta_s\left(1 - \frac{S^{eq}+R^{eq}}{K}\right) - \left[\sum_{i=1}^{n}(\overline{q_i} + \overline{\alpha_i})\frac{\Lambda_i}{\mu_i}\right] - \mu_s = 0$.

Let $S^{eq} = 0$. Then $R^{eq} = 0$ or $R^{eq} = K\frac{\beta_r - \mu_r}{\beta_r}$. Thereby, there are disease-free equilibrium point $E_0\left(0,0,\frac{\Lambda_1}{\mu_1},\frac{\Lambda_2}{\mu_2},\ldots,\frac{\Lambda_n}{\mu_n}\right)$ and endemic equilibrium point $E_1\left(0, K\frac{\beta_r - \mu_r}{\beta_r},\frac{\Lambda_1}{\mu_1},\frac{\Lambda_2}{\mu_2},\ldots,\frac{\Lambda_n}{\mu_n}\right)$, that is, $E_1\left(0, KR_r,\frac{\Lambda_1}{\mu_1},\frac{\Lambda_2}{\mu_2},\ldots,\frac{\Lambda_n}{\mu_n}\right)$ with respect to (12).

In addition that, let $\beta_s\left(1 - \frac{S^{eq}+R^{eq}}{K}\right) - \left[\sum_{i=1}^{n}(\overline{q_i} + \overline{\alpha_i})\frac{\Lambda_i}{\mu_i}\right] - \mu_s = 0$, that is, $S^{eq} + R^{eq} = K\frac{\beta_s - \left[\sum_{i=1}^{n}(\overline{q_i}+\overline{\alpha_i})\frac{\Lambda_i}{\mu_i}\right] - \mu_s}{\beta_s}$. In this case, The components of equilibrium point obtained from (14) has founded as

$$S^{eq} = K\frac{\beta_s - \left[\sum_{i=1}^{n}(\overline{q_i}+\overline{\alpha_i})\frac{\Lambda_i}{\mu_i}\right] - \mu_s}{\beta_s}\left(\frac{\beta_r\left(\frac{\beta_s - \left[\sum_{i=1}^{n}(\overline{q_i}+\overline{\alpha_i})\frac{\Lambda_i}{\mu_i}\right] - \mu_s}{\beta_s} - \frac{\beta_r-\mu_r}{\beta_r}\right)}{\left[\sum_{i=1}^{n}\overline{q_i}\frac{\Lambda_i}{\mu_i}\right]+\frac{\beta_r-\mu_r}{\beta_r}\left(\frac{\beta_s - \left[\sum_{i=1}^{n}(\overline{q_i}+\overline{\alpha_i})\frac{\Lambda_i}{\mu_i}\right] - \mu_s}{\beta_s} - \frac{\beta_r-\mu_r}{\beta_r}\right)}\right)$$

and

$$R^{eq} = K\frac{\beta_s - \left[\sum_{i=1}^{n}(\overline{q_i}+\overline{\alpha_i})\frac{\Lambda_i}{\mu_i}\right] - \mu_s}{\beta_s}\frac{\left[\sum_{i=1}^{n}\overline{q_i}\frac{\Lambda_i}{\mu_i}\right]}{\left[\sum_{i=1}^{n}\overline{q_i}\frac{\Lambda_i}{\mu_i}\right]+\beta_r\left(\frac{\beta_s - \left[\sum_{i=1}^{n}(\overline{q_i}+\overline{\alpha_i})\frac{\Lambda_i}{\mu_i}\right] - \mu_s}{\beta_s} - \frac{\beta_r-\mu_r}{\beta_r}\right)}.$$

In this sense, we have positive equilibrium point that is,

$$E_2\left(KS_0\left(\frac{\beta_r(S_0-R_r)}{\left[\sum_{i=1}^n \overline{q_i}\frac{\Lambda_i}{\mu_i}\right]+\beta_r(S_0-R_r)}\right), KS_0\frac{\left[\sum_{i=1}^n \overline{q_i}\frac{\Lambda_i}{\mu_i}\right]}{\left[\sum_{i=1}^n \overline{q_i}\frac{\Lambda_i}{\mu_i}\right]+\beta_r(S_0-R_r)}, \frac{\Lambda_1}{\mu_1}, \frac{\Lambda_2}{\mu_2}, \dots, \frac{\Lambda_n}{\mu_n}\right)$$

by (12).

In Table 1, biological existence conditions of equilibrium points of system (8) are showed.

Table 1. Biological existence conditions of the equilibria of system (8)

Equilibrium Points	Biological Existence Conditions
$E_0\left(0,0,\frac{\Lambda_1}{\mu_1},\dots,\frac{\Lambda_n}{\mu_n}\right).$	Always exists
$E_1\left(0,KR_r,\frac{\Lambda_1}{\mu_1},\dots,\frac{\Lambda_n}{\mu_n}\right).$	$R_r>0$
$E_2\left(KS_0\frac{\beta_r(S_0-R_r)}{\sum_{i=1}^n \overline{q_i}\frac{\Lambda_i}{\mu_i}+\beta_r(S_0-R_r)}, KS_0\frac{\sum_{i=1}^n \overline{q_i}\frac{\Lambda_i}{\mu_i}}{\sum_{i=1}^n \overline{q_i}\frac{\Lambda_i}{\mu_i}+\beta_r(S_0-R_r)}, \frac{\Lambda_1}{\mu_1},\dots,\frac{\Lambda_n}{\mu_n}\right)$	$S_0>0, S_0>R_0$

4.2. Stability analysis of equilibrium points of model in (8)

Proposition 4.2 The equilibrium points of system (8) satisfy

  (i)   If $S_0<0$ and $R_r<0$, then E_0 is locally asymtotically stable.

  (ii)   Let $R_r>0$. If $S_0<R_r$, then E_1 is locally asymtotically stable.

  (iii)   Let $S_0>0$ and $S_0>R_r$. Then E_2 is locally asymtotically stable.

Proof For the stability analysis, the functions of the right side of the system (8) are assigned as:

$$f(S,R,C_1,\dots,C_n)=S\left(\beta_s\left(1-\frac{S+R}{K}\right)-[\sum_{i=1}^n(\overline{q_i}+\overline{\alpha_i})C_i]-\mu_s\right)$$
$$g(S,R,C_1,\dots,C_n)=\beta_r R\left(1-\frac{S+R}{K}\right)+S[\sum_{i=1}^n \overline{q_i}C_i]-\mu_r R \quad (15)$$
$$h_i(S,R,C_1,\dots,C_n)=\Lambda_i-\mu_i C_i, \qquad i=1,2,\dots,n$$

That jacobian matrix obtained from (15) is

$$J=\begin{pmatrix} f_S & f_R & f_{C_1} & \cdots & f_{C_n} \\ g_S & g_R & g_{C_1} & \cdots & g_{C_n} \\ (h_1)_S & (h_1)_R & (h_1)_{C_1} & \cdots & (h_1)_{C_n} \\ \cdot & \cdot & \cdot & & \cdot \\ (h_n)_S & (h_n)_R & (h_n)_{C_1} & \cdots & (h_n)_{C_n} \end{pmatrix},$$

$$J=\begin{pmatrix} \beta_s-2\frac{S\beta_s}{K}-\frac{R\beta_s}{K} & -\frac{S\beta_s}{K} & -S\left(\overline{\frac{q_1}{+\alpha_1}}\right) & \cdots & -S\left(\overline{\frac{q_n}{+\alpha_n}}\right) \\ -\sum_{i=1}^n(\overline{q_i}+\overline{\alpha_i})C_i-\mu_s & & & & \\ -\frac{\beta_r R}{K}+\sum_{i=1}^n \overline{q_i}C_i & \beta_r-\frac{\beta_r S}{K}-2\frac{\beta_r R}{K}-\mu_r & +S\overline{q_1} & \cdots & +S\overline{q_n} \\ 0 & 0 & -\mu_1 & \cdots & 0 \\ \dots & \dots & \dots & \ddots & \dots \\ 0 & 0 & 0 & \cdots & -\mu_n \end{pmatrix} \quad (16)$$

Since $C_i^{eq}=\frac{\Lambda_i}{\mu_i}$ for $i=1,2,\dots,n$ in all equilibria of the system (8), the jacobian matrix showed in (16) can be rewritten as follows:

$$J=\begin{pmatrix} \beta_s\left(S_0-2\frac{S}{K}-\frac{R}{K}\right) & -\frac{S\beta_s}{K} & -S\left(\overline{\frac{q_1}{+\alpha_1}}\right) & \cdots & -S\left(\overline{\frac{q_n}{+\alpha_n}}\right) \\ -\frac{\beta_r R}{K}+\sum_{i=1}^n \overline{q_i}\frac{\Lambda_i}{\mu_i} & \beta_r\left(R_r-\frac{S}{K}-2\frac{R}{K}\right) & +S\overline{q_1} & \cdots & +S\overline{q_n} \\ 0 & 0 & -\mu_1 & \cdots & 0 \\ \dots & \dots & \dots & \ddots & \dots \\ 0 & 0 & 0 & \cdots & -\mu_n \end{pmatrix} \quad (17)$$

For ease of examination, the τ-th eigenvalue of equilibrium point E_k has shown as $\lambda_{k,\tau}$ for $k=0,1,2$ and $\tau=1,2,\dots,n+2, \quad n\in N$.

  (i)   For E_0, the jacobian matrix evaluated in (17) is

$$J(E_0)=\begin{pmatrix} \beta_s S_0 & 0 & 0 & \cdots & 0 \\ \sum_{i=1}^n \overline{q_i}\frac{\Lambda_i}{\mu_i} & \beta_r R_r & 0 & \cdots & 0 \\ 0 & 0 & -\mu_1 & \cdots & 0 \\ \dots & \dots & \dots & \ddots & \dots \\ 0 & 0 & 0 & \cdots & -\mu_n \end{pmatrix} \quad (18)$$

The eigenvalues obtained from (18) are that $\lambda_{0,1}=\beta_s S_0$, $\lambda_{0,2}=\beta_r R_r$ and $\lambda_{0,i+2}=-\mu_i<0$ for $i=1,2,\dots,n$. Because $\alpha\in(0,1]$ and $\lambda_{0,1},\lambda_{0,2}\in R$, it is sufficient to examine the Routh-Hurwitz conditions for $\lambda_{0,1},\lambda_{0,2}$. In this respect, if $S_0<0$ and $R_r<0$, then E_0 is locally asymtotically stable.

  (ii)   Let

$$R_r>0. \qquad (19)$$

Jacobian matrix evaluated at the equilibrium point E_1 is

$$J(E_1) = - \begin{pmatrix} \beta_s(R_r - S_0) & 0 & 0 & . & . & . & 0 \\ \begin{pmatrix} \beta_r R_r - \\ \sum_{i=1}^{n} \overline{q_i} \frac{\Lambda_i}{\mu_i} \end{pmatrix} & \beta_r R_r & 0 & . & . & . & 0 \\ 0 & 0 & \mu_1 & . & . & . & 0 \\ ... & & ... & ... & . & . & ... \\ 0 & 0 & 0 & . & . & . & \mu_n \end{pmatrix} \quad (20)$$

The eigenvalues obtained from (20) are that $\lambda_{1,1} = \beta_s(S_0 - R_r)$, $\lambda_{1,2} = -\beta_r R_r$ and $\lambda_{1,i+2} = -\mu_i < 0$ for $i = 1,2,\ldots,n$. From (19), it is $\lambda_{1,2} \in R^-$. it is sufficient to examine the Routh-Hurwitz conditions for $\lambda_{1,1}$ due to $\alpha \in (0,1]$ and $\lambda_{1,1} \in R$. In this sense, if $S_0 < R_r$, then the equilibrium point E_1 is locally asymtotically stable.

(iii) Lastly, let $S_0 > 0$ and $S_0 > R_r$. For E_2, the jacobian matrix evaluated in (17) is

$$J(E_2) = \begin{pmatrix} -\beta_s \frac{S^{*eq}}{K} & -\beta_s \frac{S^{*eq}}{K} & -S^{*eq}\left(\frac{\overline{q_1}}{+\alpha_1}\right) & . & . & . & -S^{*eq}\left(\frac{\overline{q_n}}{+\alpha_n}\right) \\ \begin{pmatrix} \sum_{i=1}^{n} \overline{q_i} \frac{\Lambda_i}{\mu_i} \\ -\frac{\beta_r R^{*eq}}{K} \end{pmatrix} & \beta_r \begin{pmatrix} S_0 \\ -R_r \\ +\frac{R^{*eq}}{K} \end{pmatrix} & +S^{*eq}\overline{q_1} & . & . & . & +S^{*eq}\overline{q_n} \\ 0 & 0 & -\mu_1 & . & . & . & 0 \\ ... & ... & ... & . & . & . & ... \\ 0 & 0 & 0 & . & . & . & -\mu_n \end{pmatrix} \quad (21)$$

where S^{*eq} and R^{*eq} are as illustrated in E_2. The eigenvalues of matrix (21) are $\lambda_{2,i+2} = -\mu_i < 0$ for $i = 1,2,\ldots,n$ and the others are found from following matrix;

$$J^{B(E_2)} = \begin{pmatrix} -\beta_s \frac{S^{*eq}}{K} & -\beta_s \frac{S^{*eq}}{K} \\ \left(-\beta_r \frac{R^{*eq}}{K} + \sum_{i=1}^{n} \overline{q_i} \frac{\Lambda_i}{\mu_i}\right) & \beta_r \left(R_r - \frac{R}{K} - S_0\right) \end{pmatrix} \quad (22)$$

where matrix $J^{B(E_2)}$ is the block matrix of (21). Characteristic equation of (22) is

$$\lambda^2 + a_1\lambda + a_2 = 0, \quad (23)$$

Where

$$a_1 = \left(\beta_s \frac{S^{*eq}}{K} + \beta_r \frac{R^{*eq}}{K}\right) + \beta_r(S_0 - R_r)$$

$$a_2 = \beta_s \frac{S^{*eq}}{K}\left[\sum_{i=1}^{n} \overline{q_i} \frac{\Lambda_i}{\mu_i} + \beta_r(S_0 - R_r)\right]$$

Because the biological existence condition of E_2 is $S_0 > R_r$, it is $a_1, a_2 > 0$. Therefore the eigenvalues $\lambda_{2,1}$ and $\lambda_{2,2}$ are negative or have

negative reel parts in accord with Routh-Hurwitz criteria. In this respect, the equilibrium point E_2 is locally asymtotically stable. Hence, proof is completed.

For equilibria of system (8), the conditions found for locally asymtotically stability and biological existence are summarized in the Table (2).

Table 2: The biological existence and locally asymtotically stability conditions of the equilibria of system (8)

Equilibrium Points	Biological Existence and Locally Asymtotically Stability Conditions
$E_0\left(0,0,\frac{\Lambda_1}{\mu_1},\ldots,\frac{\Lambda_n}{\mu_n}\right)$	$S_0, R_r < 0$
$E_1\left(0, KR_r, \frac{\Lambda_1}{\mu_1},\ldots,\frac{\Lambda_n}{\mu_n}\right)$	$\max\{S_0, 0\} < R_r$
$E_2\left(KS_0 \dfrac{\beta_r(S_0 - R_r)}{\sum_{i=1}^{n} \overline{q_i}\frac{\Lambda_i}{\mu_i} + \beta_r(S_0 - R_r)}, \; KS_0 \dfrac{\sum_{i=1}^{n} \overline{q_i}\frac{\Lambda_i}{\mu_i}}{\sum_{i=1}^{n} \overline{q_i}\frac{\Lambda_i}{\mu_i} + \beta_r(S_0 - R_r)}, \; \dfrac{\Lambda_1}{\mu_1},\ldots,\dfrac{\Lambda_n}{\mu_n}\right)$	$\max\{R_r, 0\} < S_0$

5. NUMERICAL STUDY FOR MODEL (8)

Among the treatment regimen recommended by WHO includes isoniazid (INH), rifampicin (RIF), streptomycin (SRT) and pyrazinamide (PZA) for some bacterial infections caused by bacteria such as mycobacterium tuberculosis [28]. In this respect, the aforementioned bacteria and antibiotics were used in our numerical study. For this infection, treatment time is about 6 months, antibiotics INH, RIF, SRT and PZA are used in the first two months and antibiotics INH and RIF are used in the remaining four months.

The parameter values used in the system (8) for numerical study are given in Table 3.

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

Parameter	Description	Value	Reference
β_s	Growth rate of sensitive Mtb	0.8 day^{-1}	[1]
β_r	Growth rate of resistant Mtb	0.4 day^{-1}	[1]
μ_s	Natural death rate of sensitive Mtb	0.312 day^{-1}	[1]
μ_r	Natural death rate of resistant Mtb	0.312-0.42 day^{-1}	[1]-Hypothesis
K	Carrying capacity of Mtb	10^9 bacteria	[29]
$\overline{q_1}$	Mutation rate of INH	10^{-6} mutxgen	[30]
$\overline{q_2}$	Mutation rate of RIF	10^{-8} mutxgen	[30]
$\overline{q_3}$	Mutation rate of SRT	0	[1]
$\overline{q_4}$	Mutation rate of PZA	0	[1]
$\overline{\alpha_1}$	Elimination rate of sensitive Mtb due INH	0.0039 day^{-1}	[31]
$\overline{\alpha_2}$	Elimination rate of sensitive Mtb due RIF	0.00375 day^{-1}	[1]
$\overline{\alpha_3}$	Elimination rate of sensitive Mtb due SRT	0.0025 day^{-1}	[29]
$\overline{\alpha_4}$	Elimination rate of sensitive Mtb due PZA	0.00001625 day^{-1}	[29]
$\overline{\Delta_1}$	Daily dose of INH	5 mg/kg/day	[30]
$\overline{\Delta_2}$	Daily dose RIF	10 mg/kg/day	[30]
$\overline{\Delta_3}$	Daily dose SRT	15-25 mg/kg/ day	[30]
$\overline{\Delta_4}$	Daily dose ZPA	20-35 mg/kg/ day	[30]
$\overline{\mu_1}$	Uptake rate of INH	0.06 day^{-1}	[32]
$\overline{\mu_2}$	Uptake rate of RIF	0.05 day^{-1}	[32]
$\overline{\mu_3}$	Uptake rate of SRT	0.04 day^{-1}	[32]
$\overline{\mu_4}$	Uptake rate of PZA	0.03 day^{-1}	[32]

The values for the first case ($\mu_r = 0.312, \overline{\Delta_3} = 15, \overline{\Delta_4} = 20$ and the remaining parameters have the values shown in the Table (3)) obtained from this Table are $S_0 = \frac{\beta_s - \left[\sum_{i=1}^{4}(\overline{q_i} + \overline{\alpha_i})\frac{\Delta_i}{\mu_i}\right] - \mu_s}{\beta_s} =$

$$\frac{0.8 - \left(\begin{array}{l}(10^{-6}+0.0039)\frac{5}{0.06} + (10^{-8}+0.00375)\frac{10}{0.05} \\ +(0+0.0025)\frac{15}{0.04} + (0+0.00001625)\frac{20}{0.03}\end{array}\right) - 0.312}{0.8} =$$

$$-1.9180$$

and $R_r = \frac{\beta_r - \mu_r}{\beta_r} = \frac{0.4 - 0.312}{0.4} = 0.22$.
We have $\max\{S_0, 0\} < R_r$ from Table 2. Therefore, locally asymtotically stable equilibrium point is

$$E = \left(S^{eq}, R^{eq}, C_1^{eq}, C_2^{eq}, \ldots, C_n^{eq}\right) =$$

$$E_1\left(0, 22.10^7, \left\{\begin{array}{l}\overbrace{\frac{250}{3}, 200, 375, \frac{2000}{3}}^{0-2\,th\,months} \\ \underbrace{\frac{250}{3}, 200, 0, 0}_{2-6\,th\,months}\end{array}\right\}\right).$$

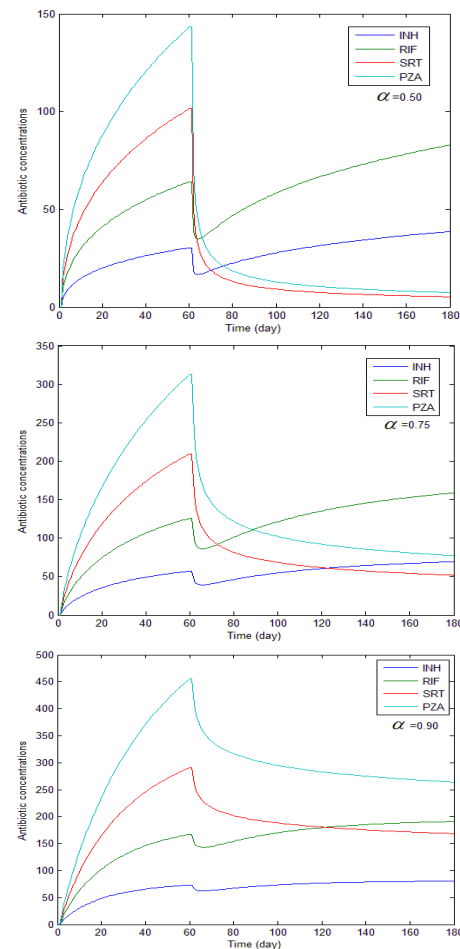This case with initial condition [10000 0 0 0 0] has monitored in Figures 2, 3 and 4.

Figure 2. In case of $\alpha = 0.50, 0.75$ and 0.90 in system (8), respectively, temporal courses of antibiotics concentrations obtained by using first column datas in the Table 3.
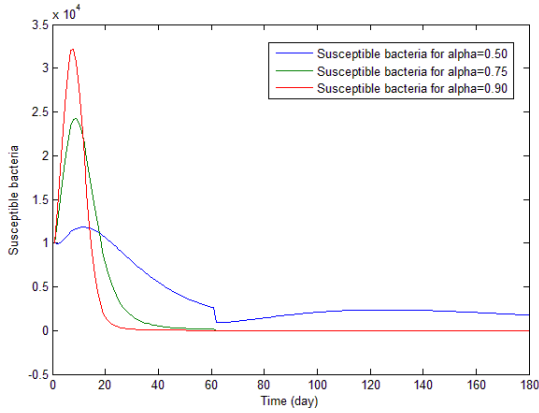
Figure 3. In case of $\alpha = 0.50, 0.75$ and 0.90 in system (8), respectively, temporal course of susceptible bacteria to multiple antibiotics obtained by using first column datas in the Table 3
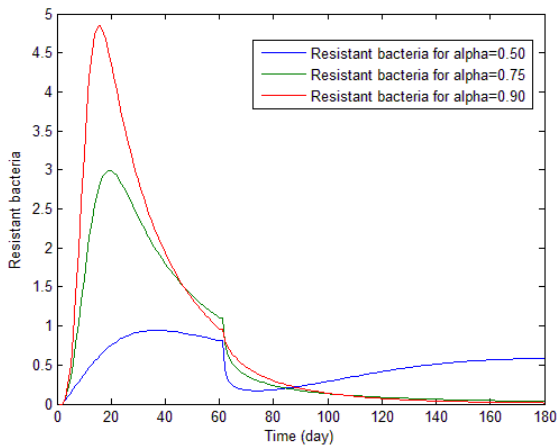

Figure 4. In case of $\alpha = 0.50, 0.75$ and 0.90 in system (8), respectively, temporal course of resistant bacteria to multiple antibiotics obtained by using first column datas in the Table 3

Let $\mu_r = 0.312, \overline{\Delta_3} = 15, \overline{\Delta_4} = 20$ and the remaining parameters have the values shown in the Table (3). The values for the second case are founded as

$$S_0 = \frac{\beta_s - \left[\sum_{i=1}^{2} (\overline{q_i} + \overline{\alpha_i}) \frac{\Lambda_i}{\mu_i} \right] - \mu_s}{\beta_s} =$$

$$\frac{0.8 - \left(\left(10^{-6} + 0.0039 \right) \frac{5}{0.06} + \left(10^{-8} + 0.00375 \right) \frac{10}{0.05} \right) - 0.312}{0.8} =$$

$$-0.73260$$

and

$$R_r = \frac{\beta_r - \mu_r}{\beta_r} = \frac{0.4 - 0.42}{0.4} = -0,05.$$

By Table 2, it is $S_0, R_r < 0$. In this respect, locally asymtotically stable equilibrium point is

$$E =$$

$$(S^{eq}, R^{eq}, C_1^{eq}, C_2^{eq}, \dots, C_n^{eq})_{E_0} \left(0, 0, \left\{ \begin{array}{c} \overbrace{\frac{250}{3}, 200, \frac{2500}{4}, \frac{3500}{3}}^{0-2\,th\,months} \\ \underbrace{\frac{250}{3}, 200, 0, 0}_{2-6\,th\,months} \end{array} \right\} \right)$$

Figures 5, 6 and 7 obtained from initial condition [10000 0 0 0 0 0] are following:
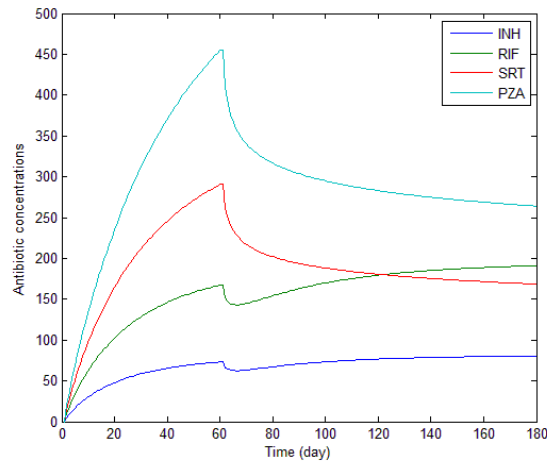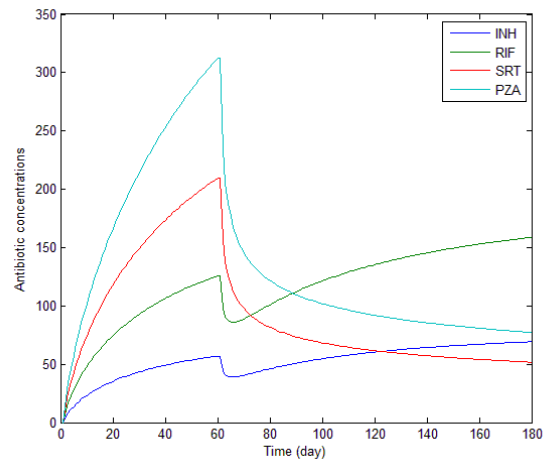

Figure 5. In case of $\alpha = 0.75$ and 0.90 in system (8), respectively, temporal course of antibiotics concentrations obtained by using second column datas in the Table 3

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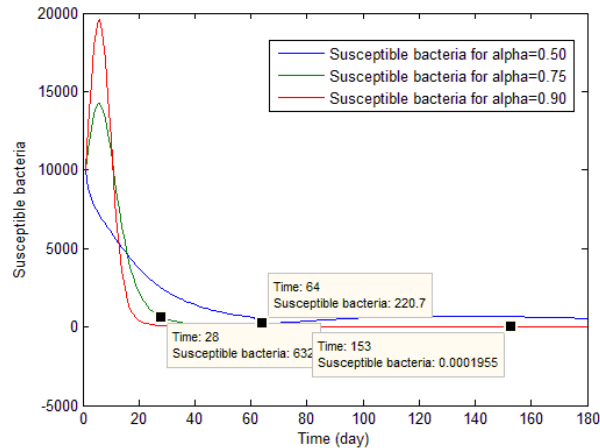

Figure 6. In case of $\alpha = 0.50, 0.75$ and 0.90 in system (8), respectively, temporal course of susceptible bacteria to multiple antibiotics obtained by using second column datas in the Table 3
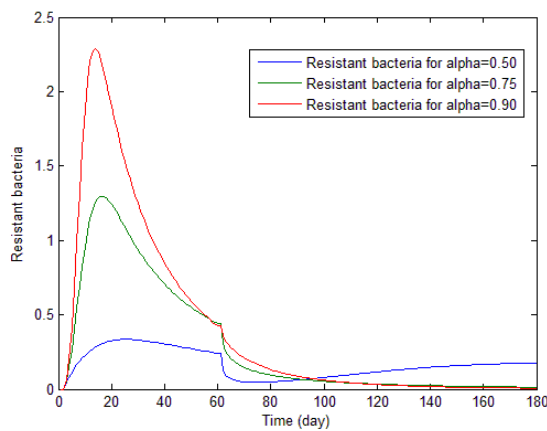

Figure 7. In case of $\alpha = 0.50, 0.75$ and 0.90 in system (8), respectively, temporal course of resistant bacteria to multiple antibiotics obtained by using second column datas in the Table 3

6. RESULTS AND DISCUSSION

As seen in the Figures, these results in the model analysis highlight the fact that some of the bacterial infections like tuberculosis believed its have limited or destroyed, may recur again. In this respect, the effects of antibiotics are much than assumed, since these are used probable inappropriately or random. Thus, the appropriate dose and duration of antibiotics play the major role in these infections. In the individuals who receive not in the appropriate dose and duration of antibiotic coctail according to the type and characteristic of the bacteria causing infection, infection is limited but persistence [33].

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