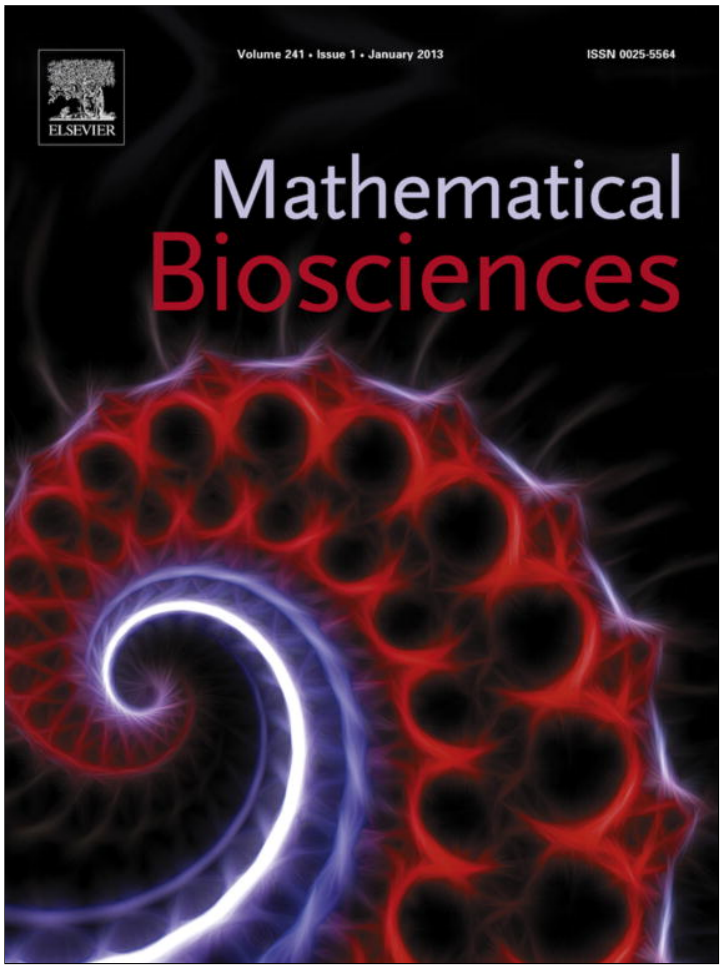

Mathematical Biosciences 241 (2013) 99–108

Contents lists available at SciVerse ScienceDirect

Mathematical Biosciences

journal homepage: www.elsevier.com/locate/mbs

An analysis of a stochastic model for bacteriophage systems ☆

X. Bardina [a], D. Bascompte [a], C. Rovira [b,*], S. Tindel [c]

[a] Departament de Matemàtiques, Facultat de Ciències, Edifici C, Universitat Autònoma de Barcelona, 08193 Bellaterra, Spain
[b] Facultat de Matemàtiques, Universitat de Barcelona, Gran Via 585, 08007 Barcelona, Spain
[c] Institut Élie Cartan Nancy, B.P. 239, 54506 Vandœuvre-lès-Nancy Cedex, France

ARTICLE INFO

Article history:
Received 23 September 2011
Received in revised form 28 September 2012
Accepted 28 September 2012
Available online 23 October 2012

Keywords:
Bacteriophage
Competition systems
Brownian motion
Large deviations

ABSTRACT

In this article, we analyze a system modeling bacteriophage treatments for infections in a noisy context. In the small noise regime, we show that after a reasonable amount of time the system is close to a bacteria free equilibrium (which is a relevant biologic information) with high probability. Mathematically speaking, our study hinges on concentration techniques for delayed stochastic differential equations.

1. Introduction

Lately Bacteriophage therapies are attracting the attention of several scientific studies. They can be seen as a new and powerful tool to treat bacterial infections or to prevent them in food, animals or even humans. Generally speaking, they consist in inoculating a (benign) virus in order to kill the bacteria known to be responsible for a certain disease. This kind of treatment is known since the beginning of the 20th century, but has been in disuse in the Western world, erased by antibiotic therapies. However, a small activity in this domain has survived in the USSR, and it is now re-emerging (at least at an experimental level). Among the reasons for this re-emergence we can find the progressive slowdown in antibiotic efficiency (antibiotic resistance). Reported recent experiments include animal diseases like hemorrhagic septicemia in cattle or atrophic rhinitis in swine, and a need for suitable mathematical models is now expressed by the community.

Let us be a little more specific about the (lytic) bacteriophage mechanism: after attachment, the virus' genetic material penetrates into the bacteria and uses the host's replication mechanism to self-replicate. Once this is done, the bacteria is completely spoiled while new viruses are released, ready to attack other bacteria. It should be noticed at this point that among the advantages expected from the therapy is the fact that it focuses on one specific bacteria, while antibiotics also attack autochthonous microbiota. Generally speaking, it is also believed that viruses are likely to adapt themselves to mutations of their host bacteria.

At a mathematical level, whenever the mobility of the different biological actors is high enough, bacteriophage systems can be modeled by a kind of predator–prey equation. Namely, set $S(t)$ (resp. $Q(t)$) for the non-infected bacteria (resp. bacteriophages) concentration at time t. Consider a truncated identity function $\sigma : \mathbb{R}_+ \to \mathbb{R}_+$, such that $\sigma \in C^\infty, \sigma(x) = x$ whenever $0 \leqslant x \leqslant M$ and $\sigma(x) = M + 1$ for $x > M + 1$. Then a model for the evolution of the couple (S, Q) is as follows:

$$\begin{cases} dS(t) = [\alpha - k\sigma(Q(t))]S(t)dt \\ dQ(t) = \left[d - mQ(t) - k\sigma(Q(t))S(t) + kbe^{-\mu\zeta}\sigma(Q(t-\zeta))S(t-\zeta)\right]dt, \end{cases} \tag{1}$$

where α is the reproducing rate of the bacteria and k is the adsorption rate. In Eq. (1), d also stands for the quantity of bacteriophages inoculated per unit of time, m is their death rate, we denote by b the number of bacteriophages which are released after replication within the bacteria cell, ζ is the delay necessary to the reproduction of bacteriophages (called latency time) and the coefficient $e^{-\mu\zeta}$ represents an attenuation in the release of bacteriophages (given by the expected number of bacteria cell's deaths during the latency time, where μ is the bacteria's death rate). A given initial condition $\{S_0(\tau), Q_0(\tau); -\zeta \leqslant \tau \leqslant 0\}$ is also specified.

Some comments on the model described above are in order:

☆ S. Tindel is member of the BIGS (Biology, Genetics and Statistics) team at INRIA. X. Bardina and D. Bascompte are supported by the grant MTM2009-08869 from the Ministerio de Ciencia e Innovación. C. Rovira is supported by the grant MTM2009-07203 from the Ministerio de Ciencia e Innovación.

* Corresponding author.
E-mail addresses: Xavier.Bardina@uab.cat (X. Bardina), David.Bascompte@uab.cat (D. Bascompte), carles.rovira@ub.edu (C. Rovira), tindel@iecn.u-nancy.fr (S. Tindel).

0025-5564/$ - see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.mbs.2012.09.009

(i) Several models describing phages dynamics have already been considered in the literature (see, for instance [6,15,16,18,23]), many elaborated variants being introduced for instance in [7,20]. We are dealing here with a basic system, except for two points:

- In most of the models alluded to above, the coefficient σ in (1) is simply the identity function. We have considered here the truncation of the identity σ in order to manipulate bounded coefficients in our equations, but our parameter M can also be interpreted as a maximal phage attack rate. This feature is also present in [20], where the author argues that the saturation in the phage attack rate is due to multiple phage binding to a cell (the likelihood of this event being higher in case of high density of phages).
- To the best of our knowledge, none of the articles mentioned above contemplates the possibility of a continuous injection of phages into the system (represented by us by the constant d in (1)). This variant corresponds to the practical problem we are starting from, which has been brought to our attention by the Molecular Biology Group of the Department of Genetics and Microbiology at *Universitat Autònoma de Barcelona*. This situation corresponds to a treatment for cattle against Salmonella,[1] for which phages are inoculated through food, with an approximate constant rate d.

Let us point out that those changes with respect to the standard deterministic models induce some additional mathematical difficulties, which are handled at Section 2. In particular, the exponential convergence of the solution to (1) towards its equilibrium has to be worked out carefully.

(ii) The range of parameters in Eq. (1) obviously varies with the bacteriophage treatment being dealt with. We shall keep in mind the values corresponding to our Salmonella experiment, recorded in Section 4. However, generally speaking, one should be aware of the fact that delay is an important feature in our system. Indeed, reported values for the lysis timing parameter ζ ranges from 15 min (such a short latency time has been observed in the adsorption of a phage called C78 by a strain of Salmonella enterica) up to 45 min in the case of other Salmonella phages for instance, while the total length of experiments we had access to is measured in hours.
(iii) According to the values of the different parameters of the system and of the initial conditions, different types of equilibriums for Eq. (1) might emerge. Indeed, given a large enough M (or taking σ the identity function), an elementary analysis (not included in this article for sake of conciseness) shows that:

- When $kd/m > \alpha$, there exists a unique stable steady state $E_0 = (0, d/m)$ for our system (in particular bacteria have been eradicated).
- When $kd/m < \alpha$, the point E_0 is still an equilibrium but it becomes unstable, while another coexistence equilibrium $E_c = (\frac{\frac{mz}{k}-d}{\alpha(b-1)}, \frac{\alpha}{k})$ emerges.

On Section 2.1 we will conduct a short study on the existence and stability of the equilibrium E_0 for any given $M > 0$, but we will not give any result on the other equilibrium E_c since we only study results concerning the bacteria-free equilibrium E_0 along this paper. Indeed, the case of a unique stable equilibrium E_0 makes the mathematical analysis easier, and let us stress the fact that it corresponds to the main practical situation we have in mind, where high doses of phages are usually introduced in the cattle food. One should also mention a natural generalization of our problem: Consider the action of several varieties of bacteriophages, which is an option widely considered among practitioners. We have restricted our analysis here to a simplified situation for sake of readability.

This being recalled for the deterministic system, the main aim of this article is to deal with a noisy version of Eq. (1). This stochastic modeling can be justified by several effects:

(a) It is perfectly assumable that noise will appear when collecting data from laboratory tests.
(b) When one wishes to go from in vitro to in vivo modeling, it is commonly accepted that noisy versions of the differential systems at stake have to be considered. Indeed, random fluctuations in parameters like temperature or exposure to sun, rain and other environmental elements yield an important variability in the coefficients of our system. These fluctuations can be accurately summarized by a noisy random coefficient.
(c) Some quantities which were assumed to be deterministic in (1) are in fact random, such as the latency time ζ (see e.g. [5,7] for contributions in this direction) and the number of phages b which are released from the lytic mechanism.

Those random effects are present in other biological systems, and stochastic equations have been introduced e.g. for HIV dynamics in [10] and for bacteriophages in marine organisms in [9]. In those references it is always assumed that the noise enters in a bilinear way, which is quite natural in this situation and ensures positivity of the solution. We shall take up this strategy here, and consider system (1) with a small random perturbation of the form

$$\begin{cases} \mathrm{d}S^\varepsilon(t) = \left[\alpha - k\sigma(Q^\varepsilon(t))\right]S^\varepsilon(t)\mathrm{d}t + \varepsilon\sigma(S^\varepsilon(t)) \circ \mathrm{d}W^1(t) \\ \mathrm{d}Q^\varepsilon(t) = \left[d - mQ^\varepsilon(t) - k\sigma(Q^\varepsilon(t))S^\varepsilon(t) + kbe^{-\mu\zeta}\sigma(Q^\varepsilon(t-\zeta))S^\varepsilon(t-\zeta)\right]\mathrm{d}t + \varepsilon\sigma(Q^\varepsilon(t)) \circ \mathrm{d}W^2(t), \end{cases} \tag{2}$$

where ε is a small positive coefficient and $W = (W^1, W^2)$ is a 2-dimensional Brownian motion defined on a complete probability space $(\Omega, \mathcal{F}, \mathbf{P})$ equipped with the natural filtration $(\mathcal{F}_t)_{t\geqslant 0}$ associated to the Wiener process W. Let us add the following remarks in order to further justify our model (2):

(i) Instead of giving a detailed model for all the random effects recalled above, we have decided to summarize them in a global stochastic term represented by the Wiener process W. This is obviously a first approximation, where one assumes that a sum of many small effects gives raise to a Gaussian random variable (as suggested by the central limit theorem). Let us mention however that more complex situations, were quantities like b are modeled e.g. by Ornstein–Uhlenbeck processes, might be the object of future extensions of the current paper. More specifically, let us examine the dynamics of S. According to the fact that this process can be expressed as an exponential, it is reasonable to think that its relative increments (namely $dS(t)/S(t)$) are governed by a trend $\alpha - k\sigma(Q(t))$ plus a small Gaussian perturbation $\varepsilon dW(t)$. We shall thus assume this additive noise perturbation for the relative increment $dS(t)/S(t)$, which yields the first equation in (2). The second relation of our system (2) can be obtained thanks to the same kind of hypothesis. Let us recall at this point that similar interpretations of random effects by an analysis of the relative increments are implicit in [9,10]. Furthermore, in spite of the fact that we cannot reproduce the data we had access to for this study (for the patent reasons alluded to above), it should also be

[1] We refer to [8] for a preliminary study on this topic lead at Universitat Autònoma de Barcelona, and to the PhD theses [4,21] where the bacteriophages have been characterized. It should be mentioned however that the data we had access to cannot be reproduced in this article for patent reasons.

mentioned that the curves $t \mapsto \log(S(t))$ and $t \mapsto \log(Q(t))$ based on real measurements are compatible with a stochastic model in which the noise enters in an additive way. We thus believe that our bilinear noisy model is a natural one, though the exploration of alternative stochastic modeling strategies as explained in [1–3] would obviously be extremely interesting. We defer these developments to a subsequent publication for sake of conciseness.

(ii) We have chosen to work with Stratonovich differentials, denoted by $\circ dW$, instead of Itô type differentials. This is harmless in terms of mathematical analysis and we believe this model to be physically accurate, in spite of the fact that it differs from the Itô type modeling of [9,10]. Indeed, our starting point here is the macroscopic system of Eq. (1), in which the internal noise due to individual phage and bacteria fluctuations has already been averaged. Then all the randomness sources alluded to at points (a)–(c) above can be considered as external contributions. We refer to [22, Chapter 5] for a thorough justification of the fact that Stratonovich type noises are applicable in this kind of situation. Let us also stress the fact that Stratonovich equations can be seen as limits of smooth noisy equations, according to the celebrated Wong–Zakai theorem [24].

With these considerations in mind, the main aim of the current paper can be summarized as follows: we wish to prove that for a time τ_0 within a reasonable range, the couple $Z^\varepsilon(\tau_0) := (S^\varepsilon(\tau_0), Q^\varepsilon(\tau_0))$ is not too far away from the stable equilibrium E_0 of Eq. (1). Note that *reasonable range* is meant here as a time which corresponds to the order of both the latency delay and the time when the immune system of the animal can cope with the remaining bacteria.

As we shall see in the sequel, the treatment of Eq. (2) involves the introduction of some rather technical assumptions on our coefficients. For sake of readability, we have thus decided to handle first the following system without delay:

$$\begin{cases} dS^\varepsilon(t) = [\alpha - k\sigma(Q^\varepsilon(t))]S^\varepsilon(t)dt + \varepsilon\sigma(S^\varepsilon(t)) \circ dW^1(t) \\ dQ^\varepsilon(t) = [d - mQ^\varepsilon(t) + k(b-1)\sigma(Q^\varepsilon(t))S^\varepsilon(t)]dt + \varepsilon\sigma(Q^\varepsilon(t)) \circ dW^2(t), \end{cases} \tag{3}$$

where we notice that the only difference between (2) and (3) is that we have set $\zeta = 0$ in the latter.

The main advantage of Eq. (3) lies in the fact that we are able to work under the following rather simple set of assumptions:

Hypothesis 1.1. We will suppose that the coefficients of Eq. (3) satisfy:

(i) The initial condition (S_0, Q_0) of the system lies into the region

$$R_0 := \left[0, \frac{mM - d}{k(b-1)M}\right] \times [d/m, M].$$

(ii) The coefficient $\gamma = kd/m - \alpha$ is strictly positive and $M > d/m$.

We shall also use extensively the following notation:

Notation 1.2. The letters $c, c_1, c_2, \ldots$ will stand for universal constants, whose exact value is irrelevant. For a continuous function f, we set $\|f\|_{\infty,I} = \sup_{x\in I}|f(x)|$.

Then the previous loose considerations about convergence to E_0 can be summarized in the following theorem, which is the main result of our paper for our bacteriophage system without delay:

Theorem 1.3. *Given positive initial conditions, Eq. (3) admits a unique solution which is almost surely an element of $\mathcal{C}(\mathbb{R}_+, \mathbb{R}_+^2)$. Assume furthermore Hypothesis 1.1, set $\eta = m/2 \wedge \gamma$ and consider 3 constants $1 < \kappa_1 < \kappa_2 < \kappa_3$. Then there exists ρ_0 such that for any $\rho \leqslant \rho_0$ and any interval of time of the form $I = [\kappa_1 \ln(c/\rho)/\eta, \kappa_2 \ln(c/\rho)/\eta]$, we have*

$$\mathbf{P}\Big(\|Z^\varepsilon - E_0\|_{\infty,I} \geqslant 2\rho\Big) \leqslant \exp\left(-\frac{c_1\rho^{2+\lambda}}{\varepsilon^2}\right), \tag{4}$$

where λ is a constant satisfying $\lambda > \kappa_3/\eta$.

Remark 1.4. Relation (4) can be interpreted in the following manner: assume that we observe a noise with intensity ε. Then the kind of deviation we might expect from the noisy system (3) with respect to the equilibrium E_0 is of order $\varepsilon^{2\vartheta}$ with $\vartheta = 2\eta/\kappa_3$. This range of deviation happens at a time scale of order $\ln(\rho^{-1})/\eta$.

A second part of our analysis is then devoted to the more realistic delayed system (2), for which we have to impose some additional technical assumptions:

Hypothesis 1.5. We will suppose that the coefficients of Eq. (3) satisfy the following conditions, valid for any $t \in [-\zeta, 0]$:

(i) The initial condition $(S_0(t), Q_0(t))$ of the system lies into the region

$$R_0 := [0, M] \times \left[\frac{d}{m}, M\right].$$

(ii) We have $be^{-\mu\zeta}Q_0(t)S_0(t) > \frac{d}{m}S_0(0)$, and $be^{-\mu\zeta} > 1$.

(iii) The condition $S_0(t) < \frac{mM-d}{kbe^{-\mu\zeta}M}$ is satisfied.

With these hypotheses in hand, we obtain a result which is analogous to Theorem 1.3:

Theorem 1.6. *Eq. (4) still holds for the delayed system (2), under Hypothesis 1.5.*

Theorem 1.6 can be seen as the main result of the current paper, and deserves some additional comments:

(1) We have produced a concentration type result instead of a large deviation principle for Eq. (3), because it seemed more adapted to our biological context. Indeed, in the current situation one wishes to know how far we might be from the desired equilibrium at a given fixed time, instead of producing asymptotic results as in the large deviation theory. At a technical level however, we rely on large deviation type tools, and in particular on an extensive use of exponential inequalities for martingales.

(2) Let us compare our result with [9,10], which deal with closely related systems. The interesting article [9] is concerned with a predator–prey system similar to ours, but it assumes that a linearization procedure around equilibrium in the highly nonlinear situation (3) can be performed. The analysis relies then heavily on this unjustified step. As far as [10] is concerned, it roughly shows that if the noise intensity of the system is high enough, then HIV epidemics can be kept under control (in terms of exponential stability). This is valuable information, but far away from our point of view which assumes a low intensity for the noise. We should mention again the related thorough deterministic studies [7,12,14,20], as well as the enlightening alternative stochastic modeling [1–3].

(3) Mathematically speaking, it would certainly be interesting to play with the rich picture produced by Eq. (1) and its perturbed version in terms of stable and instable equilibrium. We have not delved deeper into this direction because it did not seem directly relevant to the biological problem we are starting from.

Our article is structured as follows: Section 2 is devoted to some preliminary considerations (convergence to equilibrium for the deterministic equations, and then existence and uniqueness results for our stochastic systems). Then we show our concentration results in Section 3. Finally, our theoretical results are illustrated by some numerical simulations presented in Section 4.

2. Preliminaries

In this section, we give some basic results concerning our competition system. This is done in increasing order for the complexity of the system under consideration:

1. Exponential convergence to equilibrium for the deterministic counterpart of the non delayed Eq. (3).
2. Same problem for the deterministic counterpart of the delayed Eq. (2).
3. Existence and uniqueness for the solution to the perturbed system (2), starting from the simpler system (3).

Before going on with our preliminary considerations, let us label the following set of hypothesis on our coefficient σ as well as the initial conditions:

Hypothesis 2.1. The coefficients of our differential systems satisfy the following assumptions:

(i) The function $\sigma : \mathbb{R}_+ \to \mathbb{R}_+$ is such that $\sigma \in \mathcal{C}^\infty$, and satisfies $\sigma(x) = x$ for $0 \leqslant x \leqslant M$ and $\sigma(x) = M + 1$ for $x > M + 1$. We also assume that $0 \leqslant \sigma\prime(x) \leqslant C$ for all $x \in \mathbb{R}_+$, with a constant C such that $C > 1$.
(ii) As far as the initial condition is concerned, we assume that it is given as continuous positive functions $\{S_0(\tau), Q_0(\tau); -\zeta \leqslant \tau \leqslant 0\}$. In case of the non delayed systems, $\zeta = 0$, it is simply given by two positive constants (S_0, Q_0).

2.1. Analysis of the deterministic non delayed system

This section is devoted to the analysis of the non perturbed system corresponding to (3). Namely, we shall consider the following dynamical system:

$$\begin{cases} \mathrm{d}S(t) = [\alpha - k\sigma(Q(t))]S(t)\mathrm{d}t \\ \mathrm{d}Q(t) = [d - mQ(t) + k(b-1)\sigma(Q(t))S(t)]\mathrm{d}t. \end{cases} \tag{5}$$

We will give some sufficient conditions for the existence of a unique stable equilibrium E_0 and then show exponential convergence to this equilibrium.

Let us start with the basic results we shall need about equilibria of (5).

Theorem 2.2. *If either $M + 1 < \frac{\alpha}{k}$ or $M > \frac{\alpha}{k}$ and $\frac{kd}{m} \geqslant \alpha$, system (5) has a unique (positive) steady state $E_0 = (0, \frac{d}{m})$. Moreover, the bacteria-free equilibrium E_0 is asymptotically stable for $\frac{kd}{m} > \alpha$ and $M > \frac{d}{m}$.*

Proof. To obtain equilibria, we have to find the solution to the following equation:

$$\begin{cases} 0 = (\alpha - k\sigma(\hat{Q}))\hat{S} \\ 0 = d - m\hat{Q} + k(b-1)\sigma(\hat{Q})\hat{S}, \end{cases} \tag{6}$$

where $\hat{S}, \hat{Q}$ are positive constants.

Owing to the first equation we have either $\hat{S} = 0$ or $\alpha - k\sigma(\hat{Q}) = 0$. Since $\hat{S} = 0$ and the second equation imply $\hat{Q} = \frac{d}{m}$, we have that bacteria-free equilibrium E_0 exists for any value of the parameters. In the case $M + 1 < \frac{\alpha}{k}$ one can observe that no other equilibrium exists (since $\alpha - k\sigma(\hat{Q}) > 0$ for any $\hat{Q}$).

Taking $M > \frac{\alpha}{k}$, $\alpha - k\sigma(\hat{Q}) = 0$ if and only if $\hat{Q} = \frac{\alpha}{k}$. Then, using the second equation in (6), we have

$$0 = d - m\frac{\alpha}{k} + (b-1)\alpha\hat{S} \Rightarrow \hat{S} = \frac{m\alpha - kd}{k(b-1)\alpha},$$

which is positive only for $\alpha > \frac{kd}{m}$. Elsewhere, this last equation gives us another equilibrium that we shall not consider along the paper. So we have proved the first part of the result.

For the second part, the Jacobian matrix of system (5) at E_0 is

$$A_0 := \begin{pmatrix} \alpha - k\sigma(\frac{d}{m}) & 0 \\ k(b-1)\sigma(\frac{d}{m}) & -m \end{pmatrix}.$$

The eigenvalues of this matrix are easily shown to be $\lambda_0 = \alpha - k\sigma(\frac{d}{m})$ and $\lambda_1 = -m$, which are negative for $\frac{kd}{m} > \alpha$ and $M > \frac{d}{m}$. □

We now wish to study the rate of convergence towards the E_0 equilibrium in the stable case (i.e., when $kd/m > \alpha$ and $M > \frac{d}{m}$). The main result we obtain to this respect is:

Theorem 2.3. *Under Hypothesis 1.1 and 2.1, the solution of system (5) with initial condition*

$$(S_0, Q_0) \in \left[0, \frac{mM - d}{k(b-1)M}\right] \times [d/m, M]$$

exponentially converges to the equilibrium E_0:

$$|(S(t), Q(t)) - E_0| \leqslant ce^{-\eta t}, \quad \text{with} \quad \eta = \gamma \wedge \frac{m}{2}, \tag{7}$$

where we recall that $\gamma = \frac{kd}{m} - \alpha > 0$.

Proof. In order to prove our claim, we first have to show that the region $R := [0, \frac{mM-d}{k(b-1)M}] \times [\frac{d}{m}, M] \subset [0, M]^2$ is left invariant by Eq. (5). Towards this aim, we can invoke the same method we will use in Proposition 2.4, and we let the reader check the details.

Now, since we have $Q(t) \leqslant M$ for all t, we can consider $\sigma(x) = x$ in Eq. (5). We will consider a version of this system centered at E_0 by means of the change of variables $\widetilde{S} = S, \widetilde{Q} = Q - d/m$. This leads to the system

$$\begin{cases} \widetilde{S}\prime(t) = -\gamma\widetilde{S}(t) - k\widetilde{Q}(t)\widetilde{S}(t) \\ \widetilde{Q}\prime(t) = -m\widetilde{Q}(t) + \frac{kd}{m}(b-1)\widetilde{S}(t) + k(b-1)\widetilde{Q}(t)\widetilde{S}(t). \end{cases} \tag{8}$$

Notice that, according to our set of assumptions concerning the initial conditions, we have $\widetilde{S}_0 \geqslant 0$ and $\widetilde{Q}_0 \geqslant 0$. Thus the solution to (8) will remain positive for all $t > 0$ (it can be deduced from R being invariant, or can be proved just like in Proposition 2.8).

Now, from the first equation in (8), we have that $\widetilde{S}'(t) \leqslant -\gamma\widetilde{S}(t)$. This implies $\widetilde{S}(t) \leqslant \widetilde{S}_0 e^{-\gamma t}$, proving that $\widetilde{S}(t)$ exponentially converges to zero.

Owing to the second equation in (8) and using positivity properties of the solution, we also get

$$\widetilde{Q}'(t) \leqslant -m\widetilde{Q}(t) + k(b-1)\widetilde{S}_0 e^{-\gamma t}\left(\frac{d}{m} + \widetilde{Q}(t)\right).$$

Finally, the variation of constants method will lead to the stated result, following the same steps we will detail later in the proof of Theorem 2.6. □

2.2. Analysis of the deterministic delayed system

We now try to generalize the results of Section 2.1 to our deterministic delayed system (1). To this aim, recall that we work under the additional Assumptions 1.5.

A first step towards exponential stability is then the invariance of a certain region under our dynamical system:

Proposition 2.4. *Under Hypothesis 1.1, 2.1 and 1.5, the region*

$$R := \left[0, \frac{mM-d}{kbe^{-\mu\zeta}M}\right] \times \left[\frac{d}{m}, M\right] \subset [0,M]^2$$

is left invariant by Eq. (1).

Proof. We separate the analysis of S and Q in two steps.

Step 1: boundedness of S. Since S is obviously positive (along the same lines as for Eq. (11)) and owing to the fact that $S'(t) = (\alpha - k\sigma(Q(t)))S(t)$ we obtain that

$$S'(t) \leqslant 0 \quad \text{whenever} \quad Q(t) > \frac{\alpha}{k}, \quad \text{and}$$
$$S'(t) \geqslant 0 \quad \text{whenever} \quad Q(t) < \frac{\alpha}{k}.$$

Furthermore, our system starts from an initial condition $Q_0(0) \geqslant \frac{d}{m} > \frac{\alpha}{k}$. Thus S is non increasing as long as Q remains in the interval $[\frac{d}{m}, \infty)$.

Let us now observe what happens in the limiting case $Q_0(0) = \frac{d}{m}$: recalling that our initial conditions are denoted by $S_0(t), Q_0(t)$ for $t \in [-\zeta, 0]$, we have

$$\begin{aligned} Q_0'(0) &= -k\frac{d}{m}S_0(0) + kbe^{-\mu\zeta}\sigma(Q_0(-\zeta))S_0(-\zeta) \\ &= k\left(be^{-\mu\zeta}Q_0(-\zeta)S_0(-\zeta) - \frac{d}{m}S_0(0)\right) > 0, \end{aligned}$$

where we have used the fact that $be^{-\mu\zeta}Q_0(-\zeta)S_0(-\zeta) > \frac{d}{m}S_0(0)$. According to this inequality, we obtain the existence of a strictly positive ε such that $Q(t) > \frac{d}{m}$ for all $t \in (0, \varepsilon)$. We thus introduce the quantity $t_0 = \inf\{t > 0 : Q(t) = \frac{d}{m}\}$, and notice that we have

$$Q'(t_0) = -k\frac{d}{m}S(t_0) + kbe^{-\mu\zeta}\sigma(Q(t_0-\zeta))S(t_0-\zeta).$$

We can now distinguish two cases:

1. If $t_0 > \zeta$, since $S(t)$ is non-increasing in $[0, t_0]$, $S(t_0 - \zeta) \geqslant S(t_0)$ and hence
$$Q'(t_0) \geqslant kS(t_0)\left(be^{-\mu\zeta}\sigma(Q(t_0-\zeta)) - \frac{d}{m}\right) > 0,$$
due to the fact that $be^{-\mu\zeta} > 1, M > \frac{d}{m}$ and $Q(t_0 - \zeta) > \frac{d}{m}$.
2. If $t_0 \leqslant \zeta$, since $S(t_0) \leqslant S_0(0)$ we obtain
$$\begin{aligned} Q'(t_0) &\geqslant -k\frac{d}{m}S_0(0) + kbe^{-\mu\zeta}\sigma(Q_0(t_0-\zeta))S_0(t_0-\zeta) \\ &= k\left(be^{-\mu\zeta}Q_0(t_0-\zeta)S_0(t_0-\zeta) - \frac{d}{m}S_0(0)\right) > 0, \end{aligned}$$
where we have used the fact that $be^{-\mu\zeta}Q_0(t)S_0(t) > \frac{d}{m}S_0(0)$ for all $t \in [-\zeta, 0]$.

This discussion allows thus to conclude that t_0 cannot be a finite time. Indeed, we should have $Q'(t_0) > 0$ and hence Q increasing in a neighborhood of t_0, while Q should be decreasing in a neighborhood of t_0 according to its very definition. We have thus reached the following partial conclusion:

$$Q(t) \geqslant \frac{d}{m}, \quad t \mapsto S(t) \text{ decreasing}, \quad S(t) \geqslant 0.$$

In particular, any interval of the form $[0, L]$ for $L \geqslant 0$ is left invariant by $t \mapsto S_t$.

Step 2: boundedness of Q. Our claim is now reduced to prove that for $(S_0(t), Q_0(t)) \in R$ we have $Q(t) \leqslant M$ for all $t \geqslant 0$.

To this aim notice that, whenever $Q_0(0) = M$ we have

$$\begin{aligned} Q'(0) &= d - mM - kMS_0(0) + kbe^{-\mu\zeta}\sigma(Q_0(-\zeta))S_0(-\zeta) \\ &\leqslant d - mM + kbe^{-\mu\zeta}MS_0(-\zeta) < 0, \end{aligned}$$

where we recall that $S_0(-\zeta) < \frac{mM-d}{kbe^{-\mu\zeta}M}$ according to Hypothesis 1.5. This yields the existence of $\varepsilon > 0$ such that $Q(t) < M$ for all $t \in (0, \varepsilon)$.

We now define $t_1 = \inf\{t > 0 : \ Q(t) = M\}$. It is readily checked that

$$\begin{aligned} Q'(t_1) &= d - mM - kMS(t_1) + kbe^{-\mu\zeta}\sigma(Q(t_1-\zeta))S(t_1-\zeta) \\ &= d - mM - kMS(t_1) + kbe^{-\mu\zeta}Q(t_1-\zeta)S(t_1-\zeta) \\ &\leqslant d - mM + kbe^{-\mu\zeta}MS(t_1-\zeta), \end{aligned}$$

and we can distinguish again two cases:

1. If $t_1 > \zeta$, thanks to the fact that $t \mapsto S(t)$ is non-increasing on $[0, t_1]$, we have
$$Q'(t_1) \leqslant d - mM + kbe^{-\mu\zeta}MS_0(0) < 0,$$
since we have assumed that $S_0(0) < \frac{mM-d}{kbe^{-\mu\zeta}M}$.
2. If $t_1 \leqslant \zeta$ then
$$Q'(t_1) \leqslant d - mM + kbe^{-\mu\zeta}MS_0(t_1-\zeta) < 0,$$
thanks to the fact that $S_0(t) < \frac{mM-d}{kbe^{-\mu\zeta}M}$ for all $t \in [-\zeta, 0]$.

As for the discussion of the previous step, this allows thus to conclude that t_1 cannot be a finite time, due to the contradiction $Q'(t_1) < 0$ and $Q(t) < Q(t_1)$ for all $t \in (0, t_1)$. We have thus shown $Q(t) \leqslant M$ for all $t \geqslant 0$, which finishes the proof. □

Remark 2.5. Before stating the exponential convergence to the bacteria-free equilibrium result, let us observe that Theorem 2.2 still holds true for the delayed system (1). This can be easily checked, exactly along the same lines as for the non-delayed system.

We are now ready to state our result on exponential convergence of the delayed system:

Theorem 2.6. *Assume Hypothesis 1.1, 2.1, and 1.5 are satisfied, and let R be the region defined at Proposition 2.4. Then the solution of system (1) with initial condition $(S_0, Q_0) \in R$ exponentially converges to the equilibrium E_0:*

$$|(S(t), Q(t)) - E_0| \leqslant ce^{-\eta t}, \quad \text{with} \quad \eta = \gamma \wedge \frac{m}{2}, \tag{9}$$

where we recall that $\gamma = \frac{kd}{m} - \alpha > 0$.

Proof. According to Proposition 2.4, we have $Q(t) \leqslant M$ for all $-\zeta \leqslant t < \infty$ under our standing assumptions. Hence one can recast Eq. (1) as

$$\begin{cases} \mathrm{d}S(t) = (\alpha - kQ(t))S(t)dt \\ \mathrm{d}Q(t) = \left(d - mQ(t) - kQ(t)S(t) + kbe^{-\mu\zeta}Q(t-\zeta)S(t-\zeta)\right)dt \end{cases}$$

Let us perform now the change of variables $\tilde{Q} = Q - \frac{d}{m}$. This transforms the previous system into

$$\begin{cases} \mathrm{d}S(t) = \left(\alpha - k(\tilde{Q}(t) + \frac{d}{m})\right)S(t)\,\mathrm{d}t \\ d\tilde{Q}(t) = \left(d - m(\tilde{Q}(t) + \frac{d}{m}) - k(\tilde{Q}(t) + \frac{d}{m})S(t) + kbe^{-\mu\zeta}(\tilde{Q}(t-\zeta) + \frac{d}{m})S(t-\zeta)\right)\mathrm{d}t. \end{cases}$$

Equivalently, our new system is:

$$\begin{cases} \mathrm{d}S(t) = -\Big(\gamma S(t) + k\tilde{Q}(t)S(t)\Big)\,\mathrm{d}t \\ \mathrm{d}\tilde{Q}(t) = \Big(-m\tilde{Q}(t) - k\frac{d}{m}S(t) - k\tilde{Q}(t)S(t) + k\frac{d}{m}be^{-\mu\zeta}S(t-\zeta) \\ \qquad +kbe^{-\mu\zeta}\tilde{Q}(t-\zeta)S(t-\zeta)\Big)\,\mathrm{d}t. \end{cases}$$

Observe now that Proposition 2.4 asserts that $Q(t) \geqslant \frac{d}{m}$ for all $t \geqslant 0$, which means that $\tilde{Q}(t) \geqslant 0$. With our change of variables, we have also shifted our equilibrium to the point $(0,0)$. We now wish to prove that $S(t)$ and $\tilde{Q}(t)$ exponentially converge to 0.

The bound on $S(t)$ is easily obtained: just note that

$$\mathrm{d}S(t) \leqslant -\gamma S(t)\,\mathrm{d}t,$$

which yields $S(t) \leqslant S_0(0)e^{-\gamma t}$. As far as $\tilde{Q}(t)$ is concerned, one gets the bound

$$\begin{aligned} \frac{\mathrm{d}\tilde{Q}(t)}{\mathrm{d}t} &\leqslant -m\tilde{Q}(t) + k\frac{d}{m}be^{-\mu\zeta}S_0(0)e^{-\gamma(t-\zeta)} + kbe^{-\mu\zeta}\tilde{Q}(t-\zeta)S_0(0)e^{-\gamma(t-\zeta)} \\ &\leqslant -m\tilde{Q}(t) + kbe^{-\mu\zeta}S_0(0)e^{-\gamma(t-\zeta)}\left(\frac{d}{m} + M - \frac{d}{m}\right) \\ &= -m\tilde{Q}(t) + ce^{-\gamma t}, \end{aligned}$$

with $c = kbMS_0(0)e^{(\gamma-\mu)\zeta}$, and where we have used the fact that $Q(t) \leqslant M$ uniformly in t.

Invoking now the variation of constant method, it is readily checked that equation $\dot{x}(t) = -mx(t) + ce^{-\gamma t}$ with initial condition $x_0 = \tilde{Q}_0(0)$ can be explicitly solved as

$$\begin{aligned} x(t) &= e^{-mt}\left(\tilde{Q}_0(0) + \frac{c}{m-\gamma}\left(e^{(m-\gamma)t} - 1\right)\right) \\ &= \left(\tilde{Q}_0(0) - \frac{c}{m-\gamma}\right)e^{-mt} + \frac{c}{m-\gamma}e^{-\gamma t}. \end{aligned}$$

By comparison, this entails the inequality $\tilde{Q}(t) \leqslant c_1 e^{-\eta t}$, where $c_1 = \max\left(\tilde{Q}_0(0) - \frac{c}{m-\gamma}, \frac{c}{m-\gamma}\right)$ and $\eta = m \wedge \gamma$. Our proof is now finished. □

2.3. Properties of the stochastic system

Recall that we are considering the perturbed problem (2), with a coefficient σ and some initial conditions satisfying Hypothesis 2.1. In particular, due to the fact that we have assumed a bounded coefficient σ, the existence and uniqueness of the solution to our differential system is a matter of standard considerations.

Theorem 2.7 (*Global existence of solution*). *For any positive initial condition there exists a unique solution of (2), which is defined for all* $t \geqslant 0$.

Proof. It is readily checked that the coefficients of the equation are locally Lipschitz with linear growth. The existence and uniqueness of the solution is then a direct consequence of classical results (see e.g. [13, Section 5.2] for the non delayed system and [17] for the delayed one). □

Positivity of the solution is also an important feature, if we want the quantities $S(t), Q(t)$ to be biologically meaningful. Moreover, part of our analysis will rely on this property, that we label for further use:

Proposition 2.8. (Positivity) *If we take positive initial conditions* $S_0(t) \geqslant 0,\ Q_0(t) \geqslant 0$ *for all* $t \in [-\zeta, 0]$ *for the system (2), then the solution fulfills* $S^\varepsilon(t) \geqslant 0,\ Q^\varepsilon(t) \geqslant 0$ *for all* $t > 0$.

Proof. Let us first consider the system with $\sigma(x) = x$ for all x, namely:

$$\begin{cases} \mathrm{d}S^\varepsilon(t) = \big[\alpha - kQ^\varepsilon(t)\big]S^\varepsilon(t)\mathrm{d}t + \varepsilon S^\varepsilon(t) \circ \mathrm{d}W^1(t) \\ \mathrm{d}Q^\varepsilon(t) = \Big[d - mQ^\varepsilon(t) - kQ^\varepsilon(t)S^\varepsilon(t) + kbe^{-\mu\zeta}Q^\varepsilon(t-\zeta)S^\varepsilon(t-\zeta)\Big]\mathrm{d}t + \varepsilon Q^\varepsilon(t) \circ \mathrm{d}W^2(t), \end{cases} \tag{10}$$

with initial condition $(S_0(t), Q_0(t))$. Assuming existence and uniqueness of the solution to (10), we shall prove that $S^\varepsilon(t), Q^\varepsilon(t) \geqslant 0$ for all $t \geqslant 0$ almost surely.

Indeed, after the change of variables $x(t) = e^{-\varepsilon W^1(t)}S^\varepsilon(t)$, $y(t) = e^{-\varepsilon W^2(t)}Q^\varepsilon(t)$, we can recast (10) into the following system of differential equations with random coefficients:

$$\begin{cases} x'(t) = \Big(\alpha - ke^{\varepsilon W^2(t)}y(t)\Big)x(t) \\ y'(t) = de^{-\varepsilon W^2(t)} - my(t) - ke^{\varepsilon W^1(t)}x(t)y(t) \\ \quad +kbe^{-\mu\zeta-\varepsilon(W^2(t)-W^2(t-\zeta)-W^1(t-\zeta))}y(t-\zeta)x(t-\zeta), \end{cases} \tag{11}$$

with initial conditions $x^0(t) = S_0(t) \geqslant 0, y^0(t) = Q_0(t) \geqslant 0$ for all $t \in [-\zeta, 0]$. Then, the positivity of $x(t)$ is immediate from the representation

$$x(t) = x^0(0)\exp\left\{\int_0^t (\alpha - ke^{\varepsilon W^2(s)}y(s))\mathrm{d}s\right\} \geqslant 0.$$

In order to see the positivity of $y(t)$ let us observe that for $y^0(0) = 0$ we have $y\prime(0) = d + kbe^{-\mu\zeta-\varepsilon(W^2(0)-W^2(-\zeta)-W^1(-\zeta))}y(-\zeta)x(-\zeta) > 0$. Therefore, for all initial condition $y(0) \geqslant 0$ there exists $\delta > 0$ such that $y(t) > 0$ for all $t \in (0, \delta)$. Let us suppose now that $y(t) < 0$ for some $t > 0$, and let $t_0 = \inf\{t > 0 | y(t) < 0\}$. Due to the continuity of the solution we have that $y(t_0) = 0$. Then

$$\begin{aligned} y'(t_0) &= de^{-\varepsilon W^2(t_0)} + kbe^{-\mu\zeta-\varepsilon(W^2(t_0)-W^2(t_0-\zeta)-W^1(t_0-\zeta))}y(t_0-\zeta)x(t_0-\zeta) \\ &> 0, \end{aligned}$$

which is impossible since it would yield $y(t) > 0$ for $t \in (t_0, t_0 + \delta)$ for δ small enough. This contradiction means exactly that $y(t) \geqslant 0$ for all $t \geqslant 0$.

Now that we have the positivity for system (10), we can prove the positivity for (2) in the following way. Let us first handle the case of $S^\varepsilon(t)$, and assume that the initial condition is such that $S_0(0) \geqslant M$. Set then $\tau^0_{M,S} = \inf\{t \geqslant 0$ such that $S^\varepsilon(t) \leqslant M/2\}$, and observe that $\tau^0_{M,S}$ is a $\mathcal{F}_t$- stopping time (recall that $\mathcal{F}_t$ stands for the natural filtration of the Brownian motion W), such that S^ε has remained positive until $\tau^0_{M,S}$. Furthermore, the strong Markov property for $(S^\varepsilon, Q^\varepsilon)$ entails that the process

$$\left\{\Big(S^\varepsilon(\tau^0_{M,S} + t), Q^\varepsilon(\tau^0_{M,S} + t)\Big);\quad t \geqslant 0\right\}$$

also satisfies (2) on the set $\Omega_{M,S} = \{\omega \in \Omega;\ \tau^0_{M,S} < \infty\}$, with an initial condition $S_0(0) = M/2$. With these considerations in mind, we can assume that the initial condition of our differential system satisfies $S_0(0) < M$.

With such an initial condition we can conclude the positivity of $S^\varepsilon(t)$ until the stopping time $\hat{\tau}^0_{M,S} = \inf\{t \geqslant 0$ such that $S^\varepsilon(t) \geqslant M\}$ as we have done for the system (10), since up to time $\hat{\tau}^0_{M,S}$ we have $\sigma(S^\varepsilon(t)) = S^\varepsilon(t)$. Then, invoking again the strong Markov property, we can also guarantee positivity until time $\tau^1_{M,S} = \inf\{t \geqslant \hat{\tau}^0_{M,S}$ such that $S^\varepsilon(t) \leqslant M/2\}$ as above. We are now in a position to obtain the positivity of S^ε_t until time $\hat{\tau}^1_{M,S} = \inf\{t \geqslant \tau^1_{M,S}$ such that $S^\varepsilon(t) \geqslant M\}$, once again with the same reasoning than for the system (10). The global positivity of $S^\varepsilon(t)$ on any interval of the form $[\tau^k_{M,S}, \tau^{k+1}_{M,S}]$ for $k \geqslant 0$ now follows by iteration of this reasoning.

It remains to show that $\lim_{k\to\infty}\tau^k_{M,S} = \infty$. This is easily obtained by combining the following two ingredients:

(i) The increments $\{\tau^{k+1}_{M,S} - \tau^k_{M,S}; k \geqslant 0\}$ form a i.i.d sequence by a simple application of the strong Markov property.

(ii) Owing to the specific coefficients we have for Eq. (2), it can be checked that for any $\eta_2 > 0$ one can find $\eta_1 > 0$ small enough such that $\mathbf{P}(\tau^1_{M,S} > \eta_1) \geqslant 1 - \eta_2$. Details of this assertion are omitted for sake of conciseness.

We let the reader check that the positivity of $Q^\varepsilon(t)$ can be obtained along the same lines, which ends the proof. □

Remark 2.9. Using the a priori positivity properties stated above, we could have also obtained existence and uniqueness of the solution for system (10). We did not include those developments for sake of conciseness.

3. Fluctuations of the random system

Here again we shall proceed gradually, and work out the following cases:

1. Fluctuations for the non delayed system.
2. Extension to the delayed system.

Towards this aim, let us first summarize the information we have obtained up to now in the non delayed case: we are considering the system

$$\begin{cases} \mathrm{d}S^\varepsilon(t) = \big[\alpha - k\sigma(Q^\varepsilon(t))\big]S^\varepsilon(t)\mathrm{d}t + \varepsilon\sigma(S^\varepsilon(t)) \circ \mathrm{d}W^1(t) \\ \mathrm{d}Q^\varepsilon(t) = \big[d - mQ^\varepsilon(t) + k(b-1)\sigma(Q^\varepsilon(t))S^\varepsilon(t)\big]\mathrm{d}t + \varepsilon\sigma(Q^\varepsilon(t)) \circ \mathrm{d}W^2(t). \end{cases} \tag{12}$$

Under Hypothesis 1.1 and 2.1, we have shown the existence of a unique equilibrium $E_0 = (0, d/m)$ for the deterministic system (5), corresponding to (12) with $\varepsilon = 0$. Furthermore, we have constructed a region $R \in \mathbb{R}^2_+$ such that for any initial condition $(S_0, Q_0) \in R$, the solution converges exponentially to E_0, with a rate $\eta = \gamma \wedge \frac{m}{2}$. We now wish to obtain a concentration result for the perturbed system (12), that is give a proof of Theorem 1.3. To this aim, we shall divide our proof into several subsections.

Notation 3.1. We will set $Z^\varepsilon(t)$ for the couple $(S^\varepsilon(t), Q^\varepsilon(t))$, and $Z^0(t)$ for the solution to the deterministic Eq. (5).

3.1. Reduction of the problem

Recall that Theorem 1.3 states an exponential bound (valid for ρ small enough) of the form

$$\mathbf{P}\Big(\|Z^\varepsilon - E_0\|_{\infty,I} \geqslant 2\rho\Big) \leqslant \exp\left(-\frac{c_1\rho^{2+\lambda}}{\varepsilon^2}\right), \tag{13}$$

on any interval of the form $I = [\kappa_1 \ln(c/\rho)/\eta; \kappa_2 \ln(c/\rho)/\eta]$ and $1 < \kappa_1 < \kappa_2 < \kappa_3$ such that $\lambda > \kappa_3/\eta$.

A first step in this direction is to consider a generic interval of the form $\widehat{I} = [a, b]$, and write

$$\begin{aligned} \mathbf{P}\Big(\|Z^\varepsilon - E_0\|_{\infty,\widehat{I}} \geqslant 2\rho\Big) &= \mathbf{P}\Big((\|Z^\varepsilon - E_0\|_{\infty,\widehat{I}} \geqslant 2\rho) \cap (\|Z^0 - E_0\|_{\infty,\widehat{I}} \geqslant \rho)\Big) \\ &\quad + \mathbf{P}\Big((\|Z^\varepsilon - E_0\|_{\infty,\widehat{I}} \geqslant 2\rho) \cap (\|Z^0 - E_0\|_{\infty,\widehat{I}} \leqslant \rho)\Big), \end{aligned}$$

which yields

$$\mathbf{P}\Big(\|Z^\varepsilon - E_0\|_{\infty,\widehat{I}} \geqslant 2\rho\Big) \leqslant A_1 + A_2,$$

with

$$\begin{aligned} A_1 &= \mathbf{P}\Big(\|Z^0 - E_0\|_{\infty,\widehat{I}} \geqslant \rho\Big), \quad \text{and} \\ A_2 &= \mathbf{P}\Big(\|Z^\varepsilon - Z^0\|_{\infty,\widehat{I}} \geqslant \rho\Big). \end{aligned} \tag{14}$$

Moreover, the term A_1 is easily handled: owing to (9), we have $A_1 = 0$ as soon as $a = \kappa_1 \ln(c/\rho)/\eta$ with $\kappa_1 > 1$. In order to prove (13), it is thus sufficient to check the following identity:

$$\mathbf{P}\Big(\|Z^\varepsilon - Z^0\|_{\infty,I} \geqslant \rho\Big) \leqslant \exp\left(-\frac{c_1\rho^{2+\lambda}}{\varepsilon^2}\right), \tag{15}$$

on any interval of the form $I = [\kappa_1 \ln(c/\rho)/\eta; \kappa_2 \ln(c/\rho)/\eta]$ and $1 < \kappa_1 < \kappa_2 < \kappa_3$. We shall focus on this inequality in the next subsection.

3.2. Exponential concentration of the stochastic equation

We will now give a general concentration result for $Z^\varepsilon - Z^0$ on suitable time scales as follows:

Proposition 3.2. *Let Z^ε be the solution to (12). Then there exists $\varepsilon_0 = \varepsilon_0(M, \tau)$ such that, for any $\rho \leqslant 1$ and $\varepsilon \leqslant \varepsilon_0$ we have*

$$\mathbf{P}\Big(\|Z^\varepsilon - Z^0\|_{\infty,[0,\tau]} > \rho\Big) \leqslant \exp\left(-\frac{c_2\rho^2}{e^{\kappa_2\tau}\varepsilon^2}\right), \tag{16}$$

where c_2, κ_2 are strictly positive constants which do not depend on ρ, ε, but both depend on our set of parameters $\alpha, k, \sigma, d, m, b, M$.

Proof. For notational sake, let us abbreviate $\|f\|_{\infty,[0,\tau]}$ into $\|f\|_\infty$ throughout the proof. In order to bound $Z^\varepsilon - Z^0$, we first seek a bound for $S^\varepsilon - S^0$. To this aim we notice that for the deterministic function S^0 and thanks to relation (9), one can find a constant $\kappa_1 = \kappa_1(\alpha, k, \sigma, d, m, b)$ such that $\|S^0\|_\infty \leqslant \kappa_1$. Set also $J^1(t) := \int_0^t \sigma(S^\varepsilon(s)) \circ \mathrm{d}W^1(s)$. Then

$$\begin{aligned} |S^\varepsilon(t) - S^0(t)| &\leqslant \int_0^t \Big|(\alpha - k\sigma(Q^\varepsilon(s)))S^\varepsilon(s) - \Big(\alpha - k\sigma(Q^0(s))\Big)S^0(s)\Big|\mathrm{d}s \\ &\quad + \varepsilon\Big|J^1(t)\Big| \leqslant \int_0^t \Big|(\alpha - k\sigma(Q^\varepsilon(s)))(S^\varepsilon(s) - S^0(s))\Big|\mathrm{d}s \\ &\quad + \int_0^t k\Big|\sigma(Q^\varepsilon(s)) - \sigma(Q^0(s))\Big||S^0(s)|\mathrm{d}s + \varepsilon|J^1(t)| \\ &\leqslant \int_0^t (\alpha + kM)|S^\varepsilon(s) - S^0(s)|\mathrm{d}s + \kappa_1 k\int_0^t |Q^\varepsilon(s) \\ &\quad - Q^0(s)|\mathrm{d}s + \varepsilon|J^1(t)|. \end{aligned} \tag{17}$$

Analogously, setting $J^2(t) := \int_0^t \sigma(Q^\varepsilon(s)) \circ \mathrm{d}W^2(s)$, we obtain

$$\begin{aligned} |Q^\varepsilon(t) - Q^0(t)| &\leqslant \int_0^t (m + k(b-1)\kappa_1)|Q^\varepsilon(s) - Q^0(s)|\mathrm{d}s \\ &\quad + \int_0^t k(b-1)M|S^\varepsilon(s) - S^0(s)|\mathrm{d}s + \varepsilon|J^2(t)|. \end{aligned} \tag{18}$$

Hence, putting together (17) and (18), we get the existence of two positive constants κ_2, κ_3 such that

$$|Z^\varepsilon(t) - Z^0(t)|^2 \leqslant \kappa_2\varepsilon^2\Big(|J^1(t)|^2 + |J^2(t)|^2\Big) + \kappa_3\int_0^t |Z^\varepsilon(s) - Z^0(s)|^2\mathrm{d}s,$$

and by a standard application of Gronwall's lemma, we get for all $t \in [0, \tau]$:

$$\begin{aligned} |Z^\varepsilon(t) - Z^0(t)|^2 &\leqslant \kappa_2\varepsilon^2\Big[|J^1(t)|^2 + |J^2(t)|^2\Big]\exp(\kappa_3 t) \\ &\leqslant \kappa_2\varepsilon^2\Big[|J^1(t)|^2 + |J^2(t)|^2\Big]\exp(\kappa_3\tau). \end{aligned} \tag{19}$$

Let us now go back to our claim (16): thanks to inequality (19), we have

$$\mathbf{P}\Big(\|Z^\varepsilon - Z^0\|_\infty > \rho\Big) = \mathbf{P}\Big(\|Z^\varepsilon - Z^0\|_\infty^2 > \rho^2\Big) \leqslant \mathbf{P}\left(\|J^1\|_\infty^2 + \|J^2\|_\infty^2 > \frac{\rho^2}{\kappa_2\varepsilon^2\exp(\kappa_3\tau)}\right) \leqslant T_1 + T_2,$$

with

$$T_1 = \mathbf{P}\left(\|J^1\|_\infty > \frac{\kappa_4\rho}{\varepsilon\exp(\kappa_5\tau)}\right), \quad \text{and} \quad T_2 = \mathbf{P}\left(\|J^2\|_\infty > \frac{\kappa_4\rho}{\varepsilon\exp(\kappa_5\tau)}\right).$$

We now proceed to bound the quantity T_1, and to this aim we first write $J^1(t)$ in terms of Itô's integrals: according to [13, Definition 3.13 p. 156],

$$J^1(t) = \int_0^t \sigma(S^\varepsilon(s))\mathrm{d}W^1(s) + \frac{1}{2}\langle\sigma(S^\varepsilon), \quad W^1\rangle_t,$$

where $\langle\cdot,\cdot\rangle$ stands for the bracket of two semi-martingales. Invoking Eq. (12) and ordinary rules of Stratonovich differential calculus, it is also readily checked that

$$\sigma(S^\varepsilon(t)) = \sigma(S_0^\varepsilon) + \varepsilon\int_0^t \sigma\sigma'(S^\varepsilon(s))\mathrm{d}W^1(s) + V(t),$$

where V is a process with bounded variation. We thus end up with the expression $J^1(t) = \widehat{M}^1(t) + V^1(t)$, where

$$\widehat{M}^1(t) = \int_0^t \sigma(S^\varepsilon(s))\mathrm{d}W^1(s), \quad \text{and} \quad V^1(t) = \frac{\varepsilon}{2}\int_0^t \sigma\sigma'(S^\varepsilon(s))\mathrm{d}s,$$

and decompose T_1 accordingly into $T_1 \leqslant T_{1,1} + T_{1,2}$, with

$$T_{1,1} = \mathbf{P}\left(\|\widehat{M}^1\|_\infty > \frac{\kappa_4\rho}{\varepsilon\exp(\kappa_3\tau)}\right), \quad \text{and} \quad T_{1,2} = \mathbf{P}\left(\|V^1\|_\infty > \frac{\kappa_4\rho}{\varepsilon\exp(\kappa_3\tau)}\right).$$

We now bound the terms $T_{1,1}$ and $T_{1,2}$ separately.

The term $T_{1,2}$ is easily bounded thanks to some deterministic arguments. Indeed, since $\sigma\sigma'(x) \leqslant C(M+1)$ for any $x \in \mathbb{R}_+$, we have $\|V^1\|_\infty \leqslant C(M+1)\varepsilon\tau$, so that for any $\rho \leqslant 1$ and $\varepsilon \leqslant \varepsilon_1 := (\kappa_4/(C(M+1)\tau\exp(\kappa_3\tau)))^{1/2}$, we have $T_{1,2} = 0$. As far as $T_{1,1}$ is concerned, one can apply the exponential martingale inequality (see, for instance, [11]) for stochastic integrals in order to get

$$T_{1,1} \leqslant \exp\left(-\frac{\kappa_4\rho^2}{M^2\exp(\kappa_3\tau)\varepsilon^2}\right).$$

Putting together the estimates for $T_{1,1}$ and $T_{1,2}$, we have thus obtained

$$T_1 \leqslant \exp\left(-\frac{\kappa_4\rho^2}{M^2\exp(\kappa_3\tau)\varepsilon^2}\right),$$

for any $\rho \leqslant 1$ and $\varepsilon \leqslant \varepsilon_1 := (\kappa_4/(C(M+1)\tau\exp(\kappa_3\tau)))^{1/2}$. We let the reader check that the term T_2 can be handled along the same lines, which finishes our proof. □

3.3. Deviation from equilibrium

Let us now prove inequality (13): recall that we have decomposed $\mathbf{P}(\|Z^\varepsilon - E_0\|_{\infty,\widehat{I}} \geqslant 2\rho)$ into $A_1 + A_2$ defined by (14). Furthermore, $A_1 = 0$ when $\widehat{I}$ is of the form $[a,b]$ with $a = \kappa_1\ln(c/\rho)/\eta$.

In order to complete our result, let us analyze the term A_2 in the light of inequality (16). Indeed, in order to go from (15) to (16), it is sufficient to choose ρ, τ, λ such that

$$\rho^2\exp(-\kappa_2\tau) > \rho^{2+\lambda},$$

which is achieved for $\tau < b := \lambda\ln(1/\rho)/\kappa_2$. Hence our claim is satisfied on the interval $\widehat{I} = [a,b]$. We now have to verify that this interval is nonempty, namely that $a < b$. This gives a linear equation in $\ln(1/\rho)$, of the form

$$\frac{\kappa_1}{\eta}[\ln(1/\rho) + \ln(c)] \leqslant \frac{\lambda}{\kappa_2}\ln(1/\rho).$$

and the reader might easily check that the following conditions are sufficient:

(i) The linear terms satisfy $\frac{\kappa_1}{\eta} < \frac{\lambda}{\kappa_2}$, that is $\lambda > \frac{\kappa_1\kappa_2}{\eta}$.

(ii) We take ρ small enough, namely $\rho \leqslant \rho_0$ in order to compensate the term $\ln(c)$.

The proof of (13) is now finished.

3.4. Extension to the delayed system

Let us deal now with the delayed case: as mentioned in the introduction, we consider the system

$$\begin{cases} \mathrm{d}S^\varepsilon(t) = [\alpha - k\sigma(Q^\varepsilon(t))]S^\varepsilon(t)\mathrm{d}t + \varepsilon\sigma(S^\varepsilon(t)) \circ \mathrm{d}W^1(t) \\ \mathrm{d}Q^\varepsilon(t) = \left[d - mQ^\varepsilon(t) - k\sigma(Q^\varepsilon(t))S^\varepsilon(t) + kbe^{-\mu\zeta}\sigma(Q^\varepsilon(t-\zeta))S^\varepsilon(t-\zeta)\right]\mathrm{d}t + \varepsilon\sigma(Q^\varepsilon(t)) \circ \mathrm{d}W^2(t), \end{cases} \tag{20}$$

where for any $t \in [-\zeta, 0]$ and for any $\varepsilon > 0$, $(S^\varepsilon(t), Q^\varepsilon(t)) = (S^0(t), Q^0(t))$.

Under Hypothesis 1.1, 2.1 and 1.5 we have shown the existence of a unique equilibrium E_0 for the deterministic system (1), corresponding to (20) with $\varepsilon = 0$. Following the non-delayed case, we wish to obtain a concentration result for the perturbed system (20), as is given in Theorem 1.6.

The proof of this result can be carried out almost exactly as for Theorem 1.3. Let us only point out the main difference: how to get an equivalent of inequalities (17) and (18). To this aim, we set again $J^1(t) := \int_0^t \sigma(S^\varepsilon(s)) \circ \mathrm{d}W^1(s)$ and $J^2(t) := \int_0^t \varepsilon\sigma(Q^\varepsilon(s)) \circ \mathrm{d}W^2(s)$. Then in the delayed case, relations (17) and (18) become

$$|S^\varepsilon(t) - S^0(t)| \leqslant \int_0^t (\alpha + kM)|S^\varepsilon(s) - S^0(s)|\mathrm{d}s + \kappa_1 k\int_0^t |Q^\varepsilon(s) - Q^0(s)|\mathrm{d}s + \varepsilon|J^1(t)|, \tag{21}$$

and

$$\begin{aligned} |Q^\varepsilon(t) - Q^0(t)| \leqslant{}& \int_0^t (m + k\kappa_1)|Q^\varepsilon(s) - Q^0(s)|\mathrm{d}s \\ &+ \int_0^t kM|S^\varepsilon(s) - S^0(s)|\mathrm{d}s + \varepsilon|J^2(t)| \\ &+ \int_0^t kbMe^{-\mu\zeta}|S^\varepsilon(s-\zeta) - S^0(s-\zeta)|\mathrm{d}s \\ &+ \int_0^t kbk_1e^{-\mu\zeta}|Q^\varepsilon(s-\zeta) - Q^0(s-\zeta)|\mathrm{d}s. \end{aligned} \tag{22}$$

Using that for any $t \in [-\zeta, 0]$ and for any $\varepsilon > 0$, $(S^\varepsilon(t), Q^\varepsilon(t)) = (S^0(t), Q^0(t))$ we can write the bounds

$$\begin{aligned} &\int_0^t kbMe^{-\mu\zeta}|S^\varepsilon(s-\zeta) - S^0(s-\zeta)|\mathrm{d}s = \int_0^{t-\zeta} kbMe^{-\mu\zeta}|S^\varepsilon(s) - S^0(s)|\mathrm{d}s \\ &\leqslant \int_0^t kbMe^{-\mu\zeta}|S^\varepsilon(s) - S^0(s)|\mathrm{d}s, \\ &\int_0^t kbk_1e^{-\mu\zeta}|Q^\varepsilon(s-\zeta) - Q^0(s-\zeta)|\mathrm{d}s = \int_0^{t-\zeta} kbk_1e^{-\mu\zeta}|Q^\varepsilon(s) - Q^0(s)|\mathrm{d}s \\ &\leqslant \int_0^t kbk_1e^{-\mu\zeta}|Q^\varepsilon(s) - Q^0(s)|\mathrm{d}s \end{aligned}$$

Then, putting these last bounds in (21) and (22) we get the existence of two positive constants κ_2, κ_3 such that

$$|Z^\varepsilon(t) - Z^0(t)|^2 \leqslant \kappa_2\Big(|J^1(t)|^2 + |J^2(t)|^2\Big) + \kappa_3\int_0^t |Z^\varepsilon(s) - Z^0(s)|^2\mathrm{d}s.$$

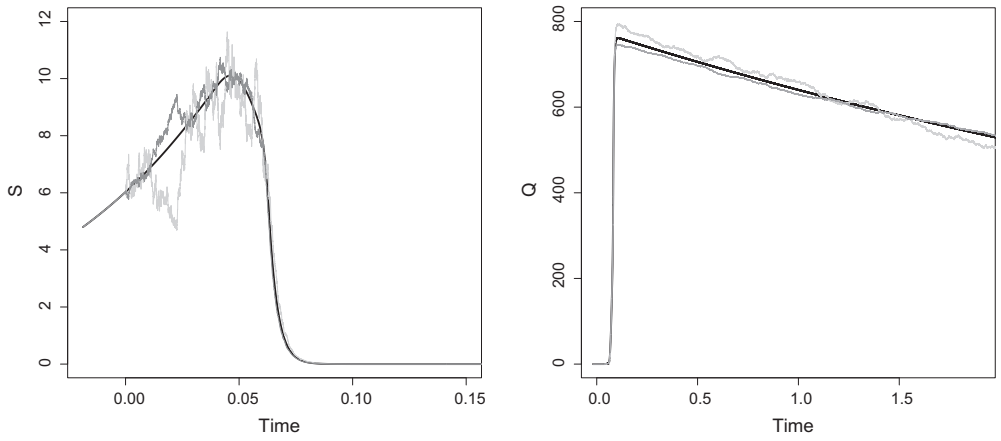

Fig. 1. Simulation of the trajectories of S and Q with real parzameters for the Salmonella ATCC14028 bacteria and UAB_Phi78 virus for the deterministic case ($\varepsilon = 0$), for $\varepsilon = -3$ and $\varepsilon = 1$.

Starting from this point, the proof follows exactly as for Theorem 1.3.

4. Numerical simulations

This final section is devoted to a presentation of some numerical simulations for the system described by Eq. (2). We have chosen the parameters $(\alpha, k, d, m, b, \zeta)$ according to some real data observed in vitro by the Molecular Biology Group of the Department of Genetics and Microbiology at *Universitat Autònoma de Barcelona*. We have also chosen to compare theoretical and noisy dynamics in order to see that the quantities S and Q are close to their equilibrium after a reasonable amount of time (in spite of randomness). We believe that this study is justified because the noise is expected to appear, either by the errors when collecting data, either by the appearance of several factors that may affect the behavior of the agents in vivo. Also, the lack of the rights to reproduce the data in the current article (for the patent reason alluded to in the introduction) does not allow us to consider other types of studies.

It is worth noticing at this point that the parameters we have chosen for our simulations do not meet the conditions stated at Hypothesis 1.5. Indeed, those conditions were imposed in order to obtain our theoretical large deviations type results with a reasonable amount of effort, but might be too restrictive to fit to real data experiments. Nevertheless, our simulations turn out to be satisfactory, since we observe that the solution $(S(t), Q(t))$ converges to E_0 for small values of ε in a reasonable amount of time, regardless of the violation of Hypothesis 1.5.

Specifically, we have simulated trajectories with parameters estimated on an experiment involving Salmonella ATCC14028 bacteria and UAB_Phi78 virus. From the experiments conducted by the mentioned group we have chosen the parameters as:

$$(\alpha, k, d, m, b, \zeta) = (12.1622, 27.36, 0.1, 0.1947, 61, 0.01875).$$

We have also put $M = 10$, $\mu = 0.5$, and we have taken the initial conditions $S_0(t) = 4.8e^{\alpha(t+\zeta)}, Q_0(t) = 0$ for $t \in [-\zeta, 0]$. The time is expressed in days and the amount of virus and bacteria are expressed in tens of millions of units.

Our simulations are summarized at Fig. 1, in which different paths of the processes S and Q are computed. We have first expressed our Stratonovich type Eq. (2) into an Itô type equation plus corrections, and then used an Euler type discretization scheme for our equations implemented with the **R** software. We have then plotted the deterministic case ($\varepsilon = 0$) plus the curves corresponding to several values of ε (namely $\varepsilon = -3, 1$). As mentioned before, the fluctuations of S and Q (which are obviously due to the randomness we have introduced) do not prevent them to converge to equilibrium. Observe that there alternative ways to Euler discretizations in order to simulate Stratonovich type equations, such as the Runge–Kutta method introduced in [19]. Since our numerical context was not too demanding, we have chosen to resort to the Euler scheme based on Itô type equations for sake of simplicity.

Acknowledgments

We would like to thank Prof. Montserrat Llagostera and the rest of the members of the Molecular Biology Group of the Department of Genetics and Microbiology at *Universitat Autònoma de Barcelona* for providing us the data we used in Section 4, and for their useful comments. We would also like to thank two anonymous referees for some enlightening discussions as well as numerous helpful suggestions and references.

References

[1] E. Allen, Modeling with Itô stochastic differential equations, Mathematical Modelling: Theory and Applications, 22, Springer, 2007.
[2] E. Allen, Derivation of stochastic partial differential equations, Stoch. Anal. Appl. 26 (2) (2008) 357.
[3] L. Allen, An introduction to stochastic processes with applications to biology, Second ed. CRC Press, 2011.
[4] C. Bardina: Estudio sobre terapia fágica contra S. enterica en Gallus gallus. PhD thesis. Universitat Autònoma de Barcelona (November 2011). Available at <https://www.educacion.es/teseo/mostrarRef.do?ref=947376>.
[5] E. Beretta, Y. Kuang, Modeling and analysis of a marine bacteriophage infection, Math. Biosci. 149 (1) (1998) 57.
[6] B.J. Cairns, A.R. Timms, V.A.A. Jansen, I.F. Connerton, R.J.H. Payne, Quantitative models of in vitro bacteriophage host dynamics and their application to phage therapy, PLoS Pathog 5 (1) (2009) e1000253, http://dx.doi.org/10.1371/journal.ppat.1000253.
[7] A. Calsina, J-M. Palmada, J. Ripoll, Optimal latent period in a bacteriophage population model structured by infection-age, Math. Models Methods Appl. Sci. 21 (4) (2011) 1–26.
[8] S. Campoy, J. Aranda, G. Alvarez, J. Barbé, M. Llagostera, Isolation and sequencing of a temperate transducing phage for pasteurella multocida, Appl. Environ. Microbiol. 72 (5) (2006) 3154–3160.
[9] M. Carletti, Mean-square stability of a stochastic model for bacteriophage infection with time delays, Math. Biosci. 210 (2) (2007) 95–414.
[10] N. Dalal, D. Greenhalgh, X. Mao, A stochastic model for internal HIV dynamics, J. Math. Anal. Appl. 341 (2) (2008) 1084–1101.
[11] M. Dozzi, Stochastic processes with a multidimensional parameter, Pitman Research Notes in Mathematics Series, Longman Scientific and Technical, Harlow, England, 1989.
[12] S. Gourley, Y. Kuang, A delay reaction–diffusion model of the spread of bacteriophage infection, SIAM J. Appl. Math. 65 (2) (2004/05) 550–566.
[13] I. Karatzas, S. Shreve, Brownian Motion and Stochastic Calculus, Second ed., Springer, 1991.
[14] Y. Kuang, Delay Differential Equations with Applications in Population Dynamics, Academic Press, 1993.

[15] B. Levin, J. Bull, Population and evolutionary dynamics of phage therapy, Nature Rev. Microbiol. 2 (2004) 166–173.
[16] S. Matsuzaki, M. Rashel, J. Uchiyama, S. Sakurai, T. Ujihara, M. Kuroda, M. Ikeuchi, T. Tani, M. Fujieda, H. Wakiguchi, S. Imai, Bacteriophage therapy: a revitalized therapy against bacterial infectious diseases, J. Infect. Chemother. 11 (2005) 211–219.
[17] S. Mohammed, Stochastic functional differential equations. Research Notes in Mathematics, vol. 99, Pitman, 1984.
[18] R. Payne, V. Jansen, Pharmacokinetic principles of bacteriophage therapy, Clin. Pharmacokinet. 42 (4) (2003) 315.
[19] W. Rümel, Numerical treatment of stochastic differential equations, SIAM J. Numer. Anal. 19 (3) (1982) 604.
[20] H. Smith, Models of virulent phage growth with application to phage therapy, SIAM J. Appl. Math. 68 (6) (2008) 1717.
[21] D.A. Spricigo: La desinfección basada en bacteriófagos como herramienta de biocontrol de Salmonella en alimentos. PhD thesis. Universitat Autònoma de Barcelona, November 2011. Available at <https://www.educacion.gob.es/teseo/mostrarRef.do?ref=947598>.
[22] N.G. Van Kampen, Stochastic Processes in Physics and Chemistry, 2nd ed., North Holland Personal Library, 2001.
[23] R. Weld, C. Butts, J. Heinemann, Models of phage growth and their applicability to phage therapy, J. Theor. Biol. 227 (2004) 1.
[24] E. Wong, M. Zakai, On the relation between ordinary and stochastic differential equations, Int. J. Eng. Sci. 3 (1965) 213.