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Fractional-order Mathematical Modeling of Bacterial Competition with Therapy of Multiple Antibiotics

Bahatdin Daşbaşı <dasbasi_bahatdin@hotmail.com>

Department of Accounting and Finance Management, Faculty of Applied Sciences, Kayseri University 38039 Kayseri, Turkey

Abstract – In this study, a mathematical model in form fractional-order differential equations (FDEs) system identifying population dynamics in two species bacteria struggling one another and exposed to multiple antibiotics simultaneously, was suggested. Stability analysis of the equilibrium points of the proposed model was also carried out. Additionally, the results of the analysis have promoted by numerical simulations.

Keywords – *Fractional-order differential equation, Stability analysis, Numerical simulation.*

1. Introduction

Mathematical modeling through fractional-orders differential and integral operators has become increasingly common in recent years. In addition, that, the various types of fractional-order differential equations are proposed for most of the standard models. Fractional-order differential equations (FDEs) are, at least, as stable as their integer order counterpart, namely ordinary differential equation [1]. Therefore, the fractional-order calculus has a considerable amount of attention for many areas of science [2-7]. In particular, biology is a very rich resource for mathematical ideas.

The behavior of most biological systems has memory or after-effects. The modeling of these systems by FDEs has more advantages than classical integer-order modeling, where such effects are neglected [2]. In this study, a continuous time mathematical model proposed in [8] is examined by using the system of FDEs.

2. Preliminaries and Definitions

In this section, the basic definitions and characteristics of fractional derivative operators is expressed.

2.1. Fractional Differential Operators

There are various descriptions of a fractional derivative with the order $\alpha > 0$. The definitions of Riemann-Liouville and Caputo are used most widely. The Riemann-Liouville fractional integral operator with order $\alpha \geq 0$ for the function $f(t)$ is described as the following:

$$J^{\alpha} f(t) = \frac{1}{\Gamma(\alpha)} \int_0^t (t-\tau)^{\alpha-1} f(\tau) d\tau \,, \alpha > 0, t > 0. \quad (2.1)$$

Some of properties of the operator J^{α} are as follows:

$$J^{\alpha} J^{\beta} f(t) = J^{\alpha+\beta} f(t)$$
$$J^{\alpha} t^{\gamma} = \frac{\Gamma(\gamma+1)}{\Gamma(\alpha+\gamma+1)} t^{\alpha+\gamma} \quad (2.2)$$

where $\mu \geq -1, \alpha, \beta \geq 0$ and $\gamma > -1$. The Caputo sense was used in this study. Taking into account the definition of Caputo sense, the fractional derivative of the function $f(t)$ is identified as

$$D^{\alpha} f(t) = J^{m-\alpha} D^m f(t) = \frac{1}{\Gamma(m-\alpha)} \int_0^t \frac{f^{(m)}(\tau)}{(t-\tau)^{\alpha-m+1}} d\tau \quad (2.3)$$

for $m-1 < \alpha \leq m$, $m \in \mathbb{N}$, $t > 0$ [9].

3. Model Formulation

The proposed model in this study is fractional-order form of model suggested in [8], which showed dynamics between antibiotics concentrations and bacteria in an individual receiving a cocktail of multi-drug treatment against bacteria. Bacteria in model have the competitive ability against each order for common host. That all bacteria have not resistance ability against to multiple antibiotics, has assumed in model. Let us denote by $B_1(t)$ and $B_2(t)$ the population sizes of first, and second bacteria to multiple antibiotics at time t, respectively; and by $A_i(t)$ the concentration of the i-th antibiotic for $i = 1,2,\ldots,n$.

The parameters used in the model are as follows: It has supposed that bacteria follow a logistic growth with different carrying capacity K_1 and K_2, respectively. In this sense, β_{B_1} and β_{B_2} are the birth rate of first and second bacteria, respectively. The first and second bacteria have per capita natural death rates μ_{B_1} and μ_{B_2}, respectively. The first bacteria also die due to the action of the antibiotics, and it has assumed that the rate at which they are killed by the i-th antibiotic is equal to $\overline{\alpha}_i B_1 A_i$. In the same mind, it is $\overline{q}_i B_2 A_i$ for other. The mutual competition between the species is dictated by M_1, M_2. Finally, the i-th antibiotic concentration is supplied at a constant rate δ_i, and is taken up at a constant per capita rate ω_i (or the excretion rate from body) [10].

Under the assumptions aforementioned and proposed in [8], it is obtained the following system of $(n+2)$ fractional-order differential equation:

$$
\begin{aligned}
D^{\alpha}B_1 &= \beta_{B_1}B_1\left(1-\frac{B_1}{K_1}\right)-\left[\sum_{i=1}^{n}\overline{\alpha_i}\,A_iB_1\right]-\mu_{B_1}B_1-M_1B_2B_1\\
D^{\alpha}B_2 &= \beta_{B_2}B_2\left(1-\frac{B_2}{K_2}\right)-\left[\sum_{i=1}^{n}\overline{q_i}\,A_iB_2\right]-\mu_{B_2}B_2-M_2B_1B_2\\
D^{\alpha}A_i &= \delta_i-\omega_iA_i, for\ i=1,2,\dots,n.
\end{aligned}
\tag{3.1}
$$

where $t \geq 0$, $n \in \mathbb{N}^+$, $D=\frac{d}{dt}$ and $\alpha \in (0,1]$, real number, is the orders of the derivatives in this system. Also, $B_1 \equiv B_1(t)$, $B_2 \equiv B_2(t)$, $A_1 \equiv A_1(t)$,…, $A_n \equiv A_n(t)$, the parameters $\beta_{B_1}, \beta_{B_2}, \mu_{B_1}, \mu_{B_2}, M_1, M_2$ and $\overline{\alpha_i}, \overline{q_i}$ for $i=1,\dots,n$ are positive constants. Additionally, the system (3.1) has to be finished with positive initial conditions $B_1(t_0)=B_{1_0}$, $B_2(t_0)=B_{2_0}$, $A_1(t_0)=A_{1_0}$,…, $A_n(t_0)=A_{n_0}$.

The above scenario related to the parameters used in the model (3.1) has been graphically described in Figure 3.1.

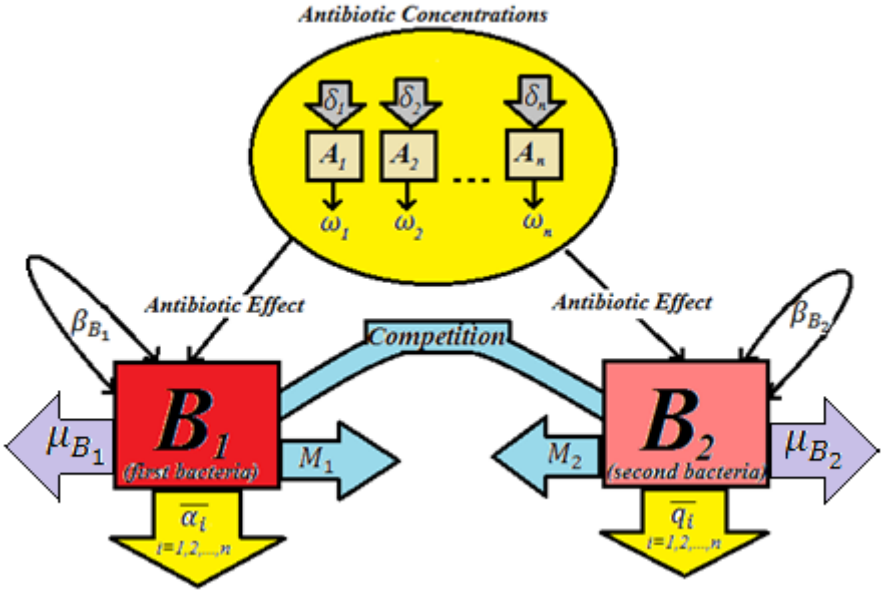

Figure 3.1. Schematic demonstration of interaction among bacteria (first and second) and concentrations of multiple antibiotic in model (3.1).

To reduce the number of parameters, it is used change of variables $b_1=\frac{B_1}{K_1}$, $b_2=\frac{B_2}{K_2}$, $a_i=\frac{A_i}{\frac{\delta_i}{\omega_i}}$. In the new variables, system (3.1) transforms to

$$
\begin{aligned}
D^{\alpha}b_1 &= \beta_{B_1}b_1(1-b_1)-\left[\sum_{i=1}^{n}\alpha_ia_ib_1\right]-\mu_{B_1}b_1-m_1b_2b_1\\
D^{\alpha}b_2 &= \beta_{B_2}b_2(1-b_2)-\left[\sum_{i=1}^{n}q_ia_ib_2\right]-\mu_{B_2}b_2-m_2b_1b_2\\
D^{\alpha}a_i &= \omega_i-\omega_ia_i, for\ i=1,2,\dots,n.
\end{aligned}
\tag{3.2}
$$

where $q_i = \overline{q}_i\left(\frac{\delta_i}{\omega_i}\right)$, $\alpha_i = \overline{\alpha}_i\left(\frac{\delta_i}{\omega_i}\right)$, $M_1 = \frac{m_1}{K_2}$ and $M_2 = \frac{m_2}{K_1}$.

Definition 3.1 The FDE model in (3.2) is rewritten the matrix form as the following:

$$\begin{aligned} &D^{\alpha}X(t) = AX(t) + x_1(t)B_1X(t) + x_2(t)B_2X(t) + H \\ &X(0) = X_0 \end{aligned} \tag{3.3}$$

where

$$X(t) = \begin{pmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \\ \vdots \\ x_{n+2}(t) \end{pmatrix} = \begin{pmatrix} b_1(t) \\ b_2(t) \\ a_1(t) \\ \vdots \\ a_n(t) \end{pmatrix}, X_0 = \begin{pmatrix} x_1(0) \\ x_2(0) \\ x_3(0) \\ \vdots \\ x_{n+2}(0) \end{pmatrix}, H = \begin{pmatrix} 0 \\ 0 \\ \omega_1 \\ \vdots \\ \omega_n \end{pmatrix},$$

$$A = \begin{pmatrix} \left(\beta_{B_1} - \mu_{B_1}\right) & 0 & 0 & \dots & 0 \\ 0 & \left(\beta_{B_2} - \mu_{B_2}\right) & 0 & \dots & 0 \\ 0 & 0 & -\omega_1 & \dots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \dots & -\omega_n \end{pmatrix},$$

$$B_1 = \begin{pmatrix} -\beta_{B_1} & -m_1 & -\alpha_1 & \dots & -\alpha_n \\ 0 & 0 & 0 & \dots & 0 \\ 0 & 0 & 0 & \dots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \dots & 0 \end{pmatrix}$$

and

$$B_2 = \begin{pmatrix} 0 & 0 & 0 & \dots & 0 \\ -m_2 & -\beta_{B_2} & -q_1 & \dots & -q_n \\ 0 & 0 & 0 & \dots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \dots & 0 \end{pmatrix}.$$

Definition 3.2 For $X(t) = \left(x_1(t)\ x_2(t)\ x_3(t)\ \dots\ x_{n+2}(t)\right)^T$, let $C^*[0,T]$ be the set of continuous column vectors $X(t)$ on the interval $[0,T]$. The norm of $X(t) \in C^*[0,T]$ definite in (3.3) is $\|X(t)\| = \sum_{i=1}^{n+2} sup_t|x_i(t)|$.

Proposition 3.1 Let considered Definition 3.1. Let $\mathbb{R}_+^{n+2} = \{X: X \geq 0\}$ and $X(t) = \left(x_1(t)\ x_2(t)\ x_3(t)\ \dots\ x_{n+2}(t)\right)^T$. Let $f(x) \in C[a,b]$ and $D^{\alpha}f(x) \in C[a,b]$ for $0 < \alpha \leq 1$, and then, by the generalized mean value theorem, it is

$f(x) = f(a) + \frac{1}{\Gamma(\alpha)}D^{\alpha}f(\xi)(x-a)^{\alpha}$ with $0 \leq \xi \leq x$, all $x \in [a,b]$.

According to this theorem,

- the function $f(x)$ is increasing for each $x \in [a,b]$, when $D^{\alpha}f(x) > 0$, all $x \in [a,b]$,
- the function $f(x)$ is decreasing for each $x \in [a,b]$, when $D^{\alpha}f(x) < 0$, all $x \in [a,b]$.

Additionally, the vector field points into $\mathbb{R}_+^{n+2}$, since $D^\alpha b_1(t)|_{b_1=b_2=a_i=0}=0$, $D^\alpha b_2(t)|_{b_1=b_2=a_i=0}=0$ and $D^\alpha a_i|_{b_1=b_2=a_i=0}=\omega_i$ for $i=1,2,\dots,n$ on each hyperplane bounding the nonnegative octant.

Proposition 3.2 Let $X(t)\in C^*[0,T]$. In this case, there is a unique solution of the system (3.2).

Proof. If $D^\alpha X(t)=F\big(X(t)\big)=AX(t)+x_1(t)B_1X(t)+x_2(t)B_2X(t)+H$, then $X(t)\in C^*[0,T]$ implies $F\big(X(t)\big)\in C^*[0,T]$. Also, considering $X(t),Y(t)\in C^*[0,T]$ and $X(t)\neq Y(t)$; it is obtained the following inequalities:

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

$$=\|(AX(t)+x_1(t)B_1X(t)+x_2(t)B_2X(t)+H)-(AY(t)+y_1(t)B_1Y(t)+y_2(t)B_2Y(t)+H)\|$$

$$=\|AX(t)+x_1(t)B_1X(t)+x_2(t)B_2X(t)-AY(t)-y_1(t)B_1Y(t)-y_2(t)B_2Y(t)\|$$

$$=\left\|\begin{matrix}A\big(X(t)-Y(t)\big)+x_1(t)B_1X(t)+x_2(t)B_2X(t)-y_1(t)B_1Y(t)-y_2(t)B_2Y(t)\\-\left(\underbrace{x_1(t)B_1Y(t)-x_1(t)B_1Y(t)}_{0}\right)-\left(\underbrace{x_2(t)B_2Y(t)-x_2(t)B_2Y(t)}_{0}\right)\end{matrix}\right\|$$

$$=\left\|\begin{matrix}A\big(X(t)-Y(t)\big)+x_1(t)B_1\big(X(t)-Y(t)\big)+x_2(t)B_2\big(X(t)-Y(t)\big)+\big(x_1(t)-y_1(t)\big)B_1Y(t)\\+\big(x_2(t)-y_2(t)\big)B_2Y(t)\end{matrix}\right\|$$

$$\leq\begin{pmatrix}\big\|A\big(X(t)-Y(t)\big)\big\|+\big\|x_1(t)B_1\big(X(t)-Y(t)\big)\big\|+\big\|x_2(t)B_2\big(X(t)-Y(t)\big)\big\|\\+\big\|\big(x_1(t)-y_1(t)\big)B_1Y(t)\big\|+\big\|\big(x_2(t)-y_2(t)\big)B_2Y(t)\big\|\end{pmatrix}$$

$$\leq\begin{pmatrix}\|A\|\big\|\big(X(t)-Y(t)\big)\big\|+|x_1(t)|\|B_1\|\big\|\big(X(t)-Y(t)\big)\big\|+|x_2(t)|\|B_2\|\big\|\big(X(t)-Y(t)\big)\big\|\\+\|B_1\|\big|\big(x_1(t)-y_1(t)\big)\big|\|Y(t)\|+\|B_2\|\big|\big(x_2(t)-y_2(t)\big)\big|\|Y(t)\|\end{pmatrix}$$

$$\leq\begin{pmatrix}(\|A\|+|x_1(t)|\|B_1\|+|x_2(t)|\|B_2\|)\big\|\big(X(t)-Y(t)\big)\big\|\\+\|B_1\|\underbrace{\big|\big(x_1(t)-y_1(t)\big)\big|}_{\leq\|(X(t)-Y(t))\|}\|Y(t)\|+\|B_2\|\underbrace{\big|\big(x_2(t)-y_2(t)\big)\big|}_{\leq\|(X(t)-Y(t))\|}\|Y(t)\|\end{pmatrix}$$

$$\leq(\|A\|+\|B_1\||x_1(t)|+\|B_1\|\|Y(t)\|+\|B_2\||x_2(t)|+\|B_2\|\|Y(t)\|)\big\|\big(X(t)-Y(t)\big)\big\|$$

$$\leq\left(\|A\|+\|B_1\|\left(\underbrace{|x_1(t)|}_{\leq\|X(t)\|}+\|Y(t)\|\right)+\|B_2\|\left(\underbrace{|x_2(t)|}_{\leq\|X(t)\|}+\|Y(t)\|\right)\right)\big\|\big(X(t)-Y(t)\big)\big\|$$

$$\leq\big(\|A\|+(\|B_1\|+\|B_2\|)(\|X(t)\|+\|Y(t)\|)\big)\big\|\big(X(t)-Y(t)\big)\big\|$$

and so, it is

$$\big\|F\big(X(t)\big)-F\big(Y(t)\big)\big\|\leq L\big\|\big(X(t)-Y(t)\big)\big\| \qquad (3.4)$$

where $L = \|A\| + (\|B_1\| + \|B_2\|)(W_1 + W_2) > 0$, and W_1 and W_2 are positive and meet the inequalities $\|X(t)\| \leq W_1$, $\|Y(t)\| \leq W_2$ due to $X(t), Y(t) \in C^*[0,T]$. Therefore, the system (3.3) has a unique solution.

Lemma 3.1. Consider the following fractional-order autonomous system

$$\begin{aligned} &D^{\alpha}X(t) = F\big(X(t)\big), D = \frac{d}{dt} \\ &X(0) = X_0 \end{aligned} \tag{3.5}$$

where $\alpha \in (0,1], X(t) = (x_1 \quad x_2 \quad \cdots \quad x_n)^T$ and $F = (f_1 \quad f_2 \quad \ldots \quad f_n)^T$. To evaluate the equilibrium points, it has been presumed as $D^{\alpha}X(t) = 0 \Rightarrow f_i(\overline{x_1}, \overline{x_2}, \ldots, \overline{x_n}) = 0$ for $i = 1,2, \ldots, n$. In this sense, the equilibrium point $(\overline{x_1}, \overline{x_2}, \ldots, \overline{x_n})$ of this system is founded. To evaluate the asymptotic stability of equilibrium points, the Jacobian matrix,

$$J = \begin{pmatrix} \frac{\partial f_1}{\partial x_1} & \frac{\partial f_1}{\partial x_2} & \cdots & \frac{\partial f_1}{\partial x_n} \\ \frac{\partial f_2}{\partial x_1} & \frac{\partial f_2}{\partial x_2} & \cdots & \frac{\partial f_2}{\partial x_n} \\ \vdots & \vdots & \ddots & \vdots \\ \frac{\partial f_n}{\partial x_1} & \frac{\partial f_n}{\partial x_2} & \cdots & \frac{\partial f_n}{\partial x_n} \end{pmatrix}$$

is used. It is assumed that the I is identity matrix with nxn. If all of the eigenvalues, $\lambda_1, \lambda_2, \ldots, \lambda_n$, obtained from the equation

$$Det\big(J_{(x_1,x_2,\ldots,x_n)=(\overline{x_1},\overline{x_2},\ldots,\overline{x_n})} - \lambda I\big) = 0 \tag{3.6}$$

satisfies either the Routh–Hurwitz stability conditions or the conditions

$$\Big(|arg(\lambda_1)| > \frac{\alpha\pi}{2}, \quad |arg(\lambda_2)| > \frac{\alpha\pi}{2}\Big), \tag{3.7}$$

then $(\overline{x_1}, \overline{x_2}, \ldots, \overline{x_n})$ is ***locally asymptotically stable (LAS)*** for system (3.5). In addition that, the characteristically equation obtained from (3.6) can be given by

$$P(\lambda) = \lambda^n + a_1\lambda^{n-1} + \ldots + a_{n-1}\lambda + a_n,$$

where the coefficients a_i for $i = 1, \ldots, n$ are real constants. In this respect, Routh-Hurwitz stability conditions for polynomial of degree $n = 2$, 3, 4 and 5 are summarized as following:

$$\begin{aligned} &n = 2: a_1, a_2 > 0, \\ &n = 3: a_1, a_3 > 0 \text{ and } a_1a_2 > a_3, \\ &n = 4: a_1, a_3, a_4 > 0 \text{ and } a_1a_2a_3 > {a_3}^2 + {a_1}^2a_4, \\ &n = 5: \begin{matrix} a_1, a_2, a_3, a_4, a_5 > 0, a_1a_2a_3 > {a_3}^2 + {a_1}^2a_4 \\ \text{and } (a_1a_4 - a_5)(a_1a_2a_3 - {a_3}^2 - {a_1}^2a_4) > a_5(a_1a_2 - a_3)^2 + a_1{a_5}^2. \end{matrix} \end{aligned} \tag{3.8}$$

Additionally, the above mentioned criteria has provided the necessary and sufficient conditions for all roots of $P(\lambda)$ to lie in the left half of the complex plane [11].

Conclusion 3.1. Let us consider Lemma 3.1. The following conclusion can be summarized from this lemma. If the eigenvalues are real numbers, it is enough to only check whether they provide the Routh-Hurwitz criteria for the stability of the equilibrium point obtained from system (3.5).

Conclusion 3.2. It is assumed that the characteristically equation is

$$\begin{aligned} P(\lambda) &= \lambda^2 + a_1\lambda + a_2 \\ &= \lambda^2 + \big(-Tr(J)\big)\lambda + (DetJ) = 0 \end{aligned} \tag{3.9}$$

for $n = 2$ in system (3.5). In this sense, the stability conditions of the equilibrium point are: either Routh–Hurwitz conditions $(a_1, a_2 > 0)$
or:

$$a_1 < 0, 4a_2 > (a_1)^2, \left| tan^{-1}\left(\frac{\sqrt{4a_2 - (a_1)^2}}{a_1}\right)\right| > \frac{\alpha\pi}{2}. \tag{3.10}$$

4. Qualitative Analysis of the System (3.2)

Proposition 4.1. The existence and stability of equilibria of the system (3.2) are analyzed in here. The equilibria of the system with the threshold parameters

$$\frac{\beta_{B_1} - [\sum_{i=1}^{n}\alpha_i] - \mu_{B_1}}{\beta_{B_1}} = A, \frac{\beta_{B_2} - [\sum_{i=1}^{n} q_i] - \mu_{B_2}}{\beta_{B_2}} = B, \frac{m_1}{\beta_{B_1}} = C, \frac{m_2}{\beta_{B_2}} = D, \tag{4.1}$$

$$0 < C, 0 < D$$

are as follows: The system (3.2) always has the infection-free equilibrium point $E_0 = (0,0,1,1,\ldots,1)$. If $A > 0$, then $E_1 = (A, 0,1,1,\ldots,1)$ reveals as another equilibrium point. Likewise, $E_2 = (0, B, 1,1,\ldots,1)$ exists, when $B > 0$. When $CD < 1$ and $BC < A < \frac{B}{D}$ or $1 < CD$ and $\frac{B}{D} < A < BC$, in addition to E_0, E_1, and E_2, there exists a fourth the equilibrium point, $E_3 = \left(\frac{BC-A}{CD-1}, \frac{DA-B}{CD-1}, 1,1,\ldots,1\right)$ [8].

Proposition 3.2. The equilibrium points of system (3.2) satisfy the followings:

- **(i)** If $A < 0$ and $B < 0$, then the infection-free equilibrium E_0 is *LAS*. If either $A > 0$ or $B > 0$, it becomes an unstable point.
- **(ii)** Let $A > 0$. If $B - DA < 0$, the equilibrium point E_1 is *LAS*, and if $B - DA > 0$, E_1 becomes an unstable point.
- **(iii)** Let $B > 0$. If $A - CB < 0$, the equilibrium point E_2 is *LAS*, and if $A - CB > 0$, E_2 becomes an unstable point.
- **(iv)** Let $CD < 1$ and $BC < A < \frac{B}{D}$ or $1 < CD$ and $\frac{B}{D} < A < BC$. If $1 < CD$ and $\frac{B}{D} > A > BC$, then E_3 is *LAS*.

Proof. For the stability analysis, the functions of the right side of the system (3.2) are suggested as follows:

$$\begin{aligned} f(b_1,b_2,a_i) &= \beta_{B_1} b_1(1-b_1) - b_1\left[\sum_{i=1}^{n}\alpha_i a_i\right] - \mu_{B_1} b_1 - m_1 b_2 b_1 \\ g(b_1,b_2,a_i) &= \beta_{B_2} b_2(1-b_2) - \left[\sum_{i=1}^{n} q_i a_i b_2\right] - \mu_{B_2}\ b_2 - m_2 b_1 b_2 \\ h_i(b_1,b_2,a_i) &= \omega_i - \omega_i a_i, \qquad i = 1,2,\dots,n. \end{aligned} \tag{4.2}$$

That Jacobean matrix obtained from equations in (4.2) is

$$J = \begin{pmatrix} \begin{pmatrix} \beta_{B_1} - 2\beta_{B_1} b_1 - \sum_{i=1}^{n}\alpha_i a_i \\ -\mu_{B_1} - m_1 b_2 \end{pmatrix} & -m_1 b_1 & -\alpha_1 b_1 & \dots & -\alpha_n b_1 \\ -m_2 b_2 & \begin{pmatrix} \beta_{B_2} - 2\beta_{B_2} b_2 - \sum_{i=1}^{n} q_i a_i \\ -\mu_{B_2} - m_2 b_1 \end{pmatrix} & -q_1 b_2 & \dots & -q_n b_2 \\ 0 & 0 & -\mu_1 & \dots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \dots & -\mu_n \end{pmatrix}. \tag{4.3}$$

In terms of ease of representation, the τ-th eigenvalue of equilibrium point E_k is shown as $\lambda^{(k)}{}_\tau$ for $k = 0,1,2,3$ and $\tau = 1,2,\dots,n+2, \quad n \in N$.

(i) From (4.3), the Jacobean matrix evaluated at the equilibrium point E_0 is given by

$$J(E_0) = \begin{pmatrix} \beta_{B_1} - \sum_{i=1}^{n}\alpha_i - \mu_{B_1} & 0 & 0 & \dots & 0 \\ 0 & \beta_{B_2} - \sum_{i=1}^{n} q_i - \mu_{B_2} & 0 & \dots & 0 \\ 0 & 0 & -\mu_1 & \dots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \dots & -\mu_n \end{pmatrix}. \tag{4.4}$$

By taking into account (4.1), the eigenvalues obtained from (4.4) are $\lambda^{(0)}{}_1 = \beta_{B_1} A$, $\lambda^{(0)}{}_2 = \beta_{B_2} B$ and $\lambda^{(0)}{}_{i+2} = -\mu_i$ for $i = 1,2,\dots,n$. It is explicit that all eigenvalues are real numbers and $\lambda^{(0)}{}_{i+2} = -\mu_i < 0$, since parameters in the proposed model are positive real number. By Conclusion 3.1., it is enough to examine whether the eigenvalues provide the Routh-Hurwitz criteria for stability analysis of E_0. Therefore, the others eigenvalues, $\lambda^{(0)}{}_1$ and $\lambda^{(0)}{}_2$, are negative real number, iff $A < 0$ and $B < 0$. In this case, E_0 is LAS.

(ii) Let $A > 0$. The jacobian matrix for the equilibrium point E_1 by taking into account (4.1) is given as

$$J(E_1)=\begin{pmatrix} -\beta_{B_1}A & -m_1A & -\alpha_1A & \dots & -\alpha_nA \\ 0 & \beta_{B_2}B-m_2A & 0 & \dots & 0 \\ 0 & 0 & -\mu_1 & \dots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \dots & -\mu_n \end{pmatrix}. \quad (4.5)$$

The eigenvalues are ${\lambda^{(1)}}_1=-\beta_{B_1}A$, ${\lambda^{(1)}}_2=\beta_{B_2}(B-DA)$ and ${\lambda^{(1)}}_{i+2}=-\mu_i<0$ for $i=1,2,\dots,n$. The eigenvalues are real numbers. From Conclusion 3.1., the eigenvalues are negative real number, iff $A>0$ and $B-DA<0$. Therefore, it is LAS.

(iii) For $B>0$, there is the equilibrium point E_2. The Jacobian matrix evaluated in this point is

$$J(E_2)=\begin{pmatrix} \beta_{B_1}A-m_1B & 0 & 0 & \dots & 0 \\ -m_2B & -\beta_{B_2}B & -q_1B & \dots & -q_nB \\ 0 & 0 & -\mu_1 & \dots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \dots & -\mu_n \end{pmatrix} \quad (4.6)$$

by (4.1). The eigenvalues of (4.6) are ${\lambda^{(2)}}_1=\beta_{B_1}A-m_1B=\beta_{B_1}(A-CB)$, ${\lambda^{(2)}}_2=-\beta_{B_2}B$ and ${\lambda^{(2)}}_{i+2}=-\mu_i<0$ for $i=1,2,\dots,n$. By the same mind in (ii), the eigenvalues are real numbers. We have Conclusion 3.1. E_2 is LAS, iff $B>0$ and $A-CB<0$.

(iv) Let

$$CD<1 \text{ and } BC<A<\frac{B}{D} \text{ or } 1<CD \text{ and } \frac{B}{D}<A<BC. \quad (4.7)$$

In this case, the stability of E_3 can be analyzed. Evaluating J for E_3, we have

$$J(E_3)=\begin{pmatrix} \beta_{B_1}\left(A-2\dfrac{BC-A}{CD-1}-C\dfrac{DA-B}{CD-1}\right) & -m_1\dfrac{BC-A}{CD-1} & -\alpha_1b_1 & \dots & -\alpha_nb_1 \\ -m_2\dfrac{DA-B}{CD-1} & \beta_{B_2}\left(B-2\dfrac{DA-B}{CD-1}-D\dfrac{BC-A}{CD-1}\right) & -q_1b_2 & \dots & -q_nb_2 \\ 0 & 0 & -\mu_1 & \dots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \dots & -\mu_n \end{pmatrix} \quad (4.8)$$

That eigenvalues of Jacobean matrix evaluated at the equilibrium point E_3 are ${\lambda^{(3)}}_{i+2}=-\mu_i<0$ for $i=1,2,\dots,n$ and the others are founded from following matrix;

$$J^{B(E_3)}=\begin{pmatrix} -\beta_{B_1}\left(\dfrac{A-BC}{1-CD}\right) & -m_1\left(\dfrac{A-BC}{1-CD}\right) \\ -m_2\left(\dfrac{B-AD}{1-CD}\right) & -\beta_{B_2}\left(\dfrac{B-AD}{1-CD}\right) \end{pmatrix} \quad (4.9)$$

where $J^{B(E_3)}$ is the block matrix of $J(E_3)$. It is clear that $\lambda^{(3)}{}_{i+2} = -\mu_i \in \mathbb{R}^-$ and so, it does not impair the stability of this point. From (4.9), it is $Tr\left(J^{B(E_3)}\right) = -\left[\beta_{B_1}\overline{b_1} + \beta_{B_2}\overline{b_2}\right]$ and $Det\left(J^{B(E_3)}\right) = \beta_{B_1}\beta_{B_2}\overline{b_1 b_2}(1 - CD)$. In this respect, it is $Tr\left(J^{B(E_3)}\right) < 0$ due to equilibrium values in E_3 and parameters in (3.1) are positive real number. Consider the parameter a_1 in (3.9), it is $a_1 > 0$, due to $Tr\left(J^{B(E_3)}\right) < 0$. Thus, the stability conditions of the equilibrium point are Routh–Hurwitz conditions $(a_1, a_2 > 0)$, due to $a_1 > 0$.

In addition, that, if $CD < 1$, (4.10). Then $a_2 = Det\left(J^{B(E_3)}\right) > 0$. By (4.7) and (4.10), if $1 < CD$ and $\frac{B}{D} < A < BC$, (4.11) then the eigenvalues are negative real number or complex number with negative real parts, and so, it is *LAS*.

As a result, the *LAS* conditions founded for equilibria of system (3.2) are summarized in the Table 4.1.

Table 4.1. The *LAS* conditions of the equilibria of FDEs system in (3.2).

Equilibrium Points	Stability Conditions
$E_0 = (0,0,1,\ldots,1)$	$A < 0, B < 0$
$E_1 = (A,0,1,\ldots,1)$	$max\left\{0,\frac{B}{D}\right\} < A$
$E_2 = (0,B,1,\ldots,1)$	$max\{0,A\} < BC$
$E_3 = \left(\frac{A-BC}{1-CD},\frac{B-AD}{1-CD},1,1,\ldots,1\right)$	$1 < CD$ and $\frac{B}{D} < A < BC$

5. Numerical Study

In the following discussion, it is demonstrated some contributions of the proposed mathematical model to the study of complex problems in host-microbe interactions. In numerical study, datas of two different streams competing each others of bacteria including Acinetobacter baumannii (b_1) and E. coli (b_2) in host were used and dynamics of multiple antibiotics against these bacteria causing infection were examined [8]. The parameters used in numerical study [12-18] are as the followings:

$$\begin{aligned}&\beta_{B_1} = 1.2\ \text{day}^{-1},\ \beta_{B_2} = 0.6\ \text{day}^{-1}, K_1 = 10^8\ \text{cell}, K_2 = 10^7\ \text{cell}, \mu_{B_1} = 0.312\ \text{day}^{-1},\\ &\mu_{B_2} = 0.179\ \text{day}^{-1}, M_1 = 10^{-7}\ \text{cell}^{-1}\text{day}^{-1}, M_2 = 10^{-7}\ \text{cell}^{-1}\text{day}^{-1}, \overline{\alpha_1} = 0.47\ \text{day}^{-1},\\ &\overline{\alpha_2} = 0.21\ \text{day}^{-1}, \overline{q_1} = 0.42\ \text{day}^{-1}, \overline{q_2} = 0.17\ \text{day}^{-1}, \delta_1 = 2\ \text{mg/kg/day},\\ &\delta_2 = 1.2\ \text{mg/kg/day}, \omega_1 = 0.04\ \text{day}^{-1}, \omega_2 = 0.03\ \text{day}^{-1} \text{ and } \alpha = 0.25,0.50,0.75,0.99.\end{aligned} \quad (5.1)$$

In the light of data obtained from (5.1), it is founded as following: the parameters

$$\sum_{i=1}^{n} \alpha_i = \alpha_1 + \alpha_2 = \overline{\alpha}_1 \frac{\delta_1}{\omega_1} + \overline{\alpha}_2 \frac{\delta_2}{\omega_2} = 0.47\frac{2}{0.04} + 0.21\frac{1.2}{0.03} = 31.9$$

$$\sum_{i=1}^{n} q_i = q_1 + q_2 = \overline{q}_1 \frac{\delta_1}{\omega_1} + \overline{q}_2 \frac{\delta_2}{\omega_2} = 0.42\frac{2}{0.04} + 0.17\frac{1.2}{0.03} = 27.8$$

$m_1 = M_1K_2 = 10^{-7} * 10^7 = 1$
$m_2 = M_2K_1 = 10^{-7} * 10^8 = 10$

the threshold parameters

$$A = \frac{\beta_{B_1} - [\sum_{i=1}^{n} \alpha_i] - \mu_{B_1}}{\beta_{B_1}} = \frac{1.2 - 31.9 - 0.312}{1.2} = -25.84$$

$$B = \frac{\beta_{B_2} - [\sum_{i=1}^{n} q_i] - \mu_{B_2}}{\beta_{B_2}} = \frac{0.6 - 27.8 - 0.179}{0.6} = -45.63$$

$$C = \frac{m_1}{\beta_{B_1}} = \frac{1}{1.2} = 0.83$$

$$D = \frac{m_2}{\beta_{B_2}} = \frac{10}{0.6} = 16.66$$

and so the equilibrium points $E_0(0,0,1,1)$, $E_1(-25.84,0,1,1)$, $E_2(0,-45.63,1,1)$ and $E_3 = (-0.9376,-29.99972,1,1,\dots,1)$. Because it is $A, B < 0$, the equilibrium point $E_0(0,0,1,1)$ is LAS and this situation is clearly seen in following figures:

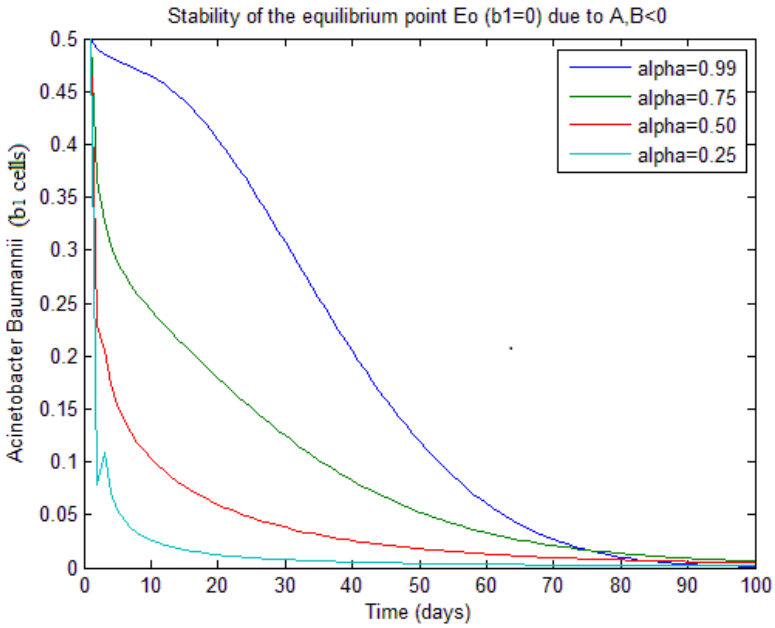

Figure 5.1. According to $\alpha = 0.25, 0.50, 0.75$ and 0.99, the trajectory of population sizes of Acinetobacter baumannii, when $A = -25.84$ and $B = -45.63$. In here, $E_0(0,0,1,1)$ is LAS, since $A, B < 0$.

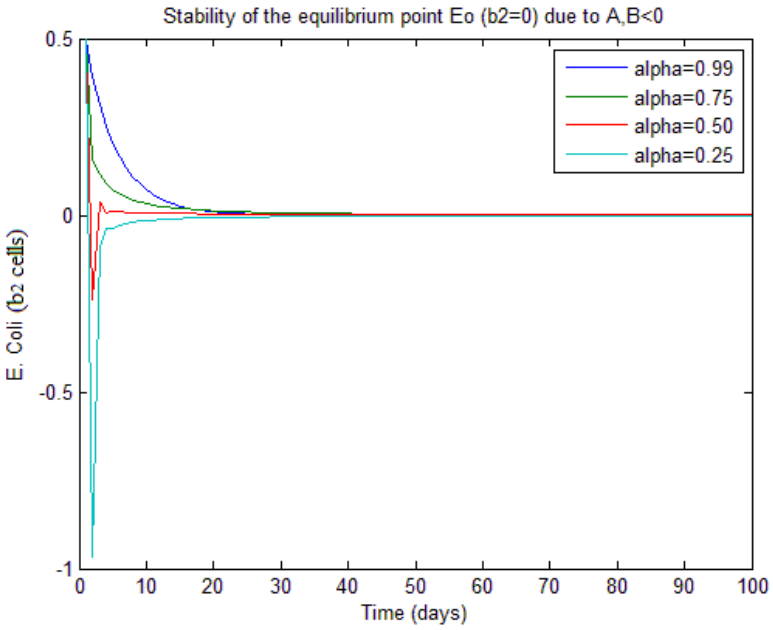

Figure 5.2. According to $\alpha = 0.25, 0.50, 0.75$ and 0.99, the trajectory of population sizes of E. coli, when $A = -25.84$ and $B = -45.63$. In here, $E_0(0,0,1,1)$ is LAS, since $A, B < 0$.

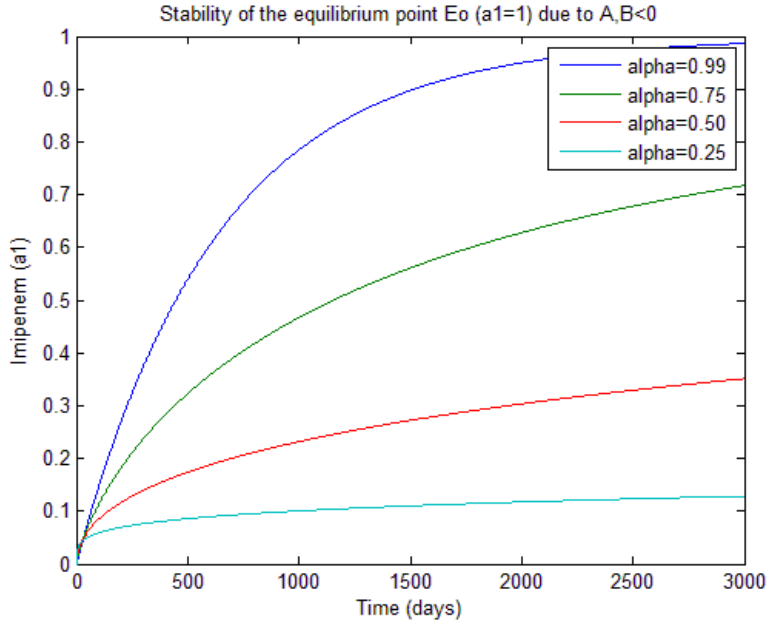

Figure 5.3. According to $\alpha = 0.25, 0.50, 0.75$ and 0.99, the trajectory of the imipenem concentration, when $A = -25.84$ and $B = -45.63$. In here, $E_0(0,0,1,1)$ is LAS, since $A, B < 0$.

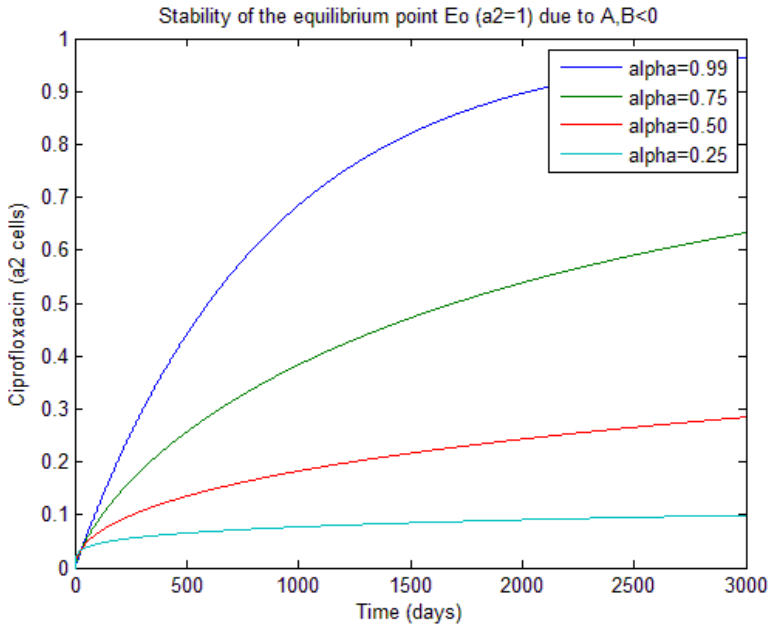

Figure 5.4. According to $\alpha = 0.25, 0.50, 0.75$ and 0.99, the trajectory of the ciprofloxacin concentration, when $A = -25.84$ and $B = -45.63$. In here, $E_0(0,0,1,1)$ is LAS, since $A, B < 0$.

In compliance with literature datas [17], while E. coli is disappeared as a result of 90-day antibiotics use and Acinetobacter baumannii is disappeared as a result of 30-day antibiotics use. This case shows that our model is very useful to explain experimental results in literatures.

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