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Research article

Dynamics of a within-host drug resistance model with impulsive state feedback control

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Abstract: Bacterial resistance poses a major hazard to human health, and is caused by the misuse and overuse of antibiotics. Thus, it is imperative to investigate the optimal dosing strategy to improve the treatment effect. In this study, a mathematical model of antibiotic-induced resistance is presented to improve the antibiotic effectiveness. First, conditions for the global asymptotical stability of the equilibrium without pulsed effect are given according to the Poincaré-Bendixson Theorem. Second, a mathematical model of the dosing strategy with impulsive state feedback control is also formulated to reduce drug resistance to an acceptable level. The existence and stability of the order-1 periodic solution of the system are discussed to obtain the optimal control of antibiotics. Finally, our conclusions are confirmed by means of numerical simulations.

Keywords: Poincaré-Bendixson theorem; optimal dosing strategy; order-1 periodic solution; semi-continuous dynamical system

1. Introduction

Drug resistance is the possibility of resisting the effects of antibiotics generated either to eradicate or to control bacteria, and it brings many important public health problems, particularly in intensive care units [1]. Many strategies have been applied to deal with drug resistance, such as drug restrictions and multiple-drug therapy [2]. However, more studies are required to evaluate the potential efficacy of both strategies in reducing or preventing drug resistance and acquire some quantitative understanding of the mechanism of drug resistance.

Drug restrictions comprise suspending a given class of antibiotics for some period of time, while other antibiotics are still used for treatment, once drug resistance emerges [2]. It stems from the reduction of drug resistance in the absence of selection pressure due to the cost of resistance. In particular, drug cycling is considered as a special case of restriction to specific classes of drugs, which is implemented by alternating drugs at a certain time interval. In preceding studies [3–7], drug cycling has been found to have a positive impact on the use of antibiotic therapy. Although one of these studies yields different results [4], there have been studies demonstrating the detrimental effects of the approach [5]. In order to better combat drug resistance, researchers acknowledge that further research on the approach is needed.

Another approach to tackle drug resistance is the multiple-drug therapy presented in [8–10]. Drug interactions often occur during multiple-drug therapy, which can be classified as synergistic or antagonistic. Synergism refers to the interaction of two drugs to amplify the effect during treatment, and can quantitatively analyze the growth rate of drug-resistant bacteria under mixed drug therapy [11], while antagonism is the opposite [12]. Drug synergy reduces the number of used antibiotics, which can effectively reduce the costs and negative effects on patients. However, it has been shown that the optimal strategy to reduce multiple-drug resistance does not always utilize synergy among drugs, and sometimes antagonism may be more beneficial to reduce the concentration of drug-resistant bacteria [13, 14].

Clinically, drug-resistant bacteria would not be so alarming if we were able to control their growth. As a resolution, many mathematical models have been established to describe the different aspects of antibiotic dynamics from the perspective of drug resistance generation and antibiotic therapy [15–17]. The mathematical models were presented to optimize the dosage of antibiotics [18–20]. Some studies have also focused on the analysis of changes in antibiotic resistance in the host [21–23]. Tetteh et al. [22] focused on the role between the host immune response and antibiotic treatment based on pharmacodynamic and pharmacokinetic approaches. In addition, Garber et al. [17] developed the following mathematical model to explore the effects of antibiotics on populations of sensitive and drug-resistant bacteria:

$$\begin{cases} \dfrac{dx}{dt} = (\alpha - ra - \beta(x+y))x + \delta y, \\ \dfrac{dy}{dt} = (\alpha - \beta(x+y))y - \delta y, \end{cases} \tag{1.1}$$

where the densities of sensitive and drug-resistant bacteria are expressed in terms of $x(t)$ and $y(t)$. α is the growth rate of strain one, less r times the antibiotic concentration a. Due to the limited nutrients in the body, competition between the two bacteria to survive will cause the bacteria to be eliminated at a rate of β. The drug-resistant bacteria after losing resistance are very similar to susceptible bacteria, and we can define the rate of conversion of drug-resistant bacteria to susceptible bacteria as δ. Through qualitative analysis, Garber obtained threshold conditions for the extinction of drug-resistant strains.

Although most of the above models of drug resistance are described by using continuous dynamics, the antibiotic dosing process is discontinuous. Therefore, it is more reasonable to describe it by using an impulsive dynamical system.

Many scholars have done extensive research on the theory and applications of impulsive dynamical systems [24–26]. For example, impulsive dynamical systems are used to study the treatment of some infectious diseases [27], impulsive differential equations are used to study population control

problems [28], and antibiotic dressing strategies are used to study the optimal timing of antibiotic treatment [29]. In a similar way as in [29], we will formulate a mathematical model of a within-host drug resistance model with impulsive state feedback control to control the development of the resistant bacteria.

The paper is organized as follows. In Section 2, a within-host drug resistance model with impulsive state feedback control is proposed. In Section 3, we determine the global asymptotic stability of continuous dynamic systems by qualitative analysis. In Section 4, the existence and uniqueness of the order-1 periodic solution are discussed, and the stability of the solutions is also proposed. Finally, we will use numerical simulations to verify the correctness of the conclusions.

2. Model description

To effectively inhibit the growth of bacteria and viruses, antibiotics are usually used in the clinic. However, it can get out of control when the same drug is used continuously for a long period of time. At the same time, the disease becomes more difficult to cure because of the bacteria becoming resistant to antibiotics. Therefore, we need to use higher concentrations of the drug or change the drug in order to effectively control the growth of the bacteria. Subsequently, we try to use other drugs to deal with the resistant bacteria. The new drugs could play a temporary role in the harmful bacteria. One scenario, however, occurs periodically when bacteria become resistant to new drugs after long-term use. Motivated by [17, 29], we consider that taking drugs not only reduces the growth rate of sensitive bacteria, but also leads to the conversion of sensitive bacteria to drug-resistant bacteria. Thus, we give the following system:

$$\begin{cases} \left.\begin{aligned} \frac{dx}{dt} &= (\alpha - ra - \beta(x+y))x + \delta y, \\ \frac{dy}{dt} &= (\alpha - \beta(x+y))y - \delta y + rax, \end{aligned}\right\} y < h, \\ \left.\begin{aligned} \Delta x &= x(t^+) - x(t^-) = \tau h, \\ \Delta y &= y(t^+) - y(t^-) = -\tau h, \end{aligned}\right\} y = h, \\ x(0) = x_0 \geq 0, \\ y(0) = y_0 \geq 0, \end{cases} \tag{2.1}$$

where ra shows conversion rate, due to the infusion of antibiotics, of the sensitive bacteria to drug-resistant bacteria. h denotes the critical threshold value of the resistant bacteria which makes the drug lose effectiveness for the patient. When the concentration of drug-resistant bacteria reaches a critical threshold value, another drug is taken to prevent the growth of drug-resistant bacteria. The antibiotic dosing strategy can be described by using impulsive state feedback control. $\tau(0 < 1 - \tau << 1)$ is the rate at which the resistant bacteria become the sensitive bacteria. The drug-resistant bacteria have become sensitive to the new drug after the antibiotic dressing strategy although few bacteria remain still resistant.

All the above parameters are nonnegative, and the biological significance of the other parameters is given in system (1.1). The aim of this paper is to derive control measures to reinforce the effect of antibiotics through pulsed kinetic studies.

For convenience, we give the following definitions and lemmas.

Definition (2.1) *[18, 27]* Suppose the state-dependent impulsive differential equations are given as follows:

$$\begin{cases} \left.\begin{array}{l} \dfrac{dx}{dt} = P(x,y), \\ \dfrac{dy}{dt} = Q(x,y), \end{array}\right\} (x,y) \notin M(x,y), \\ \left.\begin{array}{l} \Delta x = \alpha(x,y), \\ \Delta y = \beta(x,y), \end{array}\right\} (x,y) \in M(x,y), \end{cases} \tag{2.2}$$

where $M(x,y)$ is the impulsive set and a continuous mapping $g : g(M(x,y)) = N(x,y)$ is the phase set.

Definition (2.2) *[24, 29]* Let M denote the impulsive set and N is the phase set. Suppose $g : N \to N$ be a mapping. For any point $P \in N$, there exists a $t_1 > 0$ such that $F(P) = f(P,t_1) = P_1 \in M, P_1^+ = \varphi(P_1) \in N$. Then $g(P) = l(P_1^+) - l(P)$ is called the successor function of point P, and the point P_1^+ is called the successor point of P.

Lemma 2.1. *If $g(P) = 0$, the trajectory passing through point P is the order-1 periodic solution of the system.*

Lemma 2.2. *[24, 29] Assuming continuous dynamical system (X, Ψ), if there exist two points A, B in the phase set such that successor function $g(A) > 0, g(B) < 0$, we can find a point C between A and B in the phase set satisfying $g(C) = 0$. So, there must exist an order-1 periodic solution passing through point C.*

Lemma 2.3. *[25] Let $\widehat{n_1n_2} \bigcup \overline{n_2n_1}$ denote order one circles, and assume the trajectory $\widehat{n_1n_2}$ is not tangent to the impulsive set M. The successor of point $l \in N$ is φ. The position between the points n_1, l, φ and the order-1 periodic solution is divided into three types:*

Type 1: the order one circle $\widehat{n_1n_2} \bigcup \overline{n_2n_1}$ is convex, and points l, φ are at the same side of $\widehat{n_1n_2}$ (see Figure 1 (a));

Type 2: the order one circle $\widehat{n_1n_2} \bigcup \overline{n_2n_1}$ is not convex, but points l, φ are at the same side of $\widehat{n_1n_2}$ (see Figure 1 (b));

Type 3: points l, φ are at the different sides of $\widehat{n_1n_2}$ (see Figure 1 (c)).

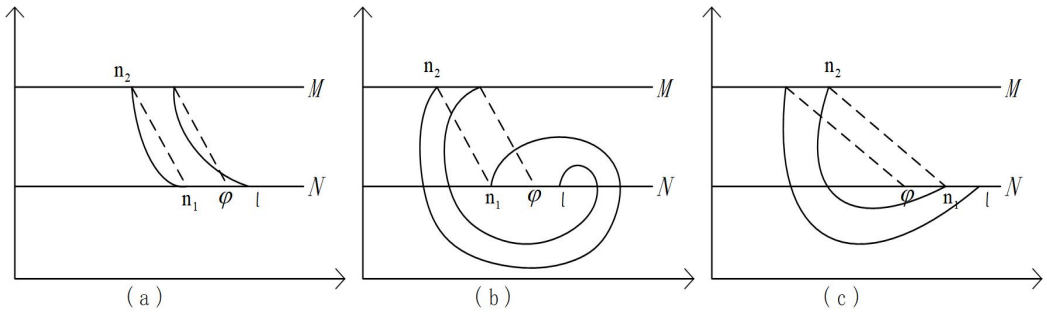

Figure 1. Three types of the order-1 periodic solution.

Theorem 2.1 *[25] If the periodic solution of the semi-continuous system is orbitally stable, it needs to satisfy*

$$\frac{\partial(P(x,y))}{\partial x} + \frac{\partial(Q(x,y))}{\partial y} < 0.$$

Theorem 2.2 *[25] If there is a convex solution with period T in the semi-continuous system, it is*

one-sided asymptotic, and the integral satisfies:

$$\int_0^T (\frac{\partial(P(x,y))}{\partial x} + \frac{\partial(Q(x,y))}{\partial y})dt < 0,$$

then the solution is orbitally stable.

3. Qualitative analysis of system (2.1)

In this section, we will consider the following system:

$$\begin{cases} \dfrac{dx}{dt} = (\alpha - ra - \beta(x+y))x + \delta y = P(x,y), \\ \dfrac{dy}{dt} = (\alpha - \beta(x+y))y - \delta y + rax = Q(x,y). \end{cases} \tag{3.1}$$

Theorem 3.1. System (3.1) is uniformly bounded.

Proof. First, the field (P, Q) of system (3.1) has the following form:

$$P(0,y) = \delta y, Q(x,0) = rax.$$

Obviously, $P(0,y) > 0$ for $y > 0$. On the positive x-axis, $Q(x,0) > 0$ means that the direction of the vector field is pointed from the negative semi-axis of y to its positive semi-axis.

Next, we take a straight line $k_1 : y - \dfrac{\alpha-\delta}{\beta} = 0$ and obtain $\dfrac{dk_1}{dt} = (-\beta y + ra)x = (-\alpha + ra + \delta)x < 0$, where $\alpha > ra + \delta$. Thus, the direction of the vector field of system (3.1) on k_1 is downward. Therefore, $y = \dfrac{\alpha-\delta}{\beta}$ is a straight line without a tangent, and the trajectory of the system (3.1) passes in a direction shown in Figure 2.

In the mean time, we define a function $k_2 : x - \dfrac{\alpha-\delta}{\beta} = 0$ and obtain $\dfrac{dk_2}{dt}|_{x=\frac{\alpha-\delta}{\beta}} = (\delta - ra)x + (\delta - \beta x)y < 0$, where $ra > \delta$. We can see that the direction of the vector field of system (3.1) on k_2 is oriented along the x-axis towards the negative semi-axis (see Figure 2). Hence, we can get the conclusion of the theorem. The proof is completed.

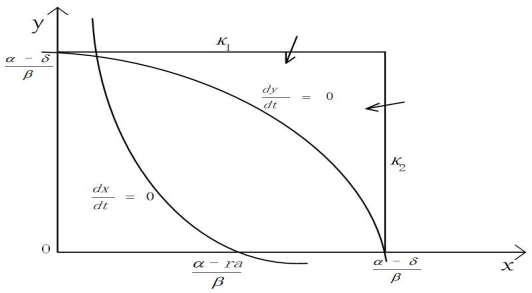

Figure 2. Boundedness of system (3.1).

We define

$$\begin{cases} (\alpha - ra - \beta(x+y))x + \delta y = 0, \\ (\alpha - \beta(x+y))y - \delta y + rax = 0, \end{cases} \tag{3.2}$$

and the system has two equilibria: one is boundary equilibrium $E_0(0,0)$, the other is positive equilibrium $E^*(x^*, y^*) = \left(\dfrac{\alpha\delta}{\beta(ra+\delta)}, \dfrac{ra\alpha}{\beta(ra+\delta)}\right)$.

We calculate the Jacobian matrix of system (3.1):

$$J(E(x,y)) = \begin{bmatrix} \alpha - ra - 2\beta x - \beta y & \delta - \beta x \\ -\beta y + ra & \alpha - \beta x - 2\beta y - \delta \end{bmatrix}.$$

Theorem 3.2. If $\alpha > \delta$, the boundary equilibrium $E_0(0,0)$ is unstable.

Proof. At the point $E_0(0,0)$, the Jacobian matrix is

$$J(E_0(0,0)) = \begin{bmatrix} \alpha - ra & \delta \\ ra & \alpha - \delta \end{bmatrix},$$

and the following eigenvalues are obtained:

$$\lambda_1 = \frac{(\alpha - ra)(\alpha - \delta) - \delta ra}{\alpha - \delta}, \lambda_2 = \alpha - \delta.$$

Obviously, $\lambda_1 > 0$ and $\lambda_2 > 0$ hold for $\alpha > \delta$. Therefore, we can obtain that $E_0(0,0)$ is unstable for $\alpha > \delta$, which shows that the sensitive and resistant bacteria cannot be completely exterminated for $\alpha > \delta$.

Theorem 3.3. The equilibrium $E^*(x^*, y^*)$ is globally asymptotically stable.

Proof. We need to determine the local asymptotical stability, and the Jacobian matrix is given as follows:

$$J(E^*(x^*,y^*)) = \begin{bmatrix} \alpha - ra - 2\beta x^* - \beta y^* & \delta - \beta x^* \\ -\beta y^* + ra & \alpha - \beta x^* - 2\beta y^* - \delta \end{bmatrix}.$$

$$\begin{aligned} det(J(E^*(x^*,y^*))) &= \begin{vmatrix} \alpha - ra - 2\beta x^* - \beta y^* & \delta - \beta x^* \\ -\beta y^* + ra & \alpha - \beta x^* - 2\beta y^* - \delta \end{vmatrix} \\ &= \alpha^2 - \alpha\delta - ra\alpha + (x^* + y^*)(2ra\beta + 2\delta\beta - \alpha\beta) \\ &= \alpha(\delta + ra) > 0, \end{aligned}$$

and

$$\begin{aligned} trace(J(E^*(x^*,y^*))) &= (\alpha - ra - 2\beta x^* - \beta y^*) + (\alpha - \beta x^* - 2\beta y^* - \delta) \\ &= -ra - \alpha - \delta < 0. \end{aligned}$$

Consequently, E^* is locally asymptotically stable in this case.

In the following, we construct the Dulac function $V(x,y) = \dfrac{1}{xy}$ and obtain

$$\frac{\partial(P(x,y)V(x,y))}{\partial x} + \frac{\partial(Q(x,y)V(x,y))}{\partial y} = -(\frac{\beta}{y} + \frac{\delta}{x^2} + \frac{\beta}{x} + \frac{ra}{y^2}) < 0,$$

which indicates that there is no limit cycle here. Hence, E^* is globally asymptotically stable.

4. The order-1 periodic solution

4.1. The existence and uniqueness of the solution

We define the impulsive set $M = \{(x, y) \in R_+^2 | x \geq 0, y_1 = h\}$ and the phase set $N = \{(x, y) \in R_+^2 | x \geq \tau h, y_2 = (1 - \tau)h\}$.

Theorem 4.1. When $h < y^*$, system (2.1) has a unique order-1 periodic solution.

Proof. From the impulsive set and phase set given above, we can obtain that point $E^*(x^*, y^*)$ must be above the sets M and N when $h < y^*$. If line $y = h$ intersects the isoclines $\frac{dx}{dt} = 0$ and $\frac{dy}{dt} = 0$ at point S^0 and S^1, the straight line $y = (1 - \tau)h$ intersects the y-axis and the isoclines $\frac{dx}{dt} = 0$ and $\frac{dy}{dt} = 0$ at points R^0, R^1 and R^2, respectively (see Figure 3(a)).

From the discussion in Section 3 and the vector field, we obtain that set S^0S^1 intersects trajectory $f(R^1, t)$ going through point $R^1(r^1, (1 - \tau)h)$ at point S^2. According to the impulsive effect, point S^2 is mapped into $R^3(r^3, (1 - \tau)h)$. From the property of the vector field, we can get $r^1 < r^3$. From Definition 2.2, point R^3 is the successor of point R^1 and satisfies

$$g(R^1) = r^3 - r^1 > 0.$$

In the same way, set S^0S^1 intersects trajectory $f(R^2, t)$ going through point $R^2(r^2, (1 - \tau)h)$ at point S^3. Point S^3 reaches the phase point $R^4(r^4, (1 - \tau)h)$. Thus, point R^4 is the successor point of point R^2. Thus, we can get $r^2 > r^4$ and

$$g(R^2) = r^4 - r^2 < 0.$$

According to Lemma 2.1, there must be a point W between R^1 and R^2. There exists a curve starting from W and intersecting the set S^0S^1. Suppose the curve intersects S^0S^1 at the point S^4, where the coordinates of the point W are denoted as $(m_1, (1 - \tau)h)$. S^4 jumps to point W^1, and the coordinates of W^1 are $(m_1, (1 - \tau)h)$. Thus, the points W and W^1 coincide on set N, and we get $g(W) = 0$. Referring to Lemma 2.2, there exists an order-1 periodic solution.

Then, we will prove the uniqueness of the above solution. First, we now choose any two points T, U in set R^1R^2. There are two points that must satisfy $x_{R^1} < x_T < x_U < x_{R^2}$. The trajectory from point T intersects at point T^1 with set S^0S^1. In the same way, the trajectory from point U intersects set S^0S^1 at point U^1 (see Figure 3(b)). Then

$$x(T^1) - x(T) = \int_{(1-\tau)h}^{h} \frac{dx}{dy} dy = \int_{(1-\tau)h}^{h} \frac{P(H_1, y)}{Q(x, y)} dy,$$

$$x(U^1) - x(U) = \int_{(1-\tau)h}^{h} \frac{dx}{dy} dy = \int_{(1-\tau)h}^{h} \frac{P(H_2, y)}{Q(x, y)} dy, \tag{4.1}$$

where H_1, H_2 represent the horizontal coordinates of T_1 and U_1 respectively. These two points should satisfy $H_1 < H_2$.

Thus,

$$\int_{(1-\tau)h}^{h} \frac{P(H_1, y)}{Q(x, y)} dy < \int_{(1-\tau)h}^{h} \frac{P(H_2, y)}{Q(x, y)} dy.$$

This is equivalent to $x(T^1) - x(T) < x(U^1) - x(U)$. From the definition of successor function, we get $g(T) = x(T_1) - x(T) = (x(T^1) + dy) - x(T)$ and $g(U) = x(U_1) - x(U) = (x(U^1) + dy) - x(U)$. For $x_T < x_U$,

$$g(T) - g(U) = (x(T^1) + dy) - x(T) - [(x(U^1) + dy) - x(U)] = [x(T^1) - x(T)] - [x(U^1) - x(U)] < 0,$$

and we have that the function g is monotonically decreasing in set R^1R^2. Therefore, there is only one point W satisfying $g(W) = 0$, and the order-1 periodic solution is unique from Lemma 2.2.

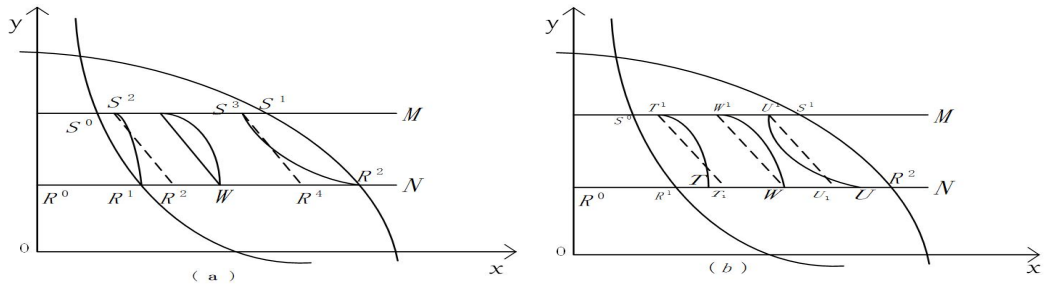

Figure 3. When $h < y^*$, (a) the existence of the order-1 periodic solution. (b) The uniqueness of the order-1 periodic solution.

4.2. Stability of the solution

To prove the stability of the order-1 periodic solution, we rewrite system (2.1) as follows:

$$\begin{cases} \left.\begin{aligned} \frac{dx}{dt} &= (\alpha - ra - \beta(x+y))x + \delta y = P(x,y), \\ \frac{dy}{dt} &= (\alpha - \beta(x+y))y - \delta y + rax = Q(x,y), \end{aligned}\right\} y < h, \\ \left.\begin{aligned} \Delta x &= x(t^+) - x(t^-) = \tau h, \\ \Delta y &= y(t^+) - y(t^-) = -\tau h, \end{aligned}\right\} y = h, \\ x(0) = x_0 \geq 0, \\ y(0) = y_0 \geq 0. \end{cases} \tag{4.2}$$

Theorem 4.2. When $h < y^*$, the order-1 periodic solution is orbitally asymptotically stable.

Proof. Obviously, we have already proved the existence and uniqueness of order-1 periodic solutions in Theorem 4.1. From Figure 2 and Theorem 4.1, we can get that the order-1 periodic solution is a convex-edge asymptotically stable type. Now, we use the Theorems 2.1 and 2.2 to prove the stability of the order-1 periodic solution.

Since

$$\frac{\partial(P(x,y))}{\partial x} + \frac{\partial(Q(x,y))}{\partial y} = 2\alpha - ra - \delta - 3\beta x - 3\beta y,$$

we cannot judge whether the above formula is positive or negative.

Then, we construct a continuously differentiable function: $V(x,y) = \frac{1}{xy}$. We have

$$\frac{\partial(P(x,y)V(x,y))}{\partial x} + \frac{\partial(Q(x,y)V(x,y))}{\partial y} = -(\frac{\beta}{y} + \frac{\delta}{x^2} + \frac{\beta}{x} + \frac{ra}{y^2}) < 0.$$

From Theorems 2.1 and 2.2, we obtain that the order-1 periodic solution is orbitally stable.

5. Numerical simulations

In this study, we formulate a mathematical model of a within-host drug resistance model with the impulsive state feedback control. We mainly consider the effect of antibiotics on the mutual transformation of both bacteria, and we fix the following parameters: $\alpha = 1$, $r = 0.1$, $\beta = 0.4$, $\delta = 0.4$, $h = 0.4$, and $\tau = 0.6$. Thus, we have the set $M = \{(x, y) \in R_+^2 | x \geq 0, y_1 = 0.4\}$ and set $N = \{(x, y) \in R_+^2 | x \geq 0.24, y_2 = 0.16\}$. We obtain the positive equilibrium $E^*(x^*, y^*) = (2.439, 0.061)$ for $a = 0.1$, which is simulated in Figure 4. With the increase of antibiotic concentration caused by the drug treatment, we get the equilibrium points $E^*(x^*, y^*) = (2.222, 0.277)$ and $E^*(x^*, y^*) = (1.818, 0.682)$ for $a = 0.5$ and $a = 1.5$, respectively, as presented in Figures 5 and 6.

At the beginning of antibiotic infusion, the concentrations of both susceptible and drug-resistant bacteria increase, and then the concentration of susceptible bacteria grows slowly and eventually stabilizes. At this time, the rate of conversion of susceptible to drug-resistant bacteria gradually decreases compared to the conversion rate of drug-resistant to susceptible bacteria (which means that rax is gradually smaller than δy), resulting in a decreasing trend in the concentration of drug-resistant bacteria, which finally tends to a stable state (Figure 4). From the comparison of Figures 4–6, it is concluded that when a is small enough, the concentration of susceptible bacteria is the highest, and the concentration of drug-resistant bacteria decreases to a very small concentration after increasing, which is one of the most desirable situations. When a increases to 0.5, there is a decrease in the concentration of the drug-resistant bacteria, but the concentration of drug-resistant bacteria is still within the critical threshold value. However, as the concentration of antibiotics increases (see Figure 6), the concentration of drug-resistant bacteria increases sharply and then stops decreasing, and the concentration exceeds the threshold range that the body can tolerate. This means that the infusion of excessive antibiotics will accelerate the growth of drug-resistant bacteria in the body and lead to an aggravation of the disease. In addition, we can also obtain that prolonged administration of the same drug can lead to an increase in antibiotics by comparing the equilibrium points at different drug concentrations, which can lead to a decrease in susceptible bacteria and an increase in drug-resistant bacteria.

As can be seen in Figure 6, continuous infusion of antibiotics into the body will result in very high concentrations of drug-resistant bacteria that exceed the critical threshold value. As a result, the model fails to effectively treat the disease if only continuous infusion of antibiotics is considered. Thus, it is necessary to implement the impulsive infusion to control the concentration of drug-resistant bacteria below the critical threshold value. Theorem 4.1 shows that an antibiotic delivery strategy is adopted when the concentration of drug-resistant bacteria exceeds the critical threshold value, followed by an oscillation of the level of drug-resistant bacteria in the host in an interval below the threshold and a stabilization of the concentration of sensitive and drug-resistant bacteria, which is simulated in Figure 7.

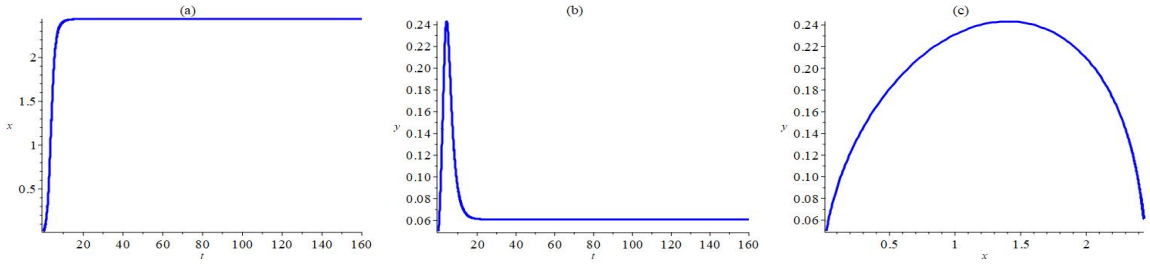

Figure 4. Time series and phase portrait of system (3.1) with $\alpha = 1, r = 0.1, \beta = 0.4, \delta = 0.4$ and $a = 0.1$.

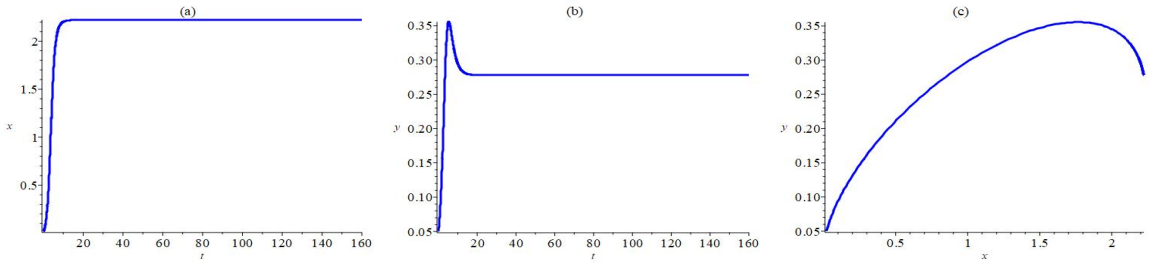

Figure 5. Time series and phase portrait of system (3.1) with $\alpha = 1, r = 0.1, \beta = 0.4, \delta = 0.4$ and $a = 0.5$.

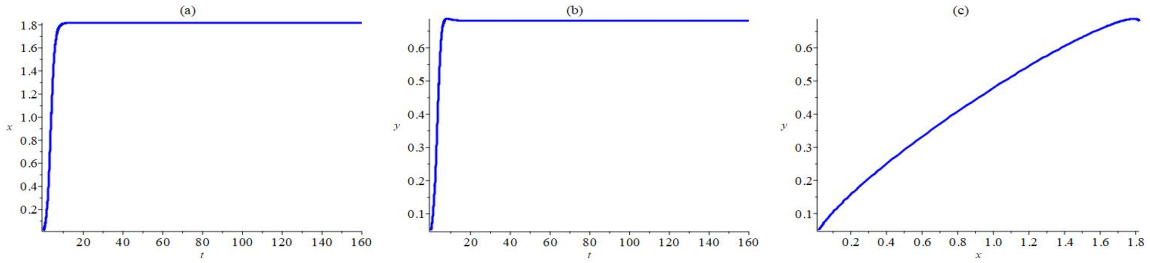

Figure 6. Time series and phase portrait of system (3.1) with $\alpha = 1, r = 0.1, \beta = 0.4, \delta = 0.4$ and $a = 1.5$.

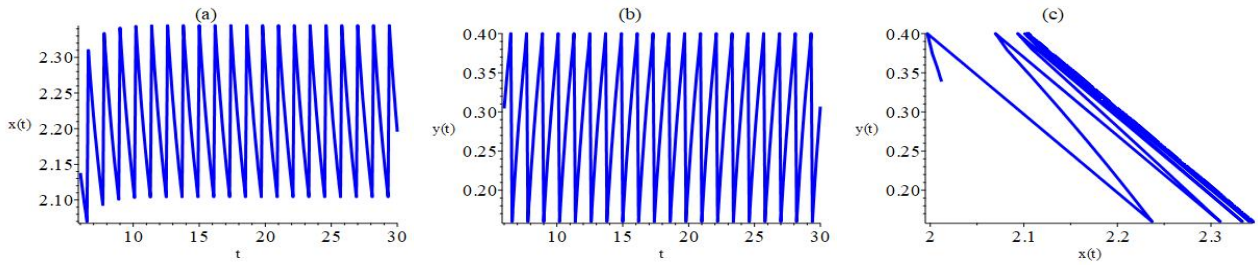

Figure 7. Time series and phase portrait of system (2.1) with $\alpha = 1, r = 0.1, \beta = 0.4, \delta = 0.4, \tau = 0.6, h = 0.4$ and $a = 1.5, E^*(1.818, 0.628)$, when $h < y^*$.

6. Conclusions

The reasonable use of antibiotics can effectively cure the disease so that bacteria are quickly cleared away. However, excessive or unreasonable use can lead to the conversion of susceptible bacteria into drug-resistant bacteria, which will not alleviate the pain of the patient but make it more severe. The long-term threat of disease exacerbated by antibiotics has reminded people to use them scientifically and reasonably. Thus, it is crucial to identify the effective methods for reducing the conversion of susceptible to resistant bacteria in the treatment of disease.

The above numerical simulations are given to compare the effects of antibiotic infusion with continuous and impulsive drug treatment. It is shown that the concentration of resistant bacteria of the model with impulsive feedback control will tend to an order-1 periodic solution. When the concentration of drug-resistant bacteria reaches a critical threshold, the concentration of drug-resistant bacteria can be controlled between 0.1 and 0.4 by means of drug infusion, so that the dynamic balance of bacterial populations in the host can be maintained, and disease progression can be effectively stopped.

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Conflict of interest

The authors declare that they have no conflict of interest in the manuscript.

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