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Modeling the role of altruism of antibiotic-resistant bacteria

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Abstract Based on the new findings in a recent experimental study (Lee et al., Nature 467, 82–86, 2010) that antibiotic resistant mutants of bacteria produce indoles to protect the wild strain bacteria, we propose a mathematical model to describe the evolution of the wild strain, resistant strain and indoles with limited nutrient. We distinguish two cases: (i) mutation is negligible and a resistant strain preexists; (ii) mutation is not negligible. For (i), we establish conditions for co-persistence of both strains, which indicate that the wild strain can survive with the help from the altruistic resistant strain, whereas it dies out in the absence of such a benefit. This consolidates the experimental findings in Lee et al. (Nature 467:82–86 2010). Further analysis and simulations also reveal some new phenomena not reported in Lee et al. (Nature 467:82–86 2010), that is, periodic oscillations of the populations may occur within certain range of the parameters, and there exists bistability in the sense that a stable positive periodic solution coexists with a stable positive equilibrium.

Keywords Antibiotic · Resistance · Altruism · Coexistence · Oscillation · Bistability

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1 Introduction

The spread of antibiotic resistance has induced difficult and complex problems in the control of bacteria diseases, and hence, posed significant clinical and societal challenges. There have been many researches in identifying and understanding the factors and biological phenomena responsible for the emergence and spread of drug resistance (see, e.g., Bjedov et al. 2003; Bohannan and Lenski 2000; Cohen et al. 2003; Dye and Williams 2000; Katouli and Komarova 2011; Kohanski et al. 2010; Komarova and Wodarz 2005; Lee et al. 2010; Levy and Marshall 2004; Livermore 2003; Smith and Walker 1998; Smith and Romesberg 2007; Wang et al. 2001). At genetic and molecular level, selection of naturally occurring resistant mutants and horizontal transfer of resistance genes play the key roles in the production of resistance strains (Livermore 2003). Within a host, the dynamics of resistance mutations depend crucially on the competition with the strain of wild type, and the establishment of a resistance strain is determined by its advantages in fitness costs and benefits (Andersson and Hughes 2011; Levin et al. 1997; Read et al. 2011). At the population level, resistance strains are transmitted through the interactions of community and health-care facilities, contacts of human populations, and the agricultural use of antibacterial (zur Wiesch et al. 2011). Antibiotic treatment can facilitate the selection and spread of antibiotic resistance via different mechanisms including the modulation of outer membrane impermeability (Hu et al. 2011), the regulation of efflux pumps (Ma et al. 1993), the stimulation of the recombinogenic capability of treated bacteria (López et al. 2007), SOS response (Dörr et al. 2009), and inducing reactive oxygen species (Kohanski et al. 2010).

Mathematical modeling of antibiotic resistance has provided useful insights into the understanding of underlying phenomena and offered helpful guidance to related public health decisions (see, e.g., Bonhoeffer et al. 1997; Bootsma et al. 2006; Cohen and Murray 2004; Colijn et al. 2010; D′Agata et al. 2009; Leenheer et al. 2010; Levin 2001; Lipsitch et al. 2000; Sun et al. 2010; Webb et al. 2005, 2006 and the survey paper Opatowski et al. 2011). For example, by modeling within-host dynamics of antibiotic resistance, paper D′Agata et al. (2008) found that shorter lengths of antibiotic therapy and early treatment interruption may facilitate resistance selection. Integrating pharmacokinetic of antibiotic therapies and bacterial population dynamics, Lipsitch and Levin (1997) analyzed conditions under which high and infrequent doses of an antibiotic can succeed in preventing the emergence of resistance, and the conditions for the success of multiple drug treatment. With the aid of mathematical models, papers Kussell et al. (2005); Levin and Rozen (2006) elucidated influences of non-inherited resistance. At the population level, paper Austin et al. (1997) studied links of antibiotic consumptions with the invasion of antibiotic resistance, and paper Lipsitch et al. (2000) proposed a mathematical model to assess the control measures to prevent the dissemination of resistant strains in hospital. Furthermore, based upon mathematical models, paper Colijn et al. (2010) demonstrated that susceptible strain may coexist with resistance strain through a simultaneous dual transmissions or the stronger intra-competitions.

Failure of an antibiotic therapeutics is commonly attributed to massive mutation of the wild strain bacteria to antibiotic resistant strains. However, in a recent experimental study (Lee et al. 2010) on the mutation mechanisms of wild-type *E. coli* facing antibiotics, the authors found that the wild strain bacteria can also survive the antibiotics without mutating, as long as a small number of highly resistant bacteria are present. Lee et al. (2010) attributed the survival of the wild strain bacteria under antibiotics to an altruistic behavior of the resistant strain bacteria representing the kin selection. Indeed, they found that when a continuous culture of *E. coli* is stressed with quinolone norfloxacin, highly resistant mutants can produce extraordinary high level of indoles (a type of signal molecules). These indoles will turn on the drug efflux pumps and oxidative-stress, which can greatly enhance the survival of the wild strain bacteria. However, there is a fitness cost for the highly drug resistant mutants for producing indoles, which is evidenced by the lower population of the mutants in the experiments conducted in Lee et al. (2010).

In order to better understand the role of the altruistic behavior of the resistant bacteria observed in Lee et al. (2010), in this paper, we formulate a mathematical model to mimic the evolution of bacterial populations described in the experimental study of Lee et al. (2010). Since the bacteria of *E. coli* in the study of Lee et al. (2010) are grown in apparatus in laboratory and reside in gut in nature, it is natural to start with a model of chemostat type. Let S denote the concentration of nutrient, B_1 denote the concentration of the wild strain of bacteria, and B_2 denote the concentration of the antibiotic resistant mutants. In the absence of the altruistic behaviors of resistant mutants, the dynamics of nutrient, wild strain and resistant strain of bacteria can be described by (see, e.g., Hsu et al. 1977; Hsu and Waltman 2004; Smith and Waltman 1995)

$$\begin{cases} \frac{dS}{dt} = A - dS - \frac{\mu_1 S}{\gamma_1(m_1+S)} B_1 - \frac{\mu_2 S}{\gamma_2(m_2+S)} B_2, \\ \frac{dB_1}{dt} = (1-p)\frac{\mu_1 S}{m_1+S} B_1 - (d+\varepsilon_1) B_1, \\ \frac{dB_2}{dt} = \frac{\mu_2 S}{m_2+S} B_2 + p\frac{\mu_1 S}{m_1+S} B_1 - (d+\varepsilon_2) B_2, \end{cases} \tag{1.1}$$

where A is the recruitment rate of nutrient, d is the washout rate of nutrient and bacteria, m_i is the Michaelis–Menten constant, γ_i is the yield constant representing the conversion efficiency of nutrient to the biomass of the organism, μ_i accounts for the maximal growth rate, ε_1 is the death rate of wild bacteria due to antibiotic influences and ε_2 is the death rate of its mutants under the antibiotic stress, and p is the mutation probability of wild bacteria. Here the backward mutation from the resistant strain to the wild strain is neglected because there is no evidence in the experimental study of Lee et al. (2010) showing that such "back" mutations are significant; and in general, "back" mutations are much rarer than "forward" mutations, because the number of ways to inactivate one gene out of thousands/millions genes is much greater than the number of ways to correct a miscopied gene (Mutation rate in Gale Genetics Encyclopedia 2012). We also assume $\mu_2 < \mu_1$ to account for the cost of resistant strain, and assume $\varepsilon_2 < \varepsilon_1$ to reflect the benefit of antibiotic resistance.

Denote by C the concentration of the antibiotic and assume that it is a constant. Then, the killing rates to both wild and mutant strains of bacteria should be a non-

decreasing function of C. In light of Austin and Anderson (1999), Levin et al. (1997), and Torella et al. (2010), we take the following forms for $\varepsilon_i(C)$:

$$\varepsilon_i(C) = \frac{k_i C}{a_i + C}, \quad i = 1, 2. \tag{1.2}$$

Note that mutation is usually considered as the consequence of errors during the DNA replication process. Recent studies indicate that a mutation rate can increase by several orders of magnitude under antibiotic stress (Kepler and Perelson 1998; Kohanski et al. 2010; Nash 2001) and may attain its maximum at an intermediate drug concentration level (Nash 2001). This means that the mutation may be adapted by the antibiotic stress. Motivated by these facts and the work of Barrett et al. (2006), we assume that the mutation rate is described by the Weibull distribution:

$$p = p_r + p_a \frac{k_0}{\lambda_0} \left(\frac{C}{\lambda_0}\right)^{k_0 - 1} \exp\left\{-\left(\frac{C}{\lambda_0}\right)^{k_0}\right\}, \tag{1.3}$$

which is versatile to accommodate various shapes. Here in (1.3), p_r is the random mutation coefficient, p_a is the adaptive coefficient, $k_0 > 0$ is the shape parameter and $\lambda_0 > 0$ is the scale parameter of the distribution.

We now incorporate the altruistic behaviors of the resistant strain into the model (1.1). Let I denote the concentration of indoles produced by resistant bacteria. In general, the rate at which the bacteria of wild strain absorb the indoles is dependent on the concentration of indoles, denoting it by $a(I)$. It is reasonable to assume that $a(I)$ is increasing and saturating. For concreteness, we choose $a(I) = \eta I/(1 + hI)$ with η/h giving the maximum absorb rate. We suppose that the probability by which the bacteria are protected by the indoles in unit time is proportional to the concentration of absorbed indoles and it takes the maximum value 1 when I becomes infinity, which leads to the protection probability $hI/(1 + hI)$. As a consequence, the probability of the bacteria being unprotected is $1/(1+hI)$. Thus, the death rate of the wild strain due to the combined effects of antibiotic stress and indole's protection is $\varepsilon_1(C)/(1 + hI)$. Furthermore, we assume that the production rate of indoles by the resistant bacteria is αB_2, where α is a proportional constant. We introduce an extra mortality rate ε_3 for the resistance bacteria to account for the cost for producing indoles, and assume that ε_4 is the natural decaying rate of indoles. Incorporating the above ingredients into (1.1), we arrive at the following model:

$$\begin{cases} \frac{dS}{dt} = A - dS - \frac{\mu_1 S}{\gamma_1(m_1+S)} B_1 - \frac{\mu_2 S}{\gamma_2(m_2+S)} B_2, \\ \frac{dB_1}{dt} = (1-p)\frac{\mu_1 S}{m_1+S} B_1 - \left(d + \frac{\varepsilon_1}{1+hI}\right) B_1, \\ \frac{dB_2}{dt} = \frac{\mu_2 S}{m_2+S} B_2 + p\frac{\mu_1 S}{m_1+S} B_1 - (d+\varepsilon) B_2, \\ \frac{dI}{dt} = \alpha B_2 - (d+\varepsilon_4) I - \frac{\eta I B_1}{1+hI}, \end{cases} \tag{1.4}$$

where $\varepsilon = \varepsilon_2 + \varepsilon_3$, and the dependence of p, ε_1 and ε on C is omitted for simplicity of notations.

For biological reason, we are only interested in non-negative initial values for (1.4). Given a set of non-negative initial values, by a standard argument, one can easily show that the model (1.4) has a unique solution satisfying the given initial conditions, and the solution remains non-negative for all those $t \geq 0$ in its existence interval.

The rest of this paper is organized as follows. In Sect. 2, we analyze (1.4) for the special case $p = 0$ to focus on the pure interactions of the two bacteria strain and the indoles. In Sect. 3, by allowing $p > 0$, we explore the influences of mutations on the coexistence of the wild strain and the resistant strain. Our analysis and numeric simulations to the model can not only explain the experimental findings that a small number of resistant mutants can enhance the survival capacity of the whole population in stressful environment, but can also predict the existence of periodic fluctuations of bacteria populations and even the occurrence of bistability in the sense that a stable positive periodic solution coexists with a stable positive equilibrium. We conclude the paper with some discussions on biological implications of the mathematical results obtained in Sects. 2 and 3, as well as some related problems for future work on this topics.

2 Dynamics without mutation

In this section, we consider the case $p = 0$ to focus on the interaction of the two strains and indoles, which can be considered as an approximation of the case when mutation rate from the wild type to the resistant type is so weak (mutation is rare) that we can ignore it. Indeed, it is estimated that the mutation rate for untreated wild-type *E. coli* is approximately 1.5×10^{-8} per cell generation (Kohanski et al. 2010), and the mutation rates from sensitive type to resistance type are often on the order of 10^{-6} to 10^{-9} (Lipsitch and Levin 1997). In the chemostat setting, this corresponds to the scenario that the resistance bacteria are brought into the chemostat from outside, and in reality can be the situation that an host is infected by both the wild strain and the drug resistant strain of bacteria. Setting $p = 0$ in (1.4), we obtain

$$\begin{cases} \frac{dS}{dt} = A - dS - \frac{\mu_1 S}{\gamma_1(m_1+S)}B_1 - \frac{\mu_2 S}{\gamma_2(m_2+S)}B_2, \\ \frac{dB_1}{dt} = \frac{\mu_1 S}{m_1+S}B_1 - \left(d + \frac{\varepsilon_1}{1+hI}\right)B_1, \\ \frac{dB_2}{dt} = \frac{\mu_2 S}{m_2+S}B_2 - (d+\varepsilon)B_2, \\ \frac{dI}{dt} = \alpha B_2 - (d+\varepsilon_4)I - \frac{\eta I B_1}{1+hI}. \end{cases} \tag{2.1}$$

Clearly (2.1) has the bacterium-free equilibrium $E_0 = (S^0, 0, 0, 0)$ where $S^0 = A/d$. The basic reproduction number of strain $\mathcal{R}_i$ in the absence of strain j, $j \neq i$ is denoted by $\mathcal{R}_i$ which can be calculated by a standard procedure (see, e.g., Diekmann et al. 1990; van den Driessche and Watmough 2002). Indeed, the $B_1'(t)$ and $B_2'(t)$ equations in the linearization of (2.1) at E_0 are

$$\frac{dB_1}{dt} = \frac{\mu_1 S^0}{m_1 + S^0}B_1 - (d+\varepsilon_1)B_1,$$

$$\frac{dB_2}{dt} = \frac{\mu_2 S^0}{m_2 + S^0} B_2 - (d + \varepsilon) B_2,$$

from which we immediately obtain

$$\mathcal{R}_1 = \frac{\mu_1 S^0}{(m_1 + S^0)(d + \varepsilon_1)}, \quad \mathcal{R}_2 = \frac{\mu_2 S^0}{(m_2 + S^0)(d + \varepsilon)}.$$

Setting

$$\lambda_1 = \frac{m_1\ (d + \varepsilon_1)}{\mu_1 - d - \varepsilon_1}, \quad \lambda_2 = \frac{m_2\ (d + \varepsilon)}{\mu_2 - d - \varepsilon},$$

it is easy to verify that

$$\mathcal{R}_1 > 1 \quad \text{iff} \quad \mu_1 > d + \varepsilon_1 \quad \text{and} \quad S^0 > \lambda_1, \tag{2.2}$$

$$\mathcal{R}_2 > 1 \quad \text{iff} \quad \mu_2 > d + \varepsilon \quad \text{and} \quad S^0 > \lambda_2. \tag{2.3}$$

When $\mathcal{R}_2 < 1$, since

$$\frac{dB_2}{dt} \le (\mu_2 - d - \varepsilon) B_2,$$

it follows that population B_2 will go extinct if $\mu_2 < d + \varepsilon$. In the case that $S^0 < \lambda_2$, we see from Wolkowicz and Lu (1992, Lemma 2.2) that population B_2 will also go to extinction. When $\mathcal{R}_2 > 1$, (2.1) admits equilibrium $E_2 = (\lambda_2, 0, B_{20}, I_2)$, where

$$B_{20} = \frac{\gamma_2 d(S^0 - \lambda_2)}{d + \varepsilon}, \quad I_2 = \frac{\alpha B_{20}}{d + \varepsilon_4}.$$

At E_2, one can define the B_2-mediated reproduction number for strain B_1 by

$$\mathcal{R}_{12} = \frac{\mu_1 \lambda_2}{(m_1 + \lambda_2)(d + \varepsilon_1/(1 + hI_2))},$$

which accounts for the expected number of offsprings produced by a single wild bacterium during its life time when the population of resistant type is fixed at B_{20} and the indole level is fixed at I_2. It is easy to verify that

$$\begin{cases} \mathcal{R}_{12} < 1 \quad \text{iff} \quad \frac{\mu_1 \lambda_2}{m_1 + \lambda_2} < d + \frac{\varepsilon_1 (d + \varepsilon_4)}{d + \varepsilon_4 + h\alpha B_{20}}, \\ \mathcal{R}_{12} > 1 \quad \text{iff} \quad \frac{\mu_1 \lambda_2}{m_1 + \lambda_2} > d + \frac{\varepsilon_1 (d + \varepsilon_4)}{d + \varepsilon_4 + h\alpha B_{20}}. \end{cases} \tag{2.4}$$

If $\mathcal{R}_1 < 1$ and the resistant strain is absent (implied by $B_2(0) = 0$), it is easy to see that the wild strain will go extinct. On the other hand, $\mathcal{R}_1 > 1$ implies the existence

of equilibrium $E_1 = (\lambda_1, B_{10}, 0, 0)$, where $B_{10} = \gamma_1 d(S^0 - \lambda_1)/(d + \varepsilon_1)$. At E_1, we can also define the B_1-mediated reproduction number for strain B_2 by

$$\mathcal{R}_{21} = \frac{\mu_2 \lambda_1}{(m_2 + \lambda_1)(d + \varepsilon)}.$$

It is easy to show that

$$\begin{aligned} &\mathcal{R}_{21} < 1 \quad \text{iff} \quad 0 < \lambda_1 < \lambda_2, \\ &\mathcal{R}_{21} > 1 \quad \text{iff} \quad \lambda_1 > \lambda_2 > 0. \end{aligned} \tag{2.5}$$

Next, we consider the local stability of E_1 and E_2, which gives the thresholds for small invasions of wild strain and resistant strain respectively.

Theorem 2.1 *The following statements hold:*

(i) *Assume $\mathcal{R}_1 > 1$. Then E_1 is asymptotically stable if $\mathcal{R}_{21} < 1$, and is unstable if $\mathcal{R}_{21} > 1$;*
(ii) *Assume $\mathcal{R}_2 > 1$. Then E_2 is asymptotically stable if $\mathcal{R}_{12} < 1$ and is unstable if $\mathcal{R}_{12} > 1$.*

Proof The Jacobian matrix of (2.1) at E_1 is

$$J_1 = \begin{bmatrix} -d - \frac{B_{10}(\mu_1 - d - \varepsilon_1)}{(m_1 + \lambda_1)\gamma_1} & -\frac{d + \varepsilon_1}{\gamma_1} & -\frac{\mu_2 \lambda_1}{(m_2 + \lambda_1)\gamma_2} & 0 \\ \frac{B_{10}(\mu_1 - d - \varepsilon_1)}{m_1 + \lambda_1} & 0 & 0 & \varepsilon_1 h B_{10} \\ 0 & 0 & \frac{\mu_2 \lambda_1}{m_2 + \lambda_1} - d - \varepsilon & 0 \\ 0 & 0 & \alpha & -d - \varepsilon_4 - \eta B_{20} \end{bmatrix}.$$

The upper-left 2×2 block matrix in J_1 is stable by (2.2), and the stability of the lower-right 2×2 block matrix is fully determined by the sign of $\mu_2 \lambda_1/(m_2 + \lambda_1) - d - \varepsilon$. Thus, (i) follows from (2.4). Similarly, we can show that E_2 is asymptotically stable if $\mathcal{R}_{12} < 1$ and it is a saddle if $\mathcal{R}_{12} > 1$, proving (ii) (also a special case of Theorem 3.1 in Sect. 3). □

The following theorem gives conditions on the persistence of bacteria populations.

Theorem 2.2 *The following statements hold:*

(i) *If either $\mathcal{R}_1 > 1$ and $\mathcal{R}_2 < 1$, or $\mathcal{R}_2 > 1$ and $\mathcal{R}_{12} > 1$, then population B_1 is uniformly persistent, i.e., there exists a $\zeta > 0$ such that positive solutions of (2.1) satisfy $\liminf_{t \to \infty} B_1(t) > \zeta$.*
(ii) *If $\mathcal{R}_2 > 1$ and $\mathcal{R}_{21} > 1$, then population B_2 is uniformly persistent.*
(iii) *Assume that $\mathcal{R}_2 > 1$, $\mathcal{R}_{21} > 1$ and $\mathcal{R}_{12} > 1$. Then both $B_1(t)$ and $B_2(t)$ are uniformly persistent.*

Proof We only give the proof of (i), since the proof of (ii) is similar and (iii) is a direct consequence of (i) and (ii).

By the form of (2.1), it is easy to see that solutions of (2.1) with nonnegative initial values are nonnegative, and the solutions with positive initial values are positive. Set

$$V_0 = S + \gamma_1 B_1 + \gamma_2 B_2.$$

Then we have

$$\frac{dV_0}{dt} \le A - dV_0. \tag{2.6}$$

This, together with the last equation in (2.1), implies that nonnegative solutions of (2.1) exist for all forward times. The inequality (2.6) also leads to

$$V_0(t) \le \frac{A}{d} + 1, \quad \text{for all large } t.$$

On the other hand, the non-negativity of solutions leads to

$$\frac{dI}{dt} \le \alpha B_2 - (d + \varepsilon_4)I \le \frac{\alpha}{\gamma_2}\left(\frac{A}{d} + 1\right) - (d + \varepsilon_4)I, \tag{2.7}$$

which implies that the $I(t)$ component of a nonnegative solution of (2.1) is also ultimately bounded.

Let us consider the case where $\mathcal{R}_1 > 1$ and $\mathcal{R}_2 < 1$. We have $B_2(t) \to 0$ as $t \to \infty$ because $\mathcal{R}_2 < 1$ implies $I(t) \to 0$ as $t \to \infty$. It follows from the techniques of Wang and Zhao (2004) and Xiao and Zou (2008) that positive solutions of (2.1) satisfy $S(t) \to \lambda_1$ and $B_1(t) \to B_{10}$ as $t \to \infty$, implying the uniform persistence of population B_1.

Now we consider the case that $\mathcal{R}_2 > 1$ and $\mathcal{R}_{12} > 1$. Set

$$\begin{aligned} X &= \mathcal{R}^4_+ = \{(S, B_1, B_2, I) : S \ge 0, B_1 \ge 0, B_2 \ge 0, I \ge 0\}, \\ X_0 &= \{(S, B_1, B_2, I) \in X : B_1 > 0\}, \\ Y &= X/X_0 = \{(S, 0, B_2, I) : S \ge 0, B_2 \ge 0, I \ge 0\}. \end{aligned}$$

It then suffices to show that (2.1) is uniformly persistent with respect to (X_0, Y). First, it is easy to see that both X and X_0 are positively invariant. Further, (2.6) and (2.7) imply that system (2.1) is point dissipative.

Notice that there are two equilibria E_0 and E_2 in Y for (2.1). Let us consider

$$\begin{cases} \frac{dS}{dt} = A - dS - \frac{\mu_2 S}{\gamma_2(m_2+S)}B_2, \\ \frac{dB_2}{dt} = \frac{\mu_2 S}{m_2+S}B_2 - (d+\varepsilon)B_2, \\ \frac{dI}{dt} = \alpha B_2 - (d+\varepsilon_4)I, \end{cases} \tag{2.8}$$

which describes the dynamics of (2.1) in Y. Notice that $\mathcal{R}_2 > 1$. Using similar arguments to those in Hsu et al. (1977) and Wolkowicz ans Lu (1992), we see that $E_2^0 = (\lambda_2, B_{20}, I_2)$ is globally stable for the solutions $(S(t), B_2(t), I(t))$ of (2.8) with

$B_2(0) > 0, S(0) \geq 0, I(0) \geq 0$. Furthermore, if $Y_0 = \{(S, 0, I) : S \geq 0, I \geq 0\}$, it is easy to see that Y_0 is positively invariant for (2.8) and the solutions of (2.8) in Y_0 approach $E_0^0 = (S^0, 0, 0)$ as $t \to \infty$ and become unbounded as $t \to -\infty$. These facts indicate that equilibria E_0 and E_2 are acyclic in Y.

To show that E_0 and E_2 is isolated in X, it suffices to verify that E_0 and E_2 are hyperbolic. The Jacobian matrix of (2.1) at E_2 is

$$J_2 = \begin{bmatrix} -d - \frac{\mu_2 B_{20}}{(m_2+\lambda_2)\gamma_2} + \frac{\mu_2 \lambda_2 B_{20}}{\gamma_2 (m_2+\lambda_2)^2} & -\frac{\mu_1 \lambda_2}{(m_1+\lambda_2)\gamma_1} & -\frac{\mu_2 \lambda_2}{(m_2+\lambda_2)\gamma_2} & 0 \\ 0 & \frac{\mu_1 \lambda_2}{m_1+\lambda_2} - d - \frac{\varepsilon_1}{1+hI_2} & 0 & 0 \\ \left(\frac{\mu_2}{m_2+\lambda_2} - \frac{\mu_2 \lambda_2}{(m_2+\lambda_2)^2}\right) B_{20} & 0 & 0 & 0 \\ 0 & -\frac{\eta I_2}{1+hI_2} & \alpha & -d - \varepsilon_4 \end{bmatrix}. \quad (2.9)$$

Clearly, J_2 has an eigenvalue $\Lambda_2 = \frac{\mu_1 \lambda_2}{m_1+\lambda_2} - d - \frac{\epsilon_1}{1+hI_2}$, which is positive because $\mathcal{R}_{12} > 1$, and has an eigenvalue $\Lambda_4 = -(d + \varepsilon_4) < 0$. The other two eigenvalues of J_2 are determined by the matrix:

$$J_{20} = \begin{bmatrix} -d - \frac{\mu_2 B_{20}}{(m_2+\lambda_2)\gamma_2} + \frac{\mu_2 \lambda_2 B_{20}}{\gamma_2 (m_2+\lambda_2)^2} & -\frac{\mu_2 \lambda_2}{(m_2+\lambda_2)\gamma_2} \\ \left(\frac{\mu_2}{m_2+\lambda_2} - \frac{\mu_2 \lambda_2}{(m_2+\lambda_2)^2}\right) B_{20} & 0 \end{bmatrix}.$$

Since $\mathcal{R}_2 > 1$, direct calculations lead to $\mathrm{tr}(J_{20}) < 0$ and $\det(J_{20}) > 0$. Thus, the eigenvalues of J_{20} have negative real part. Hence, E_2 is hyperbolic. Similarly, one can verify that E_0 is hyperbolic. Therefore, we have verified that E_0 and E_2 are isolated in X and $\{E_0, E_2\}$ is an acyclic covering.

We now show that $W^s(E_2) \cap X_0 = \emptyset$ where $W^s(E_2)$ denotes the stable manifold of E_2. Suppose not. Then there is a solution of (2.1) such that

$$\lim_{t\to\infty} (S(t), B_1(t), B_2(t), I(t)) \to (\lambda_2, 0, B_{20}, I_2). \quad (2.10)$$

As a consequence, it follows from the second equation of (2.1) that

$$\frac{dB_1}{dt} \geq B_1 \left[\frac{\mu_1(\lambda_2 - \xi)}{m_1 + \lambda_2 - \xi} - d - \frac{\varepsilon_1}{1 + h(I_2 - \xi)}\right] := B_1 q(\xi) \quad (2.11)$$

where $\xi > 0$ is sufficiently small. Since $\mathcal{R}_{12} > 1$, one can restrict $\xi > 0$ small enough such that $q(\xi) > 0$. Then (2.11) implies that $B_1(t) \to \infty$ as $t \to \infty$. This contradicts the fact that positive solutions are ultimately bounded. Therefore, $W^s(E_2) \cap X_0 = \emptyset$. Similarly, we can verify $W^s(E_0) \cap X_0 = \emptyset$, where $W^s(E_0)$ denotes the stable manifold of E_0.

In summary, the conditions of Thieme (1993, Theorem 4.6) (see also Hirsch 2001, Theorem 4.3 and Remark 4.3, or Butler et al. 1986; Zhao 2003) are satisfied. Therefore, we conclude that system (2.1) is uniformly persistent with respect to (X_0, Y). This proves the uniform persistence of population B_1. □

Remark 2.3 The second set of conditions in Theorem 2.2(i) deserve more discussions. The condition $\mathcal{R}_2 > 1$ means that B_2 strain can persist in the absence of B_1 strain, and $\mathcal{R}_{12} > 1$ implies that B_2 strain can help B_1 strain survive by its altruistic behavior even if $\mathcal{R}_1 < 1$, which means that B_1 strain faces a strong antibiotic stress. This theorem clearly supports the experimental results in Lee et al. (2010): altruism of the antibiotic-resistant strain can help the wild strain survive the antibiotic (under certain ranges of parameters).

By Theorem 2.1, E_2 is locally asymptotically stable under the conditions $\mathcal{R}_2 > 1$ and $\mathcal{R}_{12} < 1$. In the next theorem, we show that E_2 actually can be globally asymptotically stable under some extra conditions.

Theorem 2.4 *Assume that $\mathcal{R}_2 > 1$ and $\mathcal{R}_{12} < 1$. Then E_2 is globally asymptotically stable in the set $D_1 = \{(S, B_1, B_2, I) : S > 0, B_1 \geq 0, B_2 > 0, I > 0\}$ if*

$$\frac{\alpha A}{(d+\varepsilon_4)d\gamma_2} < \frac{\varepsilon_1 - \varepsilon}{h\varepsilon} \tag{2.12}$$

and

$$\begin{cases} \frac{\mu_1 m_2}{\mu_2 m_1} \leq 1, & \text{if } m_2 \geq m_1, \\ \frac{(m_2 d + A)\mu_1}{(m_1 d + A)\mu_2} \leq 1, & \text{if } m_1 > m_2. \end{cases} \tag{2.13}$$

Proof We define a Lyapunov function by

$$\begin{aligned} V_1 = &\left(1 - \frac{d+\varepsilon}{\mu_2}\right)(S - \lambda_2) - \frac{m_2(d+\varepsilon)}{\mu_2} \ln \frac{S}{\lambda_2} + \frac{1}{\gamma_1} B_1 \\ &+ \frac{1}{\gamma_2}\left(B_2 - B_{20} - B_{20} \ln \frac{B_2}{B_{20}}\right). \end{aligned} \tag{2.14}$$

Calculating the derivative of V_1 along solutions of (2.1) in D_1, we obtain

$$\begin{aligned} \frac{dV}{dt} &= A - dS - \frac{\mu_1 S}{\gamma_1(m_1 + S)} B_1 - \frac{\mu_2 S}{\gamma_2(m_2 + S)} B_2 \\ &\quad -(d+\varepsilon)\left[(A - dS)\Big/\frac{\mu_2 S}{m_2 + S} - \frac{\mu_1 S}{m_1 + S}\Big/\frac{\gamma_1 \mu_2 S}{m_2 + S} B_1 - \frac{1}{\gamma_2} B_2\right] \\ &\quad + \frac{\mu_1 S}{\gamma_1(m_1 + S)} B_1 - \frac{1}{\gamma_1}\left(d + \frac{\varepsilon_1}{1 + hI}\right) B_1 + \frac{\mu_2 S}{\gamma_2(m_2 + S)} B_2 - \frac{d+\varepsilon}{\gamma_2} B_2 \\ &\quad - \frac{B_{20}}{\gamma_2}\left(\frac{\mu_2 S}{m_2 + S} - d - \varepsilon\right) \\ &= (A - dS)\left(1 - (d+\varepsilon)/\frac{\mu_2 S}{m_2 + S}\right) - \frac{B_{20}}{\gamma_2}\left(\frac{\mu_2 S}{m_2 + S} - d - \varepsilon\right) \\ &\quad + \frac{1}{\gamma_1}\left((d+\varepsilon)\frac{\mu_1 S}{m_1 + S}\Big/\frac{\mu_2 S}{m_2 + S} - d - \frac{\varepsilon_1}{1 + hI}\right) B_1. \end{aligned} \tag{2.15}$$

In view of (2.6) and the last equation of (2.1), one can assume, for the simplicity of notations, that for large t,

$$S(t) \le S^0, \quad B_1(t) \le \frac{S^0}{\gamma_1}, \quad B_2(t) \le \frac{S^0}{\gamma_2}, \quad I(t) \le \frac{\alpha S^0}{\gamma_2(d+\varepsilon_4)}. \tag{2.16}$$

Note that (2.13) leads to

$$\frac{\mu_1 S}{m_1+S} \Big/ \frac{\mu_2 S}{m_2+S} \le 1, \quad \text{for} \quad 0 \le S \le S^0. \tag{2.17}$$

It follows from (2.16), (2.17) and (2.12) that

$$(d+\varepsilon)\frac{\mu_1 S}{m_1+S} \Big/ \frac{\mu_2 S}{m_2+S} - d - \frac{\varepsilon_1}{1+hI} < 0 \tag{2.18}$$

for all large t. Consequently

$$\frac{dV_1}{dt} \le (A-dS)\left(1-(d+\varepsilon)\Big/\frac{\mu_2 S}{m_2+S}\right) - \frac{B_{20}}{\gamma_2}\left(\frac{\mu_2 S}{m_2+S} - d - \varepsilon\right) \triangleq F(S). \tag{2.19}$$

Next, we show that $F(S)$ satisfies

$$F(S) < 0, \quad \text{for} \quad 0 < S \le S^0 \ \text{ and } S \ne \lambda_2. \tag{2.20}$$

Using the transformation

$$u = \frac{\mu_2 S}{m_2+S}, \quad \text{or equivalently} \quad S = \frac{um_2}{\mu_2 - u}$$

with $0 < u < \mu_2$, we obtain

$$\begin{aligned} F(S) &= \left(A - \frac{dm_2 u}{\mu_2 - u}\right)\left(1 - \frac{d+\varepsilon}{u}\right) - \frac{B_{20}}{\gamma_2}(u - d - \varepsilon) \\ &= -\frac{(d+\varepsilon-u)\left(\gamma_2 A\mu_2 - (\gamma_2 A + \gamma_2 dm_2 + B_{20}\mu_2)u + B_{20}u^2\right)}{(\mu_2-u)u\gamma_2}. \end{aligned} \tag{2.21}$$

Substituting $B_{20} = \gamma_2(A - d\lambda_2)/(d+\varepsilon)$ with $\lambda_2 = (d+\varepsilon)m_2/(\mu_2 - d - \varepsilon)$ into (2.21) leads to

$$F(S) = -\frac{(d+\varepsilon-u)^2 L(u)}{(\mu_2-u)u(\mu_2-\varepsilon-d)(d+\varepsilon)} \tag{2.22}$$

where

$$L(u) = [A(\varepsilon + d - \mu_2) + dm_2(d+\varepsilon)]u + A\mu_2(\mu_2 - \varepsilon - d).$$

This, together with (2.3), implies that $L(u) > 0$ for $0 < u < \mu_2$. It follows that $F(S)$ satisfies (2.20). Moreover, (2.22) also implies that $F(s) = 0$ if and only $u = d + \varepsilon$, that is, $S = \lambda_2$.

Set

$$D_{01} = \left\{ (S(t), B_1(t), B_2(t), I(t)) : \frac{dV_1}{dt} = 0 \right\}.$$

From the above we know that $\frac{dV_1}{dt} = 0$ implies $S(t) = \lambda_2$. Then the third equation of (2.1) implies that $B_2(t)$ is a constant. As a consequence, it follows from the first equation of (2.1) that $B_1(t)$ is also a constant. Since $\frac{dB_1(t)}{dt} = 0$, we have

$$\left[\frac{\mu_1 S}{m_1 + S} - \left(d + \frac{\varepsilon_1}{1 + hI} \right) \right] B_1 = \left[\frac{\mu_1 \lambda_2}{m_1 + \lambda_2} - \left(d + \frac{\varepsilon_1}{1 + hI} \right) \right] B_1 = 0. \quad (2.23)$$

Note that $\mathcal{R}_2 > 1$ implies that $\lambda_2 < S^0$. From (2.17) and (2.18) it follows that

$$\frac{\mu_1 \lambda_2}{m_1 + \lambda_2} - \left(d + \frac{\varepsilon_1}{1 + hI} \right) < 0.$$

Hence, (2.23) leads to $B_1 = 0$. Then from the right-hand of (2.1) we further obtain $B_2 = B_{20}$. Using $B_1 = 0$ and $B_2 = B_{20}$, we see, from the last equation of (2.1), that $I(t) \to I_2$ as $t \to \infty$. Thus, the largest invariant set of (2.1) contained in D_{01} is $\{E_2\}$. By the Lyapunov–LaSalle theorem (Hale and Verduyn Lunel 1993), all solutions of (2.1) in D_1 approach E_2 as $t \to \infty$.

Parallel to Theorem 2.4, we have the following theorem on the global asymptotic stability of E_1.

Theorem 2.5 *Assume that $\mathcal{R}_1 > 1$ and $\mathcal{R}_{21} < 1$. Then E_1 is globally stable in the set $D_2 = \{(S, B_1, B_2, I) : S > 0, B_1 > 0, B_2 \geq 0, I > 0\}$ if the following condition holds:*

$$\begin{cases} \alpha \frac{\varepsilon_1 h}{\gamma_1 \eta} + \frac{(d+\varepsilon_1)\mu_2 m_1}{\gamma_2 \mu_1 m_2} < \frac{d+\varepsilon}{\gamma_2}, & \text{if } m_1 \geq m_2, \\ \alpha \frac{\varepsilon_1 h}{\gamma_1 \eta} + \frac{(d+\varepsilon_1)\mu_2 (m_1 d + A)}{\gamma_2 \mu_1 (m_2 d + A)} < \frac{d+\varepsilon}{\gamma_2}, & \text{if } m_1 > m_2. \end{cases} \quad (2.24)$$

Proof Define a Lyapunov function by

$$V_2 = \left(1 - \frac{d + \varepsilon_1}{\mu_1} \right) (S - \lambda_1) - \frac{m_1 (d + \varepsilon_1)}{\mu_1} \ln \frac{S}{\lambda_1} + \frac{1}{\gamma_2} B_2 + \frac{1}{\gamma_1} \left(B_1 - B_{10} - B_{10} \ln \frac{B_1}{B_{10}} \right) + \frac{\varepsilon_1 h}{\gamma_1 \eta} I. \quad (2.25)$$

Calculating the derivative of V_2 along solutions of (2.1) in D_2, we obtain

$$\begin{aligned}\frac{dV_2}{dt} &= A - dS - \frac{\mu_1 S}{\gamma_1(m_1+S)}B_1 - \frac{\mu_2 S}{\gamma_2(m_2+S)}B_2\\ &\quad -(d+\varepsilon_1)\left[(A-dS)\Big/\frac{\mu_1 S}{m_1+S} - \frac{1}{\gamma_1}B_1 - \frac{\mu_2 S}{m_2+S}\Big/\frac{\gamma_2\mu_1 S}{m_1+S}B_2\right]\\ &\quad +\frac{\mu_1 S}{\gamma_1(m_1+S)}B_1 - \frac{1}{\gamma_1}\left(d+\frac{\varepsilon_1}{1+hI}\right)B_1\\ &\quad -\frac{B_{10}}{\gamma_1}\left(\frac{\mu_1 S}{m_1+S} - d - \frac{\varepsilon_1}{1+hz}\right) + \frac{\mu_2 S}{\gamma_2(m_2+S)}B_2 - \frac{d+\varepsilon}{\gamma_2}B_2\\ &\quad +\frac{\varepsilon_1 h}{\gamma_1\eta}\left(\alpha B_2 - (d+\varepsilon_4)I - \frac{\eta I B_1}{1+hI}\right)\\ &\le (A-dS)\left(1-(d+\varepsilon_1)\Big/\frac{\mu_1 S}{m_1+S}\right) - \frac{B_{10}}{\gamma_1}\left(\frac{\mu_1 S}{m_1+S} - d - \varepsilon_1\right)\\ &\quad -(d+\varepsilon_4)\frac{\varepsilon_1 h}{\gamma_1\eta}I + \left((d+\varepsilon_1)\frac{\mu_2(m_1+S)}{\gamma_2\mu_1(m_2+S)} - \frac{d+\varepsilon}{\gamma_2} + \alpha\frac{\varepsilon_1 h}{\gamma_1\eta}\right)B_2.\end{aligned} \tag{2.26}$$

As discussed in the proof of Theorem 2.4, we can confine ourselves to the set described in (2.16). Then it is easy to see that (2.24) implies

$$(d+\varepsilon_1)\frac{\mu_2(m_1+S)}{\gamma_2\mu_1(m_2+S)} - \frac{d+\varepsilon}{\gamma_2} + \alpha\frac{\varepsilon_1 h}{\gamma_1\eta} < 0, \quad \text{for } 0 < S \le S^0. \tag{2.27}$$

Let

$$G(S) = (A-dS)\left(1-(d+\varepsilon_1)\Big/\frac{\mu_1 S}{m_1+S}\right) - \frac{B_{10}}{\gamma_1}\left(\frac{\mu_1 S}{m_1+S} - d - \varepsilon_1\right).$$

By similar discussions to those in the proof of Theorem 2.4, we see that

$$G(S) < 0, \quad \text{for } 0 < S \le S^0 \text{ and } S \ne \lambda_2. \tag{2.28}$$

Set

$$D_{02} = \left\{(S(t), B_1(t), B_2(t), I(t)) : \frac{dV_2}{dt} = 0\right\}.$$

Clearly, $\frac{dV_2}{dt} = 0$ implies $S(t) = \lambda_1$, $B_2(t) = 0$ and $I(t) = 0$. Then the first equation of (2.1) implies $B_1(t) = B_{10}$. As a consequence, the largest invariant set of (2.1) contained in D_{02} is $\{E_1\}$. It follows from the Lyapunov–LaSalle Theorem (Hale and Verduyn Lunel 1993) that all solutions in D_2 approach E_1 as $t \to \infty$. □

Our next goal is to look for conditions under which there exists a positive equilibrium for (2.1), accounting for co-existence of the two strains. For this purpose,

we assume $\mathcal{R}_2 > 1$ in the sequel. Otherwise, population B_2 may go to extinct, and consequently, the indole population I is eliminated. To be succinct, we assume that both strains have the same metabolic parameters, i.e., $\mu_1 = \mu_2 = \mu, m_1 = m_2 = m, \gamma_1 = \gamma_2 = \gamma$. Then a positive equilibrium satisfies

$$\begin{cases} A - dS - \frac{\mu S}{\gamma(m+S)}(B_1 + B_2) = 0, \\ \frac{\mu S}{m+S} - \left(d + \frac{\varepsilon_1}{1+hI}\right) = 0, \\ \frac{\mu S}{m+S} - (d+\varepsilon) = 0, \\ \alpha B_2 - (d+\varepsilon_4)I - \frac{\eta I B_1}{1+hI} = 0. \end{cases} \tag{2.29}$$

Solving (2.29) gives a unique positive solution $E^* = (\lambda_2, B_1^*, B_2^*, I^*)$ where

$$\lambda_2 = \frac{m(d+\varepsilon)}{\mu - d - \varepsilon}, \quad I^* = \frac{\varepsilon_1 - \varepsilon}{h\varepsilon},$$

and (B_1^*, B_2^*) is the unique solution of the linear system

$$\begin{cases} B_1 + B_2 = \frac{(A - d\lambda_2)\gamma}{d+\varepsilon} \\ \frac{-\eta I^*}{1+hI^*} B_1 + \alpha B_2 = (d+\varepsilon_4) I^*. \end{cases} \tag{2.30}$$

Since we have assumed $\varepsilon_1 > \varepsilon$ (see Sect. 1) and $\mu > d + \varepsilon$ (implied by $\mathcal{R}_2 > 1$), it follows from (2.30) that B_1^* and B_2^* are positive if and only if

$$\alpha h \varepsilon (A - d\lambda_2)\gamma > (d+\varepsilon_4)(\varepsilon_1 - \varepsilon)(d+\varepsilon). \tag{2.31}$$

The Jacobian matrix at E^* is

$$\begin{bmatrix} -\frac{A\mu\gamma - (B_1^* + B_2^*)(d+\varepsilon)^2}{\mu\gamma S} & -\frac{d+\varepsilon}{\gamma} & -\frac{d+\varepsilon}{\gamma} & 0 \\ \frac{(d+\varepsilon)(\mu - d - \varepsilon)B_1^*}{\mu\lambda_2} & 0 & 0 & \frac{\varepsilon^2 h B_1^*}{\varepsilon_1} \\ \frac{(d+\varepsilon)(\mu - d - \varepsilon)B_2^*}{\mu\lambda_2} & 0 & 0 & 0 \\ 0 & \frac{\eta(\varepsilon - \varepsilon_1)}{\varepsilon_1 h} & \alpha & -\frac{\alpha B_2^* {\varepsilon_1}^2 + \eta B_1^*(\varepsilon^2 I^* - \varepsilon I^* \varepsilon_1)}{I^* {\varepsilon_1}^2} \end{bmatrix}.$$

Its characteristic equation is

$$\lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4 = 0, \tag{2.32}$$

where

$$a_1 = \frac{\lambda_2\mu\gamma[\eta B_1^*\varepsilon(\varepsilon - \varepsilon_1)I^* + \alpha B_2^*\varepsilon_1^2 + I^*{\varepsilon_1}^2(A\mu\gamma - (B_1^* + B_2^*)(d+\varepsilon)^2)]}{\mu\gamma\lambda_2 I^* {\varepsilon_1}^2},$$

$$
\begin{aligned}
a_2 &= \frac{1}{\mu\,\gamma\,\lambda_2 {I^*}{\varepsilon_1}^2}[(B_1^*+B_2^*)^2 I^*\eta\,\varepsilon\,(d+\varepsilon)^2(\varepsilon_1-\varepsilon)+\gamma\mu B_2^*(I^*\eta\,\varepsilon^2\lambda_2(\varepsilon-\varepsilon_1)\\
&\quad +A(\varepsilon_1{}^2\alpha-\eta\,\varepsilon^2 z+\eta\,\varepsilon\,z\varepsilon_1))+(B_1^*+B_2^*)(-\lambda_2\varepsilon_1{}^2 y\alpha\,(d+\varepsilon)^2\\
&\quad +A\eta\,\varepsilon\,(d+\varepsilon)^2(\varepsilon-\varepsilon_1)+\varepsilon_1{}^2(d+\varepsilon)^2(\mu-d-\varepsilon))],\\
a_3 &= \frac{1}{\mu\,\gamma\,\lambda_2 {I^*}{\varepsilon_1}^2}[(B_1^*+B_2^*)^2\varepsilon\,\eta\,I^*(d+\varepsilon)^2(\varepsilon-\varepsilon_1)(\mu-d)\\
&\quad +\gamma\,\mu\,AB_2^* I^*\eta\,\varepsilon^2(\varepsilon-\varepsilon_1)\\
&\quad +(B_1^*+B_2^*)(I^*\varepsilon\eta(\varepsilon_1-\varepsilon)(B_2^*(d+\varepsilon)^2(\mu-d)+\varepsilon\gamma\mu A)\\
&\quad +\alpha\,B_2^*\varepsilon_1{}^2(d+\varepsilon)^2(\mu-d-\varepsilon))],\\
a_4 &= \frac{\varepsilon^2 B_1^* B_2^*(d+\varepsilon)^2(\alpha\,h\varepsilon_1-\varepsilon\,\eta+\eta\,\varepsilon_1)(\mu-d-\varepsilon)}{\gamma\,\mu\,\lambda_2\varepsilon_1{}^2}.
\end{aligned}
$$

It is clear that $a_3 > 0$ and $a_4 > 0$. Some algebraic calculations also show that $a_1 > 0$. By the Routh–Hurwitz criteria, we can obtain the following theorem.

Theorem 2.6 *Assume $\mathcal{R}_2 > 1$ and (2.31) hold so that E^* exists. Then E^* is asymptotically stable if*

$$
\Delta_2 := \begin{vmatrix} a_1 & a_3 \\ 1 & a_2 \end{vmatrix} > 0 \quad \text{and} \quad \Delta_3 := \begin{vmatrix} a_1 & a_3 & 0 \\ 1 & a_2 & a_4 \\ 0 & a_1 & a_3 \end{vmatrix} > 0, \tag{2.33}
$$

and is unstable if either $\Delta_2 < 0$ or $\Delta_3 < 0$.

Due to the complexity of the formulas for $a_i's$, $i = 1, 2, 3, 4$, it is difficult, if not impossible, to further identify the full range of parameters for (2.33). However partial ranges are possible. For example, we can show that $\Delta_2 > 0$ when $\eta \geq 0$ is small. Indeed, when $\eta = 0$, direct calculations gives $\Delta_2 = T_2/H_2$ where H_2 is a positive constant and

$$
T_2 = [A(\mu-d-\varepsilon)^2 + dm(d+\varepsilon)^2]\chi,
$$

where

$$
\chi = A(\mu-d-\varepsilon)^2(2d+\varepsilon_4+\varepsilon) - \mu(d\varepsilon-2d\varepsilon_4-\varepsilon_4^2) + d(d+\varepsilon)(2d+\varepsilon+\varepsilon_4).
$$

Noting that $A > d\lambda_2$, it follows that

$$
\begin{aligned}
\chi &> d\lambda_2(\mu-d-\varepsilon)^2(2d+\varepsilon_4+\varepsilon) - \mu(d\varepsilon-d\varepsilon_4-\varepsilon_4^2) + d(d+\varepsilon)(2d+\varepsilon+\varepsilon_4)\\
&= (2d+\varepsilon_4)(d+\varepsilon)(d+\varepsilon_4)\mu m > 0.
\end{aligned}
$$

Hence, $T_2 > 0$, implying that $\Delta_2 > 0$. Since Δ_2 depends continuously on η, we conclude that $\Delta_2 > 0$ when $\eta \geq 0$ is small. This leads to the following corollary.

Corollary 2.7 *Let $0 \leq \eta \ll 1$. Assume that $\mathcal{R}_{21} > 1$ and (2.31) hold so that E^* exists. Then E^* is asymptotically stable if $\Delta_3 < 0$ and is unstable if $\Delta_3 > 0$.*

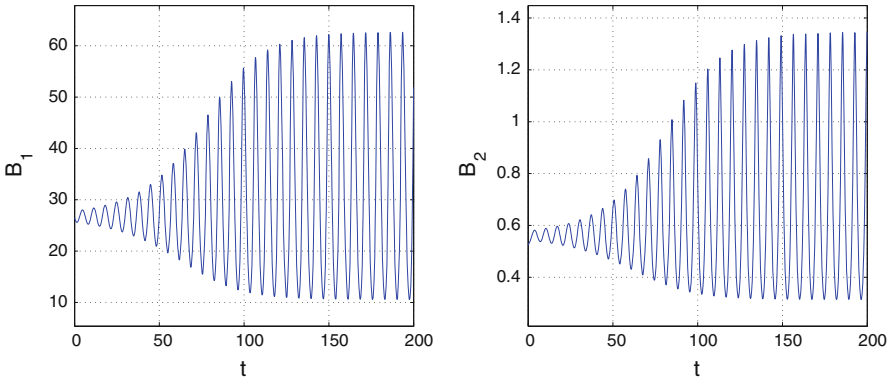
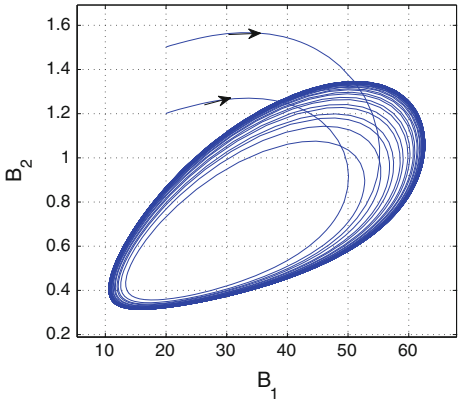


Fig. 1 Periodic solution arising from the Hopf bifurcation when E^* becomes unstable

Fig. 2 Periodic solution from the Hopf bifurcation is stable



Note that $\Delta_3 = a_3\Delta_2 - a_4a_1^2$. Thus, Δ_2 can not cross zero as long as Δ_3 remains positive. Thus, if Δ_2 and Δ_3 change signs from positive to negative, Δ_3 must change its sign first. It follows from Yu (2005) that E^* can only lose its stability through a Hopf bifurcation, giving rise to periodic solutions surrounding E^*.

Detailed analysis of the Hopf bifurcation via sign change(s) of Δ_3 is lengthy and quite technical. Since this is not the focus of this paper, we will not further explore here along this line. But our numeric simulations show that the Hopf bifurcation is possible. To see this, we take $A = 4.9846, d = 0.0035, \mu = 3.8799, m = 9.7723, \gamma = 6.0260, \varepsilon_4 = 4.0731, h = 5.3871, \alpha = 7.9668$ and $\eta = 0.01$, and fix $a_1 = a_2 = 1, k_1 = 10, k_2 = 1.46, \varepsilon_3 = 0.001$. Then Δ_3 changes signs as antibiotic concentration C varies. Indeed, E^* is asymptotically stable when $0 \le C < 2.4213$, and it becomes unstable when $C > 2.4213$, giving rise to a stable periodic solution (see Figs. 1, 2).

One more interesting observation from simulations is that the model (2.1) may admit the coexistence of a stable positive equilibrium and a stable periodic solution. To see this, we fix $A = 5.0683, d = 0.5701, \mu = 3.9010, m = 2.5580, \gamma = 7.5510, \varepsilon_4 = 0.0207, h = 0.4812, \alpha = 6.8250, \eta = 0.01$, and $\varepsilon_1 = 10C/(1 + C), \varepsilon_2 = 1.373C/(1 + C), \varepsilon_3 = 0.001$, Then E^* is stable for $0 < C < 9.8143$ and becomes

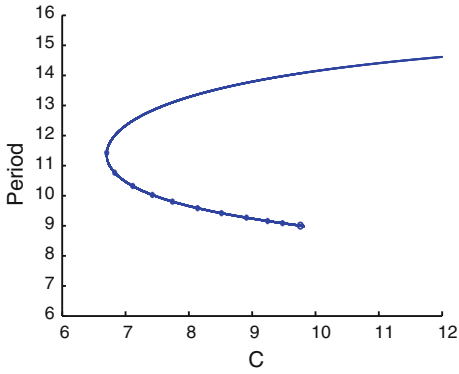


Fig. 3 Subcritical bifurcation curve where the lower part with dots marked denotes the unstable branch and the upper part is the stable branch

unstable when $C > 9.8143$. With the aid of Mactone package (Dhooge et al. 2003), we find a *subcritical* Hopf bifurcation, shown in Fig. 3. Specifically, there are two branches in the bifurcation curve when $6.709 < C < 9.8143$. The upper branch represents a family of stable periodic solutions, which coexist with stable positive equilibrium E^*. Therefore, the dynamics of populations in model (2.1) can evolve to a stable periodic solution, or tend to the stable positive equilibrium, depending upon initial values.

3 Impact of mutation

In this section, we consider influences of mutation rate p on evolutionary behaviors of two bacteria strains described by (1.4). Unlike the case $p = 0$ where $B_2(0) = 0$ implies $B_2(t) = 0$ for all $t \geq 0$ and $I(t) \to 0$ as $t \to \infty$, positive p can activate $B_2(t)$ and $I(t)$, even if $B_2(0) = 0$. Indeed, if $p > 0$, then a standard argument shows that $S(0) \geq 0$, $B_1(0) > 0$, $B_2(0) \geq 0$ and $I(0) \geq 0$ imply that $S(t)$, $B_1(t)$, $B_2(t)$ and $I(t)$ are strictly positive for $t > 0$.

$E_0 = (S^0, 0, 0, 0)$ remains the bacterium-free equilibrium of (1.4), and equilibrium $E_2 = (\lambda_2, 0, B_{20}, I_2)$ still exists if $\mathcal{R}_2 > 1$. At E_2, the B_2-mediated reproduction number for strain B_1 is modified to

$$\mathcal{R}_{12}^p = \frac{(1-p)\mu_1\lambda_2}{(m_1+\lambda_2)[d+\varepsilon_1/(1+hI_2)]}.$$

The stability/instability of E_2 is closely related to extinction/persistence of the wild strain, and we address it in the next theorem.

Theorem 3.1 *Assume that $\mathcal{R}_2 > 1$. Then boundary equilibrium E_2 of (1.4) is asymptotically stable if $\mathcal{R}_{12}^p < 1$, and is unstable if $\mathcal{R}_{12}^p > 1$.*

Proof The Jacobian matrix of (1.4) at E_2 is

$$\begin{bmatrix} -\frac{A}{\lambda_2}+\frac{(d+\varepsilon)^2 B_{20}}{\gamma_2\mu_2\lambda_2} & -\frac{\mu_1\lambda_2}{(m_1+\lambda_2)\gamma_1} & -\frac{d+\varepsilon}{\gamma_2} & 0 \\ 0 & \frac{(1-p)\mu_1\lambda_2}{m_1+\lambda_2}-d-\frac{\varepsilon_1}{1+hI_2} & 0 & 0 \\ \left(d+\varepsilon-\frac{(d+\varepsilon)^2}{\mu_2}\right)\frac{B_{20}}{\lambda_2} & \frac{p\mu_1\lambda_2}{m_1+\lambda_2} & 0 & 0 \\ 0 & -\frac{\eta I_2}{1+hI_2} & \alpha & -(d+\varepsilon_4) \end{bmatrix}.$$

Its characteristic equation can be written as

$$(\lambda+d+\varepsilon_4)\left[(1+hI_2)(m_1+\lambda_2)\lambda+\xi\right]Q_2(\lambda)=0, \tag{3.1}$$

where

$$\begin{aligned} \xi &= m_1(d+dhI_2+\varepsilon_1)+[I_2h(d-\mu_1+p\mu_1)-\mu_1+p\mu_1+d+\varepsilon_1]\lambda_2, \\ Q_2(\lambda) &= \gamma_1\gamma_2\mu_2\lambda_2\lambda^2+\lambda\gamma_1[\mu_2\gamma_2 A-B_{20}(d+\varepsilon)^2] \\ &\quad +B_{20}\gamma_2(d+\varepsilon)^2(\mu_2-d-\varepsilon). \end{aligned}$$

Equation (3.1) has an eigenvalue $\lambda=-(d+\varepsilon_4)$. Note that (2.3) implies that the last term of $Q_2(\lambda)$ is positive. Moreover, direct calculations give

$$\mu_2\gamma_2 A-B_{20}(d+\varepsilon)^2=\gamma_2\frac{A(\mu-d-\varepsilon)^2+dm_2(d+\varepsilon)^2}{\mu-d-\varepsilon}>0.$$

Thus, all roots of the equation $Q_2(\lambda)=0$ have negative real parts. As a consequence, we are left to consider the sign of ξ. Set

$$\kappa=(1-p)\frac{\mu_1\lambda_2}{m_1+\lambda_2}-\left(d+\frac{\varepsilon_1}{1+hI_2}\right).$$

After some algebraic computations, we obtain

$$\kappa=\xi(m_1+\lambda_2)[-(d+\varepsilon)(d+\varepsilon_4)-h\gamma_2(A-d\lambda_2)\alpha],$$

which means that κ has the opposite sign of ξ. Consequently, all roots of (3.1) have negative real parts if $\kappa<0$ (i.e., $\mathcal{R}_{12}^p<1$), and (3.1) admits a positive root if $\kappa>0$ (i.e., $\mathcal{R}_{12}^p>1$), completing the proof. □

The following two theorems present impacts of mutations on the co-survival of the two strains.

Theorem 3.2 *Assume that $\mathcal{R}_2>1$ and $\mathcal{R}_{12}^p>1$. Then population B_1 and population B_2 in (1.4) are uniformly persistent.*

Theorem 3.3 *Let $(1-p)\mathcal{R}_1>1$ and $\mathcal{R}_2<1$. Then population B_1 and population B_2 in (1.4) are uniformly persistent.*

The proofs of these theorems are similar to that of Theorem 2.2, and are thus omitted.

Remark 3.4 The above theorems show the influence of mutation rate $p > 0$. Comparing Theorem 3.2 with Theorem 2.2(iii), one finds that the condition $\mathcal{R}_{21} > 1$ is no longer needed in Theorem 3.2 to guarantee the persistence of both strains B_1 and B_2. This is due to the positive mutation rate. Indeed, $\mathcal{R}_2 > 1$ and $\mathcal{R}_{12}^p > 1$ imply that B_1 is uniformly persistent, providing a long term source for mutation. This, together with a positive mutation rate p, guarantees the persistence of B_2 strain. Theorem 3.3 means that a small mutation rate p is beneficial to the coexistence of strain B_1 and B_2 when $\mathcal{R}_1 > 1$ and $\mathcal{R}_2 < 1$, where the resistant strain B_2 dies out in the absence of the mutation.

We now use numerical simulations to explore the combinational effects of adaptive mutation and protections from altruistic resistant strain on the dynamics of (1.4). For illustration purpose, we fix $A = 0.02, d = 0.1, \mu_1 = 0.3026, \mu_2 = 0.17027, \gamma_1 = \gamma_2 = 0.5\times10^6, m_1 = 0.0727, m_2 = 0.09, \varepsilon_1 = 0.15C/(1+C), \varepsilon_2 = 0.13C/(1+C)$. Then $\mathcal{R}_1 > 1$ and $\mathcal{R}_{21} < 1$ when $0 < C < 4.3436$ in the *absence* of the mutation and the protection from altruistic resistant strain. Thus, B_1 population is persistent and B_2 population will go extinct for $0 < C < 4.3436$. However, when the adaptive mutation is given by

$$p = 0.6C^{0.5}\exp(-C^{1.5})$$

and the protection from altruistic resistant strain is still absent, B_2 population is persistent for $0 < C < 0.6253$ and $1.1443 < C < 4.3373$ due to the benefit of mutations, but there is a cost to B_1 which can drive the B_1 population to extinction for $0.6253 < C < 1.1443$ (see Fig. 4). Now, if we keep the adaptive mutation rate as above and incorporate the protection of altruistic resistant strain by choosing $\varepsilon_3 = 0.01, \varepsilon_4 = 0.02, \alpha = 3, h = 0.48$ and $\eta = 0.01$. Then the altruistic protection from the resistance strain to the wild strain helps the survival of the wild strain, which in return helps its own survival through the mutation from wild type to resistant type (see Fig. 5).

4 Discussions

In this paper, motivated by the experimental findings in Lee et al. (2010) that the resistant mutants of bacteria produce indoles to protect the wild strain, we have formulated a dynamical system to mimic the interactions of the populations of the wild strain, the resistance strain and the indoles. To separate influences of mutation from the interactions of the populations, in Sect. 2 we have neglected the mutation from the wild strain to the resistant strain and only considered the interaction of the wild strain with a preexisting resistant strain. We have obtained some explicit threshold conditions for the persistence of the bacteria populations. Our theoretic results on the model explain very well the experimental findings in Lee et al. (2010) that the altruistic behaviors of

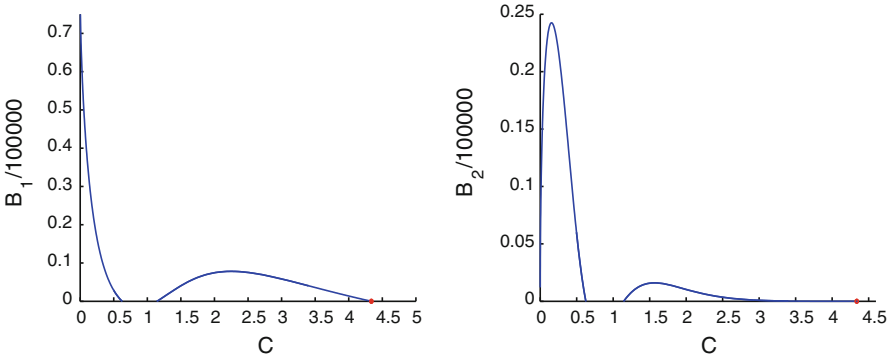


Fig. 4 The persistence and extinction of wild strain and resistance strain due to the adaptive mutations

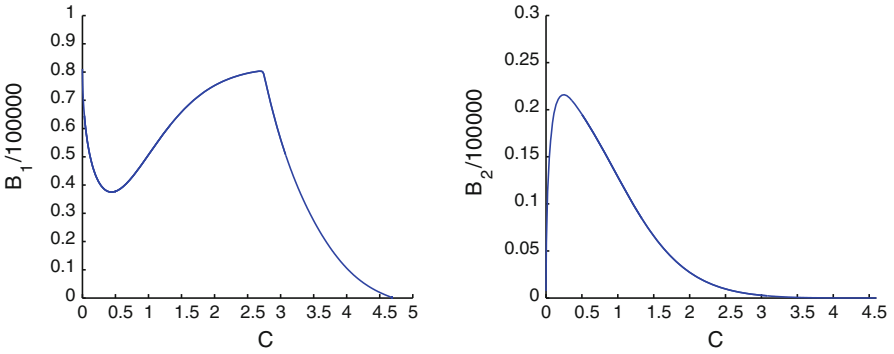


Fig. 5 The mutation and altruistic behaviors of resistant strain enhance the survival of both wild strain and resistant strain

the resistant mutants can enhance the survival of the wild type bacteria facing antibiotics stress. An obvious advantage of the explicit threshold conditions is that they may be used to select parameters for experiments to observe the co-persistence of the bacteria populations of both strains. In Sect. 3, our analysis of the model focuses on the influence of mutation rate p which is dependent on antibiotic concentration C. Our analytical results, together with numerical simulations, reveal that the adaptive mutation can facilitate the survival of resistant strain at the cost of wild strain, and the altruistic protection from the resistance strain to the wild strain helps the survival of the wild strain, which in return helps its own survival through the mutation from wild type to resistant type.

Another implication of Theorems 2.1 and 2.2, in addition to persistence/extinction conclusion, is that the antibiotic-resistance will increase the threshold of the dosage (reflected by C) of the antibiotics for eradicating the bacterial population of wild strain. Indeed, assuming $\mathcal{R}_2 > 1$ (existence of antibiotic-resistance), then the wild strain dies out if $\mathcal{R}_{12} < 1$ but becomes persistent if $\mathcal{R}_{12} > 1$; this together with the equivalent conditions in (2.4) clearly shows the impact of C (through ε_1) on the threshold value $\mathcal{R}_{12} = 1$.

One new phenomenon that is revealed by our model, but was not reported in the experimental study (Lee et al. 2010), is that the bacteria populations may experience periodic fluctuations within a certain range of model parameters. This should help avoid misreading some sample isolates in experiments: a very low count of bacteria in a sample at some time does not necessarily imply that the outcome of the bacteria is extinct; in order to obtain reliable information of the population, sampling in a sufficiently long period should be sought.

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