Stability analysis of an enteropathogen population growing within a heterogeneous group of animals *

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Abstract

An autonomous semi-linear model for the proliferation of bacteria within a heterogeneous population of animals is developed. It is assumed that bacteria grow inside the intestines and that they can be either attached to the epithelial wall or as free particles in the lumen. A condition involving ecological parameters is given, which can be used to decide the existence of endemic equilibria as well as local stability properties of the non-endemic one. Some implications on phage therapy are addressed.

1 Introduction

Most enteropathogenic microorganisms such as *Salmonella*, enterotoxigenic *Escherichia*, *Yersinia* or protozoans within the *Giarda* genus have the potential to infect a broad spectrum of animals, including humans and livestock. They are able to adhere to the intestinal epithelium in order to persist in the gut in a way that they may damage some tissues and promote harmful inflammatory responses. As a consequence, the absorption of nutrients by the infected animal becomes severally reduced. Hence, epidemics driven by enteropathogens must be controlled in farms not only to improve production and the animal welfare, but also to prevent infection of people through food derivatives, eggs and meat primarily, or by contamination of rivers and lakes. Nowadays, the rising levels of multidrug resistant bacteria make the use of antibiotics a controversial option [17], while more ecologically based alternatives are becoming more popular, such as viral therapy with bacteriophage [1] or probiotic usage [13].

It is well known that the complex relations between the agents in such epidemiological scenarios make mathematical modelling a powerful tool to better understand the infection progression as well as to search and test different strategies designed to prevent and/or eradicate it (reviewed in [14] and [4]). Several theoretical results exist relating the epidemics evolution with bacteria-bacteriophage interactions

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[19, 5, 6], competition between virulent and innocuous strains [20, 10, 2], or the spatial and physiological structures of the host populations [15, 22]. They provide valuable information on how we can take advantage of certain processes in order to treat a group of animals just changing some ecological parameter. However, the link between the pathogen ecology inside and outside the host is in general not considered explicitly. From our point of view this issue deserves to be analysed carefully when dealing with living beings as therapeutic agents. This may give clues about how the cleaning of animals enclosures affects the bacterial growth. For example, if the detergents are much harmful for bacteriophage than for bacteria, then it could be better doing nothing instead of adopting an intensive hygienic policy. This work is partially motivated by this idea. Although we are not attempting to give precise therapeutic protocols, the qualitative results we derive shed some light on how the external environment together with the structure of the susceptible population affect the epidemic progression.

Our main goal is to present a rather general mathematical model about the dynamics of microorganisms that grow within the guts of animals. To this end, we somehow extend the linear PDE system introduced by Barbara Boldin to explore the *Escherichia coli* growth within a pig intestine [3], whose main feature is to distinguish those microbes present in the lumen from the ones attached to the epithelium. Thus, the former are affected by the intestinal flow while the latter are not. One of the incorporations we propose is nothing but to assume non-linear relations between the variables. Although it is a quite natural procedure since it allows to consider competition interactions or relations between bacteria and bacteriophage, some care must be taken from the mathematical point of view due to the fact that the variables belong to an infinite dimensional space. The aim of applying rigorously mathematical tools such as the linear stability principle lead us to make use of the so-called sun-dual formulation developed in [8] and [9] (see [11] for an application of the theory to population dynamics and [16] where it is used to treat a non-linear hyperbolic system similar to ours). Another important difference with respect to Boldin paper is that our framework makes possible to consider the spread of bacteria trough an heterogeneous group of hosts, while the model in [3] assumes an isolated animal. This is done just adding a new scalar variable that represents the amount of microbes in the external media. With this new ingredient we can also study which actions not on the animals but on the environment could be useful to control the spread of bacteria. The model analysis leads to a set of quantitative expressions that determines the stability of the non-endemic steady state. Several biological conclusions can be drawn from such magnitudes, and many of them will be highlighted along the text as *Biological remarks*.

The structure of the paper is the following: section 2 is devoted to the formulation of a rather general model to study how microbes behave within the gastrointestinal ecosystem. In section 3, we focus on a specific competition scenario and we give conditions on the parameters that ensure the existence of an endemic steady state (Theorem 3.7). In Theorem 3.13 we show that this equilibrium is stable whenever it exists. Finally, in section 4 we consider the possible effects on such equilibrium of a phage therapy consisting in the administration to the host animals of a certain dose of bacteriophage mixed with their food.

2 A rather general model for the gastrointestinal ecosystem

Consider a population with n hosts and m microbial types (bacteria and bacteriophage for example). Let $H = \{1, 2, \cdots, n\}$ and $S = \{1, 2, \cdots, m\}$ be the indexes for the host and the microbial types (or strains) respectively. Let us call $u_{h,s}(x,t)$ and $v_{h,s}(x,t)$ the densities of attached and luminal microbes of type s in the host h respectively, and $r_s(t)$ the density of strain s in the soil. Then the set of equations describing the dynamics of the microorganisms can be written as

$$\begin{cases} \partial_t u_{h,s} = g_{h,s}(x, u_h, v_h), \\ \partial_t v_{h,s} = -\partial_x(c_h(x)v_{h,s}) + f_{h,s}(x, u_h, v_h) & \forall (h,s) \in H \times S. \\ \frac{\mathrm{d}r_s}{\mathrm{d}t} = m_s(r) + \sum_{h\in H} k_{h,s}(c_h(l_h)v_{h,s}(t, l_h)) - \sum_{h\in H} \lambda_{h,s} r_s, \end{cases} \tag{1}$$

Here, $u_h = (u_{h,1}, \ldots, u_{h,m})$, $v_h = (v_{h,1}, \ldots, v_{h,m})$ and $r = (r_1, \ldots, r_m)$. The parameter l_h is the intestine length of host h and $c_h(x)$ stands for the celerity of its intestinal flow. As a first approximation we assume this is autonomous for mathematical convenience. The functions $g_{h,s}$ and $f_{h,s}$ take into account the ecological processes happening locally at the position x of the intestine. Besides replication and mortality of bacteria, these functions may also reflect migration between epithelium and lumen, competition interactions or whatever we are interested in. Similarly, function m_s describes the ecology in the external media of the population of type s, and $k_{h,s}$ gives the amount of strains s leaving the intestine of host h. Finally, we assume that microbes enter the intestine proportionally to their amount in the soil. Thus, $\lambda_{h,s}$ represents a kind of ingestion rate of particles of type s by host h. Consequently, a boundary condition for $v_{h,s}$ must be incorporated relating such reinfection term, which is

$$c_h(0)v_{h,s}(0,t) = \lambda_{h,s} r_s \qquad \forall (h,s) \in H \times S.$$

For the purposes of this paper, all functions introduced above (c_h, $g_{h,s}$, $f_{h,s}$ and $k_{h,s}$) are assumed to be differentiable.

In this article stability properties and processes of equilibria bifurcation of system (1) are addressed for a particular class of functions f and g. We proceed in a quite formal way, leaving the theory that justifies some key properties of (1) for a second publication. However, next we give some clues about such a theory, which is based on the sun-dual semilinear formulation developed in [8, 9] and which has been applied in previous biological and physical models [16, 11] (see also [18] where the standard semilinear formulation is presented). The idea is to treat (1) as the semilinear evolution problem

$$\begin{cases} \frac{\mathrm{d}u}{\mathrm{d}t} = \mathcal{G}(u, v), \\ \frac{\mathrm{d}v}{\mathrm{d}t} = -\partial_x(cv) + \mathcal{F}(u, v), \\ \frac{\mathrm{d}r}{\mathrm{d}t} = \mathcal{K}(v, r) - \Lambda r, \\ (v(0), u(0), r(0)) = (v_0, u_0, r_0) \in X, \end{cases} \tag{2}$$

X being the Banach space

$$X = \prod_{s\in S} \left(\left(\prod_{h\in H} L^\infty(0, l_h) \right) \times C_s \right)$$

where

$$C_s = \left\{ (v,r) \in \left(\prod_{h\in H} C([0,l_h],\mathbb{R}) \right) \times \mathbb{R} \quad | \quad c_h(0)v_h(0) = \lambda_{h,s} r \quad \forall h \in H \right\}.$$

If the right hand side of (2) is written as the sum of a linear unbounded operator plus a Lipschitz non-linear operator, then a generalized version of the variation of constants equation can be used to prove important properties about the dynamics of (1). Specifically, it can be shown that for any $x \in X$ there exists one, and only one, mild solution of the system. Although the term mild solution has a precise definition, for the purpose of this work it is enough to say that a mild solution could be non differentiable with respect time in the classical sense, but it has good regularity properties that make the equations in (2) meaningful. It can also be shown that a point $(u,v,r) = x \in X$ is a stationary state of (2) if and only if $v_{h,s}$ is Lipschitz for all pair $(h,s) \in H \times S$ and

$$\begin{cases} 0 = g_{h,s}(x,u_h,v_h), \\ 0 = -\partial_x(c_h(x)v_{h,s}) + f_{h,s}(x,u_h,v_h), & \forall (h,s) \in H \times S \\ 0 = m_s(r) + \sum_{h\in H} k_h(c_h(l_h)v_{h,s}(l_h)) - \sum_{h\in H} \lambda_{h,s} r_s, \end{cases}$$

where we take ∂_x as the derivative in distributional sense. Moreover, the stability of a given steady state $(u,v,r) = x \in X$ can be determined taking into account properties of the linearized generator of (2) around x, namely the linear operator

$$A \begin{pmatrix} \xi \\ \zeta \\ \rho \end{pmatrix} = \begin{pmatrix} D_2 g(\cdot,u(\cdot),v(\cdot))\xi + D_3 g(\cdot,u(\cdot),v(\cdot))\zeta \\ -\partial_x(c\zeta) + D_2 f(\cdot,u(\cdot),v(\cdot))\xi + D_3 f(\cdot,u(\cdot),v(\cdot))\zeta \\ \sum_{h\in H} k_h'(c_h(l_h)v_h(l))c_h(l_h)\zeta_h(l) + (m'(r) - \sum_{h\in H}\lambda_h)\rho \end{pmatrix} \tag{3}$$

with domain

$$D(A) = \{ (\xi,\zeta,\rho) \in X \mid \text{ each component of } \zeta \text{ is Lipschitz and } A(\xi,\zeta,\rho) \in X \}.$$

An important theorem relating the operator A with the stability of the steady state (u,v,r) is the following.

Theorem 2.1. *Let us assume that the spectrum of A can be written as a disjoint union $\sigma(A) = \Sigma_1 \dot\cup \Sigma_2$ satisfying:*

- *Σ_1 is finite and for all $\eta \in \Sigma_1$, η is an eigenvalue with finite algebraic multiplicity,*
- *there exists $\omega \in \mathbb{R}$ such that $Re(\eta_1) > \omega > Re(\eta_2)$ for all $\eta_1 \in \Sigma_1$ and $\eta_2 \in \Sigma_2$ and*

$$\omega > \operatorname{ess\,sup} D_2 g(\cdot,u(\cdot),v(\cdot)).$$

Then the equilibrium (u,v,r) is exponentially asymptotically stable if $\max_{\eta\in\Sigma_1} Re(\eta) < 0$ and unstable if $\max_{\eta\in\Sigma_1} Re(\eta) > 0$.

In this article we do not give a proof of the above result because it would be quite long and technical and we prefer to first illustrate the theory with particular scenarios. Let us just say that difficulties arise because of the unboundedness status of the generator A so typical of partial differential equations, forcing us to verify some compactness properties of the associated semigroup in order to relate the non-linear dynamics of (2) with the spectral properties of A. The methodology to overcome these problems is similar to the one used in the monograph [23] by G. F. Webb.

3 Spread of bacteria within a population of multiple hosts

In this section we consider a strain of bacteria growing within the intestines of an heterogeneous group of n animals enclosed in the same pen. Let $h \in H = \{1, 2, \ldots, n\}$ be an index for each animal and consider

$$\begin{cases} \partial_t u_h = \gamma_1^h(u_h)u_h + \alpha_h v_h - \delta_h u_h \\ \partial_t v_h = -c_h \partial_x v_h + \gamma_2^h(v_h)v_h - \alpha_h v_h + \delta_h u_h \\ \dot{r} = \sum_{h\in H}(c_h v_h(l_h, t) - \lambda_h r) - \mu r \\ c_h v_h(0, t) = \lambda_h r \end{cases} . \tag{4}$$

The parameters α and δ are per capita attachment and detachment rates to the epithelium respectively. The functions γ_1 and γ_2 are per capita growth rates. The sub and super indexes h indicate that these parameters may depend on which host the bacteria is inside. We make the assumption that

$$\begin{array}{l} \forall h \in H,\ \gamma_1^h \text{ and } \gamma_2^h \text{ are smooth functions on } [0, \infty), \text{ have negative} \\ \text{derivative and are negative valued for large enough arguments,} \end{array} \tag{5}$$

thus reflecting competition interactions both in the epithelium and in the lumen. We also assume that the transport speeds are constant. The free bacteria in the media are degraded at a per capita rate μ. Notice that the proposed model assumes a stable background bacterial community, whose effects on the modelled bacteria are constant in time. In this sense, the model may serve to decide if a foreign microorganism such as Salmonella can spread and persist within a mature intestine. The linear approximation of the attachment and detachment rates keeps the equations tractable and allows us to give qualitative results of the asymptotic behaviour of the population depending on α and δ. However, we are aware that it seems very difficult to determine experimentally how bacterial cells move from the epithelium to the lumen and vice versa. The stationary states of the system above are the solutions of

$$\begin{cases} 0 = \gamma_1^h(u_h)u_h + \alpha_h v_h - \delta_h u_h \\ 0 = -c_h \partial_x v_h + \gamma_2^h(v_h)v_h - \alpha_h v_h + \delta_h u_h \\ 0 = \sum_{h\in H}(c_h v_h(l_h) - \lambda_h r) - \mu r \\ c_h v_h(0) = \lambda_h r \end{cases} . \tag{6}$$

Clearly $(u, v, r) = (0, 0, 0)$ is always an equilibrium point, which corresponds to the infection free scenario. The interesting question is when positive solutions exist depending on the parameters. To address this issue, we will assume $\lambda_h > 0$ for all $h \in H$, which implies that every host is susceptible to be infected by environmental bacteria. We refer to such situation as the reinfection case. At the end of section 3 it is shown that if $\lambda_h = 0$ for some h, then system (4) becomes degenerate in some sense and a non-numerable set of equilibria may exist.

3.1 Stationary states in the reinfection case

3.1.1 Existence of an endemic equilibrium

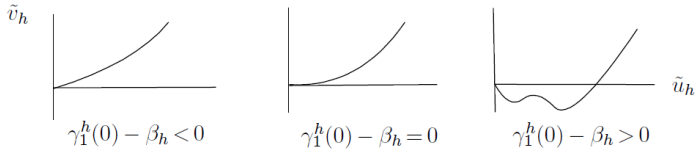
First of all notice that, using the monotony properties of γ_1^h, one easily proves that for every $\tilde{v}_h > 0$ there is a unique value $\tilde{u}_h = \tilde{u}_h(\tilde{v}_h)$ satisfying

$$\gamma_1^h(\tilde{u}_h)\tilde{u}_h + \alpha_h \tilde{v}_h - \delta_h \tilde{u}_h = 0$$

(see the graphical proof in Proposition 3.1 below). Moreover, the corresponding function $\tilde{u}_h(\tilde{v}_h)$ is increasing, regular and unbounded from above in the domain $\tilde{v}_h \in (0, \infty)$. We may denote $\tilde{u}_h(0)$ as the limit of $\tilde{u}_h(\tilde{v}_h)$ as $\tilde{v}_h$ decreases to zero. The following property relates $\tilde{u}_h(0)$ with the sign of $\gamma_1^h(0) - \delta_h$.

Proposition 3.1. *If $\gamma_1^h(0) - \delta_h \leq 0$, then $\tilde{u}_h(0) = 0$, and if $\gamma_1^h(0) - \delta_h > 0$, then $\tilde{u}_h(0) > 0$.*

Proof. Realize that $\tilde{u}_h(\tilde{v}_h)$ is nothing but the inverse function of $\tilde{v}_h(\tilde{u}_h) = -(\gamma_1^h(\tilde{u}_h) - \delta_h)\tilde{u}_h/\alpha_h$, which takes the following forms depending on the hypotheses.



Notice that if $\tilde{v}_h(\tilde{u}_h) > 0$, then necessarily $\tilde{v}_h'(\tilde{u}_h) > 0$ and that $\tilde{v}_h'(\tilde{u}_h) > \delta_h/\alpha_h$ for large values $\tilde{u}_h$. □

Let (u, v, r) be an endemic equilibrium. The relation between u_h and $\tilde{u}_h$ is given by $u_h(x) = \tilde{u}_h(v_h(x))$ provided $v_h(x) > 0$.

Proposition 3.2. *The component r of any endemic equilibrium (u, v, r) satisfying (6) must be positive.*

Proof. Suppose $r = 0$. Then $v_h(0) = v_h(l_h) = 0$ for all host h since we are assuming $\lambda_h > 0$ for all h. If $v_h(x) \equiv 0$, then the second equation in (6) gives $u_h(x) \equiv 0$. Otherwise, $v_h(x)$ is solution of the scalar differential equation $c_h v_h' = \gamma_2^h(v_h)v_h - \alpha_h v_h + \delta_h \tilde{u}_h(v_h)$, which is autonomous and whose right hand side is smooth for $v_h > 0$. Hence, $v_h(x)$ is necessarily monotone, which is not compatible with the boundary conditions $v_h(0) = v_h(l_h) = 0$ unless $v_h(x) \equiv 0$. □

The above observations reduce system (6) to

$$\begin{cases} v_h' = (\gamma_2^h(v_h)v_h - \alpha_h v_h + \delta_h\, \tilde{u}_h(v_h))/c_h =: g_h(v_h), \\ v_h(0) = \lambda_h r/c_h, \\ 0 = \sum_{h \in H}(c_h v_h(l_h) - \lambda_h r) - \mu r. \end{cases} \tag{7}$$

Next we are going to show that all equations $v_h' = g_h(v_h)$ have a well defined solution $\varphi_h(x; v_h(0)) > 0$ for all $x \geq 0$ provided $v_h(0) > 0$, so that there are as many non trivial solutions of (6) as positive solutions $\bar{r} > 0$ the equation

$$0 = \sum_{h \in H}(c_h \varphi_h(l_h; \lambda_h r/c_h) - \lambda_h r) - \mu r \tag{8}$$

has. The equilibrium is expressed in terms of $\bar{r}$ as

$$\bar{u}_h(\cdot) = \tilde{u}_h(\bar{v}_h(\cdot)) \quad \text{and} \quad \bar{v}_h(\cdot) = \varphi_h(\cdot; \lambda_h \bar{r}/c_h) \qquad \forall h \in H.$$

In order to prove the existence of the functions $\varphi_h(x; v_h(0))$ we use the lemmas below. We omit the indexes h because all we need to use are the structural properties of γ_1^h and γ_2^h given in (5), which are shared by all hosts.

Lemma 3.3. *The function* $\frac{c\,g(v)}{v} = \frac{\gamma_2(v)v - \alpha v + \delta\tilde{u}(v)}{v}$ *is strictly decreasing for* $v > 0$ *and it is either always negative or it vanishes at some value* $v_\infty > 0$.

Proof. First we prove the monotony property. Since $\gamma_2(v)$ decreases, it is enough to show that $h(v) := \tilde{u}(v)/v$ is strictly decreasing. From the definition of $\tilde{u}(v)$ we obtain the equation $(\gamma_1(vh(v)) - \delta)h(v) + \alpha = 0$, and taking the derivative we have

$$\gamma_1'(vh(v))(h(v) + vh'(v))h(v) + (\gamma_1(vh(v)) - \delta)h'(v) = 0.$$

Therefore, the derivative $h'(v)$ can only vanish if $h(v)$ vanishes too. In addition it is easily seen that $h'(v) < 0$ for some v small enough, since $\lim_{v\downarrow 0} h(v) = \infty$ if $\gamma_1(0) - \delta \geq 0$ and, on the other hand, using L'Hôpital's rule and the second derivative of the inverse function, we have

$$\lim_{v\downarrow 0} h'(v) = \frac{1}{2}\tilde{u}''(0) = -\frac{1}{2}\,\frac{\tilde{v}''(0)}{\tilde{v}'(0)^3} = -\alpha^2\frac{\gamma_1'(0)}{(\gamma_1(0) - \delta)^3} < 0$$

if $\gamma_1(0) - \delta < 0$. Finally, as $h(v)$ is always positive for $v > 0$, we conclude that $h'(v) < 0$ for all $v > 0$.

Now we show that $\gamma_2(v)v - \alpha v + \delta\tilde{u}(v)$ is negative for v large enough, which implies the second claim of the lemma. Since $\gamma_2(v)$ eventually becomes negative, it suffices to prove $\delta\,\tilde{u}(v) < \alpha\,v$ for large values of v. Taking into account the negativeness of $\gamma_1(u)$ for large arguments, and also that $\tilde{u}(v)$ is an increasing function of v unbounded from above, it follows $-\gamma_1(\tilde{u}(v))\tilde{u}(v) > 0$ for v large enough. Then, using that $\gamma_1(\tilde{u}(v))\tilde{u}(v) + \alpha v - \delta\tilde{u}(v) = 0$ we finally obtain $\alpha v = \delta\tilde{u}(v) - \gamma_1(\tilde{u}(v))\tilde{u}(v) > \delta\tilde{u}(v)$, for v large enough. □

Lemma 3.4. *Let* $\varphi(x;\varphi_0)$ *be the solution of the initial value problem*

$$\varphi'(x) = f(\varphi(x))\varphi(x), \qquad \varphi(0) = \varphi_0 > 0,$$

where f *is a strictly decreasing smooth function defined on* $(0,\infty)$. *Then,* $\varphi(x;\varphi_0)$ *is uniquely defined and positive for all* $x \geq 0$. *Moreover, for any* $l > 0$, *the function*

$$h(\varphi_0; l) := \frac{\varphi(l;\varphi_0)}{\varphi_0}$$

is a strictly decreasing function of $\varphi_0 \in (0,\infty)$.

Proof. We start by proving that $\varphi(x;\varphi_0)$ is uniquely defined for all $x \geq 0$. On the one hand, either $f(\varphi) > 0$ for some $\varphi > 0$ and therefore $\varphi(x;\varphi_0)$ increases for φ_0 small enough, or $f(\varphi) < 0$ for all $\varphi > 0$, in which case one easily obtains the lower bound $\varphi(x;\varphi_0) \geq \varphi_0 e^{f(\varphi_0)x}$. In any case $\varphi(x;\varphi_0)$ keeps away from 0 and positive for finite x. On the other hand, $\varphi(x;\varphi_0)$ cannot grow up to infinity for finite positive values of x because, for any $\varepsilon > 0$, $f(\varphi)\varphi < f(\varepsilon)\varphi$ when $\varphi \geq \varepsilon$.

Having established that $h(\varphi_0; l)$ is well defined for all $l > 0$, we show that it is strictly decreasing. Consider $0 < \varphi_1 < \varphi_2$. It is clear that, for any s, $0 < \varphi(s;\varphi_1) < \varphi(s;\varphi_2)$ holds, so that $f(\varphi(s;\varphi_1)) > f(\varphi(s;\varphi_2))$ due to the monotony of f. Finally, since $\ln h(\varphi_0; l) = \int_0^l f(\varphi(s;\varphi_0))\mathrm{ds}$, it follows that $h(\varphi_1; l) > h(\varphi_2; l)$ for all $l \in (0,\infty)$. □

Lemma 3.5. *Under the hypotheses of Lemma 3.4,*

i) If $\lim_{\varphi\downarrow 0} f(\varphi) = \infty$, *then* $\lim_{\varphi_0\downarrow 0} \frac{\varphi(l;\varphi_0)}{\varphi_0} = \infty$.

ii) If $f(0) := \lim_{\varphi\downarrow 0} f(\varphi) < \infty$, *then* $\lim_{\varphi_0\downarrow 0} \frac{\varphi(l;\varphi_0)}{\varphi_0} = e^{f(0)l}$

Proof. Notice that $\varphi(l;\varphi_0)$ is a positive increasing function of φ_0. In case *i*), if $\varphi(l;\varphi_0)$ tends to a positive limit when φ_0 goes to 0, the conclusion is obvious. Otherwise, since $\varphi(x;\varphi_0)$ increases with x (when φ_0 is small) and f is a decreasing function, we easily obtain $\varphi(l;\varphi_0) \geq \varphi_0 + lf(\varphi(l;\varphi_0))\varphi_0$ which clearly implies

$$\lim_{\varphi_0\downarrow 0} \frac{\varphi(l;\varphi_0)}{\varphi_0} \geq \lim_{\varphi_0\downarrow 0} (1 + lf(\varphi(l;\varphi_0))) = 1 + l \lim_{\varphi\downarrow 0} f(\varphi) = \infty.$$

In case *ii*), $\lim_{\varphi_0\downarrow 0} \varphi(l;\varphi_0) = 0$ and the limit of the ratio $\varphi(l;\varphi_0)/\varphi_0$ turns out to be undetermined. To resolve this, we compute the first variation $\partial_2\varphi(l;0)$ and we get

$$\varphi(l;\varphi_0) = \varphi(l;0) + \partial_2\varphi(l;0)\varphi_0 + o(\varphi_0) = \varphi_0 e^{f(0)l} + o(\varphi_0),$$

which gives the claim. □

Remark 3.6. *In case i), $\varphi(l;\varphi_0)$ can indeed tend to 0 as φ_0 goes to 0. An example is given by $f(\varphi) = -\ln(\varphi)$.*

Realize that Lemma 3.3 ensures that $g_h(v)/v$ satisfies the hypotheses on f of Lemma 3.4, so that not only $\varphi_h(x;v)$ exists for any initial condition $v > 0$, but also satisfies that $\varphi_h(x;v)/v$ is a decreasing function with respect to v. Moreover, since $g_h(v) < 0$ if v is large enough, $\varphi_h(x;v)/v < 1$ for such large v values. These properties allows us to prove that (8) has at most one positive solution. Indeed, dividing (8) by $r > 0$ we get

$$0 = \sum_{h\in H} \left(\lambda_h \frac{\varphi_h(l;\lambda_h r/c_h)}{\lambda_h r/c_h} - \lambda_h \right) - \mu =: k(r).$$

The properties of φ_h mentioned above clearly imply that $k(r)$ is an eventually negative decreasing function. So, equation (8) has one unique solution if and only if $\lim_{r\downarrow 0} k(r) > 0$, that is if

$$\lim_{r\downarrow 0} \sum_{h\in H} \lambda_h \frac{\varphi_h(l_h;\lambda_h r/c_h)}{\lambda_h r/c_h} > \mu + \sum_{h\in H} \lambda_h \quad . \tag{9}$$

Defining

$$\varepsilon_h := \frac{\lambda_h}{\mu + \sum_{h\in H} \lambda_h} \quad ,$$

we proceed to prove a theorem which gives necessary and sufficient conditions for the existence of an endemic equilibrium of system (4).

Theorem 3.7. *In the reinfection case (i.e., if $\lambda_h > 0$ for all $h \in H$), system (4) has an endemic equilibrium if and only if*

i) $\gamma_1^h(0) \geqslant \delta_h$ *for some* $h \in H$, *or*

ii) $\gamma_1^h(0) < \delta_h$ *for all* $h \in H$ *and*

$$\sum_{h\in H} \varepsilon_h e^{\frac{l_h}{c_h}\left(\gamma_2^h(0) - \alpha_h + \frac{\alpha_h\delta_h}{\delta_h - \gamma_1^h(0)}\right)} > 1\,. \tag{10}$$

Proof. Recall that for each $g_h(v)$, the function

$$f_h(v) := \frac{g_h(v)}{v} = \frac{\gamma_2^h(v)v - \alpha_h v + \delta_h \tilde{u}_h(v)}{c_h\, v}$$

satisfies the hypotheses on f of Lemma 3.4 (due to Lemma 3.3).

In case i), $f_h(v)$ tends to infinity at the origin for some host h. Indeed, this is clear if $\gamma_1^h(0) > \delta_h$ since then $\tilde{u}_h(0) > 0$, whereas if $\gamma_1^h(0) = \delta_h$ then $\tilde{v}_h(u)/u = (\delta_h - \gamma_1^h(u))/\alpha_h \to 0$ as u tend to 0 and so $\tilde{u}_h(v)/v \to \infty$ as v tends to 0 (recall Proposition 3.2 and the definition of $\tilde{v}_h(u)$ therein). Hence,

$$\lim_{r\downarrow 0} \frac{\varphi_h(l_h; \lambda_h r/c_h)}{\lambda_h r/c_h} = \infty$$

by Lemma 3.5. Therefore, the limit in (9) equals infinity and an endemic equilibrium must exist.

In case ii), $f_h(v)$ tends to

$$\frac{1}{c_h}\left(\gamma_2^h(0) - \alpha_h + \frac{\delta_h \alpha_h}{\delta_h - \gamma_1^h(0)}\right)$$

at the origin for all h (since now $\lim_{v\downarrow 0} \tilde{u}_h(v)/v = \tilde{u}_h'(0) = 1/\tilde{v}_h'(0) = \alpha_h/(\delta_h - \gamma_1^h(0))$. Therefore, by Lemma 3.5,

$$\lim_{r\to 0} \frac{\varphi_h(l_h; \lambda_h r/c_h)}{\lambda_h r/c_h} = e^{\frac{l_h}{c_h}\left(\gamma_2^h(0) - \alpha_h + \frac{\alpha_h \delta_h}{\delta_h - \gamma_1^h(0)}\right)}.$$

Then, condition (9) can be rewritten as (10) and the theorem is proven. □

3.1.2 Stability of the equilibria

Next we give stability results related to the steady states of system (4). Recall that we take perturbations within the Banach space $X = (\prod_{h\in H} L^\infty(0, l_h)) \times C$, where

$$C := \left\{ (v, r) \in \left(\prod_{h\in H} C([0, l_h], \mathbb{R}) \right) \times \mathbb{R} \mid c_h v_h(0) = \lambda_h r \right\}.$$

Let $(\bar{u}, \bar{v}, \bar{r})$ be an equilibrium of (4), where $\bar{u}$ and $\bar{v}$ have n components, one for each host. In view of (3), $(u, v, r) \in X$ belongs to $D(A)$ if, for all $h \in H$, v_h is Lipschitz, $\hat{v}_h := -c_h {v_h}' + (\gamma_2^h(\bar{v}_h) - \alpha_h + \left(\gamma_2^h\right)'(\bar{v}_h)\bar{v}_h)v_h + \delta_h u_h$ is continuous on $[0, l_h]$ and

$$c_h \hat{v}_h(0) = \lambda_h \hat{r},$$

where $\hat{r} := \sum_{h\in H}(c_h v_h(l_h, t) - \lambda_h r) - \mu r$ (recall that v' indicates the weak derivative of v). If we define

$$\begin{aligned} a_1^h(x) &:= \gamma_1^h(\bar{u}_h(x)) - \delta_h + \left(\gamma_1^h\right)'(\bar{u}_h(x))\bar{u}_h(x) \\ a_2^h(x) &:= \gamma_2^h(\bar{v}_h(x)) - \alpha_h + \left(\gamma_2^h\right)'(\bar{v}_h(x))\bar{v}_h(x) \end{aligned}$$

then

$$A\begin{pmatrix} u \\ v \\ r \end{pmatrix} = \begin{pmatrix} \hat{u} \\ \hat{v} \\ \hat{r} \end{pmatrix} \qquad \text{where} \qquad \begin{aligned} \hat{u}_h &= a_1^h(x)u_h + \alpha_h v_h \\ \hat{v}_h &= -c_h v_h' + a_2^h(x)v_h + \delta_h u_h \\ \hat{r} &= \textstyle\sum_{h\in H}(c_h v_h(l_h) - \lambda_h r) - \mu r \end{aligned} \quad . \tag{11}$$

Lemma 3.8. *The spectrum of the linear operator A is the set*

$$\sigma(A) = \sigma_{ess}(A) \bigcup \{\eta \in \mathbb{C} \setminus \sigma_{ess}(A) | \Gamma(\eta) = 0\},$$

where $\sigma_{ess}(A) = \bigcup_{h \in H} \operatorname{ess\,range} a_1^h(\cdot)$ *is the essential spectrum of* A *and* $\Gamma(\eta)$ *is the characteristic function*

$$\Gamma(\eta) := \mu + \eta + \sum_{h \in H} \lambda_h - \sum_{h \in H} \lambda_h \exp\left(\frac{1}{c_h} \int_0^{l_h} a_2^h(s) - \frac{\delta_h \alpha_h}{a_1^h(s) - \eta} - \eta \, ds \right). \quad (12)$$

Proof. By definition, $\eta \in \sigma(A)$ if the operator $A - \eta \mathrm{Id} : D(A) \to X$ does not have a continuous inverse. Take $(\hat{u}, \hat{v}, \hat{r}) \in X$ and consider the system

$$\begin{cases} a_1^h(x) u_h + \alpha_h v_h - \eta u_h = \hat{u}_h \\ -c_h v_h' + a_2^h(x) v_h + \delta_h u_h - \eta v_h = \hat{v}_h \\ \sum_{h \in H} (c_h v_h(l_h) - \lambda_h r) - \mu r - \eta r = \hat{r} \\ c_h v_h(0) = \lambda_h r \end{cases} . \quad (13)$$

Clearly, the system above fails to have a solution for all $(\hat{u}, \hat{v}, \hat{r})$ if $a_1^h(x) - \eta = 0$ for some $h \in H$, and this condition determines the set $\sigma_{\mathrm{ess}}(A)$. If $\eta \notin \sigma_{\mathrm{ess}}(A)$, the component u_h can be isolated and the equations for v_h in (13) reduce to

$$\begin{cases} -v_h' + \frac{1}{c_h}(a_2^h(x) - \eta - \delta_h \frac{\alpha_h}{a_1^h(x) - \eta}) v_h = \frac{1}{c_h} \left(\hat{v}_h - \delta_h \frac{\hat{u}_h}{a_1^h(x) - \eta} \right) \\ v_h(0) = \frac{\lambda_h}{c_h} r \end{cases} . \quad (14)$$

Solving the above differential equations by means of the variation of constants formula, one in particular gets

$$v_h(l_h) = \frac{\lambda_h}{c_h} r \exp\left(\frac{1}{c_h} \int_0^{l_h} a_2^h(s) - \eta - \delta_h \frac{\alpha_h}{a_1^h(s) - \eta} ds \right) + I_h(\eta, \hat{u}_h, \hat{v}_h) \quad (15)$$

where $I_h(\eta, \hat{u}_h, \hat{v}_h)$ depends continuously on the pair $(\hat{u}_h, \hat{v}_h)$ and can be given explicitly. Finally, we use (15) in the equation for r of system (13), so that r must satisfy

$$-\Gamma(\eta)\, r = \hat{r} - \sum_{h \in H} c_h I_h(\eta, \hat{u}_h, \hat{v}_h). \quad (16)$$

Therefore, since the right hand side of (16) can be any real value because it depends on the arbitrary elements $\hat{u}_h$, $\hat{v}_h$ and $\hat{r}$, we conclude that system (13) fails to have a unique solution for all points $(\hat{u}, \hat{v}, \hat{r}) \in X$ if $\Gamma(\eta) = 0$. □

Proposition 3.9. *If A has a real eigenvalue η_d greater than $\max_{h \in H} \operatorname{ess\,sup} a_1^h(\cdot)$, then there exists $\omega \in \mathbb{R}$ such that $\eta_d > \omega > \sup_{\eta \in \sigma(A), \eta \neq \eta_d} \mathrm{Re}(\eta)$.*

Proof. Notice that $\Gamma_{|\mathbb{R}} : (\max_{h \in H}(\operatorname{ess\,sup} a_1^h(\cdot)), \infty) \longrightarrow \mathbb{R}$ is a strictly increasing function, so that only one real eigenvalue greater than $\max_{h \in H} \operatorname{ess\,sup} a_1^h(\cdot)$ may exist. Assume such a real eigenvalue, referred as η_d, exists. Now we show that all other complex eigenvalues are located to the left of η_d. Define, for real ρ and y,

$$f_h(\rho, y) := \frac{1}{c_h} \left(\alpha_h \delta_h \int_0^{l_h} \frac{(\rho - a_1^h(x)) dx}{y^2 + (\rho - a_1^h(x))^2} + \int_0^{l_h} a_2^h(x) dx - \rho \, l_h \right)$$

and

$$g_h(\rho, y) := -\frac{1}{c_h}\left(\alpha_h\delta_h\int_0^{l_h}\frac{y\,dx}{y^2+(\rho-a_1^h(x))^2}+y\,l_h\right),$$

which are, respectively, the real and the imaginary part of

$$\frac{1}{c_h}\int_0^{l_h} a_2^h(x)-\frac{\delta_h\alpha_h}{a_1^h(x)-(\rho+iy)}-(\rho+iy)\,dx.$$

Then, for all $(\rho+iy)\in\mathbb{C}$ with $y\neq 0$ satisfying $\max_{h\in H}(\operatorname{ess\,sup} a_1^h(\cdot))<\rho$, clearly $f_h(\rho,y)<f_h(\rho,0)$ for all $h\in H$ and

$$\begin{aligned}\operatorname{Re}(\Gamma(\rho+iy)) = \quad & \rho+\mu+\textstyle\sum_{h\in H}\lambda_h-\sum_{h\in H}\lambda_h e^{f_h(\rho,y)}\cos g_h(\rho,y) > \\ & > \rho+\mu+\textstyle\sum_{h\in H}\lambda_h-\sum_{h\in H}\lambda_h e^{f_h(\rho,0)}=\Gamma(\rho).\end{aligned}$$

This inequality implies that, if $\rho\geq\eta_d$, then $\operatorname{Re}(\Gamma(\rho+iy))>\Gamma(\rho)\geq\Gamma(\eta_d)=0$ (recall $\Gamma_{|\mathbb{R}}$ is increasing), so that $(\rho+iy)$ cannot be an eigenvalue.

Finally, let us prove that there exists a stripe $(\omega,\eta_d)\times i\,\mathbb{R}$ in the complex plane which does not include any spectral value. Choose $\omega>\max_{h\in H}\operatorname{ess\,sup} a_1^h(\cdot)$. Next we show that function Γ can only have a finite number of zeros in the stripe determined by such an ω. On the one hand, since

$$\lim_{|y|\to\infty}|\operatorname{Im}(\Gamma(\rho+iy))|=\lim_{|y|\to\infty}\left|y-\sum_{h\in H}\lambda_h e^{f_h(\rho,y)}\sin g_h(\rho,y)\right|=\infty\quad\forall\rho\in(\omega,\eta_d),$$

the solutions of $\Gamma(\rho+iy)=0$ within the stripe are a bounded set. On the other hand, since Γ is holomorphic in the stripe, the set of its zeros cannot have accumulation points. These two facts clearly imply that $\Gamma(\eta)$ only vanishes for finitely many values η within the stripe. Hence, for an ω close enough to η_d the stripe will not include any solution of Γ. □

Theorem 3.10. *In the reinfection case ($\lambda_h>0$ for all $h\in H$),*

i) If a non-trivial equilibrium of (4) exists, then the trivial one is unstable.

ii) If the trivial equilibrium is the only stationary solution of (4), then it is asymptotically stable or it is non-hyperbolic (more precisely, such that $s(A)=0$).

Proof. Setting $(\bar u,\bar v,\bar r)=(0,0,0)$, we obtain $a_1^h(x)\equiv\gamma_1^h(0)-\delta_h$ and $a_2^h(x)\equiv\gamma_2^h(0)-\alpha_h$, so the characteristic function (12) reduces to

$$\Gamma(\eta)=\eta+\mu+\sum_{h\in H}\lambda_h-\sum_{h\in H}\lambda_h e^{\frac{l_h}{c_h}\left(\gamma_2^h(0)-\alpha_h-\frac{\alpha_h\delta_h}{\gamma_1^h(0)-\delta_h-\eta}-\eta\right)}.$$

Denote $a_1^h=\gamma_1^h(0)-\delta_h$. Since $\lim_{\rho\downarrow\max_{h\in H}a_1^h}\Gamma(\rho)=-\infty$ and $\lim_{\rho\uparrow\infty}\Gamma(\rho)=\infty$, there exists a real number $\eta_d>\max_{h\in H}a_1^h$ such that $\Gamma(\eta_d)=0$. Hence, by proposition 3.9, the stability of the trivial state depends on the sign of η_d (see proposition 2.1). Let us first assume either $\gamma_1^h(0)\geq\delta_h$ for some h or $\gamma_1^h(0)<\delta_h$ for all h and

$$\sum_{h\in H}\varepsilon_h e^{\frac{l_h}{c_h}\left(\gamma_2^h(0)-\alpha_h+\frac{\alpha_h\delta_h}{\delta_h-\gamma_1^h(0)}\right)}>1$$

(i.e. that there exists a non-trivial equilibrium by Theorem 3.7). Then, in the first case $\eta_d > \max_{h\in H}(\operatorname{ess\,sup} \gamma_1^h(0) - \delta_h) \geq 0$, while in the second case we obtain $\Gamma(0) < 0$ which also implies $\eta_d > 0$. Thus the trivial steady state is unstable (by propositions 2.1 and 3.9). On the other hand, let us now assume that the trivial state is the only steady state and that the strict inequality

$$\sum_{h\in H} \varepsilon_h e^{\frac{l_h}{c_h}\left(\gamma_2^h(0)-\alpha_h+\frac{\alpha_h\delta_h}{\delta_h-\gamma_1^h(0)}\right)} < 1$$

holds. Then $\Gamma(0) > 0$, so that η_d is negative. In this case, the trivial steady state is stable (by propositions 2.1 and 3.9).

Finally notice that the remaining special case $\gamma_1^h(0) < \delta_h$ for all h and equality in (10), implies $\Gamma(0) = 0$ and $\eta_d = s(A) = 0$, where $s(A)$ denotes the spectral bound of A. In order to determine the trivial state stability in this situation other non-linear techniques should be used, but such an analysis is beyond our scope. □

The combination of Theorems 3.7 and 3.10 allows us to give the following biological interpretations of the system.

Biological remark 3.11. *If one animal houses an attached bacteria whose growth rate is bigger than its detachment rate, then an outbreak occurs. Alternatively, if the previous condition does not hold, then an outbreak occurs if the residence time of a bacterium within the intestine of one animal is large enough. Notice that both conditions involve only the features of one animal, but the epidemic will spread trough all the population. Hence, treatments targeted to some special animal could be more effective than treating all the population in the same way.*

Biological remark 3.12. *Notice that if all the animals are physiologically equivalent, then the condition in Theorem 3.7 becomes*

$$e^{\frac{l}{c}\left(\gamma_2(0)+\frac{\alpha\gamma_1(0)}{\delta-\gamma_1(0)}\right)} > \frac{\mu+n\lambda}{n\lambda} \quad .$$

In particular, we see that bacteria are always able to grow and persist if the number of animals is large enough and $\gamma_2(0) > 0$.

Theorem 3.13. *The endemic equilibrium is locally asymptotically stable whenever it exists.*

Proof. Since, for all $h \in H$, the functions $\bar{u}_h(x)$ and $\bar{v}_h(x)$ are positive and differentiable (it is easy to check that), then $a_1^h(x)$ and $a_2^h(x)$ are also differentiable within $[0, l_h]$. In particular, this implies that $\Gamma(\rho) \to -\infty$ as ρ tends to $\max_{h\in H}(\operatorname{ess\,sup} a_1^h(\cdot))$ from above. Next we show that $\Gamma(0) > 0$, which ensures the existence of a unique $\eta_d \in (\max_{h\in H}(\operatorname{ess\,sup} a_1^h(\cdot)), 0)$ satisfying $\Gamma(\eta_d) = 0$) due to the monotony and continuity of Γ. Recall

$$\Gamma(0) = \mu + \sum_{h\in H} \lambda_h - \sum_{h\in H} \lambda_h e^{f_h(0,0)},$$

where f_h is defined in proposition 3.9. Next we show that

$$f_h(0,0) < \ln\frac{\bar{v}_h(l_h)}{\bar{v}_h(0)} \qquad \text{for all} \quad h \in H.$$

Using the positiveness of $\bar{u}_h$ and $\bar{v}_h$, the assumption (5) on the γ functions, and the equilibrium conditions of (6), namely $0 = \gamma_1^h(\bar{u}_h)\bar{u}_h + \alpha_h\bar{v}_h - \delta_h\bar{u}_h$ and $c_h\,\bar{v}_h' = \gamma_2^h(\bar{v}_h)\bar{v}_h - \alpha_h\bar{v}_h + \delta_h\bar{u}_h$, we obtain (recall the definitions of a_1^h and a_2^h in (11))

$$a_1^h(x) < -\alpha_h\frac{\bar{v}_h(x)}{\bar{u}_h(x)} < 0 \quad \text{and} \quad a_2^h(x) < \frac{c_h\bar{v}_h'(x) - \delta_h\bar{u}_h(x)}{\bar{v}_h(x)}.$$

Therefore,

$$f_h(0,0) = \frac{1}{c}\left(\alpha\delta\int_0^l \frac{dx}{-a_1(x)} + \int_0^l a_2(x)dx\right) < \frac{1}{c}\left(\alpha\delta\int_0^l \frac{\bar{u}(x)}{\alpha\bar{v}(x)}dx + \right.$$

$$\left. + \int_0^l \frac{c\bar{v}'(x) - \delta\bar{u}(x)}{\bar{v}(x)}dx\right) = \int_0^l \frac{\bar{v}'(x)}{\bar{v}(x)}dx = \ln\frac{\bar{v}_h(l_h)}{\bar{v}_h(0)},$$

where the subindex h is supressed in the intermediate steps for ease of reading. Since $\bar{v}_h(0) = \lambda_h\bar{r}/c_h$ (boundary condition), then

$$\Gamma(0) = \mu + \textstyle\sum_{h\in H}\lambda_h - \sum_{h\in H}\lambda_h e^{f_h(0,0)} >$$

$$> \mu + \textstyle\sum_{h\in H}\lambda_h - \sum_{h\in H}\lambda_h\frac{\bar{v}_h(l_h)}{\bar{v}_h(0)} = \mu + \sum_{h\in H}\lambda_h - \sum_{h\in H}c_h\frac{\bar{v}_h(l_h)}{\bar{r}} = 0$$

where the last equality is due to the equilibrium condition $0 = \sum_{h\in H}(c_h v_h(l_h) - \lambda_h r) - \mu r$. Finally, by means of propositions 2.1 and 3.9 the asymptotic stability of the endemic equilibrium is proven. □

3.2 Stationary states in the case of no reinfection

In the case $\lambda = 0$ similar results exist, although the uniqueness of endemic equilibria does not hold any more. We may restrict to the case $n = 1$ without loss of generality. This is so because any animal satisfying $\lambda_h = 0$ does not depend on the infection state of the other animals. Next we show that when $\gamma_1(0) = \delta$ a kind of non-standard bifurcation occurs in which an uncountable set of equilibriums are suddenly generated. We must say that this subsection is more a mathematical curiosity rather a useful biological result. This is because the continuum of endemic equilibria disappears if diffusion is taken into account, which would be the case in a more realistic situation.

Theorem 3.14. *If $\lambda = 0$ and $\gamma_1(0) < \delta$, then the only equilibrium state is the trivial one.*

Proof. If $\gamma_1(0) < \delta$, then the equation $0 = \gamma_1(u)u + \alpha v - \delta u$ defines a unique function $\tilde{u}(v)$ on $[0,\infty)$ which is Lipschitz and satisfies $u(0) = 0$. Therefore, a solution $(\bar{u},\bar{v},\bar{r})$ of (6) must satisfy

$$\begin{cases} c\,\bar{v}' = \gamma_2(\bar{v})\bar{v} - \alpha\bar{v} + \delta\tilde{u}(\bar{v}), \\ \bar{v}(0) = 0, \end{cases} , \tag{17}$$

$\bar{u}(x) = \tilde{u}(\bar{v}(x))$, and $\bar{r} = c\bar{v}(l)/\mu$. However, problem (17) has a unique solution $\bar{v}(x) = 0$ because the right hand side of the differential equation is Lipschitz and it vanishes at zero, so that $(\bar{u},\bar{v},\bar{r}) = (0,0,0)$. □

Theorem 3.15. *If $\lambda = 0$ and $\gamma_1(0) > \delta$, then there is an uncountable set of non-trivial equilibrium states.*

Proof. If $\gamma_1(0) > \delta$, then the equation $0 = \gamma_1(u)u + \alpha v - \delta u$ defines two functions of $v \in [0, \infty)$ that only differ at $v = 0$. The first one referred as $\tilde{u}(v)$ is Lipschitz on $[0, \infty)$ and satisfies $\tilde{u}(0) > 0$. The second one is a version of $\tilde{u}(v)$ that vanishes at $v = 0$, so it is not continuous at this point. This phenomenon implies that the initial value problem (17) has multiple solutions of the form

$$\bar{v}_{x_0}(x) = \bar{v}_0(x - x_0)\mathbb{1}_{[x_0,l]}(x),$$

where $\bar{v}_0(x)$ is the unique solution of (17) satisfying $\bar{v}_0(0) = 0$ and $\bar{v}_0(x) > 0$ for all $x \in (0, l]$. Such solution is unique because $\tilde{u}(v)$ is positive and smooth within $[0, \infty)$. Therefore, for each $x_0 \in [0, l)$ there is an associated non trivial equilibrium of the form

$$(\bar{u}_{x_0}(x), \bar{v}_{x_0}(x), \bar{r}_{x_0}) = (\tilde{u}(\bar{v}_{x_0}(x))\mathbb{1}_{[x_0,l]}(x), \bar{v}_{x_0}(x), c\,\bar{v}_{x_0}(l)/\mu).$$

Notice that $\bar{u}_{x_0}$ is not continuous at x_0 (it has a jump discontinuity of height $\tilde{u}(0)$, so that the endemic equilibria are isolated as points of X. □

At the bifurcation point $\gamma_1(0) = \delta$, the equation $0 = \gamma_1(u)u + \alpha v - \delta u$ still defines a unique function $\tilde{u}(v)$ on $[0, \infty)$ satisfying $u(0) = 0$, though $\tilde{u}(v)$ fails to be Lipschitz at $v = 0$. In this case two situations may occur depending on some integrability properties of the function $h(v) := (\gamma_2(v)v - \alpha v + \delta\tilde{u}(v))/c$, specifically on the value of the limit

$$\Delta_0(v_0) := \lim_{\epsilon \downarrow 0} \int_\epsilon^{v_0} \frac{dy}{h(y)},$$

where $v_0 > 0$ is any value such that $h(y) > 0$ for all $y \in (0, v_0]$. Notice that $h(v)$ is positive for v small enough since, when $\gamma_1(0) = \delta$, $\tilde{u}(v)/v$ tends to infinity as $v \downarrow 0$ (see the proof of Theorem 3.7).

Theorem 3.16. *In the case $\lambda = 0$ and $\gamma_1(0) = \delta$,*

i) if $\Delta_0(v_0) = \infty$, then the trivial equilibrium is the only solution of (6),

ii) if $\Delta_0(v_0) < \infty$, then (6) has an uncountable set of solutions.

Proof. Consider the differential equation $v'(x) = h(v(x))$ (the same equation as in (17)) with initial condition $v(0) = v_0$. Since $h(y) > 0$ for all $y \in (0, v_0]$, $\Delta_0(v_0)$ is nothing but the distance to the left of 0 at which the trajectory through v_0 reaches 0, so that $v(-\Delta_0(v_0); v_0) = 0$ and $v(-x; v_0) > 0$ if $x < \Delta_0(v_0)$. Therefore, any solution of (17) satisfying $\bar{v}(x_0) > 0$ for some $x_0 > 0$ must reach zero at some point in $[0, x_0)$, which implies $\Delta_0(\bar{v}(x_0)) \leq x_0$. This clearly proves *i*), and to conclude *ii*) we can use the same arguments as in Theorem 3.15. However, notice that in this case the functions $\bar{u}_{x_0}$ are continuous, so that the endemic equilibria form a connected set in X. □

4 Effects of bacteriophage therapy on the spread of bacteria

System (4) can be extended in order to include a bacteriophage population used to control an epidemics in a farm. As a first approximation to this scenario we may neglect the effects of latency periods of viruses, so that the associated dynamical system takes the form

$$\begin{cases} \partial_t u_h = \gamma_1^h(u_i)u_h + \alpha_h v_h - \delta_h u_h - \kappa_1^h u_h p_h \\ \partial_t v_h = -c_h \partial_x v_h + \gamma_2^h(v_h)v_h - \alpha_h v_h + \delta_h u_h - \kappa_2^h v_h p_h \\ \dot{r} = \sum_{h\in H}(c_h v_h(l_h,t) - \lambda_1^h r) - \mu_1 r \\ \partial_t p_h = -c_h \partial_x p_h + b(\kappa_1^h u_h + \kappa_2^h v_h)p_h \\ \dot{q} = \sum_{h\in H}(c_h p_h(l_h,t) - \lambda_2^h q) - \mu_2 q \\ c_h v_h(0,t) = \lambda_1^h r \\ c_h p_h(0,t) = \lambda_2^h q + q_0^h \end{cases} . \tag{18}$$

Notice that two families of new dependent variables have been added to system (4), namely $p_h(x,t)$ which represent the bacteriophage in host h being drafted by the intestinal flow of host h, and $q(t)$ which is the amount of bacteriophage in the soil. We assume a mass action law for the infection process, where κ_1 and κ_2 are phage adsorption constants rates in the epithelium and lumen respectively. Parameter b stands for the amount of viruses released per infected cell and q_0 is the amount of bacteriophage given to the animals as part of the therapy.

Our main goal in this section is to show that a non-endemic stationary state always exist and give a condition on the parameters that determines if it is stable or it is not. We are specially interested in the dependence of the terms q_h^0 in the previous condition, since such parameters are the ones that can be tuned as part of the viral therapy. In the calculations below we avoid writing as many details as in the previous section since they can be done essentially in the same way.

A mere checking shows that the point $(u,v,r,p,q) = (0,0,0,\bar{p},\bar{q})$, with

$$\bar{p}_h(x) \equiv \frac{\lambda_2^h \bar{q} + q_0^h}{c_h} \qquad \text{and} \qquad \bar{q} = \sum_{h\in H} \frac{q_0^h}{\mu_2}, \tag{19}$$

is a steady state of (18), which corresponds to the bacteria free scenario. According to (3), the linearized system around this equilibrium is given by the operator

$$A\begin{pmatrix} u \\ v \\ r \\ p \\ q \end{pmatrix} = \begin{pmatrix} \hat{u} \\ \hat{v} \\ \hat{r} \\ \hat{p} \\ \hat{q} \end{pmatrix} \quad \text{where} \quad \begin{array}{l} \hat{u}_h = (\gamma_1^h(0) - \delta_h - \kappa_1^h \bar{p}_h)u_h + \alpha_h v_h \\ \hat{v}_h = -c_h v_h' + (\gamma_2^h(0) - \alpha_h - \kappa_2^h \bar{p}_h)v_h + \delta_h u_h \\ \hat{r} = \sum_{h\in H}(c_h v_h(l_h) - \lambda_1^h r) - \mu_1 r \\ \hat{p}_h = -c_h p_h' + b\kappa_1^h \bar{p}_h u_h + b\kappa_2^h \bar{p}_h v_h \\ \hat{q} = \sum_{h\in H}(c_h p_h(l_h) - \lambda_2^h q) - \mu_2 q \end{array} , \tag{20}$$

with (u,v,r,p,q) in the domain of A if, for all $h \in H$, v_h and p_h are Lipschitz, $\hat{v}_h$ and $\hat{p}_h$ are continuous, and the boundary conditions $c_h \hat{v}_h(0) = \lambda_1^h \hat{r}$ and $c_h \hat{p}_h(0) = \lambda_2^h \hat{q}$ hold (notice that the constant quantities q_0^h do not appear in the last boundary condition because they cancel out due to the linearisation). In order to simplify the coefficients let us denote

$$a_1^h = \gamma_1^h(0) - \delta_h - \kappa_1^h \bar{p}_h \quad \text{and} \quad a_2^h = \gamma_2^h(0) - \alpha_h - \kappa_2^h \bar{p}_h.$$

Lemma 4.1. *The spectrum of the operator A is the set*

$$\sigma(A) = \sigma_{ess}(A) \bigcup \{\eta \in \mathbb{C} \setminus \sigma_{ess}(A) | \Gamma^1(\eta)\Gamma^2(\eta) = 0\},$$

where

$$\sigma_{ess}(A) = \bigcup_{h\in H} \{a_1^h\},$$

$$\Gamma^1(\eta) = \eta + \mu_1 + \sum_{h\in H} \lambda_1^h - \sum_{h\in H} \lambda_1^h e^{\frac{l_h}{c_h}\left(\gamma_2^h(0) - \kappa_2^h \bar{p}_h - \alpha_h - \frac{\alpha_h \delta_h}{\gamma_1^h(0) - \kappa_1^h \bar{p}_h - \delta_h - \eta} - \eta\right)}, \tag{21}$$

$$\Gamma^2(\eta) = \mu_2 + \sum_{h\in H} \lambda_2^h - \sum_{h\in H} \lambda_2^h e^{-\frac{l_h}{c_h}\eta}. \tag{22}$$

Proof. We can start proceeding exactly in the same way as in the proof of Lemma 3.8. Simply notice that the components u, v and r of the preimages of $(\hat{u}, \hat{v}, \hat{r}, \hat{p}, \hat{q})$ by $(A - \eta\, I)$ only depend on $(\hat{u}, \hat{v}, \hat{r})$. This implies that if $\eta \notin \sigma_{\text{ess}}(A)$ and $\Gamma^1(\eta) \neq 0$, then for all $(\hat{u}, \hat{v}, \hat{r}, \hat{p}, \hat{q})$ the triple (u, v, r) of the preimage is always well defined. Once we dispose of (u, v, r) in terms of $(\hat{u}, \hat{v}, \hat{r})$ we can use them to compute p and q. First we solve the differential equations for $p_h(x)$ taking into account the boundary conditions $p_h(0) = \lambda_2^h q$. Secondly using the resulting expressions for $p_h(l_h)$ in the last equation of (20) we obtain a scalar equation for q. Specifically,

$$-\left(\mu_2 + \sum_{h\in H} \lambda_2^h - \sum_{h\in H} \lambda_2^h e^{-\frac{l_h}{c_h}\eta}\right) q = \hat{q} + R(\eta, \hat{u}, \hat{v}, \hat{r}, \hat{p}).$$

where R is a residual term that depends continuously on their arguments. Since the right hand side can be any value, the above equation fails to have a solution for q if $\Gamma^2(\eta) = 0$. □

Notice that all the solutions of $\Gamma^2(\eta) = 0$ have negative real part. Therefore, in order to study if the spectral bound of A is positive we may focus on the zeros of Γ^1. Since $\Gamma^1(\eta)$ restricted to $(\sup_{h\in H} a_1^h, \infty)$ is increasing and it is unbounded as η goes to both interval limits, we conclude that a real positive solution η_d of $\Gamma(\eta) = 0$ exists if and only if, $\sup_{h\in H} a_1^h \geq 0$ or $\Gamma^1(0) < 0$. This implies that bacteriophage will prevent the spread of bacteria if $a_1^h = \gamma_1^h(0) - \delta_h - \kappa_1^h \bar{p}_h < 0$ for all $h \in H$ and

$$\Gamma^1(0) = \left(\mu_1 + \sum_{h\in H} \lambda_1^h\right)\left(1 - \sum_{h\in H} \varepsilon_1^h\, e^{\frac{l_h}{c_h}\left(\gamma_2^h(0) - \alpha_h - \kappa_2^h \bar{p}_h + \frac{\alpha_h\, \delta_h}{\delta_h + \kappa_1^h \bar{p}_h - \gamma_1^h(0)}\right)}\right) > 0, \tag{23}$$

where $\varepsilon_1^h = \lambda_1^h/(\mu_1 + \sum_{j\in H} \lambda_1^j)$. The negation of these conditions are nothing but extended versions of the ones appearing in Theorem 3.7. Here they include the bacteriophage dose given to the animals (in terms of $\bar{p}_h$ defined in (19)).

Notice that if $q_0^h = 0$ for all hosts h, then the above condition reduces to the one in Theorem 3.7. Therefore, the bacteriophage population cannot prevent a bacterial outbreak by themselves, but an external source of viruses is needed in order to reduce the last term of the left hand side of (23) below 1. In other words, without an administration of new viral particles to the system, phage only partially reduce

the mean level of bacteria when these are able to grow in a free-phage environment. Conversely, if q_0^h is large enough for some h, then the stability of the free bacteria state is guaranteed. Indeed, the left hand side of (23) converges to $\sum_{h\in H} \varepsilon_1^h < 1$ as $\bar{p}_h$ grows to infinity for all h, and this condition holds provided $q_0^h \to \infty$ for some h. Such a behaviour depending on the phage dose is not a big surprise, since something similar happens in the simplified system

$$\begin{cases} \dot{S} = (a - S)S - k\,SP \\ \dot{P} = bSP - mP + P_0 \end{cases},$$

in which the only equilibrium in the $S = 0$ axis is $(0, P_0/m)$ and it is asymptotically stable if and only if $P_0 \geq a\,m/k$. However, in our case condition (23) may be used to compute efficient phage doses in non homogeneous populations, such as the ones found when a pen houses animals of different species or ages. For example, it could be useful to decide whether to split a given dose among all the animals or, alternatively, to treat only a few of them and take advantage of their capacity to produce bacteriophage particles.

5 Discussion

Reinfection phenomena of enteropathogens may have a critical role in epidemic outbreaks. In the present paper we have followed the ideas in [3] to show how the structure of the host population determines the proliferation of bacteria within the ecosystem. This relation is illustrated by means of a condition involving important ecological parameters, such as reinfection probabilities, residence times of bacteria within the intestines and local bacterial growth rates (see Theorem 3.7). Interestingly, the condition we are referring to is neither the reproduction number $\mathcal{R}$ of the bacterial population nor its population growth rate [21, 12]. Rather, it resembles the expected number of bacteria that will leave the intestines as a result of a founder bacterium in the soil. We think that this quantity emerge as a result of the different scales of the model, namely the dynamics within the intestines and the dynamics in the soil. This suggests that other biologically relevant values that determine the dynamics of a given population may exist, whose empirical computation could be easier and more natural in comparison with the one used to obtain, for example, $\mathcal{R}$. More studies are needed in this direction in order to deepen into such an issue.

This paper leaves many open questions related to the asymptotic behaviour of the trajectories. Preliminary simulations suggest that the only locally stable equilibrium found in system (4) is indeed a global atractor. However we could not find a formal proof for that. In relation to the extended system with bacteriophage (18), such a global property could not hold. In fact, in this scenario it is not easy at all to prove the existence of an endemic equilibrium when the trivial one is locally unstable (at least using the same techniques of this paper). This implies solving a system of two differential equations with a boundary condition that links the trajectory endpoints. In order to address this problem general results from bifurcation theory could be applied [7]. Finally, we must say something about possible extensions of systems (4) and (18). Among the many refinements these models may include, we are specially interested in generalizing the constants c_h, which give the celerities of the intestinal flows, into time-periodic functions $c_h(t)$. This not only would improve the model

realism, but it would also represent a tool for studying how feeding patterns may affect the microbial dynamics.

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