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Comparison of stochastic and random models for bacterial resistance

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Abstract

In this study, a mathematical model of bacterial resistance considering the immune system response and antibiotic therapy is examined under random conditions. A random model consisting of random differential equations is obtained by using the existing deterministic model. Similarly, stochastic effect terms are added to the deterministic model to form a stochastic model consisting of stochastic differential equations. The results from the random and stochastic models are also compared with the results of the deterministic model to investigate the behavior of the model components under random conditions.

MSC: Primary 34F05; secondary 92D30

Keywords: stochastic differential equation; random differential equation; Milstein scheme; Euler-Maruyama scheme; antibiotic resistance

1 Introduction

Epidemic diseases, the effects of drugs and many other phenomena in the fields of health, medicine, biology etc. have been widely analyzed through the use of mathematical models in the last century. The majority of the models used in epidemiology include systems of deterministic differential equations. However, it is well known that some of the deterministic quantities used in modeling, *e.g.* epidemiological, biological events are acquired through statistical analysis of the real-life data. Many of the numerical values of the parameters used in modeling studies, especially for newly emerging diseases, the modification of an existing model for a new disease or for trial of new drugs/treatments, are determined from the statistical investigation of the limited number of data available on the event. Thus, the uncertainty of these parameters is neglected in deterministic models. This uncertainty can be modeled in the equation systems using random variables or stochastic processes. By implementing random components into the deterministic equation system and analyzing the statistical properties of the results, we aim to obtain information on the properties of the randomness of these parameters. The use of random and stochastic terms is more effective in this sense, compared with other tools of deterministic analysis or fractional calculus. In this context, we will be using random effect and stochastic noise terms on a mathematical model for antibiotic resistance to analyze the randomness of results.

The World Health Organization (WHO) describes 'Antimicrobial Resistance (AMR)' as follows: Resistance of a microorganism to an antimicrobial drug that was originally effective for treatment of infections caused by it. WHO reports that without effective anti-

infective treatment, many standard medical treatments will fail or turn into very high risk procedures [1]. Antibiotic therapy is the most common method for battling bacterial infections worldwide. Most of the classes of antibiotics used today have been introduced in the 'golden era of antibiotics' 1940s-1960s [2]. However, various factors have caused a decline in research aimed at the discovery of novel antibacterial agents [3, 4]. Only five new significant classes of antibiotics were discovered in the last 40 years [5]. A novel treatment for bacterial infections is necessary, since the introduction of every antibiotic is followed by the occurrence of new bacteria resistant to that class [6]. Resistance is acquired either through mutations in the chromosome (vertical evolution) or through conjugation and transduction which can take place between the same or different bacteria that may also cause multiple drug resistance (horizontal evolution) [5, 7, 8]. The public threat of antibiotic resistance is also affected by inappropriate use of anti-infective medicine for human and animal food production, together with inadequate measures to control the spread of diseases. Increasing resistance of bacteria has social and economic implications like growing morbidity and mortality from infections and the rise of treatment costs [1, 8].

There are many other mathematical models which analyze antibiotic resistance from different perspectives: Dasbasi and Ozturk investigated a model of bacterial resistance to multiple drugs and immune system response [9]; Ternent *et al.* used a model of combined antibiotic and anti-virulent treatment to monitor the population dynamics of bacteria [5]; Ibarguen-Mondragon *et al.* evaluated a model on bacterial resistance to multiple antibiotics caused by spontaneous mutations [10]; D'Agata *et al.* studied a model of antibiotic resistance in hospitals [8]; Austin and Anderson investigated antibiotic resistance within patient, hospital and the community using a simple mathematical model [11]. Most of the models on bacterial resistance are compartmental models, investigating the course of the event through changes in the compartments of the model using deterministic differential equation systems. There are also some mathematical models that study fractional derivation on several phenomena like river blindness disease [12]; lassa hemorrhagic fever [13]; rubella disease [14]; immunegenic tumors [15] and heat transfer [16]. Since we concentrate on the random nature of the parameters of the antibiotic resistance model, we will be implementing random effects into the deterministic system rather than fractional derivation. Some modeling studies which compare stochastic and deterministic models in this regard can be given as follows: Imran *et al.* compared the models for analyzing Hepatitis C [17]; Lahrouz *et al.* used a SIRS epidemic model for comparison [18] and Bekiryazici *et al.* compared the results of models for Dengue disease [19].

In this study, we will be using a deterministic model of immune system response and bacterial resistance with antibiotic therapy to form random and stochastic models of the event [9]. The random and stochastic models will be obtained by adding random effect and stochastic noise terms into the deterministic model to analyze the uncertainty of the antibiotic resistance. The motivation of this work is the previous studies of the authors where the random dynamics of an avian-human influenza model [20] and a biochemical reaction model [21] were analyzed. Similarly, the random behavior of the solutions of our model will be analyzed from the simulations and solutions of the random and stochastic models. First, the deterministic solution of the model will be given along with the phase portraits to investigate the deterministic behavior of the model components. Using the deterministic model, a random model of antibiotic resistance will be obtained by adding random effect terms to the parameters of the equation system. The random parameters

will represent the uncertainty in the nature of the parameters and, thus, we will be able to analyze the randomness of the system though the solutions of the random system. Also, a stochastic model of antibiotic resistance will be obtained by adding stochastic noise terms to the deterministic model. Solutions of all three models will be given in the conclusion, where a comparison of the results will underline the random behavior of the model and the interpretations of variations from the deterministic model. The statistical properties of the random results will provide useful insights for the uncertainty in the behavior of antibiotic resistance which cannot be modeled by using deterministic equations.

2 Deterministic model of antibiotic resistance

The deterministic model in [9] is used in this study:

$$\begin{aligned}
\frac{dS}{dt} &= \beta_S S\left(1-\frac{S+R}{T}\right) - \bar{\eta}SB - S\frac{E_{\max}A}{E_{50}+A} - \mu SA - \sigma SR,\\
\frac{dR}{dt} &= (1-c)\beta_S R\left(1-\frac{S+R}{T}\right) - \bar{\eta}RB + \mu SA + \sigma SR,\\
\frac{dB}{dt} &= \beta_B B\left(1-\frac{B}{\Lambda}\right) - \lambda B(S+R),\\
\frac{dA}{dt} &= -\alpha A.
\end{aligned} \tag{1}$$

The variables of this model are as follows: $S(t)$ is the size of the population of susceptible bacteria at time t, $R(t)$ is the size of the population of resistant bacteria at time t, $B(t)$ is the size of the population of immune cells at time t and $A(t)$ is the concentration of antibiotic at time t. Basically, the model consists of four differential equations describing the change in the bacteria, immune cells and antibiotics in time. Note that this model is a modified version of some equation systems used for analyzing bacterial resistance under various situations (see, *e.g.*, [7, 8, 10]). The initial values of the variables are needed for simulations of the model:

$$S(0) = 6\times 10^3 \text{ cells}, \qquad R(0) = 20 \text{ cells}, \qquad B(0) = 1 \text{ cell}, \qquad A(0) = 4\ \mu\text{g/ml}.$$

The flowchart of model (1) is given in [5] (Figure 1). The actions illustrated with arrows going in and out of the variables are described by the parameters of the model. The values of the parameters and the initial conditions have been taken from [5, 7, 10] (Table 1). The time variable t indicates the number of days. The initial conditions imply an environment where there are susceptible bacteria, resistant bacteria and immune cells of the given values and the given concentration of the antibiotic is administered. It should also be noted that various other values can be obtained for the initial conditions and the parameters from the literature [22, 23].

2.1 Deterministic results

The numerical solutions of the deterministic equation system are obtained as follows. Note that the built-in low order methods of MATLAB are used to obtain these results (Figure 2).

The maximum and minimum values of the numerical solutions of the variables of the deterministic model are obtained in Table 2.

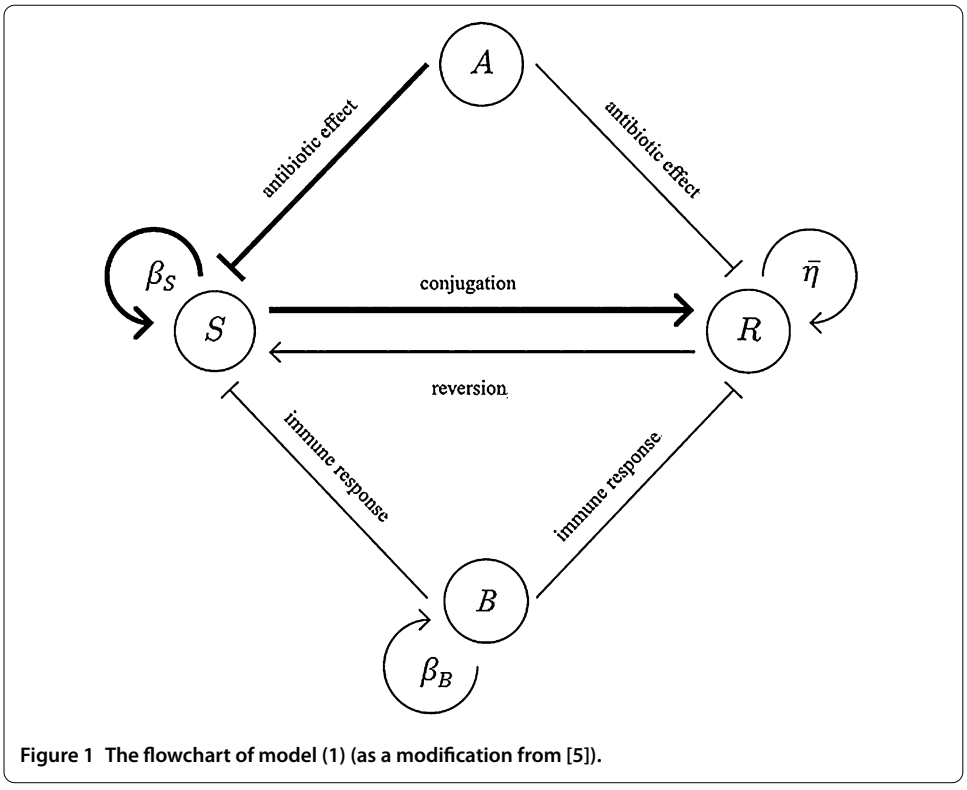

Figure 1 The flowchart of model (1) (as a modification from [5]).

Table 1 Descriptions and values of the parameters

Parameter	Description	Value
β_S	Birth rate of sensitive bacteria	0.8 day^{-1}
T	Carrying capacity of bacterial population	10^9 cells
c	Fitness cost	0.5 (dimensionless)
$\bar{\eta}$	Death rate of sensitive and resistant bacteria	0.3 day^{-1}
μ	Sensitive bac. mutation rate by exposure to antibiotic	10^{-6} mut × gen
σ	Conjugation rate of bacteria	10^{-5} day^{-1}
E_{max}	Maximum killing rate of antibiotic	26.4 day^{-1}
E_{50}	Antibiotic concentration for half max. kill rate	5 μg/ml
β_B	Recruitment rate of immune cells	3 day^{-1}
Λ	Carrying capacity of immune cells	1.8×10^5 cells
λ	Loss rate of immune cells by apoptosis	6×10^{-6} $cells^{-1}$ $days^{-1}$
α	Dose of antibiotic administration	5 mg/kg/day

The number of susceptible cells decreases to 5.824 around $t = 1.09$ meaning almost all of the susceptible bacteria either gain resistance or are destroyed through the process. Taking the changes in the number of resistant bacteria into account, it can be said that a part of the susceptible bacteria turn to resistant bacteria in the beginning, but all of these are destroyed afterwards. The number of resistant bacteria slightly increases in the beginning of the process and hits its maximum value 20.16 at $t = 0.09$, after which it starts decreasing. This shows that susceptible bacteria conjugate with resistant bacteria and some of the susceptible bacteria gain resistance to antibiotics. However, both the resistant bacteria and the susceptible bacteria are almost cleared through the end of the process. The size of the immune cell population keeps increasing and hits its maximum value 89.91 at the end of the process, $t = 1.5$, meaning the body keeps sending immune cells to the region of infection until all the bacteria are cleared. The concentration of the antibiotic

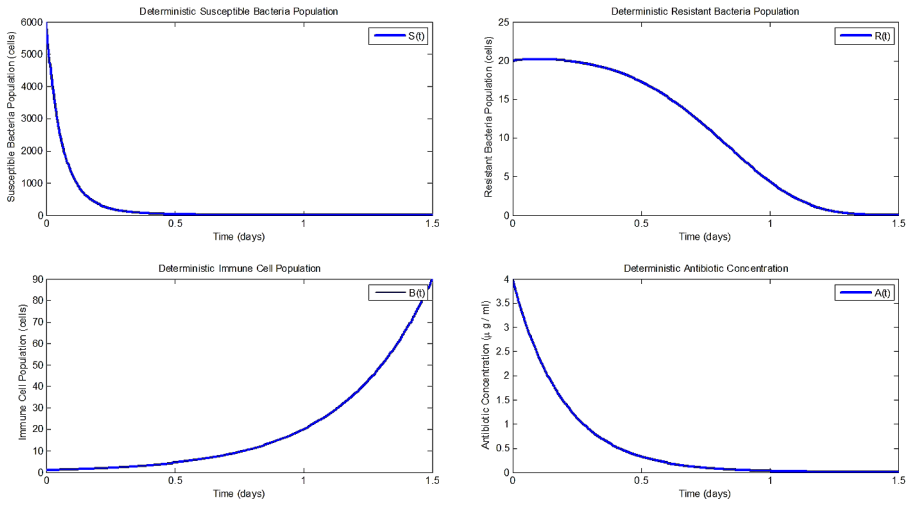

Figure 2 Solutions of the deterministic model.

Table 2 Extremum values obtained for the variables

Variable	Maximum	Time	Minimum	Time
$S(t)$	6,000	0	5.824	1.09
$R(t)$	20.16	0.09	0.004912	1.5
$B(t)$	89.91	1.5	1	0
$A(t)$	4	0	0.002193	1.5

keeps decreasing throughout the process until its hits its minimum value 0.002193 at the end of the process $t = 1.5$. The equation system used in this study is a well-posed model and the results obtained from the model are compatible with the results of the referred study for the parameters under consideration. The results for the deterministic, random and stochastic models will be investigated for the first 36 hours of the event ($t \in (0, 1.5)$). Although the random nature of the model components is the main focus of this study, the steady states and other dynamics of the model can provide an in-depth analysis of the deterministic event [24, 25].

2.2 Deterministic behavior of model components

The 2-dimensional and 3-dimensional phase portraits of system (1) are given in Figures 3 and 4 for various values of the parameters. The trajectories in the graphs demonstrate the behavior of the model components and the mutual relation of the dynamics of the variables of the system.

3 Random model of antibiotic resistance

The coefficients of the deterministic model are calculated through statistical evaluation of data obtained from various cases around the world. The values of the coefficients are assumed to be constant at the mean of their distribution for the deterministic analysis. However, in reality, these values are not constant and vary for every different case. For instance, the rate of loss of immune cells due to pathogen-induced apoptosis is considered to be constant at 6×10^{-6}, whereas this should be a random value distributed around 6×10^{-6}. A different approach to this event by taking the coefficients are random variables

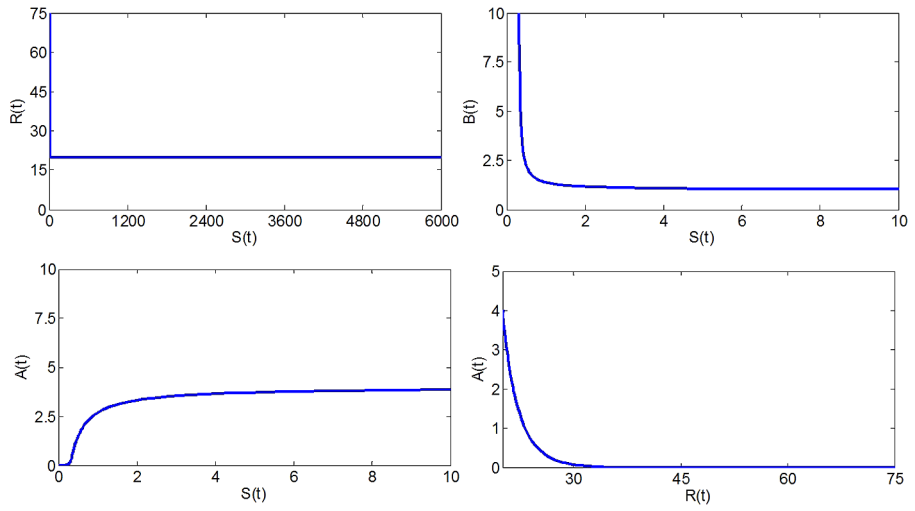

Figure 3 Two-dimensional phase portraits of the deterministic system.

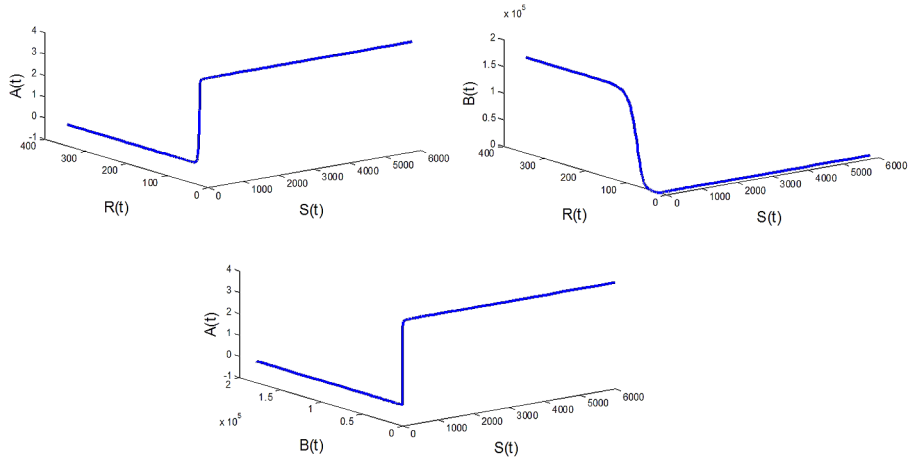

Figure 4 Three-dimensional phase portraits of the deterministic system.

could produce a model that describes the possible variations in the results [26]. Since the coefficients of the deterministic equation system are known to be random numbers in nature, we build the system of random differential equations by transforming the coefficients of system (1) to random variables. Hence, by using normal distribution, we will obtain the new set of random coefficients:

$$\begin{aligned}
&\beta_S \sim N\left(a_1, s_1^2\right), \quad T \sim N\left(a_2, s_2^2\right), \quad c \sim N\left(a_3, s_3^2\right), \quad \bar{\eta} \sim N\left(a_4, s_4^2\right),\\
&\mu \sim N\left(a_5, s_5^2\right), \quad \sigma \sim N\left(a_6, s_6^2\right), \quad E_{\max} \sim N\left(a_7, s_7^2\right), \quad E_{50} \sim N\left(a_8, s_8^2\right),\\
&\beta_B \sim N\left(a_9, s_9^2\right), \quad \Lambda \sim N\left(a_{10}, s_{10}^2\right), \quad \lambda \sim N\left(a_{11}, s_{11}^2\right), \quad \alpha \sim N\left(a_{12}, s_{12}^2\right),
\end{aligned}$$

where a_i, $i = \overline{(1,12)}$ and s_i, $i = \overline{(1,12)}$ are the means and the standard deviations of the normal distributions, respectively. The values of the coefficients are affected by various factors like temperature, host anatomy, environmental conditions etc. Random variables

that are expected to be a sum of independent quantities often have a normal distribution. Also, the central limit theorem states that, for large numbers of random variables whose distributions are not known, a normal distribution can be used. Thus, considering we will be simulating a large number of random numbers for the coefficients, the use of normal distribution seems reasonable. The mean values of the distributions used for the coefficients will be chosen according to the deterministic values of the coefficients. Standard deviations of the distributions will be 5% of the same value.

A $N(a,b^2)$ distributed random variable X can be written as $X = a + b\chi$, where $\chi \sim N(0,1)$ is the standard normally distributed random variable [27]. Using this property, random variables can be rewritten as

$$\begin{aligned}
&\beta_S = a_1 + s_1\chi_1, \qquad T = a_2 + s_2\chi_2, \qquad c = a_3 + s_3\chi_3, \qquad \bar{\eta} = a_4 + s_4\chi_4,\\
&\mu = a_5 + s_5\chi_5, \qquad \sigma = a_6 + s_6\chi_6, \qquad E_{\max} = a_7 + s_7\chi_7, \qquad E_{50} = a_8 + s_8\chi_8,\\
&\beta_B = a_9 + s_9\chi_9, \qquad \Lambda = a_{10} + s_{10}\chi_{10}, \qquad \lambda = a_{11} + s_{11}\chi_{11}, \qquad \alpha = a_{12} + s_{12}\chi_{12},
\end{aligned}$$

for independent random variables χ_i, $i = \overline{(1,12)}$ with distribution $N(0,1)$. Setting the appropriate values of a_i, $i = \overline{(1,12)}$ and s_i, $i = \overline{(1,12)}$ yields

$$\begin{aligned}
&\beta_S = 0.8 + 0.04\chi_1, \qquad T = 10^9 + 5\times 10^7\chi_2, \qquad c = 0.5 + 0.025\chi_3,\\
&\bar{\eta} = 0.3 + 0.015\chi_4, \qquad \mu = 10^{-6} + 5\times 10^{-8}\chi_5, \qquad \sigma = 10^{-5} + 5\times 10^{-7}\chi_6,\\
&E_{\max} = 26.4 + 1.32\chi_7, \qquad E_{50} = 5 + 0.25\chi_8, \qquad \beta_B = 3 + 0.15\chi_9,\\
&\Lambda = 1.8\times 10^5 + 9\times 10^3\chi_{10}, \qquad \lambda = 6\times 10^{-6} + 3\times 10^{-7}\chi_{11}, \qquad \alpha = 5 + 0.25\chi_{12}.
\end{aligned}$$

Hence, in particular, we changed the deterministic parameter β_B, which had a numerical value 3, to a normally distributed random variable $\beta_B \sim N(3, 0.15^2)$ with 68.27% of its values in the interval $(2.85, 3.15)$. Using all of the similar transformed random parameters, the random model of the antibiotic resistance thus becomes

$$\begin{aligned}
\frac{dS}{dt} &= (0.8 + 0.04\chi_1)S\left(1 - \frac{S+R}{(10^9 + 5\times 10^7\chi_2)}\right) - (0.3 + 0.015\chi_4)SB\\
&\quad - S\frac{(26.4 + 1.32\chi_7)A}{(5 + 0.25\chi_8) + A} - \left(10^{-6} + 5\times 10^{-8}\chi_5\right)SA - \left(10^{-5} + 5\times 10^{-7}\chi_6\right)SR,\\
\frac{dR}{dt} &= \left(1 - (0.5 + 0.025\chi_3)\right)(0.8 + 0.04\chi_1)R\left(1 - \frac{S+R}{(10^9 + 5\times 10^7\chi_2)}\right)\\
&\quad - (0.3 + 0.015\chi_4)RB + \left(10^{-6} + 5\times 10^{-8}\chi_5\right)SA + \left(10^{-5} + 5\times 10^{-7}\chi_6\right)SR, \qquad (2)\\
\frac{dB}{dt} &= (3 + 0.15\chi_9)B\left(1 - \frac{B}{(1.8\times 10^5 + 9\times 10^3\chi_{10})}\right)\\
&\quad - \left(6\times 10^{-6} + 3\times 10^{-7}\chi_{11}\right)B(S+R),\\
\frac{dA}{dt} &= -(5 + 0.25\chi_{12})A.
\end{aligned}$$

3.1 Random results

Matlab produces random numbers according to the standard normal distribution with the *randn* command. We simulate the numerical solutions of the random system using

the fourth order Runge-Kutta method. We produce more than 10^5 simulations of the random model. The characteristics of the random systems obtained by using these simulations will be used to interpret the random behavior of the model. Note that although the equations contain random numbers, a system of deterministic equations is obtained for every simulation. The coefficients vary from simulation to simulation, but the equations and therefore the derivatives are deterministic.

3.1.1 Solution curves

The solution curves obtained from the 10^5 simulations are shown in Figure 5. We select an arbitrary realization from these simulations to investigate the dynamics of the random event.

It should be noted that the solution curves of the random model indicate the behavior of the system under random effects which are simulated for this study. These results may vary for other simulations and hence they are only added to show the similar behavior of the model components in the random and deterministic models. However, expected values, variances and confidence intervals are valid for all possible occurrences of the random event and therefore are more reliable indicators. Figure 5 shows that the behavior of the random variables and the deterministic variables are compatible and hence our random model is meaningful. The extremum values of the solution curves are obtained in Table 3.

3.1.2 Expected values

The expected values of the variables are shown in Figure 6.

The extremum values of the expected values are obtained in Table 4.

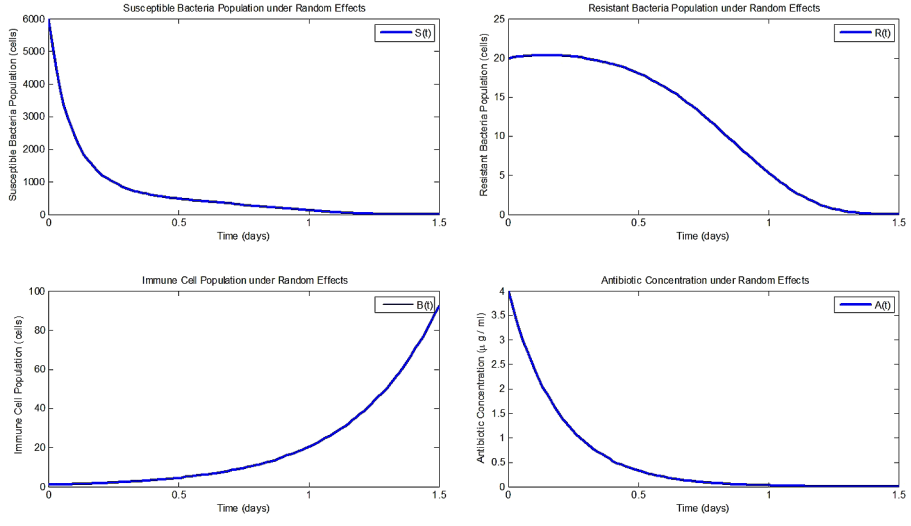

Figure 5 Solution curves of the random model.

Table 3 Extremum values of variables

Variable	Maximum	Time	Minimum	Time
$S(t)$	6,000	0	0.3081	1.5
$R(t)$	20.31	0.15	0.01054	1.5
$B(t)$	92.42	1.5	1	0
$A(t)$	4	0	0.002193	1.5

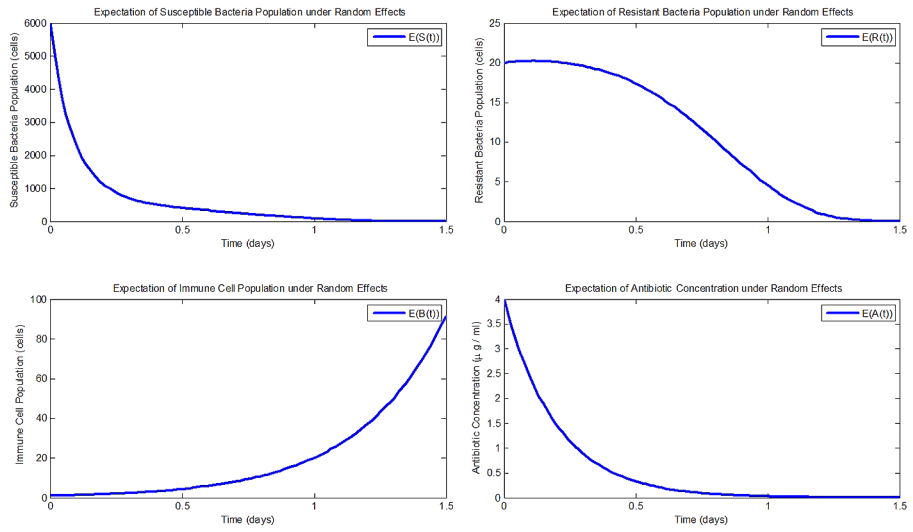

Figure 6 Expectations of the random model.

Table 4 Extremum values of the expected values

Variable	Maximum	Time	Minimum	Time
$E[S(t)]$	6,000	0	0.3442	1.5
$E[R(t)]$	20.18	0.135	0.01376	1.5
$E[B(t)]$	91.59	1.5	1	0
$E[A(t)]$	4	0	0.002386	1.5

Figure 6 shows the expectations of the random variables. These expectations are approximately valid for all possible trials of the event under the assumed random conditions. The expected values are similar to the deterministic results, as expected.

3.1.3 Variances

The variances of the variables are shown in Figure 7.

The extremum values of the variances are obtained in Table 5.

Figure 7 shows the variance of the random variables. A high variance of the model components show that some of the variables may produce significantly different behavior from the suggestions of the deterministic results. Once again, the results for the variance are approximately valid for all trials.

3.1.4 Confidence intervals

The confidence intervals of the variables are shown in Figure 8.

Note that these are approximately 99% confidence intervals for the mean values of the random variables which have the form

$$\left[E\big(X(t)\big) - K\sigma\big(X(t)\big), E\big(X(t)\big) + K\sigma\big(X(t)\big)\right]$$

for a random variable X with a standard deviation $\sigma(X)$. Alternatively for $K = 2$, this interval gives approximately 95% confidence interval. The blue lines in the graphs represent the upper end of the intervals while the green lines represent the lower end. Figure 8 shows

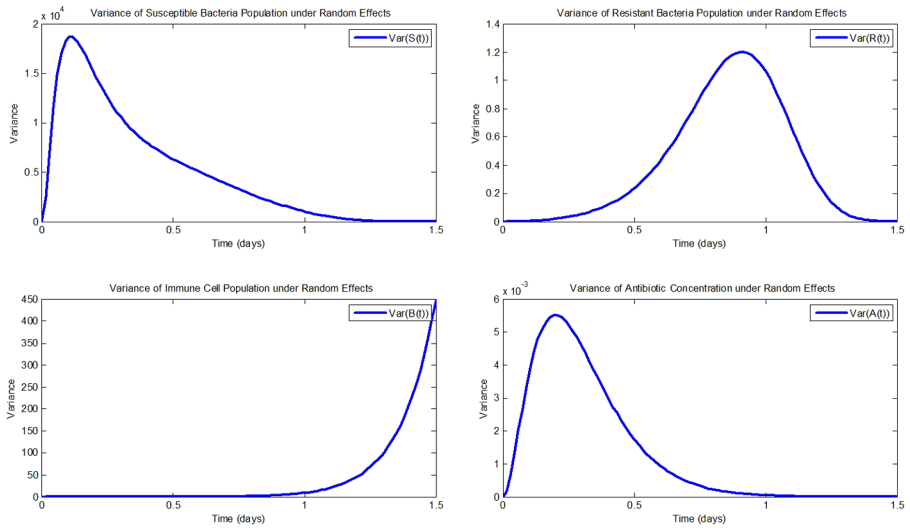

Figure 7 Variances of the random model.

Table 5 Extremum values of the variances

Variable	Maximum	Time	Minimum	Time
Var[$S(t)$]	18,740	0.105	0	0
Var[$R(t)$]	1.202	0.915	0	0
Var[$B(t)$]	447.6	1.5	0	0
Var[$A(t)$]	0.005509	0.195	0	0

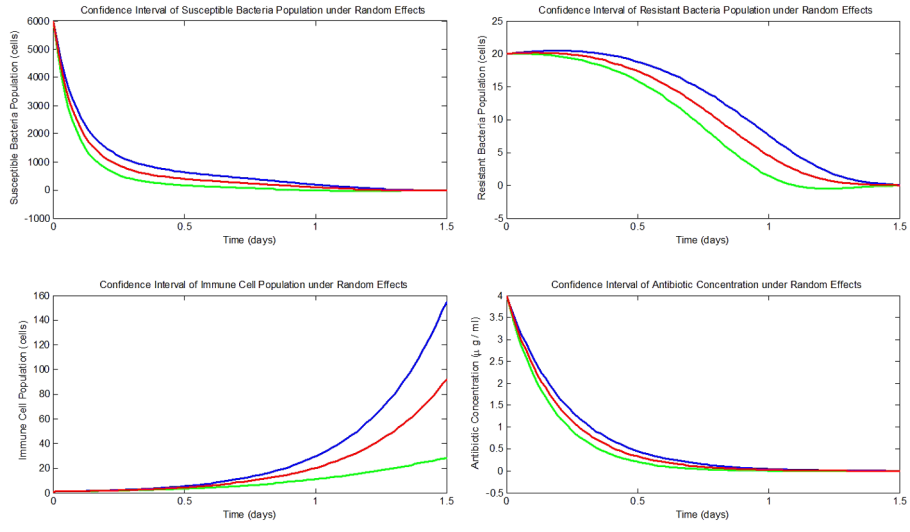

Figure 8 Confidence intervals of the random model.

that there is a significantly large confidence interval for $R(t)$ and $B(t)$, meaning that these variables have a high level of randomness in their nature. Also note that, while the simulations tend to produce values below zero for populations, the smallest positive value has been chosen for the minimum points.

The extremum values of the confidence intervals are obtained in Table 6.

Table 6 Extremum values of the confidence intervals

Variable	Maximum	Time	Minimum	Time
CI[$S(t)$]	6,000	0	0.3442	1.5
CI[$R(t)$]	20.5	0.18	0.01376	1.5
CI[$B(t)$]	155.1	1.5	1	0
CI[$A(t)$]	4	0	6.083×10^{-5}	1.275

The random behavior of the components of the model can be seen in the graphs. It is seen that the random behavior of the variables are similar to their deterministic behavior. Although there are numerical differences in the solutions of the random system (2), the graphs of the solutions are almost the same. Considering the random results, it can be said that the model produces the same results under random conditions, only at different quantities. It should be noted that the simulations of the model are compatible with the deterministic results and the real-life behavior of the components. The confidence intervals are obtained by using the results for the variance and the expectations of the components and may tend to provide negative results when the expectation of a variable tends to zero. However, these should be neglected since the results for the subpopulations of an epidemic model can only assume positive values [24, 25].

Deterministic results indicate that the population of resistant bacteria will reach its maximum value $\max(R(t)) = 20.16$ at $t = 0.09$, which is roughly about 2 hours after the start of the process. Random results suggest that the rise in the number of resistant bacteria is expected to continue a little longer until about 3.5 hours into the process, when $\max(R(t)) = 20.31$ will be obtained at $t = 0.15$. On the other hand, deterministic results and random results are quite similar in numerical values besides the behavior for the variables $S(t)$, $B(t)$ and $A(t)$. $S(t)$, the population of susceptible bacteria, decreases throughout the process in both cases, though slower in the random model, reaching very similar extremum values in both ends. Similarly, $B(t)$, the population of immune cells, increases throughout the process in both cases, reaching very similar extremum values at both ends. $A(t)$, the concentration of the antibiotic, also decreases through the process in both cases, reaching very similar extremum values at both ends.

4 Stochastic model of antibiotic resistance

Random outcomes in real life can be modeled in equation systems by the use of stochastic differential equations too. Their difference from random DEs is that stochastic differential equations contain noise terms in terms of Wiener processes. Although these equations are written as differential equations, they are interpreted as integral equations. In this study, we will be interested in the numerical solutions of SDEs.

One of the simplest approximations of an Ito process is the Euler-Maruyama scheme. Consider $X = X_t$, $t_0 \leq t \leq T$ satisfying the SDE on $t_0 \leq t \leq T$ with the initial value $X_{t_0} = X_0$. For a discretization of the interval $[t_0, T]$ as $t_0 = \tau_1 < \cdots < \tau_n < \cdots < \tau_N = T$ ($n = 0, 1, 2, \ldots, N-1$), the Euler-Maruyama approximation is a stochastic process $Y = Y_t$, $t_0 \leq t \leq T$ satisfying the iterative scheme [28, 29]

$$Y_{n+1} = Y_n + a(\tau_n, Y_n)(\tau_{n+1} - \tau_n) + b(\tau_n, Y_n)(W_{n+1} - W_n).$$

Another method that will be used is the Milstein scheme. The Milstein approximation is a stochastic process $Y = Y_t$, $t_0 \le t \le T$ satisfying the iterative scheme

$$Y_{n+1} = Y_n + a\Delta + b\Delta W + \frac{1}{2}bb'(\Delta W)^2,$$

where $\Delta = (\tau_{n+1} - \tau_n)$ [28]. The stochastic model of the antibiotic resistance can be given as

$$\begin{aligned}
\frac{dS}{dt} &= \left(\beta_S S\left(1 - \frac{S+R}{T}\right) - \bar{\eta}SB - S\frac{E_{\max}A}{E_{50}+A} - \mu SA - \sigma SR\right)dt + \gamma_1 S(t)\,dW_1 t,\\
\frac{dR}{dt} &= \left((1-c)\beta_S R\left(1 - \frac{S+R}{T}\right) - \bar{\eta}RB + \mu SA + \sigma SR\right)dt + \gamma_2 R(t)\,dW_2 t,\\
\frac{dB}{dt} &= \left(\beta_B B\left(1 - \frac{B}{\Lambda}\right) - \lambda B(S+R)\right)dt + \gamma_3 B(t)\,dW_3 t,\\
\frac{dA}{dt} &= (-\alpha A)\,dt + \gamma_4 A(t)\,dW_4 t,
\end{aligned} \tag{3}$$

for independent Wiener processes W_i, $i = \overline{(1,4)}$. Approximate numerical solutions of the stochastic differential equations in model (3) are needed since the equations are nonlinear and hence cannot be solved explicitly. Numerical solutions of the stochastic model are analyzed for small diffusion with $\gamma_i = 0.5$, $i = \overline{(1,4)}$. A small amount of diffusion is added to the models to indicate a small difference between the anticipated and the real-life realizations of the event. A Milstein approximation is expected to produce more accurate results compared to the Euler-Maruyama method, since the Milstein method has both a weak and a strong order of convergence Δt, while the Euler method has a weak order of convergence Δt but a strong order of convergence of only $\sqrt{\Delta t}$ [28].

4.1 Stochastic results

4.1.1 Euler-Maruyama

A realization of the approximate solutions of equation system (3) is given in Figure 9. Similar to the random solutions, an arbitrary realization of the stochastic event is used to analyze the stochastic dynamics of the model. The figure shows that while the stochastic behaviors of the variables are similar to their deterministic and random counterparts, the volatility in the variables $R(t)$ and $B(t)$ indicates the highly random nature of these components.

The extremum values of the realizations are obtained in Table 7.

4.1.2 Milstein

A realization of the approximate solutions of equation system (3) is given in Figure 10. Once again, the volatility in the variables $R(t)$ and $B(t)$ is significant.

The extremum values of the realizations are obtained in Table 8.

It can be seen that the expectations of the random model and the realizations of the stochastic model produce similar patterns throughout the process. The similarity in the results of these two models will be investigated in the next part.

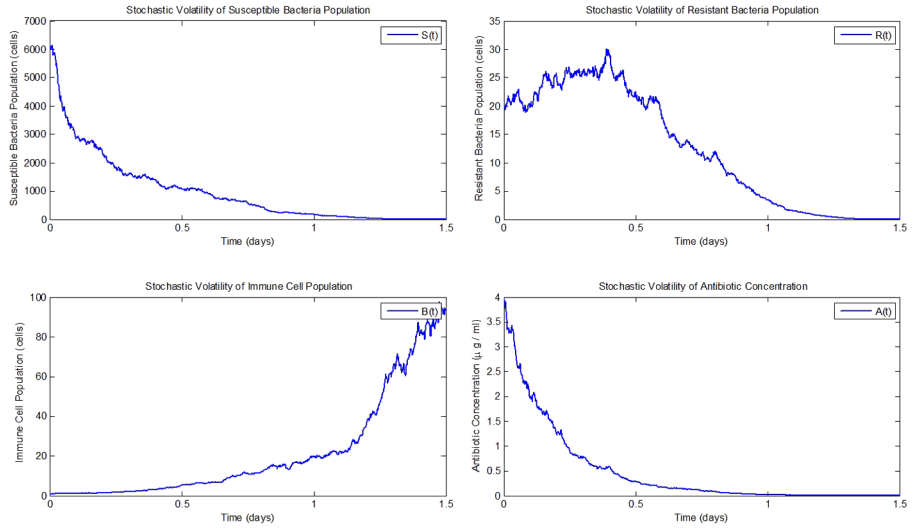

Figure 9 Realizations of the approximate solutions of the stochastic model.

Table 7 Extremum values of the realizations

Variable	Maximum	Time	Minimum	Time
$S(t)$	6,206	0.001	0.1078	1.5
$R(t)$	30.13	0.39	0.002046	1.5
$B(t)$	97.83	1.477	0.9254	0.008
$A(t)$	4	0	0.001317	1.499

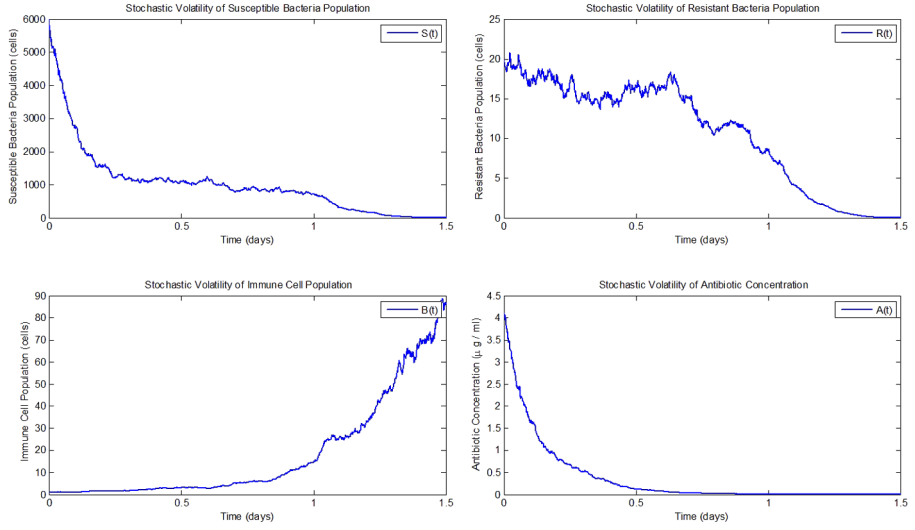

Figure 10 Realizations of the approximate solutions of the stochastic model.

Table 8 Extremum values of the realizations

Variable	Maximum	Time	Minimum	Time
$S(t)$	6,000	0	1.229	1.5
$R(t)$	20.78	0.024	0.01164	1.5
$B(t)$	88.59	1.487	0.946	0.071
$A(t)$	4.114	0.001	0.0006289	1.475

5 Comparison of random and stochastic results

Table 9 shows the extremum values obtained for the deterministic, random and stochastic models. The results for the random model are the expectations. Results from the Milstein approximation are used for the stochastic model.

Table 9 shows the impact of the random effects and stochastic noise on the extreme values of the variables. While there are some numerical differences in some of the values, together with the graphs, it can be said that the stochastic and random models are meaningful and successful in displaying the randomness of bacterial resistance.

In Figure 11, the random graph represents the results for the expectation of $S(t)$, while the stochastic results are from the Euler-Maruyama approximation. It can be seen that the behavior of the total number of susceptible bacteria in the deterministic case is in accordance with its behavior under normally distributed random effects and stochastic noise. It should be noted that there seems to be a slower decrease in both random and stochastic results, meaning that the number of susceptible bacteria should be expected to decrease more slowly under random conditions.

In Figure 12, once again the random graph is from the expectations and the stochastic graph is from the Euler-Maruyama approximation. It can be seen in the graphs that while the increase in $R(t)$ stops at $t = 0.09$ in the deterministic case at the value of 20.16, this increase should be expected to continue a while longer under random conditions until it becomes 20.18 at $t = 0.15$. Considering the behavior in the stochastic results, it can be said that the population of resistant bacteria is expected to be similar in random cases.

Table 9 Extremum values in deterministic, random and stochastic models

	Det. Max	Rand. Max	Stoch. Max	Det. Min	Rand. Min	Stoch. Min
S	(6,000, 0)	(6,000, 0)	(6,000, 0)	(5.824, 1.09)	(0.3442, 1.5)	(1.229, 1.5)
R	(20.16, 0.09)	(20.18, 0.135)	(20.78, 0.024)	(0.004912, 1.5)	(0.01376, 1.5)	(0.01164, 1.5)
B	(89.91, 1.5)	(91.59, 1.5)	(88.59, 1.487)	(1, 0)	(1, 0)	(0.946, 0.071)
A	(4.0)	(4, 0)	(4.114, 0.001)	(0.002193, 1.5)	(0.002386, 1.5)	(0.0006289, 1.475)

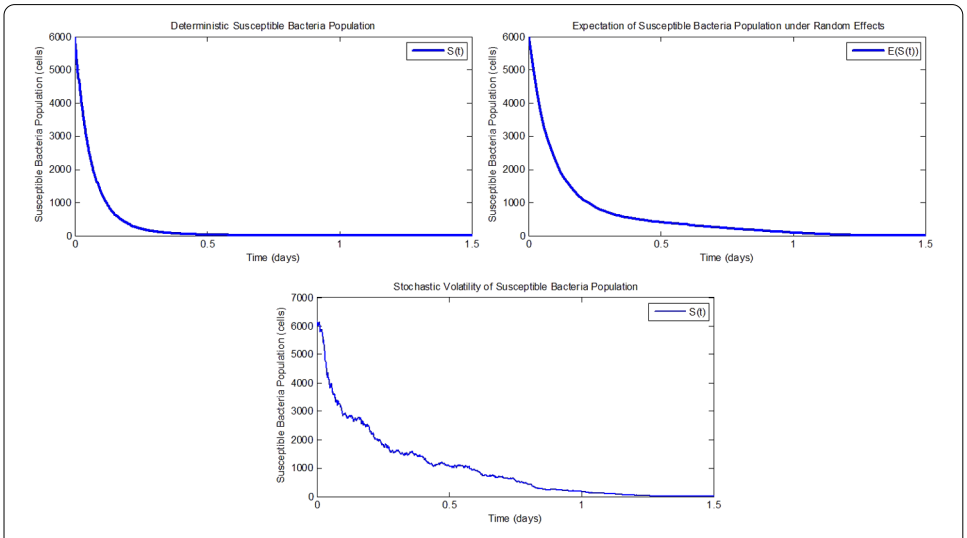

Figure 11 Deterministic, random and stochastic results for $S(t)$, respectively.

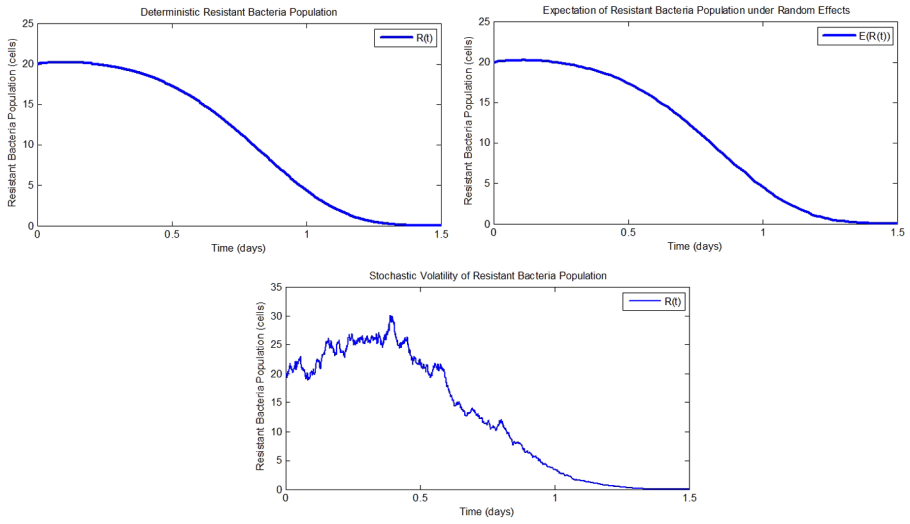

Figure 12 Deterministic, random and stochastic results for $R(t)$, respectively.

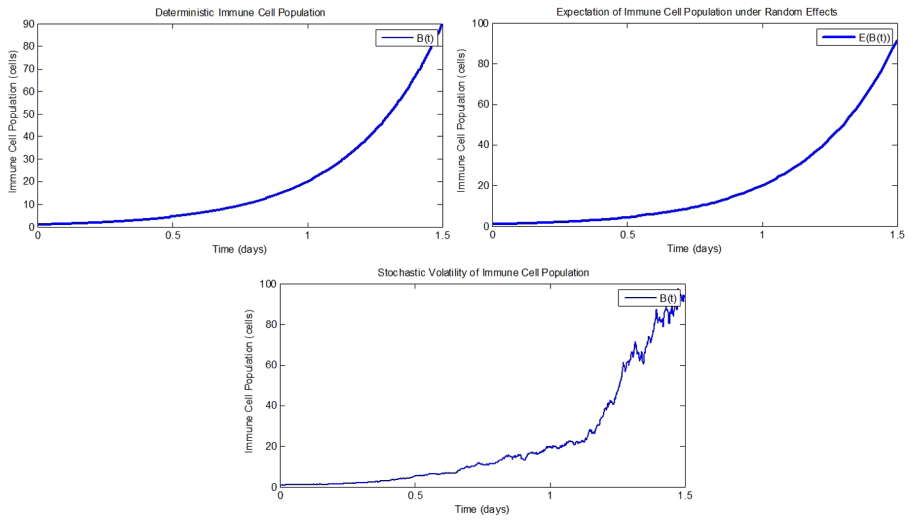

Figure 13 Deterministic, random and stochastic results for $B(t)$, respectively.

Using Figure 13, it can be said that the results for the population of immune cells are similar both in magnitudes and behavior in all three cases, meaning the immune cells behave similarly under random conditions too.

Using Figure 14, it can be seen that the results for the concentration of antibiotic are similar in all three cases as well, meaning that the antibiotic acts similarly under random conditions too.

The similarity of the behaviors of susceptible bacteria populations in the random and stochastic cases can be seen in Figure 15. The graphs show that there is little volatility in the stochastic results until $t = 1$, which is the same time period that the confidence interval grows a bit larger.

As seen in Figure 16, the stochastic and random cases for $R(t)$, the population of resistant bacteria is an indicator of the correspondence of these two models. There is a large

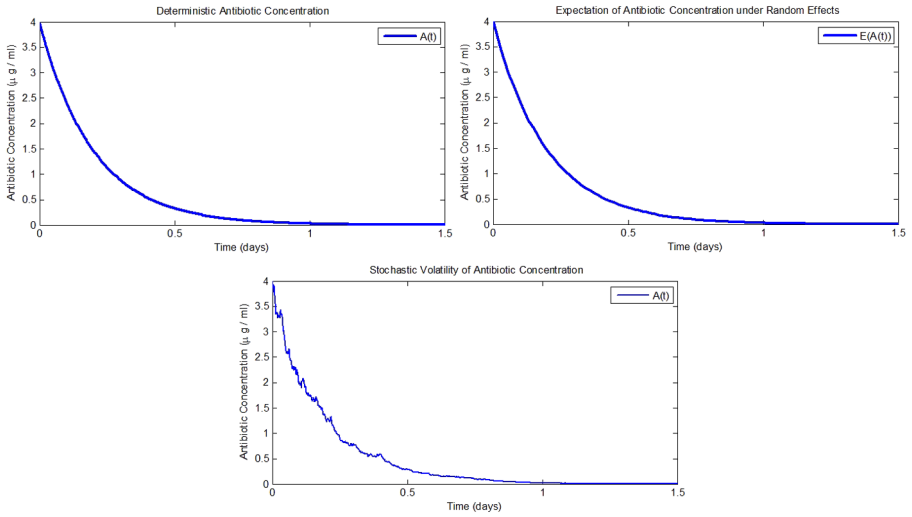

Figure 14 Deterministic, random and stochastic results for $A(t)$, respectively.

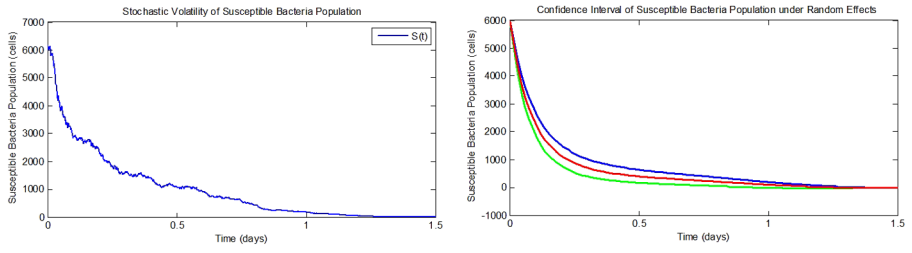

Figure 15 Stochastic volatility and confidence interval of $S(t)$, respectively.

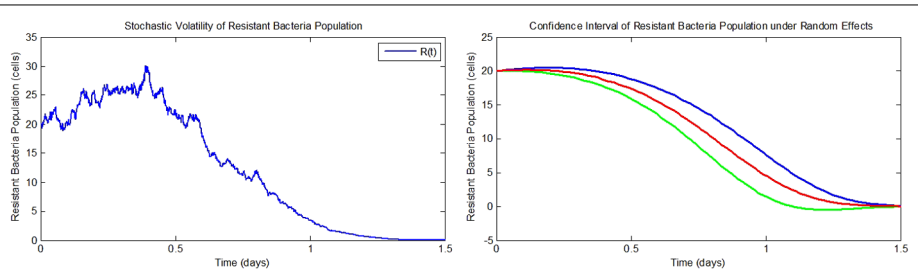

Figure 16 Stochastic volatility and confidence interval of $R(t)$, respectively.

volatility in the stochastic results for $R(t)$, which can also be seen in the graph for the confidence interval of random results. A large confidence interval implies that large variations in the results should be expected, as in the stochastic case.

The graphs for the confidence interval and volatility of $B(t)$ are also compliant, as Figure 17 suggests. The 99% confidence interval of the expectation of the population of immune cell grows large in the time period where there seems to be large volatility in the stochastic case.

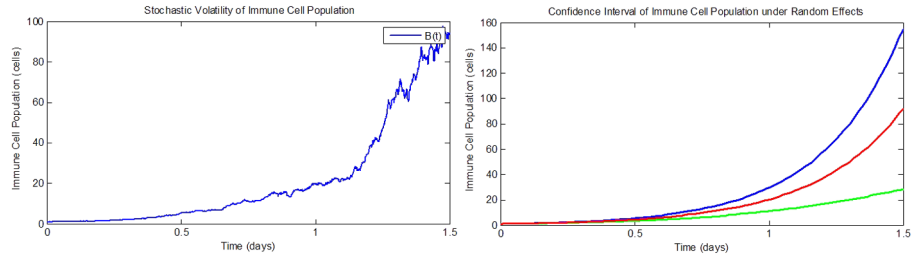

Figure 17 Stochastic volatility and confidence interval of $B(t)$, respectively.

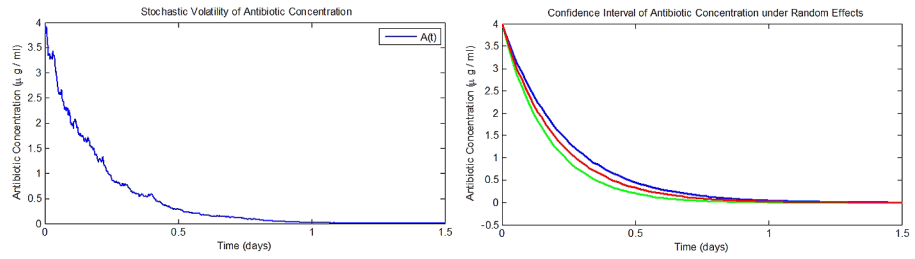

Figure 18 Stochastic volatility and confidence interval of $A(t)$, respectively.

In Figure 18, it can be seen that there is not much volatility in the results for the concentration of antibiotic, which is compliant with a small confidence interval in the random case.

6 Conclusion

In this study, the existing deterministic model for bacterial resistance with immune system response and antibiotic therapy was used to form random and stochastic models of the case. The parameters of the deterministic model are obtained from a statistical evaluation of various bacterial resistance cases from around the world, but the deterministic analysis neglects the randomness of these parameters and regards these quantities as stable values. Thus, by introducing Gaussian distributed random effect terms, we formed a random equation system that models the real-life randomness of bacterial resistance. A random analysis for the dynamics of the antibiotic resistance model is authentic and shows that, even under small random effects, some of the components produce very unlikely results. The comparison between the deterministic and random results shows a correspondence between the behaviors of the models, while the random effects cause an inevitable difference in the random case, as expected. Although the standard deviations of the random effects added to the parameters were 5% of their deterministic values, it can be seen from the results that especially the population of resistant bacteria and the population of immune cells are significantly affected from these variations. The immune cell population size, $B(t)$, gets its maximum expected value 92.42 at $t = 1.5$. The maximum standard deviation of $B(t)$ is estimated as 21.16 at $t = 1.5$ using the results of its variance. This value is approximately 22.89% of its expectation, meaning that under the assumed random conditions, the immune cell population could vary at most about 22.89% from its expectation, or similarly from the estimations of the deterministic model, which neglects the randomness of the event. Similarly, the population size of the resistant bacteria, $R(t)$, gets a maximum

standard deviation at $t = 0.915$ with an approximate value of 1.10. On the other hand, $R(t)$ has an approximate expected value of 6.849 at $t = 0.915$. Thus, the number of resistant bacteria could vary up to 16.06% at the time of its maximum standard deviation. The amount of randomness in these two variables can also be visualized from the confidence interval graphs. Confidence interval graphs of 99% show the intervals within three standard deviations from the expectation and a large interval for these two variables show that neglecting the randomness in the model could result in seriously misleading information. A deviation of 5% in the parameters of the random model causes a maximum of 22.89% deviation for $B(t)$, 16.06% maximum deviation for $R(t)$, 6.19% maximum deviation for $S(t)$ and 4.88% maximum deviation for $A(t)$. The significant deviations in $B(t)$ and $R(t)$ were also seen in the stochastic graphs. The volatility in the realizations of the model under stochastic noise is in correspondence with the confidence intervals of the random variables. For instance, $R(t)$ gets values between 18.51 and 12.639 in the time interval $[0.7, 0.824]$, just as the 99% confidence interval suggests.

The non-negligible deviation and volatility in the random and stochastic models show that the deterministic analysis of bacterial resistance is incapable of modeling the real-life randomness of the event. Our analysis shows that even with small random effects and small diffusion coefficients, the populations of resistant bacteria and immune cells show significant deviations from the deterministic results. The analyses in this study could be continued by using various values for the parameters or various distributions for the random effects. The magnitudes of the random effects or the diffusion coefficients of the stochastic noise could also be altered to monitor the effects of these changes on the results. These suggestions provide a basis for new studies and these options for random models will be evaluated in new papers. Hence, we believe this study will stimulate similar random investigations of models from all areas of science.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
All authors have contributed to all parts of the article. All authors have read and approved the final manuscript.

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