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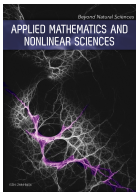

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A mathematical model of plasmid-carried antibiotic resistance transmission in two types of cells

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Abstract

Antibiotic resistance is a significant public health problem. When resistance genes are being carried on plasmids, the spread can be greatly accelerated. In this paper, the transmission of antibiotic resistance in two types of cells is discussed. A mathematical model is established to describe the dynamics of the transmission of plasmids. The effects of different parameters on the stable solution and sensitivity analysis are studied by numerical simulation. The conclusions show that the concentration of antibiotics must reach a certain level to kill the pathogenic bacteria. If the concentration of antibiotics is not high to a certain extent, the treatment becomes ineffective. If the cost of cells carried on plasmids and the rate of resistance plasmids segregation too high, the drug-resistant cells will gradually die out in the system. The rate of horizontal transfer of resistance plasmids is directly related to the spread of drug resistance. With the increase in the horizontal transfer rate of resistance plasmids, cells in the body gradually turn into cells with antibiotic resistance, which causes substantial difficulties in the treatment of diseases.

Keywords: antibiotic resistance, plasmids, horizontal gene transfer

1 Introduction

With the development of modern medical technology, a large number of antibiotics have been developed to kill microorganisms that pose a threat to human health. However, the misuse of antibiotics has led to widespread antibiotic resistance, which is now a significant public issue [1]. Antibiotic resistance, also known as drug resistance, refers to the resistance of microorganisms, parasites and tumour cells to the effects of chemotherapy antibiotics [2, 3]. Antibiotic resistance can be divided into two types: acquired antibiotic resistance and natural antibiotic resistance. Pathogens in nature, such as a strain of bacteria, can also have natural resistance, regardless of increasing doses of the antibiotic [4]. Acquired resistance occurs due to specific changes in the DNA

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(mutation) or through contact with external sources such as plasmids, transposons or integrons [5]. At present, acquired drug resistance is considered as the main cause for the prevalence of antibiotic resistant. Bacterial cells are capable of transferring genes horizontally. When resistance genes are mobile, being carried on plasmids or phages, their spread can be greatly accelerated [6,7]. A plasmid is a small piece of extra-chromosomal DNA that may be easily transferred between bacteria via horizontal gene transfer and, in particular, has been implicated in the acquisition of antibiotic resistance genes to many antibiotics [8]. In this paper, we investigate the problem of cell-to-cell transmission of antibiotic resistance caused by plasmids carrying resistance genes.

When antibiotics are applied for a long time, the majority of the sensitive bacteria are killed continuously, and the antibiotic resistant bacteria will keep multiplying in large numbers, so that the resistance rate of the bacteria to the antibiotic keeps rising [2]. The experiments show that the use of antibiotics will promote the transmission of plasmids in the colonies [9]. In fact, the concentration of antibiotics in the environment is not static, but changes continuously during the absorption. We analyse the effect of the drug concentration in the numerical simulation section. The speed at which the bacteria gets wiped out depends on the duration of administration of the antibiotic [10]. Researchers find that the optimal dosing does not necessarily correspond to the continuous administration of the antibiotics [11].

A mathematical model that describes the population dynamics of bacteria exposed to multiple antibiotics simultaneously is formulated [12], assuming the acquisition of resistance is through mutations from antibiotics exposure. In general, the specific mutations that confer resistance to antibiotic control have a cost, which may manifest as a reduction in reproductive capacity or the ability to compete. In the absence of medications, the infection rate of resistant bacteria is less or equal than the infection rate of sensitive bacteria; nevertheless, the population of resistant bacteria could increase to far exceed the population of sensitive bacteria under treatment [13]. Under the condition of decreasing drug concentration, the development of antibiotic resistance may be reversible [14]. This has implications for the management of antibiotic resistance, which can not only be managed by reducing the development of resistance, but also requires the restoring of existing resistance.

Assuming that drug resistance is acquired through mutations and plasmids transmission, a deterministic model for the population dynamics of sensitive and resistant bacteria to multiple bactericidal and bacteriostatic antibiotics is formulated and analysed [15]. Svara and Rankin [16] established an ordinary differential equation model to investigate the dynamics of plasmid-carried antibiotic resistance. By numerical simulations, it is shown that the transmission of plasmids is the key factor influencing plasmid-borne antibiotic resistance, and the dosage of antibiotic and the interval between treatments are also important. By employing qualitative analysis of ordinary differential equations, Xu et al. [17] investigate the collective resistance of the bacteria population with resistant horizontal gene transfer under sublethal bactericide pressure. The results show that the possible mechanism of variations in antibiotic susceptibility is the dominance of different bacterial genotypes under sublethal bactericide pressure, rather than persistence, tolerance or resistance. As a matter of fact, this can be seen as one of the innate characteristics of interaction between bacteria and bactericides.

In a systematic review, Quentin et al. [18] searched for mathematical modelling studies that focus on horizontal transfer of antimicrobial resistance (AMR) genes. Their findings highlight the existence of a research gap in the dynamics of transformation and transduction, and the overall public health implications of the horizontal transfer of AMR genes.

Because horizontal transfer of plasmids is an important mechanism, whereby resistance is spread through bacterial populations, we develop a mathematical model to describe this process quantitatively, using it to optimise antimicrobial dosage regimens to minimise resistance development. The transmission of antibiotic resistant plasmids in the co-existing environment of two types of bacteria is discussed in this paper.

2 Basic model

In this article, we assume that cells are divided into normal cells and pathogenic bacteria. In the mathematical model we established, the letter ‘a’ represents normal cells and the letter ‘b’ represents pathogenic bacteria. We

assume that when antibiotics are used, they only kill the pathogenic bacteria and have no effect on normal cells.

To simplify the model, we assume as follows:

1. The density-dependent death rates of the two types of cells are equal, and is given by. It means that whether a cell is antibiotic resistant or not has no effect on its natural growth rate or density-dependent death rate.

2. We assume an antibiotic-induced fitness cost, that is, antibiotics can have two effects on a cell: they can either kill the bacteria or they can prevent their reproduction.

3. To keep our model simple, we assume that genes for resistance against antibiotics are carried by a plasmid rather than by the chromosome.

4. Due to the absence of resistance genes, the plasmid-free types of pathogenic bacteria are more sensitive to antibiotics. Mathematically, it is reasonable to assume that.

5. Details of parameters used in our model are given in Table 1.

Table 1 Model variables and parameters

Variable and Parameter	Description
a_S	Density of plasmid-free type of normal cells
a_I	Density of normal cells infected with a resistance-carrying plasmid
b_S	Density of plasmid-free type of pathogenic bacteria
b_I	Density of pathogenic bacteria infected with a resistance-carrying plasmid
r	Intrinsic per-capita growth rate of cells
α	Extrinsic density-dependent death rate of cells
N	Total density of cells $N = a_S + a_I + b_S + b_I$
β_a	Rate of horizontal transfer of resistance plasmid from infected normal cells
β_b	Rate of horizontal transfer of resistance plasmid from infected pathogenic bacteria
k_a	Rate of the resistance plasmid segregation from normal cells
k_b	Rate of the resistance plasmid segregation from pathogenic bacteria
k_b	Rate of the resistance plasmid segregation from pathogenic bacteria
c_a	Cost of infected normal cells carried on plasmid
c_b	Cost of antibiotic resistance when pathogenic bacteria is carried on resistance plasmid
A	Concentration of antibiotic
m_S	Death rate of plasmid-free type of pathogenic bacteria due to antibiotics
m_I	Death rate of pathogenic bacteria with resistance-carrying plasmid due to antibiotics

Assuming logistic growth, with a growth rate of r, the dynamics of normal cells and pathogenic bacteria now become:

$$\begin{cases} \frac{da_s}{dt} = ra_s - \alpha a_s N - \beta_a a_s a_I - \beta_b a_s b_I + k_a a_I \\ \frac{da_I}{dt} = (r - c_a)a_I - \alpha a_I N + \beta_a a_s a_I + \beta_b a_s b_I - k_a a_I \\ \frac{db_s}{dt} = (r - m_s A)b_s - \alpha b_s N - \beta_a b_s a_I - \beta_b b_s b_I + k_b b_I \\ \frac{db_I}{dt} = (r - c_b - m_I A)b_I - \alpha b_I N + \beta_a b_s a_I + \beta_b b_s b_I - k_b b_I \end{cases} \tag{1}$$

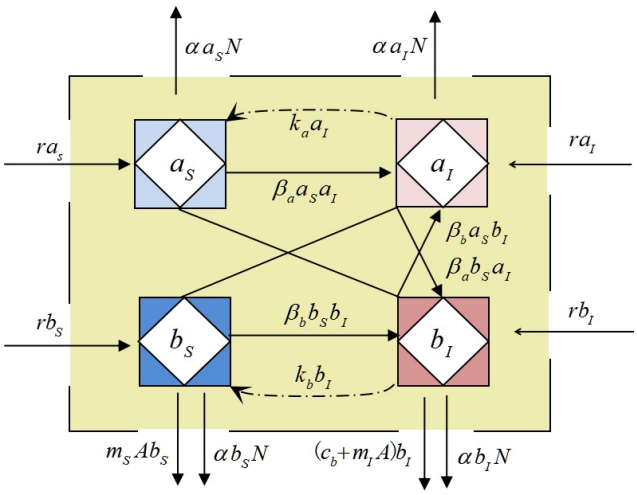


Fig. 1 Plasmid-carried antibiotic resistance transmission in two types of cells

3 Mathematical results and biological interpretation

3.1 Some theoretical results

For the sake of simplicity, let $\beta_a = \beta_b = \beta$, $k_a = k_b = k$, then the detailed analysis of the dynamic behaviours of system (1) is shown in supplemental documents. The main mathematical results are as follows: system (1) has six possible equilibria, including five boundary equilibria and a unique positive equilibrium. The conditions for all five boundary equilibria are given in Table 2.

Table 2 Boundary equilibria and conditions

Boundary equilibria	Conditions
$E_0(a_I = 0, a_S = 0, b_I = 0, b_S = 0)$	Always exist
$E_{as}(a_I = 0, a_S = \frac{r}{\alpha}, b_I = 0, b_S = 0)$	Always exist
$E_{bs}(a_I = 0, a_S = 0, b_I = 0, b_S = \frac{r - m_S A}{\alpha})$	$r > m_S A$
$E_a(a_I = a_I^+, a_S = a_S^+, b_I = 0, b_S = 0)$	It is too complicated to express
$E_b(a_I = 0, a_S = 0, b_I = b_I^+, b_S = b_S^+)$	It is too complicated to express

The boundary equilibria are analysed using stability theory. Through analysis, we can draw the following conclusions.

Theorem 1. *E_0 is always stable.*

Theorem 2. *When $\frac{\beta a_s}{\alpha a_s + k - r + c_a} < 1$, E_{as} is locally asymptotically stable.*

Theorem 3. *When $\frac{\beta b_s}{\alpha b_s + k - r + c_b + m_I A} < 1$, E_{bs} is locally asymptotically stable.*

3.2 Proof

The proofs of Theorems 1–3 are as follows.

$$\mathrm{F} = \begin{pmatrix} F_1 \\ F_2 \\ F_3 \\ F_4 \end{pmatrix} = \begin{pmatrix} \beta a_S a_I + \beta a_S b_I \\ \beta b_S a_I + \beta b_S b_I \\ 0 \\ 0 \end{pmatrix}$$

$$\text{And } v = V^- - V^+ = \begin{pmatrix} V_1 \\ V_2 \\ V_3 \\ V_4 \end{pmatrix} = \begin{pmatrix} \alpha a_I N + k a_I - (r - c_a) a_I \\ \alpha b_I N + k b_I - (r - c_b - m_I A) b_I \\ \alpha a_S N + \beta a_S a_I + \beta a_S b_I - r a_S - k a_I \\ \alpha b_S N + \beta b_S a_I + \beta b_S b_I - (r - m_S A) b_S - k b_I \end{pmatrix}$$

Then

$$F = \begin{pmatrix} \frac{\partial F_1}{\partial a_I} & \frac{\partial F_1}{\partial b_I} \\ \frac{\partial F_2}{\partial a_I} & \frac{\partial F_2}{\partial b_I} \end{pmatrix} = \begin{pmatrix} \beta a_S & \beta a_S \\ \beta b_S & \beta b_S \end{pmatrix}$$

Similarly,

$$V = \begin{pmatrix} \alpha N + \alpha a_I + k - r + c_a & a_I \\ b_I & \alpha N + \alpha b_I + k - r + c_a + m_I A \end{pmatrix}$$

1. For E_0, the

$$F = \begin{pmatrix} 0 & 0 \\ 0 & 0 \end{pmatrix}, \quad V = \begin{pmatrix} k - r + c_a & 0 \\ 0 & k - r + c_b + m_I A \end{pmatrix},$$

which implies that the spectral radius of the matrix FV^{-1} is

$$\rho = 0.$$

Meaning: E_0 is always stable.

2. For E_{as}, the

$$F = \begin{pmatrix} \beta a_S & \beta a_S \\ 0 & 0 \end{pmatrix}, \quad V = \begin{pmatrix} \alpha a_S + k - r + c_a & 0 \\ 0 & \alpha a_S + k - r + c_b + m_I A \end{pmatrix},$$

which implies that the spectral radius of the matrix FV^{-1} is

$$\rho = \max\left\{0, \frac{\beta a_s}{\alpha a_s + k - r + c_a}\right\}.$$

When $\frac{\beta a_s}{\alpha a_s + k - r + c_a} < 1$, E_{as} is locally asymptotically stable.

3. For E_{bs}, the

$$F = \begin{pmatrix} 0 & 0 \\ \beta b_S & \beta b_S \end{pmatrix}, \quad V = \begin{pmatrix} \alpha b_S + k - r + c_a & 0 \\ 0 & \alpha b_S + k - r + c_b + m_I A \end{pmatrix},$$

which implies that the spectral radius of the matrix FV^{-1} is

$$\rho = \max\left\{0, \frac{\beta b_S}{\alpha b_S + k - r + c_b + m_I A}\right\}.$$

When $\frac{\beta b_s}{\alpha b_s + k - r + c_a + m_I A} < 1$, E_{bs} is locally asymptotically stable.

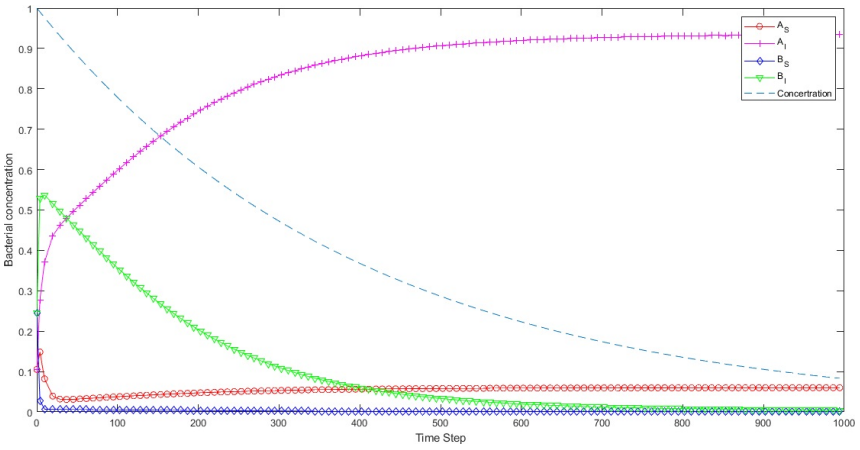
4 Numerical analysis

We built numerical simulations to investigate how parameters affect the variation of system (1). To attain a more realistic model, we assume that the antibiotic degrade at an exponential rate [19]:

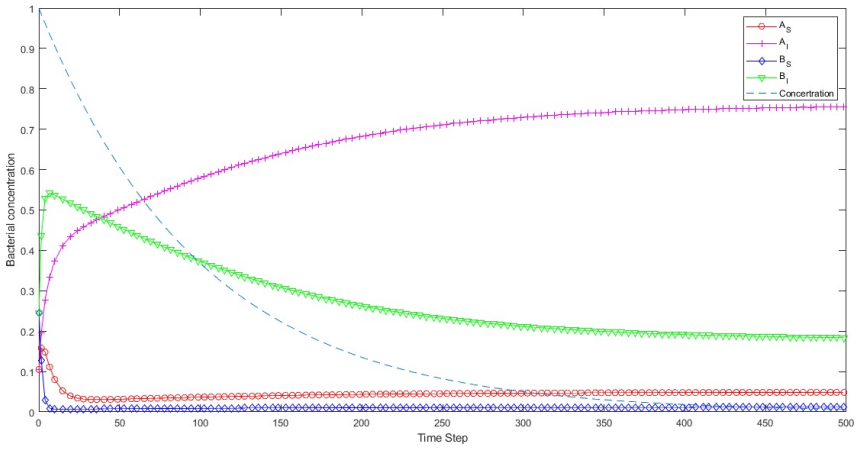
$$\frac{dA}{dt} = -lA \tag{2}$$

4.1 The role of dosage concentration

When using an antibiotic to treat the disease caused by pathogenic bacteria, the concentration of the drug must reach a certain level; otherwise, it cannot kill the pathogenic bacteria. In other words, if the concentration of the antibiotic is not high to some extent, it becomes ineffective at treating the disease. The drug concentration over time is marked by a blue dotted curve in each figure for clearer emphasis. The four other lines show the density variations of cells. As we know from Eq. (2), this means that the smaller the l is, the higher the concentration of antibiotics will be. In Figure 2, the concentration of antibiotics in Figure 2(a) is higher than that in Figure 2(b); the pathogenic bacteria are extinct in Figure 2(a) but still exist in Figure 2(b).



(a) $l = 0.05$



(b) $l = 0.1$

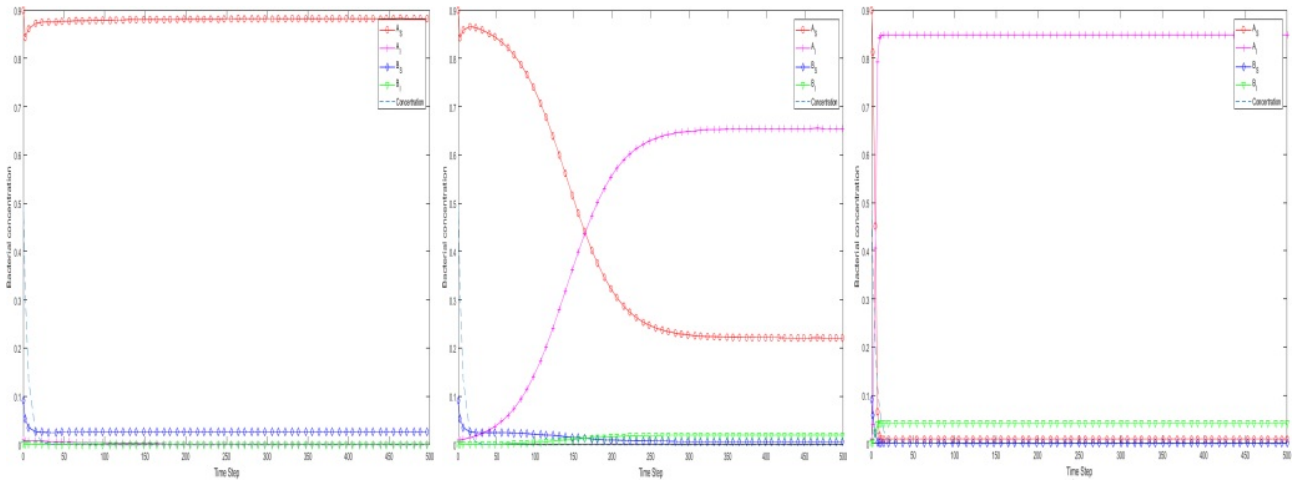
Fig. 2 The effect of antibiotic concentration

Here, the plots are calculated by running the simulation for a number of parameter values for over 500 time steps. Parameters used are: $r = 2$, $\alpha = 0.7$, $\beta = 0.06$, $k = 0.01$, $m_s = 0.7$, $m_i = 0.0001$.

4.2 The role of transmission rate β

With the increase of β, the number of cells infected with resistance-carrying plasmids increases; finally, only the cells infected with resistance-carrying plasmids exist in the system. The red curve shows the variation of a_s, which represents the density of normal cell without drug resistant plasmids. As can be seen from Figure 3, as the value of β increases, a_s decreases continuously, eventually dying out in the system. The biological

significance of this is that with the enhancement of the spread of drug resistance, the number of cells infected with resistance-carrying plasmids in the system keeps increasing until the susceptible cells in the system are transformed into drug-resistant cells.

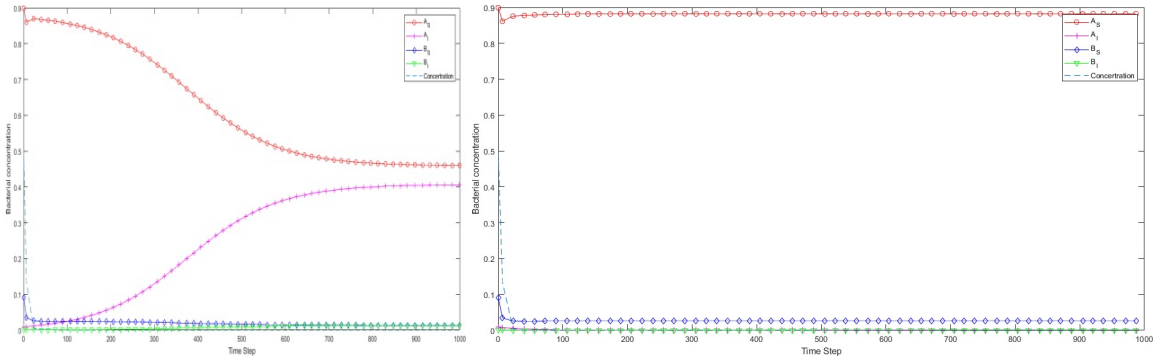


(a) $\beta = 0.01$ (b) $\beta = 0.05$ (c) $\beta = 0.5$

Fig. 3 The effect of transmission rate

4.3 The role of cost parameter c

As for the parameter of cost, when cells are carrying plasmids, the corresponding number of cells infected with resistance-carrying plasmids decreases with the increase of cost value. In Figure 4(a), when $c_a = c_b = 0.04$, cells carried on plasmids still exist in the system, which are distinct when $c_a = c_b = 0.07$. This means that if the cost of cells carried on plasmid is too high, the drug-resistant cells will gradually die out in the system.

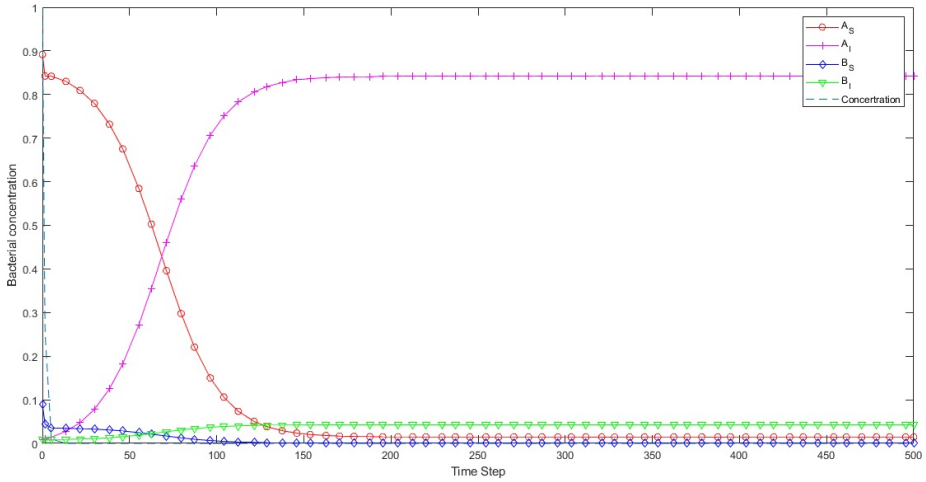


(a) $c_a = c_b = 0.04$ (b) $c_a = c_b = 0.07$

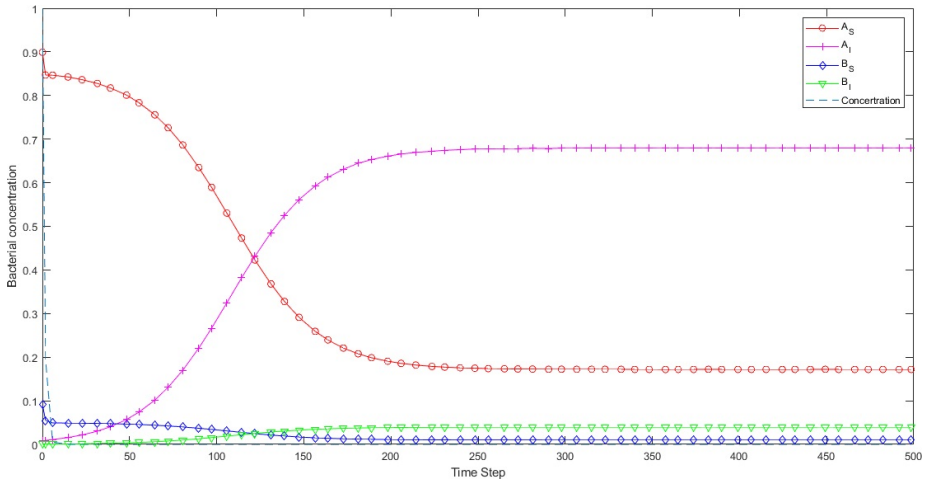
Fig. 4 The effect of cost parameter

4.4 The role of parameters of segregation rate k

Figure 5 shows the role of parameters involved in the segregation rate of plasmids. We can see from Figure 5 that the ability of resistance-carried plasmids to spread is reduced with the increasing segregation rate value k. The density of plasmid-free type of normal cells is higher in Figure 5(b) than in Figure 5(a).



(a) $k_a = k_b = 0.001$



(b) $k_a = k_b = 0.01$

Fig. 5 The effect of segregation rate

5 Sensitivity analysis

The goals of sensitivity analysis with respect to random perturbations of the model parameters is as follows:

- To show how robust the simplified uncomplicated bacteria resistance model is in relation to perturbed parameter values.
- To explore which parameters the system is more sensitive to understand the key process and bacteria resistance system mechanisms.

5.1 The sensitivity of drug degradation rates

The sensitivity of drug degradation rates is considered in this section. Figure 6 shows the effect of drug degradation rates on the population of bacteria. The values of l are 0.1, 0.3, 0.5 and 0.7, respectively, while other parameters remain unchanged. There are four small pictures in Figure 6, each of which represents the changes of a type of bacteria. In the small figure, the four curves represent the variation of one type of bacteria when l takes different values, respectively. The smaller the value is, the smaller the drug attenuation rate will be, which means the drug acts longer in the environment. The horizontal axis represents drug concentration,

so the curve from right to left shows the attenuation of drug concentration with time. In the four pictures, the curves of same colour represent the change in the proportion of bacteria under the same set of parameters. As we can see from the Figure 6, the number of drug-resistant pathogens decreases with time and remains controlled only when $l = 0.1$. Under the other three groups of parameters, although the susceptible pathogens are controlled, the proportion of drug-resistant pathogens increases, and the treatment is ineffective. Therefore, treatment effectiveness is improved by increasing the duration of the drug, which means that the sustained-release tablets are more effective in killing drug-resistant pathogens.

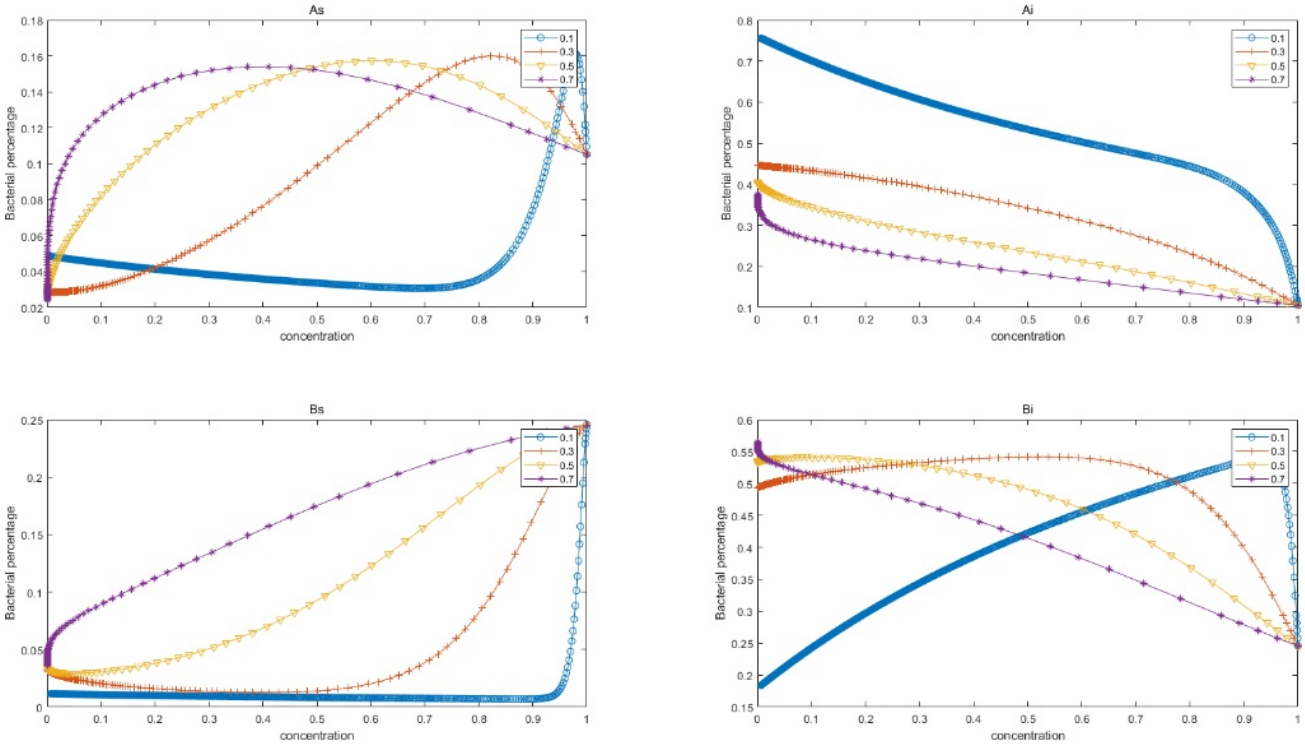


Fig. 6 The sensitivity of degradation rate

5.2 The sensitivity of transmission rate

The sensitivity of the parameter β_b is considered in this section. The Figure 7 shows the effect of the plasmid transfer rate from flora B to A. The values of parameter β_b are 0, 0.3, 0.5 and 0.7, respectively, with the other parameters remaining unchanged. The four curves represent the variations of population when β_b is taken in different values, among which, the transfer rate of the plasmid from pathogenic bacteria to normal cells is smaller for smaller values of β_b, meaning that it is difficult for the plasmid to transfer. The horizontal axis represents drug concentration, so the curve from right to left shows the attenuation of drug concentration with time. In the four pictures, the curves of same colour represents the change in the proportion of bacteria under the same set of parameters. As can be seen from the figure above, β_b has no effect on the variation trend of the four populations, but only affects the final numerical state.

5.3 The sensitivity of cost parameter

The sensitivity of the parameter c_b is considered in this part. Figure 8 shows the cost of bacteria when they are carrying on plasmids. The values of parameter c_b are 0, 0.3, 0.5 and 0.7, respectively, with the other parameters remaining unchanged. There are four small pictures in Figure 8, each of which represents the changes of a type of bacteria. In the small figure, the four curves represent the variation of one type of bacteria when c_b

takes on different values, respectively. The cost of bacteria carrying on plasmid is smaller for smaller values of c_b. The horizontal axis represents drug concentration, so the curve from right to left shows the attenuation of

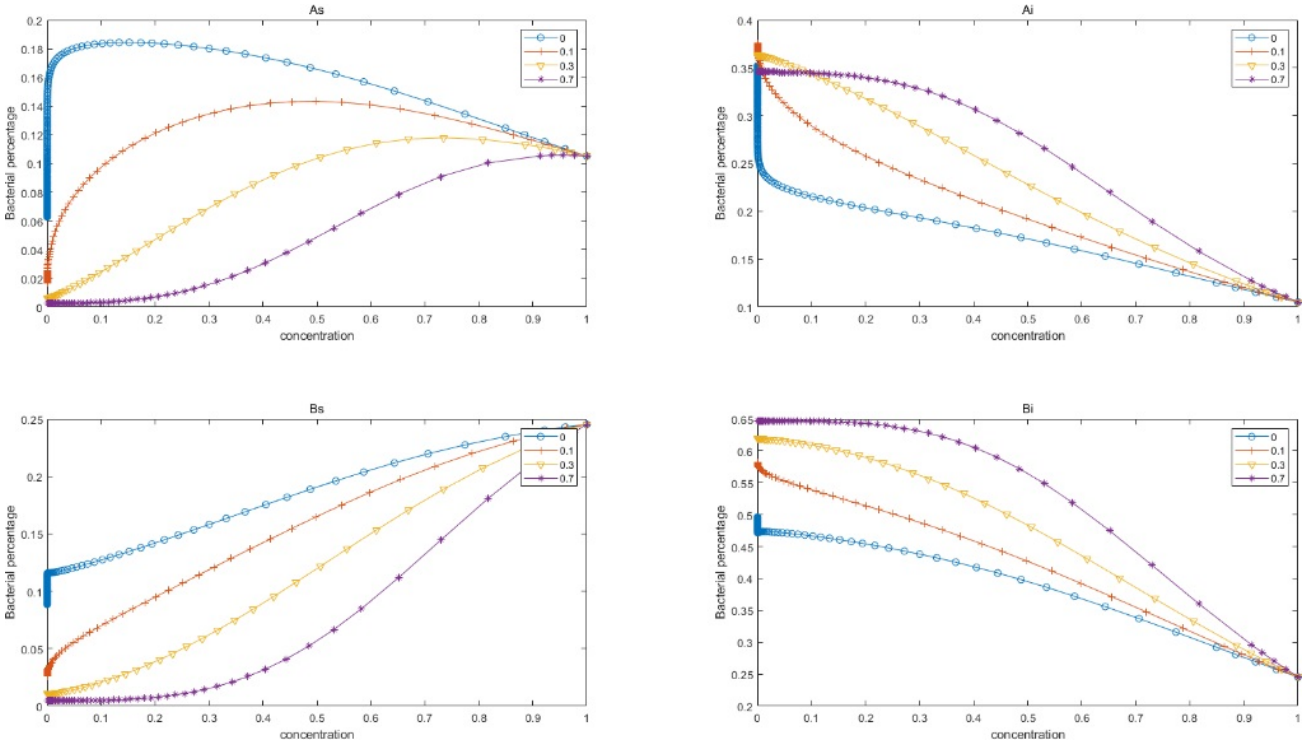


Fig. 7 The sensitivity of transmission rate

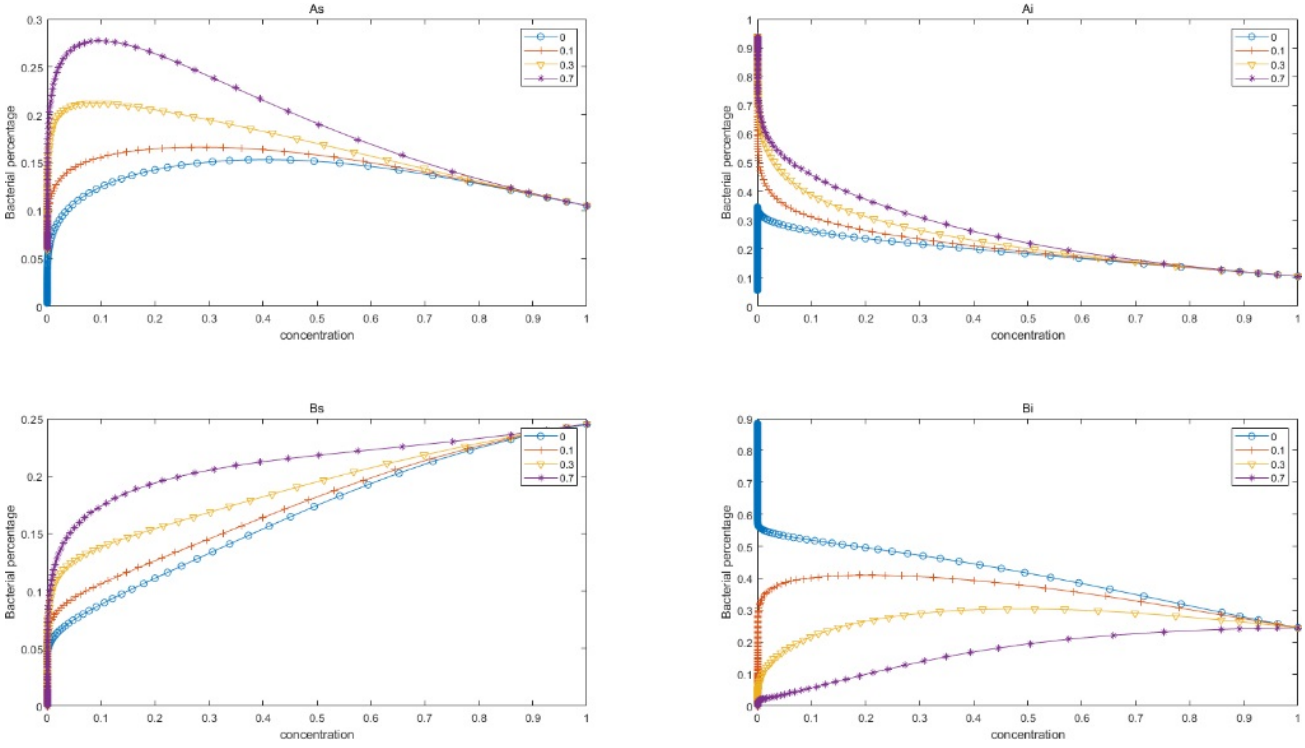


Fig. 8 The sensitivity of cost parameter c_b

drug concentration with time. In the four pictures above, the curves of same colour represents the change in the proportion of bacteria under the same set of parameters. As can be seen from Figure 8, when $c_b = 0.1, 0.3, 0.7$, the number of drug-resistant pathogens decreases over time and is controlled. When $c_b = 0$, the proportion of drug-resistant pathogens increases, and the treatment becomes ineffective.

5.4 The sensitivity of segregation rate

The sensitivity of segregation rate k is considered in this part. In Figure 9, the influence of k on the population of cells is investigated. The values of k are 0, 0.3, 0.5 and 0.7, respectively, with the other parameters remaining unchanged. The four curves in each small picture represent the changes in the population at different values of k. Where, the smaller the k value is, the smaller the plasmid segregation rate of the corresponding flora is, meaning that it is not easy for the plasmids to disappear. The horizontal axis represents the concentration of the drug, so the curve from right to left shows the decline of the concentration of the drug over time.

In Figures 9 and 10, curves of the same colour show the variations of the proportion of the bacteria under the same set of parameters. As we can see from the figures, the effect of k on the system is relatively complex. First of all, the influence of k on the same species of cells (such as k_a on normal cells) is greater than that that on the heterogeneous bacteria (such as k_a on pathogenic bacteria). For example, different values of k_a can significantly change the final value of normal cells, but have little influence on pathogenic bacteria. This is mainly due to the competitive relationship among the species, and the population of cells in a limited environment fluctuates from one to the other. Second, a higher plasmid segregation rate will lead to a lower ability of the plasmid to transfer from one flora to another, which is not conducive to the formation of antibiotic resistant pathogenic bacteria.

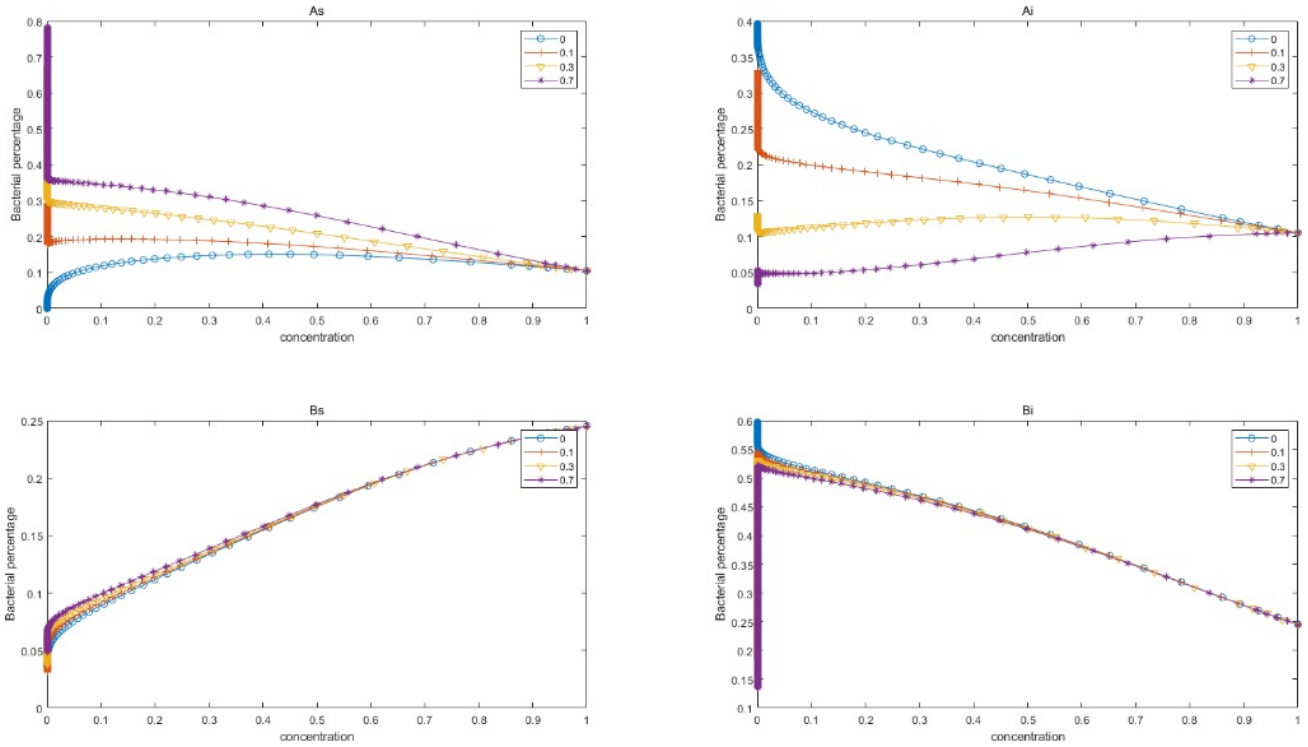


Fig. 9 The sensitivity of segregation rate k_a

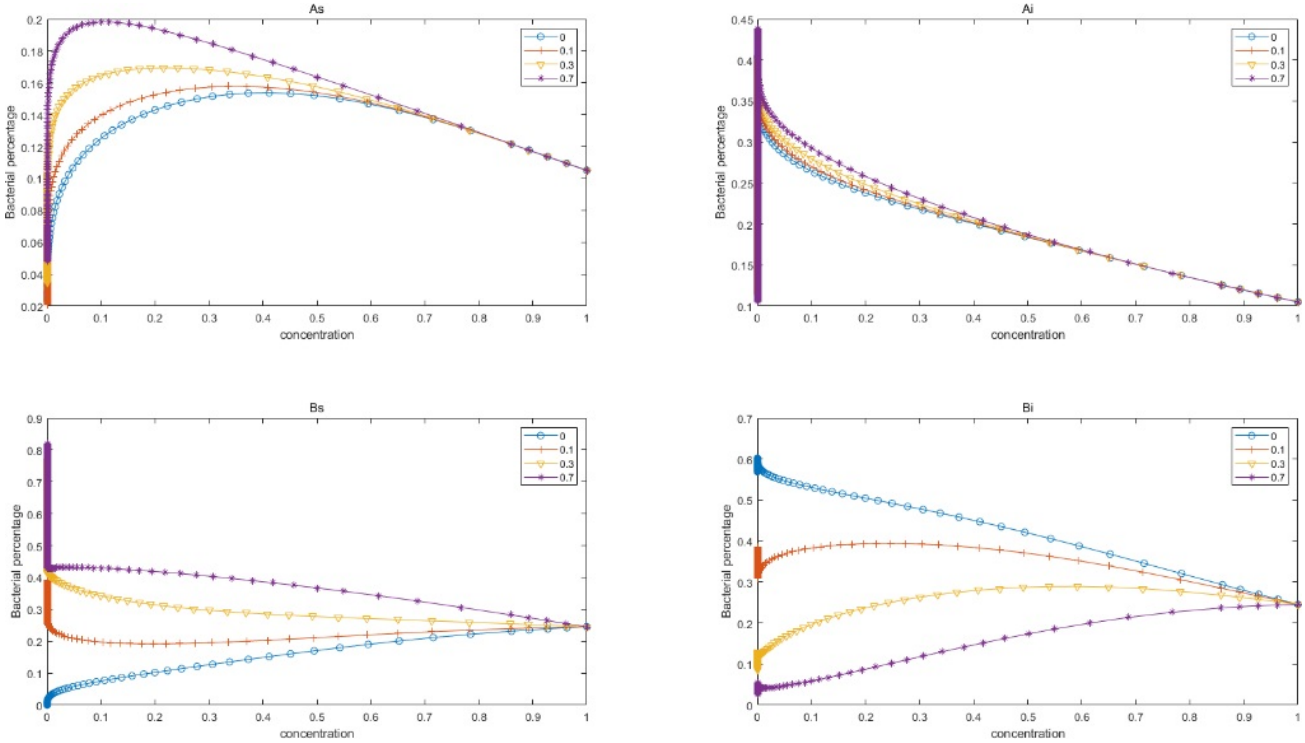


Fig. 10 The sensitivity of segregation rate k_b

6 Conclusion

It is shown that the concentration of antibiotic drugs must reach a certain level to kill the pathogenic bacteria. If the concentration of antibiotic is not high to some extent, it becomes an ineffective treatment. The rate of horizontal transfer of resistance plasmids is directly related to the spread of drug resistance. With the increase in the horizontal transfer of resistance plasmids, cells in the body gradually turn into cells with antibiotic resistance, which cause great difficulties in the treatment of diseases.

In addition, the risks associated with the development of antibiotic resistance in populations are often latent and undetectable. However, when people get sick, it will be much harder for them to heal because of antibiotic resistance. Therefore, the potential threat of drug resistance to people's health cannot be ignored.

Conflict of interest.
The authors declare that there is no conflict of interests regarding the publication of this paper.

Availability of Data and Material.
Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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Authors' Contributions.
Leilei Qu conceived and designed the study. Ziang Chen performed the simulation. Leilei Qu and Ziang Chen wrote the paper.

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