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Fractional-Order Model for Multi-Drug Antimicrobial Resistance

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Abstract: Drug resistance is one of the most serious phenomena in financial, economic and medical terms. The present paper proposes and investigates a simple mathematical fractional-order model for the phenomenon of multi-drug antimicrobial resistance. The model describes the dynamics of the susceptible and three kinds of infected populations. The first class of the infected society responds to the first antimicrobial drug but resists to the second one. The second infected individuals react to the second antimicrobial drug but resist to the first one. The third class shows resistance to both of the two drugs. We formulate the model and associate it with some of its properties. The stability conditions of the multi-drug antimicrobial resistance equilibrium states are derived. We illustrate the analytical results by some numerical simulations.

Keywords: Susceptible, infectious, drug resistance, stability, predictor-corrector method.

1 Introduction

Recently, some diseases (Measle, Poliomyelitis, Mumps, …), that were thought to have disappeared, have reappeared [Lewnard and Grad (2018)]. The most common causes are developing resistance to antimicrobial drugs (AMR) [Nguyen, Contamin, Nguyen et al. (2018); Gabryszewski, Modchang, Musset et al. (2016); Wilson, Garud, Feder et al. (2016); Welch, Fricke and McDermott (2007)]. According to the World Health Organization (WHO), AMR and multi-drug resistance (MDR) are among the top ten essential threats to human health in 2019 [Li, Plesiat and Nikaido (2015); Paul and Moye-Rowley (2014); Moreno-Gamez, Hill, Rosenbloom et al. (2018)]. This resistance resulted from the disuse of antibiotics either by the patients or by the doctors themselves. Antibiotics are widely used to treat both small infections and fatal human diseases. Furthermore, they are used extensively for animal farming and agricultural purposes. Antibiotics have been frequently and successfully used to control both human and animal epidemic outbreaks. Also, they play an essential role in many medical procedures.

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Unfortunately, the disuse of antimicrobial drugs can transform organisms to other antigenic agents that resist medication. Even the new one may be more active. This transformation was evident in appearing of new viral, bacterial, and fungal strains, which is more virulent and resistant. The reasons for these transformations can be: Firstly, it may occur naturally during the bacteria replication process. Secondly, the misuse of antibiotics in both humans and animals accelerates the process. Thirdly, low investments in both hospital infection control and scientific research for discovering new types of antibiotics. Fourthly, the absence of decisive governmental regulations on medical facilities in some regions of the world. Fifthly, pollution has a prominent role in elevating AMR and MDR development.

AMR and MDR are some of the complicated threats to global health, food security, economics, and development nowadays. Mathematical models have played an essential role in improving the perception of several biological phenomena [Elettreby, Ahmed and Safan (2019); Elettreby and Aly (2015); Nowak and May (2000); Perelson and Nelson (1998); Roy, Zhang, Ghosh et al. (2018)]. The authors have developed many mathematical models for exploring several aspects of epidemics [Daley and Gani (2001); Martcheva (2015)]. Also, Integer order dynamical systems are used to model optimization of antibiotic use [Massad, Burattini and Coutinho (2008); Sun and Hu (2018)]. Both AMR and MDR depend on exposure time. Hence, memory effects are crucial for both phenomena. Consequently, the fractional-order formulation is quite relevant because it is related to systems with memory [Capponetto, Dongola, Fortuna et al. (2010); Cao, Datta, Al Basir et al. (2018); Elettreby, Nabil and Al-Raezah (2017); Elettreby, Al-Raezah and Nabil (2017); Ahmed, Elgazzar and Elsadany (2020)].

Other mathematical topics relevant to AMR and MDR are network theory, game theory, optimization theory, and seasonality modeling. Here, we present a simple model for multi-drug antimicrobial resistance. In Section 2, we proposed the model, proved the existence and uniqueness of the solution of the model. In Section 3, we investigated the stability of the equilibrium points of the model. Finally, in Section 4, we used the Adams-type predictor-corrector method for the numerical solution of the model.

2 Two-drug antimicrobial resistance fractional-ordered model

Fractional calculus generalizes the concept of ordinary differentiation and integration to noninteger order. Fractional calculus is a fertile field for researchers to study very important real phenomena in many fields like physics, engineering, biology, and so forth [Ross (1977); Ding and Ye (2009); Hanert, Schumacher and Deleersnijder (2011); Kleinert and Korbel (2016); Garrappa (2016); Magin (2006); Kilbas, Srivastava and Trujillo (2006); Magin, Ortigueira, Podlubny et al. (2011); Zhao, Zheng, Zhang et al. (2016); Arenas, González-Parra and Chen-Charpentier (2016)]. The fractional differential equations are naturally related to systems with memory. Also, they are closely related to fractals which are numerous in biological system. The definition of fractional derivative

involves an integration which is non local operator. The obtained results by studying the solutions of the fractional differential equations are more general and are as stable as their integer-order counter-part. So, we consider a two-drug antimicrobial resistance fractional-order model. Also, studying a dynamical system in the fractional-ordered form shows a lot of complex behaviors that can not appear in the ordinary form. There are a lot of approaches to define the fractional differential operator such as Grunwald-Letnikov, Riemann-Liouville, Caputo, and Hadamard. The Riemann-Liouville and Caputo approaches are the most widely used in applications [Ding and Ye (2009); Hanert, Schumacher and Deleersnijder (2011); Zhao, Zheng, Zhang et al. (2016); Diethelm (2010)]. The Caputo fractional derivative of order α (>0) is denoted by D_*^α and it is given in the following form [El-Sayed (1993, 1998); Podlubny (1999); Diethelm, Ford and Freed (2002); Ben Adda and Cresson (2005)]:

$$D_*^\alpha f(t) = I^{n-\alpha}(D^n f(t))$$

where $n = \lceil \alpha \rceil$, $t \in \mathbb{R}^+$, $D = \frac{d}{dt}$ and the fractional integral of order α (>0), is defined by using Gamma function as follows;

$$I^\alpha f(t) = \int_0^t \frac{(t-x)^{\alpha-1}}{\Gamma(\alpha)} f(x)\,dx$$

Consider a given community that is invaded by a bacterial infection. Let S be the fraction of the susceptible population, I_1 be the fraction of the infected population which response, only, to the first antimicrobial drug (Chloramphenicol). I_2 be the fraction of the infected population which response, only, to the second antimicrobial drug (Augmentin), and I_{12} be the fraction of the infected population which shows resistance to both of the two drugs, respectively. The response to one drug but not the other is due to acquired immunity caused by the intensive use of antibiotics. The positive constants μ_1, μ_2, μ_{12} are the natural death rates of the three infected populations, respectively. Let the positive constants b_1, b_2, b_{12} are the encounter rates of the susceptible population S with the infected populations I_1, I_2, I_{12} per unit time. Also, let the positive constants b_4, b_5 are the encounter rates of the infected populations I_1 with I_{12} and I_2 with I_{12} per unit time, respectively. Let r be the growth rate of the susceptible S. We assume that the three types of infected individuals can recover, but their recovery rates are meager by comparison with the susceptible individuals so that we will ignore them. Also, the infected individuals of class three I_{12} (with two-drug resistant bacteria) can infect both of the susceptible individuals S, the first I_1 and the second I_2 classes of the infected individuals (drug-resistance transmission). Also, we assume that there is a super-infection of I_1 and I_2 individuals by I_{12} individuals but not from $I_{2(1)}$ individuals to $I_{1(2)}$ individuals due to some acquired immunity. There is a class of infected individuals by bacteria that are sensitive to both drugs. Here, we concern only on the classes of the infected individuals that are resistant to antimicrobial drugs. Then, our model takes the following form;

$$\begin{aligned}
D_*^{\alpha} S(t) &= f_1(S, I_1, I_2, I_{12}) = rS(1-S) - b_1 SI_1 - b_2 SI_2 - b_{12} SI_{12} \\
D_*^{\alpha} I_1(t) &= f_2(S, I_1, I_2, I_{12}) = b_1 SI_1 - \mu_1 I_1 - b_4 I_1 I_{12} \\
D_*^{\alpha} I_2(t) &= f_3(S, I_1, I_2, I_{12}) = b_2 SI_2 - \mu_2 I_2 - b_5 I_2 I_{12} \\
D_*^{\alpha} I_{12}(t) &= f_4(S, I_1, I_2, I_{12}) = b_{12} SI_{12} + b_4 I_1 I_{12} + b_5 I_2 I_{12} - \mu_{12} I_{12}
\end{aligned} \tag{1}$$

with the initial non-negative values;

$$(S(t),\ I_1(t),\ I_2(t),\ I_{12}(t))|_{t=0} = (S(0),\ I_1(0),\ I_2(0),\ I_{12}(0)) \tag{2}$$

where $\alpha \in (0,\ 1]$, $t \in (0,\ T]$, $S(t)$, $I_1(t)$, $I_2(t)$, $I_{12}(t) \in [0,\infty)$.

2.1 Existence of the unique non-negative solution

Theorem 2.1. The initial value problems (1), (2) has a unique solution.

Proof. System (1) can be written as the following matrix form;

$$D_*^{\alpha} X(t) = AX(t) + S(t)BX(t) + I_1(t)CX(t) + I_2(t)DX(t),\ X(0) = X_0, \tag{3}$$

where;

$$X(t) = \begin{bmatrix} S(t) \\ I_1(t) \\ I_2(t) \\ I_{12}(t) \end{bmatrix},\ X_0 = \begin{bmatrix} S(0) \\ I_1(0) \\ I_2(0) \\ I_{12}(0) \end{bmatrix},\ A = \begin{bmatrix} r & 0 & 0 & 0 \\ 0 & -\mu_1 & 0 & 0 \\ 0 & 0 & -\mu_2 & 0 \\ 0 & 0 & 0 & -\mu_{12} \end{bmatrix}$$

$$B = \begin{bmatrix} r & 0 & 0 & -b_{12} \\ 0 & b_1 & 0 & 0 \\ 0 & 0 & b_2 & 0 \\ 0 & 0 & 0 & b_{12} \end{bmatrix},\ C = \begin{bmatrix} -b_1 & 0 & 0 & 0 \\ 0 & 0 & 0 & -b_4 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & b_4 \end{bmatrix} \text{ and } D = \begin{bmatrix} -b_2 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -b_5 \\ 0 & 0 & 0 & b_5 \end{bmatrix}$$

Definition 2.1. *Let C** $[0,T]$ be the class of continuous column vector $X(t)=(S(t), I_1(t), I_2(t), I_{12}(t))^{\tau}$ where $C[0,T]$ is the class of continuous functions defined on the interval $[0,T]$.

Now, let $F(X(t))=A\,X(t)+S(t)\,B\,X(t)+I_1(t)\,C\,X(t)+I_2(t)\,D\,X(t)$ be a continuous function where $X(t)$ is a continuous column vector. Suppose that $X(t)$ and $Y(t)$ are two distinct continuous column vectors solutions of the initial value problems (1), (2) such that;

$X(t)=(S(t), I_1(t), I_2(t), I_{12}(t))^{\tau}$, $Y(t)=(Sy(t), Iy_1(t), Iy_2(t), Iy_{12}(t))^{\tau}$.

Then;

$$\begin{aligned}\|F(X)-F(Y)\| &= \|(AX(t)+S(t)BX(t)+I_1(t)CX(t)+I_2(t)DX(t))\\ &\quad -(AY(t)+Sy(t)BY(t)+Iy_1(t)CY(t)+Iy_2(t)DY(t))\|\\ &\le \|A(X(t)-Y(t))\|+\|S(t)B(X(t)-Y(t))\|+\|(S(t)-Sy(t))BY(t)\|\\ &\quad +\|I_2(t)C(X(t)-Y(t))\|+\|(I_2(t)-Iy_2(t))CY(t)\|\\ &\quad +\|I_{12}(t)D(X(t)-Y(t))\|+\|(I_{12}(t)-Iy_{12}(t))DY(t)\|.\end{aligned}$$

Since $|S(t)-Sy(t)|$, $|I_1(t)-Iy_1(t)|$, $|I_2(t)-Iy_2(t)|$, $|I_{12}(t)-Iy_{12}(t)|\le X(t)-Y(t)$, then, we have;

$$\begin{aligned}\|F(X)-F(Y)\| &\le [\|A\|+\|B\|(|S(t)|+\|Y(t)\|)+\|C\|(I_1(t)+\|Y(t)\|)\\ &\quad +\|D\|(|I_2(t)|+\|Y(t)\|)]\|X(t)-Y(t)\|.\end{aligned}$$

Let

L=[||A||+||B|| (|*S*(*t*)|+||*Y*(*t*)||)+||*C*|| (*I*$_1$(*t*)+||*Y*(*t*)||)+||D|| (|*I*$_2$(*t*)|+||*Y*(*t*)||)] ||*X*(*t*)-*Y*(*t*)||. It is clear that $L>0$. Then;

$$\|F(X)-F(Y)\| \le L\|X(t)-Y(t)\|.$$

So, the continuous function $F(X(t))$, satisfies the Lipschitz condition and the system (1) has a unique solution [Wang, Cheng and Zhang (2013)].

3 Stability analysis of the equilibria of the model

Model (1) is a nonlinear and has no time-dependent explicit solution. Therefore, we study the model for a long time run. On putting the derivatives in the left-hand side of (1) equal zero;

$$D_*^{\alpha}S(t)=D_*^{\alpha}I_1(t)=D_*^{\alpha}I_2(t)=D_*^{\alpha}I_{12}(t)=0 \tag{4}$$

to evaluate the equilibrium points of system (1). Solving the resulting nonlinear algebraic system with respect to the equilibrium state variables $\tilde{S},\tilde{I}_1,\tilde{I}_2,\tilde{I}_{12}$. Then, we get the equilibrium points;

$$\begin{aligned}&E_1=(0,0,0,0), \quad E_2=(1,0,0,0), \quad E_3=(\bar{S},\bar{I}_1,0,0), \quad E_4=(\bar{\bar{S}},0,\bar{I}_2,0)\\ &E_5=(\bar{\bar{\bar{S}}},0,0,\bar{I}_{12}), \quad E_6=(\underline{S},\underline{I}_1,0,\underline{I}_{12}), \quad E_7=(\tilde{S},0,\tilde{I}_2,\tilde{I}_{12}), \quad E_8=(\hat{S},\hat{I}_1,\hat{I}_2,\hat{I}_{12})\end{aligned}$$

where;

$$\bar{S}=\frac{\mu_1}{b_1},\bar{I}_1=\frac{r}{b_1}\left(1-\frac{\mu_1}{b_1}\right),\bar{\bar{S}}=\frac{\mu_2}{b_2},\bar{I}_2=\frac{r}{b_2}\left(1-\frac{\mu_2}{b_2}\right),\bar{\bar{\bar{S}}}=\frac{\mu_{12}}{b_{12}},\bar{I}_{12}=\frac{r}{b_{12}}\left(1-\frac{\mu_{12}}{b_{12}}\right)$$

$$\underline{S}=1-\frac{b_1\mu_{12}-b_{12}\mu_1}{rb_4},\underline{I}_1=\frac{\mu_{12}-b_{12}\underline{S}}{b_4},\underline{I}_{12}=\frac{b_1\underline{S}-\mu_1}{b_4}$$

$$\tilde{S}=1-\frac{b_2\mu_{12}-b_{12}\mu_2}{rb_5},\tilde{I}_2=\frac{\mu_{12}-b_{12}\tilde{S}}{b_5},\tilde{I}_{12}=\frac{b_2\tilde{S}-\mu_2}{b_5}$$

and;

$$\hat{S}=\frac{\mu_1 b_5-\mu_2 b_4}{b_1 b_5-b_2 b_4},\hat{I}_1=\frac{rb_5(1-\hat{S})-b_{12}b_5\hat{I}_{12}-\mu_{12}b_2+b_{12}b_2\hat{S}}{b_1 b_5-b_2 b_4}$$

$$\hat{I}_2=-\frac{rb_4(1-\hat{S})-b_{12}b_4\hat{I}_{12}-\mu_{12}b_1+b_{12}b_1\hat{S}}{b_1 b_5-b_2 b_4},\hat{I}_{12}=\frac{\mu_1 b_2-\mu_2 b_1}{b_1 b_5-b_2 b_4}$$

Since, the stability of the integer order system implies the stability of its corresponding fractional-order; we will consider the local stability of the system (1).

The local stability analysis of these equilibria is established by studying the following Jacobian matrix of system (1) at these equilibria;

$$J=\begin{pmatrix} r(1-2S)-b_1I_1-b_2I_2-b_{12}I_{12} & -b_1S & -b_2S & -b_{12}S \\ b_1I_1 & b_1S-\mu_1-b_4I_{12} & 0 & -b_4I_1 \\ b_2I_2 & 0 & b_2S-\mu_2-b_5I_{12} & -b_5I_2 \\ b_{12}I_{12} & b_4I_{12} & b_5I_{12} & b_{12}S+b_4I_1+b_5I_2-\mu_{12} \end{pmatrix}$$

A sufficient condition to say that an equilibrium point is a locally asymptotically stable is that all eigenvalues λ satisfy $|arg(\lambda)|>\alpha\ \pi/2$ [Matignon (1996)]. For α=1 this stability condition will be the Routh-Hutwitz conditions. Otherwise, these conditions are sufficient but not necessary. This condition implies that the characteristic polynomial of that point should satisfy Routh-Hurwitz conditions [Ahmed, El-Sayed and El-Saka (2006)]. For n=4, if H_1, H_2, H_3 and H_4 are the Routh-Hutwitz determinants, then the conditions $|H_1|>0$, $|H_2|>0$, $|H_3|>0$ and $a_4>0$ are the sufficient conditions that $|arg(\lambda)|>\alpha\ \pi/2$ is valid for all $\alpha\in[0,1)$.

Proposition 3.1. Model (1) has a boundary trivial unstable equilibrium E_1.

Proposition 3.2. *If* $b_1<\mu_1$, $b_2<\mu_2$ and $b_{12}<\mu_{12}$, then the full healthy second equilibrium point E_2 is locally asymptotically stable whenever it exists.

Proof. Similarly, the Jacobian matrix computed at the boundary equilibrium E_2 (fully healthy case) is;

$$J_2=\begin{pmatrix} -r & -b_1 & -b_2 & -b_{12} \\ 0 & b_1-\mu_1 & 0 & 0 \\ 0 & 0 & b_2-\mu_2 & 0 \\ 0 & 0 & 0 & b_{12}-\mu_{12} \end{pmatrix}$$

It has the eigenvalues $-r<0$, $b_1-\mu_1$, $b_2-\mu_2$ and $b_{23}-\mu_{12}$. Then, the full healthy equilibrium state E_2 is stable if $b_1<\mu_1$, $b_2<\mu_2$ and $b_{12}<\mu_{12}$.

This means that the encounter rates should be less than the death rates. Biologically, it means that susceptible individuals should avoid the infected ones. Since we concerned with the multi-drug resistance, so, we will ignore the study of the equilibrium points that do not have a multi-drug resistance (i.e., $I_{12}=0$).

Proposition 3.3. The multi-drug resistance equilibrium state E_5 is locally asymptotically stable if $\frac{\mu_{12}}{b_{12}} < min\left(1, \frac{\mu_1+b_4}{b_1}, \frac{\mu_2+b_5}{b_2}\right)$.

Proof. Since $\bar{\bar{S}}, \bar{I}_{12} \in (0,1)$, then the conditions of the existence of E_5 are;

$0<\mu_{12}<b_{12}$ and $0<r(b_{12}-\mu_{12})<b_{12}^2$

The local stability analysis of the multi-drug resistance fifth equilibrium state can establish by studying the following Jacobian matrix of system (1) at E_5;

$$J_5=\begin{pmatrix} -r\bar{\bar{S}} & -b_1\bar{\bar{S}} & -b_2\bar{\bar{S}} & -b_{12}\bar{\bar{S}} \\ 0 & b_1\bar{\bar{S}}-\mu_1-b_4\bar{I}_{12} & 0 & 0 \\ 0 & 0 & b_2\bar{\bar{S}}-\mu_2-b_5\bar{I}_{12} & 0 \\ b_{12}\bar{I}_{12} & b_4\bar{I}_{12} & b_5\bar{I}_{12} & 0 \end{pmatrix}$$

Since, $\bar{\bar{S}}=\frac{\mu_{12}}{b_{12}}$, $\bar{I}_{12}=\frac{r}{b_{12}}\left(1-\frac{\mu_{12}}{b_{12}}\right)$, we get the following characteristic equation;

$(b_1\bar{\bar{S}}-\mu_1-b_4\bar{I}_{12}-m)(b_2\bar{\bar{S}}-\mu_2-b_5\bar{I}_{12}-m)(m^2+r\bar{\bar{S}}m+b_{12}\bar{I}_{12}\mu_{12})=0,$

where m is the eigenvalues of the Jacobian matrix J_5. So, the eigenvalues are $m_1=b_1\bar{\bar{S}}-\mu_1-b_4\bar{I}_{12}$, $m_2=b_2\bar{\bar{S}}-\mu_2-b_5\bar{I}_{12}$ and the other two values $m_{3,\,4}$ are the solutions of the equation $m^2+r\bar{\bar{S}}m+b_{12}\bar{I}_{12}\mu_{12}=0$. This equation has two negative real parts. Then, multi-drug resistance fifth equilibrium state E_5 is stable if $b_1\bar{\bar{S}}<\mu_1-b_4\bar{I}_{12}$ and $b_2\bar{\bar{S}}<\mu_2-b_5\bar{I}_{12}$. Using the values of $\bar{\bar{S}}$, $\bar{I}_{12}$ and the conditions of the existence of the equilibrium point E_5, we get the following conditions;

$0<\frac{\mu_{12}}{b_{12}}<1, \frac{\mu_{12}}{b_{12}}<\frac{\mu_1+b_4}{b_1}$ and $\frac{\mu_{12}}{b_{12}}<\frac{\mu_2+b_5}{b_2}$

which is equivalent to the condition;

$\frac{\mu_{12}}{b_{12}}<\min\left(1, \frac{\mu_1+b_4}{b_1}, \frac{\mu_2+b_5}{b_2}\right)$

Note that, the condition of the existence of the equilibrium point E_5 is the condition of the instability of the full healthy state E_2.

This means that after some time the population will turn to only susceptible and multi-drug resistance. There will not be any individuals that can response to the existence drugs. This is a very dangerous case.

Proposition 3.4. The multi-drug resistance equilibrium state E_6 is locally asymptotically stable if $\underline{S}=1-\frac{b_1\mu_{12}-b_{12}\mu_1}{rb_4}<\frac{b_4\mu_2-b_5\mu_1}{b_4b_2-b_5b_1}$.

Proof. Since $\underline{S},\underline{I}_1,\underline{I}_{12}\in(0,1)$, then the conditions of the existence of E_6 are;

$$0<b_1\mu_{12}-b_{12}\mu_1<rb_4,\frac{\mu_{12}-b_4}{b_{12}}<\underline{S}<\frac{\mu_{12}}{b_{12}}\text{ and }\frac{\mu_1}{b_1}<\underline{S}<\frac{\mu_1+b_4}{b_1}$$

The local stability analysis of the multi-drug resistance sixth equilibrium state can established by studying the following Jacobian matrix of system (1) at E_6;

$$J_6=\begin{pmatrix}-r\underline{S} & -b_1\underline{S} & -b_2\underline{S} & -b_{12}\underline{S}\\ b_1\underline{I}_1 & 0 & 0 & -b_4\underline{I}_1\\ 0 & 0 & b_2\underline{S}-\mu_2-b_5\underline{I}_{12} & 0\\ b_{12}\underline{I}_{12} & b_4\underline{I}_{12} & b_5\underline{I}_{12} & 0\end{pmatrix}$$

which has the characteristic equation $(\lambda-b_2\underline{S}+\mu_2+b_5\underline{I}_{12})(\lambda^3+a_1\lambda^2+a_2\lambda+a_3)=0$, where λ is the eigenvalues of the Jacobian matrix J_6 and $a_1=r\underline{S}(>0)$, $a_2=\underline{S}(b_1^2\underline{I}_1+b_{12}^2\underline{I}_{12})+b_4^2\underline{I}_1\underline{I}_{12}(>0)$ and $a_3=rb_4^2\underline{S}\underline{I}_1\underline{I}_{12}(>0)$. So, the eigenvalues are $\lambda_1=b_2\underline{S}-\mu_2-b_5\underline{I}_{12}$, and the other three values $\lambda_{2,\ 3,\ 4}$ are the solutions of the characteristic equation $\lambda^3+a_1\ \lambda^2+a_2\ \lambda+a_3=0$. The Routh-Hurwitz matrices of the above characteristic equation are;

$$H_1=[a_1],H_2=\begin{bmatrix}a_1 & 1\\ a_3 & a_2\end{bmatrix},H_3=\begin{bmatrix}a_1 & 1 & 0\\ a_3 & a_2 & a_1\\ 0 & 0 & a_3\end{bmatrix}$$

According to Proposition. 1 Ahmed et al. [Ahmed, El-Sayed and El-Saka (2006)] the condition $|arg(\lambda)|>\alpha\ \pi/2$ is satisfied for $\lambda_{2,\ 3,\ 4}$ since $a_1>0$, $a_1\ a_2>a_3$, $a_3>0$ and $D(P)>0$, where $D(P)=18\ a_1\ a_2\ a_3+(a_1\ a_2)^2-4\ a_3\ (a_1)^3-4\ (a_2)^3-27\ (a_3)^2$. Then, the condition of the stability of the multi-drug resistance sixth equilibrium state E_6 is $\lambda_1=b_2\underline{S}-\mu_2-b_5\underline{I}_{12}<0$;

$$\underline{S}<\frac{b_4\mu_2-b_5\mu_1}{b_4b_2-b_5b_1}\Leftrightarrow\frac{\mu_1}{\mu_2}<\frac{b_4}{b_5}<\frac{\mu_1-b_1}{\mu_2-b_2}$$

Note that, the condition of the existence of the equilibrium point E_6 is the condition of the instability of the multi-drug equilibrium state E_5.

Similarly, the conditions of the existence of multi-drug resistance equilibrium point E_7 are;

$$0 < b_2\mu_{12} - b_{12}\mu_2 < rb_5, \frac{\mu_{12} - b_5}{b_{12}} < \tilde{S} < \frac{\mu_{12}}{b_{12}} \text{ and } \frac{\mu_2}{b_2} < \tilde{S} < \frac{\mu_2 + b_5}{b_2}$$

Proposition 3.5. The multi-drug resistance equilibrium state E_7 is locally asymptotically stable if $\underline{S} = 1 - \dfrac{b_2\mu_{12} - b_{12}\mu_2}{rb_5} < \dfrac{b_5\mu_1 - b_4\mu_2}{b_5b_1 - b_4b_2}$.

Proposition 3.6. The coexistence multi-drug resistance equilibrium state E_8 is locally asymptotically stable whenever it exists.

Proof. Since $\hat{S}, \hat{I}_1, \hat{I}_2, \hat{I}_{12} \in (0, 1)$, then the conditions of the existence of E_8 are;

$$0 < \mu_1 b_5 - \mu_2 b_4 < b_1 b_5 - b_2 b_4, 0 < \mu_1 b_2 - \mu_2 b_1 < b_1 b_5 - b_2 b_4$$

$$\begin{aligned} 0 &< (rb_5 - \mu_{12} b_2)(b_1 b_5 - b_2 b_4) - (rb_5 - b_{12} b_2)(\mu_1 b_5 - \mu_2 b_4) - b_{12} b_5 (\mu_1 b_2 - \mu_2 b_1) \\ &< (b_1 b_5 - b_2 b_4)^2 \end{aligned}$$

$$\begin{aligned} 0 &< -(rb_4 - \mu_{12} b_1)(b_1 b_5 - b_2 b_4) + (rb_4 - b_{12} b_1)(\mu_1 b_5 - \mu_2 b_4) + b_{12} b_4 (\mu_1 b_2 - \mu_2 b_1) \\ &< (b_1 b_5 - b_2 b_4)^2 \end{aligned}$$

The local stability analysis of the multi-drug resistance eight equilibrium state can establish by studying the following Jacobian matrix of system (1) at E_8;

$$J_8 = \begin{pmatrix} -r\hat{S} & -b_1\hat{S} & -b_2\hat{S} & -b_{12}\hat{S} \\ b_1\hat{I}_1 & 0 & 0 & -b_4\hat{I}_1 \\ b_2\hat{I}_2 & 0 & 0 & -b_5\hat{I}_2 \\ b_{12}\hat{I}_{12} & b_4\hat{I}_{12} & b_5\hat{I}_{12} & 0 \end{pmatrix}$$

which has the characteristic equation $\lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4 = 0$, where λ is the eigenvalues of the Jacobian matrix J_8 and;

- $a_1 = r\hat{S} > 0$,
- $a_2 = \hat{S}(b_1^2\hat{I}_1 + b_2^2\hat{I}_2 + b_{12}^2\hat{I}_{12}) + (b_4^2\hat{I}_1 + b_5^2\hat{I}_2) > 0$,
- $a_3 = r(b_4^2\hat{I}_1 + b_5^2\hat{I}_2)\hat{S}\hat{I}_{12} > 0$,
- $a_4 = (b_1^2b_5^2 - b_1b_2b_4b_5 + b_2^2b_4^2)\hat{S}\hat{I}_1\hat{I}_2\hat{I}_{12} > (b_1b_5 - b_2b_4)^2\hat{S}\hat{I}_1\hat{I}_2\hat{I}_{12} > 0$.

The Routh-Hurwitz matrices of the above characteristic equation are;

$$H_1=[a_1], H_2=\begin{bmatrix} a_1 & 1 \\ a_3 & a_2 \end{bmatrix}, H_3=\begin{bmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ 0 & a_4 & a_3 \end{bmatrix}, H_4=\begin{bmatrix} a_1 & 1 & 0 & 0 \\ a_3 & a_2 & a_1 & 1 \\ 0 & a_4 & a_3 & a_2 \\ 0 & 0 & 0 & a_4 \end{bmatrix}$$

Since n=4, then the conditions $|H_1|=a_1=r\hat{S}>0$, $|H_2|=a_1a_2-a_3=r\hat{S}^2(b_1^2\hat{I}_1+b_2^2\hat{I}_2+b_{12}^2\hat{I}_{12})>0$, $a_4>0$ and $|H_3|=a_3(a_1a_2-a_3)-a_1^2a_4=r^2(b_1^2b_4^2\hat{I}_1^2+b_2^2b_5^2\hat{I}_2^2+(b_4^2\hat{I}_1^2+b_5^2\hat{I}_2^2)b_{12}^2\hat{I}_{12}+b_1b_2b_4b_5\hat{I}_1\hat{I}_2)\hat{S}^3\hat{I}_{12}>0$ are sufficient conditions that $|arg(\lambda)|>\alpha\ \pi/2$ is valid for all $\alpha\in[0,1)$. Then, the multi-drug resistance eighth equilibrium state E_8 is stable whenever it exists. Note that, the condition of the existence of the equilibrium point E_8 is the condition of the instability of all the previous multi-drug equilibrium states. Also, that the conditions in Propositions (2)−(4) implies the existence of MDR. In general any stable equilibrium with $I_{12}>0$ will imply MDR.

4 Numerical results

In this paper, we used the Adams-type predictor-corrector method for the numerical solution of our fractional-order system [Diethelm and Ford (2002)]. First, we will give the Adams-type predictor-corrector method for solving general initial value problem with Caputo derivative;

$$D_*^{\alpha}y(t)=f(t,y(t))$$

with the initial condition $y(0)=y_0$ and $t\in(0,T]$. We assumed a set of points $\{t_j,y_j\}$, where $y_j=y(t_j)$, are the points used for our approximation and $t_j=j\,h$, j=0, 1, ….., N (*integer*), $h=\frac{T}{N}$. The general formula for Adams-type predictor-corrector method is;

$$y_{n+1}=\sum_{k=0}^{\lceil\alpha\rceil-1}\frac{t_{n+1}^k}{k!}y_0^{(k)}+\frac{h^{\alpha}}{\Gamma(\alpha+2)}\sum_{j=0}^{n}\sigma_{j,n+1}f(t_j,y_j)+\frac{h^{\alpha}}{\Gamma(\alpha+2)}\sigma_{n+1,n+1}f(t_{n+1},y_{n+1}^P)$$

where;

$$\sigma_{j,n+1}=\begin{cases} n^{\alpha+1}-(n-\alpha)(n+1)^{\alpha}, & \text{if } j=0 \\ (n-j+2)^{\alpha+1}+(n-j)^{\alpha+1}-2(n-j+1)^{\alpha+1}, & \text{if } 1\le j\le n \\ 1, & \text{if } j=n+1 \end{cases}$$

and;

$$y_{n+1}^P=\sum_{k=0}^{\lceil\alpha\rceil-1}\frac{t_{n+1}^k}{k!}y_0^{(k)}+\frac{1}{\Gamma(\alpha)}\sum_{j=0}^{n}\rho_{j,n+1}f(t_j,y_j),$$

$$\rho_{j,n+1}=\frac{h^{\alpha}}{\alpha}\left((n+1-j)^{\alpha}-(n-j)^{\alpha}\right).$$

Applying the above algorithm for the system (1), we have the following;

$$\begin{aligned}
S_{n+1}&= S_0+\frac{h^{\alpha}}{\Gamma(\alpha+2)}\sum_{j=0}^{n}\sigma_{1,j,n+1}\left(rS_j(1-S_j)-b_1S_jI_{1,j}-b_2S_jI_{2,j}-b_{12}S_jI_{12,j}\right)\\
&\quad+\frac{h^{\alpha}}{\Gamma(\alpha+2)}\sigma_{1,n+1,n+1}\left(rS^P_{n+1}(1-S^P_{n+1})-b_1S^P_{n+1}I^P_{1,n+1}-b_2S^P_{n+1}I^P_{2,n+1}\right.\\
&\quad\left.-b_{12}S^P_{n+1}I_{12,n+1}\right)\\
I_{1,n+1}&=I_{1,0}+\frac{h^{\alpha}}{\Gamma(\alpha+2)}\sum_{j=0}^{n}\sigma_{2,j,n+1}\left(b_1S_jI_{1,j}-\mu_1I_{1,j}-b_4I_{1,j}I_{12,j}\right)\\
&\quad+\frac{h^{\alpha}}{\Gamma(\alpha+2)}\sigma_{2,n+1,n+1}\left(b_1S^P_{n+1}I^P_{1,n+1}-\mu_1I^P_{1,n+1}-b_4I^P_{1,n+1}I^P_{12,n+1}\right)\\
I_{2,n+1}&=I_{2,0}+\frac{h^{\alpha}}{\Gamma(\alpha+2)}\sum_{j=0}^{n}\sigma_{3,j,n+1}\left(b_2S_jI_{2,j}-\mu_2I_{2,j}-b_5I_{2,j}I_{12,j}\right)\\
&\quad+\frac{h^{\alpha}}{\Gamma(\alpha+2)}\sigma_{3,n+1,n+1}\left(b_2S^P_{n+1}I^P_{2,n+1}-\mu_2I^P_{2,n+1}-b_5I^P_{2,n+1}I^P_{12,n+1}\right)\\
I_{12,n+1}&=I_{12,0}+\frac{h^{\alpha}}{\Gamma(\alpha+2)}\sum_{j=0}^{n}\sigma_{4,j,n+1}\left(b_{12}S_jI_{12,j}+b_4I_{1,j}I_{12,j}+b_5I_{2,j}I_{12,j}-\mu_{12}I_{12,j}\right)\\
&\quad+\frac{h^{\alpha}}{\Gamma(\alpha+2)}\sigma_{4,n+1,n+1}\left(b_{12}S^P_{n+1}I^P_{12,n+1}+b_4I^P_{1,n+1}I^P_{12,n+1}+b_5I^P_{2,n+1}I^P_{12,n+1}-\mu_{12}I^P_{12,n+1}\right)
\end{aligned}$$

where;

$$S^P_{n+1}=S_0+\frac{1}{\Gamma(\alpha)}\sum_{j=0}^{n}\sigma_{1,j,n+1}\left(rS_j(1-S_j)-b_1S_jI_{1,j}-b_2S_jI_{2,j}-b_{12}S_jI_{12,j}\right)$$

$$I^P_{1,n+1}=I_{1,0}+\frac{1}{\Gamma(\alpha)}\sum_{j=0}^{n}\sigma_{2,j,n+1}\left(b_1S_jI_{1,j}-\mu_1I_{1,j}-b_4I_{1,j}I_{12,j}\right)$$

$$I^P_{2,n+1}=I_{2,0}+\frac{1}{\Gamma(\alpha)}\sum_{j=0}^{n}\sigma_{3,j,n+1}\left(b_2S_jI_{2,j}-\mu_2I_{2,j}-b_5I_{2,j}I_{12,j}\right)$$

$$I^P_{12,n+1}=I_{12,0}+\frac{1}{\Gamma(\alpha)}\sum_{j=0}^{n}\sigma_{4,j,n+1}\left(b_{12}S_jI_{12,j}+b_4I_{1,j}I_{12,j}+b_5I_{2,j}I_{12,j}-\mu_{12}I_{12,j}\right)$$

Therefore, for i=1, 2, 3, 4,

$$\sigma_{i,j,n+1}=\begin{cases} n^{\alpha+1}-(n-\alpha)(n+1)^{\alpha} & \text{, if } j=0 \\ (n-j+2)^{\alpha+1}+(n-j)^{\alpha+1}-2(n-j+1)^{\alpha+1} & \text{, if } 1\leq j\leq n \\ 1 & \text{, if } j=n+1 \end{cases}$$

and;

$$\rho_{i,j,n+1}=\frac{h^{\alpha}}{\alpha}((n+1-j)^{\alpha}-(n-j)^{\alpha}).$$

Numerical simulations for the model (1) have been carried out, where it is revealed that the solutions do not depend on the initial conditions. So, we will use the initial point (0.4, 0.3, 0.1, 0.2) and the parameter values r=0.1, b_1=0.1, b_2=0.11, b_{12}=0.09, b_4=0.08, b_5=0.1, μ_1=0.11, μ_2=0.12, and μ_{12}=0.1 for the following figures. Also, we will plot the time t versus the susceptible S, and the three kinds of the infected individuals I_1, I_2, I_{12} to check the qualitative behavior of the system.

In Fig. 1, we vary the value of the fractional-order α to test its impact on the behavior of the individuals. The figure shows that all curves of the three kinds of the infected individuals tend to zero as t increases and the susceptible goes to one, whenever the stability conditions of the equilibrium point E_2 are satisfied. This means the extinction of them and the system approaches a healthy state. We observed that increasing the parameter α increases the rate to reach to the steady state.

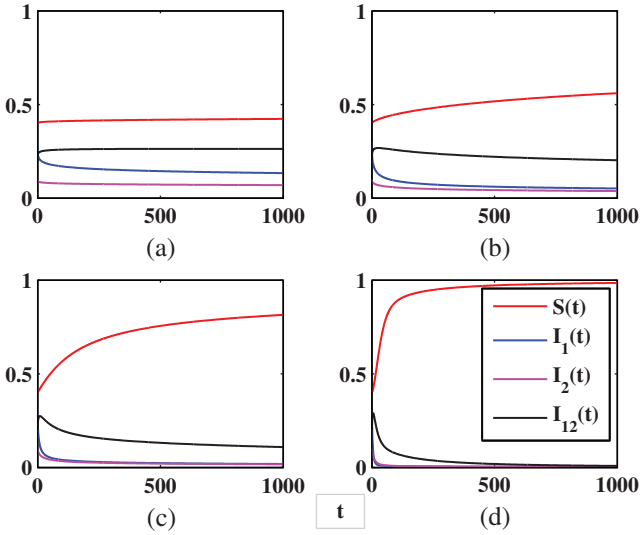

Figure 1: The figure shows the curves of the susceptible $S(t)$ and the other three represent the three kinds of the infected $I_1(t)$, $I_2(t)$ and $I_{12}(t)$ at r=0.1, b_1=0.1, b_2=0.11, b_{12}=0.09, b_4=0.08, b_5=0.1, μ_1=0.11, μ_2=0.12, μ_{12}=0.1. (a) α=0.2. (b) α=0.4. (c) α=0.6. (d) α=0.9

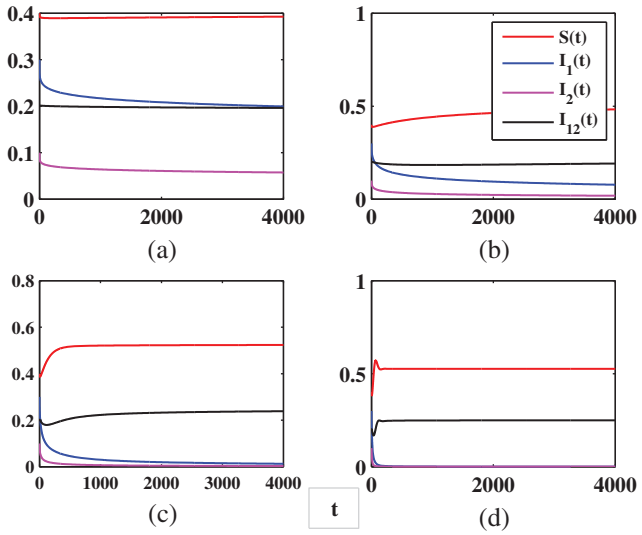

Figure 2: The figure shows the stability of E_5. (a) α=0.2. (b) α=0.4. (c) α=0.6. (d) α=0.9

In Figs. 2(a)–2(d), we used the parameter value b_{12}=0.19 to satisfies the stability conditions of the equilibrium point E_5. The figures show that the two kinds of infected I_1 and I_2 tend to zero as the time increases. The susceptible S and the MDR I_{12} approach to $\bar{\bar{S}}$=0.52632 and $\bar{I}_2 = 0.24931$, respectively. After some time, the system approaches the multi-drug resistance state.

In Figs. 3(a)–3(d) shows that the infected I_2 tends to zero as the time increases. The susceptible S, the infected I_1 and the MDR I_{12} approach to $(\underline{S}, \underline{I}_1, 0, \underline{I}_{12})$=$(0.4656, 0.6680, 0, 0.1572)$.

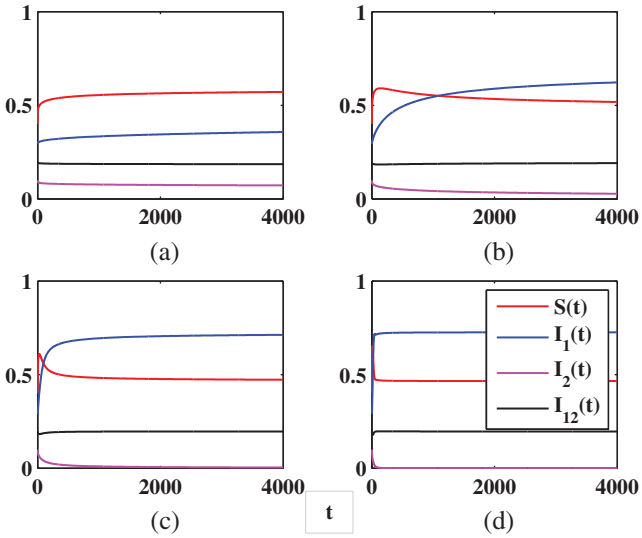

Figure 3: The figure shows the stability of E_6. (a) α=0.2. (b) α=0.4. (c) α=0.6. (d) α=0.9

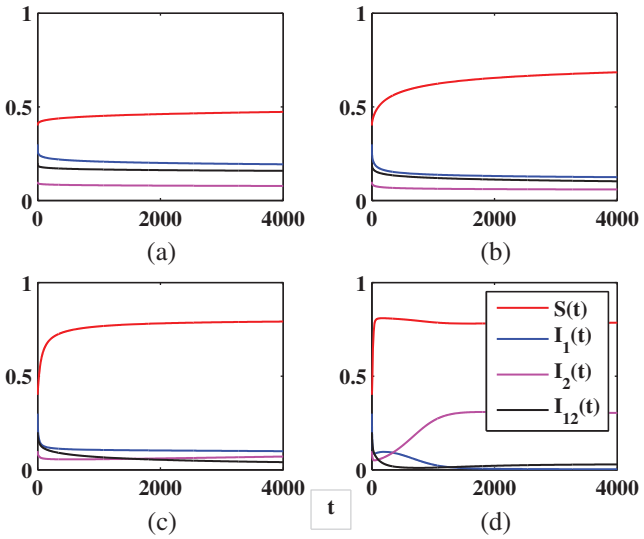

Figure 4: The figure shows the stability of E_7. (a) α=0.2. (b) α=0.4. (c) α=0.6. (d) α=0.9

This means that after some time the individual that responses to the second drug will disappear. Also, this is a problem because the second antibiotic becomes non-effective.

In Figs. 4(a)–4(d) shows that the infected I_1 tends to zero as the time increases. The susceptible S, the infected I_2 and the MDR I_{12} approach to $(\underline{S}, 0, \underline{I}_2, \underline{I}_{12}) = (0.7857, 0, 0.3061, 0.0306)$. This means that after some time the individual

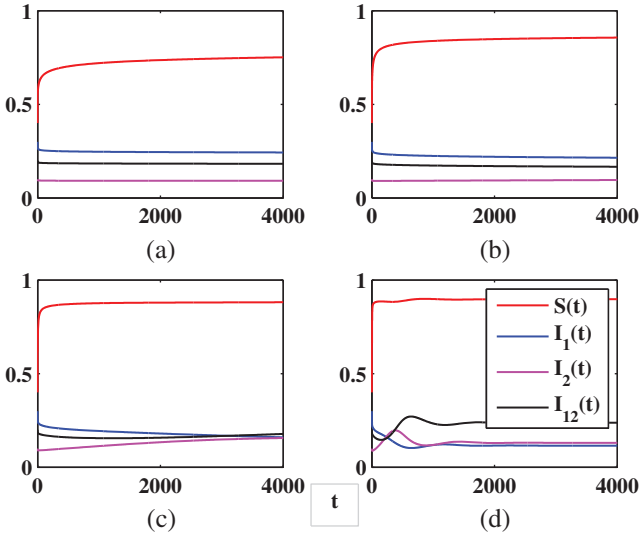

Figure 5: The figure shows the stability of E_8. (a) α=0.2. (b) α=0.4. (c) α=0.6. (d) α=0.9

that responses to the first drug will disappear. Also, this is a problem because the first antibiotic becomes non-effective.

In Figs. 5(a)–5(d), the susceptible S, the infected I_1, the infected I_2 and the MDR I_{12} approach to $(\hat{S}, \hat{I}_1, \hat{I}_2, \hat{I}_{12}) = (0.8977, 0.1143, 0.1298, 0.2386)$.

In Figs. 1–5 we noted that increasing the fractional-ordered parameter α increases the rate to reach to the steady state.

5 Summary and conclusion

There is increasing evidence showing that antimicrobial usage provides a powerful selective force that promotes the emergence of resistance in both humans and animals. The emergence, persistence, and spread of resistant bacteria are of great concern since they may lead to an overall increase in disease transmission, morbidity, mortality and sometimes to economic losses to both humans and animal production industry where tonnes of antimicrobial agents are consumed yearly.

The current paper has introduced a fractional-order model for multi-drug antimicrobial resistance. The main idea is to describes and studies the effect of the emergence of antimicrobial drug resistance on the existing antibiotics. The steady states of the model are obtained. There are seven boundary steady states and a unique interior steady state. The conditions of local stability of these states have been proved. We have made some numerical simulations to confirm our theoretical results.

Our model proved some important results, mathematically. Firstly, we proved the coexistence of drug sensitive and drug resisting strains, which is an observed phenomena. Secondly, the healthy state persists if the encounter rates are less than the death rates. Medically, it means that susceptible individuals should avoid infected ones, or the infected individuals should be isolated. Thirdly, we calculate the conditions that prevent individuals who, only, responds to the first antimicrobial drug I_1, and those, only, respond to the second antimicrobial drug from fading. These cases are very dangerous as the disappearance of these individuals makes the current drugs out of effect, and these are major economical and medical losses. Fifthly, we found the stability conditions of the coexistence state which is less dangerous than the others. Finally, we test the effect of the parameter fractional-order α on the system.

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