Coinfection in a stochastic model for bacteriophage systems

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Abstract

A system modeling bacteriophage treatments with coinfections in a noisy context is analysed. We prove that in a small noise regime, the system converges in the long term to a bacteria-free equilibrium. Moreover, we compare the treatment with coinfection with the treatment without coinfection, showing how coinfection affects the convergence to the bacteria-free equilibrium.

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1 Introduction

The emergence of pathogenic bacteria resistant to most currently available antimicrobial agents has become a critical problem in medicine. The development of alternative antiinfection modalities has become a priority. Bacteriophage therapies are one of these alternatives. Prior to the discovery and widespread use of antibiotics, it has been suggested that bacterial infections could be treated by the administration of bacteriophages, but early clinical studies with bacteriophages were not pursued in the United States and Western Europe. Nowadays, these therapies are reemerging and attracting the attention of the scientific community.

Let us explain the (lytic) bacteriophage mechanism: the first step of an infection of a bacterium by a bacteriophage is the adsorption, i.e., the attachment of the virus to a given receptor of the bacterium surface (notice that in the literature often the word infection is simply used for adsorption, but it is not always the case that adsorption and infection can be used interchangeably [2]). After attachment, the virus' genetic material penetrates into the bacterium and uses the host's replication mechanism to self-replicate. After some latency time τ,

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the bacterium encounters death releasing some new viruses (lysis), free to attack other bacteria.

Host-pathogen interactions can vary from single to multiple infections. For multiple infections, the term *coinfection* is used when the host can be infected at the same time by more than one pathogen whereas *superinfection* stands for subsequent infections of an infected host at a later time.

In the case of bacteriophages, it has been seen [23, 25] that multiple phage can be adsorbed to a single bacterium which will imply a bigger rate of loss of phage in the population than if adsorption would happen only between one phage and one bacterium.

There is a long history of mathematical modelling of phage dynamics. One of the first papers was the work of Campbell [13] where he proposed a model based on a system of delay differential equations. Deterministic models can be found, for instance, in [8], [10], [11], [17], [19], [21], [26]. The literature about stochastic models is scarce. For instance, in [23] the authors give a stochastic model allowing multiple bacteriophage adsorption to host. On the other hand, [12] was one of the first papers dealing with coinfection and superfinfection models in evolutionary epidemiology, as previous models took only first infections into account. A general discussion about how superinfections and coinfections have been modeled in evolutionary epidemiology can be found in [4] and [20].

In [5] we have considered a stochastic model with a constant injection of phages into the system. This variant corresponds to a treatment for cattle against Salmonella, which was brought to our attention by the Molecular Biology Group of the Department of Genetics and Microbiology at *Universitat Autònoma de Barcelona*. We modeled the bacteria-phage dynamics by a system of predator prey type equations.

Let $S(t)$ (resp. $Q(t)$) denote the non-infected bacteria (resp. bacteriophages) concentration at time t. Consider a truncated identity function $\sigma : \mathbb{R}_+ \to \mathbb{R}_+$, such that $\sigma \in \mathcal{C}^\infty$, $\sigma(x) = x$ whenever $0 \leq x \leq M$ and $\sigma(x) = M + 1$ for $x > M + 1$. Then the model reads:

$$\begin{cases} dS(t) = [\alpha - k_1\sigma(Q(t))]\, S(t)dt \\ dQ(t) = \left[\delta - mQ(t) - k_1\sigma(Q(t))S(t) + k_1\, b\, e^{-\mu\tau}\sigma(Q(t-\tau))S(t-\tau)\right] dt, \end{cases} \tag{1}$$

where α is the growth rate of bacteria, k_1 is the adsorption rate, δ stands for the quantity of bacteriophages inoculated per unit of time (dose), m is their death rate, b is the burst size, i.e., the number of bacteriophages that are released after replication within the bacteria cell, τ is the delay necessary for the reproduction of bacteriophages (called latency time) and the coefficient $e^{-\mu\tau}$ 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 death rate of bacteria). In fact, $\alpha = \beta - \mu$ where β is the reproduction rate of bacteria. A given initial condition $\{S_0(t), Q_0(t); -\tau \leq t \leq 0\}$ is also specified.

Note that we have considered a coefficient σ that is a truncation of the identity. It is useful in order to manipulate bounded coefficients in our equations and our parameter M can be interpreted as a maximal phage attack rate.

Given a large enough M we showed that when $k_1\delta/m > \alpha$, there exists a unique stable steady state of (1), $E_0 = (0, \delta/m)$ (bacteria have been eradicated), while when $k_1\delta/m < \alpha$, the point E_0 is still an equilibrium but it becomes unstable and there exists another coexistence equilibrium. The paper only studies results regarding the bacteria-free equilibrium E_0, since it corresponds to the main practical situation, where high doses of phages are usually introduced in cattle feed.

Our main interest was in fact a noisy version of system (1). In this type of models there exist several random effects as the noise that can appear when collecting data from laboratory tests, random fluctuations in parameters (like temperature) that can affect the coefficients of our system or some randomness in the latency times. We summarized all these random effects in a small global stochastic term represented by a Wiener process W. That is, we considered a small random perturbation of the form

$$\begin{cases} dS^\varepsilon(t) = \left[\alpha - k_1\sigma(Q^\varepsilon(t))\right] S^\varepsilon(t)dt + \varepsilon\sigma(S^\varepsilon(t)) \circ dW^1(t) \\ dQ^\varepsilon(t) = \left[\delta - mQ^\varepsilon(t) - k_1\sigma(Q^\varepsilon(t))S^\varepsilon(t) + k_1\, b\, e^{-\mu\tau}\sigma(Q^\varepsilon(t-\tau))S^\varepsilon(t-\tau)\right] dt \\ \qquad\qquad + \varepsilon\sigma(Q^\varepsilon(t)) \circ dW^2(t), \end{cases} \tag{2}$$

where ε is a small positive coefficient and $W = (W^1, W^2)$ is a 2-dimensional Brownian motion and with Stratonovich differentials, denoted by $\circ\, dW$. We obtained a concentration result for the perturbed system around E_0.

Our aim in this paper is to study the problem of coinfection in the models we have presented in [5]. As mentioned before, due to the ambiguity in terminology we have to specify what we understand by coinfection in our model: after the first infection by a bacteriophage and before the death of the bacterium we will assume that more bacteriophages can be adsorbed to the bacterium. These later adsorptions will not affect the behaviour of the bacteria but they cause an extra loss in the free bacteriophage population. Thus, coinfection means here an extra mortality in the bacteriophage population.

We will show existence of a steady state $E_0 = (0, 0, \delta/m)$ (bacteria-free equilibrium) and we we will give conditions for its stability and also for the existence of a coexistence steady state. Furthermore, we will obtain a concentration result around E_0 for a perturbed system. These results are similar to those obtained in [5]. Furthermore, we will compare both models to determine the role of the coinfection in the behaviour of the system. Since some of the proofs are similar to those given in [5], we only will give some details of the proofs with new arguments and we will refer to those in [5] in the other cases.

Our article is structured as follows: in Section 2 we introduce both the deterministic and the stochastic model, in Section 3 we study the deterministic model showing positivity and boundedness of solutions in subsection 3.1 and computing the steady states and analysing the stability of the boundary steady state in subsection 3.2. Section 4 is devoted to the analysis of the stochastic system and in Section 5 we finish with some concluding remarks.

2 Formulation of the models

In order to consider coinfection, we introduce a new state variable $I(t)$, that gives the infected bacteria concentration at time t. Thus, we transform model (1) into the following

$$\begin{cases} dS(t) &= (\alpha - k_1\sigma(Q(t)))S(t)dt \\ dI(t) &= [k_1\sigma(Q(t))S(t) - \mu I(t) - k_1 e^{-\mu\tau}\sigma(Q(t-\tau))S(t-\tau)]dt \\ dQ(t) &= [\delta - mQ(t) - k_1\sigma(Q(t))S(t) - k_2\sigma(Q(t))I(t) \\ & \quad +k_1 be^{-\mu\tau}\sigma(Q(t-\tau))S(t-\tau)]dt, \end{cases} \tag{3}$$

where $\alpha > 0$ denotes the growth rate of bacteria, $k_1 > 0$ is the adsorption rate for noninfected bacteria, $k_2 > 0$ is the adsorption rate by infected ones, $\mu > 0$ denotes the death rate of infected bacteria, $m > 0$ is the death rate of bacteriophages and $b > 0$ is the burst size (i.e., the average number of virus released per infected cell).

The first term on the right hand side of the equation for the infected bacteria, $k_1\sigma(Q(t))S(t)$, stands for the rate of infection, i.e., the number of new infected bacteria per unit of time (assuming a "truncated" law of mass action) whereas the terms $k_1 e^{-\mu\tau}\sigma(Q(t-\tau))S(t-\tau)$ and $\mu I(t)$ stand for loss of infected bacteria because of lysis (after a latency time τ) and because of a different reason than lysis (with death rate μ) respectively. On the other hand, in the last equation, the term $-k_2\sigma(Q(t))I(t)$ accounts for the bacteriophages that the system loses when they try to infect infected bacteria (coinfection).

For the stochastic model we will introduce the random effects following the ideas we have used in [5]. Thus, we consider system (3) with a small random perturbation of the form

$$\begin{cases} dS^\varepsilon(t) &= \big(\alpha - k_1\sigma(Q^\varepsilon(t))\big)S^\varepsilon(t)dt + \varepsilon\sigma(S^\varepsilon(t)) \circ dW^1(t), \\ dI^\varepsilon(t) &= \big[k_1\sigma(Q^\varepsilon(t))S^\varepsilon(t) - \mu I^\varepsilon(t) - k_1 e^{-\mu\tau}\sigma(Q^\varepsilon(t-\tau))S^\varepsilon(t-\tau)\big]dt \\ dQ^\varepsilon(t) &= \big[\delta - mQ^\varepsilon(t) - k_1\sigma(Q^\varepsilon(t))S^\varepsilon(t) - k_2\sigma(Q^\varepsilon(t))I^\varepsilon(t) \\ & \quad +k_1 be^{-\mu\tau}\sigma(Q^\varepsilon(t-\tau))S(t-\tau)\big]dt + \varepsilon\sigma(Q^\varepsilon(t)) \circ dW^2(t), \end{cases} \tag{4}$$

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 $(\Omega, \mathcal{F}, P)$ equipped with the natural filtration $(\mathcal{F}_t)_{t\geq 0}$ associated to the Wiener process W. Recall that $\circ dW(t)$ denotes a Stratonovich integral.

Let us note that we assume that the noise enters in a bilineal way and that we consider the random effects in the coefficients in the noise in the first and third equation. We do not introduce an additive noise in the new state variable $I(t)$ to ensure the positivity of the solution.

3 Analysis of the deterministic model

This section is devoted to the study of the deterministic coinfection model (3). Before going on with the study of the deterministic model, let us present a set

of hypotheses on the coefficient σ and on the initial condition. The hypotheses on σ will be the same as those in [5].

Nonnegative initial data for S and Q must be given on $[-\tau, 0]$ whereas for I it only has to be given at $t = 0$. However (see [9], [22], [24]) I_0 cannot be given by any nonegative value, it will depend on S and Q.

Indeed (see [22],[24]), it can be seen that

$$I(t) = \int_{t-\tau}^{t} k_1 e^{-\mu(t-\theta)} \sigma(Q(\theta)) S(\theta) d\theta = \int_0^{\tau} k_1 e^{-\mu s} \sigma(Q(t-s)) S(t-s) ds \quad (5)$$

is a solution to the second equation in (3) which is biologically meaningful because it is the summation of all the rates of infection at previous times (up to $-\tau$, i.e., the ones that have not lysed yet), $k_1\sigma(Q(t-s))S(t-s)$, multiplied by the survival probability of infected bacteria $e^{-\mu s}$.

To ensure that (5) is then the only solution to the equation for $I(t)$ in (3), the initial value must be chosen so that (5) holds at $t = 0$, i.e.

$$I_0 := I(0) = \int_0^{\tau} k_1 e^{-\mu s} \sigma(Q(-s)) S(-s) ds. \quad (6)$$

Hypothesis 3.1 *We will make the following assumptions on our models:*
(i) *The function $\sigma : \mathbb{R}_+ \to \mathbb{R}_+$ is such that $\sigma \in \mathcal{C}^\infty$, and satisfies $\sigma(x) = x$ for $0 \le x \le M$ and $\sigma(x) = M + 1$ for $x > M + 1$. We also assume that $0 \le \sigma'(x) \le C$ 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 nonnegative functions $\{S_0(t), Q_0(t); -\tau \le t \le 0\}$ and a constant I_0 given by* (6).

3.1 Positivity and boundedness of solutions

The first step to analyse the model is to obtain existence and uniqueness of a global nonnegative solution.

Proposition 3.2 *Under hypothesis 3.1 the initial value problem for system (3) has a unique global nonnegative solution.*

Proof: Local existence of a unique solution follows from standard results for delay differential equations ([16], [22]). Let us study the positivity of the solution. Note that $\{(S, I) = (0, 0)\}$ is an invariant subspace. Clearly,

$$S(t) = S(0) \exp\left(\alpha - k_1 \sigma(Q(t)\right) > 0.$$

On the other hand, if for some t_0 it holds that $Q(t_0) = 0$ then $Q'(t_0) \ge \delta > 0$. So, $Q(t) \ge 0$ for all t.

Since

$$I(t) = \int_{t-\tau}^{t} k_1 e^{-\mu(t-\theta)} \sigma(Q(\theta)) S(\theta) d\theta$$

and $Q(t)$ and $S(t)$ are nonnegative on $[-\tau, +\infty)$ we obtain $I(t) \ge 0$ for all $t \ge 0$.

In order to get the existence of global solution it is enough to check that the local solutions are bounded (see for instance [14]). Since $S'(t) \leq \alpha S(t)$, we get that for all $t > 0$, $S(t) \leq S(0)e^{\alpha t}$. On the other hand, $Q'(t) \leq \delta + k_1 b e^{-\mu\tau}\sigma(Q(t-\tau))S(t-\tau)$. Using that $\sigma(x) \leq x$ we get that

$$Q'(t) \leq \delta + k_1 b e^{-\mu\tau} S(0) e^{\alpha t} Q(t-\tau).$$

Applying a Gronwall's lemma (see [15] Lemma A.1) we obtain that

$$Q(t) \leq (Q(0) + \delta t + k_1 b S(0) e^{-\mu\tau} \int_{-\tau}^{0} e^{\alpha s} ds) \exp\left(k_1 b S(0) e^{-\mu\tau} \int_0^t e^{\alpha s} ds\right).$$

Finally, notice that $I'(t) \leq k_1 \sigma(Q(t))S(t) \leq k_1 Q(t)S(t)$. So, fixed T, the local solutions are bounded in $[0, T]$. □

In order to obtain a result giving the boundedness of the solution we will first formulate some more hypotheses on the initial condition and on the ingredients of the model.

Hypothesis 3.3 *We will suppose that the ingredients satisfy the following conditions, valid for any $t \in [-\tau, 0]$:*
(i) *The initial condition $(S_0(t), I_0, Q_0(t))$ of the system lies into the region*

$$R_0 := [0, M] \times [0, M] \times \left[\frac{\delta(be^{-\mu\tau}\mu)}{mbe^{-\mu\tau}\mu + k_2(mM - \delta)}, M\right].$$

(ii) *We have $(mb\, e^{-\mu\tau}\mu + k_2(mM - \delta))Q_0(t)S_0(t) > \delta\mu S_0(0)$, and $b\, e^{-\mu\tau} > 1$.*
(iii) *The condition $S_0(t) < \frac{mM-\delta}{k_1 be^{-\mu\tau}M}$ holds.*
(iv) $I_0 < \frac{mM-\delta}{be^{-\mu\tau}\mu}$.

Hypothesis 3.4 *We will suppose that $\frac{\delta}{m} < M$ and*

$$\delta > \frac{\alpha m}{k_1} \frac{be^{-\mu\tau}\mu + k_2(M - \frac{\delta}{m})}{be^{-\mu\tau}\mu}.$$

Then under Hypothesis 3.4,

$$\frac{\alpha}{k_1} < \frac{\delta(be^{-\mu\tau}\mu)}{mbe^{-\mu\tau}\mu + k_2(mM - \delta)} < \frac{\delta}{m} < M.$$

Notice that when $k_2 = 0$ we get the same hypothesis as in the model without coinfection. Moreover, when k_2 is increasing, we find that the constant dose δ must increase, i.e., if we lose more bacteriophages by coinfection we need to introduce a bigger dose of them. On the other hand, the region where the initial condition Q_0 lives can have smaller lower boundary. It means that since the dose will be bigger, the concentration of viruses in the initial condition can be smaller.

Remark: System (3) has two steady states (see Section 3.2), $E_0 = (0, 0, \frac{\delta}{m})$ (for any value of the parameters) and, under certain conditions, a coexistence equilibrium. Under Hypothesis 3.4, E_0 will be asymptotically stable (see Proposition 3.6). Moreover, if $b > 1$ (which holds under Hypothesis 3.3) and the latency time is below a threshold that depends on b, ($\tau^* = -\frac{1}{\mu}\ln(\frac{k_1+k_2\frac{\alpha}{\mu}}{k_1 b+k_2\frac{\alpha}{\mu}})$, see Section 3.2) E_0 is the unique steady state.

For simplicity, set

$$\nu = \frac{\delta(be^{-\mu\tau}\mu)}{mbe^{-\mu\tau}\mu + k_2(mM-\delta)}. \tag{7}$$

Proposition 3.5 *Under Hypotheses 3.1, 3.4 and 3.3, the region*

$$\begin{aligned} &R := R_1 \times R_2 \times R_3 \\ =&\left[0, \frac{mM-\delta}{k_1 be^{-\mu\tau}M}\right] \times \left[0, \frac{mM-\delta}{be^{-\mu\tau}\mu}\right] \times \left[\frac{\delta(be^{-\mu\tau}\mu)}{mbe^{-\mu\tau}\mu + k_2(mM-\delta)}, M\right] \subset [0, M]^3 \end{aligned}$$

is left invariant by equation (3).

Proof: We organize the proof in five steps.

Step 1: While $Q(t) \geq \nu$ then $S(t) \in R_1$ and is nonincreasing. Since S is positive it is clear that

$$S'(t) \leq 0 \text{ whenever } Q(t) > \frac{\alpha}{k_1}, \quad \text{and} \quad S'(t) \geq 0 \text{ whenever } Q(t) < \frac{\alpha}{k_1}.$$

On the other hand, our system starts from an initial condition

$$Q_0(0) \geq \nu \geq \frac{\alpha}{k_1}.$$

Thus S is non increasing and remains in R_1 as long as $Q \geq \nu$.

Step 2: There exists a strictly positive ε such that $Q(t) > \nu$ for all $t \in (0, \varepsilon)$. Notice that here a ε_0 exists such that $I(t) < \frac{mM-\delta}{be^{-\mu\tau}\mu}$ for all $t \in (0, \varepsilon_0)$. So, we have, if $Q(0) = \nu$,

$$\begin{aligned} Q'(0) &\geq \delta - m\nu - k_1\nu S_0(0) - k_2\nu\frac{mM-\delta}{be^{-\mu\tau}\mu} + k_1 be^{-\mu\tau}Q_0(-\tau)S_0(-\tau) \\ &= k_1\left(be^{-\mu\tau}Q_0(-\tau)S_0(-\tau) - \nu S_0(0)\right) > 0, \end{aligned}$$

where we have used Hypothesis (ii) of 3.3.

Step 3: If $S(t)$ is nonincreasing and $I(t)$ remains in R_2 for any $t \leq T$ and $Q(T) = \nu$ then $Q'(T) > 0$. Let us consider what happens when $Q(t_0) = \nu$. We now introduce the quantity $t_0 = \inf\{t > 0 : \ Q(t) = \nu\}$, and notice that we have

$$Q'(t_0) = \delta - m\nu - k_1\nu S(t_0) - k_2\nu\frac{mM-\delta}{be^{-\mu\tau}\mu} + k_1 be^{-\mu\tau}\sigma(Q(t_0-\tau))S(t_0-\tau).$$

We can now distinguish two cases:

1. If $t_0 > \tau$, since $S(t)$ is nonincreasing in $[0, t_0]$, $S(t_0 - \zeta) \geq S(t_0)$ and hence
$$Q'(t_0) \geq k_1 S(t_0) \left(be^{-\mu\tau} \sigma(Q(t_0 - \tau)) - \nu \right) > 0,$$
due to the fact that $be^{-\mu\tau} > 1$, $M > \nu$ and $Q(t_0 - \zeta) > \nu$.

2. If $t_0 \leq \tau$, since $S(t_0) \leq S_0(0)$ we obtain
$$Q'(t_0) \geq k_1 \left(be^{-\mu\tau} Q_0(t_0 - \tau) S_0(t_0 - \tau) - \nu S_0(0) \right) > 0,$$
where we have used again Hypothesis (ii) of 3.3.

This discussion allows thus to conclude that t_0 cannot be a finite time.

Step 4: If $S(t)$ is nonincreasing for any $t \leq T$ and $Q(T) = M$ then $Q'(T) < 0$. To this aim notice that, whenever $Q_0(0) = M$ we have
$$Q'(0) \leq \delta - mM + k_1 be^{-\mu\tau} M S_0(-\tau) < 0,$$
where we recall that $S_0(-\tau) < \frac{mM - \delta}{k_1 be^{-\mu\tau} M}$ according to Hypothesis 3.3. 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
$$\begin{aligned} Q'(t_1) &\leq \delta - mM + k_1 be^{-\mu\tau} \sigma(Q(t_1 - \tau)) S(t_1 - \tau) \\ &= \delta - mM + k_1 be^{-\mu\tau} M S(t_1 - \tau), \end{aligned}$$
and we can distinguish again two cases:

1. If $t_1 > \tau$, thanks to the fact that $t \mapsto S(t)$ is non-increasing on $[0, t_1]$, we have
$$Q'(t_1) \leq \delta - mM + k_1 be^{-\mu\tau} M S_0(0) < 0,$$
since we have assumed that $S_0(0) < \frac{mM - \delta}{k_1 be^{-\mu\tau} M}$.

2. If $t_1 \leq \tau$ then
$$Q'(t_1) \leq \delta - mM + k_1 be^{-\mu\tau} M S_0(t_1 - \tau) < 0,$$
thanks to the fact that $S_0(t) < \frac{mM - \delta}{k_1 be^{-\mu\tau} M}$ for all $t \in [-\tau, 0]$.

We have thus shown $Q(t) \leq M$ for all $t \geq 0$, which finishes the proof.

Step 5: While S remains in R_1 and Q remains in R_3 then I lives in R_2. Notice first that
$$\begin{aligned} I'(t) &\leq k_1 M \frac{mM - \delta}{k_1 be^{-\mu\tau} M} - \mu I(t) - k_1 e^{-\mu\tau} \sigma(Q(t - \tau)) S(t - \tau) \\ &= \frac{mM - \delta}{be^{-\mu\tau}} - \mu I(t) - k_1 e^{-\mu\tau} \sigma(Q(t - \tau)) S(t - \tau). \end{aligned}$$
We have seen before that I is always nonnegative. Assume now that there exist t_1 such that $I(t_1) = \frac{mM - \delta}{be^{-\mu\tau}\mu}$. Then
$$I'(t_1) \leq -k_1 e^{-\mu\tau} \sigma(Q(t - \tau)) S(t - \tau) \leq 0,$$
and so, $I(t) \leq \frac{mM - \delta}{be^{-\mu\tau}\mu}$ for all $t \geq 0$.

Conclusion: From the previous steps we get that there exists $\varepsilon > 0$ such that $(S(t), I(t), Q(t)) \in R$ for any $t \in [-\tau, \varepsilon)$. Combining all the steps it is clear that they can not leave the region. □

3.2 Steady states. Stability

Let us study the equilibrium points. We have to solve the following equations:

$$\begin{cases} 0 = & (\alpha - k_1\sigma(Q))S \\ 0 = & k_1\sigma(Q)S - \mu I - k_1 e^{-\mu\tau}\sigma(Q)S \\ 0 = & \delta - mQ - k_1\sigma(Q)S - k_2\sigma(Q)I + k_1 b e^{-\mu\tau}\sigma(Q)S. \end{cases} \tag{8}$$

Clearly, when $S = 0$ we get that $I = 0$ and $Q = \frac{\delta}{m}$. So, we obtain the bacteria-free equilibrium $E_0 = (0, 0, \frac{\delta}{m})$ that exists for any value of the parameters. In the case $M + 1 < \frac{\alpha}{k_1}$ it is clear that no other equilibrium exists (because then $\alpha - k_1\sigma(Q) > 0$ for any Q).
Furthermore, if $M \geq \frac{\alpha}{k_1}$ a possible coexistence equilibrium should be

$$Q_c = \frac{\alpha}{k_1}, \qquad I_c(S) = \frac{\alpha}{\mu}(1 - e^{-\mu\tau})S,$$

and

$$S_c = \frac{m - \frac{k_1\delta}{\alpha}}{k_1(be^{-\mu\tau} - 1) - k_2\frac{\alpha}{\mu}(1 - e^{-\mu\tau})}.$$

Notice that the function in the denominator of S_c,

$$f(\tau) := e^{-\mu\tau}(k_1 b + \frac{k_2\alpha}{\mu}) - (k_1 + k_2\frac{\alpha}{\mu})$$

is a decreasing function of τ for which we have

a) $f(0) < 0 \iff b < 1$,

b) $f(0) > 0 \iff b > 1$. in this case there exists a unique $\tau^* = -\frac{1}{\mu}\ln(\frac{k_1 + k_2\frac{\alpha}{\mu}}{k_1 b + k_2\frac{\alpha}{\mu}})$ such that $f(\tau^*) = 0$.

The coexistence equilibrium should be positive. We can distinguish the cases

1) $\frac{\delta}{m} > \frac{\alpha}{k_1}$. Then, if $b < 1$ there is always (for any latency time τ) a coexistence equilibrium (S_c, I_c, Q_c). If $b > 1$ the coexistence equilibrium exists only for $\tau > \tau^*$.

2) $\frac{\delta}{m} < \frac{\alpha}{k_1}$. Then the coexistence equilibrium exists only if $b > 1$ and $\tau < \tau^*$.

From the biological point of view, these situations correspond to the cases of a "large" dose of "nonefficient" viruses, "large" dose of viruses with burst size bigger than one but "big" latency time and "small" dose of viruses with burst size bigger than one and "small" latency time respectively.

As we have explained in the introduction we are interested in the behaviour of the bacteria-free equilibrium $E_0 = (0, 0, \frac{\delta}{m})$. We now state the local stability result for this boundary equilibrium which ensures local stability when the "carrying capacity" ([7]) of phages, $\frac{\delta}{m}$, is bigger than the one for susceptible bacteria, $\frac{\alpha}{k_1}$.

Notice that, if we assume $\frac{\delta}{m} > \frac{\alpha}{k_1}$ (large dose) and $b > 1$ then E_0 is the unique steady state as long as $\tau < \tau^*$ (which implies in particular that $be^{-\mu\tau} > 1$ i.e., that the viruses are "efficient" in the sense that the expected increase in the virus population by infection is positive) .

Proposition 3.6 *The bacteria-free equilibrium $E_0 = (0, 0, \frac{\delta}{m})$ is asymptotically stable if $\alpha - k_1\frac{\delta}{m} < 0$ and unstable if $\alpha - k_1\frac{\delta}{m} > 0$.*

Proof: When $\tau = 0$, using that $\sigma(Q(t)) = Q(t)$, around E_0 the differential matrix is:

$$\begin{pmatrix} \alpha - k_1\frac{\delta}{m} & 0 & 0 \\ 0 & -\mu & 0 \\ k_1(b-1)\frac{\delta}{m} & -k_2\frac{\delta}{m} & -m \end{pmatrix},$$

with eigenvalues $\lambda_0 = \alpha - k_1\frac{\delta}{m}$, $\lambda_1 = -\mu < 0$ and $\lambda_2 = -m < 0$. Thus E_0 is stable if and only if $\alpha - k_1\frac{\delta}{m} < 0$. In order to study the system with delay, we linearize it around E_0, i.e, $S(t) = 0 + s(t), I(t) = 0 + i(t)$ and $Q(t) = \frac{\delta}{m} + q(t)$ and we assume that the solutions are exponential, i.e. (abusing the notation) $s(t) = e^{\lambda t}s, i(t) = e^{\lambda t}i$ and $q(t) = e^{\lambda t}q$. We get

$$\begin{cases} \lambda e^{\lambda t}s = (\alpha - k_1\frac{\delta}{m})e^{\lambda t}s \\ \lambda e^{\lambda t}i = k_1\frac{\delta}{m}e^{\lambda t}s - \mu e^{\lambda t}i - k_1 e^{-\mu\tau}\frac{\delta}{m}e^{\lambda(t-\tau)}s \\ \lambda e^{\lambda t}q = -me^{\lambda t}q - k_1\frac{\delta}{m}e^{\lambda t}s - k_2\frac{\delta}{m}e^{\lambda t}i + k_1 be^{-\mu\tau}\frac{\delta}{m}e^{\lambda(t-\tau)}s. \end{cases} \tag{9}$$

Thus the characteristic equation is

$$p(\lambda) = \begin{vmatrix} \lambda - (\alpha - k_1\frac{\delta}{m}) & 0 & 0 \\ -k_1\frac{\delta}{m} + k_1 e^{-(\mu+\lambda)\tau}\frac{\delta}{m} & \lambda + \mu & 0 \\ k_1\frac{\delta}{m} - k_1 be^{-(\mu+\lambda)\tau}\frac{\delta}{m} & k_2\frac{\delta}{m} & \lambda + m \end{vmatrix} = 0,$$

and the eigenvalues will be $\lambda_1 = \alpha - k_1\frac{\delta}{m}$, $\lambda_2 = -\mu < 0$ and $\lambda_3 = -m < 0$ and so E_0 is stable under the same condition that when $\tau = 0$. □

The previous result implies that the stability of the bacteria-free steady state is assured by supplying a large dose of viruses (notice that the condition implying this stability was also needed in order to obtain boundedness of the solutions (hypothesis 3.4)).

Characteristic equations for delay differential equations are usually trascendental. However, for our model, due to the type of nonlinearity of the model, this characteristic equation is a cubic polynomial which implies that we have exactly three eigenvalues.

We state now the result about the exponential convergence to the bacteria-free equilibrium point.

Theorem 3.7 *Let us assume that Hypotheses 3.1, 3.3 and 3.4 hold. Let R be the region defined in Proposition 3.5. Then the solution of system (3) with initial condition $(S_0, I_0, Q_0) \in R$ exponentially converges to the equilibrium E_0:*

$$|(S(t), I(t), Q(t)) - E_0| \leq c\, e^{-\eta t}, \quad \textit{with} \quad \eta = \gamma \wedge m \wedge \mu, \tag{10}$$

where $\gamma = \nu k_1 - \alpha > 0$ and ν is given by (7).

Remark: Notice that γ is decreasing with respect to k_2 (adsorption rate of infected bacteria) and that if $k_2 = 0$ then $\gamma = \frac{k_1\delta}{m} - \alpha$ as in [5].

Proof: According to Proposition 3.5, we have $Q(t) \leq M$ for all t. Doing now the change of variables $\tilde{Q} = Q - \frac{\delta}{m}$ we get:

$$\begin{aligned}
dS(t) &= -\left((\tfrac{k_1\delta}{m} - \alpha)S(t) + k_1\tilde{Q}(t)S(t)\right)\,dt,\\
dI(t) &= \Big(k_1\tfrac{\delta}{m}S(t) + k_1\tilde{Q}(t)S(t) - \mu I(t) - k_1\tfrac{\delta}{m}e^{-\mu\tau}S(t-\tau)\\
&\qquad -k_1e^{-\mu\tau}\tilde{Q}(t-\tau)S(t-\tau)\Big)\,dt,\\
d\tilde{Q}(t) &= \Big(-m\tilde{Q}(t) - k_1\tfrac{\delta}{m}S(t) - k_1\tilde{Q}(t)S(t) - k_2\tfrac{\delta}{m}I(t) - k_2\tilde{Q}(t)I(t)\\
&\qquad +k_1\tfrac{\delta}{m}be^{-\mu\tau}S(t-\tau) + k_1be^{-\mu\tau}\tilde{Q}(t-\tau)S(t-\tau)\Big)\,dt.
\end{aligned}$$

With this change of variables, we have also shifted the equilibrium to the point $(0,0,0)$. We now wish to prove that $S(t), I(t)$ and $\tilde{Q}(t)$ exponentially converge to 0.

The bound on $S(t)$ is easily obtained: just note that by Proposition 3.5, we have $Q(t) \geq \nu$ and since by Hypothesis 3.4 we have $\frac{\alpha}{k_1} < \nu < \frac{\delta}{m}$

$$S'(t) = -\left((\tfrac{k_1\delta}{m} - \alpha)S(t) + k_1\tilde{Q}(t)S(t)\right) \leq -(\nu k_1 - \alpha)S(t)$$

which yields $S(t) \leq S_0(0)\,e^{-\gamma t}$ where $\gamma = (\nu k_1 - \alpha) > 0$.

As far as $\tilde{Q}(t)$ is concerned, one gets the bound

$$\begin{aligned}
\tilde{Q}'(t) &\leq -m\tilde{Q}(t) + k_1be^{-\mu\tau}(\frac{\delta}{m} + \tilde{Q}(t-\tau))S_0(0)\,e^{-\gamma(t-\tau)}\\
&\leq -m\tilde{Q}(t) + c\,e^{-\gamma t},
\end{aligned}$$

with $c = 2k_1bMS_0(0)\,e^{(\gamma-\mu)\tau}$, and where we have used the fact that $Q(t) \leq M$ uniformly in t. Using that equation $x'(t) = -mx(t) + c\,e^{-\gamma t}$ with initial condition $x_0 = \tilde{Q}_0(0)$ can be explicitly solved as

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

and by comparison, this entails the inequality $\tilde{Q}(t) \leq c_1\,e^{-(m\wedge\gamma)t}$, where $c_1 > 0$.

Finally, let us consider $I(t)$. Clearly

$$I'(t) \leq k_1\frac{\delta}{m}S(t) + k_1\tilde{Q}(t)S(t) - \mu I(t) \leq 2k_1MS_0(0)e^{-\gamma t} - \mu I(t).$$

Following the same method, we get that $I(t) \leq c_2\,e^{-(\mu\wedge\gamma)t}$. □

Summarizing, the boundary equilibrium point is, in some sense, the same point that in the model without coinfection [5]. That is, the concentration of bacteria is 0 and the concentration of bacteriophages is $\frac{\delta}{m}$. We also have exponential convergence but in our model with coinfection it will be slower or

equal that in the model without coinfection. More precisely, in [5] it was of order $e^{-(\gamma' \wedge m)t}$ with $\gamma' = \frac{k_1 \delta}{m} - \alpha$ whereas in the model with coinfection we treat here it is of order $e^{-(\gamma \wedge m \wedge \mu)t}$ with $\gamma = \nu k_1 - \alpha$ (ν given by (7)), a decreasing function of k_2.

4 Analysis of the stochastic model

For the stochastic model (4) existence of solution follows from the fact that the coefficients of the equation are locally Lipschitz with linear growth (see Theorem 2.7 in [5]). The positivity holds using the same arguments that in Proposition 2.8 in [5]. In order to give the convergence result for the stochastic model (4) we will introduce some notation: for a continuous function f, we set $\|f\|_{\infty,L} = \sup_{x \in L} |f(x)|$ and $Z^\varepsilon = (S^\varepsilon, I^\varepsilon, Q^\varepsilon)$. Let us also recall that $\gamma = \nu k_1 - \alpha > 0$ where ν is given by (7). Then we can state the result about convergence to E_0 as follows:

Theorem 4.1 *Given positive initial conditions and assuming that Hypotheses 3.4, 3.1, and 3.3 hold, equation (4) admits a unique solution which is almost surely an element of $\mathcal{C}(\mathbb{R}_+, \mathbb{R}^3_+)$. Set $\eta = m \wedge \gamma \wedge \mu$ and consider three constants $1 < \kappa_1 < \kappa_2 < \kappa_3$. Then there exists ρ_0 such that for any $\rho \leq \rho_0$ and any interval of time of the form $L = [\kappa_1 \ln(c/\rho)/\eta, \kappa_2 \ln(c/\rho)/\eta]$, we have*

$$P\left(\|Z^\varepsilon - E_0\|_{\infty,L} \geq 2\rho\right) \leq \exp\left(-\frac{c_1 \rho^{2+\lambda}}{\varepsilon^2}\right), \tag{11}$$

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

The last theorem can be interpreted as follows: assume that we observe a small noise with intensity ε, then the deviation we can expect from the noisy system with respect to the equilibrium E_0 is of order $\varepsilon^{2\theta}$ with $\theta = 2\eta/\kappa_3$. This range of deviation happens at a time scale of order $\ln(\rho^{-1})/\eta$. As in the exponential convergence for deterministic model, the convergence of the stochastic model with coinfection will be slower or equal that the convergence of the stochastic model without coinfection.

Proof: Since we have exponential convergence for the deterministic delayed system, it is enough to check (see subsection 3.1 in [5]) that for any $\varepsilon \leq \varepsilon(M, T)$

$$P(\|Z^\varepsilon - Z^0\|_{\infty,[0,T]} \geq \rho) \leq \exp -\big(\frac{c_2 \rho^2}{e^{K_2 T} \varepsilon^2}\big).$$

Recall that $\|S^0\|_\infty + \|I^0\|_\infty \leq c_4$ and set $J_1(t) = \int_0^t \sigma(S^\varepsilon(t)) \circ dW^1(t)$ and $J_2(t) = \int_0^t \sigma(Q^\varepsilon(t)) \circ dW^2(t)$. Then, using that σ is a truncated identity function,

we can write

$$
\begin{aligned}
|S^\varepsilon(t) - S^0(t)| &\leq \int_0^t |(\alpha - k_1\sigma(Q^\varepsilon(s)))(S^\varepsilon(s) - S^0(s))|ds \\
&\quad + \int_0^t |k_1(\sigma(Q^\varepsilon(s)) - \sigma(Q^0(s)))S^0(s)|ds + \varepsilon|J_1(t)| \\
&\leq \int_0^t (\alpha + k_1 M)|S^\varepsilon(s) - S^0(s)|ds + \int_0^t k_1 c_4 C|Q^\varepsilon(s) - Q^0(s)|ds \\
&\quad + \varepsilon|J_1(t)|, \\
|Q^\varepsilon(s) - Q^0(s)|ds &\leq \int_0^t m|Q^\varepsilon(s) - Q^0(s)|ds \\
&\quad + \int_0^t k_1 b e^{-\mu\tau}[|\sigma(Q^\varepsilon(s-\tau)) - \sigma(Q^0(s-\tau))||S^0(s-\tau)| \\
&\qquad\qquad + |S^\varepsilon(s-\tau) - S^0(s-\tau)||\sigma(Q^\varepsilon(s-\tau)|]ds \\
&\quad + \int_0^t k_2[|\sigma(Q^\varepsilon(s)) - \sigma(Q^0(s))||I^0(s)| + |I^\varepsilon(s) - I^0(s)||\sigma(Q^\varepsilon(s)|]ds \\
&\quad + \int_0^t k_1[|\sigma(Q^\varepsilon(s)) - \sigma(Q^0(s))||S^0(s)| + |S^\varepsilon(s) - S^0(s)||\sigma(Q^\varepsilon(s)|ds \\
&\quad + \varepsilon|J_2(t)|]ds \\
&\leq \int_0^t (m + c_4 C(k_1 + k_1 b e^{-\mu\tau} + k_2))|Q^\varepsilon(s) - Q^0(s)|ds \\
&\quad + \int_0^t (M k_1(1 + b e^{-\mu\tau}))|S^\varepsilon(s) - S^0(s)|ds \\
&\quad + \int_0^t M k_2 |I^\varepsilon(s) - I^0(s)|ds + \varepsilon|J_2(t)|
\end{aligned}
$$

and doing the same computations

$$
\begin{aligned}
|I^\varepsilon(t) - I^0(t)| &\leq \int_0^t \mu|I^\varepsilon(s) - I^0(s)|ds \\
&\quad + \int_0^t M k_1(1 + e^{-\mu\tau})|S^\varepsilon(s) - S^0(s)|ds \\
&\quad + \int_0^t k_1 c_4 C(1 + e^{-\mu\tau})|Q^\varepsilon(s) - Q^0(s)|ds.
\end{aligned}
$$

Thus

$$
|Z^\varepsilon(t) - Z^0(t)|^2 \leq c_5\varepsilon^2(|J_1(t)|^2 + |J_2(t)|^2) + c_6 \int_0^t |Z^\varepsilon(s) - Z^0(s)|^2 ds.
$$

The proof finishes using a Gronwall's lemma type and exponential inequalities for martingales (see the proof of Proposition 3.2 in [5] for the detailed methods). □

5 Concluding Remarks

Bacteriophage therapy has lately been considered an alternative to the increasing resistance of pathogenic bacteria to antibiotic treatment ([3, 18, 21]). Mathematical modelling of bacteria-phage interactions could then be a helpful tool for this therapy. Since the first work of Campbell [13] there have been quite some papers devoted to bacteria-phage dynamics, most of them considering deterministic models of ordinary differential equations or delay differential equations. In order to consider random effects (noise in data, random fluctuations in parameters...) it is also important to study stochastic models of bacteria-phage dynamics. In [5] we studied a stochastic model of susceptible bacteria and free phages with a constant injection of phages into the system, inspired by the experiments carried in [6].

Since it has been seen that many bacteriophages can be adsorbed to a single bacterium, we consider in the present paper a variant (both deterministic and stochastic) of the model in [5] where we add infected bacteria and include the possibility of this multiple adsorption which is what we call coinfection (meaning an extra mortality for the bacteriophage population).

We have then a system of susceptible bacteria, infected bacteria and free bacteriophages for which we have assumed a constant supply of viruses in order to model therapy. We have also assumed a constant latency time (time passing between the phage-bacteria binding and the lysis of the virus) which introduces a delay in the system. We have shown global existence of a unique positive solution of the initial value problem for both models, the deterministic and the stochastic and we have proved boundedness of the solutions. Moreover we have seen (also for both models) that for any value of the parameters a bacteria-free equilibrium exists which is locally asymptotically stable if a large dose of phages is supplied (if this large dose is given and the phages are "efficient" the bacteria-free equilibrium is unique as long as the latency time is not too big) and we have shown exponential convergence to this steady state. This convergence decreases when the adsorption rate of infected bacteria increases and it is slower than the exponential convergence to the bacteria-free equilibrium of the model without coinfection in [5].

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