BACTERIOPHAGE-RESISTANT AND
BACTERIOPHAGE-SENSITIVE BACTERIA IN A CHEMOSTAT

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Abstract. In this paper a mathematical model of the population dynamics of a bacteriophage-sensitive and a bacteriophage-resistant bacteria in a chemostat where the resistant bacteria is an inferior competitor for nutrient is studied. The focus of the study is on persistence and extinction of bacterial strains and bacteriophage.

1. **Introduction.** Mathematical models of viral predation on bacteria (bacterio-phagy) have been extensively studied since the pioneering work of Campbell [7] and Levin, Stewart and Chao [16]. Recent work appears in both the ecological [15, 28, 19, 6] and the biomathematical literature [1, 2, 3, 4, 20, 22, 17]. However, a mathematically rigorous study providing sharp conditions for persistence/extinction of both the virus and the bacteria has only very recently appeared and this study, see [22], considered only the simplest scenario consisting of a single phage-sensitive bacterial population and a population of virulent phages in the setting of a chemo-stat.

Experimental studies of the interaction of bacteria and phages typically result in the appearance of various mutants of both bacteria and phage. For example, experimental studies by Chao, Levin, and Stewart [8] of bacteria-phage interaction in continuous culture (chemostat), using a strain of *E. coli* bacteria and phage T7 resulted in two distinct outcomes. In one of these, a mutant strain of *E. coli*, resistant to phage infection, evolved within a few hundred hours and, later, a mutant phage evolved that was capable of infecting both the original *E. coli* strain and the resistant strain. In other replicates of the experiment, the same mutants appeared as before, and in addition, a mutant bacterial strain evolved that was resistant to both phage strains. Pairwise competition experiments between the phage-sensitive bacterial strain and the resistant mutant strains in a virus-free chemostat, described in [8], showed that the resistant mutants were inferior competitors relative to the susceptible strain.

Bohannan and Lenski [6] note that bacterial resistance is generally due to loss or modification of the receptor molecule to which a phage binds and that often this receptor is involved in bacterial metabolism. This explains the observed tradeoff

between resistance and competitive fitness. Based on experimental findings, Bohannan and Lenski stress that establishment of the resistant bacterial population does not cause extinction of the sensitive population or the extinction of phage provided that, (1) the resistant mutant suffers some cost of resistance in the form of reduced competitive ability for limiting resource with respect to the sensitive strain, and (2) the mutant's resistance to phage infection is absolute.

Our aim in this paper is to build on the work in [22] by studying a mathematical model of the interaction of a phage-sensitive bacteria, a virulent phage, and a fully phage-resistant bacterial mutant which is an inferior competitor for nutrient relative to the phage-sensitive bacteria, in a chemostat setting. We aim to confirm the predictions of Bohannan and Lenski that sensitive bacteria and phage persist in the presence of resistant bacteria provided (1) and (2) hold. Furthermore, we examine whether (1) and (2) are sufficient for the persistence of a resistant bacterial strain. Persistence is used here in the technical sense typically referred to as uniform persistence or permanence, as described in [21].

Our main analytical findings based on (1) and (2) are the following:

1. Sharp criteria for persistence/extinction of the sensitive bacteria, obtained for a model that did not include a resistant mutant in [22], are unaffected by the presence of the resistant bacteria. The same is true for persistence/extinction of the phages. Therefore, the evolution of a resistant bacteria cannot cause extinction of sensitive bacteria or phages.
2. A necessary condition for the resistant mutant to persist is that the growth rate advantage of the sensitive organism be, on average, balanced by the phage adsorption rate to sensitive bacteria.
3. Sufficient conditions for persistence of the resistant organism in the chemostat are that, (i) when it is absent, the phages and sensitive bacteria coexist in a globally stable equilibrium, and (ii) the resistant bacteria can grow at the equilibrium nutrient level set by this equilibrium.
4. If the resistant organism suffers no growth rate disadvantage relative to the sensitive bacteria, then the phages are eliminated.

Obviously, our sufficient conditions for persistence of the resistant bacteria are not optimal and they are difficult to verify. Numerical simulations suggest that these conditions are satisfied for a large set of parameter values. We show that the conditions for persistence of the resistant bacteria are met when the latent period is sufficiently short.

It is well-known that predator-prey models, like those used to model phages and bacteria, can lead to coexistence of predator and prey in a stable periodic solution [1, 2, 4, 20] as well as a stable equilibrium. We find this to be the case in our model as well. Numerical simulations and Hopf bifurcation calculations reveal attracting periodic orbits with and without the resistant bacteria. These may oscillate strongly such that bacteria and phages reach perilously low densities in parts of the cycle and quite large levels at other times. Such strong oscillations indicate that while phages and bacteria may persist in a technical mathematical sense, they are unlikely to survive over long periods due to demographic stochasticity.

Our numerical simulations reveal interesting phenomena. We simulate the behavior of our ecosystem when all parameters except for the cost of resistance born by the resistant bacteria and the virulence of the phages, as measured by the burst size, are held constant. Then, fixing the cost of resistance, we find that the largest

interval of burst size for which the resistant bacteria can persist in a stable equilibrium with phages and sensitive bacteria occurs for an intermediate value of the cost of resistance. For burst sizes beyond the upper limit of this interval, oscillations develop and their amplitude increases. Furthermore, if the cost of resistance is fixed at a low value (20%) and virulence allowed to vary over a wide range, we find the chemostat is dominated by bacteria, a majority being resistant and a minority being sensitive, whose combined density is essentially at levels typical of the phage-free system. Bacterial densities are controlled by nutrient levels which are reduced to very low levels. If the cost of resistance is fixed at a relatively large value (60%) and virulence ranges over a wide range, we observe that bacteria are controlled by a much more numerous phage population, resistant bacteria are non-existent or rare depending on virulence, resource is high and goes unused, and strong oscillations may be present.

2. **The model.** Our model, an elaboration on the one in [22], includes phage P, phage-sensitive bacteria S that are uninfected, infected bacteria I, phage-resistant bacteria M, and nutrient R supporting bacterial growth in a well-stirred chemostat with dilution rate D and nutrient supply concentration R_0. The resistant organism is assumed to enjoy complete resistance to phage infection.

$$
\begin{aligned}
R'(t) &= \underbrace{-DR(t)}_{\text{dilution}} + \underbrace{DR_0}_{\text{input}} - \underbrace{\gamma_S f_S(R(t))S(t)}_{\text{consumption by } S} - \underbrace{\gamma_M f_M(R(t))M(t)}_{\text{consumption by } M}, \\
S'(t) &= \underbrace{-DS(t)}_{\text{dilution}} + \underbrace{f_S(R(t))S(t)}_{\text{growth}} - \underbrace{kS(t)P(t)}_{\text{adsorption}}, \\
M'(t) &= \underbrace{-DM(t)}_{\text{dilution}} + \underbrace{f_M(R(t))M(t)}_{\text{growth}} \\
I'(t) &= \underbrace{-DI(t)}_{\text{dilution}} + \underbrace{kS(t)P(t)}_{\text{adsorption}} - \underbrace{k\int_0^\infty e^{-D\tau}S(t-\tau)P(t-\tau)d\nu(\tau)}_{\text{lysis}}, \\
P'(t) &= \underbrace{-DP(t)}_{\text{dilution}} - \underbrace{kS(t)P(t)}_{\text{adsorption}} + \underbrace{k\int_0^\infty e^{-D\tau}b(\tau)S(t-\tau)P(t-\tau)d\nu(\tau)}_{\text{lysis}}.
\end{aligned}
\tag{1}
$$

Yield constants γ_S and γ_M may be scaled out by using auxiliary variables $\widetilde{S} = \gamma_S S$, $\widetilde{M} = \gamma_M M$, $\widetilde{I} = \gamma_S I$, $\widetilde{P} = \gamma_S P$ and $\widetilde{k} = k/\gamma_S$. Therefore, we will hereafter assume that:

$$
\gamma_i = 1, \ i = S, M
\tag{2}
$$

$f_S(R)$ and $f_M(R)$ are the nutrient uptake functions for microbes S and M. They are assumed to be continuously differentiable functions, vanishing at zero nutrient, with positive derivative. We assume, for simplicity, that infected bacteria do not uptake nutrient. As we do not wish to waste effort on trivial cases, we make the following hypotheses:

(F1) $f_i(R_0) > D$, $i = S, M$.
(F2) $f_S(R) > f_M(R)$, $0 < R \le R_0$.

Therefore, phage-sensitive bacteria can survive in the chemostat with nutrient feed concentration R_0 and dilution rate D in the absence of phages and resistant organisms. The resistant bacteria suffers a cost of resistance to phage infection in the

form of a reduced growth rate. It is assumed that its growth rate is not so reduced as to be unable to survive in the chemostat with nutrient feed concentration R_0 and dilution rate D in the absence of the sensitive strain because then it cannot survive in the presence of sensitive bacteria, with or without the presence of phages. Indeed, if either of the inequalities in (F1) are reversed, the corresponding bacteria cannot survive in the chemostat.

A popular choice of f_S and f_M are Michaelis-Menten type functions given by $f_i(R) = \frac{v_i R}{u_i + R}$ where $v_i, u_i > 0$ for $i = S, M$. Bohannan and Lenski [6] note that bacterial resistance is generally due to loss or modification of the receptor molecule to which a phage binds and that often this receptor is involved in bacterial metabolism. It is plausible that $u_S < u_M$ or that $v_M < v_S$ or both. For mathematical simplicity, we will take $f_M = (1 - \varepsilon) f_S$ for our numerical simulations, where $\varepsilon \in (0, 1)$ represents the cost of resistance.

Following [22], we describe variation in the latent period by a cumulative probability distribution $\eta(\tau)$. To be precise, for $\tau > 0$, $\eta(\tau)$ is the probability that an infected bacterium lyses during the time period $[0, \tau]$ following infection. Mathematically, $\eta(\tau) = \nu([0, \tau])$ where ν is a probability measure on $[0, \infty)$ so $\int_0^\infty d\nu(s) = 1$.

$b(\tau)$ is the average burst size of phage with latent period τ. Generally an infected bacterium releases more than 50 phage particles [9]. The average number of new phages eventually released by an infected bacterium, B, (taking into account that it could be washed out before doing so) is given by the Laplace transform of the measure $b\nu$ evaluated at D,

$$B = \int_0^\infty e^{-D\tau} b(\tau) d\nu(\tau). \tag{3}$$

We also assume there exists $b_0 > 1$ such that $b(\tau) \le b_0$ for all $\tau \ge 0$.

Our theoretical results are derived for a general latent period distribution η and burst-size function $b(\cdot)$; however, for our numerical simulations, we choose a gamma-distributed latent period and a constant burst size, independent of the length of the latent period. This allows the reduction of our model to ordinary differential equations by the "linear chain trick".

As shown in [22], the initial data for I must satisfy a constraint in order for solutions to be positive. Moreover, the differential equation for I can be integrated directly:

$$I(t) = \int_0^\infty \left(\int_{t-\tau}^t e^{-D(t-r)} k S(r) P(r) dr \right) d\nu(\tau)$$
$$= \int_0^\infty \mathfrak{F}(s) e^{-Ds} k S(t-s) P(t-s) ds$$

where $\mathfrak{F}$ is the sojourn function for the latency stage [27, Sec.12.1], i.e.,

$$\mathfrak{F}(s) = \int_s^\infty d\nu(\tau) = 1 - \eta(s) \tag{4}$$

is the probability that an infected bacterium has not yet lysed s time units after infection. As a consequence of (4), the equation for I can be dropped from our system. However, it will occasionally be useful to include it. For example,

$$X(t) = R(t) + S(t) + M(t) + I(t) + P(t)/b_0$$

satisfies the differential inequality

$$X' \le D(R_0 - X), \tag{5}$$

and consequently

$$X(t) \le X(0)e^{-Dt} + R_0(1 - e^{-Dt}). \tag{6}$$

Since (1) involves a potentially infinite distributed delay, the phase space must be chosen very carefully. See e.g., [13] and [11]. Here we let $\mathcal{B} = C^0 \times C_\gamma \times C^0 \times C_\gamma$. Here C^0 is the space of all constant functions on $(-\infty, 0]$. And C_γ is defined by $C_\gamma = \{\varphi \in C((-\infty, 0], \mathbb{R}) : \lim\limits_{s \to -\infty} e^{\gamma s}\varphi(s) \text{ exists}\}$, where $\gamma > 0$ is a fixed number. To make the integral in the differential equation of $P(t)$ in (1) valid, we also need $\gamma < \frac{D}{2}$. A norm on C_γ is defined as $|\varphi|_\gamma = \sup\{e^{\gamma s}|\varphi(s)| : -\infty < s \le 0\}$. $\mathcal{B}$ is given the maximum norm $\|\cdot\|$. All biologically reasonable solutions should be non-negative so we take the state space to be the positive cone $\mathcal{B}_+$ in $\mathcal{B}$. More precisely, the initial data is given by $x = (R(0), S_0, M(0), P_0) \in \mathcal{B}_+$.

More importantly, by using the framework developed in [13] and [11], we can prove the local existence and uniqueness of solutions. With these preliminaries and Theorem 9.1 in [12, Chap. 12], we can prove (1) has a compact global attractor K:

Theorem 2.1. *Solutions of* (1) *corresponding to nonnegative initial data in* $\mathcal{B}_+$ *exists for all* $t \ge 0$ *and are nonnegative. Moreover, there exists a maximal compact invariant set* $K \subset \mathcal{B}_+$ *such that* K *attracts all bounded sets in* $\mathcal{B}_+$.

3. **Equilibria and local stability.** Equilibria of (1) and their stability properties are studied in this section. As the infected cell density is determined by the other densities via (4), the state vector is taken as (R, S, M, P).

Our assumptions (F1)–(F2) ensure that three equilibria without phage always exist:

$$E_0 = (R_0, 0, 0, 0), \ E_S = (R_S, \overline{S}, 0, 0), \ E_M = (R_M, 0, \overline{M}, 0,),$$

where $f_i(R_i) = D$, $i = S, M$, $\overline{S} = R_0 - R_S$, and $\overline{M} = R_0 - R_M$. E_0 and E_M are unstable; E_0 is unstable to colonization by either S or M and E_M is unstable to invasion by S which can out compete M in the absence of phage by our assumptions (F1)–(F2).

As noted in [22], the stability of E_S is determined by the "Phage Reproduction Number". Define the "Phage Reproduction Number at bacteria density S" by:

$$PRN(S) = \frac{BkS}{D + kS}. \tag{7}$$

The Phage Reproduction Number is $PRN = PRN(\overline{S})$, the evaluation of $PRN(S)$ at $S = \overline{S}$.

Lemma 3.1. E_S *is asymptotically stable if* $PRN < 1$ *and unstable if* $PRN > 1$.

There are two more possible equilibria of (1) which include phage:

$$E_{SP} = (R^*, S^*, 0, P^*), \ E_{SMP} = (R_M, S^*, \widehat{M}, \widehat{P}).$$

It is intuitively evident that the total bacteria population cannot exceed the level $\overline{S}$ supported in E_S: $\widehat{M} + S^* \le \overline{S}$. See Lemma 7.2.

Necessary and sufficient conditions for existence and positivity of equilibria are summarized in the table below.

Equilibrium	existence conditions	stability
$E_R = (R_0, 0, 0, 0)$	none	unstable by (F1)
$E_S = (R_S, \overline{S}, 0, 0)$	$\frac{f_S(R_0)}{D} > 1$	see Lemma 3.1
$E_M = (R_M, 0, \overline{M}, 0)$	$\frac{f_M(R_0)}{D} > 1$	unstable by (F2)
$E_{SP} = (R^*, S^*, 0, P^*)$	$PRN = Bk\overline{S}/(D + k\overline{S}) > 1$	see Theorem 3.2
$E_{SMP} = (R_M, S^*, \widehat{M}, \widehat{P})$	$MRN = f_M(R^*)/D > 1$	unknown

The phage-susceptible bacterial density S^* at $E_{SP} = (R^*, S^*, 0, P^*)$ is characterized as the unique solution of $PRN(S^*) = 1$. $R^* < R_0$ satisfies $DR^* + f_S(R^*)S^* = DR_0$ and $kP^* + D = f_S(R^*)$.

The resistant bacteria M can survive only in the presence of the phage so it is natural to ask whether M can invade E_{SP}. This is easily seen to be the case if and only if

$$MRN = f_M(R^*)/D > 1, \tag{8}$$

where the nutrient level R^* is determined by E_{SP}. Indeed, E_{SMP} exists and is positive if and only if $MRN > 1$. Similarly as for PRN, MRN is the resistant bacteria's reproductive number in the E_{SP} environment.

Notice that the nutrient density at E_{SMP} is the same as at E_M and E_{SMP} has the same density of sensitive bacteria as E_{SP}. Phage density is determined by $D + k\widehat{P} = f_S(R_M)$ and density of the resistant organism satisfies $D(R_M + \widehat{M}) + f_S(R_M)S^* = DR_0$.

It is very difficult to give criteria for stability and instability of E_{SP} and even more so for E_{SMP}. However, stability properties of E_{SP} and the existence of E_{SMP} are linked. We say an equilibrium is linearly asymptotically stable if all characteristic roots of the characteristic equation associated to the linearized system have negative real part; it is said to be linearly unstable if a characteristic root has positive real part. The next result is a consequence of the fact that the characteristic equation associated to E_{SP} factors with one factor representing the linearization of the system without resistant bacteria and a simple linear factor measuring potential invasibility by the resistent bacteria.

Theorem 3.2. *E_{SP} is linearly asymptotically stable for* (1) *if it is linearly asymptotically stable for the system without M and if $MRN < 1$. It is linearly unstable for* (1) *if it is linearly unstable for the system without M or if $MRN > 1$.*

It is well-known that E_{SP} can lose stability through a supercritical Hopf bifurcation for the system without M (see [4, 20]) for the special case of fixed latent period duration.

Figure 1 and Figure 2 illustrate the regions of stability of E_{SP}, represented by a pentagram, and E_{SMP}, represented by a triangle, and the existence of periodic orbits arising from Hopf bifurcation from these equilibria as two key parameters, ε and b, are varied. The burst-size distribution is assumed constant ($b(\tau) \equiv b$) so that b represents a measure of phage virulence and resistent bacteria are assumed to grow at rate $f_M = (1 - \varepsilon)f_S$ so ε represents the cost of phage-resistance. All other parameters are fixed. The latent period obeys a gamma distribution, allowing us to use the linear chain trick to rewrite the system as a system of ODEs. See section 5 for more details of the simulations. A solid symbol (pentagram or triangle) indicates a locally asymptotically stable equilibrium and a hollow one indicates it is unstable. Circles are periodic orbits, a solid circle represents a stable orbit and
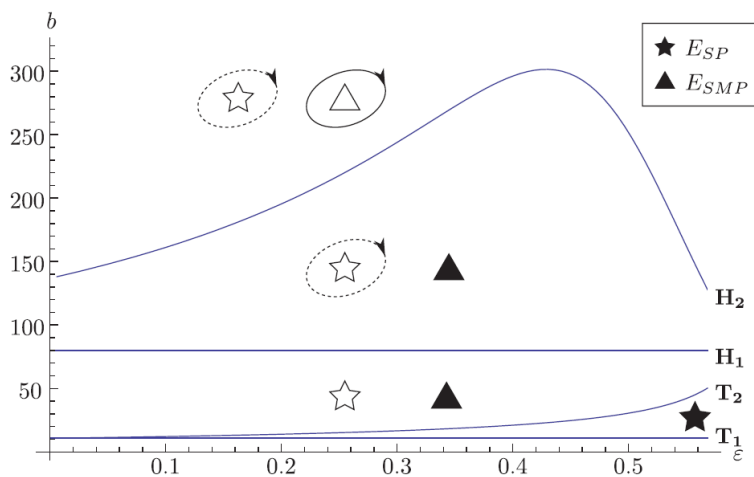
FIGURE 1. Equilibria, periodic orbits, and their stability in ε-b parameter space. Small ε. Recall that ε is the fitness cost of resistance to phage while b is the number of phage released when an infected cell lyses. Black fill indicates stable equilibrium, unfilled indicates unstable equilibrium; solid loop indicates stable periodic orbit, dashed loop indicates an unstable one.
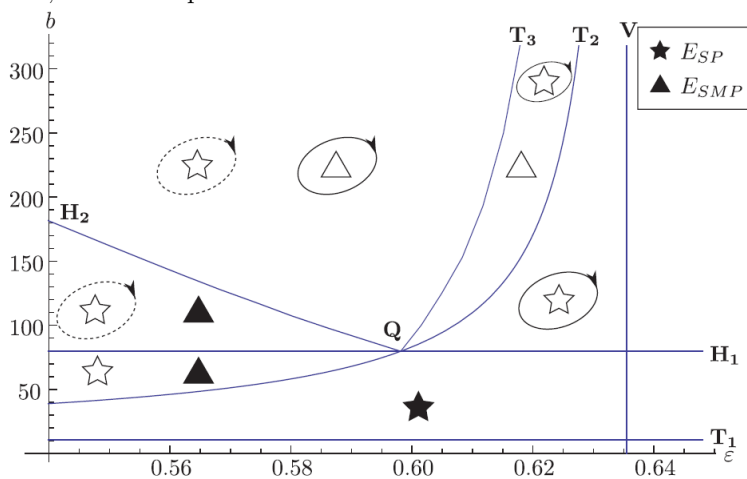

FIGURE 2. Equilibria, periodic orbits and their stability in ε-b parameter space. Blow-up of large ε.

the dashed line means it is unstable. In order to more clearly display the dynamics for larger values of ε, we use two figures; Figure 2 is a continuation of Figure 1 for larger ε and the ε-scale is expanded.

We proceed to describe the curves appearing in Figure 1 and Figure 2. The horizontal line $\mathbf{T}_1$ in both figures is determined by $PRN = 1$; for values of b below it, phage cannot survive so neither E_{SP} nor E_{SMP} exists. E_{SP} exists above $\mathbf{T}_1$ and it is stable in the region immediately above $\mathbf{T}_1$. The other horizontal line, i.e., $\mathbf{H}_1$, is the line along which a periodic orbit appears with $M = 0$ as a result of a

Hopf bifurcation from E_{SP} as b is varied with fixed ε. It is computed numerically using Mathematica to find purely imaginary roots of the characteristic equation associated with E_{SP} for the system with $M = 0$, so it is independent of ε. The increasing curve $\mathbf{T}_2$ above $\mathbf{T}_1$ in Figure 1 is determined analytically by $MRN = 1$, that is, by $(1 - \varepsilon)f_S(R^*)/D = 1$. E_{SMP} bifurcates from E_{SP} as b is increased with fixed ε such that (ε, b) crosses above $\mathbf{T}_2$. In Figure 1, E_{SP} is stable below $\mathbf{T}_2$ and unstable above it while E_{SMP} becomes stable, at least near the curve. Notice that in Figure 2, $\mathbf{H}_1$ meets $\mathbf{T}_2$. At this point, which we designate $\mathbf{Q} = (\varepsilon_c, b_c)$, the steady state and Hopf bifurcation coincide. At $\mathbf{Q}$, the characteristic equation associated with E_{SP} has a pair of purely imaginary roots and a zero root. E_{SMP} may undergo a Hopf bifurcation as well and curve $\mathbf{H}_2$ in Figure 1, terminating at $\mathbf{Q}$, is determined by this bifurcation. It is also computed numerically using Mathematica to find, for each fixed ε, the critical value of b such that the characteristic equation associated with E_{SMP} has purely imaginary roots. Remarkably, $\mathbf{H}_1$ and $\mathbf{H}_2$, the curves along which E_{SP} and E_{SMP} undergo Hopf bifurcation from their respective equilibria, and the curve $\mathbf{T}_2$, along which E_{SMP} bifurcates from E_{SP}, meet at $\mathbf{Q} = (\varepsilon_c, b_c)$. Unfortunately, the fold-Hopf bifurcation that might be expected at this point is degenerate.

If $\varepsilon < \varepsilon_c$ is fixed and b is increased, according to the figures, bifurcations and exchanges of stability occur as follows $E_S \to E_{SP} \to E_{SMP} \to POM$ where POM denotes a stable periodic orbit with $M > 0$ bifurcating from E_{SMP}. Here, we have ignored the unstable Hopf bifurcation from the unstable E_{SP}. If $\varepsilon_c < \varepsilon$ is fixed and b is increased, according to Figure 2, bifurcations and exchanges of stability occur as $E_S \to E_{SP} \to PO$ where now PO denotes a stable periodic orbit with $M = 0$ bifurcating from E_{SP}. However, as b is increased still further, PO becomes unstable to "invasion by M" and a periodic orbit with small M-component bifurcates from PO. This bifurcation occurs as the Floquet exponent of PO,

$$\frac{1}{T} \int_0^T (1 - \varepsilon)f_S(R(t)) - D dt,$$

changes sign. This "lift-off" bifurcation is described in Chapter 3, sec. 6 of [24] for a food chain model. The curve $\mathbf{T}_3$, along which this Floquet multiplier vanishes, also meets at $\mathbf{Q}$. Finally, the vertical line $\mathbf{V}$ in Figure 2 represents the value of ε at which (F1) $((1 - \varepsilon)f_S(R_0) > D)$ is violated. For values of ε exceeding this threshold, M could not survive alone in the chemostat.

The curves described above partition parameter space into open regions in each of which numerical simulations suggest that there is a unique attractor of positive initial data indicated by solid pentagram or solid triangle or a periodic orbit with solid circle surrounding pentagram or triangle. Notable among these regions is the very large one in Figure 1 where E_{SMP} is stable. Above it, for large values of b, a stable periodic orbit with $M > 0$ exists. The boundary of this oscillatory region consists of the E_{SMP} Hopf bifurcation curve below and the curve along which the periodic orbit merges with the periodic orbit in the $M = 0$ subspace on the right. As one expects, when the cost of resistance is large, the region where E_{SP} is stable is larger and it gives way to a region above it where there is a stable periodic orbit with no resistant bacteria present. As noted earlier, the oscillatory solutions may oscillate so strongly that bacteria and phage reach perilously low densities in parts of the cycle and quite large levels at other times. Such strong oscillations indicate that while phages and bacteria may persist in a technical mathematical sense, they

are unlikely to survive over long periods due to demographic stochasticity. Therefore, we may regard the large region in which E_{SMP} is stable as the region in which coexistence of sensitive-bacteria, resistant-bacteria and bacteriophages is most stable. It is notable that this region reaches maximum height at intermediate cost of resistance.

4. **Persistence and extinctions.** Our main results of an analytical nature are contained in this section. The following result focuses on persistence and extinction.

Theorem 4.1. *The following hold:*
- (a) *Sensitive bacteria persist.*
- (b) *If $PRN < 1$, then $P(t) \to 0$; indeed, all solutions with $S(0) > 0$ converge to equilibrium E_S.*
- (c) *Phage persist if $S(0) > 0, P(0) > 0$ and if $PRN > 1$.*
- (d) *Resistant bacteria persist if either of the following hold:*
    - (i) *$S(0) = 0$, or*
    - (ii) *$PRN > 1$, $MRN > 1$, $S(0) > 0$, $P(0) > 0$, and E_{SP} is asymptotically stable and attracts all solutions with $S(0) > 0, P(0) > 0$ for system (1) with $M = 0$.*

More precisely, Theorem 4.1 (a) means that there exists $\varepsilon_S > 0$ such that

$$S(0) > 0 \Rightarrow \liminf_{t \to \infty} S(t) > \epsilon_S.$$

We emphasize that ε_S is independent of initial data satisfying $S(0) > 0$. Sensitive bacteria satisfy $S(t) > \varepsilon_S$ for all sufficiently large t. Theorem 4.1 (c) means that there exists $\epsilon_P > 0$

$$S(0) > 0 \text{ and } P(0) > 0 \Rightarrow \liminf_{t \to \infty} P(t) > \epsilon_P.$$

Theorem 4.1 (d) gives conditions for persistence of the resistant bacteria. Obviously, resistant bacteria persist if they do not have to compete with phage-sensitive microbes since they are immune to phage infection. More interestingly, they also persist if both phage and sensitive microbes are present provided that E_{SP} is asymptotically stable and attracts all solutions with $S(0) > 0, P(0) > 0$ of system (1) with $M = 0$. Sufficient conditions for E_{SP} to be asymptotically stable for the system without M are known. See [4, 20]. In Theorem 7.4, we prove that in the special case that the latent period is of fixed duration, then E_{SP} attracts all solutions with $S(0) > 0, P(0) > 0$ for system (1) with $M = 0$ provided that the latent period is sufficiently small.

Persistence of the resistant bacteria clearly requires the presence of the phage to counter its fitness disadvantage relative to the sensitive bacteria. The following result merely phrases this in mathematical language.

Theorem 4.2. *Let $(R(t), S(t), M(t), P(t))$ be a solution of (1) with initial condition $S(0) > 0, M(0) > 0$ and suppose that there exists $\epsilon > 0$ and $T > 0$ such that $M(t) > \epsilon$, $t > T$. Then*

$$\lim_{t \to \infty} \frac{1}{t} \int_0^t f_S(R(t)) - f_M(R(t)) - kP(t)dt = 0 \tag{9}$$

Equation (9) says the the growth rate advantage of the sensitive organism relative to the resistant organism $(f_S - f_M)$ is, on average, balanced by the phage infection rate (kP) of sensitive bacteria.

It is of interest to consider the special case that the resistant organism suffers no loss of fitness relative to the phage sensitive organism. The phage cannot survive in this case.

Theorem 4.3. *Suppose that (F1) holds but (F2) is replaced by $f_S = f_M$. Let $\overline{R} = f_S^{-1}(D) = f_M^{-1}(D)$, then system* (1) *has a line segment of equilibria:*

$$L = \{(\overline{R}, S, M, 0) : S + M = R_0 - \overline{R},\ S \geq 0,\ M \geq 0\}.$$

Every solution with $S(0) + M(0) > 0$ converges to an equilibrium point on L. In particular,

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

Moreover, if $PRN > 1$ and $P(0) > 0, M(0) > 0$, then M persists uniformly, that is, we have $M(\infty) := \lim_{t \to \infty} M(t) \geq R_0 - \overline{R} - S^* > 0$.

5. **Gamma distributed latent period and numerical results.** An important special case of (1) is the case that the latent period obeys a Gamma distribution, namely,

$$\eta(\tau) = \int_0^\tau g_m(s, a)ds = \int_0^\tau \frac{a^m s^{m-1}}{(m-1)!} e^{-as}ds,$$

where $g_m(s, a)$ is the probability density function with $m \in \mathbb{Z}_+$ and $a > 0$. The mean of this distribution is $\frac{m}{a}$, which also represents the average latent period.

For simplicity, we assume $b(\tau) = b$ is a constant in this section.

By following the "linear chain trick" as discussed in [20] and [14], we can transform (1) into an ODE system. To perform this procedure, we introduce some new variables I_j for $1 \leq j \leq m$:

$$I_j(t) = \frac{k}{a} \int_0^\infty e^{-D\tau} g_j(\tau, a) S(t - \tau)P(t - \tau)d\tau. \tag{10}$$

Note that these equations also give the initial condition for each I_j.

Any solution of (1) gives rise, via (10), to a solution of

$$\begin{aligned}
R'(t) &= D(R_0 - R(t)) - f_S(R(t))S(t) - f_M(R(t))M(t),\\
S'(t) &= (f_S(R(t)) - D)S(t) - kS(t)P(t),\\
M'(t) &= (f_M(R(t)) - D)M(t),\\
I_1'(t) &= kS(t)P(t) - (a + D)I_1(t),\\
I_j'(t) &= aI_{j-1}(t) - (a + D)I_j(t), \qquad 2 \leq j \leq m,\\
P'(t) &= -DP(t) - kS(t)P(t) + abI_m(t),
\end{aligned} \tag{11}$$

and

$$I'(t) = -DI(t) + kS(t)P(t) - aI_m(t). \tag{12}$$

Moreover, any solution of (11) which exists and is bounded on $\mathbb{R}$ is a solution of (1). See Prop. 7.3 of [20].

We use the following parameter values from [5] for the simulations:

$$R_0 = 0.178212,\ D = 0.2,\ k = 0.15.$$

We choose $m = 5$ and $a = 10$ as gamma distribution parameters, and consequently the mean is 0.5 (the average latent period is 0.5 hour) and the variance is 0.05. Also,

$$f_S(R) = \frac{0.7726R}{0.0727 + R}.$$

We also assume $f_M(R) = (1 - \varepsilon)f_S(R)$, where $\varepsilon \in (0, 1)$ is not so large that (F1) fails to hold.

Two bifurcation diagrams, computed using XPP-AUTO, are presented using burst size b as the bifurcation parameter. In Figure 3, we fix the cost of resistance at the relatively low value $\varepsilon = 0.2$ and in Figure 4 it is $\varepsilon = 0.61$. Four plots are shown in each figure for variables R, S, M, P. Burst size b is plotted on the horizontal axis and max/min values of equilibria or periodic solutions are plotted on the vertical axis. In these diagrams, thick lines are locally asymptotically stable equilibria, thin lines are unstable ones. Hollow circles are unstable periodic orbits and solid dots are stable ones.
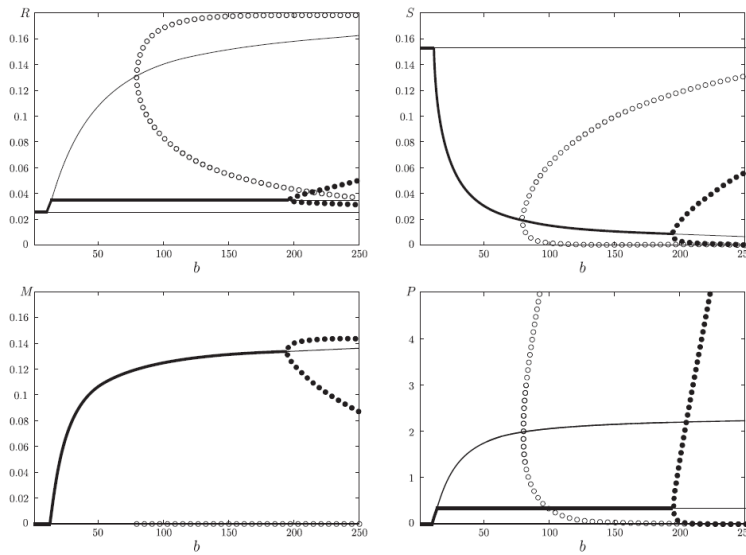

FIGURE 3. Bifurcation diagram with burst-size parameter b where the cost of resistance is 20%, i.e., $\varepsilon = 0.2$. Plots depict maximum and minimum values of R top left, S top right, M bottom left, P bottom right.

Starting from the left ($b = 0$) in Figure 3, when b is small $PRN < 1$ and E_S is stable; it has a low nutrient level R but S is large while both M and P vanish in E_S. As b increases, E_{SP} becomes a stable equilibrium, from the R-plot and Figure 1, we observe that E_{SP} is stable when b is approximately between 10 and 14. For larger b, E_{SMP} becomes a positive equilibrium and it is stable. Since E_{SP} and E_{SMP} share the same S-component, they are not distinguishable from the S-diagram. At $b \approx 80$, E_{SP} undergoes a Hopf bifurcation, an unstable periodic orbit appears. Since this orbit lies entirely in the subspace $\{M \equiv 0\}$, we see hollow circles on the b axis in the M-plot. At $b \approx 190$, there is another Hopf bifurcation at E_{SMP} resulting in a stable periodic orbit, and E_{SMP} becomes unstable. It should be noted that although in S and P plots the periodic orbits appear to have zero minima, they are actually bounded away by uniform persistence (the lower bound is uniform for all initial data but can be extremely small).

We infer from Figure 3 that at low cost of resistance, the combined density of bacteria is essentially at levels typical of the phage-free system, a majority being resistant and a minority being sensitive. Bacterial densities are controlled by nutrient levels which are reduced to very low levels rather than by phage predation.
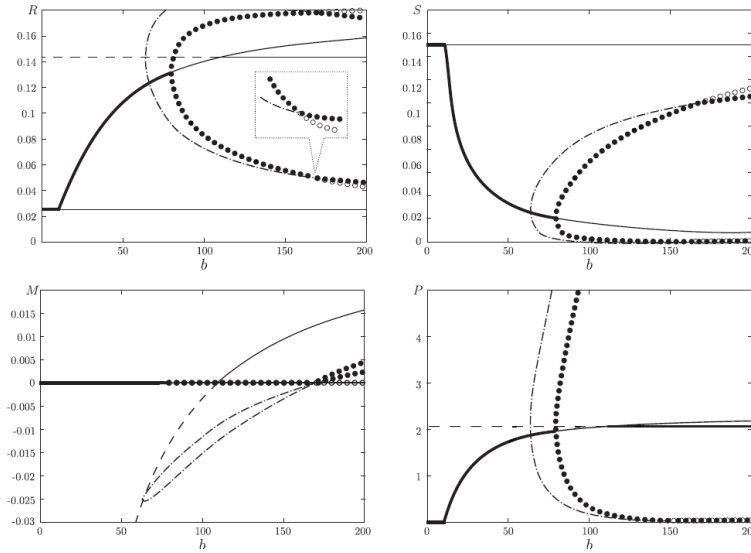

FIGURE 4. Bifurcation diagram with burst-size parameter b as in Figure 3 but with a 61% cost of resistance.

In Figure 4, when b is small, E_S is stable. Then, as b increases, E_{SP} becomes stable, until at $b \approx 80$, it undergoes a Hopf bifurcation and a stable period orbit appears. Since both E_S and E_{SP}, as well as the periodic orbit, are in $\{M \equiv 0\}$, it is easier to study these equilibria and periodic orbit in the R-plot. At $b \approx 110$, E_{SMP} becomes a positive equilibrium (the rising curve in M-diagram). Interestingly, at $b \approx 170$, the periodic solution in the $M = 0$ hyperplane becomes unstable and a "lift-off bifurcation" occurs as a stable periodic orbit with $M > 0$, but small, bifurcates from the periodic solution in the $M = 0$ hyperplane. This lift-off bifurcation is similar to that described for the food-chain model in Chapter 3, sec. 6 of [24]; it is not a small amplitude orbit. It occurs as the Floquet multiplier associated with the M-equation becomes unity as b is varied. For super-threshold values of $b > 170$, the bifurcating periodic orbit has small but positive M values while for sub-threshold $b < 170$ values the periodic orbit has small but negative M values. The particular region in the M-plot shows the periodic orbit with negative M values, see dot-dash lines, which is traced back to a Hopf point at E_{SMP}, see dashed lines, which also has a negative M-component.

In order to clarify this lift-off bifurcation phenomena, we provide two simulations, one at the sub-threshold $b = 150$ and one at super-threshold $b = 200$. Initial data are $R(0) = 0.1, S(0) = 0.1, M(0) = 0.005, I_1(0) = \cdots = I_5(0) = 0.001, P(0) = 1$. At sub-threshold $b = 150$, the only positive periodic orbit lies in the $M = 0$ hyperplane and Figure 5 depicts $M(t)$ converging to 0 as the solution approaches the periodic orbit in the $M = 0$ hyperplane.
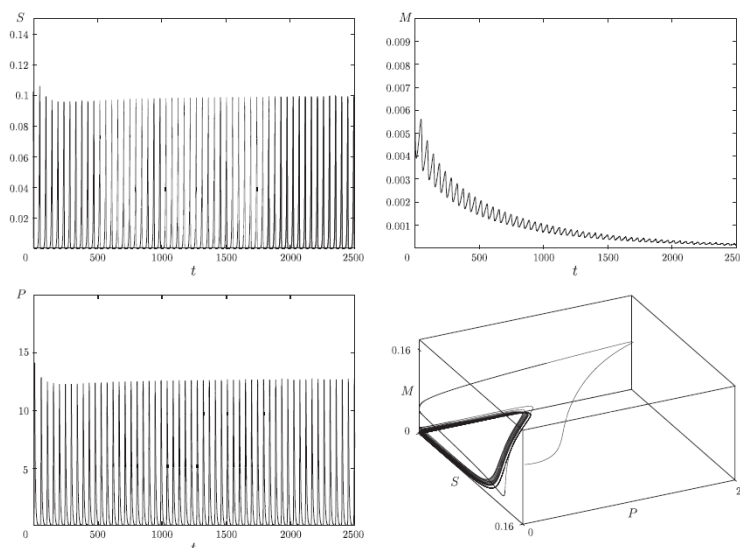
FIGURE 5. Numerical simulation with 61% cost of resistance and burst size of $b = 150$.

At super-threshold $b = 200$, there are two periodic orbits, one in $M = 0$ and one with small but positive M-component. These are shown in Figure 6. The one with positive M-component is stable and the other one is unstable (though stable in $\{M \equiv 0\}$). The simulation shows the solution is attracted by the stable periodic orbit.

We infer from Figure 4 that at high cost of resistance, bacteria are controlled by a much more numerous phage population, resistant bacteria are non-existent or rare depending on virulence (b), available resource goes unused, and strong predator-prey oscillations may be present.

6. **Summary.** The mathematical modeling of bacteriophage predation on bacteria in the setting of the chemostat goes back to the classical work of Levin, Stewart and Chao [16]. Unfortunately, our ability to analyze these highly nonlinear models with time-delays for virus latency in a mathematically rigorous way is lacking. Recently, one of the authors, together with H. Thieme, has provided sharp sufficient conditions for the persistence of both bacteria and phage in [22]. Essentially, bacteria persist provided they can survive in the absence of phage and the phage persist provided a basic phage reproductive number exceeds unity, implying that phage can successfully invade the phage-free equilibrium. However, numerous experimental works, e.g. [8, 5, 6], show that the bacteria may evolve resistance to phage infection via mutation to a phage-resistant phenotype, usually at some cost to its fitness relative to the original phage-susceptible bacteria, such that the latter can out-compete the resistant organism for limiting nutrient in the absence of the phage. Our aim in this paper is to shed light on this trade-off between resistance to infection and reduced ability to compete for nutrient by seeking sufficient conditions for the persistence of the phage-resistant bacteria. Our analytical results provide a set of sufficient conditions, namely: (1) the phage reproductive number must exceed unity, (2) phage-susceptible bacteria and phage coexist in a globally stable
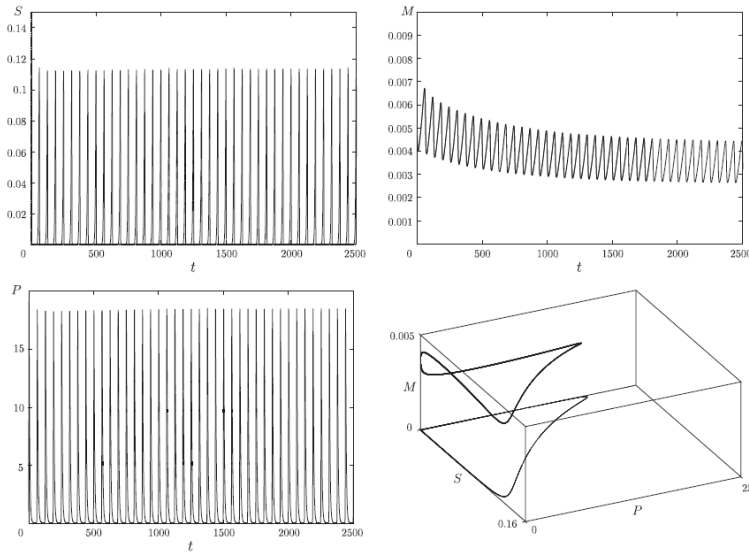
FIGURE 6. Numerical simulation with 61% cost of resistance and burst size of $b = 200$.

(for positive initial data) equilibrium in the absence of the phage-resistant bacteria, and (3) that there is sufficient nutrient for the phage-resistant bacteria to grow at this equilibrium. Conditions (1) is clearly a necessary conditions for persistence of the phage-resistant bacteria since they cannot survive without the presence of the phage. Condition (2) is not a necessary condition for persistence of the phage-resistant bacteria; we assume it because it allows us to verify the hypotheses of an abstract persistence theorem. Given that condition (2) holds, then (3) is necessary for persistence of the phage-resistant bacteria. Unfortunately, we are only able to verify that (2) holds in the special case of small fixed delay, a result we defer to Theorem 7.4 in Section 7. Our numerical simulations show that persistence of the phage-resistant bacteria holds for a broad set of parameter values.

While this paper was under review, we learned of recent work of Northcott, Imran, and Wolkowicz [17] which focuses on the same issue of persistence of phage-susceptible and phage-resistent bacteria in a chemostat. These authors take a different modeling approach that makes their model more mathematically tractable. They do not model phage directly; instead, they assume that phage infection of susceptible bacteria is mediated by phage-infected bacteria leading to an SIS infection model for phage-susceptible bacteria. Furthermore, as there are no phage in their model, there is no need to model virus latency, so they can avoid modeling with delay differential equations. Northcott et. al. obtain sufficient conditions for the persistence of the phage-resistant organism (and all other constituents) which are essentially the same conditions that we find. Rather surprisingly, they find a richer bifurcation scenario for their system than we do.

7. **Proofs.** This section contains all proofs of main lemmas and theorems in this paper.

The last part of this section is devoted to a special case of (1). In this case, we assume that the latent period is a fixed number τ, for each sufficiently small τ, we

prove that M persist uniformly by using Theorem 4.1 (d) (ii). The main result of this subsection is summarized by Theorem 7.4.

7.1. **Preliminary results.** Theorem 2.1 and local stability results are proved here.

Proof of Theorem 2.1. Proofs of existence and positivity of solutions are omitted since they are similar to ones in [22]. Therefore, the solutions of (1) generate a semiflow $\Phi : \mathbb{R}_+ \times \mathcal{B}_+ \to \mathcal{B}_+$ defined by $\Phi(t, x) = (R(t), S_t, M(t), P_t)$ for $x = (R(0), S_0, M(0), P_0) \in \mathcal{B}_+$. To show the existence of the compact attractor K for Φ, by Theorem 9.1 [12, Chap 12], it suffices to show positive orbits of bounded sets are bounded and Φ is point dissipative.

Recall that $2\gamma < D$ and define $\alpha = \frac{k}{D-2\gamma}$. Then, by (4) and $\mathfrak{F}(s) \leq 1$, for any $x \in \mathcal{B}_+$,

$$I(0) \leq \int_0^\infty e^{-Ds} kS(0-s)P(0-s)ds \leq k \int_0^\infty e^{-(D-2\gamma)s} \|S\|_\gamma \|P\|_\gamma ds \leq \alpha \|x\|^2$$

Let U be an arbitrary bounded set in $\mathcal{B}_+$, so there exists $L > 0$ such that $\|x\| < L, \forall x \in U$ and $I(0) \leq \alpha L^2$. If $(R, S, M, P)(t) = \Phi(t, x)(0)$ and $Y = R + S + M + P/b_0$, then (6) implies

$$Y(t) \leq X(t) \leq (Y(0) + I(0)) + R_0 \leq L + \alpha L^2 + R_0.$$

Recall that for any $\varphi \in C_\gamma$,

$$\|\varphi\|_\gamma = \sup\{e^{\gamma s}|\varphi(s)| : -\infty < s \leq 0\},$$

thus for any $t_0 < 0$,

$$\begin{aligned}
\|\varphi\|_\gamma &= \max\left\{\sup_{t_0 < s \leq 0} e^{\gamma s}|\varphi(s)|, \sup_{-\infty < s \leq t_0} e^{\gamma s}|\varphi(s)|\right\} \\
&\leq \sup_{t_0 < s \leq 0} e^{\gamma s}|\varphi(s)| + \sup_{-\infty < s \leq t_0} e^{\gamma s}|\varphi(s)| \\
&\leq \sup_{t_0 < s \leq 0} |\varphi(s)| + \sup_{-\infty < s \leq 0} e^{\gamma(s+t_0)}|\varphi(s+t_0)| \leq \sup_{t_0 < s \leq 0} |\varphi(s)| + e^{\gamma t_0} \|\varphi_{t_0}\|_\gamma,
\end{aligned}$$

where $\varphi_{t_0} \in C_\gamma$ is defined as $\varphi_{t_0}(r) = \varphi(r + t_0)$ for all $r \leq 0$.

Therefore, for any fixed $t \geq 0$, each component of $\Phi(t, x)(0)$ is less than $b_0 Y(t)$ (recall $b_0 > 1$),

$$\|\Phi(t, x)\| \leq \sup_{0 \leq s \leq t} b_0 Y(s) + e^{-\gamma t}\|x\| \leq (b_0 + 1)L + \alpha b_0 L^2 + b_0 R_0.$$

Hence positive orbits of bounded subsets of $\mathcal{B}_+$ are bounded.

To show Φ is point dissipative, we prove that there exists a bounded set V that attracts all points in $\mathcal{B}_+$. Let $x \in \mathcal{B}_+$ be an arbitrary point. Note that (5) also implies that there exists some $T_1 > 0$ such that $X(t) \leq R_0 + 1$ for all $t > T_1$. Therefore, $Y(t) \leq X(t) \leq R_0 + 1$ when $t > T_1$. Also there exists $T_2 > 0$ such that $e^{-\gamma t}\|x\| < 1$ for all $t > T_2$. Let $T = \max\{T_1, T_2\}$, we have

$$\|\Phi(t, x)\| \leq \sup_{0 \leq s \leq t} b_0 Y(s) + e^{-\gamma t}\|x\| \leq b_0 R_0 + b_0 + 1$$

for all $t > T$. Define $V = \{x \in \mathcal{B}_+ : \|x\| \leq b_0 R_0 + b_0 + 1\}$ then $\Phi(t, x) \to V$, and the proof is complete. □

Proof of Lemma 3.1. The linearization of (1) about E_S is given by

$$R'(t) = -(D + \overline{S}f_S'(R_S))R(t) - DS(t) - f_M(R_S)M(t)$$
$$S'(t) = f_S'(R_S)\overline{S}R(t) - k\overline{S}P(t)$$
$$M'(t) = (f_M(R_S) - D)M(t) \tag{13}$$
$$P'(t) = -DP(t) - k\overline{S}P(t) + k\overline{S}\int_0^\infty b(\tau)e^{-D\tau}P(t-\tau)d\nu(\tau).$$

Setting $(R, S, M, P) = xe^{\lambda t}$ we find that λ and x must satisfy $A(\lambda)x = 0$ where $A(\lambda)$ is given by

$$\begin{pmatrix} -D - f_S'(R_S)\overline{S} - \lambda & -D & -f_M(R_S) & 0 \\ \overline{S}f_S'(R_S) & -\lambda & 0 & -k\overline{S} \\ 0 & 0 & f_M(R_S) - D - \lambda & 0 \\ 0 & 0 & 0 & -D - k\overline{S} - \lambda + k\overline{S}\widetilde{B} \end{pmatrix}$$

and $\widetilde{B} = \widehat{b\nu}(\lambda + D)$ is the Laplace transform of $b\nu$.

Because $(R_S, \overline{S})$ is asymptotically stable in the linear approximation for the subsystem with $M, P = 0$ and because

$$f_M(R_S) - D < f_S(R_S) - D = 0,$$

it is easily seen that the stability analysis is reducible to the following scalar "phage invasion equation":

$$P'(t) = -(D + k\overline{S})P(t) + k\overline{S}\int_0^\infty b(\tau)e^{-D\tau}P(t-\tau)d\nu(\tau). \tag{14}$$

The characteristic equation associated with (14) is obtained by inserting the ansatz $P = e^{\lambda t}$. The equation for λ is

$$\lambda + D + k\overline{S} = k\overline{S}\int_0^\infty b(\tau)e^{-(D+\lambda)\tau}d\nu(\tau). \tag{15}$$

It has a positive real root if $PRN > 1$. To see this simply plot both sides of (15) and note that they intersect for positive λ precisely when $PRN > 1$ holds. On the other hand, if there is a root λ of (15) with $\Re\lambda \geq 0$ then it is easy to see that $PRN \geq 1$. Indeed, if $\Re\lambda \geq 0$ then

$$D + k\overline{S} \leq |\lambda + D + k\overline{S}| = |k\overline{S}\int_0^\infty b(\tau)e^{-D\tau}e^{-\lambda\tau}d\nu(\tau)| \leq Bk\overline{S}$$

Therefore, $\Re\lambda < 0$ for all roots of (15) if $PRN < 1$. The stability assertions now follow from standard results for delay equations: for finite delays, see [12], and for infinite delay see [18]. □

Proof of Theorem 3.2. We again calculate the linearization of (1) about E_{SP} and set $(R, S, M, P) = xe^{\lambda t}$, then λ and x satisfy $A(\lambda)x = 0$, where $A(\lambda)$ is

$$\begin{pmatrix} -D - f_S'(R^*)S^* - \lambda & -f_S(R^*) & -f_M(R^*) & 0 \\ S^*f_S'(R^*) & -\lambda & 0 & -kS^* \\ 0 & 0 & f_M(R^*) - D - \lambda & 0 \\ 0 & kP^*(\widetilde{B} - 1) & 0 & -D - kS^*(1 - \widetilde{B}) - \lambda \end{pmatrix}$$

and $\widetilde{B} = \widehat{b\nu}(\lambda + D)$.

If E_{SP} is asymptotically stable for the system without M, then the linearized stability of E_{SP} with M is determined by the characteristic root $f_M(R^*) - D$. In

this case, $MRN < 1$ is equivalent to $f_M(R^*) - D < 0$ and all roots have negative real parts.

If $MRN > 1$ or if E_{SP} is unstable for the system without M, then there must be at least one characteristic root λ such that $\Re\lambda > 0$ so E_{SP} is unstable for the system with M. $\qquad\square$

7.2. **Proof of Theorem 4.1.** Before proving the statements of Theorem 4.1, we need the following lemma:

Lemma 7.1. *Let $\pi_P : \mathcal{B}_+ \to C_\gamma$ be the projection map defined by $\pi_P(x) = P(\cdot)$ for $x = (R, S(\cdot), M, P(\cdot))$. If $\pi_P(\Phi(t,x))(0) \to 0$ and $S(0) > 0$, then $\Phi(t,x) \to E_S$.*

Proof. It is easy to see $\pi_P(\Phi(t,x))(0) \to 0$ is equivalent to $P(t) \to 0$.

Now we consider the following 3-dimensional non-autonomous ODE system by taking $P(t)$ as a time-dependent function:

$$
\begin{aligned}
R'(t) &= D(R_0 - R(t)) - f_S(R(t))S(t) - f_M(R(t))M(t), \\
S'(t) &= (f_S(R(t)) - D)S(t) - kS(t)P(t), \\
M'(t) &= (f_M(R(t)) - D)M(t).
\end{aligned}
\tag{16}
$$

By Corollary 4.3 in [26], since $P(t) \to 0$, (16) is an asymptotically autonomous system with limiting system:

$$
\begin{aligned}
R'(t) &= D(R_0 - R(t)) - f_S(R(t))S(t) - f_M(R(t))M(t), \\
S'(t) &= (f_S(R(t)) - D)S(t), \\
M'(t) &= (f_M(R(t)) - D)M(t).
\end{aligned}
\tag{17}
$$

By Theorem 3.2 in [24], all trajectories of (17) are attracted by one of its equilibria: $E_0 = (R_0, 0, 0)$, $E_S = (R_S, \overline{S}, 0)$ or $E_M = (R_M, 0, \overline{M})$. By Corollary 4.3 in [26], every solution of (16) is attracted by an equilibrium of (17).

On the other hand, the formal solution of $S(t)$ is given by

$$
S(t) = S(t_0) \exp\left(\int_{t_0}^t f_S(R(s)) - D - kP(s)ds \right).
\tag{18}
$$

Suppose $R(t) \to R_M > R_S = f_S^{-1}(D)$, i.e., the solution is attracted by E_M, then $S(t) \to 0$. Since $P(t) \to 0$, we can find a $\delta > 0$ and $T > 0$ such that $f_S(R(t)) - D - kP(t) > \delta$ when $t > T$. Also, $S(T) > 0$ because $S(0) > 0$, hence

$$
S(t) > S(T)e^{\delta(t-T)} \to \infty
$$

as $t \to \infty$, which contradicts that $S(t) \to 0$. Thus the solution cannot be attracted by E_M. Similarly, it cannot converge to E_0 either. Therefore, E_S attracts the solution. $\qquad\square$

Now we proceed to the proof of Theorem 4.1. For simplicity, we prove each statement of Theorem 4.1 separately.

Proof of Theorem 4.1 (a). In this proof we show $S^\infty := \limsup_{t\to\infty} S(t) \geq \min\{\overline{S}, \dfrac{D}{Bk}\}$ for all solutions with $S(0) > 0$. Thus S persists uniformly weakly, and by Theorem 4.13 in [21], S persists uniformly.

Suppose $S(0) > 0$ but $S^\infty < \frac{D}{Bk}$. Fix $\epsilon > 0$. By suitably translating the solution, we may assume that $S(t) < S^\infty + \epsilon$ and $P(t) < P^\infty + \epsilon$ for all $t \geq 0$. By the

fluctuation argument, we can choose $\{t_j\}_{j=1}^\infty$ in $\mathbb{R}_+$ such that $t_j \to \infty$, $P'(t_j) \to 0$, and $P(t_j) \to P^\infty$. Then

$$P'(t_j) \leq -DP(t_j) + k\int_0^\infty e^{-D\tau}b(\tau)S(t_j - \tau)P(t_j - \tau)d\nu(\tau)$$

$$= -DP(t_j) + k\int_0^\infty e^{-D\tau}b(\tau)(S^\infty + \epsilon)(P^\infty + \epsilon)d\nu(\tau).$$

Therefore

$$0 \leq -DP^\infty + Bk(S^\infty + \epsilon)(P^\infty + \epsilon).$$

Since $\epsilon > 0$ is arbitrary,

$$0 \leq -DP^\infty + BkS^\infty P^\infty.$$

By the assumption, $S^\infty < \frac{D}{Bk}$, thus $P^\infty = 0$. By Lemma 7.1, $S(t) \to \overline{S}$.

Therefore, either $S^\infty \geq \frac{D}{Bk}$ or $S(t) \to \overline{S}$, and $S^\infty \geq \min\{\overline{S}, \frac{D}{Bk}\}$ follows. □

To prove statement (b) and (c) in Theorem 4.1, we adapt the method used in [22] involving the Laplace transform. The Laplace transform of function $f(t)$ is defined as

$$\widehat{f}(\lambda) = \int_0^\infty e^{-\lambda t}f(t)dt,$$

for all $\lambda \geq 0$. If $f(t)$ is a non-negative function, then its Laplace transform $\widehat{f}(\lambda)$ is also a non-negative function.

We take the Laplace transform of both sides of the $P'(t)$ equation to obtain

$$(\lambda + D)\widehat{P}(\lambda) = P(0) - k\widehat{SP}(\lambda) \\ + k\int_0^\infty e^{-\lambda t}\int_0^\infty b(\tau)e^{-D\tau}S(t - \tau)P(t - \tau)d\nu(\tau)dt. \tag{19}$$

Since $\widehat{P}(\lambda)$ and $\widehat{SP}(\lambda)$ both exist, the integral exists. And by the Fubini-Tonelli Theorem (Theorem 2.37 in [10]), we can interchange the order of the iterated integral. Thus

$$(\lambda + D)\widehat{P}(\lambda) = P(0) - k\widehat{SP}(\lambda) \\ + k\int_0^\infty b(\tau)e^{-D\tau}\int_0^\infty e^{-\lambda t}S(t - \tau)P(t - \tau)dtd\nu(\tau) \\ = P(0) - k\widehat{SP}(\lambda) \\ + k\int_0^\infty b(\tau)e^{-D\tau}\int_{-\tau}^\infty e^{-\lambda(r+\tau)}S(r)P(r)drd\nu(\tau) \\ = P(0) - k\widehat{SP}(\lambda) + kC_0 + k\widehat{SP}(\lambda)\int_0^\infty b(\tau)e^{-(\lambda+D)\tau}d\nu(\tau), \tag{20}$$

where, as $2\gamma < D$,

$$C_0 = \int_0^\infty b(\tau)e^{-(\lambda+D)\tau}\left(\int_{-\tau}^0 e^{-\lambda r}S(r)P(r)dr\right)d\nu(\tau) \\ \leq \int_0^\infty b(\tau)e^{-(\lambda+D)\tau}\left(\tau e^{(\lambda+2\gamma)\tau}\|S\|_\gamma\|P\|_\gamma\right)d\nu(\tau) \\ \leq b_0\|S\|_\gamma\|P\|_\gamma\int_0^\infty \tau e^{-(D-2\gamma)\tau}d\nu(\tau) < \infty.$$

We need the auxiliary estimate $S^\infty \leq \overline{S}$.

Lemma 7.2. *The total population of bacteria in the chemostat satisfies* $(S + M + I)^\infty \leq \overline{S}$.

Proof. Define $Y = (S + M + I)$, note

$$Y'(t) = f_S(R(t))S(t) + f_M(R(t))M(t) - DY(t)$$

$$- k \int_0^\infty e^{-D\tau} b(\tau)S(t - \tau)P(t - \tau)d\nu(\tau)$$

$$\leq f_S(R(t))(S(t) + M(t)) - DY(t) \leq (f_S(R(t)) - D)Y(t).$$

By (6), $(Y + R)^\infty \leq X^\infty \leq R_0$. Hence by the fluctuation lemma,

$$0 \leq (f_S((R + Y)^\infty - Y^\infty) - D)Y^\infty \leq (f_S(R_0 - Y^\infty) - D)Y^\infty.$$

So either $Y^\infty = 0$ or $f_S(R_0 - Y^\infty) \geq D$; the latter case is equivalent to $Y^\infty \leq R_0 - R_S = \overline{S}$. Therefore, in both cases we obtain $Y^\infty \leq \overline{S}$. $\qquad\square$

Now we are ready to prove statement (b) and (c) of Theorem 4.1.

Proof of Theorem 4.1 (b). By the previous lemma, $S^\infty \leq \overline{S}$, so for any $\epsilon > 0$, there exists a $T > 0$ such that for all $t > T$, $S(t) < \overline{S} + \epsilon$. Thus we can assume $S(t) < \overline{S} + \epsilon$ for all $t \geq 0$ after a time-shift.

Note $\lambda \geq 0$ and $\widehat{P}(\lambda) \geq 0$ imply that $e^{-(\lambda + D)\tau} \leq e^{-D\tau}$ and thus

$$D\widehat{P}(\lambda) \leq (\lambda + D)\widehat{P}(\lambda) \leq P(0) + kC_0 + k(B - 1)\widehat{SP}(\lambda).$$

If $k(B - 1) \leq 0$, $D\widehat{P}(\lambda) \leq P(0) + kC_0$ so $\widehat{P}(\lambda)$ is bounded for $\lambda \geq 0$. If $k(B - 1) > 0$, $\widehat{SP}(\lambda) \leq (\overline{S} + \epsilon)\widehat{P}(\lambda)$ and

$$(D - k(B - 1)(\overline{S} + \epsilon))\widehat{P}(\lambda) \leq P(0) + kC_0$$

Since $PRN < 1$, we can pick ϵ small enough to make $D - k(B - 1)(\overline{S} + \epsilon) > 0$. Therefore, in both cases, $\widehat{P}(\lambda)$ is uniformly bounded for $\lambda \geq 0$. Let $\lambda \to 0$ and apply the monotone convergence theorem to get $\widehat{P}(0) = \int_0^\infty P(t)dt < \infty$. Since $P'(t)$ is bounded, $P(t)$ is uniformly continuous and $P(t) \to 0$ as $t \to \infty$. Lemma 7.1 implies that the solution converges to E_S. $\qquad\square$

Proof of Theorem 4.1 (c). We will use Theorem 8.17 in [21] and follow the notation therein. Define the state space as $X = \{x \in \mathcal{B}_+ : \pi_S(x)(0) > 0\}$, where $\pi_S : \mathcal{B}_+ \to C_\gamma$ is the projection map from X to C_γ defined by $\pi_S(x) = S(\cdot)$. Note that X is positively invariant for Φ. Because S persists uniformly and our semiflow has a compact attractor of bounded sets in $\mathcal{B}_+$, the restriction of Φ to X has a compact attractor of points in X.

Let $\rho : X \to [0, \infty)$, defined as $\rho(x) = \pi_P(x)(0)$, be our persistence function. Define $X_0 = \{x \in X : \rho(\Phi(t, x)) = 0, \forall t \geq 0\}$. It is easy to see X_0 is not empty because $C^0 \times C_\gamma \times C^0 \times \{0\} \subset X_0$, where 0 represents the 0 function in C_γ. In X_0, since $P(t) \equiv 0$ for all $t \geq 0$, system (1) becomes (17). Since $S(0) > 0$, by Theorem 3.2 in [24] and $P(t) \equiv 0$, $(R(t), S(t), M(t), P(t)) \to E_S = (R_S, \overline{S}, 0, 0)$ as $t \to \infty$. This implies that E_S, viewed as an element of X, attracts all orbits starting in X_0.

We also need to show $\{E_S\}$ is compact, invariant, weakly ρ-repelling, isolated in X and acyclic. The proof of the first two properties is trivial.

Suppose $\{E_S\}$ is not a weak ρ-repeller, that is, there exists some $x_0 \in X$ such that $\rho(x_0) > 0$ and $\Phi(t, x_0) \to E_S$. Then, for arbitrary $\epsilon \in (0, \overline{S})$, we can assume,

after a time shift of the solution $\Phi(t, x_0)$, that $\overline{S} - \epsilon \le S(t) \le \overline{S} + \epsilon$ for all $t \ge 0$. Now we apply these inequalities in the final inequality of (20) to obtain

$$(D + \lambda)\widehat{P}(\lambda) \ge (-k(\overline{S} + \epsilon) + k(\overline{S} - \epsilon)\int_0^\infty b(\tau)e^{-(\lambda+D)\tau}d\nu(\tau))\widehat{P}(\lambda)$$

Since $P(t) > 0$ for $t > 0$, $\widehat{P}(\lambda)$ is positive and finite for $\lambda > 0$ so we conclude that

$$(D + \lambda) \ge -k(\overline{S} + \epsilon) + k(\overline{S} - \epsilon)\int_0^\infty b(\tau)e^{-(\lambda+D)\tau}d\nu(\tau)$$

Letting $\lambda \to 0$ we find that $D + k\overline{S} - kB\overline{S} \ge -k\epsilon(1 + B)$. Since $\epsilon > 0$ is arbitrary, this contradicts that $PRN > 1$ so $\{E_S\}$ is weakly ρ-repelling.

Now we show $\{E_S\}$ is isolated in X and acyclic in X_0. First, $\{E_S\}$ is isolated in X_0 since in X_0 our system reduces to the ODEs (17) and E_S is asymptotically stable for (17). This also shows that E_S is acyclic in X_0.

To show $\{E_S\}$ is isolated in X, we choose a neighborhood U_ϵ of $\{E_S\}$ as the ϵ-ball centered at E_S in X. By picking ϵ small enough, we can make $U_\epsilon \cap X_0$ be an isolating neighborhood of $\{E_S\}$ in X_0.

Suppose K is a compact invariant set in U_ϵ other than $\{E_S\}$. If $K \cap X_0$ is not empty, by the forward invariance of X_0, $K \subset X_0$. However, since $U_\epsilon \cap X_0$ is an isolating neighborhood of $\{E_S\}$ in X_0, we have $K \cap X_0$ is empty. So $K \subset X\backslash X_0$. But then we can use the same argument that established that E_S is ρ-repelling to obtain a contradiction to $PRN > 1$. Thus, no such compact invariant set $K \subset U_\epsilon$, distinct from E_S, exists and $\{E_S\}$ is isolated in X.

By Theorem 8.17 in [21], Φ is uniformly weakly ρ-persistent, and by Theorem 4.13 in [21], P persists uniformly as claimed. $\square$

Proof of Theorem 4.1 (d). If $S(0) = 0$, $S(t) = 0$ for all $t \ge 0$ and $P(t) \to 0$, thus our system reduces to

$$R'(t) = D(R_0 - R(t)) - f_M(R(t))M(t),$$
$$M'(t) = (f_M(R(t)) - D)M(t),$$

By Theorem 3.2 in [24], all trajectories with $M(0) > 0$ converge to $(R_M, \overline{M})$. Thus M persists uniformly.

Now we assume that $S(0) > 0, P(0) > 0, PRN > 1, MRN > 1$, and that E_{SP} attracts all solutions with $S(0) > 0, P(0) > 0$ and $M(0) = 0$. Then, $S(t), P(t) > 0$ for all $t > 0$.

Let $X = \{x \in \mathcal{B}_+ : \pi_S(x)(0) > 0, \pi_P(x)(0) > 0\}$. Because S and P persist uniformly, by parts (a) and (c), and Φ has a compact attractor of bounded sets in $\mathcal{B}_+$, it follows that the restriction of Φ to X has a compact attractor of points, as required for Theorem 8.17 in [21].

Define $\rho : X \to [0, \infty)$ as $\rho(x) = \pi_M(x) = M(0)$. Let $X_0 = \{x \in X : \rho(\Phi(t, x)) = 0, \forall t \ge 0\} = \{x \in X : M(t) = 0, t \ge 0\}$. By assumption, E_{SP} attracts all solutions in X_0. $\{E_{SP}\}$ is clearly compact, invariant and acyclic in X_0.

E_{SP} is also weakly ρ-repelling. Suppose there exists $x_0 \in X$ such that $\rho(x) > 0$ and $\Phi(t, x_0) \to E_{SP}$, then $R(t) = \pi_R(\Phi(t, x)) \to R^*$. Since $MRN > 1$, $f_M(R^*) > D$, so there exists some $T > 0$ and $\epsilon > 0$ such that for all $t > T$, $f_M(R(t)) - D > \epsilon$. This implies that $M(t) \to \infty$ as $t \to \infty$, a contradiction. Hence there is no $x_0 \in X$ with $\rho(x) > 0$ satisfying $\Phi(t, x_0) \to E_{SP}$.

As E_{SP} is asymptotically stable in X_0, it is isolated and acyclic in X_0. It is also isolated in X because if there is an entire trajectory in X, in a sufficiently small

neighborhood of E_{SP}, with $M(0) > 0$, then as $R(t) - R^*$ is small, so $f_M(R(t)) - D > \epsilon$ for some positive ϵ. This is a contradiction to the boundedness of M.

By Theorem 8.17 and Theorem 4.13 in [21], M persists uniformly. $\qquad \square$

7.3. **Proof of Theorem 4.2 and Theorem 4.3.**

Proof of Theorem 4.2. Let $Y = \frac{S}{M}$, then

$$Y'(t) = (f_S(R(t)) - f_M(R(t)) - kP(t))Y(t),$$

Since $S_\infty > 0$ and $M > \epsilon$ when $t > T$, $Y(t)$ is bounded and $Y_\infty > 0$. Thus

$$(\ln Y(t))' = \frac{Y'(t)}{Y(t)} = f_S(R(t)) - f_M(R(t)) - kP(t).$$

And

$$\lim_{t \to \infty} \frac{1}{t} \int_0^t (\ln Y(s))' ds = \lim_{t \to \infty} \frac{1}{t}(\ln Y(t) - \ln Y(0)) = 0,$$

because $|\ln Y(t)|$ is bounded. Consequently,

$$\lim_{t \to \infty} \frac{1}{t} \int_0^t f_S(R(s)) - f_M(R(s)) - kP(s) ds = 0$$

as claimed. $\qquad \square$

To prove Theorem 4.3, we need the following lemma, also used in [22].

Lemma 7.3. *Suppose $h(t)$ is a non-negative and continuously differentiable function on $[0, \infty)$ and $|h'(t)|$ is bounded, then $h^\infty > 0$ implies $\int_0^\infty h(s)ds = \infty$.*

And now we are ready to prove Theorem 4.3.

Proof of Theorem 4.3. Since $f_S(R)$ and $f_M(R)$ are identical, we write $f(R)$ as the uptake function. Now let $Y = I + \frac{1}{b_0}P$. We divide the proof into a few steps below.

Step 1: Both I and P converge to 0.

Suppose that $P^\infty > 0$, so $\int_0^\infty P(s)ds = \infty$ by Lemma 7.3. Formal solutions of $S(t)$ and $M(t)$ imply that

$$S(t) = \frac{S(0)}{M(0)} M(t) \exp\left(-k \int_0^t P(s)ds\right). \tag{21}$$

By the boundedness of $M(t)$, we have $S(t) \to 0$. Note

$$Y'(t) = -DY(t) + \frac{b_0 - 1}{b_0} kS(t)P(t)$$
$$+ k \int_0^\infty e^{-D\tau} \left(\frac{b(\tau)}{b_0} - 1\right) S(t - \tau)P(t - \tau)d\nu(\tau)$$
$$\leq -DY(t) + \frac{b_0 - 1}{b_0} kS(t)P(t).$$

By an application of fluctuation argument, we have $0 \leq -DY^\infty$, and by non-negativity of solutions, $Y^\infty = 0$. This contradiction shows that $P^\infty = 0$ and consequently, $I^\infty = 0$.

Step 2: Every solution with $S(0), M(0) > 0$ converges to a point on L.

We consider the following 2-dimensional non-autonomous system by taking $P(t)$ as a time-dependent function:

$$R'(t) = D(R_0 - R(t)) - f(R(t))(S + M)(t),$$
$$(S + M)'(t) = (f(R(t)) - D)(S + M)(t) - kS(t)P(t). \tag{22}$$

It is asymptotically autonomous and its limiting equation is

$$R'(t) = D(R_0 - R(t)) - f(R(t))(S+M)(t),$$
$$(S+M)'(t) = (f(R(t)) - D)(S+M)(t).$$
(23)

This is a classical chemostat model, every solution of (23) converges to $E_0 = (R_0, 0)$ or $E^* = (\overline{R}, R_0 - \overline{R})$. In particular, E^* attracts all solutions with $S(0) > 0, M(0) > 0$. By Corollary 4.3 in [26], every solution of (22) converges to an equilibrium of (23). However, no trajectory with $(S+M)(0) > 0$ converges to $(R_0, 0)$ because if so, there exists $T_0 > 0$ such that for all $t \geq T_0$, $R(t) > \frac{1}{2}(R_0 + \overline{R}) > \overline{R}$ and thus

$$(S+M)(t) = (S+M)(t_0) \exp\left(\int_{t_0}^t f(R(t)) - D ds\right)$$

$$> (S+M)(t_0) \exp\left(\int_{t_0}^t f\left(\frac{1}{2}(R_0 + \overline{R})\right) - D ds\right) \to \infty$$

as $t \to \infty$, which contradicts $(S+M)(t) \to 0$. So all solutions of (22) with $(S+M)(0) > 0$ are attracted by $(\overline{R}, R_0 - \overline{R})$.

Note

$$\frac{S(t)}{M(t)} = \frac{S(0)}{M(0)} \exp\left(-k\int_0^t P(s)ds\right),$$

the integral is an increasing function of t, thus it either diverges to ∞ or converges to a finite limit. In both cases,

$$\lim_{t\to\infty} \frac{S(t)}{M(t)} = \frac{S(0)}{M(0)} \lim_{t\to\infty} \exp\left(-k\int_0^t P(s)ds\right)$$

exists. Together with $\lim_{t\to\infty}(S+M)(t) = R_0 - \overline{R}$, both $\lim_{t\to\infty} S(t)$ and $\lim_{t\to\infty} M(t)$ exist.

Therefore, every solution of (1) with $S(0) > 0, M(0) > 0$ is attracted by a point on L.

Step 3: $S^\diamond := \lim_{t\to\infty} S(t) > 0$ and $M^\diamond := \lim_{t\to\infty} M(t) > 0$.

Suppose $M^\diamond = 0$, then $S^\diamond = R_0 - \overline{R}$. By (21) and non-negativity of $P(t)$, we have $S^\diamond \leq \frac{S(0)}{M(0)} M^\diamond = 0$, which forms a contradiction. Thus $M^\diamond > 0$.

Now suppose $S^\diamond = 0$, note $\frac{1}{b_0} P(t) \leq Y(t)$, thus

$$Y'(t) \leq -DY(t) + \frac{b_0 - 1}{b_0} kS(t)P(t) \leq -DY(t) + (b_0 - 1)kS(t)Y(t).$$

Since $S(t) \to 0$, we can assume $S(t) < \frac{D}{2(b_0-1)k}$ after a time-shift, thus $Y'(t) \leq -\frac{D}{2}Y(t)$, and consequently,

$$\int_0^\infty P(s)ds \leq b_0 \int_0^\infty Y(s)ds \leq b_0 \int_0^\infty Y(0)e^{-\frac{D}{2}s}ds = \frac{2b_0}{D}Y(0).$$

Since the integral of P is a finite number, by taking the limit of both sides of (21), $S^\diamond > \frac{S(0)}{M(0)} M^\diamond \exp(-\frac{2k}{Db_0}Y(0)) > 0$, which contradicts the assumption that $S^\diamond = 0$.

Step 4: S does not persist uniformly. If $PRN > 1$ and $P(0), M(0) > 0$, M persists uniformly.

For any $\epsilon > 0$, without loss of generality, assume $\epsilon < R_0 - \overline{R}$. Let $S(0) = \epsilon$ and $M(0) = R_0 - \overline{R} - \epsilon$, $P(0) > 0$, then by (21), since the integral of P is strictly positive, $\frac{S^\diamond}{M^\diamond} < \frac{S(0)}{M(0)}$. However, $S^\diamond + M^\diamond = S(0) + M(0) = R_0 - \overline{R}$, so $S^\diamond < S(0) = \epsilon$. Therefore, for any $\epsilon > 0$, we can always find a trajectory such that $S^\diamond < \epsilon$.

By Laplace transform (20),

$$(\lambda + D)\widehat{P}(\lambda) \geq -k\widehat{SP}(\lambda) + k\widehat{SP}(\lambda) \int_0^\infty b(\tau)e^{-(\lambda+D)\tau} d\nu(\tau).$$

Since $S(t) \to S^\diamond$, for any $\epsilon > 0$, we can assume $S(t) > S^\diamond - \epsilon$ after a possible time-shift. Therefore,

$$(\lambda + D)\widehat{P}(\lambda) \geq k(S^\diamond - \epsilon)\widehat{P}(\lambda) \left(\int_0^\infty b(\tau)e^{-(\lambda+D)\tau} d\nu(\tau) - 1 \right).$$

By taking $\lambda \to 0$, and dividing both sides by $\widehat{P}(0) > 0$, we have $D \geq k(B-1)(S^\diamond - \epsilon)$. Since this inequality holds for any $\epsilon > 0$, we let $\epsilon \to 0$ and get

$$D \geq k(B - 1)S^\diamond. \tag{24}$$

And (24) is exactly $S^\diamond \leq S^*$. Therefore, $M^\diamond \geq R_0 - \overline{R} - S^*$. Note $R_0 - \overline{R} - S^* > 0$ if and only if $PRN > 1$ and the proof is complete. □

7.4. **Small delay case.** In this section we consider a special case of (1), i.e, when the latent period is a single fixed delay τ for some $\tau \geq 0$. In this case (1) becomes

$$\begin{aligned}
R'(t) &= -DR(t) + DR_0 - f_S(R(t))S(t) - f_M(R(t))M(t), \\
S'(t) &= -DS(t) + f_S(R(t))S(t) - kS(t)P(t), \\
M'(t) &= -DM(t) + f_M(R(t))M(t), \\
I'(t) &= -DI(t) + kS(t)P(t) - ke^{-D\tau}S(t-\tau)P(t-\tau), \\
P'(t) &= -DP(t) - kS(t)P(t) + kbe^{-D\tau}S(t-\tau)P(t-\tau),
\end{aligned} \tag{25}$$

where $b > 1$ is a constant.

For system (25), we will show that when $\tau > 0$ is small, M persists uniformly. The main conclusion of this section is summarized below:

Theorem 7.4. *If $bk\overline{S} > D + k\overline{S}$, then there exists $\tau_0 > 0$ such that for each $\tau \in [0, \tau_0]$, we can find $\epsilon_\tau > 0$ satisfying*

$$\liminf_{t\to\infty} M(t) > \epsilon_\tau$$

provided $S(0) > 0$, $P(0) > 0$ and $M(0) > 0$.

This is a direct application of part (d) of Theorem 4.1, if we can show E_{SP} attracts all orbits in $\{M \equiv 0\}$ with positive initial data. To see that this sufficient condition is true, we first prove that E_{SP} is "globally" stable in $\{M \equiv 0\}$ when $\tau_0 = 0$, and then analyze the stability of E_{SP} for small $\tau > 0$ by a perturbation argument. Without loss of generality, we assume $\tau_0 \leq 1$.

System (25) can be obtained by letting the probability distribution of the latent period be a Delta distribution. All results regarding equilibria, boundedness, positivity and persistence obtained for (1) still hold for (25). Since components of E_{SP} depend on τ, we write E_{SP}^τ to emphasize that it is an equilibrium of (25) with the given delay parameter τ. Since E_0 and E_S remain the same for all $\tau \geq 0$, we skip the superscript to simplify notation. Nevertheless, it is worth mentioning that the phage reproduction number now becomes

$$PRN = \frac{e^{-D\tau}bk\overline{S}}{D + k\overline{S}}.$$

Again, since $I(t)$ can be solved by its formal solution, we omit the differential equation of $I(t)$ in (25) hereafter. Our main focus is the stability of E_{SP} given that $M \equiv 0$, so it suffices to consider the following system:

$$
\begin{aligned}
R'(t) &= -DR(t) + DR_0 - f_S(R(t))S(t) - f_M(R(t))M(t), \\
S'(t) &= -DS(t) + f_S(R(t))S(t) - kS(t)P(t), \\
P'(t) &= -DP(t) - kS(t)P(t) + kbe^{-D\tau}S(t-\tau)P(t-\tau),
\end{aligned}
\tag{26}
$$

Let the phase space of (26) be

$$
\mathcal{C} = \mathbb{R}_+ \times C \times C,
$$

where $C = C([-1,0], \mathbb{R}_+)$ equipped with the supremum norm $\|\cdot\|_\infty$. Moreover, let $\mathcal{C}$ take the maximum norm.

Let $\Psi^\tau : \mathbb{R}_+ \times \mathcal{C} \to \mathcal{C}$ be the semiflow induced by (26) on $\mathcal{C}$ with the given delay parameter τ. Define two projection maps $\widetilde{\pi}_S, \widetilde{\pi}_P : \mathcal{C} \to C$ as: for each $x = (R, S(\cdot), P(\cdot)) \in \mathcal{C}$, $\widetilde{\pi}_S(x) = S(\cdot)$ and $\widetilde{\pi}_P(x) = P(\cdot)$. Define $\widetilde{\pi}_R : \mathcal{C} \to \mathbb{R}_+$ as $\widetilde{\pi}_R(x) = R$.

The first lemma shows that E_{SP} attracts all orbits in $\{M \equiv 0\}$ with positive initial data if $\tau = 0$.

Lemma 7.5. *Suppose $bk\overline{S} > D + K\overline{S}$ and $\tau = 0$, then E_{SP}^0 attracts all orbits of* (26) *with $S(0) > 0$ and $P(0) > 0$.*

Proof. Given that $\tau = 0$, (26) is reduced to

$$
\begin{aligned}
R'(t) &= -D(R(t) - R(0)) - f_S(R(t))S(t), \\
S'(t) &= (f_S(R(t)) - D)S(t) - kS(t)P(t), \\
P'(t) &= -DP(t) + (b-1)kS(t)P(t).
\end{aligned}
\tag{27}
$$

Define an auxiliary variable $Y = R + S + \frac{1}{b-1}P$. Then it is easy to see $Y'(t) = D(R_0 - Y(t))$, thus $Y(t) \to R_0$ as $t \to \infty$. By writing $R(t) = Y(t) - S(t) - \frac{1}{b-1}P(t)$ in the differential equation of $S(t)$, as treated in [24], it suffices to consider the following limiting system

$$
\begin{aligned}
S'(t) &= \left[f_S\left(R_0 - S(t) - \frac{1}{b-1}P(t) \right) - D \right] S(t) - kS(t)P(t), \\
P'(t) &= -DP(t) + (b-1)kS(t)P(t).
\end{aligned}
\tag{28}
$$

Let $F = (F_S, F_P)^T$ be the vector field of (28) on the open set $\{(S,P) \in \mathbb{R}_+^2 : S > 0, P > 0\}$. Then we have

$$
div\left(\frac{F_S}{SP}, \frac{F_P}{SP} \right) = -\frac{f_S'(R_0 - S - \frac{1}{b-1}P)}{P},
$$

which does not change sign because $f_S' > 0$. By the Poincaré-Bendixson theorem and the Dulac criteria, there are no periodic orbits in this open set and hence every solution is attracted by E_{SP}^0. $\qquad\square$

To show this is true for all small delays, we need the following lemma.

Lemma 7.6. *For each given $\tau \in [0,1]$, let*

$$
\mathcal{C}_\tau = \left\{ x = (R, S(\cdot), P(\cdot)) \in \mathcal{C} : 0 \le R + S(0) + I(0) + \frac{P(0)}{b} \le R_0 + 1 \right\},
$$

where

$$I(0) = \int_0^\tau e^{-Ds} S(-s) P(-s) ds.$$

Then

$$W := \bigcup_{\tau \in [0,1]} \Psi^\tau(2, \mathcal{C}_\tau)$$

has a compact closure in $\mathcal{C}$.

Proof. First let τ be fixed. In (25), let $Y(t) = R(t) + S(t) + I(t) + P(t)/b$. As $M(t) \equiv 0$, we have

$$Y'(t) \leq D(R_0 - Y(t)).$$

Therefore, $\mathcal{C}_\tau$ is forward invariant for Ψ^τ and it attracts all orbits.

Now, if $y = (R, \phi(\cdot), \psi(\cdot))$ is an arbitrary point in W, then there exists some $\tau > 0$ and $x \in \mathcal{C}_\tau$ such that $y = \Psi^\tau(2, x)$. Since $\mathcal{C}_\tau$ is forward invariant, $\Psi^\tau(s, x) \in \mathcal{C}_\tau$ for all $s \in [0, 2]$. Note that for all $\theta \in [-1, 0]$, we have

$$\phi(\theta) = \widetilde{\pi}_S(\Psi^\tau(2 + \theta, x))(0) \leq R_0 + 1,$$

and

$$\psi(\theta) = \widetilde{\pi}_P(\Psi^\tau(2 + \theta, x))(0) \leq b(R_0 + 1).$$

So $\|\phi\|_\infty \leq R_0 + 1$ and $\|\psi\|_\infty \leq b(R_0 + 1)$. That is, by using the fact $b > 1$, $\|y\| \leq b(R_0 + 1)$.

Moreover,

$$\phi'(\theta) = S'(2 + \theta) = (f_S(R(2 + \theta)) - D)S(2 + \theta) - kS(2 + \theta)P(2 + \theta),$$

$$\psi'(\theta) = P'(2 + \theta)$$
$$= -DP(2 + \theta) - kS(2 + \theta)P(2 + \theta) + bke^{-D\tau}S(2 + \theta - \tau)P(2 + \theta - \tau).$$

Let

$$L := \max\left\{ f_S(R_0 + 1) + D + kb, D + kb(b + 1) \right\} (R_0 + 1)^2.$$

Since $R_0 + 1 < (R_0 + 1)^2$, we have that both ϕ and ψ are Lipschitz continuous on $[-1, 0]$ with constant L.

Note that $y \in W$ is arbitrary and both the upper bound $b(R_0 + 1)$ and the Lipschitz constant L are independent from the choice of y, τ, and x. Thus W is uniformly bounded and equicontinuous. By the Arzelà-Ascoli theorem, W has compact closure in $\mathcal{C}$. $\square$

Part (a) and (c) of Theorem 4.1 claim that for each fixed $\tau > 0$, S and P persist uniformly for all positive initial condition. The following lemma shows that the lower bound on the limit inferior can be chosen to be independent of the parameter τ, provided it is small.

Lemma 7.7. *Let $bk\overline{S} > D + k\overline{S}$. Let $U = \{x \in \mathcal{C} : \widetilde{\pi}_S(x)(0) > 0, \widetilde{\pi}_P(x)(0) > 0\}$ and $\partial U = \mathcal{C} \backslash U$. Define $\rho : \mathcal{C} \to \mathbb{R}_+$ as $\rho(x) = \min\{\widetilde{\pi}_S(x)(0), \widetilde{\pi}_P(x)(0)\}$. Then there exists $\epsilon_0 \in (0, 1]$ such that*

$$\liminf_{t \to \infty} \rho(\Psi^\tau(t, x)) > \epsilon_0$$

for all $\tau \in [0, \epsilon_0)$ and $x \in U$.

Proof. We use Theorem 5 in [25] to prove this lemma.

Let $\tau_{\max} = \min\{1, -\frac{1}{D}\ln\frac{D+k\overline{S}}{bk\overline{S}}\}$.

$\Psi^\tau(t,x)$ is continuous in (τ, t, x) because of the continuous dependence of solutions of (26), both in parameters and initial data. Every positive orbit of Ψ^τ has a compact closure in $\mathcal{C}$. For each given τ and $x \in \mathcal{C}$, let $\omega_\tau(x)$ be the omega-limit set of x. We claim that

$$W_1 := \bigcup_{\tau \in [0,\tau_{\max}], x \in \mathcal{C}} \omega_\tau(x)$$

has a compact closure in $\mathcal{C}$. Since $\omega_\tau(x)$ is invariant, $\omega_\tau(x) = \Psi^\tau(2, \omega_\tau(x))$. Thus we can rewrite W_1 as

$$W_1 = \bigcup_{\tau \in [0,\tau_{\max}]} \Psi^\tau \left(2, \bigcup_{x \in \mathcal{C}} \omega_\tau(x)\right)$$

We have already noted that $\omega_\tau(x) \subset C_\tau$. By Lemma 7.6, W_1 has a compact closure.

We must verify hypothesis (B1) of Theorem 5 in [25]. By Theorem 2.1, Ψ^0 has a global attractor. Moreover, for every $x \in \partial U$, $\Psi^0(t,x)$ either converges to E_0 or E_S. Note that $\{\{E_0\}, \{E_S\}\}$ is acyclic in ∂U and both $\{E_0\}$ and $\{E_S\}$ are isolated in $\mathcal{C}$. Moreover, both stable manifolds $W^s(E_0)$ and $W^s(E_S)$ are disjoint from $\rho^{-1}(0,\infty)$. Therefore, hypothesis (B1) is verified.

Now we turn to hypothesis (B2) of Theorem 5 in [25]. In the proof of part (a) of Theorem 4.1, we have shown $S^\infty \geq \min\{\overline{S}, \frac{D}{e^{-D\tau}bk}\}$, hence $S^\infty \geq \min\{\overline{S}, \frac{D}{bk}\} > 0$, and this inequality is independent from τ. So as a consequence,

$$\limsup_{t \to \infty} \|\Psi^\tau(t,x) - E_0\| \geq S^\infty \geq \min\{\overline{S}, \frac{D}{bk}\} > 0.$$

for all $\tau \in [0, \tau_{\max}]$ and $x \in U$.

For E_S, we would like to show there exists $\epsilon_0 \in (0, \tau_{\max}]$ such that for any $\tau \in (0, \epsilon_0)$ and any $x \in U$,

$$\limsup_{t \to \infty} \|\Psi^\tau(t,x) - E_S\| \geq \epsilon_0 > 0. \tag{29}$$

If this is not true, then for any $n \in \mathbb{N}$, there exists $\tau_n \in (0, \frac{1}{n})$ and $x_n \in U$ such that

$$\limsup_{t \to \infty} \|\Psi^{\tau_n}(t,x_n) - E_S\| < \frac{1}{n}. \tag{30}$$

After a suitable time shift, we may assume that $S_n(t) = \tilde{\pi}_S(\Psi^{\tau_n}(t,x_n))(0)$ satisfies $S_n(t) > \bar{S} - \frac{1}{n}$ for all $t \geq 0$. Let $P_n(t) = \tilde{\pi}_P(\Psi^{\tau_n}(t,x_n))(0)$ for $t \geq 0$. In the proof of part (c) of Theorem 4.1, we used the Laplace transform of P to show that E_S is a repeller for phage P and we would like to use a similar argument to show that (30) is impossible.

Taking the Laplace transform of the P_n equation in (26), we find that

$$(\lambda + D)\widehat{P_n}(\lambda) \geq k\widehat{S_nP_n}(\lambda)\left[be^{-(\lambda+D)\tau} - 1\right].$$

Letting $\lambda \to 0$ gives

$$D\widehat{P_n}(0) \geq k\widehat{S_nP_n}(0)\left[be^{-D\tau} - 1\right].$$

For each $n \in \mathbb{N}$, by (30), after a possible time-shift, we have

$$D\widehat{P_n}(0) \geq k(\bar{S} - \frac{1}{n})\widehat{P_n}(0)\left[be^{-D\tau_n} - 1\right],$$

that is,

$$D \geq k(\overline{S} - \frac{1}{n}) \left[be^{-D\tau_n} - 1 \right],$$

because $\widehat{P_n}(0) > 0$. However, for n large enough, $\tau_n < \frac{1}{2}\tau_{\max}$ and hence

$$D \geq k(\overline{S} - \frac{1}{n}) \left[be^{-\frac{1}{2}D\tau_{\max}} - 1 \right].$$

Since this inequality is true for all large n, we take $n \to \infty$ and get

$$D \geq k\overline{S} \left[be^{-\frac{1}{2}D\tau_{\max}} - 1 \right] > k\overline{S} \left[be^{-D\tau_{\max}} - 1 \right] = D,$$

which is a contradiction. Thus (29) is true.

All hypotheses of Theorem 5 in [25] have been verified and the conclusion of the lemma is an application of this theorem. □

Now we are ready to show that the global stability of E_{SP}^τ holds for all small $\tau > 0$.

Lemma 7.8. *There exists some $\tau_0 > 0$ such that for every $\tau \in [0, \tau_0)$ fixed, E_{SP}^τ attracts all orbits of* (26) *with $S(0) > 0$ and $P(0) > 0$.*

Proof. This claim follows from Theorem 2.2 in [23].

Let $B(E_{SP}^0, \delta)$ be the open ball of radius δ about E_{SP} in $\mathcal{C}$ and $\Lambda = [0, \epsilon_0)$, where $\epsilon_0 \leq 1$ is the same as in Lemma 7.7. Recall that $U = \{x \in \mathcal{C} : \widetilde{\pi}_S(x)(0) > 0, \widetilde{\pi}_P(x)(0) > 0\}$.

We can find $\delta > 0$ such that $B(E_{SP}^0, \delta) \in U$ and $D_x\Psi^\tau(t, x)$ exists for $(t, x, \tau) \in [0, \infty) \times B(E_{SP}^0, \delta) \times \Lambda$ and it is continuous on $B(E_{SP}^0, \delta) \times \Lambda$. Since E_{SP}^0 is a locally asymptotically stable equilibrium of (26), $\Psi^0(t, E_{SP}^0) = E_{SP}^0$ and $D_x\Phi^0(t, E_{SP}^0)$ has a negative growth bound $-\omega$. Moreover, $\Psi^0(t, x) \to E_{SP}^0$ as $t \to \infty$ for $x \in U$ by Lemma 7.5.

Define

$$V_\tau = \left\{ x \in U \cap C_\tau : \min \{ \widetilde{\pi}_S(x)(0), \widetilde{\pi}_P(x)(0) \} > \frac{\epsilon_0}{2} \right\}.$$

By Lemma 7.7, for each $\tau \in \Lambda$ and $x \in U$ fixed, $\Psi^\tau(t, x) \in V_\tau$ for all large t.

Moreover, by Lemma 7.6,

$$W_2 := \overline{\bigcup_{\tau \in \Lambda} \Psi^\tau(2, V_\tau)}$$

is compact in $\mathcal{C}$.

It remains to show $W_2 \subset U$. For any $x \in \bigcup_{\tau \in \Lambda} \Psi^\tau(2, V_\tau)$, there exists some $\tau \in \Lambda$ and $y \in V_\tau$ such that $x = \Psi^\tau(2, y)$. Let $y = (R, S(\cdot), P(\cdot))$, then

$$S'(t) > -DS(t) - kS(t)P(t) \geq -S(t)(D + kb(R_0 + 1)),$$

so $S(0) > \frac{\epsilon_0}{2}$ implies that $S(t) > \frac{\epsilon_0}{2}e^{-2q}$ for $0 \leq t \leq 2$, where $q = D + kb(R_0 + 1)$. Thus $\widetilde{\pi}_S(x)(0) = S(2)$ is bounded away from 0 by a constant independent from τ. The parallel result holds for P as well. Therefore, $W_2 \subset U$ and it is relatively compact in U.

By Theorem 2.2 in [23], there exists $\tau_0 > 0$ and a continuous map $\widehat{x} : [0, \tau_0) \to U$ such that $\widehat{x}(0) = E_{SP}^0$, $\Psi^\tau(t, \widehat{x}(\tau)) = \widehat{x}(\tau)$ for $t \geq 0$ and $\Psi^\tau(t, x) \to \widehat{x}(\tau)$ for all $x \in U$ and $\tau \in [0, \tau_0)$. However, for every $\tau \in [0, \tau_0)$, since E_{SP}^τ is the only equilibrium in U, we conclude that $\widehat{x}(\tau) = E_{SP}^\tau$. Moreover, for every given $\tau \in [0, \tau_0)$, E_{SP}^τ attracts all points in U. □

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