We study the lysis timing of a bacteriophage population by means of a continuously infection-age-structured population dynamics model. The features of the model are the infection process of bacteria, the death process, and the lysis process which means the replication of bacteriophage viruses inside bacteria and the destruction of them. The time till lysis (or latent period) is assumed to have an arbitrary distribution. We have carried out an optimization procedure, and we have found that the latent period corresponding to maximal fitness (i.e. maximal growth rate of the bacteriophage population) is of fixed length. We also study the dependence of the optimal latent period on the amount of susceptible bacteria and the number of virions released by a single infection. Finally, the evolutionarily stable strategy of the latent period is also determined as a fixed period taking into account that super-infections are not considered.

**Keywords**: Bacteriophage infection; random lysis timing; partial differential equations; fitness optimization.

AMS Subject Classification: 35L, 47D06, 92

1. **Introduction**

Most bacteriophage viruses (etymologically “bacteria eater”) replicate inside bacteria causing the death of their host. This process starts when a phage (for short) is adsorbed by the receptors of the cell membrane and injects its genetical material through it.
After some time interval the cell machinery of the bacterium synthesizes copies of the virus nucleic acid, the proteins of the capsules and the tails of the new phages. Finally the bacterium lyses (“explodes” and dies) releasing an amount of new virions (called burst size) which widely varies between 5 and 250 depending on the strain. This process, replication of phages linked to destruction of bacteria, obviously indicates that the treatment of bacterial infections using phages can be useful as a therapeutic tool. Indeed, after being almost forgotten due to the discovery of antibiotics, the so-called phage therapy is nowadays becoming more popular since the emergence of the antibiotic resistances. In particular, this work, though it has no therapeutic implications, was partially motivated by a research project of the Department of Genetics and Microbiology at the Universitat Autònoma de Barcelona, whose goal is the control of Salmonella infections in animal farms by means of bacteriophages.

The already mentioned period of time between the infection (the adsorption of a virus particle by a bacterium) and the lysis is called lysis timing or latent period. According to experimentalists, the average length of the lysis timing is from 15 minutes (such a short latency time has been observed in the adsorption of a phage called C78 by a strain of Salmonella enterica) up to 45 minutes in the case of other Salmonella phages for instance. Here we focus on this latent period and how it is related to the virus population growth rate. More precisely, we compute the latent period giving the maximal growth rate of the phage population, among a very general form of latent periods. In Ref. 11, a similar computation was performed in order to find the optimal age at sex-reversal in sequential hermaphrodite populations, also assuming an a priori very general form of the possible distributions of the age at sex-reversal. See also Ref. 29, Chap. 22 and Ref. 24 for a computation of optimal vaccination schedules among all possible age-dependent vaccination strategies.

In many papers of epidemiological models, latent periods (understood in general as the period when infected individuals are not infectious yet) are typically assumed to be either exponentially distributed or fixed. This assumption yields ordinary differential equations in the first case, and delay differential equations in the second one. Nevertheless, an epidemic model where all infection stages have arbitrary length distributions is considered in Refs. 18 and 19 for instance.

In this paper, we introduce and analyze a structured bacteriophage population model where we extend the previous assumptions in the sense that we consider a general probability distribution function for the length of the latent period.

In the literature we find several papers on the dynamics of marine plankton bacteriophage infections. In Ref. 3, the latent period is assumed to be exponentially distributed and in Ref. 4 instead, the latent period has a fixed length. Moreover, in Ref. 20 the authors include in addition spatial diffusion of the population. See also Refs. 5 and 28.

The main goal of the paper is to show the existence of an optimal lysis timing which can be observed in laboratory experiments (also in phage therapy) for short periods of time. These experiments pretend to annihilate the maximum number of
bacteria, by infecting them, in a short period of time. Therefore the paper focuses on
the initial phase of the infection, as described by a linear model, and considers the
phage growth rate as a fitness measure which is not necessarily related to a long-term
evolutionary process. In laboratory experiments, the interest is often limited to short
periods of time for several reasons, the rise of resistant bacteria populations being the
most important. More importantly, in phage therapy of bacterial infections, the goal
is to reduce the bacteria population in a short term to give the immune system the
opportunity to strike back and eliminate the bacteria before the resistant bacteria
population can grow. So the phage strain with the fastest growth rate during the
initial phase of the infection is the appropriate strain for these purposes.

References 1, 2, 21, 26, 33, and 34 use the phage growth rate as a fitness measure to
address a study of the latent period, both from the modeling and experimental points
of view. The authors always assume a fixed latent period and artificially keep con-
stant (in experiments) and consider constant (in models) the density of uninfected
bacteria. For a discussion on the suitability of the phage growth rate as a good
predictor of the long-term evolution, see Sec. 5.

The paper is organized as follows. In Sec. 2, a bacteriophage infection is described
and a linear (infection age)-structured population model with a general lysis timing is
introduced. Two versions of the system are stated depending on whether the prob-
ability distribution of the latent period is assumed to be absolutely continuous (to
have a density function) or not. In the first case the model reduces to an age-structured
population dynamics system given by a partial differential equation coupled to an
integro-differential equation whereas the second, which includes the former as a par-
ticular case, is directly formulated as a delay equation. Existence and uniqueness of
global solutions, which yield a strongly continuous positive linear semigroup, is shown
in Appendix A through the reduction to a single (Volterra) integral equation for the
number of phages. In Sec. 3, the bacteriophage fitness is defined as the growth bound of
the solution semigroup. Exponentially growing solutions (separate variables sol-
utions) are computed. The phage reproduction number (i.e. the expected number
of virions produced by a single phage) is also given. The control of the growth bound
is reduced to the computation of the eigenvalues of the infinitesimal generator.
There exists at most one real eigenvalue. Finally, Sec. 4 contains the main result
(Theorem 4.1) which states that the latent period giving the maximal fitness corre-
sponds to a fixed length period even when it is admitted that potentially the lysis
process may take place at a different infection-age for each bacterium. Moreover, we
show that the optimal value of the latent period is a decreasing function of the quality
of the bacteria (e.g. the maximum burst size) and that it is also decreasing with respect
to the number of uninfected bacteria provided their mortality is smaller than a critical
value. We have found that the quality of the bacteria has a stronger influence on the
optimal latent period than the quantity of the disease-free ones. In Sec. 5, in addition,
we change the goal to the study of the evolution of lysis timing in a large time scale, and
we have determined the evolutionarily stable strategy (ESS) of the latent period using
either the phage growth rate or equivalently the phage reproduction number as the fitness measure.

2. Model Formulation

We consider a micro-epidemiology model made up of free bacteriophage viruses infecting a population of bacteria with variable *lysis timing* (also called latent period) as the main new feature of the model.

In the *lytic cycle*, the interaction between phages and bacteria is described as follows: viruses attack susceptible bacteria which get infected in the sense that a virus successfully injects its genetical material (adsorption) through the bacterial membrane. Then, after an *eclipse period* $E \geq 0$ (where no viral particles can be seen inside the cell, and possibly even outside, and the bacterium is forced to manufacture viral products which will become part of the new virions), the assembly of new virions starts until the bacterium dies by lysis, that is, the bacterium explodes releasing new virions which are then free to attack other infected-free bacteria. The number of particles released in each lysis is called the *burst size*. See Fig. 1 for a schematic representation of the process. Let us remark that we are considering a type of bacteriophages (e.g. T4 phages) that inhibits the replication of the infected bacteria, so only uninfected bacteria are capable of reproducing by division, see Ref. 33, p. 22, or Ref. 2, p. 4234. We assume that these populations inhabit a solution and are measured in units of number of viruses/bacteria per unit of volume.

**Fig. 1.** Viral-bacteria model. Free bacteriophages (“bacteria-eater”) encounter susceptible bacteria that become infected at a rate $kSP$, where $k$ is the adsorption rate. The latent period $T$, the time-span from infection to lysis which include an eclipse period $E$, is taken as a random variable. After lysis, new virions are released according to $L(t) = \int_0^t B(\tau)e(\tau, t) \frac{dF(\tau)}{1-F(\tau)}$, where $B(\tau)$ is the burst size and $F(\tau)$ is the probability distribution of the latent period. $\frac{1}{1-e} + E[T]$ is the expected time of the infection cycle.
The variability of the lysis timing in the bacterial population is incorporated into the model by considering that this latent period \( T > 0 \), which is defined as the time elapsed between infection and lysis, is a positive random variable with a given probability distribution function \( P(T \leq \tau) = F(\tau) \), where \( \tau \) is the time since infection. So, the precise meaning of the latent period in this paper is the random period between the moment of being infected and the moment of releasing the infecting agent. The eclipse period \( E \) (i.e. from infection until the appearance of new virions inside the bacterium) constrains the random latent period in the sense that \( P(T \leq E) = 0 \).

Bacteria are divided according to the disease stage: uninfected (susceptible) \( S(t) \) and infected (but not infectious). Since we are considering that the lysis timing (latent period) may differ from one bacterium to another, we introduce the variable \( v(\tau, t) \) as the density of infected bacteria with respect to the infection age (i.e. the time that has passed since the infection) at time \( t \). On the other hand, the infecting agent is the free bacteriophage virus population \( P(t) \).

We also consider the demographic processes of natural mortality \( \delta > 0 \) in bacteria and the degradation of viruses \( m > 0 \).

Finally, let us point out that we are considering populations homogeneously distributed in space, and that super-infections are ignored.

For a general nonlinear model, one can consider that the dynamics for the susceptible bacteria in the absence of viruses is given by \( S'(t) = r(S(t), t) \) with the latter function being defined according to a specific situation, whereas in case of viral infection one has \( S'(t) = r(S(t), t) - kS(t)P(t) \) if we assume that the incidence rate (number of new infected bacteria per unit of time) follows the law of mass action. The proportionality factor \( k > 0 \) is called adsorption rate. However, here, we will assume that the population of susceptible bacteria is at equilibrium \( S(t) = S^* \). For simplicity, from now on, let \( S \) denote the constant \( S^* \). For instance one can think in a laboratory population where there is a suitable inflow of uninfected bacteria in order for this population to maintain constant, see Refs. 1, 2, 21, 26, 33, and 34. Also one can think in the initial phase of the infection where a small amount of phages is introduced in a population of totally infected-free bacteria at equilibrium and a linear exponential growth/decay of the infected bacteria and phages takes place.

Now, let us assume for awhile that the latent period \( T > 0 \) is an absolutely continuous random variable, i.e. its probability distribution function is an absolutely continuous function. In this case the (infection age)-structured model can be described by the following linear system which is a combination of a first-order partial differential equation with a boundary condition and an ordinary differential equation:

\[
\begin{align*}
\frac{\partial v}{\partial t}(\tau, t) + \frac{\partial v}{\partial \tau}(\tau, t) &= -\delta v(\tau, t) - \frac{F'(\tau)}{1 - F(\tau)} v(\tau, t), \quad \tau < l, \\
v(0, t) &= kSP(t), \\
\frac{dP}{dt}(t) &= -mP(t) - kSP(t) + \int_0^l B(\tau)v(\tau, t) \frac{dF(\tau)}{1 - F(\tau)}.
\end{align*}
\] (2.1)
The second term on the right-hand side of the third equation takes into account only the losses due to adsorptions of phages by uninfected bacteria. The consideration of super-infections, i.e. adsorptions of phages by infected bacteria, would add an extra nonlinear term in the equation for phages. This possibility will be ignored here.

See Refs. 25 and 23 for general physiologically structured population models using PDEs. See also Ref. 9 for a class of PDE models with distributed state-at-birth. We recall that the latent period is distributed according to $F(\tau) = 0$ and, accordingly, the maximum age of infection $l$ ($> E$) is given by

$$l := \sup\{\tau : F(\tau) < 1\} \leq \infty,$$

that is, the lysis may occur between 0 and $l$, and the rate $F'(\tau) / (1 - F(\tau))$ represents the per capita virus-induced mortality rate or the per capita lysis rate. Notice that if the maximum age of infection is finite (the maximum value of the latent period), then it is $l = F^{-1}(1)$, with the latter being the generalized inverse of $F$.

On the other hand, the burst size $B(\tau)$ (the amount of new virions released per lysis) as a function of the infection age at lysis is assumed to be bounded and continuous, $B(\tau) \equiv 0$ for $\tau \leq E$ and strictly increasing for $\tau > E$. Moreover, we assume that the maximum burst size

$$R := \lim_{\tau \to l} B(\tau)$$

is larger than 1 since otherwise there is no possibility for the spread of the infection. The quantity $R$ is interpreted as a measure of the quality of the bacteria. The total amount of new virions released per unit of time is given by

$$\int_{E}^{l} B(\tau) v(\tau, t) \frac{d\tau}{1 - F(\tau)} \leq \int_{E}^{l} B(\tau) v(\tau, t) \frac{F'(\tau)}{1 - F(\tau)} d\tau.$$

The lysis rate and the number of particles released are derived as follows. The number of lysis occurred in the time interval from $t$ to $t + dt$ of bacteria with infection age between $\tau < l$ and $\tau + dt$ is the number of bacteria with infection age between $\tau$ and $\tau + dt$, at time $t$, times the probability that a $\tau$-aged bacterium at time $t$ dies by lysis between $t$ and $t + dt$. In symbols,

$$v(\tau, t) dt P(\tau < T \leq \tau + dt | T > \tau) = v(\tau, t) dt \frac{P(\tau < T \leq \tau + dt)}{P(T > \tau)}$$

$$= v(\tau, t) dt \frac{F(\tau + dt) - F(\tau)}{1 - F(\tau)}.$$

Therefore, dividing by $dt$ and taking the limit as $dt \to 0$, one has that the measure of lysis per unit of time is

$$v(\tau, t) \frac{F'(\tau)}{1 - F(\tau)} d\tau = v(\tau, t) \frac{dF(\tau)}{1 - F(\tau)},$$

that is, the instantaneous lysis rate at infection age $\tau$ is $v(\tau, t) F'(\tau) / (1 - F(\tau))$. Finally, multiplying the measure of lysis by the burst size and integrating over the age-span, one
gets the total number of new virions released per unit of time

\[ \int_0^t B(\tau)v(\tau, t) \frac{dF(\tau)}{1 - F(\tau)}. \]

Let us point out that this total number, for some initial condition \((v(\tau, 0), P(0)) = (v_0(\tau), P_0)\), with \(v_0(\cdot) \in L^1_{\text{loc}}(0, l)\) and \(P_0 \geq 0\), and for a particular probability distribution, could be infinite. See Ref. 29, Sec. 13.6, for a general discussion on the output of a stage with arbitrary length duration.

In order to extend the model to a general random variable \(T > 0\), e.g. not necessarily absolutely continuous, we can write an “integrated” version of system (2.1) where the derivative \(F'\) of the probability distribution of the latent period disappears from the system. Indeed, defining

\[ \nu := m + kS > 0, \]

integrating along the characteristic lines the partial differential equation in (2.1), and using the variation of the constants formula to the ordinary differential equation in (2.1), we obtain the following linear system in integrated form

\[
\begin{cases}
\nu(\tau, t) = \\
\quad \begin{cases}
  kSP(t - \tau)(1 - F(\tau))e^{-\nu\tau}, & \tau < t, \\
  v_0(\tau - t) \frac{1 - F(\tau)}{1 - F(\tau - t)} e^{-\nu\tau}, & \tau > t,
\end{cases}\\
\quad P(t) = P_0 e^{-\nu t} + \int_0^t L(s)e^{-\nu(t-s)} ds, \\
\quad L(t) = \int_{(0,t]} B(\tau)v(\tau, t) \frac{dF(\tau)}{1 - F(\tau)},
\end{cases}
\]

where \(dF\) is defined by \(P(\tau_1 < T \leq \tau_2) = \int_{(\tau_1, \tau_2]} dF(\tau)\) as it is usual in probability/measure theory. The system above is interpreted as follows. The first equation says that the density of bacteria with infection age \(\nu < t\) at time \(t\) is equal to the density of bacteria infected at time \(t - \nu\), \(v(0, t - \nu) = kSP(t - \nu)\), times the probability of not yet lysed at age \(\nu\), and times the probability of surviving to age \(\nu\). On the other hand, the second equation says that the density of bacteria with infection age \(\nu > t\) at time \(t\) is equal to the initial density of bacteria with infection age \(\nu - t\), \(v(\nu - t, 0) = v_0(\nu - t)\), times the probability of not yet lysed at age \(\nu\) provided that it has no lysed at age \(\nu - t\), and times the probability of surviving from age \(\nu - t\) to age \(\nu\). The third equation in (2.3) is just the integral version of the linear inhomogeneous ordinary differential equation in (2.1).

If the latent period \(T > 0\) is an absolutely continuous random variable, it can be shown that systems (2.1) and (2.3) are equivalent in the sense that a solution of (2.1) with initial condition \((v_0(\cdot), P_0)\) is also solution of (2.3), and that all solutions of (2.3) fulfill the differential system (2.1) taking into account that the left-hand side of the partial differential equation is understood as the “directional derivative” in the direction of the vector \((1, 1)\), and understanding that a solution of (2.1)_3 is given by the variation of the constants formula by definition.
In Appendix A, we show the existence and uniqueness of global solutions to the general model (2.3) which yield a strongly continuous positive semigroup of bounded (linear) operators. The key point is that system (2.3) can be rewritten as a single integral equation for the number of phages $P(t)$:

$$
P(t) = P_0 e^{-\nu t} + \int_0^t \left( kS \int_{[0,s]} B(\tau) P(s - \tau) e^{-\delta \tau} dF(\tau) \right) d\tau + e^{-\delta s} \int_{[s,l]} B(\tau) v_0(\tau - s) \frac{dF(\tau)}{1 - F(\tau - s)} e^{-\nu (t-s)} ds,
$$

(2.4)

with $\bar{s} := \min\{s, l\}$. Once we know the solution of (2.4), the density of infected bacteria $v(\tau, t)$ is recovered by the first equation in (2.3). For nonlinear equations in a similar form of Eq. (2.4) arising in structured population dynamics, see Refs. 14 and 15.

In addition, Eq. (2.4) can be rewritten as a Volterra integral equation. Indeed, defining the function

$$
P_1(t) = e^{-\nu t} \left( P_0 + \int_0^t \int_{[s,l]} B(\tau) v_0(\tau - s) \frac{dF(\tau)}{1 - F(\tau - s)} e^{(\nu - \delta)s} ds \right),
$$

which depends on the initial condition, and using Fubini’s theorem several times, one has that

$$
P(t) = P_1(t) + kS \int_{[0,l]} B(\tau) P(s - \tau) e^{-\nu(t-s)} e^{-\delta \tau} \chi_{[0,\infty)}(s - \tau) dF(\tau) ds
$$

$$
= P_1(t) + kS \int_{[0,l]} B(\tau) e^{-\delta \tau} \left( \int_0^t P(s - \tau) e^{-\nu(t-s)} ds \right) dF(\tau)
$$

$$
= P_1(t) + kS \int_{[0,l]} B(\tau) e^{-\delta \tau} \left( \int_0^{t-\tau} P(s) e^{-\nu(t-s-\tau)} ds \right) dF(\tau)
$$

$$
= P_1(t) + kS \int_0^t P(s) \left( \int_{[0,t-s]} B(\tau) e^{-\delta \tau} e^{-\nu(t-s-\tau)} dF(\tau) \right) ds.
$$

Hence, with a change of variables we arrive at a linear integral convolution equation for the number of phages,

$$
P(t) = P_1(t) + \int_0^t P(t-s) \gamma(s) ds,
$$

(2.5)

with $\gamma(s) := kS \int_{[0,s]} B(\tau) e^{-\delta \tau} e^{-\nu(s-\tau)} dF(\tau)$. The approach to structured population dynamics using Volterra integral equations can be found in Refs. 29, 16, 17, or 22 where there are theorems on existence and uniqueness, and asymptotic behavior of the solutions. Nevertheless, we follow the approach of the theory of operator semigroups, see, for instance, Ref. 35.

Next, let us illustrate two examples which are particular cases of the present model.
Firstly, if we assume a latent period exponentially distributed thereafter the eclipse period, that is, $F(\tau) = 1 - e^{-\alpha(\tau-E)}$ for $\tau \geq E, \alpha > 0$, then the expected latent period turns out to be $E[T] = E + \frac{1}{\alpha}$. If in addition we replace the burst size $B(\tau)$ by its mean value $\bar{B} > 1$ and introduce two new state variables $I_0(t) := \int_0^E v(\tau, t)\, d\tau$ and $I_E(t) := \int_E^\infty v(\tau, t)\, d\tau$, then the linear system (2.1) reduces by integration over $(0, \infty)$ to the following system of linear delay differential equations

$$
\begin{align*}
\frac{dI_0}{dt}(t) &= kSP(t) - v(E, t) - \delta I_0(t), \\
\frac{dI_E}{dt}(t) &= v(E, t) - (\delta + \alpha)I_E(t), \\
\frac{dP}{dt}(t) &= -(m + kS)P(t) + \alpha\bar{B}I_E(t),
\end{align*}
$$

with $v(E, t) := v_0(E - t) e^{-\delta t}$ for $t < E$ and $v(E, t) := kSP(t - E) e^{-\delta t}$ for $t > E$. Notice that if the eclipse period is neglected, i.e. $E = 0$, then the system further reduces to a planar system of ordinary differential equations for the population sizes of infected bacteria and phages. In Ref. 3 a nonlinear ordinary differential equation-based ecological model of marine bacteriophages is studied, where the latent period is taken exponentially distributed.

The second example is the following. If we assume a fixed latent period instead, that is, $F(\tau) = \chi_{[l, \infty)}(\tau)$ with $E[T] = l > E$, and introduce a new state variable $I(t) := \int_0^l v(\tau, t)\, d\tau$ which is the total number of infected bacteria, then from (2.4) and (2.3), the model reduces to the following system of linear delay differential equations

$$
\begin{align*}
\frac{dI}{dt}(t) &= kSP(t) - v_-(l, t) - \delta I(t), \\
\frac{dP}{dt}(t) &= -(m + kS)P(t) + B(l)v_-(l, t),
\end{align*}
$$

with $v_-(l, t) := v_0(l - t) e^{-\delta t}$ for $t < l$ and $v_-(l, t) := kSP(t - l) e^{-\delta t}$ for $t > l$. Indeed, the second equation in (2.7), which is uncoupled from the first one, is the differential version of Eq. (2.4) at $F = \chi_{[l, \infty)}$, and the first equation in (2.7) is the differential form of $I(t) = kS\int_0^l P(t - \tau) e^{-\delta \tau}\, d\tau + e^{-\delta l} \int_l^1 v_0(\tau - t)\, d\tau$, with $\bar{l} := \min\{t, l\}$, which comes from the first equation in (2.3) also for $F = \chi_{[l, \infty)}$. See Refs. 4 and 20 where the previously cited model is treated assuming a fixed value of the latent period which leads to delay equations as in (2.7). Even though in Ref. 20 the authors already suggest the possibility of considering the latent period as given by a probability distribution function, as in systems (2.1) and (2.3).

3. Bacteriophage Fitness

3.1. Growth bound of the solution semigroup

We are interested in the optimal probability distribution function of the latent period, in the sense that this probability distribution gives the maximal growth rate
of the viral population (i.e. the maximal growth bound of the solution semigroup of (2.3), see Proposition A.2).

In order to reduce the control on the growth bound \( \omega_0 \) of the semigroup, denoted by \( S(t) \), to the computation of the eigenvalues of its infinitesimal generator, it is very useful to use the definition of the so-called essential growth bound:

\[
\omega_e = \lim_{t \to 0} \frac{\ln(d(S(t), \mathcal{K}))}{t},
\]

where \( \mathcal{K} \) is the set of all compact linear operators and for a bounded linear operator \( B \), the distance to this set is defined by \( d(B, \mathcal{K}) = \inf_{K \in \mathcal{K}} \|B - K\| \). Indeed, the following holds:

\[
\omega_0 = \max\{\omega_e, s(A)\},
\]

where \( s(A) \) is the spectral bound, i.e. the supremum of the real parts of the spectral values of the infinitesimal generator \( A \). Moreover, any spectral value with real part larger than \( \omega_e \) is necessarily an eigenvalue (see, for instance, Ref. 12, Proposition 8.6).

Next we show

**Proposition 3.1.** The essential growth bound of the solution semigroup \( S(t) \) of system (2.3) is less than or equal to \( -\delta \) (the mortality of infected bacteria).

**Proof.** As usual in structured population dynamics, this follows from a decomposition of the solution semigroup for any \( t \) in sum of two operators as follows:

\[
S(t) (v_0(\cdot), P_0) := \left( v(\cdot, t) \chi_{[0, \min\{t, l\}]}(\cdot) P(t) \right) + \left( v(\cdot, t) \chi_{[\min\{t, l\}, l]}(\cdot) 0 \right),
\]

where \( v(\tau, t) \) is given by (2.3). The second term on the right-hand side is obviously exponentially decaying at a rate at least equal to \( -\delta \). The first one is, for a fixed \( t \), a compact operator on \( X := L^1(0, t) \times \mathbb{R} \) since it can be written as a composition of three bounded linear operators, the second of which is compact. Namely, \( T_1 \) mapping the initial condition \( (v_0, P_0) \) in \( X \) to the function \( P \) in \( W^{1,1}(0, t) \) (see Appendix A), \( T_2 \) mapping \( W^{1,1}(0, t) \) to \( L^1(0, t) \times \mathbb{R} \) and defined by

\[
T_2 P = \left( \begin{array}{c} P \\ P(t) \end{array} \right),
\]

whose first component, the injection of \( W^{1,1} \) in \( L^1 \), is a compact Sobolev embedding whereas the second is the evaluation at the final point of the interval (continuous, and obviously compact, on \( W^{1,1}(0, t) \)) and, finally \( T_3 \), mapping \( L^1(0, t) \times \mathbb{R} \) in \( L^1(0, l) \times \mathbb{R} \), its first component given by the first equation in (2.3) extended to \( (0, l) \) as in (3.1), and the second one by the identity operator in \( \mathbb{R} \).

As a consequence, the existence of an eigenvalue with a real part larger than \( -\delta \) will imply \( \omega_0 = s(A) \), which will then be a (real) eigenvalue (the spectral bound of a positive semigroup always belongs to the spectrum of the generator). Hence the computation of \( \omega_0 \) will reduce to finding the larger real solution of the characteristic
equation (see below) whenever we show that there is a real solution larger than $-\delta$ of this equation. Actually we will show that the characteristic equation has at most a real solution.

3.2. Characteristic equation

In this section, we are going to compute the point spectrum of the infinitesimal generator of the solution semigroup, in order to determine the growth bound of the semigroup.

Let $A$ be the infinitesimal generator of the solution semigroup $S(t)$. If $\lambda$ is an eigenvalue of $A$, then $e^{\lambda t}$ is an eigenvalue of the operator $S(t)$. So, the eigenfunctions, $c(\varphi(\tau), 1)$ with $c$ an arbitrary constant, corresponding to an eigenvalue $\lambda$ are computed as solutions of system (2.3) in the form:

\[
\begin{align*}
 v(\tau, t) &= e^{\lambda t} \varphi(\tau), \\
P(t) &= e^{\lambda t},
\end{align*}
\]

Therefore,

\[
\begin{align*}
 e^{\lambda t} \varphi(\tau) &= \begin{cases} 
 kSe^{\lambda(t-\tau)}(1 - F(\tau))e^{-\delta \tau} & \tau < t \\
 \varphi(\tau - t) \frac{1 - F(\tau)}{1 - F(\tau - t)} e^{-\delta t} & \tau > t
\end{cases} \\
 \lambda &= -\nu + \hat{L}, \quad \hat{L} = \int_{(0, l]} B(\tau) \frac{\varphi(\tau)}{1 - F(\tau)} dF(\tau),
\end{align*}
\]

where the first equality follows by direct substitution whereas the second one comes from a change of integration variables and an explicit integration in (2.3) after substitution of (3.2). For fixed $\tau$ and $t > \tau$, the first equation in (3.3) yields $\varphi(\tau) = kSe^{-(\lambda + \delta)\tau}(1 - F(\tau))$, which solves the second part for $\tau > t$, as it is easily checked.

Accordingly, $\hat{L} = kS \int_{(0, l]} B(\tau) e^{-(\lambda + \delta)\tau} dF(\tau)$ and we get the following characteristic equation for $\lambda \in \mathbb{C}$:

\[
\lambda = -\nu + kS \int_{(0, l]} B(\tau) e^{-(\lambda + \delta)\tau} dF(\tau).
\]

Notice that this equation can be written as

\[
1 = \frac{kS \int_{(0, l]} B(\tau) e^{-(\lambda + \delta)\tau} dF(\tau)}{\lambda + m + kS},
\]

where the expression on the right-hand side at $\lambda = 0$ is the parameter $\mathcal{R}_0$:

\[
\mathcal{R}_0(S, F) = \frac{kS}{m + kS} \int_{(0, l]} B(\tau) e^{-\delta \tau} dF(\tau)
\]

which is interpreted here as the expected number of virions produced by a phage during its lifetime (phage reproduction number). Indeed, it is the product of the
probability that a virus is adsorbed before being destroyed \( \frac{kS}{m+kS} \) times the expected number of virions released by a single infection.

To end this section, let us show two results about Eq. (3.4) which will be used in the next section.

Firstly, let us show that Eq. (3.4) implicitly defines a real function \( \lambda_F \), i.e. a real eigenvalue as a function of the probability distribution \( F \). Let us define the function \( G \) as

\[
G(\lambda, F) := \lambda + \nu - kS \int_{[0,l]} B(\tau) e^{-(\lambda+\delta)\tau} dF(\tau),
\]

for \( \text{Re}(\lambda) \geq -\delta \) and for all probability distribution function \( F \). For every probability distribution \( F \), if there exists a real-valued \( \lambda_F \) such that \( G(\lambda_F, F) = 0 \), then it is unique. Indeed, this follows from the fact that the real function \( \lambda \in (-\delta, \infty) \mapsto G(\lambda, F) \) is strictly increasing and continuous. Notice also that a necessary and sufficient condition for the existence of \( \lambda_F \geq -\delta \) is \( G(-\delta, F) \leq 0 \).

Now, let us see that we can restrict the characteristic equation to real values if we are interested in the rightmost eigenvalue (i.e. the eigenvalue with larger real part).

**Lemma 3.1.** If \( \lambda \in \mathbb{C} \setminus \mathbb{R} \) is such that \( G(\lambda, F) = 0 \), then there exists a unique real value \( \tilde{\lambda} \) with \( \text{Re}(\lambda) < \tilde{\lambda} \) fulfilling \( G(\tilde{\lambda}, F) = 0 \).

**Proof.** First notice that \( \text{Re} G(\lambda, F) \geq G(\text{Re} \lambda, F) \), and that equality implies

\[
\text{supp} \ dF \subset \{ \tau > 0 : \cos(\tau \text{Im} \lambda) = 1 \} \subset \{ \tau > 0 : \sin(\tau \text{Im} \lambda) = 0 \}
\]

and hence, \( \text{Im} G(\lambda, F) = \text{Im} \lambda \). Since \( \lambda \) is not real and \( G(\lambda, F) = 0 \), it follows that \( G(\text{Re} \lambda, F) < 0 \). Finally, since for real \( z \), \( G(z, F) \) strictly increases and has an infinity limit at infinity, the latter gives the claim.

Finally, notice that it readily follows from (3.4) and (3.6) that \( \lambda_F \) has the same sign as \( \mathcal{R}_0 - 1 \). This is a general result which is shown in Ref. 32 for ODE models and in Ref. 30 for infinite-dimensional models.

### 4. Optimization of the Latent Period

If condition \( m - \delta \geq kS(R - 1) \) holds, where \( R > 1 \) is defined in (2.2), then the growth bound of the solution semigroup satisfies \( \omega_0 \leq -\delta < 0 \). Indeed, let us assume the contrary, i.e. \( \omega_0 > -\delta \), which implies that the growth bound is equal to the dominant eigenvalue of the infinitesimal generator and therefore it coincides with the unique real solution of the characteristic equation. However, this is not possible since the function \( G(\lambda, F) \) is strictly increasing in \( \lambda \) and

\[
G(-\delta, F) = -\delta + \nu - kS \int_{[0,l]} B(\tau) dF(\tau) > -\delta + \nu - kSR
\]

\[
= m - \delta - kS(R - 1) \geq 0,
\]

and therefore the claim follows.
Moreover, since here $\omega_0 < 0$ then it follows that the bacteriophage virus population $P(t)$ goes to extinction. Let us remark that in this case it would still make sense to find the probability distribution that optimizes the decay of the population of phages in the sense that the extinction of the phages occurs in the slowest possible way. Nevertheless, we will concentrate on the biologically more interesting case which follows from assuming the strict opposite inequality since then the growth bound of the semigroup can be positive. In this new situation, i.e.

$$m - \delta < kS(R - 1), \tag{4.1}$$

we can readily assure that there exist some probability distribution functions $F$ for which a real solution $\lambda_F$ of the characteristic equation (3.4) exists and $\lambda_F > -\delta$. For instance, one can take the distribution $F(\tau) := X_{[\tau_0, \infty)}(\tau)$ with $\tau_0$ any number large enough to fulfill $G(-\delta, X_{[\tau_0, \infty)}) = m - \delta - kS(B(\tau_0) - 1) < 0$. So, we will assume (4.1) throughout this section.

If $F$ is a probability distribution such that $\lambda_F > -\delta$ then, since $\omega_e \leq -\delta$, $\lambda_F$ is the growth bound of the solution semigroup and also the dominant eigenvalue of the infinitesimal generator. Next, we will focus on the computation of the probability distribution $\tilde{F}$ which maximizes the nonlinear functional $F \mapsto \lambda_F$, implicitly defined by $G(\lambda, F) = 0$, see (3.7).

Let $\tilde{M}$ be the vector space of the real functions $F(x) = \mu([0, x])$ for some real measure $\mu$ on $\mathbb{R}^+$ such that the norm $\|F\|_{\tilde{M}} := \int_0^\infty e^{-x} |F(x)| \, dx$ is finite. Notice in particular that these functions are right-continuous. In this space let us define the following subsets:

$$M := \{ F \in \tilde{M} : \text{non-decreasing and } F(x) \in [0, 1] \}$$

and $M_1$ the subset of $M$ of the functions satisfying in addition that

$$\lim_{x \to \infty} F(x) = 1.$$

**Proposition 4.1.** The set $M$ is a compact subset of the normed vector space $\tilde{M}$.

**Proof.** Let us consider a sequence $\{ F_n \} \in M$. We have to show that there exists a subsequence which is convergent in $M$. By the selection theorem of Helly and Bray (see e.g. the Appendix in Ref. 11, or Ref. 7, Theorem 8.6), there exists a subsequence $\{ F_{n_k} \}$ which converges pointwise to a non-decreasing and right-continuous function $F$ from $\mathbb{R}^+$ to $[0, 1]$, for all continuity points of the limit function and hence almost everywhere in $\mathbb{R}^+$.

On the one hand, $F_{n_k}$ tends to $F$: $\|F_{n_k} - F\|_{\tilde{M}} = \int_0^\infty e^{-x} |F_{n_k}(x) - F(x)| \, dx \to 0$ by the dominated convergence theorem. On the other hand, obviously $F \in M$. Therefore $M$ is a compact set. \qed

For the functions $F$ in $M$ we recall the definition of the generalized inverse function $J_F = J$ defined on $[0, F(\infty))$ (where $F(\infty) := \lim_{x \to \infty} F(x) \leq 1$) by $J_F(y) = \inf\{ x \geq 0 : F(x) \geq y \}$. It is easy to see that $J(y) \leq x$ if and only if $y \leq F(x)$.

Now we state an auxiliary lemma that will be used in the proof of Proposition 4.2.
Lemma 4.1. Let $F \in M$ and let $h(x)$ be an integrable function on $[0, \infty)$ with respect to the measure $dF$. Then
\begin{equation}
\int_{[0, \infty)} h(x) dF(x) = \int_0^{F(\infty)} h(J(y)) dy = \int_0^1 g(y) dy,
\end{equation}
where $g(y) = h(J(y))$ for $y < F(\infty)$ and $g(y) = 0$ otherwise.

Proof. Let us write $\mu$ for the Lebesgue measure (and $d\mu(x) = dx$). Then we have, for any $0 \leq x' < x$,
\begin{align}
(\mu J^{-1})(x', x] &:= \mu(J^{-1}(x', x]) = \mu(\{y \geq 0 : J(y) \in (x', x]\}) \\
&= \mu(\{y \geq 0 : F(x') < y \leq F(x]\}) = F(x) - F(x') = dF((x', x]).
\end{align}

So, by the change of variable theorem (see, for instance, Ref. 6, Theorem 16.12),
\begin{equation}
\int_0^{F(\infty)} h(J(y)) dy = \int_{[0, \infty)} h(x) d(\mu J^{-1})(x) = \int_{[0, \infty)} h(x) dF(x).
\end{equation}

Let us now rewrite the function $G$ defined in (3.7) as follows:
\begin{equation}
G(\lambda, F) = \lambda + m + kS(1 - L(\lambda)F),
\end{equation}
where
\begin{equation}
L(\lambda) F := \int_{\mathbb{R}^+} B(\tau) e^{-(\lambda + \delta)\tau} dF(\tau)
\end{equation}
and consider now $G(\lambda, \cdot)$ defined on all $M$.

The first part of the following proposition is a slight variant of the well-known result on equivalence of the definitions of convergence in law and weak convergence of probability measures (see, for instance, Ref. 6), being the main difference that we have convergence of the distribution functions in the norm of $M$.

Proposition 4.2. The following holds:

(1) The functional $L(\lambda) : M \to \mathbb{R}$ is well-defined for all $\lambda \geq -\delta$ and it is continuous if and only if $\lambda > -\delta$.
(2) The function $G : (-\delta, \infty) \times M \to \mathbb{R}$ is continuous.

Proof. (1) The first part of the claim is obvious. Now, let $\lambda > -\delta$ and $\{F_n\} \in M$ be a convergent sequence with limit $F \in M$. Let us show $L(\lambda) F_n \to L(\lambda) F$.

First notice that $L(\lambda) F_n$ is a bounded sequence of real numbers. Let us consider any convergent subsequence $L(\lambda) F_{n_k}$ and note that, as $F_{n_k}$ tends to $F$ in $M$, i.e. $e^{-\tau} F_{n_k}(x)$ tends to $e^{-\tau} F(x)$ in $L^1$, we then have, for a subsequence, that $e^{-\tau} F_{n_k}(x) \to e^{-\tau} F(x)$ a.e. (see Ref. 27), and consequently, $F_{n_k}(x) \to F(x)$ a.e.

For simplicity, let us denote this subsequence $F_n$. Let us also denote $J_n = J_{F_n}$ and notice that for $\lambda > -\delta$, $h(x) := B(x) e^{-\lambda - \delta x}$ is a continuous function with limit 0 at infinity.
By Lemma 4.1, the convergence of $L(\lambda)F_n$ to $L(\lambda)F$ reduces to prove that \( \int_0^1 g_n(y) \, dy \) tends to \( \int_0^1 g(y) \, dy \), and the latter follows from the bounded convergence theorem since we have \( g_n(y) \to g(y) \) a.e.

Indeed, if \( y > F(\infty) \), it reduces to show \( J_n(y) \to \infty \), since then \( h(J_n(y)) \to 0 = g(y) \). On the contrary, let us assume that there exists a bounded subsequence \( J_{n_k}(y) \) and let us choose an upper bound \( L \) such that it is a point where \( F_n \) converges. Since \( F \) is non-decreasing, we will have, using \( J_{n_k}(y) \leq L \), that \( F(L) + \varepsilon \leq F(\infty) + \varepsilon \leq y \leq F_{n_k}(L) \) for some \( \varepsilon > 0 \), a contradiction.

On the other hand, \( y < F(\infty) \) implies \( y < F_n(\infty) \) for \( n \) large enough since there exists \( \varepsilon > 0 \) and \( x \) such that \( F(x) > y + \varepsilon \) and \( F_n(x) \to F(x) \), and hence \( F_n(\infty) \geq F_n(x) \geq y + \varepsilon \) for \( n \) large enough. Then one has \( J_n(y) \to J(y) \) if \( J \) is continuous at \( y \), and so a.e. (see Ref. 6, Theorem 25.6, for instance). Finally, for \( n \) large enough, the continuity of \( h \) gives \( g_n(y) = h(J_n(y)) \to h(J(y)) = g(y) \) a.e.

Hence, going back to the subsequences notation, \( L(\lambda)F_{n_k} \to L(\lambda)F \) and therefore \( L(\lambda)F_n \to L(\lambda)F \) since we know that \( L(\lambda)F_{n_k} \) is convergent. Thus any convergent subsequence of \( L(\lambda)F_n \) has the same limit and the "if" claim follows.

On the other hand, if \( \lambda = -\delta \), then the functional \( L(\lambda) \) is not continuous. Indeed, for instance a sequence of translated Heaviside functions \( H_n \) consisting of unitary steps at \( x = n \), converges to zero in \( \mathcal{M} \):

\[
\|H_n\|_{\mathcal{M}} = \int_{\mathbb{R}} e^{-x} \, dx = e^{-n},
\]

but \( L(-\delta)H_n = \int_{\mathbb{R}} B(x) \, dH_n(x) = B(n) \), which tends to \( R > 0 \).

(2) It suffices to show the continuity of \( (\lambda, F) \mapsto L(\lambda)F \). Let \( (\lambda, F) \in (-\delta, \infty) \times M \) and let \( (\lambda_n, F_n) \) be a sequence tending to the former. Now let \( \varepsilon > 0 \), we have that

\[
|L(\lambda_n)F_n - L(\lambda)F| \leq |L(\lambda_n)F_n - L(\lambda)F_n| + |L(\lambda)F_n - L(\lambda)F|.
\]

The second term on the right-hand side is less than \( \frac{\varepsilon}{2} \) for \( n \) large enough by Part 1. The first term can be bounded as follows.

\[
|L(\lambda_n)F_n - L(\lambda)F_n| = \left| \int_{\mathbb{R}^+} B(\tau)(e^{-(\lambda_n+\delta)\tau} - e^{-(\lambda+\delta)\tau}) \, dF_n(\tau) \right|
\]

\[
\leq R \int_{\mathbb{R}^+} |e^{-(\lambda_n+\delta)\tau} - e^{-(\lambda+\delta)\tau}| \, dF_n(\tau)
\]

\[
\leq c|\lambda_n - \lambda| < \frac{\varepsilon}{2},
\]

for a suitable positive constant \( c \) whenever \( n \) is sufficiently large. Here, we have used the mean value theorem:

\[
|e^{-\tau x} - e^{-\tau x'}| \leq \tau e^{-\tau \min(x, x')} |x - x'| \leq \frac{1}{\varepsilon \min(x, x')} |x - x'|,
\]

and the fact that \( \inf_n(\lambda_n + \delta) > 0 \). \( \Box \)
Now we are concerned with the continuity of the functional \( \lambda_F \) defined on a compact subset. Let us start by choosing a \( \delta < \delta \) sufficiently close to \( \delta \) in order that \( G(-\delta, F) \leq 0 \) for some \( F \in M \). Recall that the latter is possible under assumption (4.1).

Let us define the set
\[
M_K := \{ F \in M : G(-\tilde{\delta}, F) \leq 0 \}.
\]
This set is obviously non-empty and closed by Proposition 4.2, and hence compact using Proposition 4.1.

**Lemma 4.2.** Under the condition \( m - \delta < kS(R - 1) \), the range of the functional \( F \mapsto \lambda_F \) restricted to the compact set \( M_K \) is contained in the interval
\[
[-\delta, kS(R - 1) - m].
\]

**Proof.** For all \( F \in M_K \), we have that \( \lambda_F \geq -\tilde{\delta} \). On the other hand, \( G(kS(R - 1) - m, F) = kS(R - L(\lambda)F) > 0 = G(\lambda_F, F) \). Hence \( \lambda_F \leq kS(R - 1) - m \) since the function \( \lambda \mapsto G(\lambda, F) \) is increasing.

**Proposition 4.3.** Under the condition \( m - \delta < kS(R - 1) \), the following holds:

1. The functional \( F \mapsto \lambda_F \) is continuous on the compact set \( M_K \).
2. The functional \( F \mapsto \lambda_F \) restricted to \( M_K \) has an absolute maximum point \( \hat{F} \).

**Proof.** Let \( \{ F_n \} \in M_K \) be a sequence with limit \( F \in M_K \).

Let us consider \( \lambda_n := \lambda_{F_n} \geq -\tilde{\delta} \) fulfilling \( G(\lambda_n, F_n) = 0 \). By Lemma 4.2, there exist convergent subsequences \( \{ \lambda_{n_k} \} \). It suffices to see that their limit \( \bar{\lambda} \geq -\tilde{\delta} \) is equal to \( \lambda_F \). Since \( G(\lambda, F) \) is continuous at \( (\bar{\lambda}, F) \) by Proposition 4.2, then \( 0 = G(\lambda_{n_k}, F_{n_k}) \rightarrow G(\bar{\lambda}, F) \), and hence \( G(\bar{\lambda}, F) = 0 \). Therefore \( \bar{\lambda} = \lambda_F \).

Concerning the maximum of the previous proposition, we have the following

**Proposition 4.4.** Let \( \hat{F} \) be an absolute maximum point of the continuous functional \( F \mapsto \lambda_F \) restricted to \( M_K \). Then \( \hat{F} \) is also an absolute maximum point of the continuous functional \( F \mapsto L(\lambda_{\hat{F}})F \) defined on \( M \).

**Proof.** First assume that \( F \in M_K \). Since \( \hat{F} \) is an absolute maximum point of \( \lambda_F \), \( \lambda_F \leq \lambda_{\hat{F}} \) and since \( G(\lambda, F) \) is an increasing function of \( \lambda \), one has that \( G(\lambda_{\hat{F}}, \hat{F}) = 0 = G(\lambda_F, F) \leq G(\lambda_{\hat{F}}, F) \). On the other hand, if \( F \in M \setminus M_K \), then \( G(\lambda_{\hat{F}}, \hat{F}) = 0 < G(-\tilde{\delta}, F) \leq G(\lambda_{\hat{F}}, F) \), using \( \lambda_{\hat{F}} \geq -\tilde{\delta} \). Therefore,
\[
0 \leq G(\lambda_{\hat{F}}, F) - G(\lambda_{\hat{F}}, \hat{F}) = kS(-L(\lambda_{\hat{F}})F + L(\lambda_{\hat{F}})\hat{F}),
\]
and consequently, \( L(\lambda_{\hat{F}})\hat{F} \geq L(\lambda_{\hat{F}})F \) in both cases.

Before stating the main result of the section we still need the following (see also Ref. 29, Theorem B.25).

**Lemma 4.3.** Let \( \psi : \mathbb{R}^+ \rightarrow \mathbb{R}^+ \) be a continuous function with a unique absolute maximum point \( \hat{x} \). Then the functional on \( M \) defined by \( T(F) := \int_{[0, \infty]} \psi dF \) has a
unique absolute maximum point $H_\hat{x}(x) := H(x - \hat{x})$, where $H$ is the Heaviside function.

**Proof.** If $F = pH_\hat{x}$ with $p \in [0, 1)$, then obviously $T(F) < T(H_\hat{x})$. On the other hand, if $F \in M$ is different from $pH_\hat{x}$ for any $p$, then there exists a closed interval $I$ with $\mu(I) > 0$ (where $\mu$ is the real measure associated to $F$) such that $\hat{x} \notin I$. Therefore,

$$T(F) = \int_{[0,\infty)} \psi dF = \int_{I^c} \psi dF + \int_I \psi dF \leq \psi(\hat{x}) \mu(I^c) + \psi(\hat{x}) \mu(I) = \psi(\hat{x}) = T(H_\hat{x}),$$

where the strict inequality follows from the fact that $\max_I \psi < \psi(\hat{x})$. \hfill \Box

Next theorem assures the existence and uniqueness of the optimal latent period in a bacteriophage infection where the lysis timing may be variable. Moreover, we are going to show that the optimal latent period is decreasing with respect to both the number of susceptible bacteria (under a suitable bacterial mortality) and the quality of bacteria quantified by the parameter $R$ (the maximum burst size), as in a similar way in Refs. 34, 33 and 2. See also Refs. 1, 21 and 26.

Let us recall the assumptions on the burst size given in Sec. 2, $B(\tau) \equiv 0$ for $\tau \leq E$, strictly increasing for $\tau > E$, and the maximum burst size is

$$\lim_{\tau \to -1} B(\tau) = R > 1.$$

Let us rewrite the burst size as

$$B(\tau) = Rb(\tau)$$

so that the function $b(\tau)$ represents a normalized burst size with $\lim_{\tau \to -1} b(\tau) = 1$. Now we are ready to state the main result of the section.

**Theorem 4.1.** (Optimal latent period) Under the condition $m - \delta < kS(R - 1)$ and assuming that $\ln B(\tau)$ is a strictly concave function for $\tau > E$, there exists a unique probability distribution function $\hat{F}$ such that the growth bound of the solution semigroup of (2.3) $\lambda_F$ is maximal. $\hat{F}$ has the form $\hat{F}(\tau) = \mathcal{X}[\hat{l}_\lambda, \infty)(\tau)$ where $\hat{l} > E$ is the unique maximum point of the function $\tau \mapsto Rb(\tau)e^{-(\lambda + \delta)\tau}$, $\hat{\lambda} := \lambda_F$.

Moreover, if $b(\tau)$ is differentiable for $\tau > E$ then

1. $\hat{l}$ is given by the unique solution of the nonlinear equation

$$\frac{b'(l)}{b(l)} + m - \delta = kS(Rb(l)e^{-\frac{\lambda}{R}l} - 1). \tag{4.3}$$

2. Let $\ln b(\tau)$ be twice differentiable at $\tau = \hat{l}$. The optimal latent period $\hat{l}$ is strictly decreasing with respect to $R$. On the other hand, there exists a critical value $\delta_c > m$ of the bacterial mortality such that $\hat{l}$ is strictly decreasing with respect to the number of susceptible bacteria $S$ if and only if $\delta < \delta_c$. 


**Proof.** Let condition \( m - \delta < kS(R - 1) \) hold.

If \( F \in M_1 \setminus M_K \) then either \( \lambda_F \) does not exist and the growth bound of the solution semigroup is less than or equal to \( -\delta \), or \( G(-\delta, F) > 0 \) and \( \lambda_F < -\delta \). Therefore we can restrict the optimization of the growth bound to \( F \in M_K \).

By Proposition 4.3 the functional \( F \mapsto \lambda_F \) restricted to \( M_K \) has an absolute maximum point \( \hat{F} \) with value \( \hat{\lambda} := \lambda_{\hat{F}} \), which by Proposition 4.4 is also an absolute maximum point of the functional \( F \mapsto L(\hat{\lambda})F \) defined on \( M \). According to (4.2),

\[
L(\hat{\lambda})F = \int_{\mathbb{R}^+} \psi(\tau)dF(\tau)
\]

with

\[
\psi(\tau) := R b(\tau) e^{-(\hat{\lambda} + \delta)\tau}.
\]  (4.4)

The continuous function \( \psi : \mathbb{R}^+ \to \mathbb{R}^+ \) defined above has a unique absolute maximum point \( \tilde{\lambda} > E \) since \( \ln \psi(\tau) = \ln(R b(\tau)) - (\hat{\lambda} + \delta)\tau \) is strictly concave. By Lemma 4.3 with \( \psi \) defined by (4.4), the functional \( F \mapsto L(\hat{\lambda})F \) has a unique absolute maximum point \( \mathcal{X}_{[\tilde{\lambda}, \infty)} \). Therefore \( \hat{F} \), which is an absolute maximum point given by Proposition 4.3, must be \( \mathcal{X}_{[\tilde{\lambda}, \infty)} \). Furthermore, this probability distribution function is the unique absolute maximum point of the functional \( F \mapsto L(\lambda_F)F \) but \( \lambda_F = \lambda_{\hat{F}} = \hat{\lambda} \) and consequently \( \hat{F} = \mathcal{X}_{[\tilde{\lambda}, \infty)} \).

Now, assuming in addition the differentiability of \( b(\tau) \) for \( \tau > E \),

\[
\psi'(\tau) = \Re e^{-(\hat{\lambda} + \delta)\tau}(b'(\tau) - (\hat{\lambda} + \delta)b(\tau))
\]

and thus we have that the critical points are the solutions of

\[
\hat{\lambda} = \frac{b'(\tau)}{b(\tau)} - \delta, \quad \tau > E.
\]  (4.5)

To conclude, we have that

1. Combining the characteristic equation (3.4) at \( F = \mathcal{X}_{[\tilde{\lambda}, \infty)} \), that is \( G(\hat{\lambda}, \mathcal{X}_{[\tilde{\lambda}, \infty)}) = 0 \), with the condition of critical point \( \hat{\lambda} = \frac{b'(\tilde{\lambda})}{b(\tilde{\lambda})} - \delta \), we get that \( \tilde{\lambda} > E \) is a solution of the scalar nonlinear equation (4.3). Actually, it is the unique solution since according to the type of monotonicity assumed on the burst size, the left-hand side of (4.3) is strictly decreasing and the right-hand side is strictly increasing.

2. To prove the second part of the claim we have to compute the sign of two derivatives. Indeed, the optimal latent period \( \tilde{\lambda} > E \) is strictly decreasing with respect to \( R \) since

\[
\frac{d \tilde{\lambda}}{dR} = \frac{kSb(\tilde{\lambda})e^{-\frac{\psi'(\tilde{\lambda})}{\psi(\tilde{\lambda})}}}{(kSRb(\tilde{\lambda})e^{\frac{\psi'(\tilde{\lambda})}{\psi(\tilde{\lambda})}} + 1)} \frac{d^2 b(\tau)}{d\tau^2} |_{\tau = \tilde{\lambda}}
\]  (4.6)
is negative according to the type of monotonicity that we have assumed on the normalized burst size, i.e. \( \frac{d^2}{d\tau^2} \ln b(\tau)_{|\tau=\hat{l}} < 0 \). The expression in (4.6) follows from Eq. (4.3) at \( \hat{l} = \hat{l} \) as an implicit derivative rewriting \( \frac{b'(\tau)}{b(\tau)} = \frac{d}{d\tau} \ln b(\tau) \).

On the other hand, the fact that the optimal latent period \( \hat{l} > E \) is strictly decreasing with respect to \( S \) under a suitable condition is derived as follows. Implicitly differentiating in Eq. (4.3) at \( l = \hat{l} \), we have that

\[
\frac{d\hat{l}}{dS} = \frac{k(Rb(\hat{l})e^{\frac{\lambda\hat{l}}{m}} - 1)}{(kSRb(\hat{l})e^{\frac{\lambda\hat{l}}{m}} + 1) \frac{d^2}{d\tau^2} \ln b(\tau)_{|\tau=\hat{l}}},
\]

which is negative if and only if

\[
Rb(\hat{l})e^{\frac{\lambda\hat{l}}{m}} > 1. \tag{4.8}
\]

Now, there exists a critical value of the bacterial mortality \( \delta_c := m + \frac{b'(l^*)}{b(l^*)} > m \), where \( l^* > E \) cancels the right-hand side of (4.3), i.e. \( Rb(l^*)e^{\frac{\lambda\hat{l}}{m}} = 1 \), such that \( \hat{l} = l^* \) is also solution of Eq. (4.3) for \( \delta = \delta_c \). Moreover, condition (4.8) holds if and only if \( \delta < \delta_c \). This result follows from condition \( m - \delta < kS(R - 1) \) and the fact that the left-hand side of (4.3) is a strictly decreasing function of \( l > E \) (with limit at infinity \( m - \delta \)) and the right-hand side is a strictly increasing function of \( l > E \) (with limit at infinity \( kS(R - 1) \)).

According to (4.5) at \( \tau = \hat{l} \), once we know the optimal latent period \( \hat{l} \) as the solution of Eq. (4.3), the maximal fitness (the maximal growth bound of the solution semigroup) is given by

\[
\hat{\lambda} = \frac{b'(\hat{l})}{b(\hat{l})} - \delta = \frac{B'(\hat{l})}{B(\hat{l})} - \delta > -\delta. \tag{4.9}
\]

Finally as in Ref. 34, we can find which factor, \( R \) or \( S \), has a stronger influence on the optimal latent period \( \hat{l} \). Computing the ratio of the elasticity coefficients of \( \hat{l} \) with respect to \( R \) and \( S \), we have that (\( \delta < \delta_c \)):

\[
\frac{\frac{d\hat{l}}{dR}}{\frac{d\hat{l}}{dS}} = \frac{Rb(\hat{l})e^{\frac{\lambda\hat{l}}{m}}}{\frac{d\hat{l}}{dS}} > 1.
\]

Therefore, the quality of the bacteria, \( R \), has a greater influence on the optimal latent period than the quantity of the disease-free ones, \( S \).

5. Concluding Remarks and Multi-Strain Competition

We have introduced an original model for a bacteriophage population with a random lysis timing (latent period) and a variable burst size. The asymptotic behavior (see, e.g. Ref. 29) of the phage population is given by \( P(t) \sim p_0 e^{\lambda t} \), as \( t \to \infty \), whenever a
real solution $\lambda_F$ of the characteristic equation (3.4) exists. We have computed the probability distribution of the lysis timing giving the maximal bacteriophage fitness $\lambda_F$, and it corresponds to a latent period taking a single value with probability one. This value is determined by the unique solution of a nonlinear equation, see (4.3).

Furthermore, since super-infections have been ignored and system (2.3) is linear, this system can also be interpreted as a model for the so-called linear invasion dynamics which is related to an evolutionary process in a large time scale (see, e.g. Refs. 11 and 10 and references therein). Specifically, it is a model for the growth/decay of a (small) mutant population of phages with evolutionary trait $F$ (the distribution function of the latent period) invading a resident population with another trait value and which is at equilibrium with an uninfected bacteria population $S$. As a consequence, Theorem 4.1 and the consideration that $\lambda$ given by (4.9) vanishes, gives the evolutionarily stable strategy of the latent period in the form $F_{\text{ESS}}(\tau) = X_{(l_{\text{ESS}}, \infty)}(\tau)$ with $l_{\text{ESS}} > E$ satisfying

$$\frac{B'(l_{\text{ESS}})}{B(l_{\text{ESS}})} = \delta = 0,$$

where we recall that $B(\tau) = Rb(\tau)$ is the burst size and $\delta$ is the per capita bacterial mortality rate. Alternatively, this evolutionarily stable strategy could also have been found maximizing the function $R_0(S, F) = \frac{ks}{m+kS} \int_{(0,\infty)} B(\tau) e^{-\delta \tau} dF(\tau)$, already given in (3.6), with respect to $F$. This is done with the help of Lemma 4.3, since the optimal point is obviously independent of $S$ as $R_0(S, F)$ is the product of functions of each variable. So, we arrive at the same Eq. (5.1).

It turns out that the $F$ giving the maximal phage growth rate for fixed $S$ can be different from the one giving the maximal phage reproduction number $R_0$. The first one is given by Eq. (4.3) whereas the second one is given by Eq. (5.1), and they only coincide if $\lambda = 0$ (equivalently $R_0 = 1$).

At this point, we wonder which one, if any, is the outcome of the evolution of the lysis timing. In Ref. 8, a nonlinear multi-strain epidemiological model is completely analyzed, being the main result that the strain with the maximum value of $R_0$ leads the others to extinction. In the spirit of this paper, one can consider the following nonlinear multi-strain bacteriophage model:

$$S'(t) = r(S(t))S(t) - kS(t) \sum_{j=1}^{n} P_j(t),$$

$$P'_j(t) = -(m + kS(t))P_j(t)$$

$$+ k \int_{(0, \tau]} B(\tau) S(t - \tau) P_j(t - \tau) e^{-\delta \tau} dF_j(\tau), \quad j = 1, \ldots, n,$$

with suitable initial conditions. Here, $r(S)$ is a strictly decreasing function which stands for the per capita growth rate of bacteria in the absence of phages, and the phage strain $j$ corresponds to $F_j(\tau)$. The system above has three types of equilibria:
the extinction equilibrium, the disease-free equilibrium \((S^*, 0)\) (here \(r(S^*) = 0\)), and generically, \(n\) endemic equilibria \((S^*_j, r(S^*_j)/k) e_j\), \(j = 1, \ldots, n\), where \(\{e_j\}\) is the canonical basis and \(\mathcal{R}_0(S^*_j, F_j) = \frac{kS^*_j}{m + kS^*_j} \int_{[0, l]} B(\tau) e^{-\delta \tau} dF_j(\tau) = 1\). The complete analysis of the asymptotic behavior of the solutions of (5.2) goes beyond the scope of this paper. However, an easier approach is the standard point of view of adaptive dynamics, where one assumes a resident phage strain \(j\) at endemic equilibrium with a bacteria population \(S^*_j\), and the linear growth of a small population of an invader phage strain \(i\) described by

\[
P'_i(t) = -(m + kS^*_j)P_i(t) + kS^*_j \int_{[0, l]} B(\tau) P_i(t - \tau) e^{-\delta \tau} dF_i(\tau). \tag{5.3}
\]

A small phage population of strain \(i\) invades a resident strain \(j\), at endemic equilibrium, if and only if \(\mathcal{R}_0(S^*_j, F_i) > \mathcal{R}_0(S^*_j, F_j) = 1\) which is equivalent to \(\mathcal{R}_0(S^*, F_i) > \mathcal{R}_0(S^*, F_j)\) due to the fact that \(\mathcal{R}_0(S^*, F)\) is the product of functions of each variable.

On basis of a sequential substitution\(^{13}\) of different phage strains (one strain at a time) and assuming convergence stability\(^{13}\) of the adaptive dynamics, the winning strain for the long-term evolution of the lysis time would be the one which produces the largest expected number of virions per phage in the initial phase of the infection, i.e. the largest \(\mathcal{R}_0\). Hence the appropriate fitness in this context is \(\mathcal{R}_0\) (see Refs. 8 and 31 for a similar result in another epidemic model) since, on the other hand, the phage growth rate of the strain \(i\) at disease-free equilibrium being larger than that of strain \(j\) does not guarantee a successful invasion of strain \(j\) by strain \(i\) nor the invasibility of a resident \(i\) against invasions by strain \(j\). Reference 31 also surveys epidemic models in which \(\mathcal{R}_0\) is not a good predictor of the winning strain.

**Appendix A. Existence and Uniqueness of Solutions**

In this Appendix, we show the existence and uniqueness of solutions of the model described by system (2.3), or equivalently by (2.4) as a single equation. Let us consider an initial condition \((v_0(\cdot), P_0) \in X := L^1(0, l) \times \mathbb{R}\) and a fixed interval of time \([0, t_f]\) with \(t_f < l\). Now Eq. (2.4) for \(P(t), 0 \leq t \leq t_f\), reads as

\[
P(t) = P_0 e^{-\nu t} + \int_0^t \left( k S \int_{[0, s]} B(\tau) P(s - \tau) e^{-\delta \tau} dF(\tau) \right. \\
+ \left. e^{-\delta s} \int_{(s, \tau]} B(\tau) v_0(\tau - s) \frac{dF(\tau)}{1 - F(\tau - s)} \right) e^{-\nu (t - s)} ds. \tag{A.1}
\]

We recall that \(\nu := m + kS > 0, \sup_{\tau \geq 0} B(\tau) = R\), and \(F(\tau)\) is a general probability distribution function. Let \(C := C([0, t_f], \mathbb{R})\) be the Banach space of continuous functions with the supremum norm. Let \(B : C \to C\) be the following linear operator

\[
(BP)(t) := kS \int_0^t e^{-\nu(t - s)} \int_{[0, s]} B(\tau) P(s - \tau) e^{-\delta \tau} dF(\tau) ds,
\]
and, for \( v_0 \in L^1(0, l) \) and \( P_0 \) a real value, let \( P_1(t) \) be the function

\[
P_1(t) := P_0 e^{-vt} + \int_0^t e^{-v(t-s)-\delta s} \int_{(s,\ell]} B(\tau) v_0(\tau - s) \frac{dF(\tau)}{1 - F(\tau - s)} ds.
\]

Thus, Eq. (A.1) is written in short as

\[
P(t) = (BP)(t) + P_1(t).
\] (A.2)

**Proposition A.1.** The operator \( B \) is well-defined and \( P_1(\cdot) \in C \).

**Proof.** Firstly, we have to show that if \( P(\cdot) \in C \), then \( (BP)(\cdot) \in C \). Indeed, let us define \( L_1(s) := kS \int_{(s,\ell]} B(\tau) P(s - \tau) e^{-\delta \tau} dF(\tau) \), then \( (BP)(t) = \int_0^t e^{-v(t-s)} L_1(s) ds \). It suffices to show that \( L_1(\cdot) \in L^1(0, t_\ell) \):

\[
\int_0^{t_\ell} |L_1(s)| ds \leq kS \int_0^{t_\ell} \int_{(s,\ell]} B(\tau) |P(s - \tau)| e^{-\delta \tau} dF(\tau) ds
\]

\[
\quad \leq kSR \int_{(0, t_\ell]} \int_\tau^{t_\ell} |P(s - \tau)| ds dF(\tau)
\]

\[
= kSR \int_{(0, t_\ell]} \int_0^{t_\ell - \tau} |P(\sigma)| d\sigma dF(\tau)
\]

\[
\quad \leq kSR \|P\|_{L^1(0, t_\ell)}.
\] (A.3)

On the other hand, let us show the continuity of \( P_1 \) by means of a similar argument. Making the linear change of variables \( \tau - s = \sigma, \tau = \tau \) to the double integral \( \int_0^{t_\ell} \int_{(s,\ell]} v_0(\tau - s) \frac{dF(\tau)}{1 - F(\tau - s)} ds \), the region of integration is transformed into \( \{(\tau, \sigma) \in [0, l]^2 : \tau - t_\ell < \sigma < \tau \} \) and therefore

\[
\int_0^{t_\ell} \int_{(s,\ell]} v_0(\tau - s) \frac{dF(\tau)}{1 - F(\tau - s)} ds
\]

\[
= \left( \int_0^{t_\ell - \tau} \int_{\sigma}^{\sigma + t_\ell} + \int_0^{t_\ell - \tau} \int_{\sigma}^{\tau} \right) \frac{v_0(\sigma)}{1 - F(\sigma)} dF(\tau) d\sigma
\]

\[
= \int_0^{t_\ell - \tau} \frac{F(\sigma + t_\ell) - F(\sigma)}{1 - F(\sigma)} v_0(\sigma) d\sigma
\]

\[
+ \int_0^{t_\ell} \frac{1 - F(\sigma)}{1 - F(\sigma)} v_0(\sigma) d\sigma \leq \|v_0\|_{L^1(0, l)}.
\] (A.4)

Thus it follows that the function \( L_0(s) := e^{-\delta s} \int_{(s,\ell]} B(\tau) v_0(\tau - s) \frac{dF(\tau)}{1 - F(\tau - s)} \) belongs to \( L^1(0, t_\ell) \) with

\[
\|L_0\|_{L^1(0, t_\ell)} \leq R \|v_0\|_{L^1(0, l)}.
\] (A.5)
Then \( P_1(\cdot) \in \mathcal{C} \), using the same argument as before, with norm
\[
\|P_1\|_{\mathcal{C}} \leq \max(1, R) \|(v_0, P_0)\|_{L^1(0, l) \times \mathbb{R}}.
\] (A.6)

\[\square\]

**Theorem A.1.** For any initial condition \((v_0(\cdot), P_0) \in X\), system (2.3) has a unique local solution. Moreover, if the initial condition is non-negative, then the solution is non-negative.

**Proof.** As the solution of (2.3) is given by the solution of Eq. (A.2), which is a Volterra integral equation (see (2.5) for \( t \leq t_\gamma < l \)), the proof is omitted. We refer to Appendix B.6 in Ref. 29 for existence and uniqueness of solutions to Volterra integral equations (Theorem B.37, p. 487).

Let us remark that for the usual initial conditions used in laboratory experiments, i.e. \( v_0(\tau) \equiv 0 \) and \( P_0 > 0 \), then \( P_1(t) = P_0 e^{-\nu t} \) and the solution of (2.3) via (A.2) is given by \( P(t) = P_0 (\text{Id} - \mathcal{B})^{-1}\exp(-\nu t) > 0 \), and \( v(\tau, t) = kSP_0(1 - F(\tau))e^{-\beta \tau} \cdot (\text{Id} - \mathcal{B})^{-1}\exp(-\nu(t - \tau)), \tau < t \), and zero otherwise.

A standard (and tedious) computation shows that the solution of system (2.3) defines a family of bounded linear operators in \( X \),
\[
S(t) \begin{pmatrix} v_0(\cdot) \\ P_0 \end{pmatrix} := \begin{pmatrix} v(\cdot, t) \\ P(t) \end{pmatrix},
\]
which fulfills the (local) semigroup condition. Next let us show that the strong continuity condition is also satisfied. We have

**Proposition A.2.** The solution semigroup of system (2.3) yields a strongly continuous (local) semigroup of bounded linear operators on \( X \).

**Proof.** We have to show that
\[
\lim_{t \to 0^+} S(t) \begin{pmatrix} v_0(\cdot) \\ P_0 \end{pmatrix} = \begin{pmatrix} v_0(\cdot) \\ P_0 \end{pmatrix} \quad \text{in } X.
\]
The second component of the limit, \( \lim_{t \to 0^+} P(t) = P_0 \), is trivial using (A.2) and Proposition A.1. On the other hand, the first component, i.e. \( \lim_{t \to 0^+}\|v(\cdot, t) - v_0(\cdot)\|_{L^1(0, l)} = 0 \), is derived as follows. From (2.3) and \( t < l \), it reads
\[
\int_0^t kSP(t - \tau)(1 - F(\tau))e^{-\beta \tau} - v_0(\tau) \, d\tau + \int_t^l v_0(\tau - t) \frac{1 - F(\tau)}{1 - F(\tau - t)} e^{-\beta \tau} - v_0(\tau) \, d\tau.
\]
The first integral tends to 0, as time $t$ tends to $0^+$, since $P$ and $v_0$ are integrable functions. Regarding the second one,

$$\int_t^1 \left| v_0(\tau - t) \frac{1 - F(\tau)}{1 - F(t - t)} e^{-\delta t} - v_0(\tau) \right| d\tau$$

$$= \int_0^{1-t} \left| v_0(s) \frac{1 - F(t + s)}{1 - F(s)} e^{-\delta t} - v_0(s + t) \right| ds$$

$$\leq \int_0^{1-t} \left| v_0(s) \frac{1 - F(t + s)}{1 - F(s)} e^{-\delta t} - v_0(s) \right| ds$$

$$+ \int_0^{1-t} |v_0(s + t) - v_0(s)| ds.$$ 

Now, since $\left( v_0(s) \frac{1 - F(t + s)}{1 - F(s)} e^{-\delta t} - v_0(s) \right) \mathcal{X}_{[0,1-t]}(s)$ tends pointwise to 0 as time $t$ tends to $0^+$ and its absolute value is bounded above by $|v_0(s)|$, then by the dominated convergence theorem we can conclude that the convergence is in the $L^1(0, l)$ sense. Finally, the second integral above also tends to 0, as $t$ tends to $0^+$, by a well-known property of the integral. □

Finally, we have the existence and uniqueness of global solutions which follows as a corollary of the previous statements. Indeed, using the uniqueness of solutions, the semigroup property and the fact that the existence time $t_f > 0$ does not depend on the initial condition, we have the following

**Theorem A.2.** The local solution of system (2.3) given by Theorem A.1 is actually a global solution and defines a strongly continuous positive linear semigroup.

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