

An age-size structured model for bacteria-phage interaction

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Abstract

We introduce a size structured PDE model for a susceptible and a resistant bacteria populations that grow as they feed from a resource that is added at a constant rate. Bacteria populations evolve in the presence of a phage population that is adsorbed by the susceptible bacteria but also by a bulk population of phage free receptors on cell debris and on infected cells. Assuming that the individual cell growth is non negative, we compute an age function that allow us to change variables and to obtain an equivalent system with structure by the cell age and where the cell volume becomes a state variable. We characterize the steady states of these models.

1 Introduction

Bacteriophage viruses, also known as bacteriophages or simply phages, were discovered in 1915 by the English bacteriologist Frederick William Twort (1877-1950) and the French-Canadian microbiologist Félix d'Herelle (1873-1949). In a few words they are bacterial infection agents that can cause a bacterial population to be infected or to get an illness. The class of phages that we will regard in this paper are the lytic ones that, contrary to the lysogenic kind, definitively kill the host cell in a lysis process. We can think of lytic phages as bacteria predators.

One amazing fact is that phages seem to keep an around ten to one relation with bacteria in all ecosystems, pointing at them as the most abundant biological entities on the planet [8].

After their discovery and until 1940, phage therapy produced satisfactory results in the United States and other countries when used to control bacterial infections in humans. Later, almost everywhere phage therapy was abandoned and replaced by antibiotics like penicillin that was used in large scale during the Second World War. Bacteriophage use and experimentation continued only in some Europe eastern countries.

As a reference on the history and general information on phages we recommend the work of S. Matsukazi, et. al. [3], and as a critic point of view of phage therapy the article by B. Levin and J. Bull [2].

Nowadays, it is a well known fact that bacteria have been evolving by several means like mutations, selection and even the incorporation of external genetic material. A direct consequence of this evolution is that antibiotics effectiveness do not last forever and some bacterial species dangerous to human beings become resistant or even immune to specific antibiotics that initially worked very well. There is an accepted idea that microbes develop 'resistance to medicine' and there are 'antibiotics generations'. Bacteriophage therapy has been proposed as an alternative to antibiotics with some important advantages (small doses can suffice and the high phage concentrations will be found near the maximum bacterial concentrations, for instance) but with similar problems (being the outcome of resistant strains the most important one).

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In the following section we explain the biological facts that serve us to design our models. In §3 we present a cell size structured model with two PDE's that correspond to the bacterial populations or concentrations, together with three integro differential equations for the bacterial debris, the available resources and the phage count, this last one with a time delay term. Theorem (15) in this section states that if we extend the system with a previously computed age distribution function, which is possible if we assume that the cell growth is always positive, the resulting system is equivalent to a similar one structured by the cell age. In §4 we characterize the steady states of the second system of §3. In the last section we present some conclusions and remarks.

2 Description of the biological process

The lytic phages carry out a Lytic Cycle, that for our purposes is decomposed in the following steps:

- Step 1. **Approach.** It refers to the way in which the phage and its future host, the bacteria, come close enough to make contact.
- Step 2. **Attachment.** It is the moment when the phage docks onto a target cell receptor and remains in such position.
- Step 3. **Penetration or DNA-RNA absorption.** Consists of the injection of the viral DNA or RNA to the interior of the bacteria.
- Step 4. **Replication.** It is the process by which the virions¹ are assembled inside the prokaryote.
- Step 5. **Lysis.** It refers to the rupture of the cell envelope and liberation of virions to the outside environment.

It is important to notice that there are various theories regarding the approach and contact steps. It may be possible that some kind of attraction force of an electrostatic kind is what brings the virus near their host surface and makes it stay nearby [5]. In this line, the chemical composition of the surrounding environment and its physical conditions, in particular the temperature, play a crucial role. In [5] is concluded that “The rate of interaction of several viruses and their host cells in chemically defined media can be adjusted to any desired value between zero and the maximum theoretically possible rate, by control of the ionic constitution of the medium alone.”

Another belief regarding the way in which the phage finds a docking point, that is somehow natural when modeling, is pure chance, i.e. to consider that all virus move freely in the environment and occasionally find and touch a receptor. In this sense it is clear that all conditions that are external to the prokaryotes and the viruses, aside of their respective concentrations, will impact the speed at which the contact step is completed and so its frequency.

For our purposes it is not very important if the virus is attracted or if it finds its way to the bacterial cell by chance, nor is if it ‘walks’ over the surface or bounces among many cells. What is essential is to determine and measure the speed at which the bacteriophages get attached to receptors in a given medium as a function of the phage and bacteria concentrations.

Once the phage is irreversibly and permanently attached its DNA is injected into the bacteria quickly reaching its cytoplasm.

This DNA-RNA absorption automatically triggers a radical change in the metabolic functions of the prokaryote [6], in fact, it ceases to be a bacteria and becomes a virus replication facility,

¹Complete and infective virus particles.

whose only purpose is to assemble virions using all available resources from the interior of the cell. Notice that the cell envelope is essentially unaffected in this process even when the cell stops feeding itself among all other usual metabolic functions. Related to this phenomenon are the papers by Abedon *et. al.* [1] and Weld *et. al.* [9] where it is mentioned that phage infected bacterial cells do not grow.

The cycle ends with the expulsion of all existent virions to the outside by breaking the cell envelope. The number of liberated virus particles is known as the “burst size” and it can range from 1 or 2 up to one hundred, or even more.

Besides all things related with this Lytic Cycle there are many other factors that may impact the life or death of a bacteria and a phage. For the sake of clarity we consider a phage dead when it has completely and irreversibly lost its capacity to carry out the Lytic Cycle, i.e. when it is not capable of entering a cell to get offspring anymore.

Regarding the phages, some of the following things can happen at any time:

- In what we shall call Super Infections, phages can attach themselves to lipopolysaccharide receptors of an infected bacteria and also inject their genetic information. Nevertheless this extra DNA-RNA injection will not increase nor decrease the burst size, the virus is simply lost.
- Lipopolysaccharide attachments followed by expulsion of the DNA-RNA outside of the virus, can occur even if the host cell is dead. It doesn't matter if the prokaryotic cell remains entire or the cell envelope is broken after the lysis explosion, the lipopolysaccharide molecules can adsorb phages at any time, as long as the bond of attachment is present on the lipopolysaccharide protein. These cell envelope fragments together with the membranes from cells that remain entire, is what we shall refer as “bacterial debris” or simply “debris”. We give this debris a very important role and impact in our models. In [6] we find arguments that support this great impact of bacterial debris, even conceiving it as the mechanism for bacteria-phage coexistence.
- Bacteriophages may also attach to inorganic particles [5].
- Viral DNA-RNA can not penetrate a bacteria by itself in normal conditions, the only possible way for this to occur is by completing its corresponding step of the Lytic Cycle. So, if occasionally the DNA-RNA is expelled from the virus to the environment, it will not penetrate a bacterium in a successful manner.

3 The models

We will regard the bacterial cell size to influence the viral adsorption by assuming that the phage adsorption speed is proportional to the individual cell envelope surface. We consider that the phage receptors are uniformly distributed on the cell membrane as if they were part of building blocks of fixed size.

To begin with, we let $U(v, t)$ to be a bacteria population structured by the individual cell volume or cell size v that evolves on a time variable t . In fact we can think indistinctively of a population or a bacterial concentration per volume unit. We will also consider $W(v, t)$ to be the concentration of “mutant” or resistant bacteria depending on the same variables that U does.

We will suppose that susceptible bacteria will die at a constant rate $\mu_1 > 0$ while mutants will do so at some other constant rate $\mu_2 > 0$ and we will assume the existence of a maximum volume at which cells must divide into two new bacteria of identical size. Normalizing this maximum volume it will happen that all cells will divide when they reach $v = 1$ and that the division will be sharp resulting into two daughter cells of volume $v = \frac{1}{2}$ each one of them. In this way $v \in [\frac{1}{2}, 1]$.

All bacteria will feed from a resource $R(t)$ that promotes cell growth and diminishes accordingly. The resource consumption and cell growth will depend on the actual cell size and existing resources and will be controlled by a positive function $f(v, R(t))$. The cell growth will be proportional to the resource consumption with proportion constant $\gamma > 0$. The resource $R(t)$ will be externally increased by a fixed quantity $d \geq 0$ by time unit and will decay at a constant rate $\lambda \geq 0$.

The phage concentration at time t will be given by $P(t)$ and their interaction with all bacteria will take place according to the mass action law with an adsorption function $k_1 v^{\frac{2}{3}}$ with $k_1 > 0$, i.e. the number of infections for a phage concentration $P(t)$ and a bacterial density $U(v, t)$ will be equal to $k_1 v^{\frac{2}{3}} P(t) U(v, t)$, thus the specific adsorption rate will be proportional to the number of membrane phage receptors and so to the cell surface. The number of receptors on the surface of a cell of the maximum size will be a positive fixed integer r . The constant k_1 will represent the usual adsorption constant for full grown cells of volume $v = 1$. In the absence of bacteria, $P(t)$ will decay at a constant rate $m \geq 0$.

After a latency period $L > 0$ the surviving infected cells will lyse and each one will release bv new virions with $b > 0$. We suppose that once a cell is infected the growth process is completely stopped and then the production of virions will result proportional to the available material inside the bacterium. So, b will stand for the burst size of the infected cells that have the maximum volume.

Viral adsorption will also take place on receptors of infected and dead cells, we will treat all these receptors as docking points aside of its origin and thus define $D(t)$ to represent the bulk concentration of free docking points. The adsorption will occur obeying the mass action law with constant $k_2 > 0$, i.e. the number of adsorptions for a phage concentration $P(t)$ and free docking points $D(t)$ will be equal to $k_2 P(t) D(t)$. The receptors on dead and infected cells will degrade at a constant rate $\delta > 0$.

It is important to notice that in real situations where r is typically above one hundred, while k_1 is the adsorption constant for a whole cell with r receptors, k_2 is the adsorption constant for one receptor alone, then k_2 will be comparable to k_1/r but not to k_1 .

At the start, i.e. $t = 0$, since we are modeling an ongoing process and we are assuming that $\mu_1 > 0$, then, in the presence of bacterial cells, there must always be some dead cells too allowing us to consider $D(0) = D_0 > 0$. Also, if $d > 0$ there will be no chance for the resources to extinguish completely and we can assume that $R(0) = R_0 > 0$ whenever $d > 0$ and $R(0) = R_0 \geq 0$ if $d = 0$.

In this way given an initial state $U(v, 0) = U_0(v) \geq 0$, $W(v, 0) = W_0(v) \geq 0$ for all $v \in [\frac{1}{2}, 1]$,

$P(0) = P_0 \geq 0$, $D(0) = D_0 > 0$, $R(0) = R_0 \geq 0$, it will evolve obeying

$$\begin{aligned}
U_t(v, t) + \gamma \frac{\partial}{\partial v} [f(v, R(t))U(v, t)] &= - \left(\mu_1 + k_1 v^{\frac{2}{3}} P(t) \right) U(v, t), \\
W_t(v, t) + \gamma \frac{\partial}{\partial v} [f(v, R(t))W(v, t)] &= -\mu_2 W(v, t), \\
\dot{P}(t) &= - \left(m + k_1 \int_{\frac{1}{2}}^1 v^{\frac{2}{3}} U(v, t) dv + k_2 D(t) \right) P(t) \\
&\quad + \chi_{[L, \infty)}(t) k_1 b e^{-\mu L} P(t - L) \int_{\frac{1}{2}}^1 v^{\frac{5}{3}} U(v, t - L) dv, \quad (1) \\
\dot{D}(t) &= -(\delta + k_2 P(t)) D(t) + \mu_1 r \int_{\frac{1}{2}}^1 v^{\frac{2}{3}} U(v, t) dv \\
&\quad + k_1 P(t) \int_{\frac{1}{2}}^1 v^{\frac{2}{3}} (r v^{\frac{2}{3}} - 1) U(v, t) dv, \\
\dot{R}(t) &= d - \lambda R(t) - \int_{\frac{1}{2}}^1 f(v, R(t)) (U(v, t) + W(v, t)) dv,
\end{aligned}$$

with $f(\frac{1}{2}, R(t)) U(\frac{1}{2}, t) = 2f(1, R(t))U(1, t)$ and $f(\frac{1}{2}, R(t)) W(\frac{1}{2}, t) = 2f(1, R(t))W(1, t)$ as the boundary conditions.

We consider the resource consumption function $f = f(x, y) \in C^1([\frac{1}{2}, 1] \times [0, \infty))$, bounded by some positive constant $k > 0$ and such that:

1. $f(x, y) > 0$ if and only if $y > 0$.
2. $f_x(x, y) < 0$.
3. $f_y(x, y) > 0$.

Assumption 1 implies that the existence of resources leads to cell growth which is impossible otherwise.

The second assumption is related to an experimentally observed property that points an inverse relation between the size and the growth speed. The size of cells a few minutes after partitioning is not very far from the maximum feasible size, so we can assume fast growth for small cells and slow growth for bigger ones.

The last assumption just represents a direct relation between the amount of available resources and the growth speed, i.e. there can not be less growth when there are more available resources for the same bacterial concentration and cell size.

Typically we can think for example of

$$f(x, y) = \frac{k}{x} \left(\frac{y}{j + y} \right)$$

that, for each fixed $x \in [\frac{1}{2}, 1]$, is a Michaelis-Menten function of y bounded by k/x , like the ones used to describe the rate of enzymatic reactions.

Although system (1) has all components needed to entirely determine the bacterial distributions behavior in time, once defined the resource consumption function and given the initial state and parameter values, moreover it posses intrinsically sufficient information to compute a bacterial age distribution function $A(v, t)$, whenever we provide the corresponding initial state $A_0(v) = A(v, 0)$, i.e. the age distribution of the initial concentrations $U_0(v)$ and $W_0(v)$.

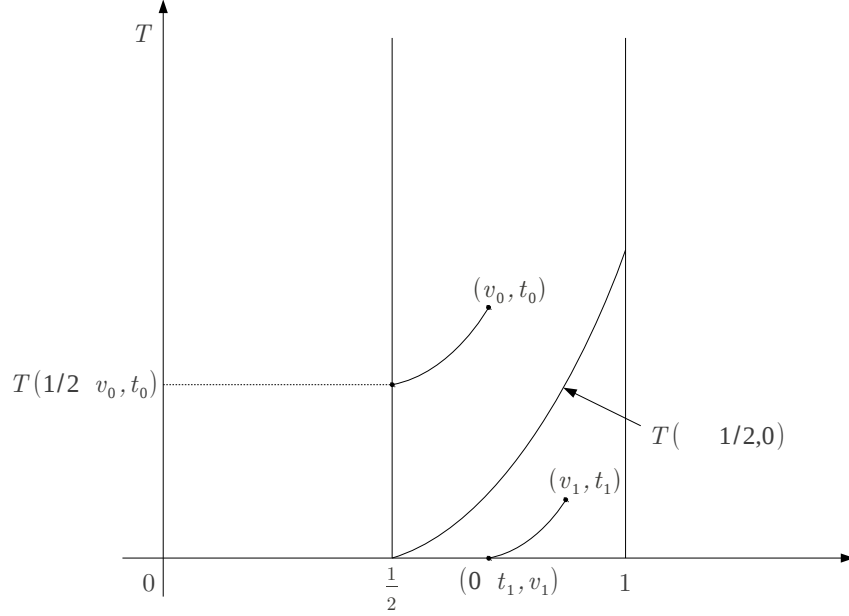


Figure 1: Computation of the age function $A(v, t)$.

The characteristic curves for (1) on the (v, t) plane will be the solutions of the planar system determined by the vector field $(\gamma f(v, R(t)), 1)$ for $(v, t) \in [\frac{1}{2}, 1] \times [0, \infty)$ that can also be presented as either of the following ordinary differential equations

$$\frac{dv}{dt} = \gamma f(v, R(t)) =: g(v, t) \quad \text{or} \quad \frac{dt}{dv} = \frac{1}{\gamma f(v, R(t))} =: h(v, t) \quad (2)$$

also with $(v, t) \in [\frac{1}{2}, 1] \times [0, \infty)$. We notice that h is well defined because f is strictly positive since $R(t)$ is strictly positive too, as we will show later.

We will denote $V(T; t, v)$ and $T(V; v, t)$ the respective solutions to (2) passing through the point (v, t) , where $T(V; v, t) = V^{-1}(T; t, v)$, i.e. T and V are the inverse functions of each other.

As shown in figure 1, there is a special solution by $(\frac{1}{2}, 0)$ namely

$$T(V; \frac{1}{2}, 0) = V^{-1}(T; 0, \frac{1}{2})$$

that divides the domain of (2) into two regions. Above this curve we will find trajectories of (2) that intersect the line $v = \frac{1}{2}$ while below it all solutions will intersect the v -axis. The first of these intersection points determines the time of birth while the other determines the volume at time zero. This allow us to define the age distribution function

$$A(v, t) := \begin{cases} t - T(\frac{1}{2}; v, t) & \text{if } T(\frac{1}{2}; v, t) \geq 0, \\ A_0(V(0; t, v)) + t & \text{otherwise.} \end{cases} \quad (3)$$

remembering that $A_0(v) = A(v, 0)$ is the age distribution for the initial population $U_0(v) = U(v, 0)$. Because of its biological meaning $A_0(\frac{1}{2}) = 0$ and $A_0(v) > 0$ for all $v > 0$.

Putting together (1) and (3) we can state the following result.

Lemma 3.1. *If $A_0(v_1) < A_0(v_2)$ for all $v_1, v_2 \in [\frac{1}{2}, 1]$ such that $v_1 < v_2$ then $A(v_1, t) < A(v_2, t)$ for all $(v_1, t), (v_2, t) \in [\frac{1}{2}, 1] \times [0, \infty)$ such that $v_1 < v_2$, i.e. if the age distribution function is strictly increasing at time zero then it will remain strictly increasing for all positive time values.*

Proof. By *reductio ad absurdum*, we suppose that there exist $(v_1, t), (v_2, t) \in [\frac{1}{2}, 1] \times [0, \infty)$ such that $v_1 < v_2$ and $A(v_1, t) \geq A(v_2, t)$. This situation leads to three possible cases:

- i) $T(\frac{1}{2}; v_1, t), T(\frac{1}{2}; v_2, t) \geq 0$ (both points not below $T(V; \frac{1}{2}, 0)$),
- ii) $T(\frac{1}{2}; v_1, t) \geq 0$ but $T(\frac{1}{2}; v_2, t) < 0$ (one point above or in $T(V; \frac{1}{2}, 0)$ and the other below), and
- iii) $T(\frac{1}{2}; v_1, t), T(\frac{1}{2}; v_2, t) < 0$ (both points below $T(V; \frac{1}{2}, 0)$).

In case i), from (3) $A(v_1, t) \geq A(v_2, t)$ implies that $T(\frac{1}{2}; v_1, t) \leq T(\frac{1}{2}; v_2, t)$ which means that these two trajectories of (2) intersect at some point, contrary to the existence and uniqueness theorem for ordinary differential equations.

In case ii), also from (3), $A(v_2, t) \geq t$, while $A(v_1, t) \leq t$, forcing $A(v_1, t) = A(v_2, t)$, which again is contrary to the existence and uniqueness theorem for ordinary differential equations.

For the last case, we use the second line of (3) from where $A(v_1, t) \geq A(v_2, t)$ will imply $A_0(V(0; t, v_1)) \geq A_0(V(0; t, v_2))$, since A_0 is strictly increasing it will force $V(0; t, v_1) \geq V(0; t, v_2)$, which again means that two trajectories of (2) intersect at some point, contrary to the existence and uniqueness theorem for ordinary differential equations. ■

This result points that if $A(v, 0)$ is strictly increasing as a function of v it will remain strictly increasing and thus invertible as a function of v for all $t \geq 0$. This will mean that at any time the volume of a cell will provide its age and vice versa. There exists a function $V(a, t)$, the inverse of $A(v, t)$ for a fixed t , such that $V(A(v, t), t) = v$ for every $t \geq 0$.

Lemma 3.2. *If $A'_0(v) > 0$ for all $v \in [\frac{1}{2}, 1]$ then $A_v(v, t) > 0$ for all $(v, t) \in [\frac{1}{2}, 1] \times [0, \infty)$.*

Proof. First let us assume $T(\frac{1}{2}; v, t) \geq 0$ in (3). Recalling that $T(V; v, t)$ is the solution of the right side of (2) passing through (v, t) , we take the partial derivative with respect to v of the whole equation

$$T_V(V; v, t) = h(V, T(V; v, t)),$$

together with the initial condition $T(v; v, t) = t$, and get

$$(T_V(V; v, t))_v = (T_v(V; v, t))_V = h_T(V, T(V; v, t))T_v(V; v, t) \quad (4)$$

and, for the initial condition,

$$\begin{aligned} T_V(v; v, t) + T_v(v; v, t) &= 0 \\ \text{if and only if } T_v(v; v, t) &= -T_V(v; v, t) = -h(v, T(v; v, t)) = h(v, t). \end{aligned}$$

Then, from (3) we have that

$$A_v(v, t) = -T_v(\frac{1}{2}; v, t)$$

and, being T_v the solution of the linear ordinary differential equation (4) with an initial condition $T_v(v; v, t)$, we can write

$$T_v(V; v, t) = -h(v, t)e^{\int_v^V h_T(s, T(s))ds}$$

and then

$$A_v(v, t) = h(v, t)e^{\int_v^{\frac{1}{2}} h_T(s, T(s))ds} > 0, \quad (5)$$

whenever $T(\frac{1}{2}; v, t) \geq 0$ in (3).

Similarly, for the case when $T(\frac{1}{2}; v, t) < 0$ in (3), recalling that $V(T; t, v)$ is the solution of the left side of (2) passing through (v, t) , we take the derivative with respect to v of the whole equation

$$V_T(T; t; v) = g(V(T; t, v), T)$$

together with the initial condition $V(t; t, v) = v$, and get

$$(V_T(T; t, v))_v = (V_v(T; t, v))_T = g_V(V(T; t, v), T)V_v(T; t, v) \quad (6)$$

and, for the initial condition,

$$V_v(t; t, v) = 1.$$

Then, from (3) we have that

$$A_v(v, t) = A'_0(V(0; t, v))V_v(0; t, v), \quad (7)$$

and being V_v the solution of the linear ordinary differential equation (6) with an initial condition $V_v(t; t, v) = 1$ we can write

$$V_v(T; t, v) = e^{\int_t^T g_V(V(s), s)ds}$$

and then

$$A_v(v, t) = A'_0(v)e^{\int_t^T g_V(V(s), s)ds} > 0, \quad (8)$$

whenever $T(\frac{1}{2}; v, t) < 0$ in (3), because $A'_0(v) > 0$ for all $v \in [\frac{1}{2}, 1]$ by hypothesis. \blacksquare

Related to $A(v, t)$ there is another important function that we will call the “age of division” $a_d(t)$ and measures, for each time t , the age value at which bacteria will divide, corresponding to the moment at which the volume reaches the maximum value equal to 1, i.e. $V(a_d(t), t) = 1$, or equivalently $a_d(t) = A(1, t)$, for all $t \geq 0$.

By (3) it will also occur that $A(\frac{1}{2}, t) = 0$ for all $t \geq 0$, biologically meaning that just born cells have age zero. Also, The maximum age of bacteria at time t will be precisely $a_d(t)$.

In this way, we may be able to construct a system equivalent to (1) where the cell age replaces the cell volume as an independent variable. For this purpose we will regard a , the age, and t , the time, as independent variables and consider the functions $S(a, t)$ to be the susceptible bacterial concentration and $M(a, t)$ the phage resistant concentration, both of age a at time t , whose volume distribution function is $V(a, t)$ with $P(t)$ being the free phage concentration, $D(t)$ the docking points concentration and $R(t)$ the available amount of resources, all three at time t .

If we calculate the total susceptible bacterial concentration of (1) for $U(v, t)$ at a given time t (recalling A and V are the inverse function of each other at a fixed time) and change variables we get

$$\int_{\frac{1}{2}}^1 U(v, t)dv = \int_{A(\frac{1}{2}, t)}^{A(1, t)} U(V(a, t), t)V_a(a, t)da = \int_0^{a_d(t)} S(a, t)da \quad (9)$$

which means that for any value $t \geq 0$ we must write

$$S(a, t) = U(V(a, t), t)V_a(a, t) = \frac{U(V(a, t), t)}{A_v(V(a, t), t)} \quad (10)$$

or

$$U(v, t) = S(A(v, t), t)A_v(v, t) = \frac{S(A(v, t), t)}{V_a(A(v, t), t)}. \quad (11)$$

Based on the same reasoning, for the mutant bacterial concentration we have

$$\int_0^{a_d(t)} M(a, t) da = \int_{\frac{1}{2}}^1 W(V(a, t), t)V_a(a, t) da, \quad (12)$$

so we notice that for any $t \geq 0$

$$M(a, t) = W(V(a, t), t)V_a(a, t) = \frac{W(V(a, t), t)}{A_v(V(a, t), t)} \quad (13)$$

or

$$W(v, t) = M(A(v, t), t)A_v(v, t) = \frac{M(A(v, t), t)}{V_a(A(v, t), t)}. \quad (14)$$

Theorem 3.3. *Let us assume a solution of system (1), together with its initial and boundary conditions and with a given strictly increasing initial age distribution $A_0(v)^2$. Then, (S, M, V, P, D, R) , where S and M are defined by (10) and (13), V is the inverse of A (given in (3)) with respect to a , $V_0(a) = A_0^{-1}(a)$, $S_0(a) = U_0(V_0(a))V_0'(a)$ and $M_0(a) = W_0(V_0(a))V_0'(a)$ is a solution to the system*

$$\begin{aligned} S_t(a, t) + S_a(a, t) &= -\left(\mu_1 + k_1 V^{\frac{2}{3}}(a, t)P(t)\right) S(a, t) \\ M_t(a, t) + M_a(a, t) &= -\mu_2 M(a, t) \\ V_t(a, t) + V_a(a, t) &= \gamma f(V(a, t), R(t)) \\ \dot{P} &= -\left(m + k_1 \int_0^{a_d(t)} V^{\frac{2}{3}}(a, t)S(a, t) da + k_2 D(t)\right) P(t) \\ &\quad + \chi_{[L, \infty)}(t) k_1 b e^{-\mu_1 L} P(t-L) \int_0^{a_d(t-L)} V^{\frac{5}{3}}(a, t-L) S(a, t-L) da, \quad (15) \\ \dot{D} &= -(\delta + k_2 P(t))D(t) + \mu_1 r \int_0^{a_d(t)} V^{\frac{2}{3}}(a, t)S(a, t) da \\ &\quad + k_1 P(t) \int_0^{a_d(t)} V^{\frac{2}{3}}(a, t) \left(r V^{\frac{2}{3}}(a, t) - 1\right) S(a, t) da, \\ \dot{R} &= d - \lambda R(t) - \int_0^{a_d(t)} f(V(a, t), R(t)) (S(a, t) + M(a, t)) da \end{aligned}$$

with $f(v, R(t))$ as for (1), $\gamma > 0$, $\lambda, d \geq 0$ and

- *Initial conditions:* $S(a, 0) = S_0(a)$, $M(a, 0) = M_0(a)$, $V(a, 0) = V_0(a)$, $P(0) = P_0 \geq 0$, $D(0) = D_0 > 0$ and $R(0) = R_0 \geq 0$.

²Regarding the fact that the initial volume distribution function is a picture of an ongoing process and that in the proof of the previous result it is possible to see that $V_a(A(v, t), t) = \frac{1}{A_v(v, t)} > 0$ after all existing cells related to the initial state have divided, it is natural to assume that older cells have bigger size at the beginning of the dynamics.

- *Boundary conditions:* $V(0, t) = \frac{1}{2}$, $S(0, t) = 2S(a_d(t), t)[1 - a'_d(t)]$ and $M(0, t) = 2M(a_d(t), t)[1 - a'_d(t)]$, where $a_d(t)$ is such that $V(a_d(t), t) = 1$, holding for all $t \geq 0$ which includes the initial conditions.

Conversely, given a solution of (15), together with its initial and boundary conditions, then (U, W, V, P, D, R) where U and W are defined by (11) and (14), with $A(v, t)$ being the inverse function of $V(a, t)$ for a fixed t , is a solution of (1).

Proof. We prove that a solution of (15) solves (1). By the first equation in (15) and (10) we have

$$\begin{aligned} -\left(\mu_1 + k_1 V^{\frac{2}{3}}(a, t) P(t)\right) U(V(a, t), t) V_a(a, t) &= -\left(\mu_1 + k_1 V^{\frac{2}{3}}(a, t) P(t)\right) S(a, t) \\ &= S_t(a, t) + S_a(a, t). \end{aligned} \quad (16)$$

Now (10) implies that

$$\begin{aligned} S_t(a, t) &= \frac{\partial}{\partial t} [U(V(a, t), t) V_a(a, t)] \\ &= [(U_v(V(a, t), t), U_t(V(a, t), t)) \cdot (V_t(a, t), 1)] V_a(a, t) + U(V(a, t), t) V_{at}(a, t) \\ &= [U_v(V(a, t), t) V_t(a, t) + U_t(V(a, t), t)] V_a(a, t) + U(V(a, t), t) V_{at}(a, t) \end{aligned}$$

and also

$$\begin{aligned} S_a(a, t) &= \frac{\partial}{\partial a} [U(V(a, t), t) V_a(a, t)] \\ &= [(U_v(V(a, t), t), U_t(V(a, t), t)) \cdot (V_a(a, t), 0)] V_a(a, t) + U(V(a, t), t) V_{aa}(a, t) \\ &= U_v(V(a, t), t) V_a^2(a, t) + U(V(a, t), t) V_{aa}(a, t). \end{aligned}$$

In short notation we will have that

$$\begin{aligned} -\left(\mu_1 + k_1 V^{\frac{2}{3}} P(t)\right) UV_a &= [U_v V_t + U_t] V_a + UV_{at} + U_v V_a^2 + UV_{aa} \\ &= [U_v (V_t + V_a) + U_t] V_a + U \frac{\partial}{\partial a} (V_t + V_a). \end{aligned}$$

Moreover, differentiating $V_t + V_a$ in (15) we have that

$$\frac{\partial}{\partial a} (V_t(a, t) + V_a(a, t)) = \gamma \frac{\partial}{\partial a} f(V(a, t), R(t)) = \gamma f_v(V(a, t), R(t)) V_a(a, t).$$

So, considering also that $V_t + V_a = \gamma f$, we have

$$\begin{aligned} -\left(\mu_1 + k_1 V^{\frac{2}{3}} P(t)\right) UV_a &= [U_v \gamma f + U_t] V_a + U \gamma f_v V_a \\ &= V_a \left[U_t + \gamma \frac{\partial}{\partial v} (fU) \right], \end{aligned}$$

that divided by V_a and in full notation can be written as

$$U_t(V(a, t), t) + \gamma \frac{\partial}{\partial v} (f(V(a, t), R(t)) U(V(a, t), t)) = -\left(\mu_1 + k_1 V^{\frac{2}{3}} P(t)\right) U(V(a, t), t), \quad (17)$$

which is the first equation of system (1) with $v = V(a, t)$.

Since this calculation is reversible, we have shown that $S(a, t)$ and $V(a, t)$ are solutions of (15) if and only if $U(v, t)$ is a solution of (1).

It is possible to reproduce this first step of the proof, i.e. from (16) to (17), to show that $M(a, t)$ and $V(a, t)$ are solutions of (15) if and only if $W(v, t)$ is a solution of (1), we only need to replace $-\left(\mu_1 + k_1 V^{\frac{2}{3}} P(t)\right)$ with μ_2 , U with W and S with M .

The equivalence of the equations for $P(t)$, $D(t)$, and $R(t)$ in both systems is a consequence of (9) and (12) because we can reduce the equality of the involved integrals to be a particular case of the following change of variables

$$\begin{aligned}
& \int_{\frac{1}{2}}^1 g(v, R(t)) [\alpha U(v, t) + \beta W(v, t)] dv \\
&= \int_{A(\frac{1}{2}, t)}^{A(1, t)} g(V(a, t), R(t)) [\alpha U(V(a, t), t) + \beta W(V(a, t), t)] V_a(a, t) da \\
&= \int_0^{a_d(t)} g(V(a, t), R(t)) [\alpha U(V(a, t), t) V_a(a, t) + \beta W(V(a, t), t) V_a(a, t)] da \\
&= \int_0^{a_d(t)} g(V(a, t), R(t)) [\alpha S(a, t) + \beta M(a, t)] da
\end{aligned} \tag{18}$$

The function $A(v, t)$ is directly calculated as pointed in (3).

For what has to do with the initial conditions, we notice that given $U_0(v)$ and $V_0(a) := A_0^{-1}(a)$ taking $t = 0$ in (11) and $v = V(a, t)$ we can use (10) to calculate

$$S_0(a) = S(a, 0) = \frac{U(V(a, 0), 0)}{A_v(V(a, 0), 0)} = U_0(V_0(a)) V_0'(a).$$

Conversely, given $S_0(a)$ and $V_0(a)$, using (11), we can compute

$$U_0(v) = U(v, 0) = \frac{S(A(v, 0), 0)}{V_a(A(v, 0), 0)} = \frac{S_0(V_0^{-1}(v))}{V_0'(V_0^{-1}(v))}$$

where V_0^{-1} is the inverse function of V_0 .

The same $P_0 = P(0)$, $D_0 = D(0)$ and $R_0 = R(0)$ work for both systems.

Regarding the boundary conditions, from (11), $f\left(\frac{1}{2}, R(t)\right) U\left(\frac{1}{2}, t\right) = 2f(1, R(t))U(1, t)$ holds if and only if

$$\begin{aligned}
& f\left(\frac{1}{2}, R(t)\right) \frac{S(0, t)}{V_a(0, t)} = 2 \frac{S(a_d(t), t)}{V_a(a_d(t), t)} f(1, R(t)) \\
& \text{if and only if } S(0, t) = 2S(a_d(t), t) \frac{V_a(0, t)}{V_a(a_d(t), t)} \frac{f(1, R(t))}{f\left(\frac{1}{2}, R(t)\right)}.
\end{aligned} \tag{19}$$

On the other hand, $V(0, t) = \frac{1}{2}$ is a constant, then $V_t(0, t) = 0$ and so, from (15),

$$V_a(0, t) = \gamma f(V(0, t), R(t)) = \gamma f\left(\frac{1}{2}, R(t)\right)$$

and differentiating $V(a_d(t), t) = 1$ with respect to t we have that $V_a(a_d(t), t) a_d'(t) + V_t(a_d(t), t) = 0$ and from the equation for V in (15) we know that $V_t = \gamma f - V_a$ allowing us to write

$$V_a(a_d(t), t) a_d'(t) + \gamma f(V(a_d(t), t), R(t)) - V_a(a_d(t), t) = 0$$

$$\text{if and only if } V_a(a_d(t), t) = \frac{\gamma f(V(a_d(t), t), R(t))}{1 - a'_d(t)} = \frac{\gamma f(1, R(t))}{1 - a'_d(t)} \quad (20)$$

which means that

$$S(0, t) = 2S(a_d(t), t)[1 - a'_d(t)].$$

Replacing U with W and S with M in this last procedure we will prove that $f(\frac{1}{2}, R(t)) W(\frac{1}{2}, t) = 2f(1, R(t))W(1, t)$ if and only if $M(0, t) = 2M(a_d(t), t)[1 - a'_d(t)]$. ■

Corollary 3.4. *For all t ,*

$$a'_d(t) < 1. \quad (21)$$

Proof. From (20) we notice that

$$1 - a'_d(t) = \frac{\gamma f(1, R(t))}{V_a(a_d(t), t)} > 0$$

from where the result follows. ■

4 Equilibria

The global existence, uniqueness and non negativity of solutions of (15) is proved in [7]. For a wide survey on related topics, we suggest the classical books [10] and [4].

We now look for steady states of system (15) that may occur once the latency period has expired, this is when $t \geq L$. Since this situation implies no changes along time we assume all time values and all time derivatives to be zero, what causes all the state variables to become time independent, yielding the following equations

$$\begin{aligned} \dot{S}(a) &= -\left(\mu_1 + k_1 P V^{\frac{2}{3}}(a)\right) S(a), \\ \dot{M}(a) &= -\mu_2 M(a), \\ \dot{V}(a) &= \gamma f(V(a), R), \\ 0 &= -\left(m + k_1 \int_0^{a_d} V^{\frac{2}{3}}(a) S(a) da + k_2 D\right) P \\ &\quad + k_1 b e^{-\mu_1 L} P \int_0^{a_d} V^{\frac{5}{3}}(a) S(a) da, \\ 0 &= -(\delta + k_2 P) D + \mu_1 r \int_0^{a_d} V^{\frac{2}{3}}(a) S(a) da \\ &\quad + k_1 P \int_0^{a_d} V^{\frac{2}{3}}(a) \left(r V^{\frac{2}{3}}(a) - 1\right) S(a) da, \\ 0 &= d - \lambda R - \int_0^{a_d} f(V(a), R) (S(a) + M(a)) da, \end{aligned} \quad (22)$$

where all parameter values are given as for (15), a_d, D and R are positive unknown constants, P is a non negative fixed unknown value and the boundary conditions, being time independent are now simple restrictions for the functions S, M, V expressed by

$$\begin{aligned} S(0) &= 2S(a_d), \\ M(0) &= 2M(a_d), \\ V(0) &= \frac{1}{2}, \\ V(a_d) &= 1. \end{aligned} \quad (23)$$

We now focus on the third equation of (22) and for a given fixed R , we define $f_R(x) = \gamma f(x, R)$ together with

$$F_R(x) = \int_{\frac{1}{2}}^x \frac{ds}{f_R(s)}, \quad (24)$$

a primitive of $\frac{1}{f_R(x)}$. In this way we have that the solution of this third equation of (22) is

$$V(a) = V_R(a) = F_R^{-1}(a), \quad (25)$$

setting the stationary volume distribution whenever R is determined.

From (25), the age of division a_d defined as the solution of $V(a_d) = 1$ will be given by

$$a_d = a_d(R) = F_R(1). \quad (26)$$

To follow, in order to determine R , we will obtain general solutions by integration of the separated variables for the first two equations of (22) that setup four different scenarios that we will analyze separately in order to find some new unknown values when it is required.

From the second equation of (22) we have that

$$M(a) = M_0 e^{-\mu_2 a} \quad (27)$$

and, according to (23) the boundary condition $M_0 = 2M(a_d)$ must hold, implying that $M_0 = 2M_0 e^{-\mu_2 a_d}$. So, either

$$M(a) = M_0 = 0, \quad \text{for all } a \in [0, a_d], \quad \text{or} \quad \left(M_0 > 0 \text{ and } a_d = \frac{\ln 2}{\mu_2} \right), \quad (28)$$

setting up a scenario “ $\overline{\mathbf{M}}$ ”, in case $M_0 = 0$, and scenario “ \mathbf{M} ”, in case $M_0 > 0$. In the latter M_0 is the new unknown that allows to find $M(a)$ using equation (27).

Similarly, from the first equation of (22) we can write

$$S(a) = S_0 e^{-\mu_1 a - k_1 P \int_0^a V^{\frac{2}{3}}(s) ds} \quad (29)$$

and apply the boundary condition to obtain either

$$S(a) = 0, \quad \text{for all } a \in [0, a_d], \quad \text{or} \quad \left(S_0 > 0 \text{ and } a_d = \frac{\ln 2 - k_1 P \int_0^{a_d} V^{\frac{2}{3}}(s) ds}{\mu_1} \right), \quad (30)$$

where we obtain scenario “ $\overline{\mathbf{S}}$ ”, in case $S_0 = 0$, and scenario “ \mathbf{S} ”, in case $S_0 > 0$. In the second, S_0 is the new incognita that allow us to compute $S(a)$ using (29).

So all possible outcomes are determined by the mixed scenarios $\overline{\mathbf{MS}}$, $\overline{\mathbf{MS}}$, \mathbf{MS} and \mathbf{MS} .

In scenario $\overline{\mathbf{MS}}$, $S_0 = S(a) = M_0 = M(a) = 0$, so there are no susceptible nor resistant bacteria and system (22) becomes almost trivial taking the form

$$\begin{aligned} \dot{V}(a) &= \gamma f(V(a), R), \\ 0 &= -(m + k_2 D) P, \\ 0 &= -(\delta + k_2 P) D, \\ 0 &= d - \lambda R, \end{aligned} \quad (31)$$

with $V_0 = \frac{1}{2}$. In such case we have a steady state for the volume function determined by (25) for a resource level $R = \frac{d}{\lambda}$ together with $P = 0$ and $D = 0$, i.e. no phages nor debris, because

the other alternative, i.e. $(P, D) = (-\delta/k_2, -m/k_2)$, has no biological meaning. We relate this equilibrium to state #1 in Theorem 4.1.

In scenario $\overline{\mathbf{MS}}$ there are no susceptible bacteria but the resistant bacteria concentration is assumed to be positive, i.e. $S_0 = S(a) = 0$ and $M_0 > 0$, so (22) is reduced to

$$\begin{aligned} \dot{M}(a) &= -\mu_2 M(a) \\ \dot{V}(a) &= \gamma f(V(a), R) \\ 0 &= -(m + k_2 D) P, \\ 0 &= -(\delta + k_2 P) D, \\ 0 &= d - \lambda R - \int_0^{a_d} f(V(a), R) M(a) da \end{aligned} \tag{32}$$

with $M_0 = 2M(a_d)$, and $V(0) = \frac{1}{2}$. In this case, as before, $P = D = 0$, because the other alternative is not biologically feasible. In the other hand, from (28) and (26),

$$a_d = \frac{\ln 2}{\mu_2} = \int_{\frac{1}{2}}^1 \frac{ds}{f_R(s)} = F_R(1) \tag{33}$$

is a function of R (see figure 2) such that:

- $F_R(1) \xrightarrow{R \rightarrow 0^+} \infty$, because $f(x, 0) = 0$ for all x ,
- it is monotone decreasing, because the partial derivative of f with respect to the second variable is positive, i.e. $f_y(x, y) > 0$, and so
- $F_R(1) \xrightarrow{R \rightarrow \infty} \zeta_1$, for some $\zeta_1 > 0$, because $F_R(1)$ is lower bounded as a consequence of the existence of some $k > 0$ such that $f(x, y) < k$ (see the characterization of $f(x, y)$ just after system (1)).

In this situation, (33) will determine a unique value of R whenever

$$\zeta_1 := \lim_{R \rightarrow \infty} F_R(1) < \frac{\ln 2}{\mu_2}. \tag{34}$$

Assuming (34) to hold and provided a fixed value for R , considering (27) and the last equation of (32) we notice that we can determine a positive density of just born resistant cells

$$M_0 = \frac{d - \lambda R}{\int_0^{a_d} e^{-\mu_2 a} f(V(a), R) da}, \quad \text{only when } R < \frac{d}{\lambda}. \tag{35}$$

Instead of (34) we can guarantee the existence of the steady state (see figure 2) when

$$\frac{\ln 2}{\mu_2} > F_{\left(\frac{d}{\lambda}\right)}(1) = \zeta^* := \int_{\frac{1}{2}}^1 \frac{ds}{\gamma f(s, d/\lambda)}, \quad \text{i. e., when } 2e^{-\mu_2 \zeta^*} > 1. \tag{36}$$

We will recall this equilibrium as state #2 in Theorem 4.1.

In scenario \mathbf{MS} we have the susceptible and resistant bacteria concentrations both positive, i.e. $S_0 > 0$ and $M_0 > 0$, thus (22) can not be reduced. Under these circumstances we can proceed

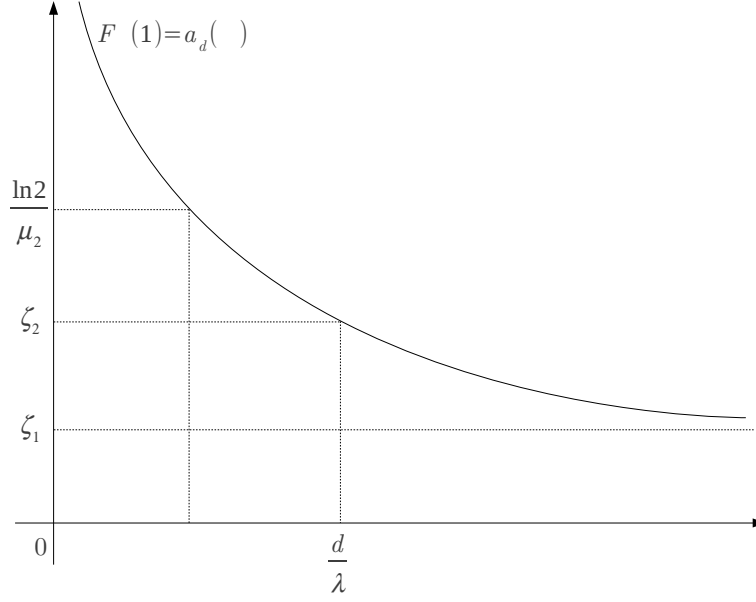


Figure 2: The age of division as a function R . R^* stands for the actual steady state value.

as in scenario \mathbf{MS} up to (33) and assume it to hold and provide us a fixed value for R so that we can compute $V(a)$ and a_d based on (25) and (26), respectively.

At this point we have determined $V(a)$ (thus a_d) and R and we notice that (28) and (30) imply that

$$a_d = \frac{\ln 2}{\mu_2} = \frac{\ln 2 - k_1 P \int_0^{a_d} V^{\frac{2}{3}}(s) ds}{\mu_1}, \quad \text{forcing} \quad \mu_1 \leq \mu_2, \quad (37)$$

and determining

$$P = \frac{\ln 2(\mu_2 - \mu_1)}{k_1 \mu_2 \int_0^{a_d} [F_R^{-1}(s)]^{\frac{2}{3}} ds} = \frac{a_d(\mu_2 - \mu_1)}{k_1 \int_0^{a_d} [F_R^{-1}(s)]^{\frac{2}{3}} ds} = \frac{\mu_2 - \mu_1}{\bar{k}_1}, \quad (38)$$

where

$$\bar{k}_1 = \frac{k_1 \int_0^{a_d} [F_R^{-1}(s)]^{\frac{2}{3}} ds}{a_d} \quad (39)$$

is the average of the adsorption capacity (cell surface times adsorption constant) taken over all possible normalized cell sizes between one half and one.

To continue let us define

$$I(p/q) := \int_0^{a_d} V^{\frac{p}{q}}(a) e^{-\mu_1 a - k_1 P \int_0^a V^{\frac{2}{3}}(s) ds} da$$

and

$$I^* := \int_0^{a_d} V^{\frac{2}{3}}(a) \left(r V^{\frac{2}{3}}(a) - 1 \right) e^{-\mu_1 a - k_1 P \int_0^a V^{\frac{2}{3}}(s) ds} da \quad (40)$$

allowing us to abbreviate

$$\int_0^{a_d} V^{\frac{p}{q}}(a)S(a)da = S_0I(p/q)$$

and

$$\int_0^{a_d} V^{\frac{2}{3}}(a) \left(rV^{\frac{2}{3}}(a) - 1 \right) S(a)da = S_0I^*.$$

Profiting from this notation and being P determined, in order to obtain S_0 and D , we simultaneously solve the fourth and fifth equations of (22) that are rewritten as

$$\begin{aligned} k_1S_0 [be^{-\mu_1L}I(5/3) - I(2/3)] - m - k_2D &= 0, \\ -(\delta + k_2P)D + S_0 [\mu_1rI(2/3) + k_1PI^*] &= 0, \end{aligned} \quad (41)$$

setting

$$D = \frac{m(\mu_1rI(2/3) + k_1PI^*)}{k_1(\delta + k_2P)[be^{-\mu_1L}I(5/3) - I(2/3)] - k_2(\mu_1rI(2/3) + k_1PI^*)} \quad \text{and} \quad (42)$$

$$S_0 = \frac{m(\delta + k_2P)}{k_1(\delta + k_2P)[be^{-\mu_1L}I(5/3) - I(2/3)] - k_2(\mu_1rI(2/3) + k_1PI^*)}, \quad (43)$$

whenever $m > 0$ and the common denominator is positive.

Actually we have that

$$S_0 = D \frac{\delta + k_2P}{\mu_1rI(2/3) + k_1PI^*}. \quad (44)$$

We notice that the common denominator of (42) and (43) is positive whenever the subtracting terms are less than the positive terms, i.e. when

$$b > e^{\mu_1L} \frac{(k_1\delta + k_2\mu_1r)I(2/3) + k_1k_2rPI(4/3)}{k_1(\delta + k_2P)I(5/3)}, \quad (45)$$

making S_0 and D both positive.

With the density of just born cells S_0 known and positive we can obtain $S(a)$ from (29) and compute, similarly to (35), a positive density of just born resistant cells

$$M_0 = \frac{d - \lambda R - \int_0^{a_d} f(V(a), R)S(a)da}{\int_0^{a_d} e^{-\mu_2a} f(V(a), R)da}, \quad (46)$$

$$\text{whenever} \quad R < \frac{1}{\lambda} \left(d - \int_0^{a_d} f(V(a), R)S(a)da \right).$$

This equilibrium, for $P > 0$, will correspond to state #4 in Theorem 4.1.

Before going further, it is mandatory to point that if the mortality rates of susceptible and resistant bacteria happen to coincide, we will write $\mu = \mu_1 = \mu_2$ and enter a new ‘sub-scenario’ where $P = 0$ and (22) reduces to

$$\begin{aligned} \dot{S}(a) &= -\mu S(a), \\ \dot{M}(a) &= -\mu M(a), \\ \dot{V}(a) &= \gamma f(V(a), R), \\ 0 &= -\delta D + \mu r \int_0^{a_d} V^{\frac{2}{3}}(a)S(a)da \\ 0 &= d - \lambda R - \int_0^{a_d} f(V(a), R) (S(a) + M(a)) da, \end{aligned} \quad (47)$$

where we can also proceed as in scenario $\overline{\mathbf{MS}}$ up to (34) and assume it to hold and provide us a fixed value for R by which we can compute $V(a)$ and a_d based on (25) and (26), respectively.

From the second and third equations in (47) we have that

$$S(a) = S_0 e^{-\mu a} \quad \text{and} \quad M(a) = M_0 e^{-\mu a}. \quad (48)$$

We remain to determine the values of S_0 , M_0 and D from the last two equations of (47) which naturally present one degree of freedom. From the fourth line in (47)

$$D = \frac{\mu r S_0 I(2/3)}{\delta} \quad (49)$$

and from the last equation in (47)

$$S_0 + M_0 = \frac{d - \lambda R}{\int_0^{a_d} e^{-\mu a} f(V(a), R) da} =: B \quad \text{whenever} \quad \frac{d}{\lambda} > R, \quad (50)$$

establishing a linear relation between S_0 and M_0 .

In this case, (49) points that D is computed directly from S_0 , though (50) determines an equilibria continuum, i.e. the susceptible and resistant bacterial concentrations can keep any arbitrary positive ratio as long as the sum of the just born cells equals the fraction in (50). This locus is geometrically represented by the open segment that joins the point $(0, B)$ with $(B, 0)$ in the $M_0 S_0$ -plane.

This case will be referred as state C in Theorem 4.1.

For the last scenario, namely $\overline{\mathbf{MS}}$, $M_0 = 0$ and $S_0 > 0$, so (22) becomes

$$\begin{aligned} \dot{S}(a) &= -\left(\mu_1 + k_1 P V^{\frac{2}{3}}(a)\right) S(a), \\ \dot{V}(a) &= \gamma f(V(a), R), \\ 0 &= -\left(m + k_1 \int_0^{a_d} V^{\frac{2}{3}}(a) S(a) da + k_2 D\right) P \\ &\quad + k_1 b e^{-\mu_1 L} P \int_0^{a_d} V^{\frac{5}{3}}(a) S(a) da, \\ 0 &= -(\delta + k_2 P) D + \mu_1 r \int_0^{a_d} V^{\frac{2}{3}}(a) S(a) da \\ &\quad + k_1 P \int_0^{a_d} V^{\frac{2}{3}}(a) \left(r V^{\frac{2}{3}}(a) - 1\right) S(a) da, \\ 0 &= d - \lambda R - \int_0^{a_d} f(V(a), R) S(a) da, \end{aligned} \quad (51)$$

and, similarly to (33) but in this occasion from the right hand side of (30), we will have that

$$\begin{aligned} a_d &= \frac{1}{\mu_1} \left(\ln 2 - k_1 P \int_0^{a_d} V^{\frac{2}{3}}(s) ds \right) \\ &= \frac{1}{\mu_1} \left(\ln 2 - k_1 P \int_0^{F_R(1)} [F_R^{-1}(s)]^{\frac{2}{3}} ds \right) = \int_{\frac{1}{2}}^1 \frac{ds}{f_R(s)} = F_R(1) \end{aligned}$$

determining, in terms of R ,

$$P = \frac{\ln 2 - \mu_1 F_R(1)}{k_1 \int_0^{F_R(1)} [F_R^{-1}(s)]^{\frac{2}{3}} ds}, \quad (52)$$

that will be non negative for all $R \geq R^* > 0$, where R^* is such that $F_{R^*}(1) = \frac{\ln 2}{\mu_1}$, because $F_R(1)$ is strictly decreasing with respect to R . In fact, P itself is a monotone increasing function of R , for all $R \geq R^*$, because in (52) the denominator decreases (since by a change of variable, $\int_0^{F_R(1)} [F_R^{-1}(s)]^{\frac{2}{3}} ds = \int_{\frac{1}{2}}^1 \frac{V^{\frac{2}{3}}}{f_R(V)} dV$) while the numerator increases with respect to R .

Since the case $P = 0$ has already been characterized and it will appear in Theorem 4.1 as state #3 we shall assume $P > 0$ and thus $R > R^*$.

We can write $S(a)$ in terms of S_0 by means of (29) and from the third and fourth equations in (51) and recalling (40) we find non negative values

$$D = \frac{S_0 (k_1 P I^* + \mu_1 r I(2/3))}{\delta + k_2 P}, \quad (53)$$

$$S_0 = \frac{m(\delta + k_2 P)}{k_1 k_2 P (be^{-\mu_1 L} I(5/3) - r I(4/3)) + \delta k_1 be^{-\mu_1 L} I(5/3) - (\delta k_1 + k_2 \mu_1 r) I(2/3)}$$

whenever

$$(k_1 k_2 P + \delta k_1) be^{-\mu_1 L} I(5/3) > k_1 k_2 P r I(4/3) + (\delta k_1 + k_2 \mu_1 r) I(2/3) \quad (54)$$

From the last equation in (51), the unknown positive value of R will be the solution of the equation

$$\lambda R = H(R) := d - S_0 \int_0^{F_R(1)} e^{-\mu_1 a - \frac{(\ln 2 - \mu_1 F_R(1)) \int_0^a [F_R^{-1}(s)]^{\frac{2}{3}} ds}{\int_0^{F_R(1)} [F_R^{-1}(s)]^{\frac{2}{3}} ds}} f(F_R^{-1}(a), R) da. \quad (55)$$

with $\frac{d}{\lambda} > R > R^*$. This last condition is needed to guarantee $P, R > 0$.

The existence of a value of R satisfying (55) can be concluded easily from the continuity of $H(R)$ (see figure 3), which is guaranteed if (54) holds for all $R \in [R^*, \frac{d}{\lambda}]$, whenever $H(R^*) > \lambda R^*$. Under such assumptions, since $H(R)$ is upper bounded by d there is no other chance for its graph that to intersect the line λR that happens to reach the value d precisely when $R = \frac{d}{\lambda}$.

To assure that (54) holds for all $R \in [R^*, \frac{d}{\lambda}]$, we will look for a burst size b big enough to simultaneously verify

$$be^{-\mu_1 L} I(5/3) > r I(4/3) \quad \text{and} \quad be^{-\mu_1 L} I(5/3) > \left(1 + \frac{k_2 \mu_1 r}{\delta k_1}\right) I(2/3) \quad (56)$$

aside from the implicitly involved value of R .

We notice that for arbitrary values $R, \alpha, \beta > 0$ and $h_1 > h_2 > 0$, we have that

$$\begin{aligned} \alpha I(h_1) - \beta I(h_2) &= \int_0^{F_R(1)} e^{-\mu_1 a - k_1 P} \int_0^a [F^{-1}(s)]^{\frac{2}{3}} ds (\alpha [F^{-1}(a)]^{h_1} - \beta [F^{-1}(a)]^{h_2}) da \\ &= \int_0^{F_R(1)} e^{-\mu_1 a - k_1 P} \int_0^a [F^{-1}(s)]^{\frac{2}{3}} ds [F^{-1}(a)]^{h_2} (\alpha [F^{-1}(a)]^{h_1 - h_2} - \beta) da \end{aligned}$$

will be positive if $\alpha [F^{-1}(a)]^{h_1 - h_2} > \beta$. Then $[F^{-1}(a)]^{h_1 - h_2} > \left(\frac{1}{2}\right)^{h_1 - h_2}$, for all R (and $a > 0$). So,

$$\frac{\alpha}{2^{h_1 - h_2}} > \beta \quad \text{imply} \quad \alpha I(h_1) > \beta I(h_2). \quad (57)$$

Applying (57) to (56) we obtain

$$b > e^{\mu_1 L} \max \left\{ 2^{\frac{1}{3}} r, 2 \left(1 + \frac{k_2 \mu_1 r}{\delta k_1}\right) \right\} \quad (58)$$

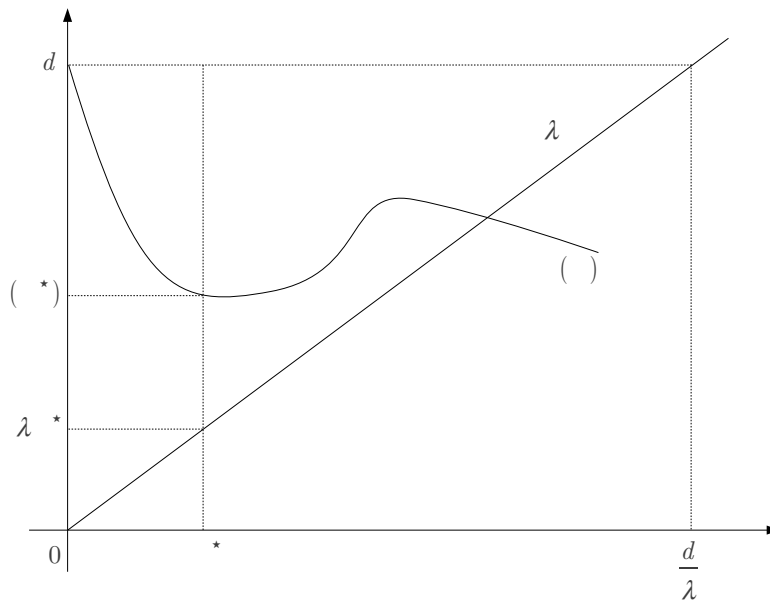


Figure 3: Existence of the steady state.

as a restriction for the existence of the steady state.

This restriction is not optimal in the sense that the steady state may exist under more relaxed conditions. What have presented for this scenario is only an existence argument not related to uniqueness nor to the necessary conditions for its existence.

This case is presented as state #5 in Theorem 4.1.

The calculations made in this subsection have proved the following result.

Theorem 4.1. *System (15) has from one up to five steady states whenever the conditions on the set of non negative parameters hold according to the following table. In the special case $\mu_1 = \mu_2$ the states 2 and 3 are the start and end points of the equilibria continuum state “C”.*

#	State	Conditions on the parameters
1	$S_0 = M_0 = P = D = 0, \quad R = d/\lambda$	none
2	$S_0 = P = D = 0,$ R such that $\int_{\frac{1}{2}}^1 \frac{ds}{\gamma f(s,R)} = \frac{\ln 2}{\mu_2},$ $M_0 = \frac{d-\lambda R}{\int_0^{a_d} e^{-\mu_2 a} f(V(s),R) ds}$	$2e^{-\mu_2 \zeta^*} > 1$
3	$M_0 = P = 0,$ R such that $\int_{\frac{1}{2}}^1 \frac{ds}{\gamma f(s,R)} = \frac{\ln 2}{\mu_1},$ $S_0 = \int_0^{a_d} \frac{d-\lambda R}{e^{-\mu_1 a} f(V(s),R) ds}, \quad D = \frac{\mu_1 r S_0 I(2/3)}{\delta}$	$2e^{-\mu_1 \zeta^*} > 1$
4	R such that $\int_{\frac{1}{2}}^1 \frac{ds}{\gamma f(s,R)} = \frac{\ln 2}{\mu_2},$ $P = \frac{\ln 2(\mu_2 - \mu_1)}{k_1 \mu_2 \int_0^{a_d} V^{\frac{2}{3}}(s) ds},$ $S_0 = \frac{m(\delta + k_2 P)}{k_1(\delta + k_2 P)Q - k_2(\mu_1 r I(2/3) + k_1 P I^*)},$ $D = S_0 \frac{\mu_1 r I(2/3) + k_1 P I^*}{\delta + k_2 P},$ $M_0 = \frac{d - \lambda R - \int_0^{a_d} f(V(a),R) S(a) da}{\int_0^{a_d} e^{-\mu_2 a} f(V(a),R) da}$	$\mu_1 < \mu_2, \quad 2e^{-\mu_2 \zeta^*} > 1,$ $b > e^{\mu_1 L} \frac{(k_1 \delta + k_2 \mu_1 r) I(2/3) + k_1 k_2 r P I(4/3)}{k_1(\delta + k_2 P) I(5/3)},$ $\frac{d - \int_0^{a_d} f(V(a),R) S(a) da}{\lambda} > R$
5	$M_0 = 0,$ R such that $\lambda R = H(R),$ with $P = \frac{\ln 2 - \mu_1 F_R(1)}{k_1 \int_0^{F_R(1)} [F_R^{-1}(s)]^{\frac{2}{3}} ds},$ D and S_0 given by (53)	$2e^{-\mu_1 \zeta^*} > 1,$ $b > e^{\mu_1 L} \max \left\{ 2^{\frac{1}{3}} r, 2 \left(1 + \frac{k_2 \mu_1 r}{\delta k_1} \right) \right\},$ $H(R^*) > \lambda R^*$
C	$P = 0, R$ such that $\int_{\frac{1}{2}}^1 \frac{ds}{\gamma f(s,R)} = \frac{\ln 2}{\mu},$ $S_0 + M_0 = \frac{d - \lambda R}{\int_0^{a_d} e^{-\mu a} f(V(a),R) da},$ $S_0, M_0 > 0, \quad D = S_0 \frac{\mu r I(2/3)}{\delta}$	$\mu = \mu_1 = \mu_2, \quad 2e^{-\mu \zeta^*} > 1$

Notation and remarks (to Theorem 4.1).

- State #5 may not be unique and may exist under more relaxed conditions on the parameters.
- In all cases, or for all states, the age structured volume distribution function is determined

as pointed by (24) and (25), i.e.

$$V(a) = V_R(a) = F_R^{-1}(a) \quad \text{with} \quad F_R(x) = \int_{\frac{1}{2}}^x \frac{ds}{f_R(s)} \quad \text{and} \quad f_R(x) = \gamma f(x, R),$$

thus setting the age of division $a_d = F_R(1)$ in concordance with (26), and the susceptible and resistant bacterial concentrations, $S(a), M(a)$, are computed from its just born cell concentrations, S_0, M_0 respectively, by means of (29) and (27), i.e.

$$S(a) = S(0)e^{-\mu_1 a - k_1 P} \int_0^a [F_R^{-1}(s)]^{\frac{2}{3}} ds \quad \text{and} \quad M(a) = M_0 e^{-\mu_2 a}.$$

- We abbreviate

$$\int_0^{a_d} V^{\frac{p}{q}}(a) S(a) da = S_0 I(p/q),$$

$$\int_0^{a_d} V^{\frac{2}{3}}(a) \left(r V^{\frac{2}{3}}(a) - 1 \right) S(a) da = S_0 I^*,$$

and we define

$$Q := b e^{-\mu_1 L} I(5/3) - I(2/3),$$

$$\zeta^* := \int_{\frac{1}{2}}^1 \frac{ds}{\gamma f(s, d/\lambda)},$$

$$H(R) := d - S_0 \int_0^{F_R(1)} e^{-\mu_1 a - \frac{(\ln 2 - \mu_1 F_R(1)) \int_0^a [F_R^{-1}(s)]^{\frac{2}{3}} ds}{\int_0^{F_R(1)} [F_R^{-1}(s)]^{\frac{2}{3}} ds}} f(F_R^{-1}(a), R) da.$$

- It is important to notice that, except for state #1, the conditions on the set of parameters can not be written without referring to the state variables because all calculations depend on the amount of available resources in equilibrium R that is implicitly determined by the resource consumption function $f(x, y)$ or even in a more complicated way in state #5. Also, since the state variables are fixed values computed based on the parameters and the resource consumption function f , we use the formers to abbreviate the conditions on the rightmost column.

Regarding Theorem 4.1, if we denote \mathcal{J}^i the set of instances of system (15) that comply with restrictions for state i , we can easily see that \mathcal{J}^1 is the set of all possible instances and that $\mathcal{J}^1 \supseteq \mathcal{J}^2 \supseteq \mathcal{J}^4$ and $\mathcal{J}^1 \supseteq \mathcal{J}^3 \supseteq \mathcal{J}^4, \mathcal{J}^5$ with $\mathcal{J}^4 \cap \mathcal{J}^5 \neq \emptyset \neq \mathcal{J}^2 \cap \mathcal{J}^3$, i.e.

- All instances present the trivial steady state # 1 with no bacteria and no phages at all.
- Some instances will have both phage free steady states # 2 (only mutants) and #3 (only susceptible cells).
- In a similar way some instances will have both steady states # 4 (coexistence of susceptible and resistant bacteria in the presence of phages) and #5 (coexistence of susceptible bacteria and phages with no resistant cells).
- The instances possessing state # 4 will have also steady states # 2 and #3.
- The instances possessing state # 5 will have also the steady state # 3.

Any instance of system (15) possessing the special state C, that represents the very particular case $\mu_1 = \mu_2$, is excluded from $\mathcal{J}^4 \cup \mathcal{J}^5$, i.e. if the mortality rates of resistant and susceptible bacteria are equal there can not be phages at all.

5 Conclusions

By means of Theorem 3.3 we have transformed system (1), that consists on two PDEs, plus definition (3) and plus three scalar integro differential equations, into (15) that happens to have gained one more PDE. The main advantage of this transformation is that the resulting characteristic curves for all three functions S, A, V in (15) are simple straight lines of slope 1, making easier some calculations but mainly the numerical simulation algorithms. The corresponding disadvantage is that we must deal with a shifting boundary condition $a_d(t)$ that is determined by the evolution of the system.

All instances of system (15), thus of system (1), will have a trivial steady state that lacks phages, susceptible and resistant bacteria.

When the bacterial basic reproduction number of either susceptible or resistant bacteria, that is computed from the resource consumption function f , the proportion constant $\gamma > 0$, the resource input speed d , the resource degradation ratio λ and the bacterial mortality rate according to (36), is greater than one, the systems will have other equilibria. This condition (36) by itself guarantees the existence of steady states with no phage presence but with susceptible or resistant bacteria alone.

More restrictive conditions, involving the viral reproduction efficiency, allow the coexistence in equilibrium of susceptible and resistant bacteria together with phages whenever the mortality rate of susceptible bacteria is less than the corresponding for resistant cells.

If the phage pressure does not revert the susceptible bacteria competitive advantage $\mu_1 < \mu_2$ (i.e. the natural death rate of resistant bacteria is bigger), then a susceptible bacteria and phages coexistence steady state will exist.

In the very special case when the mortality rate of susceptible and resistant bacteria are equal there will be a degenerate continuum of steady states that allow any given proportion of susceptible and resistant bacteria without phages.

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