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 asymptotic 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 desteklendi.

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. However, the most important problem derived from this therapy is the development of the bacteria resistance 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. ASYMPTOTIC 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

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

(1)

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

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

(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. $I^\beta L^\gamma L^\beta f = L^\gamma f$, and if $f(x) \in L^1$, then $I^\alpha I^{\gamma+\beta} f(x) = I^{\psi}(I^\gamma f(x))$,

ii. $\lim_{\beta \to 0} I^\beta f(x) = f(x)$ 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].

$$D^\alpha y_1(t) = f_1(y_1,y_2)$$  

$$D^\alpha y_2(t) = f_2(y_1,y_2)$$

with the initial values

$$y_1(t_0) = y_{10}, \quad y_2(t_0) = y_{20}.$$  

\[ y_1(0) = y_{o1} \text{ and } y_2(0) = y_{o2}. \]  

(4)

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

(7)

In this study, a continuous time model considering the main mechanisms of bacterial resistance occurring 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, \( i = 1, 2, \ldots, n \) is showed by \( C_i(t) \). Therefore, it is obtained the following system of \((n + 2)\) fractional-order differential equation:

\[ D^\alpha S(t) = S \left( \beta_s \left( 1 - \frac{S + R}{K} \right) - \left[ \sum_{i=1}^{n} (\bar{q_i} + \alpha_i) C_i \right] - \mu_s \right) \]
\[ D^\alpha R(t) = \beta_r R \left( 1 - \frac{S + R}{K} \right) + S \left[ \sum_{i=1}^{n} \bar{q_i} C_i \right] - \mu_r R \]
\[ D^\alpha C_i(t) = \lambda_i - \mu C_i, \quad i = 1, 2, \ldots, n \]

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 \( \beta_s \) and \( \beta_r \) 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

\[ \beta_s > \beta_r \]  

(9)

The sensitive and resistant bacteria to multiple antibiotics have per capita natural death rates \( \mu_{B_s} \) and \( \mu_{B_r} \), 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 \( \bar{q_i} C_i S \) where \( \bar{q_i} \) 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...
antibiotic concentration is supplied at a constant rate $A_i$, and is taken up at a constant per capita rate $\mu_i$.

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

$$D^\alpha X(t) = AX(t) + S(t)B_1X(t) + R(t)B_2X(t) + C_1(t) + \ldots + C_n(t)B_{n+2}X(t) + H$$

(10)

$$X(0) = X_0$$

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

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

$$X_0 =
\begin{pmatrix}
\beta_s - \mu_s & 0 & 0 & \ldots & 0 \\
0 & \beta_r - \mu_r & 0 & \ldots & 0 \\
0 & 0 & -\mu_1 & 0 & \ldots \\
0 & 0 & 0 & -\mu_2 & 0 \\
\vdots & \vdots & \vdots & \ddots & \vdots \\
0 & 0 & 0 & 0 & -\mu_n \\
\end{pmatrix},
$$

$$H =
\begin{pmatrix}
\beta_s & -\frac{\beta_s}{\kappa} & 0 & \ldots & 0 \\
0 & \frac{\beta_r}{\kappa} & 0 & \ldots & 0 \\
0 & 0 & \frac{\beta_s}{\kappa} & 0 & \ldots \\
0 & 0 & 0 & \frac{\beta_r}{\kappa} & 0 \\
\vdots & \vdots & \vdots & \ddots & \vdots \\
0 & 0 & 0 & 0 & \frac{\beta_s}{\kappa} \\
\end{pmatrix},
$$

$$B_1 =
\begin{pmatrix}
A_1 & 0 & 0 & \ldots & 0 \\
0 & A_1 & 0 & \ldots & 0 \\
0 & 0 & A_1 & \ldots & 0 \\
\vdots & \vdots & \vdots & \ddots & \vdots \\
0 & 0 & 0 & 0 & A_1 \\
\end{pmatrix},
$$

$$B_2 =
\begin{pmatrix}
0 & 0 & 0 & \ldots & 0 \\
0 & 0 & 0 & \ldots & 0 \\
\vdots & \vdots & \vdots & \ddots & \vdots \\
0 & 0 & 0 & 0 & 0 \\
\end{pmatrix},
$$

$$B_3 =
\begin{pmatrix}
0 & 0 & 0 & \ldots & 0 \\
0 & 0 & 0 & \ldots & 0 \\
\vdots & \vdots & \vdots & \ddots & \vdots \\
0 & 0 & 0 & 0 & 0 \\
\end{pmatrix},
$$

$$B_{n+2} =
\begin{pmatrix}
0 & 0 & 0 & \ldots & 0 \\
0 & 0 & 0 & \ldots & 0 \\
\vdots & \vdots & \vdots & \ddots & \vdots \\
0 & 0 & 0 & 0 & 0 \\
\end{pmatrix}$$

### Definition 3.1

For $X(t) = (S(t) R(t) C_1(t) \ldots C_n(t))^T$, 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 $\|X(t)\| = \sum_{t=1}^{n} \sup_{t} |x_i(t)|$ [27].

### Proposition 3.1

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

### Proof

Let $F(X(t)) = AX(t) + S(t)B_1X(t) + R(t)B_2X(t) + C_1(t) + \ldots + C_n(t)B_{n+2}X(t) + H$, 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 held the following inequality:

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

$$= ||(AX(t) + x_1(t)B_1X(t) + x_2(t)B_2X(t) + \ldots + x_n(t)B_{n+2}X(t) + H) - (AY(t) + y_1(t)B_1Y(t) + y_2(t)B_2Y(t) + \ldots + y_n(t)B_{n+2}Y(t) + H)||$$

$$= ||AX(t) + x_1(t)B_1X(t) + x_2(t)B_2X(t) + \ldots + x_n(t)B_{n+2}X(t) - AY(t) - y_1(t)B_1Y(t) - y_2(t)B_2Y(t) - \ldots - y_n(t)B_{n+2}Y(t)||$$

$$= ||A(X(t) - Y(t)) + x_1(t)(B_1X(t) - B_1Y(t)) + x_2(t)(B_2X(t) - B_2Y(t)) + \ldots + x_n(t)(B_{n+2}X(t) - B_{n+2}Y(t))||$$

$$= ||A(X(t) - Y(t)) + x_1(t)(B_1X(t) - B_1Y(t)) + x_2(t)(B_2X(t) - B_2Y(t)) + \ldots + x_n(t)(B_{n+2}X(t) - B_{n+2}Y(t))||$$

$$\leq ||A||X(t) - Y(t)|| + ||B_1||x_1(t)||X(t) - Y(t)|| + ||B_2||x_2(t)||X(t) - Y(t)|| + \ldots + ||B_{n+2}||x_n(t)||X(t) - Y(t)|| + ||y_1(t)||B_1Y(t)|| + ||y_2(t)||B_2Y(t)|| + \ldots + ||y_n(t)||B_{n+2}Y(t)||$$

$$\leq \|A\| \|X(t) - Y(t)\| + \|B_1\| \|x_1(t)\| \|X(t) - Y(t)\| + \|B_2\| \|x_2(t)\| \|X(t) - Y(t)\| + \ldots + \|B_{n+2}\| \|x_n(t)\| \|X(t) - Y(t)\| + \|y_1(t)\| \|B_1Y(t)\| + \|y_2(t)\| \|B_2Y(t)\| + \ldots + \|y_n(t)\| \|B_{n+2}Y(t)\|$$

$$\leq ||A||X(t) - Y(t)|| + \|B_1\| \|x_1(t)\| \|X(t) - Y(t)\| + \|B_2\| \|x_2(t)\| \|X(t) - Y(t)\| + \ldots + \|B_{n+2}\| \|x_n(t)\| \|X(t) - Y(t)\| + \|y_1(t)\| \|B_1Y(t)\| + \|y_2(t)\| \|B_2Y(t)\| + \ldots + \|y_n(t)\| \|B_{n+2}Y(t)\|$$

$$\leq (\|A\| + \|B_1\| + \|B_2\| + \ldots + \|B_{n+2}\| + \|y_1(t)\| + \|y_2(t)\| + \ldots + \|y_n(t)\|) \|X(t) - Y(t)\|$$
\[ \le (\|A\| + \|B_1\| |x_1(t)| + \|B_2\| \|x_2(t)| + \|B_2\| \|Y(t)\| + \ldots + \|B_{n+2}\| |x_{n+2}(t)| + \|B_2\| \|Y(t)\| + \ldots + \|B_{n+2}\| \|x_{n+2}(t)| + \|Y(t)\|) \frac{1}{3} (X(t) - Y(t)) \]

\[ \le (\|A\| + \|B_1\| |x_1(t)| + \|Y(t)\|) + \|B_2\| \|x_2(t)\| + \|Y(t)\| + \ldots + \|B_{n+2}\| \|x_{n+2}(t)\| + \|Y(t)\|) \frac{1}{3} (X(t) - Y(t)) \]

and so, we have

\[ \|F(X(t)) - F(Y(t))\| \le L \|X(t) - Y(t)\| \]

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 \( \|X(t)\| \le M_1 \), \( \|Y(t)\| \le M_2 \) as a result of \( X(t), Y(t) \in C^1[0,T] \). 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 \((S^e, R^e, C_1^e, C_2^e, \ldots, C_n^e)\) have accepted.

Proposition 4.1 Let

\[
S_0 = \frac{\beta_s - \sum_{i=1}^{n} (q_i + \bar{a}_i) \frac{\alpha_i}{\mu_i} - \mu_s}{\beta_s}, R_r = \frac{\beta_r - \mu_r}{\beta_r} \tag{12}
\]

The system (8) always has the equilibrium points \( E_0 (0,0, \frac{\alpha_1}{\mu_1}, \frac{\alpha_2}{\mu_2}, \ldots, \frac{\alpha_n}{\mu_n}) \) (namely, the infection-free equilibrium point. If \( R_r > 0 \), then \( E_1 (0, K R_r, \frac{\alpha_1}{\mu_1}, \frac{\alpha_2}{\mu_2}, \ldots, \frac{\alpha_n}{\mu_n}) \) exists. Moreover, if \( S_0 > 0 \) and \( S_0 > R_r \), then

\[
E_2 (K S_0 (\frac{\beta_r S_0 - R_r}{\sum_{i=1}^{n} \frac{q_i}{\mu_i} + \beta_r (S_0 - R_r)}), KS_0 (\frac{\beta_r S_0 - R_r}{\sum_{i=1}^{n} \frac{q_i}{\mu_i} + \beta_r (S_0 - R_r)}, K S_0 (\frac{1}{\sum_{i=1}^{n} \frac{q_i}{\mu_i} + \beta_r (S_0 - R_r)})
\]

exists as another equilibrium points.

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

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

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

\[
\alpha_i - \mu_s C_i = 0, \quad i = 1,2, \ldots, n
\]

For all the equilibrium points, it is clear that \( C_i^e = \frac{\alpha_i}{\mu_i} \)

for \( i = 1,2, \ldots, n \). Therefore, (13) transforms to

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

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

In (14), it is \( S^e = 0 \) or \( \beta_s \left( 1 - \frac{S^e + R^e}{K} \right) - \sum_{i=1}^{n} (q_i + \bar{a}_i) \frac{\alpha_i}{\mu_i} \right) - \mu_s = 0
\]

Let \( S^e = 0 \). Then \( R^e = 0 \) or \( R^e = K \frac{\beta_r - \mu_r}{\beta_r} \). Thereby, there are disease-free equilibrium point \( E_0 \left( 0,0, \frac{\alpha_1}{\mu_1}, \frac{\alpha_2}{\mu_2}, \ldots, \frac{\alpha_n}{\mu_n} \right) \) and endemic equilibrium point \( E_1 \left( 0, K R_r, \frac{\alpha_1}{\mu_1}, \frac{\alpha_2}{\mu_2}, \ldots, \frac{\alpha_n}{\mu_n} \right) \), that is, \( E_1 \left( 0, K R_r, \frac{\alpha_1}{\mu_1}, \frac{\alpha_2}{\mu_2}, \ldots, \frac{\alpha_n}{\mu_n} \right) \) with respect to (12).

In addition that, let

\[
\beta_s \left( 1 - \frac{S^e + R^e}{K} \right) - \sum_{i=1}^{n} (q_i + \bar{a}_i) \frac{\alpha_i}{\mu_i} \right) - \mu_s = 0, \quad \text{that is,}
\]

\[
S^e + R^e = K \frac{\beta_s \left( \sum_{i=1}^{n} (q_i + \bar{a}_i) \frac{\alpha_i}{\mu_i} \right) - \mu_s}{\beta_s}
\]

In this case, The components of equilibrium point obtained from (14) has founded as

\[
S^e = \frac{\beta_s \left( \sum_{i=1}^{n} (q_i + \bar{a}_i) \frac{\alpha_i}{\mu_i} \right) - \mu_s}{\beta_s} \left( \frac{\beta_s \left( \sum_{i=1}^{n} (q_i + \bar{a}_i) \frac{\alpha_i}{\mu_i} \right) - \mu_s}{\beta_s} \right) - \mu_s
\]

\[
R^e = \frac{\beta_s \left( \sum_{i=1}^{n} (q_i + \bar{a}_i) \frac{\alpha_i}{\mu_i} \right) - \mu_s}{\beta_s} \left( \frac{\beta_s \left( \sum_{i=1}^{n} (q_i + \bar{a}_i) \frac{\alpha_i}{\mu_i} \right) - \mu_s}{\beta_s} \right) - \mu_s
\]
In this sense, we have positive equilibrium point $E_2\left(KS_0\left[\frac{\beta_i(S_0 - R_2)}{\sum_{i=1}^{n} A_i \mu_i} + \beta_{R}(S_0 - R_2)\right], \frac{\sum_{i=1}^{n} A_i \mu_i}{\beta_i(S_0 - R_2)} + \frac{\beta_{R}(S_0 - R_2)}{K}\right)$ by (12).

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

<table>
<thead>
<tr>
<th>Equilibrium Points</th>
<th>Biological Existence Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_0\left(0,0,\frac{A_1}{\mu_1},\ldots,\frac{A_n}{\mu_n}\right)$</td>
<td>Always exists</td>
</tr>
<tr>
<td>$E_1\left(0, K R, \frac{A_2}{\mu_2}, \ldots, \frac{A_n}{\mu_n}\right)$</td>
<td>$R_r &gt; 0$</td>
</tr>
<tr>
<td>$E_2\left(KS_0\left[\frac{\beta_i(S_0 - R_2)}{\sum_{i=1}^{n} A_i \mu_i} + \beta_{R}(S_0 - R_2)\right], \frac{\sum_{i=1}^{n} A_i \mu_i}{\beta_i(S_0 - R_2)} + \frac{\beta_{R}(S_0 - R_2)}{K}\right)$</td>
<td>$S_0 &gt; 0, S_0 &gt; R_0$</td>
</tr>
</tbody>
</table>

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 asymptotically stable.

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

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

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

$$f(S, R, C_1, \ldots, C_n) = S\left(\beta_i \left(1 - \frac{s_k}{K}\right) - \left[\sum_{i=1}^{n} \frac{A_i \alpha_i}{\mu_i} C_1\right] - \mu_i\right)$$

$$g(S, R, C_1, \ldots, C_n) = \beta_i R \left(1 - \frac{s_k}{K}\right) + \left[\sum_{i=1}^{n} \frac{A_i \alpha_i}{\mu_i} C_1\right] - \mu_i R$$

$$h_i(S, R, C_1, \ldots, C_n) = A_i - \mu_i$$

That jacobian matrix obtained from (15) is

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

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

$$J = \begin{pmatrix}
  -\beta_i + \left[\sum_{i=1}^{n} \frac{A_i \alpha_i}{\mu_i} C_1\right] & -\beta_i R & \ldots & -\beta_i S \\
  \beta_i S & \frac{R_i}{\mu_i} & \ldots & \beta_i S \\
  \vdots & \vdots & \ddots & \vdots \\
  \beta_i S & \frac{R_i}{\mu_i} & \ldots & \beta_i S \\
  0 & 0 & \ldots & -\mu_i \\
  0 & 0 & \ldots & -\mu_i \\
  \ldots & \ldots & \ddots & \ldots \\
  0 & 0 & \ldots & -\mu_i
\end{pmatrix}$$

(17)

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

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

$$J(E_0) = \begin{pmatrix}
  \beta_i S_0 & 0 & 0 & \ldots & 0 \\
  \sum_{i=1}^{n} \frac{A_i}{\mu_i} & \beta_i S & 0 & \ldots & 0 \\
  0 & 0 & -\mu_i & \ldots & 0 \\
  \ldots & \ldots & \ldots & \ddots & \ldots \\
  0 & 0 & 0 & \ldots & -\mu_i
\end{pmatrix}$$

(18)

The eigenvalues obtained from (18) are that $\lambda_{0, 1} = \beta_i S_0$, $\lambda_{0, 2} = \beta_i R_r$, and $\lambda_{0, i+2} = -\mu_i < 0$ for $i = 1, 2, \ldots, n$. 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 asymptotically stable.

Let $R_r > 0$.

Jacobian matrix evaluated at the equilibrium point $E_1$ is
\[ J(E_1) = \begin{pmatrix} 0 & 0 & 0 & \cdots & 0 \\ \frac{\beta_S R_r - \beta_S R_r - \beta_r R_r - \sum_{i=1}^{n} \frac{A_i}{\mu_i}}{\mu_i} & \beta_r R_r & 0 & \cdots & 0 \\ 0 & 0 & \mu_i & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \cdots & \mu_n \end{pmatrix} \] 

(20)

\[ J(E_2) = \begin{pmatrix} S^{eq} - \beta_S S^{eq} & -S^{eq} \left( \frac{R_r}{K} + \frac{1}{\sigma_1} \right) & \cdots & -S^{eq} \left( \frac{R_r}{K} + \frac{1}{\sigma_n} \right) \\ \frac{\sum_{i=1}^{n} \frac{A_i}{\mu_i} \beta_S}{K} & \frac{S_0 - R_r}{R_r - S_0} & \cdots & \frac{S_0 - R_r}{R_r - S_0} \\ \frac{\beta_r S^{eq} - \beta_r S^{eq} - \beta_r R_r - \sum_{i=1}^{n} \frac{A_i}{\mu_i}}{\mu_i} & \beta_r R_r & \cdots & \beta_r (R_r - S_0) \\ 0 & 0 & \mu_i & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \cdots & \mu_n \end{pmatrix} \] 

(21)

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

\[ J^B(E_2) = \begin{pmatrix} -\beta_S S^{eq} & -S^{eq} \left( \frac{R_r}{K} + \frac{1}{\sigma_i} \right) & \cdots & -S^{eq} \left( \frac{R_r}{K} + \frac{1}{\sigma_n} \right) \\ \frac{\beta_r S^{eq} - \beta_r S^{eq} - \beta_r R_r - \sum_{i=1}^{n} \frac{A_i}{\mu_i}}{\mu_i} & \beta_r R_r & \cdots & \beta_r (R_r - S_0) \\ 0 & 0 & \mu_i & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \cdots & \mu_n \end{pmatrix} \] 

(22)

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

\[ \lambda^2 + a_1 \lambda + a_2 = 0 \] 

(23)

Where

\[ a_1 = \left( \beta_S S^{eq} + \beta_r R^{eq} + \beta_r (S_0 - R_r) \right) \]

\[ a_2 = \beta_S S^{eq} \left( \sum_{i=1}^{n} \frac{A_i}{\mu_i} \right) + \beta_r (S_0 - R_r) \]

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 real parts in accord with Routh-Hurwitz criteria. In this respect, the equilibrium point \( E_2 \) is locally asymptotically stable. Hence, proof is completed.

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

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

<table>
<thead>
<tr>
<th>Equilibrium Points</th>
<th>Biological Existence and Locally Asymptotically Stability Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>( E_0 (0, 0, \frac{A_1}{\mu_1}, \ldots, \frac{A_n}{\mu_n}) )</td>
<td>( S_0, R_r &lt; 0 )</td>
</tr>
<tr>
<td>( E_1 (0, K R_r, \frac{A_1}{\mu_1}, \ldots, \frac{A_n}{\mu_n}) )</td>
<td>( \max(S_0, 0) &lt; R_r )</td>
</tr>
<tr>
<td>( E_2 )</td>
<td>( \max(R_r, 0) &lt; S_0 )</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_s$</td>
<td>Growth rate of sensitive Mtb</td>
<td>0.8 day$^{-1}$</td>
<td>[1]</td>
</tr>
<tr>
<td>$\beta_r$</td>
<td>Growth rate of resistant Mtb</td>
<td>0.4 day$^{-1}$</td>
<td>[1]</td>
</tr>
<tr>
<td>$\mu_s$</td>
<td>Natural death rate of sensitive Mtb</td>
<td>0.312 day$^{-1}$</td>
<td>[1]</td>
</tr>
<tr>
<td>$\mu_r$</td>
<td>Natural death rate of resistant Mtb</td>
<td>0.312-0.42 day$^{-1}$</td>
<td>[1]- Hypothesis</td>
</tr>
<tr>
<td>$K$</td>
<td>Carrying capacity of Mtb</td>
<td>$10^9$ bacteria</td>
<td>[29]</td>
</tr>
<tr>
<td>$\bar{q}_1$</td>
<td>Mutation rate of INH</td>
<td>$10^{-6}$ mutxgen</td>
<td>[30]</td>
</tr>
<tr>
<td>$\bar{q}_2$</td>
<td>Mutation rate of RIF</td>
<td>$10^{-8}$ mutxgen</td>
<td>[30]</td>
</tr>
<tr>
<td>$\bar{q}_3$</td>
<td>Mutation rate of SRT</td>
<td>0</td>
<td>[1]</td>
</tr>
<tr>
<td>$\bar{q}_4$</td>
<td>Mutation rate of PZA</td>
<td>0</td>
<td>[1]</td>
</tr>
<tr>
<td>$\bar{\alpha}_1$</td>
<td>Elimination rate of sensitive Mtb due INH</td>
<td>0.0039 day$^{-1}$</td>
<td>[31]</td>
</tr>
<tr>
<td>$\bar{\alpha}_2$</td>
<td>Elimination rate of sensitive Mtb due RIF</td>
<td>0.00375 day$^{-1}$</td>
<td>[1]</td>
</tr>
<tr>
<td>$\bar{\alpha}_3$</td>
<td>Elimination rate of sensitive Mtb due SRT</td>
<td>0.0025 day$^{-1}$</td>
<td>[29]</td>
</tr>
<tr>
<td>$\bar{\alpha}_4$</td>
<td>Elimination rate of sensitive Mtb due PZA</td>
<td>0.00001625 day$^{-1}$</td>
<td>[29]</td>
</tr>
<tr>
<td>$\bar{\Delta}_1$</td>
<td>Daily dose of INH</td>
<td>5 mg/kg/day</td>
<td>[30]</td>
</tr>
<tr>
<td>$\bar{\Delta}_2$</td>
<td>Daily dose RIF</td>
<td>10 mg/kg/day</td>
<td>[30]</td>
</tr>
<tr>
<td>$\bar{\Delta}_3$</td>
<td>Daily dose SRT</td>
<td>15-25 mg/kg/day</td>
<td>[30]</td>
</tr>
<tr>
<td>$\bar{\Delta}_4$</td>
<td>Daily dose ZPA</td>
<td>20-35 mg/kg/day</td>
<td>[30]</td>
</tr>
<tr>
<td>$\overline{\mu}_1$</td>
<td>Uptake rate of INH</td>
<td>0.06 day$^{-1}$</td>
<td>[32]</td>
</tr>
<tr>
<td>$\overline{\mu}_2$</td>
<td>Uptake rate of RIF</td>
<td>0.05 day$^{-1}$</td>
<td>[32]</td>
</tr>
<tr>
<td>$\overline{\mu}_3$</td>
<td>Uptake rate of SRT</td>
<td>0.04 day$^{-1}$</td>
<td>[32]</td>
</tr>
<tr>
<td>$\overline{\mu}_4$</td>
<td>Uptake rate of PZA</td>
<td>0.03 day$^{-1}$</td>
<td>[32]</td>
</tr>
</tbody>
</table>

The values for the first case ($\mu_s = 0.312, \bar{\Delta}_3 = 15, \bar{\Delta}_4 = 20$ and the remaining parameters have the values shown in the Table (3)) obtained from this Table are $S_0 = \frac{\beta_r \cdot \sum_{i=1}^{4} (\bar{\Delta}_i + \bar{\Delta}_i \cdot \mu_s)}{\beta_s}$.

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

$$0.8 - \left(\frac{10^{-6} + 0.0039}{0.06} + (10^{-8} + 0.00375 \cdot 10^{-3})/0.05\right) - 0.312 = -1.9180$$

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 asymptotically stable equilibrium point is

$$E = \left\{\left(S^{eq}, R^{eq}, C_1^{eq}, C_2^{eq}, \ldots, C_n^{eq}\right) \in \mathbb{R}^n : \begin{array}{c} 0.22 \cdot 10^7, \\ \frac{250}{3}, 200, 375, 2000, 0, 0, 0, 0 \end{array} \right\}.$$  

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

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


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

\[
S_0 = \beta_s \left[ \frac{C_{i_1} \gamma + C_{i_2} \gamma}{P_i} \right] \mu_s =
\]

\[0.8 \left( \frac{(10^{-6} + 0.0039)}{0.06} \cdot (10^{-8} + 0.0075) \right)^{10/0.05} = -0.73260\]

and

\[
R_r = \frac{\beta_s - \mu_r}{\beta_r} = \frac{0.4 - 0.42}{0.4} = -0.05.
\]

By Table 2, it is \( S_0, R_r < 0 \). In this respect, locally asymptotically stable equilibrium point is

\[
E = \left( S^{eq}, R^{eq}, C_1^{eq}, C_2^{eq}, \ldots, C_n^{eq} \right) = \left( \frac{250}{3}, 200, \frac{250}{3}, 200,0, 0 \right)
\]

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

Figure 6.

Figure 7.
The Fractional-Order mathematical modeling of bacterial resistance against multiple antibiotics in case of local bacterial infection

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 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 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].

REFERENCES


