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Research article

Random perturbations in a mathematical model of bacterial resistance: Analysis and optimal control

Hermann Mena [1,2], Lena–Maria Pfurtscheller [2] and Jhoana P. Romero–Leiton [1,*]

[1] Escuela de Ciencias Matemáticas y Computacionales, Universidad de Investigación de Tecnología Experimental Yachay, Ecuador

[2] Institut für Mathematik, Universität Innsbruck, Austria

* **Correspondence:** Email: jpatirom3@gmail.com; Tel: +573008993635.

Abstract: In this work, we study a mathematical model for the interaction of sensitive–resistant bacteria to antibiotics and analyse the effects of introducing random perturbations to this model. We compare the results of existence and stability of equilibrium solutions between the deterministic and stochastic formulations, and show that the conditions for the bacteria to die out are weaker in the stochastic model. Moreover, a corresponding optimal control problem is formulated for the unperturbed and the perturbed system, where the control variable is prophylaxis. The results of the optimal control problem reveal that, depending on the antibiotics, the costs of the prophylaxis, such as implementation, ordering and distribution, have to be much lower than the social costs, to achieve a bacterial resistance effective control.

Keywords: sensitive bacteria; resistant bacteria; antibiotics; deterministic model; stochastic model; equilibrium solutions; stability; optimal control problem

1. Introduction

Common infections such as pneumonia, urinary infections and post–surgical infections are examples of areas where antibiotics play an important role. Historically, antibiotics have been developed to combat harmful bacteria, but not all bacteria are harmful to health, for instance, in the human organism, there are beneficial bacteria such as those that inhabit the intestines and play an important role in the digestion process [1]. To date, diseases caused by bacteria can be treated with antibiotics as long as they are not resistant to these drugs. The increase in resistance rates is a major problem in medicine because a simple infection can be lethal, also it leads to a rise of social–economical burden due to increased health care costs.

The previous scenario generates the need to research in this area, in order to create strategies that

allow to understand the evolution and propagation of bacterial resistance to antibiotics and in some way help to mitigate its evolution. From mathematics, the bacterial resistance phenomenon has been studied using a deterministic and stochastic approach, although deterministic work has dominated strongly on stochastic work [2]. From the deterministic setting, we can highlight the works focused on propagation and transmission of bacterial resistance [3–8], identifying the responsible factors of the bacterial resistance [9], examining the bacteria behaviour under the use of different antibiotic treatments [8, 10–12], optimizing the use of antibiotics [13], helping to design viable control strategies [7], modelling the acquisition of resistance from external sources [14], among others. From a stochastic approach, the works of Philipsen [1] and D'Agata et al. [10] who studied the evolution process of bacterial resistance and the impact of minimizing antibiotic treatment duration are highlighted.

Although the study of deterministic mathematical models provides important results in terms of epidemiological thresholds such as the basic reproduction number, they have some limitations, since it is quite difficult to predict the future behaviour of a biological system with precision [15]. This is due to the fact of the deterministic models do not incorporate the effect of a fluctuating environment (for example, intensity of sunlight, temperature, precipitation, among others), which yields to consider non–constant parameters in the model that oscillate around a certain average value. Therefore, the stochastic mathematical modelling of biological systems is more realistic causing a greater interest in researchers dedicated to answering questions such as: what is the probability that there is an outbreak of a certain disease? How long will a disease likely persist (with or without intervention) [15]?

The stochastic approach for a deterministic mathematical model can be introduced by including noises in the parameters involved in the model, see e.g., [16–21]. Nevertheless, there are not many results about introduction of control strategies for stochastic models. As for this topic, we can name the works given on the references [22–25].

In this work, we will first study the effects caused in the existence and stability of equilibrium solutions properties with the introduction of random perturbations to some parameters of the deterministic mathematical model proposed by Romero et al. [3], which after nondimensionalization is given by the following system of ordinary differential equations (ODEs):

$$\begin{cases} \dfrac{dS(t)}{dt} = \beta_s S[1-(S+R)] - \alpha S - \mu_s S \\ \dfrac{dR(t)}{dt} = \beta_r R[1-(S+R)] + q\alpha S - \mu_r R. \end{cases} \tag{1.1}$$

In the above mathematical model the variables S and R denote the number of sensitive and resistant bacteria population to antibiotics, respectively. The parameters β_s and β_r represent the growth rates of sensitive and resistant bacteria, respectively, being $\beta_r \leq \beta_s$ [3], and μ_s and μ_r the natural death rates of sensitive and resistant bacteria, respectively. The term $q\alpha S$ represent the number of sensitive bacteria that acquire resistance due to contact with the antibiotic, where α is the effectiveness rate of antibiotic and q is the the proportion of bacteria that mutate. A complete description of the model (1.1) can be found in Table 2 in [3]. The qualitative analysis of the previous system was done in terms of certain thresholds representing the basic reproduction numbers of resistant and sensitive bacteria. The existence and global stability conditions of the three equilibrium solutions can be found on page 66 of [3]. Secondly, we will analyse the effects of prophylaxis (such as patient education campaigns) as a control strategy, both in the deterministic and stochastic formulation, to reduce the spread of resistant

bacteria. Finally, we will do numerical experiments to validate our theoretical results.

This paper is organized as follows: first, we formulate the stochastic mathematical model and obtain conditions for the stability of equilibrium solutions in terms of the stochastic basic reproduction numbers. Then, we formulate and analyse the optimal control problems and investigate the influence of prophylaxis on the reduction of resistant bacteria. Finally, numerical simulations in both cases using data from [3] for bacteria of the genus *Staphylococus aeureus* are performed to confirm the theoretical results.

2. Stochastic mathematical model formulation

In this section we formulate the stochastic version of the mathematical model (1.1), considering the growth rates of bacteria as random rates according to [26]

$$\widetilde{\beta_s} = \beta_s + \rho_1 \dot{W}_1(t)$$
$$\widetilde{\beta_r} = \beta_r + \rho_2 \dot{W}_2(t),$$

where ρ_1 and $\rho_2 \in \mathbb{R}$ and $W_1(t)$, $W_2(t)$ are independent Brownian motions. This implies that the growth rates of sensitive and resistant bacteria are equal to an average reproduction rates plus an additional time dependent term that follow a normal distribution with a mean of zero. Thus, an stochastic version of (1.1), is given by

$$\begin{cases} dS = [\beta_s S(1-(S+R)) - (\mu_s+\alpha)S]\,dt + \rho_1 S(1-(S+R))dW_1 \\ \\ dR = [\beta_r R(1-(S+R)) + q\alpha S - \mu_r R]\,dt + \rho_2 R(1-(S+R))dW_2. \end{cases} \tag{2.1}$$

Through the rest of this paper, let $(\Omega, \mathcal{F}, \mathbb{P})$ be a complete probability space with a filtration $\{\mathcal{F}_t\}_{t\geq 0}$ satisfying the usual conditions (i.e., it is increasing and right continuous while $\mathcal{F}_0$ contains all $\mathbb{P}$-null sets). Now, we stablish a set of biological interest for the system (2.1) as follows

$$\Delta := \{(S,R) \in \mathbb{R}^2 :\ S > 0,\ R > 0,\ 0 < S+R < 1\}. \tag{2.2}$$

Theorem 2.1. *If $(S_0, R_0) \in \Delta$ is an initial condition and $q \in (0,1]$, then $\mathbb{P}[(S_t, R_t) \in \Delta] = 1$. In other words, either Δ is a set of positive invariants or Δ is a positively invariant set.*

Proof. Let us define the following functions defined on Δ:

$$f_1(S,R) = \beta_s S(1-(S+R)) - (\alpha+\mu_S)S, \qquad g_1(S,R) = \rho_1 S(1-(S+R)),$$

$$f_2(S,R) = \beta_r R(1-(S+R))) + q\alpha S - \mu_r R, \quad g_2(S,R) = \rho_2 R(1-(S+R)).$$

The Lyapunov operator associated to (2.1) is given by

$$L = \frac{\partial}{\partial t} + f_1\frac{\partial}{\partial S} + f_2\frac{\partial}{\partial R} + \frac{1}{2}g_1^2\frac{\partial^2}{\partial S^2} + \frac{1}{2}g_2^2\frac{\partial^2}{\partial R^2}. \tag{2.3}$$

Let $V : \Delta \to [0, +\infty)$ be the function defined by

$$V(S,R) = -\ln S - \ln R - \ln(1-(S+R)). \tag{2.4}$$

We claim that LV is bounded above on Δ. In order to prove this, we define

$$L_1 := \frac{\partial}{\partial t} + f_1\frac{\partial}{\partial S} + f_2\frac{\partial}{\partial R}, \quad L_2 := \frac{1}{2}g_1^2\frac{\partial^2}{\partial S^2} + \frac{1}{2}g_2^2\frac{\partial^2}{\partial R^2}.$$

Note that $L = L_1 + L_2$. Now,

$$\begin{aligned} L_1V = &-\beta_s(1-(S+R)) + (\mu_s+\alpha) + \beta_s S - \frac{(\mu_s+\alpha)S}{1-(S+R)} \\ &-\beta_r(1-(S+R)) - \frac{q\alpha S}{R} + \mu_r + \beta_r R + \frac{q\alpha S}{1-(S+R)} - \frac{\mu_r R}{1-(S+R)}. \end{aligned}$$

As $0 < q \leq 1$, $R, S \in (0,1)$ and $1-(S+R) > 0$, this yields to

$$L_1V \leq \mu_s + \alpha + \beta_s + \mu_r + \beta_r. \tag{2.5}$$

Similar calculations show that

$$L_2V \leq \rho_1^2 + \rho_2^2. \tag{2.6}$$

It follows from (2.5) and (2.6) that there is a positive constant C such that $LV \leq C$ on Δ. Continuing with the proof, for each $k \in \mathbb{N}$, we define

$$\Delta_k = \left\{(S,R) \in \mathbb{R}^2 : S > \frac{1}{k}, R > \frac{1}{k} \text{ and } S+R < 1-\frac{1}{k}\right\}.$$

Note that $\Delta_k \nearrow \Delta$ as $k \to +\infty$. Defining

$$\tau := \inf\{t \geq 0 : S(t) = 0 \vee R(t) = 0 \vee S(t) + R(t) = 1\},$$

and for each $k \in \mathbb{N}$

$$\tau_k := \inf\left\{t \geq 0 : S(t) = \frac{1}{k} \vee R(t) = \frac{1}{k} \vee S(t) + R(t) = 1 - \frac{1}{k}\right\}.$$

Therefore $\tau_k \nearrow \tau$ almost surely as $k \to +\infty$.

To prove that $\mathbb{P}[(S(t), R(t)) \in \Delta] = 1$ it is equivalent to show that $\mathbb{P}[\tau = +\infty] = 1$. If we assume that $\mathbb{P}[\tau = +\infty] < 1$, then there exists $\eta > 0$ such that $\mathbb{P}[\tau < \infty] > \eta$. As $\lim_{T\to+\infty}\mathbb{P}[\tau < T] = \mathbb{P}[\tau < \infty]$, there exists $T > 0$ such that

$$\mathbb{P}[\tau < T] > \eta. \tag{2.7}$$

As τ_k converges almost surely to τ, there exists $k_0 \in \mathbb{N}$ such that for every $k \geq k_0$ it holds that

$$\mathbb{P}[\tau_k < T] > \eta.$$

Itôs formula yields to

$$dV = LV + \frac{\partial V}{\partial S}dW_1 + \frac{\partial V}{\partial R}dW_2 \leq C + \frac{\partial V}{\partial S}dW_1 + \frac{\partial V}{\partial R}dW_2,$$

where we used that $LV \leq C$ on Δ. Therefore,

$$V(S(\tau_k \wedge T), R(\tau_k \wedge T)) \leq V(S(0), R(0)) + CT + \int_0^{\tau_k \wedge T} \frac{\partial V}{\partial S} dW_1 + \int_0^{\tau_k \wedge T} \frac{\partial V}{\partial R} dW_2,$$

and integrating both sides of the above inequality yields to

$$\mathbb{E}[V(S(\tau_k \wedge T), R(\tau_k \wedge T))] \leq V(S(0), R(0)) + CT.$$

As

$$\begin{aligned}\mathbb{E}[V(S(\tau_k \wedge T), R(\tau_k \wedge T))] &\geq \mathbb{E}[V(S(\tau_k \wedge T), R(\tau_k \wedge T)) 1_{\{\tau_k < T\}}] \\ &\geq -\ln(1/k)\mathbb{P}[\tau_k < T],\end{aligned}$$

we obtain

$$\mathbb{P}[\tau_k < T] \leq -\frac{CT + V(S(0), R(0))}{\ln(1/k)}.$$

Taking the limit $k \to \infty$, we get that $\mathbb{P}[\tau < T] = 0$ which contradicts (2.7). Therefore, it holds that $\mathbb{P}[\tau = +\infty] = 1$, which completes the proof. □

2.1. Analysis of the model

Now, based on the below definition, we will determine conditions for the stability of the equilibrium solutions of the stochastic system (2.1).

Definition 2.2 ([27])**.** Consider the general n–dimensional stochastic system

$$dX(t) = f(t, X(t))dt + g(t, X(t))dW, \tag{2.8}$$

with initial condition $X(0) = X_0$ and its solution is denoted by $X(t, X_0)$. Assume that $f(t, 0) = g(t, 0) = 0$ for all $t \geq 0$, so $X = 0$ is an equilibrium of (2.8). Then, the equilibrium $X = 0$ is said to be

(i) almost surely exponentially stable if for all $X_0 \in \mathbb{R}^n$,

$$\limsup_{t \to \infty} \frac{1}{t} \ln |X(t, X_0)| < 0 \quad \text{a.s.};$$

(ii) pth moment exponentially stable if there is a pair of positive constants C_1, C_2 such that for all $X_0 \in \mathbb{R}^n$,

$$\mathbb{E}[|X(t, X_0)|^p] \leq C_1 |X_0|^p e^{-C_2 t}, \quad \text{on } t \geq 0.$$

When $p = 2$, it is usually said to be exponentially stable in mean square and the equilibrium $X = 0$ is globally asymptotically stable.

Let us note that $E_0 := (0, 0)$ is the trivial equilibrium of the system (2.1). Conditions for exponential moment stability of E_0 in terms of Lyapunov function are given in the following lemma.

Lemma 2.3 ([27, Theorem 3]). *Suppose that there exists a function $V(t,x) \in C^{1,2}(\mathbb{R}\times\mathbb{R}^n)$ satisfying the inequalities*

$$\begin{aligned} K_1|x|^p \quad &\le V(t,x) \le K_2|x|^p \text{ and} \\ LV(t,x) \quad &\le -K_3|x|^p, \quad K_i > 0, p > 0,\ i \in \{1,2,3\}. \end{aligned} \tag{2.9}$$

Then the equilibrium of the system (2.1) *is pth moment exponentially stable.*

Theorem 2.4. *If the conditions*

$$\begin{aligned} &-\beta_s + (\alpha+\mu_s) - \tfrac{p-1}{2}\rho_1^2 > 0 \quad \text{and} \\ &-\beta_r + \mu_r - \tfrac{p-1}{2}\rho_2^2 > 0 \end{aligned} \tag{2.10}$$

hold, then the equilibrium E_0 of the system (2.1) *is pth moment exponentially stable.*

Proof. Let us consider the Lyapunov function

$$V(S,R) = \lambda_1 S^p + \lambda_2 R^p,$$

where λ_i, $i = 1,2$ are positive constants. The first inequality of (2.9) is naturally fulfilled. Next, we show the second inequality of (2.9) and apply the Lyapunov operator (2.3) to V.

$$\begin{aligned} LV &= p\lambda_1\left[\beta_s(1-(S+R)) - (\alpha+\mu_s) + \frac{p-1}{2}\rho_1^2(1-(S+R))^2\right]S^p \\ &\quad + p\lambda_2 q\alpha S R^{p-1} + p\lambda_2\left[\beta_r(1-(S+R)) - \mu_r + \frac{p-1}{2}\rho_2^2(1-(S+R))^2\right]R^p \\ &\le \left[\lambda_1\left(p\beta_s - p(\alpha+\mu_s) + \frac{p(p-1)}{2}\rho_1^2\right) + \lambda_2 q\alpha\varepsilon^{1-p}\right]S^p \\ &\quad + \lambda_2\left[p\beta_r - p\mu_r + \frac{p(p-1)}{2}\rho_2^2 + q\alpha(p-1)\varepsilon\right]R^p \\ &= -\left[\lambda_1\left(-p\beta_s + p(\alpha+\mu_s) - \frac{p(p-1)}{2}\rho_1^2\right) - \lambda_2 q\alpha\varepsilon^{1-p}\right]S^p \\ &\quad - \lambda_2\left[-p\beta_r + p\mu_r - \frac{p(p-1)}{2}\rho_2^2 - q\alpha(p-1)\varepsilon\right]R^p, \end{aligned}$$

where we used a variant of Young's inequality

$$x^{p-1}y \le \frac{p-1}{p}\varepsilon x^p + \frac{1}{p}\varepsilon^{1-p}y^p, \quad x,y>0,$$

as well as $0 < S+R < 1$. Under the conditions (2.10) we can choose ε small enough and $\lambda_1, \lambda_2 > 0$ such that the coefficients of S^p and R^p are negative. This completes the proof. □

From Theorem 2.4 we derive conditions such that the equilibrium E_0 is globally asymptotically stable.

Lemma 2.5. *If* $-\beta_s + (\alpha + \mu_s) - \frac{1}{2}\rho_1^2 > 0$ *and* $-\beta_r + \mu_r - \frac{1}{2}\rho_2^2 > 0$*, the equilibrium* E_0 *of the system* (2.1) *is globally asymptotically stable.*

Proof. Taking $p = 2$ in (2.10) yields immediately to the desired result. □

Next, we want to derive similar basic reproduction numbers for the resistant and sensitive bacteria, respectively as in the deterministic formulation. Recall, for the unperturbed model, those thresholds are given by

$$R_r = \frac{\beta_r}{\mu_r} \text{ and } S_0 = \frac{\beta_s}{\alpha + \mu_s},$$

and depending on these values, there are three equilibrium solutions, E_0 where both bacteria die out, E_1 where only resistant bacteria survives, and the equilibrium of coexistence E_2. As for the perturbed models these thresholds differ, see e.g., [28], we will study the behaviour of the stochastic model.

Theorem 2.6. *Let* $(S, R) \in \Delta$ *be the solution of* (2.1)*. The following holds:*
If either

$$S_0^S := \frac{\beta_s - \frac{1}{2}\rho_1^2}{\alpha + \mu_s} < 1, \quad \textit{and } \rho_1^2 \leq \beta_s, \tag{2.11}$$

or

$$\rho_1^2 > \max\left\{\frac{\beta_s^2}{2(\alpha + \mu_s)}, \beta_s\right\}, \tag{2.12}$$

and either

$$R_r^S := \frac{\beta_r - \frac{1}{2}\rho_2^2}{\mu_r} < 1, \quad \textit{and } \rho_2^2 \leq \beta_r, \tag{2.13}$$

or

$$\rho_2^2 > \max\left\{\frac{\beta_r^2}{2\mu_r}, \beta_r\right\}, \tag{2.14}$$

then the solution of the system (2.1) *has the following property:*

$$\limsup_{t\to\infty} \frac{\log S(t)}{t} \leq -a < 0 \quad a.s.,$$
$$\limsup_{t\to\infty} \frac{\log R(t)}{t} \leq -b < 0 \quad a.s.,$$

namely it tends to zero exponentially almost surely, where $a, b > 0$ *are positive constants. In other words, both the sensitive and the resistant bacteria die out with probability one.*

Proof. The proof follows closely the one given in [28]. By Itô's formula, it holds that

$$d\ln S = \left[\beta_s(1 - (S + R)) - (\alpha + \mu_s) - \frac{1}{2}\rho_1^2(1 - (S + R))^2\right] dt$$

$$+\frac{1}{2}\rho_1(1-(S+R))dW_1.$$

As $(S,R)\in\Delta$, we have that $S+R\in(0,1)$ and using the large number theorem for martingales [29], we get

$$\limsup_{t\to\infty}\frac{1}{t}\int_0^t(1-(S+R))dW_1=0\quad\text{a.s..}$$

Moreover the function $f:(0,1)\to\mathbb{R}$ defined by

$$f(x)=\beta_s x-\frac{\rho_1^2}{2}x^2-(\alpha+\mu_s)=-\frac{\rho_1^2}{2}\left(x-\frac{\beta_s}{\rho_1^2}\right)^2-(\alpha+\mu_s)+\frac{\beta_s^2}{2\rho_1^2}$$

has its maximum value at $x=1$ if $\rho_1^2<\beta_s$. This yields to

$$\limsup_{t\to\infty}\frac{1}{t}\ln S\le\left(-\frac{\rho_1^2}{2}+\beta_s-(\alpha+\mu_s)\right)<0\iff S_0^S<1.$$

On the other hand, if (2.12) holds, then

$$f(x)=-\frac{\rho_1^2}{2}\left(x-\frac{\beta_s}{\rho_1^2}\right)^2-(\alpha+\mu_s)+\frac{\beta_s^2}{2\rho_1^2}\le-(\alpha+\mu_s)+\frac{\beta_s^2}{2\rho_1^2}<0,$$

and therefore, also

$$\limsup_{t\to\infty}\frac{1}{t}\ln S<0.$$

Next we show that also R tends to zero exponentially almost surely by using condition (2.13). Without loss of generality it holds that $0\le S\le\varepsilon R$, as $R\in\Delta$ and S tends to zero exponentially a.s.. Then, Itô's formula gives

$$\begin{aligned}d\ln R\le&\left[\beta_r(1-(S+R))-\mu_r+q\alpha\varepsilon-\frac{1}{2}\rho_2^2(1-(S+R))^2\right]dt\\&+\frac{1}{2}\rho_2(1-(S+R))dW_2.\end{aligned}$$

Using a similar argument as above, we can define a function $\tilde{f}:(0,1)\to\mathbb{R}$, $x\mapsto\beta_r x-\mu_r-\frac{1}{2}\rho_2^2x^2$, and its maximum value is obtained at $x=1$ if $\rho_2^2\le\beta_r$. Taking the limit $t\to\infty$, $\varepsilon\to0$ yields to

$$\limsup_{t\to\infty}\frac{1}{t}\ln R\le-\frac{1}{2}\rho_2^2+\beta_r-\mu_r<0\iff R_r^S<1.$$

The same assertion can be shown when using condition (2.14). This follows analogously and will be omitted here. □

Remark 2.7. *The conditions* (2.11) *and* (2.13) *in Theorem 2.6 state that the bacteria will extinct if* $R_r^S<1$ *and* $S_0^S<1$ *and the white noise is not too large or if the white noise is large enough such that the conditions* (2.12) *and* (2.14) *are fulfilled. Moreover, the thresholds compared to the unperturbed system differ by the noise parameters* ρ_1, ρ_2, *and the conditions for the stochastic model are weaker than for the deterministic system. This will be also illustrated in more detail in Subsection 2.2.*

The remaining part of this subsection deals with the persistence of bacteria.

Theorem 2.8. *Let* $(S, R) \in \Delta$ *be the solution of* (2.1)*. Then,*

(i) If $R_r^S > 1$ *and* (2.11) *or* (2.12) *are fulfilled, then the sensitive bacteria tend to zero exponentially and the resistant bacteria satisfy*

$$\liminf_{t\to\infty} \frac{1}{t}\int_0^t R(s)ds =: \liminf_{t\to\infty}\langle R\rangle \geq \frac{R_r^S - 1}{R_r^S} > 0, \tag{2.15}$$

i.e. the resistant bacteria are persistent in mean.

(ii) If $S_0^S > 1$, $R_r < S_0^S$, $R_r^S < S_0^S$ *and* $\mu_r(S_0^S - R_r) > \frac{S_0^S - S_0}{S_0^S - 1} q\alpha S_0^S$, *then both the sensitive and resistant bacteria are persistent in mean and they satisfy*

$$\liminf_{t\to\infty}\langle R\rangle \geq \frac{q\alpha(S_0^S - 1)}{(q\alpha + \mu_r)\left(S_0^S - \frac{\mu_r}{\mu_r + q\alpha}R_r^S(S_0^S - S_0 + 1)\right)} > 0,$$

$$\liminf_{t\to\infty}\langle S\rangle \geq \frac{1}{S_0^S}\frac{(S_0^S - S_0)q\alpha + (S_0^S - 1)\mu_r\left(1 - \frac{R_r}{S_0^S}\right)}{q\alpha + \mu_r\left(1 - \frac{R_r}{S_0^S}\right)} > 0.$$

Proof. First we show (i). Since either (2.11) or (2.12) hold, it follows from Theorem 2.6 that $\lim_{t\to\infty} S(t) = 0$ a.s.. Moreover, applying Itô's formula to $V = \ln R$ yields

$$\begin{aligned} d\ln R = &\left[\beta_r(1 - (S + R)) - \mu_r + q\alpha\frac{S}{R} - \frac{\rho_2^2}{2}(1 - (S + R))^2\right]dt \\ &+ \rho_2(1 - (S + R))dW_2. \end{aligned}$$

Thus,

$$\begin{aligned} \frac{\ln R(t) - \ln R(0)}{t} \geq{}& \beta_r - \left(\beta_r - \frac{\rho_2^2}{2}\right)\langle S\rangle - \left(\beta_r - \frac{\rho_2^2}{2}\right)\langle R\rangle - \mu_r + q\alpha\langle\frac{S}{R}\rangle \\ &- \frac{\rho_2^2}{2} + \frac{\rho_2}{t}\int_0^t (1 - (S + R))dW_2, \end{aligned}$$

where we used that $0 < R < 1$ and $0 < S + R < 1$ and in particular for $0 \leq S \leq \varepsilon R$ it holds that

$$\begin{aligned} \langle R\rangle \geq{}& \frac{1}{\beta_r - \frac{\rho_2^2}{2}}\left(\beta_r - \mu_r - \frac{\rho_2^2}{2} + q\alpha\varepsilon - \left(\beta_r - \frac{\rho_2^2}{2}\right)\varepsilon\right) \\ &+ \frac{\rho_2}{t}\int_0^t (1 - (S + R))dW_2 + \frac{1}{t}\ln R(0) - \frac{1}{t}\ln R(t). \end{aligned}$$

The large number theorem for martingales [29] states that

$$\lim_{t\to\infty}\frac{\rho_2}{t}\int_0^t (1 - (S + R))dW_2 = 0, \quad \lim_{t\to\infty}\frac{\ln R(0)}{t} = 0,$$

and taking the limit $t \to \infty$ and $\varepsilon \to 0$, we obtain

$$\liminf_{t\to\infty} \langle R\rangle \geq \frac{R_r^S - 1}{R_r^S} > 0 \iff R_r^S > 1.$$

Next, we show assertion (*ii*). Itô's formula implies that

$$\begin{aligned} d\ln S &= \left[\beta_s(1-(S+R)) - (\alpha+\mu_s) - \frac{\rho_1^2}{2}(1-(S+R))^2\right]dt \\ &\quad + \rho_1(1-(S+R))dW_1, \end{aligned}$$

and in particular,

$$\begin{aligned} \langle S\rangle &\geq \frac{1}{\beta_s - \frac{\rho_1^2}{2}}\left(\beta_s - (\alpha+\mu_s) - \frac{\rho_1^2}{2} - \left(\beta_s - \frac{\rho_1^2}{2}\right)\langle R\rangle\right) + \varphi_1(t), \\ &= \left(\frac{S_0^S - 1}{S_0^S}\right) - \langle R\rangle + \varphi_1(t), \end{aligned} \tag{2.16}$$

where we used the definition of S_0^S and φ_1 is given by

$$\varphi_1(t) = \frac{\rho_1}{t}\int_0^t (1-(S+R))dW_1 - \frac{\ln S(t) - \ln S(0)}{t}.$$

Similarly we can show that

$$\begin{aligned} \langle S\rangle &\leq \frac{1}{\beta_s - \frac{\rho_1^2}{2}}\left(\beta_s - (\alpha+\mu_s) - \left(\beta_s - \frac{\rho_1^2}{2}\right)\langle R\rangle\right) + \varphi_1(t), \\ &= \frac{S_0 - 1}{S_0^S} - \langle R\rangle + \varphi_1(t). \end{aligned} \tag{2.17}$$

Integration of the second equation of (2.1) leads to

$$\begin{aligned} \frac{R(t)-R(0)}{t} &= (\beta_r\langle R(1-(S+R))\rangle - \mu_r\langle R\rangle + q\alpha\langle S\rangle)\,dt \\ &\quad + \frac{\rho_2}{t}\int_0^t R(1-(S+R))dW_2 \\ &\geq \left(\left(\beta_r - \frac{\rho_2^2}{2}\right)\langle R(1-(S+R))\rangle - \mu_r\langle R\rangle + q\alpha\langle S\rangle\right)dt \\ &\quad + \frac{\rho_2}{t}\int_0^t R(1-(S+R))dW_2, \end{aligned}$$

where we used that $0 < S + R < 1$. To this end, inserting the inequalities (2.16) and (2.17) yields to

$$\frac{R(t)-R(0)}{t} \geq \left(\left(\beta_r - \frac{\rho_2^2}{2}\right)\langle R\rangle - \left(\beta_r - \frac{\rho_2^2}{2}\right)\frac{S_0 - 1}{S_0^S}\langle R\rangle\right.$$

$$- (\mu_r + q\alpha)\langle R\rangle + \frac{S_0^S - 1}{S_0^S} q\alpha \Big) dt + \frac{\rho_2}{t} \int_0^t R(1 - (S + R)) dW_2$$
$$+ \left(q\alpha - \beta_r + \frac{\rho_2^2}{2} \right) \varphi_1(t),$$

and therefore,

$$\begin{aligned} \langle R\rangle &\geq \frac{q\alpha \frac{S_0^S - 1}{S_0^S}}{q\alpha + \mu_r - \left(\beta_r - \frac{\rho_2^2}{2}\right)\left(1 - \frac{S_0 - 1}{S_0^S}\right)} + \varphi(t) \\ &= \frac{q\alpha(S_0^S - 1)}{(q\alpha + \mu_r)\left(S_0^S - \frac{\mu_r}{\mu_r + q\alpha} R_r^S (S_0^S - S_0 + 1)\right)} + \varphi(t), \end{aligned} \tag{2.18}$$

where φ is defined by

$$\varphi(t) = \frac{\rho_2}{t} \int_0^t R(1 - (S + R)) dW_2 + \left(q\alpha - \beta_r + \frac{\rho_2^2}{2} \right) \varphi_1(t) - \frac{R(t) - R(0)}{t}.$$

Using again the large number theorem of martingales, we obtain that

$$\lim_{t\to\infty} \varphi(t) = 0.$$

Thus, it holds that

$$\liminf_{t\to\infty} \langle R\rangle \geq \frac{q\alpha(S_0^S - 1)}{(q\alpha + \mu_r)\left(S_0^S - \frac{\mu_r}{\mu_r + q\alpha} R_r^S (S_0^S - S_0 + 1)\right)} > 0,$$

if the conditions of (ii) are fulfilled. Similarly one could show that

$$\limsup_{t\to\infty} \langle R\rangle \leq \frac{q\alpha(S_0 - 1)}{(q\alpha + \mu_r)\left(S_0^S - \frac{\mu_r R_r}{q\alpha + \mu_r}\right)}. \tag{2.19}$$

Finally, we have to show that also $\liminf_{t\to\infty} \langle S\rangle > 0$. Due to (2.16) and (2.19), it holds that

$$\begin{aligned} \liminf_{t\to\infty} \langle S\rangle &\geq \frac{S_0^S - 1}{S_0^S} - \limsup_{t\to\infty} \langle R\rangle \geq \frac{S_0^S - 1}{S_0^S} - \frac{q\alpha(S_0 - 1)}{(q\alpha + \mu_r)\left(S_0^S - \frac{\mu_r R_r}{\mu_r + q\alpha}\right)} \\ &= \frac{1}{S_0^S}\left((S_0^S - 1) - \frac{q\alpha(S_0 - 1)}{q\alpha + \mu_r - \frac{\beta_r}{S_0^S}} \right) \\ &= \frac{S_0^S - 1}{S_0^S} \frac{\mu_r\left(1 - \frac{R_r}{S_0^S}\right)}{q\alpha + \mu_r\left(1 - \frac{R_r}{S_0^S}\right)} + \frac{S_0^S - S_0}{S_0^S} \frac{q\alpha}{q\alpha + \mu_r\left(1 - \frac{R_r}{S_0^S}\right)}. \end{aligned}$$

This concludes the proof. □

2.2. Numerical simulations

In this subsection, we do some numerical experiments to corroborate our theoretical results. The values of the dimensionless parameters were obtained from [3] and are given in Table 1. According to [3], the unit of time before nondimensionalization corresponds to days.

Table 1. Values of the parameters for the model (2.1).

Parameter	Definition	Value
β_s	Growth rate of S	0.4
β_r	Growth rate of R	0.1
μ_s	Natural death rate of S	0.2
μ_r	Natural death rate of R	0.5
ρ_1	Intensity of noise for β_s	0.5
ρ_2	Intensity of noise for β_r	0.5

Recall the parameter α represents the elimination rate of bacteria by antibiotic which is considered to vary depending on the antibiotic supplied: Linezolid, Penicillin G or Methicillin. Table 2 shows the values of these variations.

Table 2. Values of the parameters α and q depending on the type of antibiotic.

Parameter	Description	Linezolid	Penicillin G	Methicillin
α	Elimination rate of S	39.7	0.1204	32.4
q	Fraction of S that acquires resistance	4×10^{-3}	0.3992	0.1234

The previous section tells us, that the trivial equilibrium E_0 of the system (2.1) exists if $S_0^S < 1$ and $\rho_1^2 < \beta_s$ and $R_r^S < 1$ and $\rho_2^2 < \beta_r$, respectively or if the noise parameters are large compared to the other model parameters. The goal of this subsection is to confirm the theoretical results with numerical simulations. In the following, we approximate the mean of the solution of the stochastic system by performing a Monte–Carlo simulation using 5000 different paths and compare it with the deterministic results.

As a first example, we take the values from Table 1 and Linezolid as antibiotic. In this case it holds that $R_r = 0.2$, $S_0 = 0.01$ and $R_r^S = -0.05$ and $S_0^S = 0.069$ respectively. Thus, using the results of Table 2 from [3], we should obtain the equilibrium E_0 see Figure 1).

We see that both the resistant and the sensitive bacteria tend to zero for the deterministic model and this is also the case for the stochastic model.

As a next example, we use Methicillin and change the natural death rate of R to 0.09. Then, for the deterministic model, we have $R_r = 1.11$ and $S_0 = 0.0123$ but $\rho_2^2 > \beta_r$ respectively. The theoretical analysis of the previous section tells that in the stochastic case both bacteria dies out while in the deterministic case, the resistant bacteria survives. However, if we decrease ρ_2 to 0.1, we obtain that $R_r^S > 1$ and the behaviour of the stochastic system coincides with the deterministic one. Therefore, in

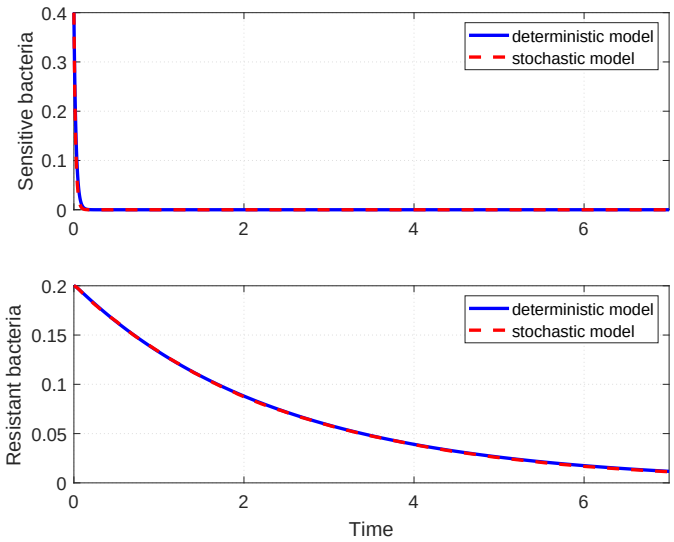

Figure 1. Approximated mean of the solution of the system (2.1) and the corresponding deterministic model (1.1) for Linezolid. The unit of time before nondimensionalization corresponds to days.

Figure 2 the mean of the solution of the stochastic model is plotted for both, $\rho_2 = 0.5$ and $\rho_2 = 0.1$ respectively.
The theoretical results for the equilibrium E_1 coincide with the numerical results as can be seen in Figure 2. For both models only the sensitive bacteria goes extinct if we use $\rho_2 = 0.1$, however, for $\rho_2 = 0.1$ both bacteria die out.
Finally, Penicillin G is taken as antibiotic. Then, $S_0 > 1$ but for the stochastic setting we have $S_0^S < 1$. Thus, we need to change ρ_1 to 0.3, which leads to $S_0^S > 1$ and both, the sensitive and resistant bacteria should be present, which is confirmed by Figure 3.
The numerical simulations of equations (1.1) and (2.1) which can be seen in Figures 1–3 confirm the theoretical results derived in Section 2 and are in line with the deterministic results from [3].

3. Optimal control problem

From a mathematical approach only a small number of studies have established analytical results for the optimal control of an infectious disease under drug resistance, see e.g., [11, 30–33]. Here, we do not consider a population–model for individuals infected with a bacterial disease, but we consider a simple model where sensitive and resistant bacteria interact. Thus, in this section we study the optimal control problem for the deterministic model (1.1) which motivates the stochastic case (2.1). We first analyse the setting, show the existence of the control and also present some numerical simulations.

3.1. Deterministic optimal control problem

In order to formulate the deterministic optimal control problem, the following additional hypothesis in the model (1.1) are considered: the population of resistant bacteria are perturbed by prophylaxis at a rate $(1 - \eta(t))q\alpha$, being $\eta(t)$ the control by prophylaxis, which assumes values between 0 and 1, where

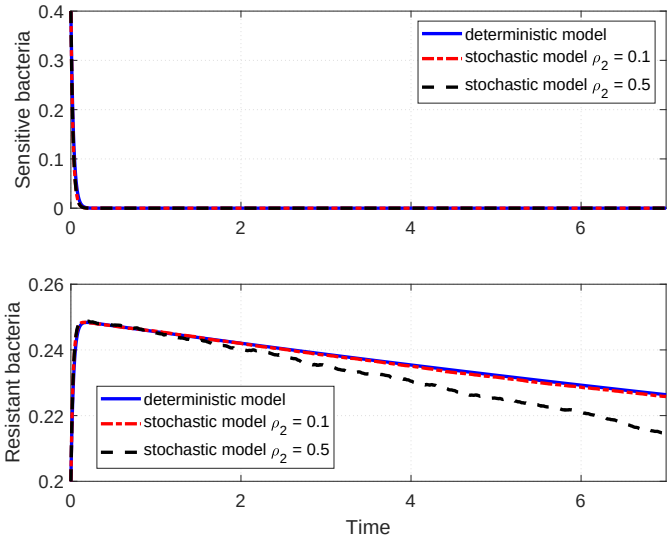

Figure 2. Approximated mean of the solution of system (2.1) and the corresponding deterministic model (1.1) for Methicillin. The unit of time before nondimensionalization corresponds to days.

$\eta = 0$ is assumed if the prophylaxis is ineffective and $\eta = 1$ if it is completely effective, that is, there is no mutation due to antibiotics. Thus, we have that the control variable $\eta(t)$ provides information about the amount of patients that must be educated.

The main goal will be to minimize the number of resistant bacteria. For this purpose, the following cost function is considered

$$J(\eta) = \int_0^T \left(aR + \frac{1}{2} b\eta^2 \right) dt. \tag{3.1}$$

In above function a represents the social cost, which depends on the number of resistant bacteria due to mutations, and the function $\frac{1}{2}b\eta^2$ defines the absolute cost associated to the control strategy, such as implementation, ordering, distribution, among others.

Taking $x = (S, R)$ and the above considerations, the following optimal control problem is formulated

$$\begin{cases} J(\eta) & = \min \int_0^T \left(aR + \frac{1}{2} b\eta^2 \right) dt \\ \dfrac{dS}{dt} & = \beta_s S[1 - (S + R)] - \alpha S - \mu_s S \\ \dfrac{dR}{dt} & = \beta_r R[1 - (S + R)] + (1 - \eta) q\alpha S - \mu_r R \\ x(0) & = (\bar{S}, \bar{R}) = x_0 \\ x(T) & = (S_f, R_f) = x_1. \end{cases} \tag{3.2}$$

In our control problem, we assume an initial time $t_0 = 0$, a final time T fixed representing the

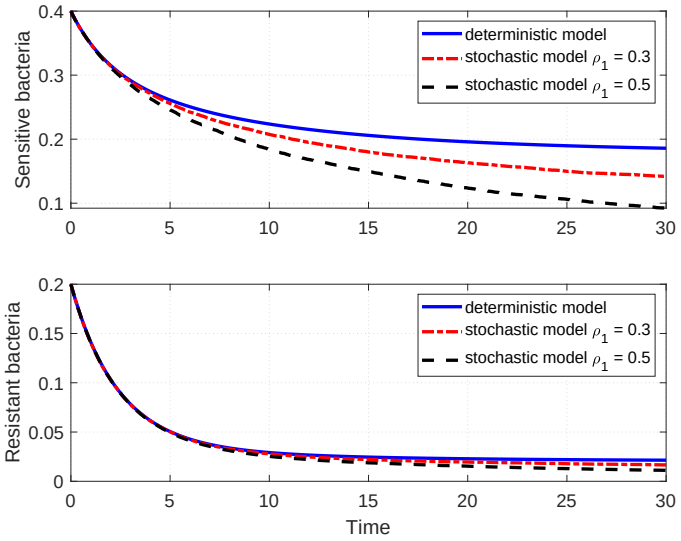

Figure 3. Approximated mean of the solution of system (2.1) and the corresponding deterministic model (1.1) for Penicillin G. The unit of time before nondimensionalization corresponds to days.

implementation time of the control strategy, and also we assume free dynamic variables x_1 at the final time, while the coordinates of the initial condition x_0 are the coordinates of a non–trivial equilibrium of the system (1.1). Additionally, we assume that control variable is in an appropriate set of admissible controls, namely $\mathcal{U} = \{\eta(t) : \eta(t)$ is Lebesgue measurable and $0 \leq \eta(t) \leq 1, t \in [0, T]\}$.

In the following, we prove the existence and uniqueness of the control η. To this end, using arguments similar to [34], we have to show that the following properties have to be fulfilled:

(i) The set of all solutions to the state equations from (3.2) with corresponding control functions in $\mathcal{U}$ is not empty.

(ii) The right side of the state equation from (3.2) is continuous, bounded above by a sum of bounded control and state, and can be written as a linear function of the control variables with coefficients dependent on time and the state variables.

(iii) The integrand in the cost function $aR + \frac{1}{2}b\eta^2$ is convex on $\mathcal{U}$ and additionally satisfies

$$aR + \frac{1}{2}b\eta^2 \geq k_1|\eta|^\delta - k_2 \quad \text{where } k_1, k_2 > 0, \delta > 1.$$

Assumption (i) is fulfilled by Theorem 1 from [4]. Rewriting the right side of the state system as $\dot{x} = f(x) + g(x)\eta$ immediately leads to Assumption (ii). Moreover, the integrand in the cost function is clearly convex and we have that

$$aR + \frac{1}{2}b\eta^2 \geq -aR + \frac{1}{2}b\eta^2 \geq -k_2 + k_1|\eta|^2,$$

such that Assumption (iii) is fulfilled. Thus, there exists an optimal control.

Now, the Pontryagin principle for bounded controls [35] is used to calculate the optimal control of (3.2). To this end, we observe that the Hamiltonian is given by

$$H = aR + \frac{1}{2}b\eta^2 + \lambda_1 \left[\beta_s S(1 - (S + R)) - \alpha S - \mu_s S\right]$$

$$+ \lambda_2 \left[\beta_r R(1 - (S + R)) + q\alpha S - \mu_r R\right], \tag{3.3}$$

where λ_i, $i = 1, 2$ are the *adjoint variables* which determine the adjoint system. The adjoint system and the formulation (3.2) define the optimal system. The main result of this section is summarized in the following theorem.

Theorem 3.1. *For* (3.2) *there exists a corresponding optimal solution* $(S^\star(t), R^\star(t))$ *that minimize* $J(\eta)$ *in* $[0, T]$. *Moreover, there exits an adjoint function* $\lambda(t) = (\lambda_1(t), \lambda_2(t))$ *such that*

$$\begin{cases} \dfrac{d\lambda_1}{dt} = & \lambda_1(2\beta_s S + \beta_s R + \mu_s + \alpha - \beta_s) - \lambda_2[\beta_r R + (1 - \eta(t))q\alpha] \\ \dfrac{d\lambda_2}{dt} = & -a + \lambda_1\beta_s S + \lambda_2(2\beta_r R + \beta_r S + \mu_r - \beta_r) \end{cases} \tag{3.4}$$

with transversality conditions $\lambda_i(t) = 0$ *for* $i = 1, 2$ *which satisfy*

$$\eta^\star = \min\left\{\max\left\{0, \frac{\lambda_2 q\alpha S}{b}\right\}, 1\right\}.$$

Proof. The Pontryagin Principle applied to (3.2) guarantees the existence of adjoint variables λ_i, $i = 1, 2$ that satisfy

$$\begin{aligned} \dot{\lambda}_1 &= -\frac{\partial H}{\partial S}, \quad \lambda_1(T) = 0, \\ \dot{\lambda}_2 &= -\frac{\partial H}{\partial R}, \quad \lambda_2(T) = 0, \\ H &= \max_{\eta \in \mathcal{U}} H. \end{aligned}$$

Replacing the derivatives of H with respect to S and R in above equations we obtain the system (3.4). The optimality condition for the Hamiltonian is given by $\dfrac{\partial H}{\partial \eta^\star} = 0$, or equivalently $b\eta^\star - \lambda_2 q\alpha S = 0$, from where $\eta^\star = \dfrac{\lambda_2 q\alpha S}{b}$. In consequence, the optimal control $\eta^\star$ is given by

$$\eta^\star = \min\left\{\max\left\{0, \frac{\lambda_2 q\alpha S}{b}\right\}, 1\right\}.$$

□

3.2. Numerical solutions

In this subsection, some numerical simulations for the problem (3.2) are performed to observe the effects of prophylaxis as control strategy. To this end, we use the forward–backward sweep method described on [36]. The implementation time of control is approximately 10 days and the values of the relative weights are $a = b = 0.002$ as it is suggested in [37]. Here we omit the case of Linezolid as the bacteria die out even without control strategy.

In Figure 4 we observe the control effectiveness. From the first moment the Methicillin–resistant bacteria population R is controlled while without control R grows. On the other hand, η starts at the

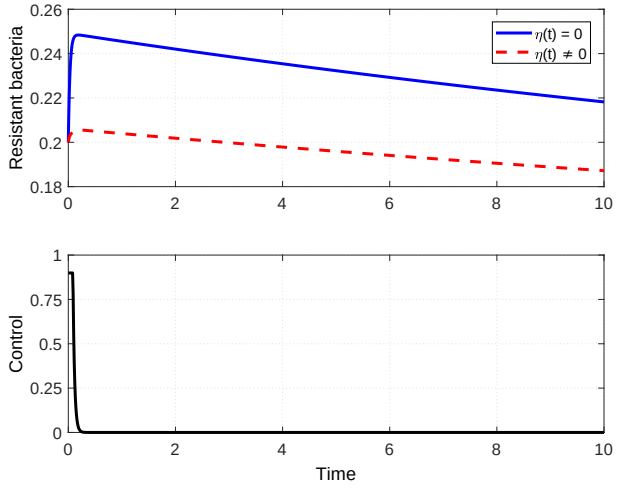

Figure 4. Methicillin–resistant bacteria with and without control. The unit of time before nondimensionalization corresponds to days.

limit of 90% during the first moment and then decreases rapidly until reaching its lower level of 0% before the first day.

Figure 5 shows the case of Penicillin G–resistant bacteria. Despite the cost and effort generated by controlling the resistance with the prophylaxis strategy, control can not be achieved. As less resistant bacteria survive, the costs of the prophylaxis, have to be much lower than the social costs, to achieve an effective control.

3.3. Stochastic optimal control problem

As discussed in the previous sections, introducing random perturbations to the deterministic system will lead to different behaviour of the bacteria. Thus, we will study in this subsection a stochastic optimal control problem where the state equations are given by

$$\begin{cases} dS &= [\beta_s S(1-(S+R)) - (\mu_s+\alpha)S]\,dt + \rho_1 S(1-(S+R))dW_1 \\ \\ dR &= [\beta_r R(1-(S+R)) + (1-\eta)q\alpha S - \mu_r R]\,dt + \rho_2 R(1-(S+R))dW_2. \end{cases} \tag{3.5}$$

The solutions (S, R) are random variables, thus we need to take the expected value of the cost function (3.1), which leads in minimizing

$$J(\eta) = \mathbb{E}\left[\int_0^T \left(aR + \frac{1}{2}b\eta^2\right)dt\right].$$

As the diffusion does not contain the control variable, the Hamiltonian H is defined by (see e.g. [38])

$$\begin{aligned} H = aR + \frac{1}{2}b\eta^2 &+ p_1\left[\beta_s S(1-(S+R)) - (\mu_s+\alpha)S\right] \\ &+ p_2\left[\beta_r R(1-(S+R)) + (1-\eta)q\alpha S - \mu_r R\right] \\ &+ q_1\left[\rho_1 S(1-(S+R))\right] + q_2\left[\rho_2 R(1-(S+R))\right], \end{aligned}$$

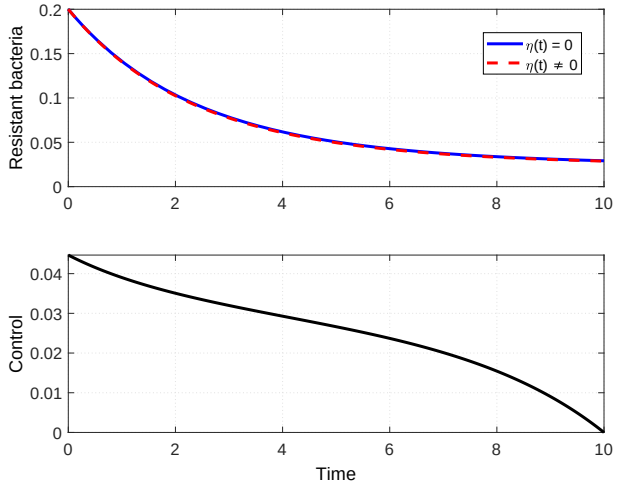

Figure 5. Penicillin G–resistant bacteria with and without control. The unit of time before nondimensionalization corresponds to days.

where the pairs (p_1, q_1) and (p_2, q_2) solve the backward stochastic differential equations

$$\begin{cases} dp_1(t) &= -\left[(\beta_s(1-(S+R)-S)-(\mu_s+\alpha))p_1 + (-\beta_r R + (1-\eta)q\alpha)p_2 \right. \\ &\quad \left. +(\rho_1(1-(S+R)-S)q_1 - \rho_2 y q_2)\right]dt + q_1 dW_1 \\ dp_2(t) &= -a - \left[-\beta_s S\, p_1 + (\beta_r(1-(S+R)-R)-\mu_r)p_2 \right. \\ &\quad \left. -\rho_1 S\, q_1 + \rho_2(1-(S+R)-R)q_2\right]dt + q_2 dW_2 \\ p_1(T) &= 0 \\ p_2(T) &= 0. \end{cases} \tag{3.6}$$

Moreover, as in the deterministic case, it holds that $\dfrac{\partial H}{\partial \eta^\star} = 0$, or equivalently

$$\eta^\star = \min\left\{\max\left\{0, \frac{p_2 q \alpha S}{b}\right\}, 1\right\}. \tag{3.7}$$

3.4. Numerical solutions

The main difficulty in the numerical simulations is the approximation of the stochastic forward–backward differential equation (3.5)–(3.6). Due to the four–step scheme [39], these equations are related to the solution of quasi–linear partial differential equations which we solve by the probabilistic approach presented by [40]. The implementation time of control strategies is again 10 days and the values of the relative weights are $a = b = 0.002$. The parameters in the equations are the same as in Subsection 2.2, and as in Subsection 3.2, only the cases of Methicillin Penicillin G resistant bacteria are considered. Moreover, from the study in Section 2, we choose for the Methicillin simulation $\rho_2 = 0.1$

and for the Penicillin simulation $\rho_1 = 0.3$, respectively, as for greater values of ρ_1 and ρ_2 both bacteria die out and no control strategy is necessary.

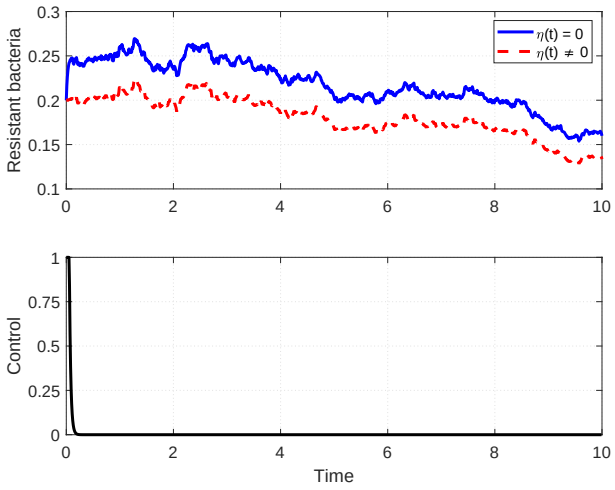

Figure 6. Methicillin–resistant bacteria with and without control. The simulations were made using the same path of the Brownian motion. The unit of time before nondimensionalization corresponds to days.

We observe a similar behaviour as in the deterministic case comparing with Figures 4–5. Again, Methicillin-resistant bacteria is controlled effectively by η and the resistant bacteria without control grows much faster than the controlled one (see Figure 6). However, repeating the experiment with Penicillin G-resistant bacteria, the uncontrolled and the controlled resistant bacteria behave similarly (Figure 7) and a lower value of b is needed in order to have an effective control strategy.

4. Discussion

This paper presented a mathematical study describing the dynamical behaviour of bacterial resistance to antibiotics model with perturbed reproduction rates. Our purpose was based on analysing this behaviour using both a deterministic model and a stochastic one. The deterministic case was studied in [3]. Concerning the stochastic model, we obtained sufficient conditions for the stability of the trivial equilibrium E_0 in the probability sense by using a suitable Lyapunov function and other techniques of stochastic analysis. The investigation of this stochastic model revealed that the stochastic stability of E_0 depends on the magnitude of the intensity of noise. Moreover, we determined the stochastic reproduction numbers for sensitive and resistant bacteria and we gave conditions for the cases that only resistant bacteria survive and that both bacteria persist.

The main result of this work was based on the formulation of optimal control problems in both cases (deterministic and stochastic). The control strategy used was prophylaxis, that is, control by patient education campaigns and an adequate supply of antibiotics. Sufficient conditions were derived to show existence and uniqueness of the control problem. The numerical simulations of the deterministic control problem were performed by using data from bacterial cells of the genus *Staphylococcus* under three types of antibiotics supply: Penicillin G (low efficacy), Methicillin (medium efficacy) and Linezolid (high efficiency). The numerical results revealed that when bacteria are treated with Linezolid they

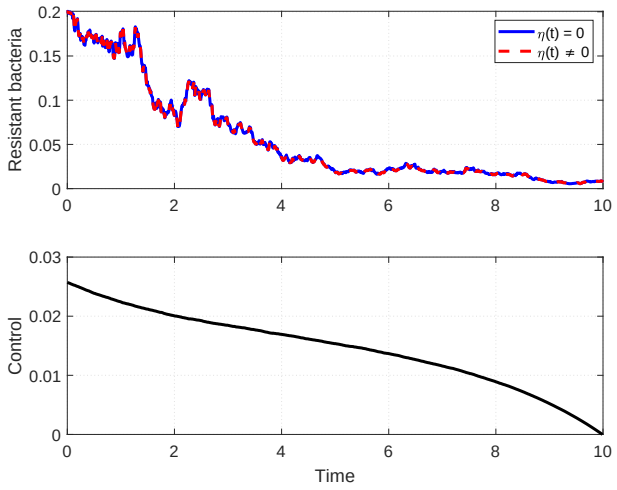

Figure 7. Penicillin G–resistant bacteria with and without control. The simulations were made using the same path of the Brownian motion. The unit of time before nondimensionalization corresponds to days.

are naturally eradicated, when they are treated with Methicillin the sensitive bacteria are eliminated and a persistence of resistant bacteria is generated, which can be reduced incorporating a prophylactic control strategy. The most interesting case occurred when bacteria are treated with Penicillin G, as there is a persistence of sensitive and resistant bacteria that cannot be controlled with the same costs for prophylaxis. Therefore, these results suggested that one has to lower the costs for the prophylaxis in comparison to the social costs to obtain an effective control strategy.

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Conflict of interest

No potential conflict of interest was reported by the authors.

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