



Universitat Autònoma de Barcelona

ADVERTIMENT. L'accés als continguts d'aquesta tesi queda condicionat a l'acceptació de les condicions d'ús establertes per la següent llicència Creative Commons:  http://cat.creativecommons.org/?page_id=184

ADVERTENCIA. El acceso a los contenidos de esta tesis queda condicionado a la aceptación de las condiciones de uso establecidas por la siguiente licencia Creative Commons:  <http://es.creativecommons.org/blog/licencias/>

WARNING. The access to the contents of this doctoral thesis it is limited to the acceptance of the use conditions set by the following Creative Commons license:  <https://creativecommons.org/licenses/?lang=en>

Semilinear hyperbolic equations and the dynamics of gut bacteria

Tesi Doctoral

Carles Barril Basil

Dirigida per Àngel Calsina Ballesta

Maig de 2018

Certifico que la present memòria
ha estat realitzada per en Carles Barril Basil,
sota la direcció d'Àngel Calsina Ballesta.
Bellaterra, maig de 2018.

Signat: Dr. Àngel Calsina Ballesta

Abstract

In this thesis we propose a mathematical framework to analyse the dynamics of microorganisms growing within the guts of animals. Such a framework consists of a hyperbolic system of PDEs with non-linear reaction terms and certain boundary conditions that link the microbes in the environment with those inside the hosts.

In chapter 1 we solve the Abstract Cauchy Problem associated to the model by considering the semilinear formulation on a certain Banach space X . The semilinear structure of the system obtained in this way is special because, on the one hand, the evolution law can be expressed as the sum of a linear unbounded operator and a non-linear Lipschitz function (which is typical) but, on the other hand, the non-linear perturbation takes values not in X but on a larger space Y which is related to X (which is atypical). In order to deal with this situation we use the theory of dual semigroups. Stability results around steady states are also given when the non-linear perturbation is Fréchet differentiable. These results are based on two propositions: one relating the local dynamics of the non-linear semiflow with the linearised semigroup around the equilibrium, and a second relating the dynamical properties of the linearised semigroup with the spectral values of its generator. The latter is proven by showing that the Spectral Mapping Theorem always applies to the semigroups one obtains when the semiflow is linearised.

In chapter 2 an autonomous semi-linear hyperbolic pde system for the proliferation of bacteria within a heterogeneous population of animals is presented and analysed. 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. In chapter 3 the basic reproduction number associated to the bacterial population, i.e. the expected number of daughter cells per bacterium, is given explicitly in terms of biological parameters. In addition, an alternative quantity is introduced based on the number of bacteria produced within the intestine by one bacterium originally in the external media. The latter depends on the parameters in a simpler way and provides more biological insight than the standard reproduction number, allowing the design of experimental procedures. Both quantities coincide and are equal to one at the extinction threshold, below which the bacterial population becomes extinct. Optimal values of both reproduction numbers are derived assuming parameter trade-offs.

Agraïments

Diuen que l'acte de donar les gràcies no només ens fa estar millor amb les altres, sinó també amb nosaltres mateixes. Agrair és, en part, quelcom íntim. És com tancar una etapa, parar el temps, i recordar totes les persones que han fet que la vida fos. Massa coses han passat durant aquests anys. A vegades no me n'adono fins que paro, i quan paro me n'adono de com us trobo a faltar. Aquesta tesi és per a vosaltres (sé que preferiríeu una novel·la i un còmic, però és el que hi ha).

Alba, Lluís, Joan i Isabel gràcies per haver fet pinya. Carmen gràcies per animar-nos quan més ho necessitàvem. Marta i Pere gràcies per estimar-me. Elisa gràcies per voler jugar. Esther, Roberto, Núria, Víctor, Claudia, Gemma, Helena, Carmelo, Bernat, Alberto i Genís gràcies per aquesta dosi diària de riure i broma. Ricard gràcies per fer-me viatjar de tant en tant pels no confins de les varietats compactes sense vora. Tomás gràcies per la ironia. Álvaro gràcies per la curiositat. Gaël gràcies per la breu incursió a part de la recerca francesa. Odo gràcies per la bondat. Àlex gràcies per l'entusiasme de les teves classes que encara recordo. Laurent, Barbara i Joan gràcies per acabar de donar sentit a aquesta tesi. Aus, arbres i felins universitaris gràcies per donar un toc salvatge a l'abstracció. Simón gràcies per cinc quarts del mateix. Jordi gràcies per compartir idees científiques i quotidianes. Sílvia gràcies per lluitar tant per tu com pels altres. Àngel gràcies per totes les converses sense final, per les reflexions sobre el món i la naturalesa, pel teu optimisme, pel teu temps, i, és clar, perquè sense tu aquest treball no existiria com a tal.

I a tu, Marina, infinites gràcies per ser-hi.

Contents

1	Semilinear formulation of a hyperbolic system of PDEs	11
1.1	Introduction	11
1.2	Sun-dual formalism and evolution equations	14
1.2.1	Linear theory	14
1.2.2	Semi-Linear theory	18
1.3	Semilinear formulation of the problem	24
1.3.1	Existence and uniqueness of solutions	24
1.3.2	Linearisation around steady states	27
1.4	A model for the gastrointestinal ecosystem	38
1.5	Discussion	39
2	Stability analysis of an enteropathogen population growing within a heterogeneous group of animals	41
2.1	Introduction	41
2.2	Spread of bacteria within a population of multiple hosts	42
2.2.1	Stationary states in the reinfection case	43
2.2.2	Stationary states in the case of no reinfection	53
2.3	Effects of bacteriophage therapy on the spread of bacteria	55
2.4	Discussion	59
3	On the reproduction number of a gut microbiota model	61
3.1	Introduction	61
3.2	Next-generation Operator framework	63
3.3	Standard generational approach of the model	66
3.3.1	Next-Generation Operator	66
3.3.2	Basic reproduction number	67
3.4	Alternative generational approach of the model	68
3.5	Optimal reproduction number	69
3.6	Suggestions for an experimental computation of $\tilde{\mathcal{R}}$	72
3.6.1	Following one infection event	72
3.6.2	Bacteria released per bacteria supplied	75
3.7	Discussion	76

Introduction

The second half of the 17th century saw a curious man entering for the first time into the bacterial world. He was Antoine van Leeuwenhoek (1632-1723) and the scene took place in Delft. Like a child with a new toy, he used a microscope designed by himself to observe nature as never before. In his journey to the universe of the tiny things, *Animalcules* (now microorganisms) were set to become the biggest surprise. In a letter sent to the Royal Society of London on 9 October 1676 [83], he described the living beings inhabiting various kinds of water and plant based infusions. In one of his observations he wrote:

For me this was among all the marvels that I have discovered in nature the most marvellous of all, and I must say that, for my part, no more pleasant sight has yet met my eye than this of so many thousands of living creatures in one small drop of water, all huddling and moving, but each creature having its own motion. And even if I said that there were a hundred thousand animalcules in one drop of water which I took from the surface of the water, I should not err. Others, seeing this, would estimate the number at quite ten times more, of which I have instances, but I give the lowest numbers.

The excitement behind these words was probably not due to the simple view of microbes: Leeuwenhoek was amazed to see that microscopic life could be so small, so diverse and so abundant. Today, more than three centuries after the first encounter, microbiologists are still astonished by the domain of bacteria.

Bacteria were the first forms of life on Earth, evolving from organic matter 4 billions years ago. Since then, they have had time to adapt to almost every niche in the planet, even in extreme conditions such as hot springs or ice. Because their metabolic repertoire has diverged in many different ways, the whole ensemble of bacteria has become a huge reservoir of genes. And what is more, these genes are not necessarily linked to a specific lineage of bacteria but, on the contrary, they can be transmitted to other individuals (either directly through bacterial conjugation or indirectly via viral particles). That is, bacterial genes move not only vertically through generations, but also horizontally within the population. These two properties, genetic diversity and genetic traffic, turn bacterial communities into complex entities which are highly adaptable to changing environments. Whereas each cell is specialized in the synthesis of a few metabolites or in the neutralization of a particular toxin, the community creates a medium rich in nutrients and produces shields against damaging substances.

It could be said that bacterial communities are plastic in the sense that the proportion of their constituents can be readjusted to exploit the environment more efficiently. Multicellular organisms, on the other side, are more rigid because the relation between their constituents is

genetically determined during development. This difference may explain why so many animals and plants live in close association with particular bacterial communities [59, 71, 74, 61]. These communities belong to what is known as the microbiome, defined as the microbial ensemble associated to a given host. Somehow, the microbiome of multicellular organisms can be thought of as an organ capable of undergoing fast reorganizations in response to environmental clues. In this sense the microbiome is far from being nothing more than unspecific bacteria acquired by chance without any functional link with the host. This possibility, although plausible, would not be evolutionarily stable. Indeed, as soon as the microbiome could respond to signals from the host and vice versa, selection for favourable partnerships would take place. This view is supported by many examples in which the microbiome is known to have multiple functions on the host. The nitrogen fixing bacteria that grow symbiotically in the roots of leguminosae are paradigmatic. The metabolic role of microbiomes in animals is also well known. Gut bacteria produce vitamins and enhance nutrient intake. In ruminants they are vital to digest the grass they eat. Microbiomes also tend to act as defensive barriers. By adhering to epithelial surfaces they may create a protective biofilm that prevents the colonization by harmful microbes. In addition, such biofilms may induce changes in the underlying epithelium, for example by regulating cell division or stimulating the immune system.

In the last decades scientists have shown that microbiomes consist of many different classes of bacteria. The human microbiome is particularly well documented for obvious reasons [23, 69], although most of its properties are presumably common to other hosts. The approximately 10^{13} bacteria carried by each human being can be classified in hundreds of different “species level” phylotypes (based on the divergence degree of a highly conserved RNA sequence). The amount of non-redundant genes stored in each of these bacterial communities is also huge: around half million, more than 10 times the number of human genes. Even more interesting is the high diversity in both bacterial composition and genes across healthy individuals. It seems that samples from the same person obtained at different times are more similar to one another than those obtained from different individuals. However, by focusing on functional diversity rather than genetic diversity, it has been shown that the metabolic profile of microbiomes is much more conserved between individuals. This suggests that multiple bacterial consortia capable of performing equivalent processes exist. Moreover, these consortia are relatively stable along time, although environmental disruptors such as antibiotic usage or strong dietary changes could drive them towards other stable configurations [56].

Since the microbiome of any individual is both unique and characterizable, the classification of microbiomes has become an important topic in current research. A special attention is given to those microbiomes associated with some kinds of pathology, such as chronic infections or inflammatory reactions. Answering how these dysfunctional consortia arise and, more importantly, how they can be modified into healthier configurations would have clear implications on the way doctors treat these patients. A recent trend in this direction consists in transplanting the fecal microbiome from a healthy donor into the gut of a receptor affected by some recurrent infection. This technique has been proved to be surprisingly effective in cases in which the only option was the continued use of antibiotics [5]. In addition to clinical issues, understanding the dynamics of microbiomes could also be useful in the design of new strategies

to control plagues and vector-borne diseases. Beyond human oriented applications, the role of microbiomes in the structure of ecosystems is important by itself and deserves to be considered carefully. In this line, an increasing number of studies are focusing on the relation between the behaviour of hosts and their microbiome, and it seems that some of the behaviours driven by the microbiome could lead to major changes in the food web. For example, it has been observed that mating choice in flies is affected by the diet through the microbiome [31]. The flies of those experiments were more likely to mate between them than the flies reared with different diets, and such preferences disappeared when the flies were treated with antibiotics [73]. From the evolutionary point of view, this could be interpreted as if the microbiome favoured the specialization of the flies to different nutritional sources. Somehow, the microbiome would be promoting a speciation event in which a generalist population of flies splits into two new specialized species.

Most studies classify the diversity of microbiomes from an empiric perspective, that is, by means of data and statistical tools. This approach is highly powerful in identifying patterns in real systems. However, the overwhelming amount of variables involved in these assays makes it difficult to focus on mechanistic processes set at the level of bacteria. At this point mathematical modelling comes into play. In order to complement available data, appropriate models can be used to get insights on how a certain bacterial property affects the microbiome (which, in turn, has an impact on the host population). In this thesis we follow this approach and propose a mathematical framework to analyse the dynamics of microorganisms growing within the guts of animals. Instead of going directly to our model and discussing its pros and cons, we first give a brief detour in order to review how mathematics started to be used in the study of populations.

Modelling populations

Not many years before Leeuwenhoek's death, Leonard Euler was born in Basel. Among his deep and broad contributions to mathematics, a relatively mundane work about the growth of human populations can be found [35]. Through a series of practical questions Euler described some relations between demographic variables in a population which grows geometrically and whose age distribution is stationary. He showed, for example, how to recover the total population and the rate at which it is increasing using the number of births, the number of deaths and the probability to survive until each year of life. This work was published in 1760 and it is important not only for being one of the first studies in which mathematics was applied to model populations [3]: the dynamical system used by Euler is specially interesting because it considers a structured population, that is, a population whose individuals are classified according to some structural variable. Indeed, the state of the system in Euler's model was not the total population but the distribution of individuals according to their age.

Euler already knew that the assumption on the geometric growth of populations was only reasonable if ecological limitations were negligible, and presumably this idea was commonly accepted among demographers of that time. Its popularization, however, occurred in 1798 due

to the economical controversies raised by Thomas Robert Malthus in his book *An essay on the Principle of Population* [58]. This is why now it is said that a population is experiencing a Malthusian growth if its individuals do not compete between them, which in some sense means that they behave as independent agents. Mathematically, the Malthusian growth is the same as the geometric growth given by

$$p_{t+1} = (1 + r)p_t \quad (0.0.1)$$

if the population is modelled at discrete times, and the same as the exponential growth given by

$$p'(t) = rp(t) \quad (0.0.2)$$

if the population is modelled continuously in time. In both cases the parameter r is the *growth rate* of the population, known also as the *Malthusian parameter*. The description given by Malthus on the population growth was purely verbal, and in this sense neither equation (0.0.1) nor equation (0.0.2) should be attributed to him. Nevertheless, the influence his book had on academia arrived to Pierre François Verhulst who, in 1838, formulated equation (0.0.2) mathematically and generalised it into

$$p'(t) = rp(t) - \varphi(p(t)) \quad (0.0.3)$$

in order to take into account the effects of resources scarcity [84]. Such effects were represented by means of function φ , whose precise expression depended on the population under study and in general was not known. With this equation Verhulst introduced the first family of non-linear population models. Among other particular cases, he considered what, in modern notation, would be written as $\varphi(p) = rp^2/K$, with K being the maximum number of individuals that the environment can support, which results in the famous logistic equation

$$p'(t) = rp(t) \left(1 - \frac{p(t)}{K}\right). \quad (0.0.4)$$

The model proposed by Euler was linear but structured. By contrast, the model of Verhulst was unstructured but non-linear. It seems that a population model combining these two properties was about to be formulated in the upcoming years. However, the spread of scientific ideas was far from being perfect at that time. During the 19th century the logistic equation was reintroduced independently by other authors. The age structured model that constituted the basis of Euler's paper had to wait until Alfred James Lotka reformulated it in 1907 [54, 55]. The population modelled by Lotka changed continuously in time, although the model was linear as the one of 1760. The non-linear version arrived many years later when, in 1974, Morton Gurtin and Richard MacCamy fused the ideas of Lotka and Verhulst [41]. By that time, other non-linear structured models had already been proposed. Instead of age, the structural variable in these models was the spatial position of the individuals. One of the most important examples is the Fisher-KPP equation, derived in 1937 independently by Ronald Fisher on one side and Andrey Kolmogorov, Ivan Petrovsky and Nicola Piskunov on the other [37, 51]. The equation takes the form

$$\partial_t p(x, t) = k \partial_{xx} p(x, t) + f(p(x, t)) \quad (0.0.5)$$

with k being the diffusion coefficient and f being a function that gives the population growth rate in the absence of diffusion. In fact, Fisher derived the equation to study how the frequency of a favourable allele spreads in a population, which resulted in $f(p) = mp(1 - p)$ with m being the relative fitness of the new allele with respect to the common one.

Whether non-linear models were structured by age, space or whatever variable of interest, it can fairly be said that the mathematics to analyse them flourished during the last century. These new mathematics were not directly inspired by structured populations; the motivation behind them was more fundamental and was related to the way deterministic dynamical systems were understood. Originally, dynamical systems were defined by means of evolution laws, that is, differential equations of the form

$$p'(t) = f(p(t)) \tag{0.0.6}$$

describing the velocity at which the state p of the system moves. The discipline took this path because the derivation of physical models relies on what happens during small intervals of time: the evolution law is the mathematical object one reaches when trying to model the motion of the universe. Using the evolution law one can define the trajectory associated to a given initial condition $p(0) = p_0$ as the solution of

$$\begin{cases} p'(t) = f(p(t)) \\ p(0) = p_0 \end{cases} . \tag{0.0.7}$$

This approach, however, raises some issues since it is not clear at all if system (0.0.7) has any solution and, in case it does have one, if it is unique. Since the existence and uniqueness of solutions are not guaranteed in general, the evolution law (0.0.6) is said to define a dynamical system if the trajectory into the future associated to any initial condition exists and it is unique. If, in addition, the trajectories are continuous in time and behave continuously with respect to the initial conditions, then the dynamical system defined by (0.0.6) is said to be well posed. The notion of continuity in the previous condition is related to the phase space of the system, which is the normed space containing all the possible states of the physical system. The question of whether a differential equation as (0.0.6) defines a well posed dynamical system in a phase space P is known as the Abstract Cauchy Problem. As one should expect, the complexity of this problem depends on the properties of f and P . Since the work of Picard and Lindelöf on ordinary differential equations, it is known that, if the phase space P is a Banach space, then the system is well posed if the function $f : P \rightarrow P$ is Lipschitz. Although this result is very useful when the dimension of P is finite, the property of being Lipschitz is quite restrictive if P has infinite dimension. Linear functions (or operators) such as those appearing in partial differential equations are not even continuous from P to P and, in fact, they fail to be defined on the whole space P . This obstacle required extending the classical theory built on finite dimensional spaces. To this end, dynamical systems were studied directly from the point of view of trajectories, thus skipping the problematic evolution law. More precisely, a well posed dynamical system was defined as a function

$$\mathcal{T} : [0, \infty) \times P \rightarrow P \tag{0.0.8}$$

satisfying:

- i. for each $p_0 \in P$, there exists $t_{p_0} \in (0, \infty]$ such that $[0, t_{p_0}) \times \{p_0\}$ is the intersection of $[0, \infty) \times \{p_0\}$ with the domain of \mathcal{T} ,
- ii. for all $p_0 \in P$, the identity $\mathcal{T}(0, p_0) = p_0$ holds,
- iii. for all $p_0 \in P$ and $t < t_{p_0}$, the semigroup property $\mathcal{T}(t, p_0) = \mathcal{T}(t - s, \mathcal{T}(s, p_0))$ holds for all $s \in [0, t]$,
- iv. the function \mathcal{T} is separately continuous in its domain, i.e. $\mathcal{T}(\cdot, p_0)$ is continuous for all p_0 (continuity with respect time) and $\mathcal{T}(t, \cdot)$ is continuous for all $t \geq 0$ (continuity with respect initial conditions).

Because of items ii and iii, the function \mathcal{T} is said to be a one-parameter semigroup or semiflow. Such a new focus allowed to ask which properties the evolution laws associated to dynamical systems must satisfy. In particular, when the semigroup T is linear with respect to the state variable, then its associated evolution law is determined by a linear operator (i.e. f in (0.0.6) is linear), although it is not necessarily continuous. The characterization of those linear operators f defining a well posed system is one of the major achievements of the theory of linear semigroups, the result now being known as the Hille-Yosida Theorem. Whereas the linear theory of dynamical systems is well understood, the theory to deal with general non-linear systems is still incomplete. However, some work has been devoted to solving the Abstract Cauchy Problem for different classes of functions f (see, for instance, the classical monographs of Pazy [68] and Henry [44] for semilinear semigroups and Miyadera [65] for dissipative systems).

In the context of population dynamics, the phase space of the system is given by all the possible configurations the population can have. In the model proposed by Verhulst it is assumed that the state of the population is given by the total number of its individuals, so that the phase space can be represented by the unidimensional space \mathbb{R} : each element $P \in \mathbb{R}$ represents a population state with P individuals. The situation is different in the model proposed by Lotka, since there the state of the population is given by the distribution of its individuals with respect to their age. A possible phase space in this case is given by the set of real functions defined on the interval $[0, \infty)$: each function P would represent a population state in which the density of individuals with respect to their age is P . This set, however, presents some inconveniences. On the one hand, the representation is not one to one: two different functions can represent the same population density. On the other hand, it includes functions that may fail to be integrable around some point, which somehow represent populations infinitely large. These inconveniences can be solved by taking the equivalent classes within the space of integrable functions, that is, $L^1(0, \infty)$. Although this is a reasonable choice, notice that when using functions to represent population densities, we are ignoring, for example, distributions in which the individuals are concentrated at a specific age. In order to take into account these states, the space of measures on $[0, \infty)$ should be used, but this would certainly complicate the analysis of the model. In any case, the phase space associated to Lotka's model is infinite-dimensional. This is also the case for any model dealing with populations structured

by a continuous variable, such as the one given by equation (0.0.5) or the one analysed in this thesis. For these kind of models, the tools of functional analysis developed to treat the Abstract Cauchy Problem are highly valuable. Many works illustrate this assertion, but, because of their relevance in the field, it is appropriate to emphasize the monographs of Glenn Webb [87], and Hans Metz and Odo Diekmann [63].

A model of gut bacteria in heterogeneous populations

In order to study how bacteria grow and move within the guts of a host population, we assume that bacteria can be found in different states. Inside the hosts they can be either attached to the intestinal epithelium or suspended in the lumen. Outside the hosts they are modelled as free living particles. Due to mechanistic effects, bacteria can detach from the epithelium and enter into the luminal compartment. Similarly, suspended bacteria can interact with the epithelium and become part of the attached community. When suspended in the lumen, bacteria move towards the anus (the end of the digestive tract) dragged by the intestinal flow. Eventually they leave the host and become environmental bacteria. The cycle is closed when hosts ingest those bacteria found in the media. This process is passive if, for example, hosts eat food which is contaminated with microbes. Sometimes, however, this process can also be active. Some insects, such as the dung beetle, feed exclusively from feces whereas a variety of species eat feces occasionally in order to obtain certain nutrients or to improve their gut flora [78]. Before moving to the specific equations of the model, notice that other microbes such as virus and inert substances such as nutrients or toxins can be modelled in the same way as we have done with bacteria.

The conceptual lines of the system presented above are formalised as follows. Consider a population with n hosts and m microbial “species” (for example, bacteria and bacteriophage or simply different types of bacteria). Let $H = \{1, 2, \dots, n\}$ and $S = \{1, 2, \dots, m\}$ be the indices sets for the hosts and the microbial species (or strains), respectively. The scalar variable x gives the position along the intestines. The point $x = 0$ indicates the start of the gut of every host. 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, all of them at time t . Then the set of equations describing the dynamics of the microorganisms can be written as

$$\begin{cases} \partial_t u_{h,s}(t, x) = g_{h,s}(x, u_h(t, x), v_h(t, x)) & \forall (h, s) \in H \times S, \\ \partial_t v_{h,s}(t, x) = -\partial_x(c_h(x)v_{h,s}(t, x)) + f_{h,s}(x, u_h(t, x), v_h(t, x)) & \forall (h, s) \in H \times S, \\ \frac{dr_s(t)}{dt} = m_s(r(t)) + \sum_{h \in H} k_{h,s}(c_h(l_h)v_{h,s}(t, l_h)) - \sum_{h \in H} \lambda_{h,s}r_s(t) & \forall s \in S. \end{cases} \quad (0.0.9)$$

Here, $u_h = (u_{h,1}, \dots, u_{h,m})$, $v_h = (v_{h,1}, \dots, v_{h,m})$ and $r = (r_1, \dots, r_m)$. The parameter l_h is the intestine length of host h (thus, the spatial domain of u_h and v_h is $[0, l_h]$) and $c_h(x)$ stands for the velocity of its intestinal flow at position x (thus, its domain is $[0, l_h]$). The functions $g_{h,s}$ and $f_{h,s}$ take into account the ecological processes occurring locally at position x of the intestine (thus, their domains are $[0, l_h] \times \mathbb{R}^m \times \mathbb{R}^m$). 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, the function m_s describes the ecology in the external media of the population of type s , and $k_{h,s}$ is a function that gives the amount of particles of type s leaving the intestine of host h per time unit. Finally, we assume that microbes enter the intestine at a rate which is proportional 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

$$c_h(0)v_{h,s}(0, t) = \lambda_{h,s}r_s \quad \forall (h, s) \in H \times S. \quad (0.0.10)$$

Notice that the above system is as a kind of metapopulation model [42], where each host acts as a distinct patch, the dynamics within each patch is structured and the transitions between patches occur through a pool of delocalised individuals.

Model (0.0.9)-(0.0.10) can be interpreted as an extension of the model formulated by Ballyk, Smith and Jones [7, 49, 76] to study the ecology of biofilms in the intestines. Both models are essentially the same inside the gut, what changes is the relation of the intestine with the external world. Whereas Ballyk and collaborators considered the input entering into the intestine to be independent from the output leaving the intestine, in our extension a link exists between these two phenomena. Such a link is similar to the one considered in the linear model used by Boldin to explore the *Escherichia coli* growth within a pig intestine [11]. As Boldin showed in her work, reinfection events can be decisive in determining the outcome of a primary infection, which means that, at least in certain circumstances, bacteria leaving the intestine should not be neglected. The model used by Boldin was specially suited to study the propagation of bacteria in an isolated animal. Our framework, on the contrary, makes it possible to study the spread of bacteria through a heterogeneous group of hosts. This is done by adding the variable r that represents the amount of microbes in the external media. In addition, by modelling the environmental bacteria it is possible to study which actions not on the animals but on the environment might have an impact on the spread of bacteria, something that was infeasible in any of the two models mentioned above.

Several simplifications are implicitly assumed in model (0.0.9)-(0.0.10). Since they may be fundamental in determining the limitations of the model, making them explicit is mandatory. Let us list them in order to be as precise as possible:

- The physiological characteristics of the hosts are constant over time.
- The intestinal flow is constant over time.
- The transversal sections of the lumen and the epithelium are well mixed compartments.
- The external media is a well mixed compartment.
- The random motion of particles along the intestine is neglected.

Although these assumptions compromise the realism of the model, avoiding them could result in a set of equations too complex to work with. A theory for the simplified model can be useful to study those dynamics in which the obviated properties do not play a major role. In

addition, when it is necessary to extend the model, the knowledge derived from the simpler one might be helpful. However, it should be pointed out that generalised versions of the dynamics within the intestines have been analysed by Smith and collaborators. In fact, in [7] longitudinal diffusion of luminal bacteria was already considered, and diffusion of both luminal and epithelial bacteria was treated later in [77]. The analysis of biofilm formations in explicit three dimensional digestive tracts can be found in [48]. Periodic advection speeds were considered not in the context of microbial growth within the intestines but to study how insect populations can persist in river ecosystems. The mathematical treatment of this problem was conducted primarily by Lutscher and collaborators, whose work was based on an earlier work by Speirs and Gurney [79]. In [67] they first considered a model analogous to the one treated in [7], in which individuals could be either immobile in the benthos or could flow along the river. In a further work, time periodic coefficients were included in order to study how seasonality could affect the population dynamics [57] (see also [88]).

Structure of the thesis

Up to our knowledge, the model proposed in this thesis is original in the sense that it combines the dynamics within the host (using the ideas presented in [49]) with the dynamics between hosts. In this sense, it is essential to study if equations (0.0.9) together with the boundary conditions (0.0.10) define a well posed dynamical system in a proper Banach space. This is addressed in the first chapter using the theory of semilinear semigroups. Specifically, the differential equations of the model are rewritten as an Abstract Cauchy Problem of the form

$$p'(t) = Ap(t) + \varphi(p(t))$$

where A is a linear (but unbounded) operator defined on a dense subspace of the phase space and φ is a Lipschitz function from the phase space to a certain extension of it. As it is shown in the first chapter, the reason why the images of function φ does not belong to the phase space is twofold. On the one side, the phase space we use depends on the boundary conditions and φ does not preserve them in general. On the other hand, the population densities of attached bacteria belong to a larger functional space than that where luminal densities belong. As a consequence, the components of φ associated to the luminal populations take values in the larger space. Such a property of function φ differs from the one needed to apply the semilinear formulation presented by Pazy, in which φ is defined from the phase space to itself. The more general framework of sun dual semigroups [18, 19], however, can be used to treat the problem and to define in which sense our model is well posed.

Once the fact that the model defines a coherent dynamical system is proven, we focus on the local behaviour around steady states, that is, those distributions of microbes within the environment and hosts that are constant with time. This is also done in the first chapter. There we show that if φ is differentiable, then the dynamics around a steady state can be linearised, in the sense that the non-linear semiflow around the steady state can be approximated by its linearisation, which is a semigroup of bounded linear operators. The generator of that

semigroup is given explicitly in terms of the parameters of the model. In addition, we show that the linearised semigroup is eventually norm continuous, which makes it possible to study certain dynamical properties of the semigroup (and hence the non-linear semiflow) in terms of the spectral properties of its generator.

In the second chapter we become less general and we consider a particular biological scenario. Our main goal there is to study how the properties of the hosts' population and the environment affect the spread of pathogenic bacteria that proliferate in the guts. This is done by identifying the stationary points of the system and analysing if they are unstable or locally asymptotically stable. As a result, we find for which parameters of the model the bacterial population is able to proliferate and persist. In order to evaluate possible strategies intended to eliminate bacteria in those systems where they are endemic, an additional population of bacteriophages is taken into account. Such scenario reflects a situation in which phage therapy is applied to treat the infection, and the model can be useful to get some intuition about the best way to distribute the viruses among the hosts.

In the third chapter, we analyse the model of pathogenic bacteria from a more biological perspective. In order to understand the meaning of some expressions derived in the second chapter, we compute the Reproduction Number of bacteria, defined as the expected offspring produced by bacteria at low densities [27]. The descendants of bacteria are counted following two different interpretations of what a birth event is. This gives rise to two non-equivalent Reproduction Numbers although both of them reflect, as expected, if an initial infection is going to spread or not. If the Reproduction Number is bigger than one, then each bacterium is, on average, able to replace itself and give rise to some more bacteria, so that the population tends to grow. Alternatively, if the Reproduction Number is smaller than one, then the population shrinks over time.

Chapter 1

Semilinear formulation of a hyperbolic system of PDEs

1.1 Introduction

In this chapter we analyse a dynamical system related to the model (0.0.9) and (0.0.10) presented in the introduction. Its formulation as a PDE system is the following. Let u and v be functions with domain $[0, 1] \times [0, \infty)$ taking values in \mathbb{R}^n and \mathbb{R}^m respectively. Let r be a \mathbb{R}^k valued function with domain $[0, \infty)$. Let

$$\begin{aligned} g &: [0, 1] \times \mathbb{R}^n \times \mathbb{R}^m \rightarrow \mathbb{R}^n \\ f &: [0, 1] \times \mathbb{R}^n \times \mathbb{R}^m \rightarrow \mathbb{R}^m \\ h &: \mathbb{R}^m \times \mathbb{R}^k \rightarrow \mathbb{R}^k \end{aligned}$$

be differentiable functions, and let $c : [0, 1] \rightarrow \mathbb{R}^m$ be a bounded function such that $c_i(x) \geq 1$ for all $x \in [0, 1]$ and $i \in \{1, \dots, m\}$, where we use an index i to denote the i th component of a vector valued function (such as u, v, r, g, f, h and c). Let Λ be a $m \times k$ real matrix. Then consider the following system of first order partial differential equations with initial condition:

$$\begin{cases} \partial_t u(x, t) = g(x, u(x, t), v(x, t)), \\ \partial_t v(x, t) = -c(x) \cdot \partial_x v(x, t) + f(x, u(x, t), v(x, t)) \\ r'(t) = h(v(1, t), r(t)) \\ u(x, 0) = u_0(x), v(x, 0) = v_0(x) \text{ and } r(0) = r_0, \end{cases} \quad (1.1.1)$$

with boundary condition

$$v(0, t) = \Lambda r(t). \quad (1.1.2)$$

The problem above is said to be well posed if, at least for small times t , it determines unambiguously the trajectory of the system and such trajectories present some continuity with respect to initial conditions. In order to prove that this is really the case the problem can be

interpreted as a semilinear evolution problem defined on a certain Banach space X ,

$$\begin{cases} \frac{du}{dt} = \mathcal{G}(u, v) \\ \frac{dv}{dt} = -c \cdot \partial_x v + \mathcal{F}(u, v) \\ \frac{dr}{dt} = \mathcal{H}(v, r) \\ (v(0), u(0), r(0)) = (v_0, u_0, r_0) \in X \end{cases}, \quad (1.1.3)$$

and then try to proceed as in the case of ordinary differential equations. The first difficulty one encounters is related to the fact that the operator defining the right hand side of (1.1.3) is not smooth enough (i.e. Lipschitz) to apply the Picard iterative scheme, being the differential operator ∂_x the reason of that. To overcome this problem Ammon Pazy [68] developed a theory to treat the system composed only by the “difficult” (but linear) *principal part* (i.e. the differential operator or whatever that creates the loss in regularity) and after consider the whole system as a smooth perturbation of the system generated by just the principal part. The tool to link the perturbed system with the unperturbed one is the variation of constants formula, which makes possible to prove not only the well posedness of the problem but also the principle of linearised stability. Although this is a typical procedure to deal with semilinear partial differential equations, in our case some difficulties arise due to the nonlinearities \mathcal{G} and \mathcal{F} involved, which take the form of Nemytskij operators defined by g and f , namely

$$\mathcal{G}(u(\cdot, t), v(\cdot, t))(x) = g(x, u(x, t), v(x, t)) \quad \text{and} \quad \mathcal{F}(u(\cdot, t), v(\cdot, t))(x) = f(x, u(x, t), v(x, t)).$$

In fact, these difficulties were also highlighted in [53] for a hyperbolic system similar, but not reducible, to (1.1.3).

First of all, we have to decide which Banach space X we could use in order to study the system above. From a conceptual point of view, if u and v are densities on the interval $[0, 1]$, it would be natural to consider spaces based on L^1 for these variables. However, the Nemytskij operators \mathcal{G} and \mathcal{F} defined on a space of integrable \mathbb{R} -valued functions on $[0, 1]$ are very often not well defined and more importantly, they are Fréchet differentiable only if g and f are affine functions (see [52]). This makes impossible to linearise the system around steady states in order to study their stability properties. Although this lack of differentiability do not invalidate the principle of linearised stability per se, it makes necessary to use ad hoc techniques to analyse the behaviour of the system around stationary points (see [30] for an example of that).

In order to avoid this lack of smoothness related to the Nemytskij operators on L^1 , we may use spaces based on the sup norm. It is easy to prove that this operators inherit the smooth properties of its associated functions in spaces with the sup norm. In particular, if g is differentiable, then the Fréchet derivative of \mathcal{G} at a point (\bar{u}, \bar{v}) is the operator

$$D\mathcal{G}(\bar{u}, \bar{v}) \begin{pmatrix} u \\ v \end{pmatrix} = D_2g(\cdot, \bar{u}(\cdot), \bar{v}(\cdot))u(\cdot) + D_3g(\cdot, \bar{u}(\cdot), \bar{v}(\cdot))v(\cdot), \quad (1.1.4)$$

and analogously for f . Specifically, the sup norm space X we are going to work with is

$$X = L_\infty^n \times C_b \quad (1.1.5)$$

where $L_\infty^n = (L^\infty(0, 1))^n$ and

$$C_b = \{(v, r) \in C([0, 1], \mathbb{R})^m \times \mathbb{R}^k \mid v(0) = \Lambda r\}.$$

Realise that the definition of space C_b comprises the boundary conditions of the system. The reason why we choose X to have this form rather than a simpler one such as $L_\infty^n \times C([0, 1], \mathbb{R})^m \times \mathbb{R}^k$ or $L_\infty^n \times L_\infty^m \times \mathbb{R}^k$ is that the trajectories would not be continuous on these spaces.

In order to follow the standard semilinear formulation of system (1.1.3) as it is described in [68], we consider the linear principal part and the nonlinear Lipschitz perturbation separately. Thus, the operator A defined as

$$A \begin{pmatrix} u \\ v \\ r \end{pmatrix} = \begin{pmatrix} 0 \\ -c \cdot v' \\ 0 \end{pmatrix} \quad (1.1.6)$$

with domain

$$D(A) = \{(u, v, r) \in X \mid (0, c \cdot v', 0) \in X\},$$

is the infinitesimal generator of a strongly continuous semigroup¹ T . The prime symbol $'$ in the previous expressions refers to the generalised notion of derivative. Being the principal part of the system specified, the perturbation is the operator \mathcal{P} that sends elements $(u, v, r) \in X$ into $\mathcal{P}(u, v, r) = (\mathcal{G}(u, v), \mathcal{F}(u, v), \mathcal{H}(v, r))$. At this point, however, we encounter an obstacle that prevents us from applying the standard semilinear formulation in a straightforward manner. It turns out that the range of the perturbation \mathcal{P} is not within X but contained in the bigger space $Y = L_\infty^n \times L_\infty^m \times \mathbb{R}^k$. Since \mathcal{P} is Lipschitz from X into Y , the problem is now not a lack of regularity but a lack of definition of the semigroup T on the space Y , in the sense that the variation of constants equation

$$\begin{pmatrix} u(\cdot, t) \\ v(\cdot, t) \\ r(t) \end{pmatrix} = T(t) \begin{pmatrix} u_0(\cdot) \\ v_0(\cdot) \\ r_0 \end{pmatrix} + \int_0^t T(t-s) \mathcal{P} \begin{pmatrix} u(\cdot, s) \\ v(\cdot, s) \\ r(s) \end{pmatrix} ds$$

is ambiguous. To overcome this difficulty the semigroup T should be extended into Y , and the natural way to do that is to define the operator A in Y instead of X . However, this procedure is not as easy as it could seem. In X some hypotheses are satisfied by A that guarantee the existence of a strongly continuous semigroup whereas in Y such hypotheses could not hold. In order to deal with semigroups that fail to be strongly continuous we apply the sun-dual framework developed in [18, 19]. This theory extends the standard semilinear formulation by allowing perturbations that take values on certain Banach space related to the phase space in which the system is defined. It is worth pointing out that this theory has commonly been used to treat systems of delay differential equations [28, 26], whereas here it is applied to a system of PDEs (similarly as in [53]).

¹A brief introduction to strongly continuous semigroups and their infinitesimal generators can be found in Appendix A.

A comprehensive review of the theory of sun dual semigroups is given in section 1.2. There we provide the main tools to give a semilinear formulation of the dynamical systems (1.1.1) and (1.1.2). This is done in section 1.3, where such a formulation allows us to solve the Abstract Cauchy Problem (Theorem 1.3.2) as well as to study the dynamics of the system around steady states by means of the linearised system at these points (Theorem 1.3.6). We also show that the semigroups associated to the linearised systems are eventually norm continuous, so that the dynamics of these semigroups can be summarised in terms of the dominant eigenvalues and eigenvectors of their generators. In the discussion we finally show how the results of section 3 can be applied to equations (0.0.9) and (0.0.10) that model the growth of microorganisms along the intestines of animals. In addition, we also illustrate how the systems introduced in this chapter are suited to study the formation of biofilms on complex networks where certain liquid is flowing and diffusion is negligible.

1.2 Sun-dual formalism and evolution equations

Next we recall the most important results (for our purposes) of the work done by Clement et al. [18, 19], which are based on a generalised version of the variation of constants formula. We will state two main theorems. The first gives a result of local existence and uniqueness of solutions, while the second is related to stability properties of the steady states. Although similar brief summaries exist written by the same authors [26], we have decided to include our own in order to present a more comprehensible work and because slight variations are introduced to deal with non sun-reflexive spaces for which the variation of constants formula is well defined (see [29] for another reference where this semilinear formulation is undertaken without the sun-reflexivity hypothesis). Thus some of the theorems stated below are not exactly the same as the ones found in [18, 19], even though the arguments to prove them can be applied essentially in the same way.

1.2.1 Linear theory

Let X be a Banach space, and denote by X^* its dual space. An element $x^* \in X^*$ is, by definition, a linear continuous operator from X to \mathbb{R} . We denote the image of an element $x \in X$ by x^* with the bracket $\langle x^*, x \rangle$.

Given a closed operator C on X , its adjoint operator C^* is a linear operator from X^* to X^* with domain

$$D(C^*) = \{x^* \in X^* \mid \exists \zeta^* \in X^* \text{ such that } \langle x^*, Cx \rangle = \langle \zeta^*, x \rangle \forall x \in D(C) \subset X\}.$$

It turns out that if $x^* \in D(C^*)$ then only one $\zeta^* \in X^*$ exists satisfying $\langle x^*, Cx \rangle = \langle \zeta^*, x \rangle$ for all $x \in D(C)$, so that the image of x^* by C^* is defined unequivocally as $C^*x^* = \zeta^*$. In particular if C is a bounded operator, then C^* is also a bounded operator and satisfies $\langle C^*x^*, x \rangle = \langle x^*, Cx \rangle$ for all $x^* \in X^*$ and $x \in X$.

Given a strongly continuous semigroup T on X , the sun-dual space of X relative to T is a subspace of the dual space X^* defined by:

$$X^{\odot T} := \{x^* \in X^* \mid \|T^*(t)x^* - x^*\| \rightarrow 0 \text{ as } t \downarrow 0\},$$

where $T^*(t)$ is the adjoint of the operator $T(t)$. We denote by $T^\odot(t)$ the restriction of $T^*(t)$ to $X^{\odot T}$, so that T^\odot is, by construction, a strongly continuous semigroup on $X^{\odot T}$ whose infinitesimal generator is denoted as A_{T^\odot} . Repeating this procedure on the pair $(T^\odot, X^{\odot T})$ we define the double-sun-dual of X relative to T as:

$$X^{\odot\odot T} := (X^{\odot T})^{\odot T^\odot}.$$

The *canonical injection* $j : X \hookrightarrow X^{\odot T^*} := (X^{\odot T})^*$ is determined by the pairing

$$\langle j(x), x^\odot \rangle = \langle x^\odot, x \rangle \quad \forall x^\odot \in X^{\odot T}.$$

In [18] it is shown that

$$\|j(x)\|_{X^{\odot T^*}} \leq \|x\|_X \leq M \|j(x)\|_{X^{\odot T^*}}, \quad (1.2.1)$$

where M is a constant which depends on T . Among other things, this implies that

$$j(X) \subset X^{\odot\odot T} \quad (1.2.2)$$

since it is easily checked that $T^{\odot*}(t)j(x) = jT(t)x$ and then

$$\|T^{\odot*}(t)j(x) - j(x)\|_{X^{\odot T^*}} \leq \|T(t)x - x\|_X \longrightarrow 0 \text{ as } t \downarrow 0.$$

The canonical injection makes possible to introduce two important concepts for the development of the theory.

Definition 1.2.1. *X is said to be sun-reflexive relative to a strongly continuous semigroup T on X if $j(X) = X^{\odot\odot T}$.*

Definition 1.2.2. *Let T be a strongly continuous semigroup on X . Let Y be a subspace of $X^{\odot T^*}$. We say that T is closed by $\odot*$ -integration on Y if, for all $f \in C([0, \infty), Y)$ and for all $t \geq 0$,*

$$\int_0^t T^{\odot*}(t-s)f(s) ds \in j(X). \quad (1.2.3)$$

The integral in (1.2.3) must be understood as an element of $X^{\odot T^*}$, and specifically (due to Bochner integral properties) as the functional satisfying

$$\left\langle \int_0^t T^{\odot*}(t-s)f(s) ds, x^\odot \right\rangle = \int_0^t \langle T^{\odot*}(t-s)f(s), x^\odot \rangle ds.$$

Notice that a semigroup T is always closed by $\odot*$ -integration on $j(X)$ since

$$\int_0^t T^{\odot*}(t-s)f(s) ds = j \int_0^t T(t-s)j^{-1}f(s) ds.$$

A well known result of the theory states that the kind of integrals given by (1.2.3) take values not in the whole space $X^{\odot T^*}$ but in the subset $X^{\odot\odot T}$.

Proposition 1.2.3. ([18], Theorem 3.2) *Let T be a strongly continuous semigroup on X and $f \in C([0, \infty), X^{\odot T^*})$. Then*

$$\int_0^t T^{\odot*}(t-s)f(s) \in X^{\odot\odot T} \quad \forall t \geq 0$$

Taking into account this proposition together with inclusion (1.2.2) it follows:

Corollary 1.2.4. *If X is sun-reflexive relative to T , then T is closed by $\odot*$ -integration on $X^{\odot T^*}$.*

As already commented, most propositions in the series of papers [18, 19] as well as in the book [28] assume that a given Banach space X is sun-reflexive relative to a semigroup T . However, it is possible to prove similar results by means of analogous arguments assuming the closedness of T by $\odot*$ -integration on a subspace Y of $X^{\odot T^*}$. Let us give the reformulated statements we need for the present thesis.

Theorem 1.2.5. ([18], Theorem 4.2) *Let T be a strongly continuous semigroup generated by A and closed by $\odot*$ -integration on $Y \subset X^{\odot T^*}$. Let B be a bounded linear operator from X into Y . Then the equation*

$$S(t)x = T(t)x + j^{-1} \int_0^t T^{\odot*}(t-s)BS(s)x ds \quad (1.2.4)$$

uniquely defines a strongly continuous semigroup S on X . The partial sums of

$$\sum_{k=0}^{\infty} S_k,$$

with $S_0 = T$ and

$$S_{k+1}(t) = j^{-1} \int_0^t T^{\odot*}(t-s)BS_k(s)ds \quad \forall t \geq 0,$$

converge towards S uniformly on compact intervals, i.e.

$$\lim_{n \rightarrow \infty} \sup_{t \in [0, \tau]} \|S(t) - \sum_{k=0}^n S_k(t)\| = 0 \quad \forall \tau > 0.$$

The generator of S is A_S with domain

$$D(A_S) = \{x \in X \mid j(x) \in D(A_{T^{\odot}}^*) \text{ and } A_{T^{\odot}}^*j(x) + Bx \in j(X)\}$$

*and images $A_Sx = j^{-1}(A_{T^{\odot}}^*j(x) + Bx)$.*

The semigroup implicitly defined by equation (1.2.4) makes natural to ask for its sun-dual spaces, that is for $X^{\odot S}$ and $X^{\odot\odot S}$. The following result shows that these spaces are determined just by the generator A , so they do not depend on the perturbation B .

Proposition 1.2.6. ([18], Lemma 4.3) *Let T , A , B and S be as in Theorem 1.2.5. Then $X^{\odot s} = X^{\odot r}$ and $X^{\odot \odot s} = X^{\odot \odot r}$.*

Not only the sun-dual spaces are invariant with respect bounded perturbations from X into Y . The property of being closed by $\odot*$ -integration on Y is also satisfied by the perturbed semigroup S . Notice that this makes sense since Proposition 1.2.6 ensures that Y is a subspace of $X^{\odot s*}$. This is stated formally in the following proposition. The same proposition relates the evolution family obtained when T is perturbed by $B + f$ with the evolution family obtained when S is perturbed by f , where f is a continuous function of time from $[0, \infty)$ into Y .

Proposition 1.2.7. ([19], Proposition 2.5) *Let T , A , B and S be as in Theorem 1.2.5. Then S is closed by $\odot*$ -integration on Y . Moreover, for every $x \in X$ and every function $f \in C([0, \infty), Y)$, $u(t; x)$ defined as*

$$u(t; x) = S(t)x + j^{-1} \int_0^t S^{\odot*}(t - \tau)f(\tau)d\tau$$

is the only solution of

$$u(t; x) = T(t)x + j^{-1} \int_0^t T^{\odot*}(t - \tau)(Bu(\tau; x) + f(\tau))d\tau.$$

Corollary 1.2.8. *Let T , A , B and S be as in Theorem 1.2.5. Let B_1 and B_2 be bounded operators from X into $Y \subset X^{\odot r*}$ such that $B = B_1 + B_2$, and let S_1 be the semigroup obtained when T is perturbed by B_1 . Then S is equal to the semigroup obtained when S_1 is perturbed by B_2 (in the sense of Theorem 1.2.5).*

The above reformulation of the perturbation theory for dual semigroups is useful when, on the one hand, the unperturbed semigroup T is defined on a non sun-reflexive space X , but, on the other hand, T is closed by $\odot*$ -integration on some subspace Y bigger than $j(X)$ (so that the standard semilinear formulation is not enough to solve the problem). At this point it is mandatory to show that semigroups satisfying these properties do exist.

Example 1.2.9. *Let $X = X_1 \times X_2$ be a Banach space and $T = \text{diag}(T_1, T_2)$ be a strongly continuous semigroup with a “diagonal” structure, i.e. $T(t)(x_1, x_2) = (T_1(t)x_1, T_2(t)x_2)$ for all $t \geq 0$. Let X_2 be sun-reflexive with respect T_2 . For $i \in \{1, 2\}$ let j_i be the canonical inclusion from X_i into $X^{\odot T_i*}$ and define $Y = j_1(X_1) \times X_2^{\odot T_2*}$. Then T is closed by $\odot*$ -integration on Y .*

Proof. Take $f \in C([0, \infty), Y)$ arbitrary, and define f_1 and f_2 the component functions of f in $j_1(X_1)$ and $X_2^{\odot T_2*}$ respectively. On the one hand, since j_1 is a linear bounded operator and $j_1 T_1(t) = T_1^{\odot*}(t)j_1$, then

$$\int_0^t T_1^{\odot*}(t - s)f_1(s)ds = j_1 \left(\int_0^t T_1(t - s)j_1^{-1}f(s)ds \right) \in j_1(X_1).$$

On the other hand, since f_2 is norm continuous from $[0, \infty)$ to $X_2^{\odot T_2^*}$, Proposition 1.2.3 implies

$$\int_0^t T_2^{\odot*}(t-s)f_2(s)ds \in X_2^{\odot\odot T_2},$$

and this is enough because $X_2^{\odot\odot T_2} = j_2(X_2)$ due to the sun-reflexivity condition. \square

Notice that the subspace Y in the previous example is in general bigger than $j(X)$ because $X_2^{\odot T_2^*}$ is in general bigger than $X_2^{\odot\odot T_2}$. Notice also that X could be non sun-reflexive if, for example, $T_1(t) = \text{Id}$ for all $t \geq 0$ and X_1 were non-reflexive. Arguably one could say that the example above is very degenerate due to the diagonal structure of the semigroup T . However, Proposition 1.2.7 allows us to take any perturbation of T by a bounded linear perturbation from X into Y , which give a collection of less trivial examples.

1.2.2 Semi-Linear theory

In some applications, as we write the evolution law of a dynamical system, we may obtain equations of the type

$$\begin{cases} \frac{dv(t)}{dt} = A_T v(t) + \mathcal{H}(v(t)) \\ v(0) = x \in X \end{cases}, \quad (1.2.5)$$

where A_T is the generator of a strongly continuous semigroup T which is closed by \odot^* -integration on Y (see Definition 1.2.2) and $\mathcal{H} : X \rightarrow Y \subset X^{\odot T^*}$ is a Lipschitz function.

Due to the fact that \mathcal{H} takes values in $Y \subset X^{\odot T^*}$, it is clear that (1.2.5) is a non-standard initial value problem which even fails to be well defined. Such an issue can be overcome reinterpreting the equation not in X but in $j(X)$. The natural way to do this is by writing

$$\begin{cases} \frac{djv(t)}{dt} = jA_T v(t) + \mathcal{H}(v(t)) \\ jv(0) = j(x) \in j(X) \end{cases}. \quad (1.2.6)$$

Alternatively, we can go a bit further thanks to the equivalence between the adjoint operator $A_{T^\odot}^*$ and the weak-star generator of $T^{\odot*}$.

Proposition 1.2.10. ([28], Theorem AII.3.5) *Let T be a strongly continuous semigroup T on X with generator A_T . Then, A_T^* coincides with the weak-star generator of T^* , that is,*

$$D(A_T^*) = \left\{ x^* \in X^* \mid \exists \omega^* \text{-}\lim_{t \rightarrow 0} \frac{T^*(t)x^* - x^*}{t} \right\}$$

and $A_T^* x^* = \omega^* \text{-}\lim_{t \rightarrow 0} \frac{T^*(t)x^* - x^*}{t}$ when $x^* \in D(A_T^*)$.

By means of such an equivalence one can check that for all $x \in D(A_T)$, $j(x) \in D(A_{T \circ}^*)$ and $jA_T x = A_{T \circ}^* j(x)$, so that if $ju(t)$ is a classical solution of (1.2.6) then it has to be a classical solution of

$$\begin{cases} \frac{dju(t)}{dt} = A_{T \circ}^* ju(t) + \mathcal{H}(j^{-1}(ju(t))) \\ ju(0) = j(x) \in j(X) \end{cases} . \quad (1.2.7)$$

Now we deal with a perfectly defined IVP. Although it is not the kind of standard Lipschitz perturbations of linear evolution equations treated in [68], it resembles them in some sense. In fact, in this case similar arguments can be made by means of a generalised version of the variation of constants equation, which takes the form

$$ju(t) = jT(t)x + \int_0^t T^{\circ*}(t-s)\mathcal{H}(v(s)) ds . \quad (1.2.8)$$

The functions $v : [0, \infty) \rightarrow X$ satisfying this integral equation are its solutions, though we also refer to the composition ju as solutions. One reason to consider such an integral equation is that any classical solution of (1.2.7) is a solution of (1.2.8). This relation suggests the notion of mild solution:

Definition 1.2.11. *A function $v : [0, \infty) \rightarrow X$ is a mild solution of (1.2.5) if it is continuous and it satisfies the integral equation (1.2.8). If v is a mild solution of (1.2.5), then we say $ju : [0, \infty) \rightarrow j(X)$ is a mild solution of (1.2.6).*

It seems evident that other notions of generalised solutions may exist, that is, sets of functions which contain all classical solution of (1.2.7). Therefore, we should justify in which sense the above definition is special. Although it is not an easy question with still open issues, the main argument is that mild solutions defined in this way behave continuously with respect to initial data (see Theorem 1.2.12 stated below). This is somehow related with the fact that for any mild solution v given by (1.2.8), there is an abstract Cauchy problem somehow close to (1.2.7) with a classical solution close to v (see Theorem 4.2.7 in [68]). Therefore, by analysing the solutions of (1.2.8), one can derive results about the trajectories of our original problem (1.2.5).

Two fundamental properties of mild solutions are given in the following theorem. It addresses the question of how many, if any, solutions the equation (1.2.8) has, as well as some regularity properties with respect to initial conditions. It was proven in [19] and the proof is based on the contraction principle as it is done in ODEs theory or in the standard semilinear formulation. The main difference is justifying that for any continuous function $f : [0, t] \rightarrow X$ the integral

$$\int_0^t T^{\circ*}(t-s)\mathcal{H}(f(s)) ds$$

belongs to $j(X)$. However, in our setting this issue presents no problems since we assume $\mathcal{H} : X \rightarrow Y$ to be Lipschitz (and in particular continuous) and T to be closed by $\circ*$ -integration on Y (see Definition 1.2.2).

Theorem 1.2.12. ([19], Theorem 3.1) For every $x \in X$ there exists a unique mild solution $v(\cdot; x)$ of (1.2.5). Moreover, v satisfies the semigroup property $v(t + s; x) = v(t; v(s; x))$ and $v(t; \cdot)$ is Lipschitz. We refer to $v(\cdot; \cdot)$ as the semiflow of (1.2.5).

Therefore, if jv is a classical solution of (1.2.6) it has to be unique. When \mathcal{H} is Fréchet differentiable, a result on the differentiability with respect to initial conditions around a steady state can be given. Here, by steady state we mean an element $\bar{x} \in X$ such that

$$j\bar{x} = jT(t)\bar{x} + \int_0^t T^{\odot*}(t-s)\mathcal{H}(\bar{x}) ds \quad \forall t \geq 0.$$

However, as it occurs in the standard semilinear formulation, the steady states satisfying the above integral conditions coincide with the equilibrium points of system (1.2.7), i.e., the points $\bar{x} \in X$ such that

$$j\bar{x} \in D(A_{T^{\odot}}^*) \quad \text{and} \quad A_{T^{\odot}}^* j\bar{x} + \mathcal{H}(\bar{x}) = 0.$$

This equivalence enables us to use, on the one hand, the differential equation (1.2.7) to find the stationary mild solutions of (1.2.5), and, on the other hand, the variation of constants formula to linearise the semiflow around such solutions as well as to give some stability results.

Theorem 1.2.13. ([28] Proposition VII.5.6) Let \bar{x} be a steady state of (1.2.8). Assume \mathcal{H} is Fréchet differentiable in \bar{x} and define $B := \mathcal{H}'(\bar{x}) \in \mathcal{B}(X, Y)$. Then the semiflow $v(\cdot; \cdot)$ given by (1.2.8) is uniformly Fréchet differentiable at \bar{x} , i.e. for all $t_1 > 0$ and all $\varepsilon > 0$ there exists $\delta > 0$ such that if $\|x - \bar{x}\| < \delta$ and $t \in [0, t_1]$ then

$$\|v(t; x) - \bar{x} - D_x v(t; \bar{x})(x - \bar{x})\| < \varepsilon \|x - \bar{x}\|.$$

The family of linear operators S defined as $S(t) := D_x v(t; \bar{x}) : X \rightarrow X$ for all $t \geq 0$, is given implicitly by

$$jS(t)x = jT(t)x + \int_0^t T^{\odot*}(t-s)BS(t)x ds \quad \forall t \geq 0, \quad (1.2.9)$$

and explicitly by the series

$$S = \sum_{n=0}^{\infty} S_n \quad (1.2.10)$$

with $S_0 = T$ and

$$S_n(t) = j^{-1} \int_0^t T^{\odot*}(t-s)BS_{n-1}(s)ds \quad \forall t \geq 0.$$

Moreover, the partial sums in (1.2.10) converge uniformly on compact intervals.

Notice that $S(t)$ is well defined because, since T is closed by \odot^* -integration on Y and B is continuous and takes values in Y , Theorem 1.2.5 ensures the existence of a unique strongly continuous semigroup S which is solution of (1.2.9). The generator of S is also given by Theorem 1.2.5.

From the previous theorem it follows that, for all fixed $t > 0$, $v(t; x)$ can be approximated by $\bar{x} + S(t)(x - \bar{x})$ for those x close enough to \bar{x} . It seems a good strategy to infer the behavior of $v(\cdot; x)$ close to \bar{x} by means of the stability properties of S . However, we must justify carefully the validity of this procedure because, a priori, the asymptotic behavior of S could not determine the stability of the equilibrium \bar{x} . To our knowledge, it is yet an open question if it could exist non-linear semiflows with an asymptotically stable equilibrium for which the linearised system around it is unstable. Fortunately, some results in the literature can be applied to our system in order to discard this pathological possibility. Before exposing them let us recall a couple of concepts.

Definition 1.2.14. *The growth bound of a strongly continuous linear semigroup T on a Banach space X is defined as*

$$\omega_0(T) := \inf\{\omega \in \mathbb{R} \mid \exists M \geq 1 \text{ such that } \|T(t)\| \leq Me^{\omega t} \quad \forall t \geq 0\}.$$

Definition 1.2.15. *A strongly continuous linear semigroup T is said to be exponentially stable if its growth bound is strictly negative. Similarly, T is said to be exponentially unstable if its growth bound is strictly positive.*

If S is exponentially stable (i.e. there exists $M \geq 1$ and $\omega > 0$ such that $\|S(t)\| \leq Me^{-\omega t}$), it can be shown that \bar{x} is a locally asymptotically stable equilibrium (the continuity of $v(\cdot; x)$ makes possible to apply essentially the same argument used in the theory of ODEs [64]).

Theorem 1.2.16. *([19] Theorem 4.2) Let \bar{x} , v and S as in Theorem 1.2.13. If $\omega_0(S) < 0$ then \bar{x} is locally asymptotically stable in the Lyapunov sense. More precisely, there exist $\omega > 0$ and $\delta > 0$ such that if $\|x - \bar{x}\| < \delta$,*

$$e^{\omega t}(v(t; x) - \bar{x}) \rightarrow 0 \quad \text{as} \quad t \rightarrow \infty.$$

In order to give an instability result some additional hypotheses other than $\omega_0(S) > 0$ have to be assumed.

Theorem 1.2.17. *([19] Theorem 4.3) Let \bar{x} , v and S as in Theorem 1.2.13, and denote A_S the generator of S . Assume $\omega_0(S) > 0$ and that X admits a decomposition*

$$X = X_1 \oplus X_2 \tag{1.2.11}$$

into S -invariant subspaces with X_1 finite-dimensional. For $i \in \{1, 2\}$ let S_i be the restriction of S to X_i and let A_{S_i} be the corresponding generators. If

$$\omega_0(S_2) < \min\{\operatorname{Re}\lambda \mid \lambda \in \operatorname{Spectrum}(A_{S_1})\}$$

then \bar{x} is unstable, i.e. there exist $M > 0$ and a sequence $\{x_n, t_n\}_{n \geq 1} \subset X \times \mathbb{R}$ satisfying $x_n \rightarrow \bar{x}$ and $t_n \rightarrow \infty$ such that $\|(v(t_n, x_n) - \bar{x})\| \geq M$.

The above results are useful provided we have a method to study the dynamics of S . In general this cannot be done in a straightforward manner because S is given either implicitly or as a series. One way to overcome this problem is by means of the generator A_S , whose expression is usually explicit and relatively simple. Indeed, some relations are known between the growth bound of a semigroup T and the spectral bound of its infinitesimal generator A_T , which is defined as follows.

Definition 1.2.18. *The spectral bound of a closed operator A , denoted by $s(A)$, is defined as*

$$s(A) := \sup\{\operatorname{Re}\lambda \mid \lambda \in \operatorname{Spectrum}(A)\}.$$

In general one can only say that $s(A_T) \leq \omega_0(T)$, since counterexamples exist in which the strict inequality holds (see chapter 5 of [33] and [66] for a review on asymptotics of semigroups). However, by imposing some further regularity on the semigroup T beyond strong continuity, one can obtain stronger results such as the relation $s(A_T) = \omega_0(T)$ or even a mapping linking the spectrum of $T(t)$ with the spectrum of A_T .

Definition 1.2.19. *A strongly continuous semigroup T is said to be eventually norm continuous if there exist $t^* \geq 0$ such that*

$$\lim_{h \rightarrow 0} \|T(t+h) - T(t)\| = 0 \quad \forall t > t^*,$$

where $\|\cdot\|$ denotes the operator norm.

Theorem 1.2.20. ([33] Theorem IV.3.10) *Let T be an eventually norm continuous semigroup on a Banach space X with generator A_T . Then T satisfies the Spectral Mapping Theorem: for all $t \geq 0$, the spectrum of $T(t)$ and the spectrum of A_T , denoted by $\sigma(T(t))$ and $\sigma(A_T)$ respectively, satisfy the following set relation*

$$\sigma(T(t)) \setminus \{0\} = e^{t\sigma(A_T)}.$$

In particular the equality $\omega_0(T) = s(A_T)$ holds.

Taking this into account, Theorems 1.2.16 and 1.2.17 can be modified in terms that they only involve information about the spectrum of A_S , i.e. the generator of the linearised semigroup S .

Theorem 1.2.21. *Let \bar{x} , v and S as in Theorem 1.2.13, and denote A_S the generator of S . If S is eventually norm continuous then*

- (i) \bar{x} is locally asymptotically stable if $s(A_S) < 0$,
- (ii) \bar{x} is unstable if there exists $\omega > 0$ such that the spectrum of A_S within the region $\{\lambda \in \mathbb{C} \mid \operatorname{Re}(\lambda) > \omega\}$ is non-empty and is composed only by a finite number of eigenvalues with finite algebraic multiplicity.

Proof. Statement (i) follows directly from Theorem 1.2.16 and the relation $s(A_S) = \omega_0(S)$ due to the eventually norm continuity of S . To prove statement (ii) we use the decomposition theorem (Theorem 6.17 in [50]) by taking a Jordan curve enclosing the eigenvalues to the right of ω . This implies that $A_S : D(A_S) \subset X \rightarrow X$ can be decomposed on $X = X_1 \oplus X_2$ as $A_S(x_1 + x_2) = A_{S_1}x_1 + A_{S_2}x_2$, with X_1 being the eigenspace associated to the eigenvalues to the right of ω and A_{S_1} and A_{S_2} being closed operators on X_1 and X_2 respectively. The assumption on the eigenvalues to the right of ω ensures that X_1 is finite-dimensional. Moreover, both A_{S_1} and A_{S_2} are generators of strongly continuous semigroups, namely S_1 on X_1 and S_2 on X_2 respectively, in such a way that $S(t)(x_1 + x_2) = S_1(t)x_1 + S_2(t)x_2$ for all $t \geq 0$ and $(x_1, x_2) \in X_1 \times X_2$. Thus, a decomposition as the one appearing in Theorem 1.2.17 is derived from the hypotheses. From the decomposition theorem it also follows that the spectrum of A_{S_1} is composed by the spectral values of A_S to the right of ω whereas the spectrum of A_{S_2} corresponds to the spectrum of A_S located to the left of ω . Finally, since S_1 is norm continuous (because X_1 is finite dimensional), the eventually norm continuity of S implies the eventually norm continuity of S_2 . Then we obtain

$$\omega_0(S_2) = s(A_{S_2}) < \omega < \min\{\operatorname{Re}\lambda \mid \lambda \in \operatorname{Spectrum}(A_{S_1})\},$$

which, through Theorem 1.2.17, implies the instability of \bar{x} . □

By analysing the previous proof one can check that the eventually norm continuity of the semigroup S is only used to derive the relations $s(A_S) = \omega_0(S)$ and $s(A_{S_2}) = \omega_0(S_2)$. Thus, similar results could be given assuming that semigroup S satisfies weaker properties than the eventual norm continuity. However, we have decided to use this version of the theorem because, as it will be shown in the next section, the linearised semigroups associated to (1.1.3) are indeed eventually norm continuous.

We finish this section recalling that the property of being eventually norm continuous is preserved under compact perturbations (Proposition III.1.14 in [33] states this result in the standard case, i.e. when the perturbation K is defined from X to X).

Theorem 1.2.22. *Let T be an eventually norm continuous semigroup generated by A and closed by \odot^* -integration on $Y \subset X^{\odot T^*}$. Let K be a compact operator from X into Y . Then the semigroup S generated by $A+K$ (in the sense of Theorem 1.2.5) is eventually norm continuous.*

Proof. By Theorem 1.2.5 we know that S is given by equation (1.2.4). Since K is compact, the integral

$$I(t) = j^{-1} \int_0^t T^{\odot^*}(t-s)KS(s)ds$$

is a compact operator from X to X for every t (see Theorem A.2 of [26] or Theorem 1.3 of [85]). Let $t^* > 0$ be the time beyond which T is norm continuous. Then, since

$$\begin{aligned} \|S(t+h) - S(t)\| &\leq \|T(t+h) - T(t)\| + \\ &+ \|j^{-1} \int_0^{t+h} T^{\odot^*}(t+h-s)KS(s)ds - j^{-1} \int_0^t T^{\odot^*}(t-s)KS(s)ds\|, \end{aligned}$$

for $t > t^*$ it follows that S is norm continuous from the right. Indeed,

$$\lim_{h \downarrow 0} \|S(t+h) - S(t)\| \leq \lim_{h \downarrow 0} \|j^{-1}(T^{\odot*}(h) - Id)jI(t)\| = \lim_{h \downarrow 0} \|(T(h) - Id)I(t)\| = 0,$$

where the limit above vanishes because the strong continuity of T implies that T is norm continuous when restricted to compact sets of X (see Lemma I.5.2 in [33]), such as the image of the unit ball by $I(t)$. Finally, using the semigroup property of S we conclude that, for $t > t^*$, S is also norm continuous from the left. Indeed, taking $\hat{t} \in (t^*, t)$, it follows

$$\lim_{h \uparrow 0} \|S(t+h) - S(t)\| \leq \lim_{h \uparrow 0} \|S(t - \hat{t} + h)\| \|S(\hat{t}) - S(\hat{t} - h)\| = 0,$$

where the limit vanishes because, on the one hand, $\|S(\hat{t}) - S(\hat{t} - h)\|$ tends to 0 due to the norm continuity from the right of S at $\hat{t} > t^*$ and, on the other hand, $\|S(t - \hat{t} + h)\|$ is uniformly bounded as h approaches 0 due to the strong continuity of S . \square

1.3 Semilinear formulation of the problem

Now we are ready to deal with problem (1.1.3). First we are going to give a formula for the semigroup T generated by A (see (1.1.6)) and then we will show that T is indeed closed by $\odot*$ -integration on Y . This is done by checking that T has the structure of Example 1.2.9. Once verified these properties about T , the well posedness of the problem will be derived by means of the theory reviewed in the previous section. Finally, we show that the linearised semigroup S around any stationary point of (1.1.3) is eventually norm continuous, so that Theorem 1.2.21 gives a method to determine the stability of equilibria based only on the spectrum of the infinitesimal generator A_S of S .

1.3.1 Existence and uniqueness of solutions

The semigroup T on X generated by A can be obtained through the method of characteristics, and acts in the following way:

$$T(t) \begin{pmatrix} u \\ v \\ r \end{pmatrix} = \begin{pmatrix} u(\cdot) \\ \tilde{v}(\cdot; t, v, r) \\ r \end{pmatrix} \quad (1.3.1)$$

where the i th component of $\tilde{v}(\cdot; t, v, r)$ is

$$(\tilde{v}(x; t, v, r))_i = \tilde{v}_i(x; t, v_i, r) = \Lambda_i r \mathbf{1}_-(\varphi_i(-t, x)) + v_i(\varphi_i(-t, x)) \mathbf{1}_+(\varphi_i(-t, x)), \quad (1.3.2)$$

being Λ_i the i th row of Λ and $\varphi_i(t, x)$ the unique function satisfying $\partial_t \varphi_i(t, x) = c_i(\varphi_i(t, x))$ and $\varphi_i(0, x) = x$ (although the function $c_i(x)$ is not necessarily Lipschitz, the uniqueness property can be deduced because $c_i(x) \geq 1$ for all x). The functions $\mathbf{1}_-$ and $\mathbf{1}_+$ stand for the indicator functions on $(-\infty, 0)$ and $[0, \infty)$ respectively. To give a meaning to $\varphi_i(-t, x)$ for any $-t < 0$

is enough to assume that the function c_i is prolonged by any positive constant (for instance 1) for negative values of their arguments. Notice that $\varphi_i(\cdot, x)$ describes, as a function of t , the characteristic curve passing through the point x at time 0, so that $\varphi_i(-t, x)$ should be interpreted as the position that a point moving with velocity c had t units of times into the past. Therefore, a point that at time t is at position x , was at position $\varphi_i(-t, x)$ at time 0. In particular, if $\varphi_i(-t, x) < 0$ then we deduce that the point was outside the interval $[0, 1]$ at time 0, hence its value is not given by the initial condition of v but by the boundary condition.

Clearly, T is a diagonal semigroup on $X = L_\infty^n \times C_b$. Let T_1 and T_2 be the associated semigroups of T on L_∞^n and C_b respectively. Since $Y = L_\infty^n \times L_\infty^m \times \mathbb{R}^k$, in order to show that T is closed by \odot^* -integration on Y it is enough to verify that i) $L_\infty^m \times \mathbb{R}^k$ can be identified with a subspace of $C_b^{\odot T_2^*}$ and that ii) C_b is sun-reflexive with respect to T_2 (as showed in Example 1.2.9). Notice that here Y has not exactly the same meaning as in the previous section. There Y was a subspace of X^{\odot^*} whereas here Y is a representation of a subspace of X^{\odot^*} . We proceed in this way because then we can consider X as a subspace of Y and avoid the use of the inclusion $j : X \rightarrow X^{\odot^*}$ in the formulation of the results. Next we show that the two conditions mentioned above (i and ii) hold and, in addition, we specify how $T_2^{\odot^*}$ is defined on $L_\infty^m \times \mathbb{R}^k$.

Proposition 1.3.1. *Let C_b and T_2 be as above. Then*

$$L_\infty^m \times \mathbb{R}^k \cong C_b^{\odot T_2^*} \quad \text{and} \quad C_b \cong C_b^{\odot \odot T_2}.$$

Moreover, $T_2^{\odot^*}$ is the natural extension of T_2 into $L_\infty^m \times \mathbb{R}^k$, i.e.

$$T_2^{\odot^*}(t) \begin{pmatrix} v \\ r \end{pmatrix} = \begin{pmatrix} \tilde{v}(\cdot; t, v, r) \\ r \end{pmatrix}$$

with \tilde{v} exactly given as in (1.3.2).

Proof. The methodology of the proof is based on the one used in section II.5 of [28], and hence we only expose the main ideas². First the Riesz representation theorem is used to represent C_b^* using the space $\mathcal{M}_b^m \times \mathbb{R}^k$, where \mathcal{M}_b is the set of real Borel measures μ satisfying $\mu(\{0\}) = 0$. Instead of $\mu(\{0\}) = 0$ other conditions could be imposed in order to identify Borel Measures (seen as functionals on $C([0, \infty), \mathbb{R})^m \times \mathbb{R}^k$) that are equivalent on C_b due to the boundary condition. The pairing between C_b^* and C_b can be written as

$$\left\langle \begin{pmatrix} \mu \\ q \end{pmatrix}, \begin{pmatrix} v \\ r \end{pmatrix} \right\rangle = \sum_{i=1}^m \int_0^1 v_i(s) d\mu_i(s) + \langle q, r \rangle.$$

In order to work with a functions rather than measures, a isometric isomorphism between real Borel measures and normalised functions of bounded variation is used, so that C_b^* is represented as $\text{NBV}_b^m \times \mathbb{R}^k$ with $\eta \in \text{NBV}_b$ if η is a function of bounded variation, right continuous in $[0, 1]$ and satisfies $\eta(0) = 0$ (the norm in NBV_b is the total variation norm).

²A more detailed version of the proof is given in Appendix B.

The next step consists in showing $C_b^{\circ T_2} \cong (L^1(0, 1))^m \times \mathbb{R}^k$ where the norm in $L^1(0, 1)^m$ is weighed by function c (in the sense that $\|\nu\| = \sum_{i=0}^m \int_0^1 |\nu_i(s)/c_i(s)| ds$). This is done taking into account the result $\overline{D(A_{T_2}^*)} = C_b^{\circ T_2}$ (which is a particular case of the equality $\overline{D(A_T^*)} = X^{\circ T}$ that holds for any strongly continuous semigroup T generated by A_T on a Banach space X , proved in Proposition AII.3.8 of [28]). To apply this result first $D(A_{T_2}^*)$ is determined, which results in the pairs $(\eta, q) \in \text{NBV}_b^m \times \mathbb{R}^k$ satisfying $q \in \mathbb{R}^k$ and for all component of η there exists $\nu_i \in \text{NBV}_b$ such that

$$\eta_i(s) = \int_0^1 \frac{\nu_i(\sigma)}{c(\sigma)} d\sigma \quad \forall s \in [0, 1].$$

Then the closure $\overline{D(A_{T_2}^*)}$ is shown to be isometrically isomorphic to $(L^1(0, 1))^m \times \mathbb{R}^k$ when using weighting by c the norm of $(L^1(0, 1))^m$.

Since we represent $C_b^{\circ T_2} \subset C_b^*$ by means of $(L^1(0, 1))^m \times \mathbb{R}^k$, we can define a pairing between $(L^1(0, 1))^m \times \mathbb{R}^k$ and C_b . The natural pairing is the one obtained as $\langle (\nu, q), (v, r) \rangle = \langle (\phi((\nu, q)), (v, r)) \rangle$ where ϕ is the isometric isomorphism between $(L^1(0, 1))^m \times \mathbb{R}^k$ and $\overline{D(A_{T_2}^*)} \subset \text{NBV}_b^m \times \mathbb{R}^k$, which is given by

$$\left\langle \begin{pmatrix} \nu \\ q \end{pmatrix}, \begin{pmatrix} v \\ r \end{pmatrix} \right\rangle = \sum_{i=0}^m \int_0^1 v_i(s) \frac{\nu_i(s)}{c_i(s)} ds + r \cdot q.$$

Finally it is proven that $C_b^{\circ \circ T_2} \cong C_b$. Indeed, using $(L^1(0, 1))^m \times \mathbb{R}^k$ as a representation of $C_b^{\circ T_2}$ clearly implies $C_b^{\circ T_2^*} \cong (L^\infty(0, 1))^m \times \mathbb{R}^k$. In this case the norm of $(L^\infty(0, 1))^m$ is the standard one (i.e. is not affected by function c) if the pairing

$$\left\langle \begin{pmatrix} v \\ r \end{pmatrix}, \begin{pmatrix} \nu \\ q \end{pmatrix} \right\rangle = \sum_{i=1}^m \int_0^1 \frac{v_i(s)}{c_i(s)} \nu_i(s) ds + r \cdot q$$

is used, as we do. On the other hand, the semigroup T_2° on $(L^1(0, 1))^m \times \mathbb{R}^k$ is specified by

$$T_2^\circ(t) \begin{pmatrix} \nu \\ q \end{pmatrix} = \begin{pmatrix} \tilde{\nu}(\cdot; t, \nu) \\ q + \sum_{i=1}^m \int_0^1 \frac{\nu_i(s)}{c_i(s)} \mathbb{1}_-(\varphi_i(-t, s)) ds \Lambda_i \end{pmatrix}$$

where the i th component of $\tilde{\nu}(\cdot; t, \nu)$ is

$$\tilde{\nu}_i(\cdot, t, \nu) = c_i(\cdot) \frac{\nu_i(\varphi_i(t, \cdot))}{c_i(\varphi_i(t, \cdot))} \partial_2 \varphi_i(t, \cdot) \mathbb{1}_+(\varphi_i(-t, 1) - \cdot).$$

Similarly, T_2° is used to give an explicit formula for the semigroup $T_2^{\circ*}$ on $L_\infty^m \times \mathbb{R}^k$, which results in the natural extension of T_2 into $L_\infty^m \times \mathbb{R}^k$.

Then, the infinitesimal generator of T_2° on $(L^1(0, 1))^m \times \mathbb{R}^k$ is determined as

$$D(A_{T_2^\circ}) = \{(\nu, q) \in (L^1(0, 1))^m \times \mathbb{R}^k \mid \nu \text{ is absolutely continuous and } \nu(1) = 0\}$$

and $A_{T^\circ}(\nu, q) = (c\nu', \sum_{i=1}^m \Lambda_i \nu_i(0))$. By saying that ν is absolutely continuous we mean that the condition is satisfied component-wise, i.e. for each component of ν . The adjoint of A_{T° is consequently determined as

$$D(A_{T^\circ}^*) = \{(v, r) \in (L^\infty(0, 1))^m \times \mathbb{R} \mid v \text{ is Lipschitz and } v(0) = \Lambda r\} \quad (1.3.3)$$

and $A_{T^\circ}^*(v, r) = (-cv', 0)$. By taking the closure of $D(A_{T^\circ}^*)$ we obtain $C_b^{\circ\circ T_2}$. When doing so we lose the Lipschitz condition on v but the continuity remains. Therefore,

$$C_b^{\circ\circ T_2} \cong \{(v, r) \in C([0, 1], \mathbb{R})^m \times \mathbb{R}^k \mid v(0) = \Lambda r\} = C_b,$$

as desired. \square

Once shown that T is closed by \circledast -integration on Y , we can use Theorem 1.2.12 to conclude that one and only one semiflow Σ associated to (1.1.3) exists. This result is stated below in the form of a theorem.

Theorem 1.3.2. *Problem (1.1.1) is well posed on $X = L_\infty^n \times C_b$ defined in (1.1.5), i.e. there exists a unique function Σ from Ω to X , with Ω being an open subset of $[0, \infty) \times X$ (in the induced topology), satisfying the following:*

- for all initial condition $x = (u_0, v_0, r_0) \in X$ there exists $t_x \in (0, \infty]$ such that $[0, t_x) \times \{x\}$ is the intersection of Ω with $[0, \infty) \times \{x\}$,
- for all $x = (u_0, v_0, r_0) \in X$, the function $\Sigma(\cdot; x)$ from $[0, t_x)$ to X is a mild solution of (1.1.1) (in the sense of Definition 1.2.11). Thus, Σ satisfies the semigroup property, i.e. $\Sigma(t+s, x) = \Sigma(t, \Sigma(s, x))$ for positive s and t with $t+s < t_x$, whereas the function $\Sigma(t; \cdot)$ is locally Lipschitz in x .

1.3.2 Linearisation around steady states

Given a steady state $(\bar{u}, \bar{v}, \bar{r}) \in X$ of the semiflow Σ , Theorem 1.2.13 ensures that there exists a strongly continuous linear semigroup $S(t)$ on X such that $S(t) = D_2\Sigma(t; (\bar{u}, \bar{v}, \bar{r}))$. Moreover, using that $(v, r) \in D(A_{T^\circ}^*)$ if and only if v is Lipschitz and $v(0) = \Lambda r$ (see (1.3.3)), it follows that the domain of A_S (see Theorem 1.2.5) can be written as

$$D(A_S) = \{(u, v, r) \in X \mid v \text{ is Lipschitz and } (0, -c \cdot v', 0) + D\mathcal{H}(\bar{u}, \bar{v}, \bar{r})(u, v, r) \in X\}$$

and then

$$A_S \begin{pmatrix} u \\ v \\ r \end{pmatrix} = \begin{pmatrix} 0 \\ -c \cdot v' \\ 0 \end{pmatrix} + D\mathcal{H}(\bar{u}, \bar{v}, \bar{r}) \begin{pmatrix} u \\ v \\ r \end{pmatrix} \quad \text{for all } \begin{pmatrix} u \\ v \\ r \end{pmatrix} \in D(A_S). \quad (1.3.4)$$

Next, in order to study the asymptotic behaviour of Σ around $(\bar{u}, \bar{v}, \bar{r})$, we show that $S(t)$ is eventually norm continuous (see Theorem , so that Theorem 1.2.21 can be applied and a

characterization of the local dynamics around $(\bar{u}, \bar{v}, \bar{r})$ can be given in terms of the eigenvalues of the operator A_S (see Theorem 1.3.6 in the end of the section). The proof is long and will occupy the rest of the section.

Let us start noticing that $D\mathcal{H}(\bar{u}, \bar{v}, \bar{r})$ has the form

$$D\mathcal{H}(\bar{u}, \bar{v}, \bar{r}) \begin{pmatrix} u \\ v \\ r \end{pmatrix} = \begin{pmatrix} B_{11}u + B_{12}v \\ B_{21}u + B_{22}v \\ \tilde{K}(v, r) \end{pmatrix}.$$

where

$$\begin{aligned} B_{11} &\in L_\infty((0, 1), \mathcal{M}_{n \times n}(\mathbb{R})), \\ B_{12} &\in L_\infty((0, 1), \mathcal{M}_{n \times m}(\mathbb{R})), \\ B_{21} &\in L_\infty((0, 1), \mathcal{M}_{m \times n}(\mathbb{R})), \\ B_{22} &\in L_\infty((0, 1), \mathcal{M}_{m \times m}(\mathbb{R})), \end{aligned}$$

and \tilde{K} is a bounded operator from C_b into \mathbb{R}^k . Thus, the generator A_S can be formally written as

$$A_S \begin{pmatrix} u \\ v \\ r \end{pmatrix} = A \begin{pmatrix} u \\ v \\ r \end{pmatrix} + B \begin{pmatrix} u \\ v \\ r \end{pmatrix} + K \begin{pmatrix} u \\ v \\ r \end{pmatrix},$$

where B and K are bounded operators from X into $X^{\odot r^*}$. Their explicit expressions are

$$B \begin{pmatrix} u \\ v \\ r \end{pmatrix} = \begin{pmatrix} B_{11}u + B_{12}v \\ B_{21}u + B_{22}v \\ 0 \end{pmatrix} \quad \text{and} \quad K \begin{pmatrix} u \\ v \\ r \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ \tilde{K}(v, r) \end{pmatrix}. \quad (1.3.5)$$

Notice that K is a compact operator because it takes values in a finite dimensional subspace of $X^{\odot r^*}$, namely $\{0\} \times \{0\} \times \mathbb{R}^k$. Thus, in order to show that S is eventually norm continuous it is enough to prove the eventually norm continuity of the simpler semigroup generated by $A + B$. This is so because compact perturbations of eventually continuous semigroups are also eventually norm continuous (see Theorem 1.2.22 in the previous section).

The proof of the eventual norm continuity of the semigroup S_B generated by $A + B$ is based on the series formula for S_B given in Theorem 1.2.5. From that theorem we know that the series

$$\sum_{k=0}^{\infty} S_k,$$

with $S_0 = T$ and $S_k = \int_0^{\cdot} T^{\odot*}(\cdot - s)BS_{k-1}(s)ds$ for $n > 1$, converge uniformly (on compact time intervals) towards S_B . By the Uniform Convergence Theorem, we know that if function S_k is continuous in $[t_0, \infty)$ for each k , then so is S_B . Therefore, it is enough to prove that each term in the series defining S_B is continuous on $[1, \infty)$ in order to conclude that S_B is eventually norm continuous from 1 onwards.

As it is seen in the proof below, the specific value at which the functions defining the series become continuous is 1 due to the fact that $c_i(x) \geq 1$ for all i , which implies that

$\varphi_i(-t, x) < 0$ for all $(t, x) \in (1, \infty) \times [0, 1]$. The proof consists in showing that the operator norm of $(S_k(t+h) - S_k(t))$ can be bounded as $\|(S_k(t+h) - S_k(t))\| < M_{t,k}|h|$ for all $k \in \mathbb{N}$, $t > 1$ and $|h|$ small enough, where $M_{t,k}$ is a constant that only depends on t and k . In order to do that the image of a point (u, v, r) by $S_k(t+h) - S_k(t)$ is expressed as the sum of several terms and each of them is properly bounded. Hence the methodology is technical, though the tricks are mostly elementary. Unfortunately, we failed in given a proof by induction on the index k . In order to keep track of the long proof, the different steps are introduced with particular font styles.

Lemma 1.3.3. *Let T and $T^{\odot*}$ be defined by (1.3.1) on X and $X^{\odot T^*}$ respectively. Let B be defined by (1.3.5). The functions*

$$\begin{aligned} S_0(t) &= T(t), \\ S_k(t) &= j^{-1} \int_0^t T^{\odot*}(t-s) B S_{k-1}(s) ds, \quad \forall k \in \mathbb{N} \end{aligned}$$

from $[0, \infty)$ into X are continuous within $[1, \infty)$.

Proof. The case $k = 0$ follows immediately from the definition of $T(\cdot)$ in (1.3.1). Indeed, let $t > 1$ and $h > 1 - t$. Then

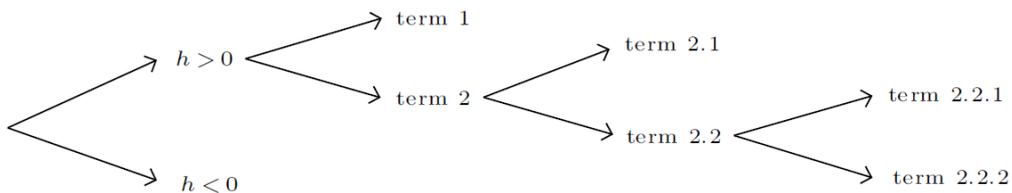
$$\left\| (T(t+h) - T(t)) \begin{pmatrix} u \\ v \\ r \end{pmatrix} \right\| = \left\| \begin{pmatrix} u - u \\ r - r \\ r - r \end{pmatrix} \right\| = 0,$$

that is $\|T(t+h) - T(t)\| = 0$ for all $h > 1 - t$, and in particular the limit as h tends to zero is also zero.

The general case $k > 0$ requires some more work. First of all let us recall that the norms of X and $j(X)$ are equivalent (Proposition 1.2.1), so that there exists $M > 0$ such that

$$\left\| j \begin{pmatrix} u \\ v \\ r \end{pmatrix} \right\|_{X^{\odot*}} \leq \left\| \begin{pmatrix} u \\ v \\ r \end{pmatrix} \right\|_X \leq M \left\| j \begin{pmatrix} u \\ v \\ r \end{pmatrix} \right\|_{X^{\odot*}}. \quad (1.3.6)$$

In the following we show that for all $t > 1$ and $h \in (\max\{1-t, -1\}, 1)$ the operator norm of $(S_k(t+h) - S_k(t))$ can be bounded as $\|(S_k(t+h) - S_k(t))\| < M_t|h|$, where M_t is a constant that only depends on t . We start considering the case $h \in (0, 1)$, since then the case $h \in (\max\{1-t, -1\}, 0)$ will be a simple consequence. In order to accomplish this $\|(S_k(t+h) - S_k(t))\|$ is split into treatable expressions according to the following diagram (which hopefully helps to follow the proof):



Case $h \in (0, 1)$

The definition of S_k implies

$$\begin{aligned}
& \left\| (S_k(t+h) - S_k(t)) \begin{pmatrix} u \\ v \\ r \end{pmatrix} \right\|_X \leq \\
& \leq M \left\| \int_0^{t+h} T^{\odot*}(t+h-s) BS_{k-1}(s) \begin{pmatrix} u \\ v \\ r \end{pmatrix} ds - \int_0^t T^{\odot*}(t-s) BS_{k-1}(s) \begin{pmatrix} u \\ v \\ r \end{pmatrix} ds \right\|_{X^{\odot*}} \leq \\
& \leq M \left\| \begin{pmatrix} \hat{u}(\cdot; t+h) - \hat{u}(\cdot; t) \\ \hat{v}(\cdot; t+h) - \hat{v}(\cdot; t) \\ 0 \end{pmatrix} \right\|_{X^{\odot*}} \leq \\
& \leq M (\|\hat{u}(\cdot; t+h) - \hat{u}(\cdot; t)\|_{L_\infty^n} + \|\hat{v}(\cdot; t+h) - \hat{v}(\cdot; t)\|_{L_\infty^m})
\end{aligned} \tag{1.3.7}$$

where, defining the projection $\pi_u : L_\infty^n \times L_\infty^m \times \mathbb{R}^m \rightarrow L_\infty^n$ so that $\pi_u(u, v, r) = u$,

$$\hat{u}(\cdot; t) = \int_0^t \pi_u BS_{k-1}(s) \begin{pmatrix} u \\ v \\ r \end{pmatrix} ds, \tag{1.3.8}$$

and, defining the projections $\pi_v : L_\infty^n \times L_\infty^m \times \mathbb{R}^m \rightarrow L_\infty^m$ so that $\pi_v(u, v, r) = v$,

$$\hat{v}(\cdot; t) = \int_0^t \pi_v T^{\odot*}(t-s) BS_{k-1}(s) \begin{pmatrix} u \\ v \\ r \end{pmatrix} ds. \tag{1.3.9}$$

From inequality (1.3.7) it follows that in order to obtain the bound $\|(S_k(t+h) - S_k(t))\| < M_t h$ we can split the proof in two parts: a part in which a bound of the type

$$\|\hat{u}(\cdot; t+h) - \hat{u}(\cdot; t)\|_{L_\infty^n} < \tilde{M}_t h$$

is provided and another part that gives a bound of the type

$$\|\hat{v}(\cdot; t+h) - \hat{v}(\cdot; t)\|_{L_\infty^m} < \tilde{M}_t h.$$

A bound for $\|\hat{u}(\cdot; t+h) - \hat{u}(\cdot; t)\|_{L_\infty^n}$

The term $\|\hat{u}(\cdot; t+h) - \hat{u}(\cdot; t)\|_{L_\infty^n}$ in (1.3.7) can be bounded properly because the operator norm of $S_{k-1}(s)$ is uniformly bounded within bounded intervals. Indeed, using expression (1.3.8),

one has

$$\begin{aligned}
& \|\hat{u}(\cdot; t+h) - \hat{u}(\cdot; t)\|_{L_\infty^n} \leq \\
& \leq \left\| \pi_u \left(\int_0^{t+h} BS_{k-1}(s) \begin{pmatrix} u \\ v \\ r \end{pmatrix} ds - \int_0^t BS_{k-1}(s) \begin{pmatrix} u \\ v \\ r \end{pmatrix} ds \right) \right\|_{L_\infty^n} \leq \\
& \leq \int_t^{t+h} \left\| BS_{k-1}(s) \begin{pmatrix} u \\ v \\ r \end{pmatrix} \right\|_{X^{\odot*}} ds \leq h \|B\| \sup_{s \in [0, t+1]} \|S_{k-1}(s)\| \left\| \begin{pmatrix} u \\ v \\ r \end{pmatrix} \right\|_X.
\end{aligned} \tag{1.3.10}$$

A bound for $\|\hat{v}(\cdot; t+h) - \hat{v}(\cdot; t)\|_{L_\infty^m}$

Let us focus now on the terms $\|\hat{v}(\cdot; t+h) - \hat{v}(\cdot; t)\|_{L_\infty^m}$ of (1.3.7). Notice that B initially defined from X into $X^{\odot*}$ can be extended to a bounded operator from $X^{\odot*}$ into itself given by the same expression of B (see (1.3.5)). Thus, it is possible to enter the operators $T^{\odot*}(t-s_k)$ and B inside the integral that defines $S_k(s)$ in (1.3.9). That is, $\hat{v}(\cdot; t)$ can be written as

$$\begin{aligned}
\hat{v}(\cdot; t) &= \int_0^t \pi_v T^{\odot*}(t-s_k) B \int_0^{s_k} T^{\odot*}(s_k-s_{k-1}) BS_{k-2}(s_{k-1}) \begin{pmatrix} u \\ v \\ r \end{pmatrix} ds_{k-1} ds_k = \\
&= \int_0^t \int_0^{s_k} \pi_v T^{\odot*}(t-s_k) BT^{\odot*}(s_k-s_{k-1}) BS_{k-2}(s_{k-1}) \begin{pmatrix} u \\ v \\ r \end{pmatrix} ds_{k-1} ds_k,
\end{aligned}$$

and, inductively, one obtains

$$\begin{aligned}
\hat{v}(\cdot; t) &= \int_0^t \int_0^{s_k} \cdots \int_0^{s_2} \\
& \pi_v T^{\odot*}(t-s_k) BT^{\odot*}(s_k-s_{k-1}) B \cdots T^{\odot*}(s_2-s_1) BT(s_1) \begin{pmatrix} u \\ v \\ r \end{pmatrix} ds_1 \cdots ds_{k-1} ds_k.
\end{aligned} \tag{1.3.11}$$

In order to simplify the above equation recall that $X^{\odot*} = L_\infty^n \times L_\infty^m \times \mathbb{R}^m$ and observe that the operators $T^{\odot*}(s_{l+1}-s_l)B : X^{\odot*} \rightarrow X^{\odot*}$ for $l \in \{1, \dots, k\}$ (setting $s_{k+1} = t$) can be synthesised as matrices of operators:

$$T^{\odot*}(s_{l+1}-s_l)B \sim \begin{pmatrix} B_{11} & B_{12} & 0 \\ \tilde{T}(s_{l+1}-s_l)B_{21} & \tilde{T}(s_{l+1}-s_l)B_{22} & 0 \\ 0 & 0 & 0 \end{pmatrix},$$

where $\tilde{T}(s) : L_\infty^m \rightarrow L_\infty^m$ is defined as

$$(\tilde{T}(s)v)_i = v_i(\varphi_i(-s, \cdot)) \mathbb{1}_+(\varphi_i(-s, \cdot)) \quad \forall i \in \{1, \dots, m\}.$$

The product of operators

$$\prod_{l=k}^1 T^{\odot*}(s_{l+1} - s_l)B = T^{\odot*}(t - s_k)BT^{\odot*}(s_k - s_{k-1})B \cdots T^{\odot*}(s_2 - s_1)B,$$

written as a matrix of operators, becomes:

$$J \sim \begin{pmatrix} J_{11} & J_{12} & 0 \\ J_{21} & J_{22} & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

where, for $(i_0, i_{k+1}) \in \{1, 2\} \times \{1, 2\}$,

$$J_{i_0 i_{k+1}} = \sum_{i_1=1}^2 \sum_{i_2=1}^2 \cdots \sum_{i_k=1}^2 J_{i_0 i_1 i_2 \cdots i_k i_{k+1}}(t - s_k, s_k - s_{k-1}, \dots, s_2 - s_1)$$

with

$$\begin{aligned} J_{i_0 i_1 i_2 \cdots i_k i_{k+1}}(t - s_k, s_k - s_{k-1}, \dots, s_2 - s_1) &= \\ &= (T^{\odot*}(t - s_k)B)_{i_0 i_1} (T^{\odot*}(s_k - s_{k-1})B)_{i_1 i_2} \cdots (T^{\odot*}(s_2 - s_1)B)_{i_k i_{k+1}}. \end{aligned} \quad (1.3.12)$$

In particular, using $\tilde{v}(\cdot; s_1, v, r)$ defined in (1.3.2) the integrand in (1.3.11) can be expressed as

$$\pi_v \left(\prod_{l=k}^1 T^{\odot*}(s_{l+1} - s_l)B \right) T(s_1) \begin{pmatrix} u \\ v \\ r \end{pmatrix} = J_{21}u + J_{22}\tilde{v}(\cdot; s_1, v, r)$$

so that (1.3.11) becomes the sum

$$\hat{v}(\cdot; t) = \sum_{i_1=1}^2 \sum_{i_2=1}^2 \cdots \sum_{i_k=1}^2 I_{2 i_1 i_2 \cdots i_k 1}(t, u) + \sum_{i_1=1}^2 \sum_{i_2=1}^2 \cdots \sum_{i_k=1}^2 I_{2 i_1 i_2 \cdots i_k 2}(t, v, r) \quad (1.3.13)$$

where

$$I_{2 i_1 i_2 \cdots i_k 1}(t, u) = \int_0^t \int_0^{s_k} \cdots \int_0^{s_2} J_{2 i_1 i_2 \cdots i_k 1}(t - s_k, s_k - s_{k-1}, \dots, s_2 - s_1) u ds_1 \cdots ds_{k-1} ds_k$$

and

$$I_{2 i_1 i_2 \cdots i_k 2}(t, v, r) = \int_0^t \int_0^{s_k} \cdots \int_0^{s_2} J_{2 i_1 i_2 \cdots i_k 2}(t - s_k, s_k - s_{k-1}, \dots, s_2 - s_1) \tilde{v}(\cdot; s_1, v, r) ds_1 \cdots ds_{k-1} ds_k.$$

Clearly, from (1.3.13) it follows

$$\begin{aligned} \|\hat{v}(\cdot; t+h) - \hat{v}(\cdot; t)\|_{L_\infty^m} &\leq \sum_{i_1=1}^2 \sum_{i_2=1}^2 \cdots \sum_{i_k=1}^2 \|I_{2 i_1 i_2 \cdots i_k 1}(t+h, u) - I_{2 i_1 i_2 \cdots i_k 1}(t, u)\|_{L_\infty^m} + \\ &+ \sum_{i_1=1}^2 \sum_{i_2=1}^2 \cdots \sum_{i_k=1}^2 \|I_{2 i_1 i_2 \cdots i_k 2}(t+h, v, r) - I_{2 i_1 i_2 \cdots i_k 2}(t, v, r)\|_{L_\infty^m} \end{aligned} \quad (1.3.14)$$

In order to give a bound for $\|\hat{v}(\cdot; t+h) - \hat{v}(\cdot; t)\|_{L_\infty^m}$, we show that each summand on the right hand side in (1.3.14) can be bounded properly, i.e. by something of the form $h\tilde{M}_t\|(u, v, r)\|$. This is done by performing a change of variables to the “shifted integrals” (the ones evaluated at $t+h$) so that the new integrand coincides with the integrand of the “unshifted integrals” (the ones evaluated at t). The equality between integrands makes, on the one hand, that the difference between integrals vanishes over the domain of integration that is common to both integrals. On the other hand, the domains of integration that are specific to each integral have a Lebesgue measure proportional to h . These statements are developed in the following. To do so we treat separately the terms in the first summation from those in the second summation.

Let us consider the terms in (1.3.14) of the form

$$\|I_{2i_1i_2\dots i_k1}(t+h, u) - I_{2i_1i_2\dots i_k1}(t, u)\|_{L_\infty^m}.$$

Applying a translation τ_h to the integration variables so that

$$\tau_h(s_1, s_2, \dots, s_k) = (s_1 + h, s_2 + h, \dots, s_k + h)$$

the integral $I_{2i_1i_2\dots i_k1}(t+h, u)$ becomes

$$\int_{-h}^t \int_{-h}^{s_k} \dots \int_{-h}^{s_2} J_{2i_1i_2\dots i_k1}(t - s_k, s_k - s_{k-1}, \dots, s_2 - s_1) u ds_1 \dots ds_{k-1} ds_k.$$

Therefore, using $\|T^{\odot*}(s)\|_{X^{\odot*}} \leq 1$ for all $s \geq 0$, one has

$$\begin{aligned} & \|I_{2i_1i_2\dots i_k1}(t+h, u) - I_{2i_1i_2\dots i_k1}(t, u)\|_{L_\infty^m} = \\ & = \left\| \int_{-h}^t \int_{-h}^{s_k} \dots \int_{-h}^{\min\{s_2, 0\}} J_{2i_1i_2\dots i_k1}(t - s_k, s_k - s_{k-1}, \dots, s_2 - s_1) u ds_1 \dots ds_{k-1} ds_k \right\|_{L_\infty^m} \leq \\ & \leq h(t+h)^{k-1} \|B\|^k \|(u, v, r)\| \leq h(t+1)^{k-1} \|B\|^k \|(u, v, r)\| \end{aligned} \tag{1.3.15}$$

as desired.

Let us consider now the terms in (1.3.14) of the form

$$\|I_{2i_1i_2\dots i_k2}(t+h, v, r) - I_{2i_1i_2\dots i_k2}(t, v, r)\|_{L_\infty^m}.$$

In this case it is not clear whether it is possible to make a change of variables that transforms the integrand of $I_{2i_1i_2\dots i_k2}(t+h, v, r)$ into the integrand of $I_{2i_1i_2\dots i_k2}(t, v, r)$. The problem is that the integration variables do not only appear in the function that determines $J_{2i_1i_2\dots i_k2}$, but they

also play a role in the term \tilde{v} . Specifically, finding a change of variables that transforms the integrand

$$J_{2i_1i_2\dots i_k2}(t+h-s_k, s_k-s_{k-1}, \dots, s_2-s_1)\tilde{v}(\cdot; s_1, v, r)$$

into

$$J_{2i_1i_2\dots i_k2}(t-\sigma_k, \sigma_k-\sigma_{k-1}, \dots, \sigma_2-\sigma_1)\tilde{v}(\cdot; \sigma_1, v, r)$$

seems to be the same as solving the following system of $k+1$ equations and k unknowns:

$$\begin{cases} t+h-s_k = t-\sigma_k \\ s_k-s_{k-1} = \sigma_k-\sigma_{k-1} \\ \vdots \\ s_2-s_1 = \sigma_2-\sigma_1 \\ s_1 = \sigma_1 \end{cases}, \quad (1.3.16)$$

which is impossible. However, the fact is that one of the equations in the system above is unnecessary to find the desired change of variables. To justify this let us distinguish the case $I_{22\dots 22}$ from the cases $I_{2i_1i_2\dots i_k2}$ in which at least one index is 1.

Consider $I_{2i_1i_2\dots i_k2}$ such that $i_l = 1$.

Then the term $(T^{\odot*}(s_k-s_{k-1})B)_{i_l i_{l+1}}$ appearing in (1.3.12) is

$$(T^{\odot*}(s_{k-l+1}-s_{k-l})B)_{i_l i_{l+1}} = (T^{\odot*}(s_{k-l+1}-s_{k-l})B)_{1i_{l+1}} = B_{1i_{l+1}},$$

so that $J_{2i_1i_2\dots i_k2}$ is independent of the difference $s_{k-l+1}-s_{k-l}$. Thus, the desired change of variables can be obtained without imposing the relation

$$s_{k-l+1}-s_{k-l} = \sigma_{k-l+1}-\sigma_{k-l}.$$

This means that this equation can be removed from system (1.3.16) so that it becomes compatible. The solution of the reduced system is the desired change of variables, which is a translation τ_h given by

$$\tau_h(s_1, s_2, \dots, s_k) = (s_1, \dots, s_{k-l}, s_{k-l+1}+h, \dots, s_k+h).$$

By using this transformation on the “shifted integral” one has

$$\begin{aligned} I_{2i_1i_2\dots i_k2}(t+h, v, r) &= \\ &= \int_{-h}^t \int_{-h}^{s_k} \dots \int_{-h}^{s_{k-l+2}} \int_0^{s_{k-l+1}+h} \int_0^{s_{k-l}} \dots \int_0^{s_2} J_{2i_1i_2\dots i_k2}(t-s_k, \dots, s_2-s_1)\tilde{v}(\cdot; s_1, v, r) ds_1 \dots ds_k, \end{aligned}$$

and, similarly as done in (1.3.15), one concludes

$$\|I_{2i_1i_2\dots i_k2}(t+h, v, r) - I_{2i_1i_2\dots i_k2}(t, v, r)\|_{L_\infty^m} \leq h(t+1)^{k-1} \|B\|^k \|(u, v, r)\|. \quad (1.3.17)$$

Consider now the particular integral $I_{222\dots 22}$.

In this case the term $J_{222\dots 22}$ depends on all the differences $s_{l+1} - s_l$ with $l \in \{1, \dots, k\}$, which means that all the first k rows of system (1.3.16) have to be imposed. The unnecessary equation in this case is the last equation of (1.3.16). Indeed, let us show that, for all $t > 1$, the following holds

$$J_{222\dots 22}(t - s_k, s_k - s_{k-1}, \dots, s_2 - s_1)\tilde{v}(\cdot; s_1, v, r) = J_{222\dots 22}(t - s_k, s_k - s_{k-1}, \dots, s_2 - s_1)\Lambda r. \quad (1.3.18)$$

First of all notice that, denoting $d_l = s_{l+1} - s_l$, the i th component of $J_{222\dots 22}(d_k, \dots, d_1)v$ is

$$\begin{aligned} (J_{222\dots 22}(d_k, \dots, d_1)v)_i &= (\tilde{T}(d_k)B_{22}\tilde{T}(d_{k-1})B_{22}\cdots\tilde{T}(d_1)B_{22}v)_i = \\ &= \sum_{l_k=1}^m \cdots \sum_{l_1=1}^m \tilde{T}_i(d_k)B_{22,il_k}\tilde{T}_{l_k}(d_{k-1})B_{22,l_k l_{k-1}} \cdots \tilde{T}_{l_2}(d_1)(B_{22,l_2 l_1}v_{l_1}) = \\ &= \sum_{l_k=1}^m \cdots \sum_{l_1=1}^m (\tilde{T}_i(d_k)B_{22,il_k}\tilde{T}_{l_k}(d_{k-1})B_{22,l_k l_{k-1}} \cdots \tilde{T}_{l_2}(d_1)B_{22,l_2 l_1}) \\ &\quad (\tilde{T}_i(d_k)\tilde{T}_{l_k}(d_{k-1}) \cdots \tilde{T}_{l_2}(d_1)v_{l_1}). \end{aligned} \quad (1.3.19)$$

In the last equality we have used that, for all $i \in \{1, \dots, m\}$ and for all $f, g \in L^\infty(0, 1)$, the operator $\tilde{T}_i(d)$ satisfies

$$\begin{aligned} \tilde{T}_i(d)(fg) &= f(\varphi_i(-d, \cdot))g(\varphi_i(-d, \cdot))\mathbf{1}_+(\varphi_i(-d, \cdot)) = \\ &= (f(\varphi_i(-d, \cdot))\mathbf{1}_+(\varphi_i(-d, \cdot)))(g(\varphi_i(-d, \cdot))\mathbf{1}_+(\varphi_i(-d, \cdot))) = (\tilde{T}_i(d)f)(\tilde{T}_i(d)g), \end{aligned} \quad (1.3.20)$$

so that for all triad $b, f, g \in L^\infty(0, 1)$ one has

$$b\tilde{T}_i(d)(fg) = (b\tilde{T}_i(d)f)(\tilde{T}_i(d)g).$$

In particular, the i th component of $J_{222\dots 22}(d_k, \dots, d_1)\tilde{v}(\cdot; s_1, v, r)$ is

$$(J_{222\dots 22}(d_k, \dots, d_1)\tilde{v}(\cdot; s_1, v, r))_i = \Sigma_v + \Sigma_r$$

with

$$\Sigma_v = \sum_{l_k=1}^m \cdots \sum_{l_1=1}^m (\tilde{T}_i(d_k)B_{22,il_k}\tilde{T}_{l_k}(d_{k-1})B_{22,l_k l_{k-1}} \cdots \tilde{T}_{l_2}(d_1)B_{22,l_2 l_1}) \\ (\tilde{T}_i(d_k)\tilde{T}_{l_k}(d_{k-1}) \cdots \tilde{T}_{l_2}(d_1)(v_{l_1}(\varphi_{l_1}(-s_1, \cdot))\mathbf{1}_+(\varphi_{l_1}(-s_1, \cdot))))$$

and

$$\Sigma_r = \sum_{l_k=1}^m \cdots \sum_{l_1=1}^m (\tilde{T}_i(d_k)B_{22,il_k}\tilde{T}_{l_k}(d_{k-1})B_{22,l_k l_{k-1}} \cdots \tilde{T}_{l_2}(d_1)B_{22,l_2 l_1}) \\ (\tilde{T}_i(d_k)\tilde{T}_{l_k}(d_{k-1}) \cdots \tilde{T}_{l_2}(d_1)(\Lambda_{l_1} r \mathbf{1}_-(\varphi_{l_1}(-s_1, \cdot)))).$$

Since the operators $\tilde{T}_i(d)$ satisfy

$$\tilde{T}_i(d)(fg) = f(\varphi_i(-d, \cdot))g(\varphi_i(-d, \cdot))\mathbf{1}_+(\varphi_i(-d, \cdot)) = (\tilde{T}_i(d)f)g(\varphi_i(-d, \cdot)),$$

for all $f \in L^\infty(0, 1)$ and $g \in L^\infty(\mathbb{R})$ (and considering that the product of a function f in $L^\infty(0, 1)$ with a function g in $L^\infty(\mathbb{R})$ is the product of f with the projection of g in $L^\infty(0, 1)$), the factors in each summand of Σ_v that depend on v , i.e the terms of the form

$$\tilde{T}_i(d_k)\tilde{T}_{l_k}(d_{k-1}) \cdots \tilde{T}_{l_2}(d_1)(v_{l_1}(\varphi_{l_1}(-s_1, \cdot))\mathbb{1}_+(\varphi_{l_1}(-s_1, \cdot))),$$

can be written as the product

$$(\tilde{T}_i(d_k)\tilde{T}_{l_k}(d_{k-1}) \cdots \tilde{T}_{l_2}(d_1)v_{l_1}(\varphi_{l_1}(-s_1, \cdot))) \\ \mathbb{1}_+(\varphi_{l_1}(-s_1, \cdot) \circ \varphi_{l_2}(-d_1, \cdot) \circ \cdots \circ \varphi_{l_k}(-d_{k-1}, \cdot) \circ \varphi_i(-d_k, \cdot)),$$

whereas the factors in each summand of Σ_r that depend on r can be written as

$$(\tilde{T}_i(d_k)\tilde{T}_{l_k}(d_{k-1}) \cdots \tilde{T}_{l_2}(d_1)\Lambda_{l_1}r) \\ \mathbb{1}_-(\varphi_{l_1}(-s_1, \cdot) \circ \varphi_{l_2}(-d_1, \cdot) \circ \cdots \circ \varphi_{l_k}(-d_{k-1}, \cdot) \circ \varphi_i(-d_k, \cdot)).$$

It turns out that the functions

$$\mathbb{1}_+(\varphi_{l_1}(-s_1, \cdot) \circ \varphi_{l_2}(-d_1, \cdot) \circ \cdots \circ \varphi_{l_k}(-d_{k-1}, \cdot) \circ \varphi_i(-d_k, \cdot))$$

and

$$\mathbb{1}_-(\varphi_{l_1}(-s_1, \cdot) \circ \varphi_{l_2}(-d_1, \cdot) \circ \cdots \circ \varphi_{l_k}(-d_{k-1}, \cdot) \circ \varphi_i(-d_k, \cdot))$$

as elements of $L^\infty(0, 1)$ are, respectively, the constant functions 0 and 1. To see that notice that for all $x \in [0, 1]$ and $t > 1$ one has

$$\varphi_{l_1}(-s_1, \cdot) \circ \varphi_{l_2}(-d_1, \cdot) \circ \cdots \circ \varphi_{l_k}(-d_{k-1}, \cdot) \circ \varphi_i(-d_k, \cdot) < 0.$$

Indeed, using that $\partial_t \varphi_j(t, x) \geq 1$ for all $j \in \{1, \dots, m\}$, which implies $\varphi_j(-d, x) \leq \varphi_j(0, x) - d = x - d$ for all $d > 0$, we deduce

$$\begin{aligned} & \varphi_{l_1}(-s_1, \cdot) \circ \varphi_{l_2}(-d_1, \cdot) \circ \cdots \circ \varphi_{l_k}(-d_{k-1}, \cdot) \circ \varphi_i(-d_k, \cdot)(x) \leq \\ & \leq \varphi_{l_2}(-d_1, \cdot) \circ \cdots \circ \varphi_{l_k}(-d_{k-1}, \cdot) \circ \varphi_i(-d_k, \cdot)(x) - s_1 \leq \\ & \leq \varphi_{l_3}(-d_2, \cdot) \circ \cdots \circ \varphi_{l_k}(-d_{k-1}, \cdot) \circ \varphi_i(-d_k, \cdot)(x) - d_1 - s_1 \leq \cdots \leq \\ & \leq \varphi_{l_k}(-d_{k-1}, \cdot) \circ \varphi_i(-d_k, \cdot)(x) - \sum_{i=1}^{k-2} d_i - s_1 \leq \\ & \leq \varphi_i(-d_k, x) - \sum_{i=1}^{k-1} d_i - s_1 \leq x - \sum_{i=1}^k d_i - s_1 = \\ & = x - \sum_{i=1}^k (s_{i+1} - s_i) - s_1 = x - t < 0 \end{aligned}$$

since $t > 1$ and $x \in [0, 1]$. Therefore, the term Σ_v is zero whereas Σ_r equals

$$\sum_{l_k=1}^m \cdots \sum_{l_1=1}^m (\tilde{T}_i(d_k) B_{22,il_k} \tilde{T}_{l_k}(d_{k-1}) B_{22,l_k l_{k-1}} \cdots \tilde{T}_{l_2}(d_1) B_{22,l_2 l_1}) (\tilde{T}_i(d_k) \tilde{T}_{l_k}(d_{k-1}) \cdots \tilde{T}_{l_2}(d_1) \Lambda_{l_1} r),$$

which clearly coincides with the i th component of $J_{222\dots 22}(d_k, \dots, d_1) \Lambda r$ if one uses the expression (1.3.19). That is, for all $i \in \{1, \dots, m\}$ one has

$$(J_{222\dots 22}(d_k, \dots, d_1) \tilde{v}(\cdot; s_1, v, r))_i = (J_{222\dots 22}(d_k, \dots, d_1) \Lambda r)_i,$$

which implies the equality stated in (1.3.18). The solution of system (1.3.16) with the last equation removed gives the desired change of variables, which is $\tau_h(s_1, s_2, \dots, s_k) = (s_1 + h, s_2 + h, \dots, s_k + h)$ and transforms the integral $I_{222\dots 22}(t + h, v, r)$ into

$$\int_{-h}^t \int_{-h}^{s_k} \cdots \int_{-h}^{s_2} J_{222\dots 22}(t - s_k, s_k - s_{k-1}, \dots, s_2 - s_1) \Lambda r ds_1 \cdots ds_{k-1} ds_k,$$

so that, similarly as done in (1.3.15) and taking into account $\Lambda r = v(0)$, one concludes

$$\|I_{222\dots 22}(t + h, v, r) - I_{222\dots 22}(t, v, r)\|_{L_\infty^m} \leq h(t + 1)^{k-1} \|B\|^k \|(u, v, r)\|. \quad (1.3.21)$$

Putting all the estimates together

By using the bounds (1.3.15), (1.3.17) and (1.3.21) in inequality (1.3.14) it follows

$$\|\hat{v}(\cdot; t + h) - \hat{v}(\cdot; t)\|_{L_\infty^m} < 2^{k+1} h(t + 1)^{k-1} \|B\|^k \left\| \begin{pmatrix} u \\ v \\ r \end{pmatrix} \right\|_X. \quad (1.3.22)$$

Finally, (1.3.10) and (1.3.22) are applied in inequality (1.3.7) to obtain

$$\|(S_k(t + h) - S_k(t))\|_X \leq h M_t \quad (1.3.23)$$

for all $t > 1$ and $h \in (0, 1)$ as stated.

Case $h \in (\max\{1 - t, -1\}, 0)$

If h is negative, that is if $t > 1$ and $h \in (\max\{1 - t, -1\}, 0)$, then inequality (1.3.23) can be applied as

$$\|(S_k(t + h) - S_k(t))\|_X = \|(S_k(t + h + |h|) - S_k(t + h))\|_X \leq k_{t+h} |h| \leq M_t |h|,$$

since, on the one hand, $t + h$ is still bigger than 1 and, on the other hand, the constant

$$M_t = M(\|B\| \sup_{s \in [0, t+1]} \|S_{k-1}(s)\| + 2^{k+1} (t + 1)^{k-1} \|B\|^k)$$

is increasing as a function of t .

Therefore, by combining the results for positive and negative h , one concludes that for $t > 1$ and $h \in (\max\{1 - t, -1\}, 1)$ exists a constant M_t (which depends on t) such that

$$\|(S_k(t+h) - S_k(t))\|_X \leq |h|M_t.$$

□

As a corollary of Lemma 1.3.3 and the uniform convergence of the series defining S_B (see the comments that motivated the lemma) we conclude:

Theorem 1.3.4. *The semigroup S_B generated by $A + B$ (in the sense of Theorem 1.2.5) is eventually norm continuous.*

Then, since K is a compact operator from X into $X^{\odot*}$, Theorems 1.3.4 and 1.2.22 imply:

Theorem 1.3.5. *The semigroup S generated by $A + B + K$ (in the sense of Theorem 1.2.5, using either $A + (B + K)$ or $(A + B) + K$) is eventually norm continuous.*

Finally, the eventual norm continuity of the linearised semigroup S makes possible to apply Theorem 1.2.21, so that the following result on linearisation specific to problem (1.1.1) can be stated:

Theorem 1.3.6. *Let $(\bar{u}, \bar{v}, \bar{r}) \in X$ be a steady state of the semiflow Σ associated to (1.1.1) and let A_S the operator defined in (1.3.4). Then,*

- (i) $(\bar{u}, \bar{v}, \bar{r})$ is locally asymptotically stable if $s(A_S) < 0$,
- (ii) $(\bar{u}, \bar{v}, \bar{r})$ is unstable if there exists $\omega > 0$ such that the spectrum of A_S within the region $\{\lambda \in \mathbb{C} \mid \operatorname{Re}(\lambda) > \omega\}$ is non-empty and is composed only by a finite number of eigenvalues with finite algebraic multiplicity.

1.4 A model for the gastrointestinal ecosystem

The diversity in gut lengths across hosts makes that, a priori, system (0.0.9) has not the form of system (1.1.1). Fortunately, we can perform a change in the spatial variables to rewrite (0.0.9) properly. Such a change is possible because microbes within a host do not affect what happens in a different host. Indeed, by defining $\tilde{v}_h(x, t) := v_h(l_h x, t)$ and $\tilde{u}_h(x, t) := u_h(l_h x, t)$, we have, on the one hand, that the spatial domains of $\tilde{u}_{h,s}$ and $\tilde{v}_{h,s}$ are the interval $[0, 1]$ for all $(h, s) \in H \times S$ and, on the other hand, that system (0.0.9) transforms into

$$\begin{cases} \partial_t \tilde{u}_{h,s}(t, x) = g_{h,s}(l_h x, \tilde{u}_h(t, x), \tilde{v}_h(t, x)), \\ \partial_t \tilde{v}_{h,s}(t, x) = -\partial_x (c_h(l_h x) \tilde{v}_{h,s}(t, x)) + f_{h,s}(l_h x, \tilde{u}_h(t, x), \tilde{v}_h(t, x)), \\ \frac{dr_s(t)}{dt} = m_s(r(t)) + \sum_{h \in H} k_{h,s}(c_h(l_h) \tilde{v}_{h,s}(t, 1)) - \sum_{h \in H} \lambda_{h,s} r_s(t). \end{cases} \quad (1.4.1)$$

with the boundary condition

$$\tilde{v}_{h,s}(0, t) = \frac{\lambda_{h,s}}{c_h(0)} r_s(t) \quad \forall (h, s) \in H \times S.$$

In particular, by considering vectors \tilde{u} and \tilde{v} to be indexed by one number instead of two, for example by writing $\tilde{u}_{m(h-1)+s}$ instead of $\tilde{u}_{h,s}$ (analogously for \tilde{v}), then the initial value problem associated to 1.4.1 has the form of problem (1.1.1). Thus, in order to apply Theorems 1.3.2 and 1.3.6 to system (1.4.1) (which is equivalent to system (0.0.9)) the phase space we have to work on is the Banach space

$$X = L^\infty(0, 1)^{n \times m} \times C_b$$

where

$$C_b = \left\{ (\tilde{v}, r) \in C([0, 1], \mathbb{R})^{n \times m} \times \mathbb{R}^m \mid \tilde{v}_{m(h-1)+s}(0) = \frac{\lambda_{h,s}}{c_h(0)} r_s \quad \forall (h, s) \in H \times S \right\}.$$

1.5 Discussion

As explained in the introduction, the system analysed in this chapter is motivated by a model of gut bacteria spreading through the fecal-oral route. The general results derived here are going to be applied in the next chapter to study the dynamics of some pathogenic bacteria. Before moving on, however, we want to mention that problem (1.1.3) can be applied not only to gut microorganisms, but also to substances or living beings inhabiting networks with a high advection to diffusion ratio and whose vertices behave as well mixed compartments. To visualise this let us consider a species whose individuals are distributed through a graph. The spatial coordinates of each individual are given by an edge and a scalar $x \in (0, 1)$ denoting the position within the edge. By using indices i to refer the edges of the graph and denoting $v_i(t, x)$ the density of individuals in position x of edge h , then the dynamics of the population in each edge can be modelled as

$$\partial_t v_i(t, x) = -\partial_x(c_i(x)v_i(t, x)) + f_i(x, v_i(t, x)) \quad (1.5.1)$$

where $c_i(x) > 0$ is the flow within the edge at position x and f_i is related to the biological processes occurring locally at x that depend on the population at that point. In order to link the dynamics of the different edges, we model the vertices of the graph as independent compartments. Then, the population $r_j(t)$ in a vertex j satisfies

$$r'_j(t) = \sum_{i \in \text{In}(j)} c_i(1)v_i(t, 1) - \sum_{i \in \text{Out}(j)} \lambda_{ji} r_j(t) + h_j(r_j(t))$$

where $\text{In}(j)$ are the edges flowing into vertex j whereas $\text{Out}(j)$ are the edges taking flow from vertex j , λ_{ji} are the per capita rates at which individuals from vertex j enter edge i and h_j

models the intrinsic population changes within the vertex. Notice that the definition of λ_{ji} implies boundary conditions at the origin of the edges, namely

$$c_i(0)v_i(t, 0) = \lambda_{j,i} r_j(t)$$

for each vertex j and each edge $i \in \text{Out}(j)$. The above equations form a system that is a particular case of the one given in (1.1.1). It is particular in the sense that does not involve the component of type u . It is easy to imagine an extension of the previous model in which the component u naturally arises. Indeed, if we let the individuals to attach to the edge, then a new set of dependent variables is needed to denote the density $u_i(t, x)$ of individuals attached at position x of edge i . In this case the arguments of f_i in (1.5.1) have to include $u_i(t, x)$ and the dynamics of attached bacteria can be modelled as

$$\partial_t u_i(t, x) = g_i(x, v_i(t, x), u_i(t, x)).$$

The above construction can be done in a similar way in order to incorporate multiple species.

Chapter 2

Stability analysis of an enteropathogen population growing within a heterogenous group of animals

The content in this chapter is published [8].

2.1 Introduction

Most enteropathogenic microorganisms such as *Salmonella*, enterotoxigenic *Escherichia*, *Yersinia* or protozoans within the *Giardia* 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 severely reduced. Hence, before humans turn into a plant based diet, 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 [60], while more ecologically based alternatives are becoming more popular, such as viral therapy with bacteriophage [2] or probiotic usage [39].

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 [45] and [12]). Several theoretical results exist relating the epidemics evolution with bacteria-bacteriophage interactions [75, 16, 15], competition between virulent and innocuous strains [20, 6, 81], or the spatial and physiological structures of the host populations [46, 86]. 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 more harmful for bacteriophage than for bacteria, then it could be better doing nothing instead of adopting certain hygienic policies. 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 analyse the dynamics of a population of enterobacteria in terms of some ecological parameters, such as number of susceptible hosts or their sizes. To this end we focus on a specific competition scenario which is a particular case of the class of models presented in the introduction, given in (0.0.9). Thus, the theoretical framework developed in chapter 1 can be applied. This is done in section 2.2, where, in addition to presenting the equations, conditions on the parameters are given ensuring the existence of an endemic steady state (Theorem 2.2.7). In Theorem 2.2.11 we apply the theorems of the previous chapter to show that this equilibrium is stable whenever it exists. In order to study the effects of a phage therapy consisting in the administration to the host animals of a certain dose of bacteriophage mixed with their food, the system is extended in order to include the population of phages. This is done in section 2.3, where the stability of the free bacteria stationary state is also addressed.

2.2 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 $h \in H = \{1, 2, \dots, n\}$ be an index for each animal and consider

$$\begin{cases} \partial_t u_h = \gamma_1^h(u_h)u_h + \alpha_h v_h - \delta_h u_h \\ \partial_t v_h = -c_h \partial_x v_h + \gamma_2^h(v_h)v_h - \alpha_h v_h + \delta_h u_h \\ \dot{r} = \sum_{h \in H} (c_h v_h(l_h, t) - \lambda_h r) - \mu r \\ c_h v_h(0, t) = \lambda_h r \end{cases}, \quad (2.2.1)$$

where, $u_h(x, t)$ and $v_h(x, t)$ are, respectively, the attached and luminal bacteria found at the position x of host h at time t , and $r(t)$ is the amount of bacteria in the environment at time t (see (0.0.9) in the introduction for further details). The parameter l_h is the gut length of host h and c_h stands for the velocity of its intestinal flow (here assumed to be constant along the intestine). Bacteria on the external environment are eliminated at a per capita rate μ and are ingested by host h at a per capita rate λ_h . 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 indices h indicate that these parameters may depend on

which host the bacteria is inside. We make the assumption that

$$\forall h \in H, \gamma_1^h \text{ and } \gamma_2^h \text{ are smooth functions on } [0, \infty), \text{ have negative derivative and are negative valued for large enough arguments,} \quad (2.2.2)$$

thus reflecting competition interactions both in the epithelium and in the lumen. Notice that we also assume that bacteria cannot grow in the external media, which means that the soil acts as a sink for the bacteria. The model may serve to decide if an infective microorganism such as Salmonella can spread and persist. 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 (see the model in [7], inspired by [38], for an example of non-linear attachment and detachment rates).

By Theorem 1.3.2 we know that system 2.2.1 together with an initial condition is a well posed problem on the Banach space

$$X = \left(\prod_{h=1}^n L^\infty(0, l_h) \right) \times C_b$$

with

$$C_b = \left\{ (v, r) \in \left(\prod_{h=1}^n C([0, l_h], \mathbb{R}) \right) \times \mathbb{R} \mid c_h v_h(0) = \lambda_h r \right\}.$$

The stationary states of the system above are the solutions of

$$\begin{cases} 0 = \gamma_1^h(u_h)u_h + \alpha_h v_h - \delta_h u_h \\ 0 = -c_h v_h' + \gamma_2^h(v_h)v_h - \alpha_h v_h + \delta_h u_h \\ 0 = \sum_{h \in H} (c_h v_h(l_h) - \lambda_h r) - \mu r \\ c_h v_h(0) = \lambda_h r \end{cases}. \quad (2.2.3)$$

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 2.2 it is shown that if $\lambda_h = 0$ for some h , then system (2.2.1) becomes degenerate in some sense and a non-numerable set of equilibria may exist.

2.2.1 Stationary states in the reinfection case

Existence of an endemic equilibrium

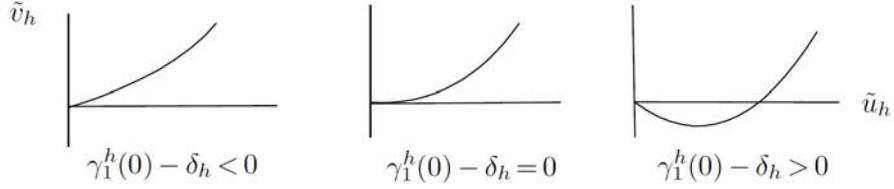
First of all notice that, using the monotony properties of γ_1^h , for every scalar $\tilde{v}_h > 0$ there is a unique value $\tilde{u}_h = \tilde{u}_h(\tilde{v}_h)$ satisfying

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

(see the graphical proof in Proposition 2.2.1 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 denote $\tilde{u}_h(0)$ 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 2.2.1. *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. Realise 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 $\tilde{v}'_h(\tilde{u}_h) > 0$, and also that $\tilde{v}'_h(\tilde{u}_h) > \delta_h/\alpha_h$ for large values \tilde{u}_h . \square

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 2.2.2. *The component r of any endemic equilibrium (u, v, r) satisfying (2.2.3) must be positive.*

Proof. Suppose $r = 0$. Then $v_h(0) = v_h(l_h) = 0$ for all host h since $c_h > 0$ for all h . If $v_h(x) \equiv 0$, then the second equation in (2.2.3) 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 $v_h(x) \equiv 0$. \square

The above observations reduce system (2.2.3) to

$$\begin{cases} v'_h = (\gamma_2^h(v_h)v_h - \alpha_h v_h + \delta_h \tilde{u}_h(v_h))/c_h =: g_h(v_h), \\ v_h(0) = \lambda_h r / c_h, \\ 0 = \sum_{h \in H} (c_h v_h(l_h) - \lambda_h r) - \mu r. \end{cases} \quad (2.2.4)$$

Next we are going to show that, if $v_h(0) > 0$, then equation $v'_h = g_h(v_h)$ with initial condition $v_h(0)$ has a well defined solution $\varphi_h(x; v_h(0)) > 0$ for all $x \geq 0$. Therefore, there are as many non trivial solutions of (2.2.3) as positive solutions $\bar{r} > 0$ has the equation

$$0 = \sum_{h \in H} (c_h \varphi_h(l_h; \lambda_h \bar{r} / c_h) - \lambda_h \bar{r}) - \mu \bar{r}. \quad (2.2.5)$$

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

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

In order to prove the existence of the functions $\varphi_h(x; v_h(0))$ we use the lemmas below. We omit the indices h because all we need to use are the structural properties of γ_1^h and γ_2^h given in (2.2.2), which are shared by all hosts.

Lemma 2.2.3. *The function $\frac{cg(v)}{v} = \frac{\gamma_2(v)v - \alpha v + \delta \tilde{u}(v)}{v}$ 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 all v large enough. \square

Now we prove two rather general lemmas on autonomous scalar ode's that will be helpful to prove existence and uniqueness of the non-trivial steady states (Theorem 2.2.7).

Lemma 2.2.4. *Let $\varphi(x; \varphi_0)$ be the solution of the initial value problem*

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

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 $\ln h(\varphi_0; l) = \int_0^l f(\varphi(s; \varphi_0)) ds$, it follows that $h(\varphi_1; l) > h(\varphi_2; l)$ for all $l \in (0, \infty)$. \square

Lemma 2.2.5. *Under the hypotheses of Lemma 2.2.4,*

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. \square

Remark 2.2.6. *In case i), $\varphi(l; \varphi_0)$ can indeed tend to 0 as φ_0 goes to 0. An example is given by $f(\varphi) = -\ln(\varphi)$.*

Realise that Lemma 2.2.3 ensures that $g_h(v)/v$ satisfies the hypotheses on f of Lemma 2.2.4, 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 (2.2.5) has at most one positive solution. Indeed, dividing (2.2.5) 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 (2.2.5) has a unique solution if and only if $\lim_{r \downarrow 0} k(r) > 0$, that is if

$$\lim_{r \downarrow 0} \sum_{h \in H} \lambda_h \frac{\varphi_h(l; \lambda_h r / c_h)}{\lambda_h r / c_h} > \mu + \sum_{h \in H} \lambda_h \quad . \quad (2.2.6)$$

Defining

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

we proceed to prove a theorem which gives necessary and sufficient conditions for the existence of an endemic equilibrium of system (2.2.1).

Theorem 2.2.7. *In the reinfection case (i.e., if $\lambda_h > 0$ for all $h \in H$), system (2.2.1) has an endemic equilibrium if and only if*

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

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

$$\sum_{h \in H} \varepsilon_h e^{\frac{l_h}{c_h} \left(\gamma_2^h(0) - \alpha_h + \frac{\alpha_h \delta_h}{\delta_h - \gamma_1^h(0)} \right)} > 1. \quad (2.2.7)$$

This endemic equilibrium is unique whenever it exists.

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 2.2.4 (due to Lemma 2.2.3).

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 $\tilde{v}_h(u)/u = (\delta_h - \gamma_1^h(u))/\alpha_h \rightarrow 0$ as u tend to 0 and so $\tilde{u}_h(v)/v \rightarrow \infty$ as v tends to 0 (recall Proposition 2.2.1 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 2.2.5. Therefore, the limit in (2.2.6) 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 2.2.5,

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

Then, condition (2.2.6) can be rewritten as (2.2.7) and the theorem is proven. \square

Stability of the equilibria

Next we give stability results related to the steady states of system (2.2.1). Recall that we take perturbations within the Banach space $X = \left(\prod_{h \in H} L^\infty(0, l_h) \right) \times C_b$, where

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

Let $(\bar{u}, \bar{v}, \bar{r})$ be an equilibrium of (2.2.1), where \bar{u} and \bar{v} have n components, one for each host. In view of section 2, let A be the generator of the linearised semigroup around $(\bar{u}, \bar{v}, \bar{r})$. According to (1.3.4), $(u, v, r) \in X$ belongs to $D(A)$ if, for all $h \in H$, v_h is Lipschitz, $\hat{v}_h := -c_h v_h' + (\gamma_2^h(\bar{v}_h) - \alpha_h + (\gamma_2^h)'(\bar{v}_h)\bar{v}_h)v_h + \delta_h u_h$ 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). In addition, denoting

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

the operator A is given by

$$A \begin{pmatrix} u \\ v \\ r \end{pmatrix} = \begin{pmatrix} \hat{u} \\ \hat{v} \\ \hat{r} \end{pmatrix} \quad \text{where} \quad \begin{aligned} \hat{u}_h &= a_1^h(x)u_h + \alpha_h v_h \\ \hat{v}_h &= -c_h v_h' + a_2^h(x)v_h + \delta_h u_h \\ \hat{r} &= \sum_{h \in H} (c_h v_h(l_h) - \lambda_h r) - \mu r \end{aligned} . \quad (2.2.8)$$

Lemma 2.2.8. *The spectrum of the linear operator A is the set*

$$\sigma(A) = \sigma_{\text{ess}}(A) \cup \{\eta \in \mathbb{C} \setminus \sigma_{\text{ess}}(A) \mid \Gamma(\eta) = 0\},$$

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

$$\Gamma(\eta) := \mu + \eta + \sum_{h \in H} \lambda_h - \sum_{h \in H} \lambda_h \exp \left(\frac{1}{c_h} \int_0^{l_h} a_2^h(s) - \frac{\delta_h \alpha_h}{a_1^h(s) - \eta} - \eta ds \right). \quad (2.2.9)$$

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

$$\begin{cases} a_1^h(x)u_h + \alpha_h v_h - \eta u_h = \hat{u}_h \\ -c_h v_h' + a_2^h(x)v_h + \delta_h u_h - \eta v_h = \hat{v}_h \\ \sum_{h \in H} (c_h v_h(l_h) - \lambda_h r) - \mu r - \eta r = \hat{r} \\ c_h v_h(0) = \lambda_h r \end{cases} . \quad (2.2.10)$$

Clearly, the system above fails to have a solution for all $(\hat{u}, \hat{v}, \hat{r})$ if, for some $h \in H$, the function $(a_1^h(\cdot) - \eta)^{-1}$ does not belong to $L^\infty(0, l_h)$, and this condition determines the set $\sigma_{\text{ess}}(A)$. If $\eta \notin \sigma_{\text{ess}}(A)$, the component u_h can be isolated and the equations for v_h in (2.2.10) reduce to

$$\begin{cases} -v_h' + \frac{1}{c_h} \left(a_2^h(x) - \eta - \delta_h \frac{\alpha_h}{a_1^h(x) - \eta} \right) v_h = \frac{1}{c_h} \left(\hat{v}_h - \delta_h \frac{\hat{u}_h}{a_1^h(x) - \eta} \right) \\ v_h(0) = \frac{\lambda_h}{c_h} r \end{cases} . \quad (2.2.11)$$

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

$$v_h(l_h) = \frac{\lambda_h}{c_h} r \exp \left(\frac{1}{c_h} \int_0^{l_h} a_2^h(s) - \frac{\delta_h \alpha_h}{a_1^h(s) - \eta} - \eta ds \right) + I_h(\eta, \hat{u}_h, \hat{v}_h) \quad (2.2.12)$$

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 (2.2.12) in the third equation of system (2.2.10), so that r must satisfy

$$-\Gamma(\eta) r = \hat{r} - \sum_{h \in H} c_h I_h(\eta, \hat{u}_h, \hat{v}_h). \quad (2.2.13)$$

Therefore, since the right hand side of (2.2.13) 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 (2.2.10) fails to have a unique solution for all points $(\hat{u}, \hat{v}, \hat{r}) \in X$ if $\Gamma(\eta) = 0$. \square

Proposition 2.2.9. *If A has a real eigenvalue η_d greater than $\max_{h \in H} (\text{ess sup } a_1^h(\cdot))$, then there exists $\omega \in \mathbb{R}$ such that $\eta_d > \omega > \sup_{\eta \in \sigma(A), \eta \neq \eta_d} \text{Re}(\eta)$.*

Proof. Notice that $\Gamma_{|\mathbb{R}} : (\max_{h \in H} (\text{ess sup } a_1^h(\cdot)), \infty) \rightarrow \mathbb{R}$ is a strictly increasing function, so that only one real eigenvalue greater than $\max_{h \in H} (\text{ess sup } a_1^h(\cdot))$ 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 $\max_{h \in H} (\text{ess sup } a_1^h(\cdot)) < \rho$, one can easily check that $f_h(\rho, y) < f_h(\rho, 0)$ for all $h \in H$ and

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

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

Finally, let us prove that there exists a strip $(\omega, \eta_d) \times i\mathbb{R}$ in the complex plane which does not include any spectral value. Choose $\omega > \max_{h \in H} \text{ess sup } a_1^h(\cdot)$. 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

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

uniformly in $\rho \in (\omega, \eta_d)$, the solutions of $\Gamma(\rho + iy) = 0$ within the strip 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 strip. Hence, for an ω close enough to η_d the strip will not include any solution of Γ . \square

Theorem 2.2.10. *In the reinfection case ($\lambda_h > 0$ for all $h \in H$),*

- i) If a non-trivial equilibrium of (2.2.1) exists, then the trivial one is unstable.*
- ii) If the trivial equilibrium is the only stationary solution of (2.2.1), then it is asymptotically stable or it is non-hyperbolic (more precisely, such that the spectral bound of A is zero).*

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 (2.2.9) 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 2.2.9, the stability of the trivial state depends on the sign of η_d (see Theorem 1.3.6). 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 2.2.7). Then, in the first case

$$\eta_d > \max_{h \in H} (\gamma_1^h(0) - \delta_h) \geq 0,$$

while in the second case we obtain $\Gamma(0) < 0$ which also implies $\eta_d > 0$. Thus the trivial steady state is unstable (by Theorem 1.3.6 and Proposition 2.2.9). 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 using 1.3.6 and 2.2.9 again).

Finally notice that the remaining special case $\gamma_1^h(0) < \delta_h$ for all h and equality in (2.2.7), 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. \square

Theorem 2.2.11. *The endemic equilibrium is locally asymptotically stable whenever it exists.*

Proof. Since, for all $h \in H$, the functions $\bar{u}_h(x)$ and $\bar{v}_h(x)$ giving the endemic equilibrium 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 $\Gamma(\rho) \rightarrow -\infty$ as ρ tends to $\max_{h \in H}(\text{ess sup } a_1^h(\cdot))$ from above. We will see that $a_1^h(\cdot) < 0$ for all h and $\Gamma(0) > 0$, which ensures, due to the monotony and continuity of Γ , the existence of a unique $\eta_d \in (\max_{h \in H}(\text{ess sup } a_1^h(\cdot)), 0)$ satisfying $\Gamma(\eta_d) = 0$. 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 2.2.9. Next we show that

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

Using the positiveness of \bar{u}_h and \bar{v}_h , the assumption (2.2.2) on the functions γ , and the equilibrium conditions of (2.2.3), 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 (2.2.8))

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

Therefore,

$$\begin{aligned} f_h(0,0) &= \frac{1}{c} \left(\alpha \delta \int_0^l \frac{dx}{-a_1(x)} + \int_0^l a_2(x) dx \right) < \frac{1}{c} \left(\alpha \delta \int_0^l \frac{\bar{u}(x)}{\alpha \bar{v}(x)} dx + \right. \\ &\quad \left. + \int_0^l \frac{c \bar{v}'(x) - \delta \bar{u}(x)}{\bar{v}(x)} dx \right) = \int_0^l \frac{\bar{v}'(x)}{\bar{v}(x)} dx = \ln \frac{\bar{v}_h(l_h)}{\bar{v}_h(0)}, \end{aligned}$$

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

$$\begin{aligned} \Gamma(0) &= \mu + \sum_{h \in H} \lambda_h - \sum_{h \in H} \lambda_h e^{f_h(0,0)} > \\ &> \mu + \sum_{h \in H} \lambda_h - \sum_{h \in H} \lambda_h \frac{\bar{v}_h(l_h)}{\bar{v}_h(0)} = \mu + \sum_{h \in H} \lambda_h - \sum_{h \in H} c_h \frac{\bar{v}_h(l_h)}{\bar{r}} = 0 \end{aligned}$$

where the last equality is due to the equilibrium condition $0 = \sum_{h \in H} (c_h v_h(l_h) - \lambda_h r) - \mu r$ (see (2.2.5)). Finally, by means of Theorem 1.3.6 and Proposition 2.2.9 the asymptotic stability of the endemic equilibrium is proven. \square

Biological interpretation and implications

The condition on the parameters appearing in Theorem 2.2.7 together with the stability results given in Theorem 2.2.10 can be used to predict in which situations bacteria can spread across the population of hosts. The theoretical results make natural to distinguish the condition involving one host from the one involving the population as a whole. Therefore, we proceed to comment them separately.

A spreading scenario will occur if there is a host in which attached bacteria at low densities proliferate more than they detach. This is what point i) in Theorem 2.2.7 says. Notice that in this case an outbreak may occur even if bacteria cannot grow in most of the population but only on a few hosts, whose intestinal epithelium act as a kind of bacterial source or reactor. One has to be specially aware of this possibility if the microbes in question exert its pathogenesis through toxins, since these substances can either accumulate to the environment or be harmful at low concentrations.

If no host has a gut epithelium acting as a bacterial source, i.e. if $\gamma_1^h(0) < \delta_h$ for all host h , then the fate of the pathogens depend on how they grow and move on the lumen as well as their degradation rate in the soil. The inequality (2.2.7) synthesizes such information. The effect of host h is represented by the h summation term. The higher it is, the more bacteria are produced within such host. As in the previous case, it is enough for the bacteria to be sufficiently well adapted to a few hosts in order to spread through all the individuals. However, an outbreak can also occur if bacteria barely grow within each intestine but the host population is big enough to compensate the losses occurring in the soil. In the first case a few terms of the summation in inequality (2.2.7) are high enough to satisfy the condition by themselves while in the second case all the terms are small but the sum of them is greater than one. Clearly, a precise biological interpretation of these summation terms is needed to use condition (2.2.7) as a tool to control epidemics driven by enteropathogens. To this end, we consider an isolated host so that the condition for bacteria to persist is

$$\frac{\lambda}{\lambda + \rho} e^{\frac{1}{c}(\gamma_2(0) - \alpha + \frac{\alpha\delta}{\delta - \gamma_1(0)})} > 1. \quad (2.2.14)$$

The term $\lambda/(\lambda + \rho)$ can be thought as the probability that a bacterium in the soil is ingested by the host before dying. Thus, the other term (the exponential factor) seems to be the expected number of descendants of this recently ingested bacteria that succeed to leave the intestine. Indeed, if the product of this two conceptual quantities is greater than one, then each cycle of infection ends with a greater number of bacteria so they persist. Otherwise, if the product is lower than one, then the converse holds and bacteria cannot spread. The relation between these facts and inequality (2.2.14) is what suggested us the interpretation of the exponential factor given above. If we now return to the system with multiple hosts, then an arbitrary term h of the summation is interpreted analogously. That is, ε_h is the probability that a bacterium in the soil enters host h before dying or being ingested by a different animal while the exponential term represents the descendants of this bacterium that will leave the intestine. Of course, this interpretation is only valid when assuming that bacteria are at low concentration so that the non-linear effects due to competition are negligible. This is why the exponential factors

in (2.2.7) only depend on the pathogen growth rates at low density (actually at zero). As expected, the exponential term increases with these growth rates in both the gut lining ($\gamma_1^h(0)$) and the lumen ($\gamma_2^h(0)$). If pathogens grow more than they die in the epithelium ($\gamma_1^h(0) > 0$, but still in the case $\gamma_1^h(0) < \delta_h$), then the exponential term also increases with the attachment rate (α_h) and decreases with the detachment rate (δ_h). Conversely, if the epithelium has a kind of bactericidal effect, then the effects of α_h and δ_h reverse. Similarly, a higher intestinal transit time (l_h/c_h) have a beneficial effect on the microbes population if

$$\frac{\gamma_2^h(0) - \alpha_h}{\alpha_h} > \frac{\delta_h}{\gamma_1^h(0) - \delta_h},$$

and it is detrimental if the parameters satisfy the converse inequality. One can easily check that, since α_h and δ_h are non-negative, the above condition is always true if both $\gamma_1^h(0)$ and $\gamma_2^h(0)$ are positive, whereas the condition is always false if they are both negative.

We end this section showing how the introduction of animals in which bacteria grow badly can affect the infection progression. In the field this could be achieved treating part of the animals in the pen or using different species with physiological particularities. In any case, they act as bacterial sinks, so that they release less pathogens to the soil than what they ingest from it. This means that the exponential factor in (2.2.14) associated to them is lower than one. The hosts producing a net amount of pathogens are characterized by an exponential part greater than one. Being that said, let us consider a population of n bacterial producers and m bacterial sinks, whose respective exponential terms are denoted by $e_p > 1$ and $e_s < 1$. We assume that all the animals have the same ingestion rate λ . Then condition (2.2.7) reduces to

$$\frac{\lambda}{\mu + (n + m)\lambda} (ne_p + me_s) > 1,$$

so that $m(1 - e_s)$ has to be greater than $n(e_p - 1) - \mu/\lambda$ in order to avoid the outbreak. Since $e_s < 1$, if m is large enough then the epidemics will be controlled. Of course, we are assuming that none of the n producers has an epithelium acting as a bacterial source. Otherwise, (2.2.7) is nonsense and eradication is no possible using animals acting as bacterial sinks. Although the previous example is rather simple, we think that it illustrates quite well how to apply the above theoretical results to real systems once information on the population structure is available.

2.2.2 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 than 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 2.2.12. *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 (2.2.3) must satisfy

$$\begin{cases} c\bar{v}' = \gamma_2(\bar{v})\bar{v} - \alpha\bar{v} + \delta\tilde{u}(\bar{v}), \\ \bar{v}(0) = 0, \end{cases}, \quad (2.2.15)$$

$\bar{u}(x) = \tilde{u}(\bar{v}(x))$, and $\bar{r} = c\bar{v}(l)/\mu$. However, problem (2.2.15) 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 $(\bar{u}, \bar{v}, \bar{r}) = (0, 0, 0)$. \square

Theorem 2.2.13. *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 (2.2.15) 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 (2.2.15) 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 . \square

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 2.2.7).

Theorem 2.2.14. *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 (2.2.3),

ii) if $\Delta_0(v_0) < \infty$, then (2.2.3) has an uncountable set of solutions.

Proof. Consider the differential equation $v'(x) = h(v(x))$ (the same equation as in (2.2.15)) 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 (2.2.15) 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 2.2.13. 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 . \square

2.3 Effects of bacteriophage therapy on the spread of bacteria

System (2.2.1) 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

$$\begin{cases} \partial_t u_h = \gamma_1^h(u_h)u_h + \alpha_h v_h - \delta_h u_h - \kappa_1^h u_h p_h \\ \partial_t v_h = -c_h \partial_x v_h + \gamma_2^h(v_h)v_h - \alpha_h v_h + \delta_h u_h - \kappa_2^h v_h p_h \\ \dot{r} = \sum_{h \in H} (c_h v_h(l_h, t) - \lambda_1^h r) - \mu_1 r \\ \partial_t p_h = -c_h \partial_x p_h + b(\kappa_1^h u_h + \kappa_2^h v_h)p_h \\ \dot{q} = \sum_{h \in H} (c_h p_h(l_h, t) - \lambda_2^h q) - \mu_2 q \\ c_h v_h(0, t) = \lambda_1^h r \\ c_h p_h(0, t) = \lambda_2^h q + q_0^h \end{cases} . \quad (2.3.1)$$

Notice that two families of new dependent variables have been added to system (2.2.1), namely $p_h(x, t)$ which represent the bacteriophage density 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 per time unit 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_0^h 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 so many details as in the previous section since they can be tackled 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

$$\bar{p}_h(x) \equiv \frac{\lambda_2^h \bar{q} + q_0^h}{c_h} \quad \text{and} \quad \bar{q} = \sum_{h \in H} \frac{q_0^h}{\mu_2}, \quad (2.3.2)$$

is a steady state of (2.3.1), which corresponds to the non-endemic state or bacteria free scenario. To study if it is stable or not, we analyse the linearised system around this equilibrium, which we call A . Specifically, we give a formula for the spectral bound of A , and we show that its sign determines the stability or instability of the non-endemic state.

Using (1.3.4), we have that A is given by

$$A \begin{pmatrix} u \\ v \\ r \\ p \\ q \end{pmatrix} = \begin{pmatrix} \hat{u} \\ \hat{v} \\ \hat{r} \\ \hat{p} \\ \hat{q} \end{pmatrix} \quad \text{where} \quad \begin{cases} \hat{u}_h = (\gamma_1^h(0) - \delta_h - \kappa_1^h \bar{p}_h)u_h + \alpha_h v_h \\ \hat{v}_h = -c_h v'_h + (\gamma_2^h(0) - \alpha_h - \kappa_2^h \bar{p}_h)v_h + \delta_h u_h \\ \hat{r} = \sum_{h \in H} (c_h v_h(l_h) - \lambda_1^h r) - \mu_1 r \\ \hat{p}_h = -c_h p'_h + b \kappa_1^h \bar{p}_h u_h + b \kappa_2^h \bar{p}_h v_h \\ \hat{q} = \sum_{h \in H} (c_h p_h(l_h) - \lambda_2^h q) - \mu_2 q \end{cases}, \quad (2.3.3)$$

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 2.3.1. *The spectrum of the operator A is the set*

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

where

$$\begin{aligned} \sigma_{\text{ess}}(A) &= \bigcup_{h \in H} \{a_1^h\}, \\ \Gamma^1(\eta) &= \eta + \mu_1 + \sum_{h \in H} \lambda_1^h - \sum_{h \in H} \lambda_1^h e^{\frac{l_h}{c_h} \left(\gamma_2^h(0) - \kappa_2^h \bar{p}_h - \alpha_h - \frac{\alpha_h \delta_h}{\gamma_1^h(0) - \kappa_1^h \bar{p}_h - \delta_h - \eta} - \eta \right)}, \end{aligned} \quad (2.3.4)$$

$$\Gamma^2(\eta) = \mu_2 + \sum_{h \in H} \lambda_2^h - \sum_{h \in H} \lambda_2^h e^{-\frac{l_h}{c_h} \eta}. \quad (2.3.5)$$

Proof. We can start proceeding exactly in the same way as in the proof of Lemma 2.2.8. 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 $p_h(0) = \frac{\lambda_2^h}{c_h} q$ as the initial condition. Secondly, using the resulting expressions for $p_h(l_h)$ in the last equation of (2.3.3), 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 $\Gamma^2(\eta) = 0$. \square

Next, the characteristic equation from the previous lemma is used to determine the spectral bound of the operator A . In addition, the conditions needed to apply Theorem 1.3.6 are verified. Altogether, these two steps prove a stability/instability result related to the non-endemic equilibrium. As before, we use ε_1^h as the quotient $\lambda_1^h/(\mu_1 + \sum_{j \in H} \lambda_1^j)$.

Theorem 2.3.2. *In the reinfection case (i.e., if $\lambda_h > 0$ for all $h \in H$), the non-endemic equilibrium of system (2.3.1) is asymptotically stable if $\gamma_1^h(0) < \delta_h + \kappa_1^h \bar{p}_h$ for all $h \in H$ and*

$$\sum_{h \in H} \varepsilon_1^h e^{\frac{l_h}{c_h} \left(\gamma_2^h(0) - \alpha_h - \kappa_2^h \bar{p}_h + \frac{\alpha_h \delta_h}{\delta_h + \kappa_1^h \bar{p}_h - \gamma_1^h(0)} \right)} < 1, \quad (2.3.6)$$

and it is unstable if

i) $\gamma_1^h(0) \geq \delta_h + \kappa_1^h \bar{p}_h$ for some $h \in H$, or

ii) $\gamma_1^h(0) < \delta_h + \kappa_1^h \bar{p}_h$ for all $h \in H$ and

$$\sum_{h \in H} \varepsilon_1^h e^{\frac{l_h}{c_h} \left(\gamma_2^h(0) - \alpha_h - \kappa_2^h \bar{p}_h + \frac{\alpha_h \delta_h}{\delta_h + \kappa_1^h \bar{p}_h - \gamma_1^h(0)} \right)} > 1 \quad (2.3.7)$$

Proof. In order to compute the spectral bound of A , denoted by $s(A)$, first notice that $s(A) \geq \sup_{h \in H} a_1^h$. Therefore, since all the solutions of $\Gamma^2(\eta) = 0$ have negative real part, to determine the sign of $s(A)$ we may focus on the zeros of $\Gamma^1(\eta)$ in the semiplane $\text{Re}(\eta) \in (\sup_{h \in H} a_1^h, \infty)$. Since $\Gamma^1(\eta)$ is increasing on the real line $(\sup_{h \in H} a_1^h, \infty)$ and it is unbounded as η goes to both interval limits, we conclude that a unique real solution $\eta_d > \sup_{h \in H} a_1^h$ of $\Gamma^1(\eta) = 0$ always exist. The inequalities $\Gamma^1(\eta) > 0$ and $\Gamma^1(\eta) < 0$ reduce to expressions (2.3.6) and (2.3.7) respectively. Moreover, we can proceed in the same way as in Proposition 2.2.9 to show that η_d is the solution of $\Gamma^1(\eta) = 0$ with higher real part and that there is a gap between η_d and the real part of the other zeros of Γ^1 . One can also check that the part of the spectrum related to the zeros of Γ^2 is also dominated by a real value. Therefore, Theorem 1.3.6 can be applied and we conclude that the non-endemic state of (2.3.1) is stable if $s(A) < 0$ and unstable if $s(A) > 0$. In other words, it is stable if $\gamma_1^h(0) < \delta_h + \kappa_1^h \bar{p}_h$ for all $h \in H$ and (2.3.6) holds, whereas it is unstable whenever condition i) or condition ii) of the statement above holds. \square

Clearly, the conditions appearing in the above result are nothing but extended versions of the ones appearing in Theorem 2.2.7. Here they include the bacteriophage dose given to the animals (in terms of \bar{p}_h defined in (2.3.2)). In fact, if $q_0^h = 0$ for all hosts h , then we recover the same conditions of Theorem 2.2.7. Therefore, the bacteriophage population cannot prevent a bacterial outbreak by themselves, but an external source of viruses is needed in order to reduce the term of the left hand side of (2.3.6) 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

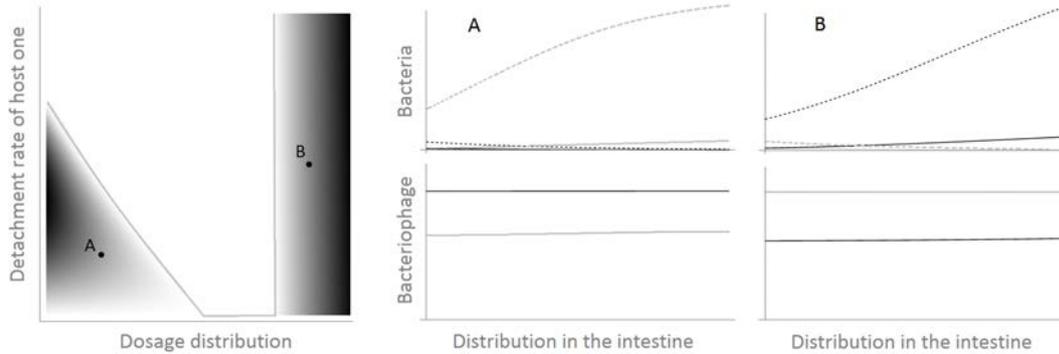


Figure 2.1: Bifurcation diagram showing epidemic progression (dark regions) or eradication (white regions) in a system with two hosts. The changing parameters are the fraction of bacteriophage given to the first host ($q_0^1/(q_0^1 + q_0^2)$ ranging from 0 to 1) and its detachment rate (δ_1 ranging from 0 to 1.5). The bacterial and bacteriophage distributions along the intestine once the system has converged to the equilibria are shown for two different set of parameters A and B. The dashed line refers to attached bacteria while gray color is used for host one and black for host two. The other fix parameters used to do the numeric simulations are the total bacteriophage dose per time unit $q_0^1 + q_0^2 = 11$ and: $c_h = l_h = 1$, $\gamma_1^h(u) = 1 - u$, $\gamma_2^h(v) = 1 - v$, $\alpha_h = 4$, $b = 4$, $\kappa_1^h = 0.06$, $\kappa_2^h = 0.1$, $\lambda_1^h = \lambda_2^h = 0.1$, $\mu_1 = 0.4$ and $\mu_2 = 0.1$ for all $h \in 1, 2$ and $\delta_2 = 0.5$. Notice that the two hosts only differ in their detachment rate (δ_1 and δ_2) and the treatment received (q_0^1 and q_0^2).

of (2.3.6) converges to 0 as \bar{p}_h grows to infinity for all h , and this condition holds provided $q_0^h \rightarrow \infty$ for some h . Such a behaviour depending on the phage dose is not a big surprise, since something similar happens in the simplified system

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

in which the only equilibrium in the $S = 0$ axis is $(0, P_0/m)$ and it is asymptotically stable if and only if $P_0 \geq am/k$. In particular, notice that both in our case and in this simplified model, the so called burst size b does not play a role in the stability of the uninfected equilibrium.

From our point of view, the main contribution of condition (2.3.6) is that it may be used to compute efficient phage doses in non homogeneous populations, such as the ones found when a pen harbours 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. To illustrate this idea we show in Figure 2.1 a bifurcation diagram for a system with two hosts. We assume that a given amount per time unit Q of bacteriophage is used to treat the animals, so that $q_0^1 + q_0^2 = Q$. All the parameters are fixed but the detachment rate of the first host and the distribution of bacteriophage given to the couple. Thus, the abscissa axis represents the proportion of bacteriophage received by the first host while the ordinate axis indicates its

detachment rate. The detachment rate of the second host is constant but its bacteriophage dose changes according to $q_0^2 = Q - q_0^1$. The gray scale in the graphic reflects the amount of bacteria in the external media once the system has converged to an equilibrium, so that parameters in the darker zones imply larger epidemic states while parameters in the white zone control the infection. The gray curve splitting these regions has been drawn taking into account the theoretical conditions of Theorem 2.3.2, so that the figure also provides a computational check to the analytical results of the paper. Observe that in this scenario a set of effective ways to dispense the viral particle among the two animals always exist, even when the detachment rate of the first host vanishes. The strategies that avoid the spread of bacteria require treating both animals when they have low detachment rates. If the detachment rate of the first host is high enough, then eradication can also be achieved by giving all the bacteriophage to the second animal. However, the black region in the right of the graphic indicates that the epidemic control is not guaranteed independently of the dosing strategy. Even when the first host has a very high detachment rate, bacteria manage to proliferate if only a small percentage of the therapy is directed to the second host which has a low detachment rate. This phenomenon in which control is possible only for some dosage patterns appears in many other sets of parameters. Although the difficulty in estimating some of the parameters appearing in condition (2.3.6), we think that this expression can be a useful starting point to get some intuition about how to distribute the bacteriophage among the animals.

2.4 Discussion

Reinfection phenomena of enteropathogens may have a critical role in epidemic outbreaks. In the present paper we have followed the ideas of [11] 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 2.2.7). Interestingly, the condition we are referring to is neither the basic reproduction number \mathcal{R} of the bacterial population nor its population growth rate [27, 80]. 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 emerges 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} . In the next chapter this issue is treated with more detail.

The results obtained in this chapter leave many open questions related to the asymptotic behaviour of the trajectories. Preliminary simulations suggest that the only locally stable equilibrium found in system (2.2.1) is indeed a global attractor. However we could not find a formal proof for that. In relation to the extended system with bacteriophage (2.3.1), 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 [17]. Finally, we must say something about possible extensions of systems (2.2.1) and (2.3.1). Among the many refinements these models may include, we are specially interested in generalising the constants c_h , which give the speeds 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.

Chapter 3

On the reproduction number of a gut microbiota model

The content in this chapter is published [9].

3.1 Introduction

Population density plays an important role in regulating the dynamics of the population. When many individuals are sharing the same niche, the interactions between them and their effects on the environment are by no means negligible. At low densities, however, these interactions and effects are rare. This implies, on the one hand, that the environment is essentially insensitive to the population and, on the other hand, that the individuals behave mainly as independent agents. Mathematically, these two properties translate into a linear dynamical system describing the changes of the modelled population. Of course, if the environment is not stable but changes according to its own dynamics (due to the seasons or to the resident communities), then the system may become non-autonomous, but it will still be linear. The linearity is commonly lost when modelling populations at higher densities, and this explains why it is easier to analyse the colonization success of a group of living beings than predicting what will happen to them in the long run. Fortunately, in many applications the interesting questions are related to the initial steps of an invasion event. Indeed, any species reintroduction program must perform studies to know under which conditions a small group of animals or plants are able to expand in a given place. Epidemiology cares about the factors that prevent the proliferation of small inoculations of microbes. Evolution itself deals with low density populations since mutants are necessarily rare (at least when they are generated).

The linear model reflecting the dynamics of a population at low densities is the main mathematical tool the (deterministic) modeller has at hand in order to answer if the population tends to grow or, alternatively, becomes extinct. The standard way to do that is by computing the highest per capita rate at which the population can grow, that is the Malthusian parameter in the terminology of demography. In principle if this rate is positive then the population

increases whereas it decreases if the rate is negative. It is worth saying that the above relation is relatively easy to formulate and prove if the linear system is autonomous and finite dimensional. Complications arise either in the non-autonomous setting (i.e., when the environment changes with time) or when the population structure cannot be specified by a finite number of quantities [87, 47, 4]. In any case, since the Malthusian parameter is a rate, it not only reflects the qualitative behaviour of the population, but it contains information about the velocity at which the changes occur.

An alternative approach to analyse the stability of the linear model is based on the population ratio between successive generations, so that values above one would imply proliferation and values below one regression. Here the term generation is not specified, but it can be defined in different ways to highlight important aspects of the model. Classically, two successive generations have been characterized by the fact that the individuals in the later generation are the offspring of the former one. When this definition is taken into account the ratios between successive generations converge to the famous *basic reproduction number* [27, 80], roughly defined as the expected number of offspring produced by each member of the population. However, as Cushing and Diekmann have noticed in a recent paper [25], different interpretations of what a birth event is, give rise to different generational schemes, and hence alternative basic reproduction numbers are obtained. See [82] where it is shown that the growth rate has the same sign as $\mathcal{R} - 1$ for ode models and [80] where this significant result is generalized to infinite dimensional models.

The range of suitable quantities to determine the growth of a population lead us to wonder if some of them are better than others. From the mathematical point of view little differences exist. The Malthusian parameter and the basic reproduction numbers are related to the spectral properties of certain operators, so that technical difficulties are more or less comparable. In contrast, some of these numbers may be much easier to compute empirically than others. Thus, it is on the biological side of the problem where one should focus on to decide which birth event, though artificial, is accessible and measurable.

In this chapter we use our model (2.2.1) for the growth of intestinal bacteria to show which kind of birth events lead to useful reproductive numbers. To this end, we consider the linearised version of (2.2.1) around the free bacteria equilibrium, which, in the case of an isolated host (i.e. $n = 1$), takes the form

$$\begin{cases} \partial_t u(x, t) = \gamma_1 u(x, t) + \alpha v(x, t) - \delta u(x, t) \\ \partial_t v(x, t) = -c \partial_x v(x, t) + \gamma_2 v(x, t) - \alpha v(x, t) + \delta u(x, t) \\ b'(t) = cv(l, t) - \rho b(t) - \mu b(t) \\ cv(0, t) = \rho b(t) \end{cases}, \quad (3.1.1)$$

with γ_1 and γ_2 being the bacterial intrinsic rates of increase in the epithelium and the lumen respectively (notice that in this chapter we use b instead of r and ρ instead of λ). The asymptotic behaviour of the bacterial population is then analysed from two generational points of view. By considering that two bacteria are born when a mother bacterium divides, the standard reproduction number is obtained. Although biologically meaningful, the derived expression this

way does not have a clear mechanistic interpretation to work with. A more understandable reproduction number is obtained when, instead, we consider that bacteria are “born” at the moment they leave the intestine. Moreover, it is shown how the rationale behind this number makes possible to design experiments for its empirical computation.

The chapter is organized as follows. Section 3.2 is a brief introduction to the generational perspective of population dynamics problems, based primarily on [27]. In Section 3.3, we properly derive the next-generation operator associated to model (3.1.1) and explicitly compute its spectral radius which gives the standard reproduction number. Similarly, Section 3.4 is devoted to the alternative reproduction number based on counting the amount of bacteria that leave the intestine and descend from a bacterium originally at the external media. A little algebra is enough to show that both reproduction numbers coincide and are equal to one at the extinction threshold. In Section 3.5, assuming trade-offs between parameters, we study if both reproduction numbers are maximized at the same parameter values. Finally, in Section 3.6 we present the design of two possible experimental procedures that could be used to approximate the determination of the alternative reproduction number in real situations.

3.2 Next-generation Operator framework

The dynamics of a population can be analysed from a generational point of view by giving the distribution of newborns of the different generations in terms of a founder population (here by distribution we refer to a non-normalized density). This is achieved by considering the next-generation operator (G_1) defined as the function that takes a founder population and returns the state-at-birth distribution of its first descendants. Clearly, in an autonomous system and under the assumption that individuals behave independently (i.e. no interactions between them), the next-generation operator becomes linear. In this case, the state-at-birth distribution of the n -th generation p_n of a founder population p_0 is given by

$$p_n = G_1^n p_0,$$

simply because the n -th generation of newborns acts as the founder population of the $(n + 1)$ -generation. This formula can be used to compute the mean offspring-per-descendant of a founder population p_0 . The concept offspring-per-descendant refers to the expected amount of newborns produced by a certain descendant. Obviously, depending on the state-at-birth of the descendant (or the state-at-foundation if the descendant is actually a founder) this number will be higher or lower. However, when we take the average of these values we end up with a number related to the fecundity of the descendants as a whole, which commonly determines the population dynamics [80]. To compute this average define the norm $\|\cdot\|$ as the one that corresponds to the total number of individuals of a population distribution, so we can think of $\|\cdot\|$ to be the L^1 norm. Then, if we distribute uniformly all the n -th descendants among the individuals in the founder population, it can be said that each founder individual has, on average,

$$\frac{\|G_1^n p_0\|}{\|p_0\|}$$

n -th descendants. Similarly, it can also be said that the offspring of each individual below the n -th generation is

$$\sqrt[n]{\frac{\|G_1^n p_0\|}{\|p_0\|}}$$

on average. This is so because the amount of individuals in each level of the genealogical tree grows geometrically if everybody has the same number of offspring. In particular, notice that the mean offspring per individual may change depending on the number of generations we use to compute it. However, if the limit

$$\lim_{n \rightarrow \infty} \sqrt[n]{\frac{\|G_1^n p_0\|}{\|p_0\|}}$$

exists, then it gives the mean offspring-per-descendant taking into account all the lineages of the founder individuals, which are represented by p_0 . In fact, the upper limit is bounded from above by

$$\limsup_{n \rightarrow \infty} \sqrt[n]{\frac{\|G_1^n p_0\|}{\|p_0\|}} \leq \lim_{n \rightarrow \infty} \sqrt[n]{\|G_1^n\|}, \quad (3.2.1)$$

and for a generic founder population p_0 , this bound is attained [27]. This motivates the definition of Reproduction number (\mathcal{R}) as the mean offspring-per-descendant of a generic founder population that has colonized the environment. Thus, \mathcal{R} is essentially independent of the founder population and coincides with the right hand side of expression (3.2.1), which in turn is equivalent to the spectral radius of the next-generation operator (denoted by $\rho(G_1)$), i.e.,

$$\mathcal{R} = \lim_{n \rightarrow \infty} \sqrt[n]{\|G_1^n\|} = \rho(G_1).$$

Alternatively, the Reproduction number can also be defined as the expected number of offspring produced by a typical individual [27], where a typical individual can be understood as a random descendant of the n -th generation of any generic founder population p_0 as n tends to infinity. Formally,

$$\mathcal{R} = \lim_{n \rightarrow \infty} E(\text{Offspring}(Z_n)) = \lim_{n \rightarrow \infty} E(\|G_1 \delta_{Z_n}\|)$$

where δ_{Z_n} is the Dirac mass at Z_n and Z_n is a random variable with probability density p_n given by

$$p_n = \frac{G_1^n p_0}{\|G_1^n p_0\|}, \quad n \geq 1.$$

Although the sequence $\{p_n\}_{n \in \mathbb{N}}$ depends on the founder population p_0 , generically, as n goes to infinity the vectors p_n tend to align along the eigenspace corresponding to the largest eigenvalue of G_1 , which is independent of p_0 and precisely

$$\lim_{n \rightarrow \infty} \sqrt[n]{\|G_1^n\|}. \quad (3.2.2)$$

In particular, the sequence of norms $\|G_1 p_n\|$ converge to the expression (3.2.2) as n goes to infinity. Thus,

$$\mathcal{R} = \lim_{n \rightarrow \infty} E(\|G_1 \delta_{Z_n}\|) = \lim_{n \rightarrow \infty} \int \|G_1 \delta_z\| p_n(z) dz = \lim_{n \rightarrow \infty} \|G_1 p_n\| = \lim_{n \rightarrow \infty} \sqrt[n]{\|G_1^n\|},$$

which gives the same value obtained in the previous interpretation. In fact, since (3.2.2) is equal to the spectral value of the next-generation operator, the reproduction number is sometimes defined directly as the spectral radius of G_1 .

In [27] it is shown how to obtain the next-generation operator from the linear dynamical system that determines the population growth. Briefly, in these cases one has to distinguish the linear operator B associated to the birth part from the linear operator $-M$, which gives the transition part in the population dynamics model. The birth part contains all the information related to new individuals entering to the system while the transition part is everything else so that $B - M$ is the operator that generates the dynamical system. For a given population p , the product $B p dt$ gives the state-at-birth distribution of the offspring produced by p during dt units of time. The problem is that p is not fixed through time since it is affected by the biological process collected by $-M$. To solve this issue, the idea is to firstly consider the system without births and study how the individuals of the population move through the state space and die. If $-M$ generates a strongly continuous semigroup $T_{-M}(t)$ on some Banach space X , then for each population distribution $p_0 \in X$ the image $T_{-M}(t)p_0$ gives the distribution of the population at time t due to transitions in the state space. The number of deaths occurred during the time window $[0, t]$ is simply $\|p_0\| - \|T_{-M}(t)p_0\|$. In principle this number cannot be negative because this would imply that some new individual has entered the system, but this is not possible by definition of the operators M and B . Moreover, since we are dealing with living beings, a reasonable and useful assumption is that the death rate of any individual is strictly positive. Mathematically, this amounts to the existence of a negative number that bounds from above the real part of all the spectral values of $-M$, so that 0 belongs to the resolvent set of $-M$ and the formula

$$\int_0^\infty T_{-M}(t)p_0 dt = M^{-1}p_0 \quad \text{holds} \quad \forall p_0 \in X. \quad (3.2.3)$$

This follows from the fact that the resolvent of the generator is equal to the Laplace transform of the semigroup [34]. Then, provided B is a bounded operator, the next-generation operator can be written as

$$G_1 p_0 = \int_0^\infty B T_{-M}(t)p_0 dt = B \int_0^\infty T_{-M}(t)p_0 dt = B M^{-1} p_0.$$

Although there are different ways to express the next-generation operator, the formula $G_1 = B M^{-1}$ is really useful when the population dynamics is given in terms of a differential equation as in (3.1.1).

3.3 Standard generational approach of the model

In this section we compute the next-generation operator associated to system (3.1.1) as well as the reproduction number of the system in terms of the model parameters. We consider that two bacteria are born when a mother cell divides (and, hence, also dies). This definition of a birth event in a bacterial population is the standard one, so that the generational approach we are going to follow is the usual one.

3.3.1 Next-Generation Operator

In order to compute the birth part B in (3.1.1) we must specify precisely the meaning of γ_1 and γ_2 in the model since for the moment these are growth rates that take into account cell division as well as cell death. It is possible to take auxiliary parameters d and m for the division and mortality rates respectively, in order to express growth rate as $\gamma = 2d - d - m$ (assuming symmetrical division, i.e., the mother cell disappears giving rise to two descendants). The value of \mathcal{R} depends then on the relation between the values of the parameters d and m . However, the critical value $\mathcal{R} = 1$ is independent of the values of d and m provided that $\gamma = d - m$. For this reason and in order to simplify notation, we will assume that the death rates of bacteria inside the intestine are zero and we will use γ as division rate. In this case,

$$B \begin{pmatrix} u \\ v \\ b \end{pmatrix} = \begin{pmatrix} 2\gamma_1 u \\ 2\gamma_2 v \\ 0 \end{pmatrix}, \quad M \begin{pmatrix} u \\ v \\ b \end{pmatrix} = \begin{pmatrix} \gamma_1 u - \alpha v + \delta u \\ cv' + \gamma_2 v + \alpha v - \delta u \\ -cv(l) + \rho b + \mu b \end{pmatrix},$$

and the next-generation operator is formally given by

$$G_1 = BM^{-1} = \begin{pmatrix} 2\gamma_1 & 0 & 0 \\ 0 & 2\gamma_2 & 0 \\ 0 & 0 & 0 \end{pmatrix} \begin{pmatrix} \gamma_1 + \delta & -\alpha & 0 \\ -\delta & c\partial_x + \gamma_2 + \alpha & 0 \\ 0 & -c\delta_l & \rho + \mu \end{pmatrix}^{-1}$$

where δ_l stands for the evaluation operator at the point $x = l$. In the expressions above we consider M as a closed linear operator on the Banach lattice $X = L^1(0, l) \times L^1(0, l) \times \mathbb{R}$ with domain $D = L^1(0, l) \times \{(v, b) \in W^{1,1}(0, l) \times \mathbb{R} : cv(0) = \rho b\}$. Notice that the space we use in this chapter does not belong to the class of spaces used in chapters 1 and 2. This is because in the previous chapters we were interested in the dynamics of non-linear systems for which the L^1 norm presented some inconveniences (see the introduction in chapter 1), whereas here we already have a linear system and we want to “count individuals” (hence we use the L^1 norm). It can be checked that $-M$ is the generator of a positive strongly continuous semigroup and that 0 does not belong to the spectrum of M , which implies that M^{-1} is a bounded positive operator on X . Therefore, since B is also a bounded positive operator, BM^{-1} turns out to be a positive bounded linear operator on X .

Throughout the rest of the paper, we avoid the degenerate case $\gamma_1 = \delta = 0$ and we assume $\gamma_1 > 0$ or $\delta > 0$ (as well as $c > 0, \rho > 0$ and $b > 0$).

3.3.2 Basic reproduction number

We are going to compute the basic reproduction number \mathcal{R} which is interpreted here as the expected number of newborns produced by each bacterium (in the long run). In our case, the limit that defines \mathcal{R} (see Section 3.2) coincides with the spectral radius of the next-generation operator, so that $\mathcal{R} = \rho(BM^{-1})$. Recall that the spectral radius of a positive bounded linear operator always belongs to the spectrum of the operator, see e.g. [72]. Thus, we restrict to the computation of real spectral values of BM^{-1} .

Let us consider the operator $L_\lambda \hat{\phi} := BM^{-1}\hat{\phi} - \lambda\hat{\phi}$ defined on X . Denoting $\phi = M^{-1}\hat{\phi}$, we have that $M\phi = \hat{\phi}$ and hence that L_λ is surjective if and only if $\text{Range}(B - \lambda M)$ is the whole space X . Notice that

$$\tilde{\lambda} = \frac{2\gamma_1}{\gamma_1 + \delta}$$

belongs to the spectrum $\sigma(BM^{-1})$. Indeed, the first component of the image by $(B - \tilde{\lambda}M)$ of any $(u, v, b) \in D$ equals to $\tilde{\lambda}\alpha v \in W^{1,1}(0, l)$. Hence, $(B - \tilde{\lambda}M)$ is not surjective. Moreover, notice that $0 \leq \tilde{\lambda} < 2$.

Now we are ready to show that BM^{-1} always has a unique real spectral value larger than the value $\tilde{\lambda}$ computed above, and therefore the former will coincide with the spectral radius. Actually, it will be a positive eigenvalue.

Indeed, let us compute the inverse of the operator $(B - \lambda M)$ for $\lambda > \tilde{\lambda}$, i.e., let us look for solutions of

$$(B - \lambda M) \begin{pmatrix} u \\ v \\ b \end{pmatrix} = \begin{pmatrix} f \\ g \\ k \end{pmatrix}.$$

From the first equation $(2\gamma_1 u(x) - \lambda(\gamma_1 u(x) - \alpha v(x) + \delta u(x))) = f(x)$ we obtain

$$u(x) = \frac{\alpha v(x)}{\gamma_1(1 - 2/\lambda) + \delta} - \tilde{f}(x), \quad (3.3.1)$$

for a suitable function \tilde{f} , where the denominator does not vanish since $\lambda > \tilde{\lambda}$. From the second equation, we obtain

$$cv'(x) = \left(-(\gamma_2 + \alpha) + \frac{\alpha\delta}{\gamma_1(1 - 2/\lambda) + \delta} + \frac{2\gamma_2}{\lambda} \right) v(x) + \tilde{g}(x) \quad \text{and} \quad cv(0) = \rho b,$$

for a suitable function \tilde{g} and setting $z = 1 - 2/\lambda$, it can be written as

$$cv'(x) = - \left(\frac{\alpha\gamma_1 z}{\gamma_1 z + \delta} + z\gamma_2 \right) v(x) + \tilde{g}(x) \quad \text{and} \quad cv(0) = \rho b. \quad (3.3.2)$$

Note that z takes values in the interval $(-\delta/\gamma_1, 1]$ which always contains the value 0. The solution of equation (3.3.2) is given by

$$v(x) = \frac{\rho b}{c} e^{-\left(\frac{\alpha\gamma_1 z}{\gamma_1 z + \delta} + z\gamma_2\right)\frac{x}{c}} + \frac{1}{c} \int_0^x e^{-\left(\frac{\alpha\gamma_1 z}{\gamma_1 z + \delta} + z\gamma_2\right)\frac{x-y}{c}} \tilde{g}(y) dy, \quad (3.3.3)$$

Finally, using the last component we obtain $\left(-\rho e^{-\left(\frac{\alpha\gamma_1 z}{\gamma_1 z + \delta} + z\gamma_2\right)\frac{l}{c}} + \rho + \mu\right) b = \tilde{k}$ for a suitable number \tilde{k} , so that, a generic (f, g, k) has a unique pre-image if and only if

$$F(z) := \frac{\rho}{\rho + \mu} e^{-\left(\frac{\alpha\gamma_1 z}{\gamma_1 z + \delta} + z\gamma_2\right)\frac{l}{c}} \neq 1 .$$

Since the function $F(z)$, defined for $z \in (-\delta/\gamma_1, 1]$, decreases, tends to infinity as $z \downarrow -\frac{\delta}{\gamma_1}$ and fulfils $F(0) = \frac{\rho}{\rho + \mu} \leq 1$, the existence of a unique $z^* \in (-\frac{\delta}{\gamma_1}, 0]$ such that $F(z^*) = 1$ is guaranteed. Moreover, $F(z^*) = 1$ is transformed into $\left(\frac{\alpha\gamma_1 z^*}{\gamma_1 z^* + \delta} + z^*\gamma_2\right) = \frac{c}{l} \ln \frac{\rho}{\rho + \mu} =: A \leq 0$ and thus

$$z^* = \frac{-(\alpha\gamma_1 + \delta\gamma_2 - \gamma_1 A) + \sqrt{(\alpha\gamma_1 + \delta\gamma_2 - \gamma_1 A)^2 + 4\gamma_1\gamma_2\delta A}}{2\gamma_1\gamma_2} . \quad (3.3.4)$$

So, $\lambda = 2/(1 - z^*) > \tilde{\lambda}$ is the largest real spectral value of BM^{-1} , and then it is the spectral radius \mathcal{R} . Actually, it is an eigenvalue with associated eigenfunction:

$$v(x) = b \frac{\rho}{c} \exp \left\{ - \left(\frac{\alpha\gamma_1 z^*}{\gamma_1 z^* + \delta} + z^*\gamma_2 \right) \frac{x}{c} \right\} ,$$

$$u(x) = \frac{\alpha}{\gamma_1 z^* + \delta} v(x) , \quad \text{and} \quad b \neq 0 .$$

In summary, the basic reproduction number for the gut microbiota model (3.1.1) is explicitly given by

$$\mathcal{R} = \frac{2}{1 - z^*} \quad (3.3.5)$$

with $z^* \leq 0$ defined in (3.3.4). As expected, it is not bigger than 2.

3.4 Alternative generational approach of the model

This section is as the previous one with the difference that we depart from a different definition of birth event. Here we consider that the offspring of a mother cell originally in the external media are all the bacteria that leave the intestine and descend from her. Somehow one can think of the mother cell as an extended organism composed by all its clones while in the intestine. When each of these clones leaves the host it becomes a new individual, in fact it becomes a daughter of the mother cell. Although this interpretation is certainly strange and artificial, it leads to an alternative reproduction number closely related to the biology of the problem.

The birth part B and the transition part M in (3.1.1) assuming that births occur at the moment that bacteria leave the intestine is simply

$$B \begin{pmatrix} u \\ v \\ b \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ cv(l) \end{pmatrix}, \quad M \begin{pmatrix} u \\ v \\ b \end{pmatrix} = \begin{pmatrix} -\gamma_1 u - \alpha v + \delta u \\ cv' - \gamma_2 v + \alpha v - \delta u \\ \rho b + \mu b \end{pmatrix},$$

where we recall that δ_l is the evaluation operator at the point $x = l$. As in the previous section, we consider M as a closed linear operator on the Banach lattice $X = L^1(0, l) \times L^1(0, l) \times \mathbb{R}$ with domain $D = L^1(0, l) \times \{(v, b) \in W^{1,1}(0, l) \times \mathbb{R} : cv(0) = \rho b\}$.

Since now we are dealing with a special birth definition, some individuals may be produced in the transition part. This invalidates the formula given in (3.2.3) when the spectral bound of the semigroup generated by $-M$ is positive. In fact, this is the case if $\gamma_1 \geq \delta$, which means that the attached bacteria grow faster than they detach. In terms of the concepts introduced at the beginning of this section, this implies that a part of the mother (some of its clones) is attached forever and never leaves the intestine, so that it is immortal and produces infinitely many daughters. Thus the reproduction number in this case is infinite. If $\gamma_1 < \delta$, then the spectral bound of $-M$ is negative and the next-generation operator becomes

$$G_1 = BM^{-1} = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & c\delta_l & 0 \end{pmatrix} \begin{pmatrix} -\gamma_1 + \delta & -\alpha & 0 \\ -\delta & c\partial_x - \gamma_2 + \alpha & 0 \\ 0 & 0 & \rho + \mu \end{pmatrix}^{-1}.$$

Clearly, due to the birth part B , the operator G_1 can only have eigenvectors which are multiples of $(0, 0, 1)$. By performing a calculation similar to the one in the previous section, we obtain that the eigenvalue associated to $(0, 0, 1)$ is $\frac{\rho}{\rho + \mu} e^{\left(\frac{\alpha\gamma_1}{\delta - \gamma_1} + \gamma_2\right)\frac{l}{c}}$. So, the alternative reproduction number obtained with the birth events detailed above is given by

$$\tilde{\mathcal{R}} = \frac{\rho}{\rho + \mu} e^{\left(\frac{\alpha\gamma_1}{\delta - \gamma_1} + \gamma_2\right)\frac{l}{c}} \quad (3.4.1)$$

if $\gamma_1 < \delta$ and $\tilde{\mathcal{R}} = \infty$ if $\gamma_1 \geq \delta$.

Finally, we can check that $\mathcal{R} > 1$ if and only if $\tilde{\mathcal{R}} > 1$ (and the same respectively when $\mathcal{R} = 1$ and $\mathcal{R} < 1$). Indeed, recall that $\mathcal{R} = 2/(1 - z^*)$ where z^* is the only solution of

$$F(z) = \frac{\rho}{\rho + \mu} e^{-\left(\frac{\alpha\gamma_1 z}{\gamma_1 z + \delta} + z\gamma_2\right)\frac{l}{c}} = 1,$$

within the interval $(-\delta/\gamma_1, 0)$ (see section 3.3). Therefore, if $\gamma_1 \geq \delta$ (so that $\tilde{\mathcal{R}} = \infty > 1$), then necessarily $z^* \in (-1, 0)$ which implies $\mathcal{R} > 1$. Otherwise, i.e. if $\gamma_1 < \delta$, then $z^* \in (-1, 0)$ if and only if $F(-1) > 1$ (recall that $F(z)$ is decreasing). Since $F(-1)$ is precisely $\tilde{\mathcal{R}}$ when $\gamma_1 < \delta$, the previous equivalence implies that $\mathcal{R} > 1$ if and only if $\tilde{\mathcal{R}} > 1$. Analogously, one can prove that $\mathcal{R} < 1$ if and only if $\tilde{\mathcal{R}} = F(-1) < 1$.

3.5 Optimal reproduction number

So far we have obtained two explicit expressions of the basic reproduction number for the gut microbiota model, coming from two interpretations of what a birth event is for such a population. Namely, the standard one

$$\mathcal{R} = \frac{2}{1 - z^*}$$

with z^* the non-positive solution of the quadratic equation $\left(\frac{\alpha\gamma_1 z^*}{\gamma_1 z^* + \delta} + z^* \gamma_2\right) = A$ with $A = \frac{c}{l} \ln \frac{\rho}{\rho + \mu}$, and the alternative one

$$\tilde{\mathcal{R}} = \frac{\rho}{\rho + \mu} e^{\left(\frac{\alpha\gamma_1}{\delta - \gamma_1} + \gamma_2\right) \frac{l}{c}}.$$

The parameters of the model can be classified into two groups. Increasing each parameter in the first group enhances the probability of infection (ρ), the proliferation (γ_1 and γ_2) and the permanence time of the bacteria inside the intestine (l and α), respectively, whereas increasing each parameter in the second group enhances the exterior mortality (μ) and the expulsion rate of bacteria from the intestine (δ and c), respectively. Note that an increase of the environmental bacteria mortality reduces the reinfection probability and that an increase of the bacteria expulsion rate reduces the average time of permanence within the host. This means that both reproduction numbers, \mathcal{R} and $\tilde{\mathcal{R}}$, are increasing in $\rho, \gamma_1, \gamma_2, \alpha, l$ and decreasing in μ, δ, c . Therefore, in absence of trade-offs between ecological parameters of the model, a competition between types of bacteria would evolve to ever-increasing or ever-decreasing values of any single parameter of the model. However, if there exists some trade-off between two parameters one would expect to find a type of bacteria maximizing the basic reproduction number and therefore being a candidate to persist among the other types. See e.g. the papers [62, 70] on the evolution of virulence in epidemic models. Since we have taken two different approaches, one question arises here: assuming the same trade-off function, would standard and alternative reproduction numbers maximize at the same point?

To answer the question and in order to illustrate the richness of the model we have considered, on the one hand, a trade-off between detachment rate and division rate of attached bacteria: $\delta(\gamma_1)$ as an increasing function, and on the other hand, a trade-off between attachment rate and division rate of free bacteria: $\alpha(\gamma_2)$ as a decreasing function. The first situation reflects the feasible fact that, during mitosis, attached bacteria lose adherence to the epithelium. The second situation assumes that free bacteria with high division rates tend to be less sticky, possibly because adhesion molecules are not synthesized.

Let us study which value of γ_1 maximizes \mathcal{R} and $\tilde{\mathcal{R}}$ under the assumption that δ increases with γ_1 . To this end we consider

$$\mathcal{R}(\gamma_1) = \frac{2}{1 - z^*(\gamma_1)} \quad \text{and} \quad \tilde{\mathcal{R}}(\gamma_1) = \frac{\rho}{\rho + \mu} e^{\left(\frac{\alpha\gamma_1}{\delta(\gamma_1) - \gamma_1} + \gamma_2\right) \frac{l}{c}},$$

with $z^*(\gamma_1)$ satisfying $\left(\frac{\alpha\gamma_1 z^*(\gamma_1)}{\gamma_1 z^*(\gamma_1) + \delta(\gamma_1)} + z^*(\gamma_1) \gamma_2\right) = A$. The critical points of $z^*(\gamma_1)$ are given implicitly as the solutions of

$$\frac{d}{d\gamma_1} \left(\frac{\alpha\gamma_1 z^*(\gamma_1)}{\gamma_1 z^*(\gamma_1) + \delta(\gamma_1)} + z^*(\gamma_1) \gamma_2 \right) = 0,$$

which implies, using $\frac{d}{d\gamma_1} z^*(\gamma_1) = 0$, that γ_1 is a critical point of $z^*(\gamma_1)$ if and only if

$$\frac{d}{d\gamma_1} \frac{\delta(\gamma_1)}{\gamma_1} = 0. \tag{3.5.1}$$

Since \mathcal{R} is increasing with z^* , see (3.3.5), the above equation also gives a characterization of the critical points of $\mathcal{R}(\gamma_1)$. On the other hand, the critical points of $\tilde{\mathcal{R}}(\gamma_1)$ satisfy

$$\frac{d}{d\gamma_1} \left(\frac{\rho}{\rho + \mu} e^{\left(\frac{\alpha\gamma_1}{\delta(\gamma_1) - \gamma_1} + \gamma_2\right) \frac{1}{c}} \right) = 0,$$

which reduce precisely to condition (3.5.1). Thus, the critical points of $\mathcal{R}(\gamma_1)$ coincide with the critical points of $\tilde{\mathcal{R}}(\gamma_1)$, and it is the case that γ_1 is a local maximum of $\mathcal{R}(\gamma_1)$ if and only if it is a local maximum of $\tilde{\mathcal{R}}(\gamma_1)$ (see Figure 3.1, left).

Interestingly, the previous equivalence does not hold if, instead of γ_1 , we analyse the effects of γ_2 in \mathcal{R} and $\tilde{\mathcal{R}}$. In this case we assume that α decreases with γ_2 , so that \mathcal{R} and $\tilde{\mathcal{R}}$ can be written as

$$\mathcal{R}(\gamma_2) = \frac{2}{1 - z^*(\gamma_2)} \quad \text{and} \quad \tilde{\mathcal{R}}(\gamma_2) = \frac{\rho}{\rho + \mu} e^{\left(\frac{\alpha(\gamma_2)\gamma_1}{\delta - \gamma_1} + \gamma_2\right) \frac{1}{c}},$$

with $z^*(\gamma_2)$ satisfying $\left(\frac{\alpha(\gamma_2)\gamma_1 z^*(\gamma_2)}{\gamma_1 z^*(\gamma_2) + \delta} + z^*(\gamma_2)\gamma_2\right) = A$. As we did before, the critical points of $z^*(\gamma_2)$, which coincide with the critical points of $\mathcal{R}(\gamma_2)$, are given as the solutions of

$$\frac{d}{d\gamma_2} \left(\frac{\alpha(\gamma_2)\gamma_1 z^*(\gamma_2)}{\gamma_1 z^*(\gamma_2) + \delta} + z^*(\gamma_2)\gamma_2 \right) = 0,$$

which implies, using $\frac{d}{d\gamma_2} z^*(\gamma_2) = 0$, that

$$\gamma_1 \alpha'(\gamma_2) + \gamma_1 z^*(\gamma_2) + \delta = 0. \quad (3.5.2)$$

Alternatively, the critical points of $\tilde{\mathcal{R}}(\gamma_2)$ are given by

$$\frac{d}{d\gamma_2} \left(\frac{\rho}{\rho + \mu} e^{\left(\frac{\alpha(\gamma_2)\gamma_1}{\delta - \gamma_1} + \gamma_2\right) \frac{1}{c}} \right) = 0,$$

or equivalently

$$\gamma_1 \alpha'(\gamma_2) - \gamma_1 + \delta = 0,$$

which is not the same as condition (3.5.2) unless $z^*(\gamma_2) = -1$, but this is not true in general. Thus, the local maxima of $\mathcal{R}(\gamma_2)$ are different to the local maxima of $\tilde{\mathcal{R}}(\gamma_2)$ (see Figure 3.1, right).

In addition, one may wonder which optimal division rate, if any, is selected by evolutionary changes. See e.g. the adaptive dynamics framework [40, 70]. We want to point out that, although the trade-off approach can not assess which is the evolutionary outcome [24], at least it can give some sound clues on evolutionary issues of the ecological problem. For instance, in the second trade-off considered here, where the optimal division rate is different for the standard and the alternative threshold, we can guess that in most cases, evolution does not lead to the maximization of the basic reproduction number since it depends on the interpretation of what a birth event is in this case.

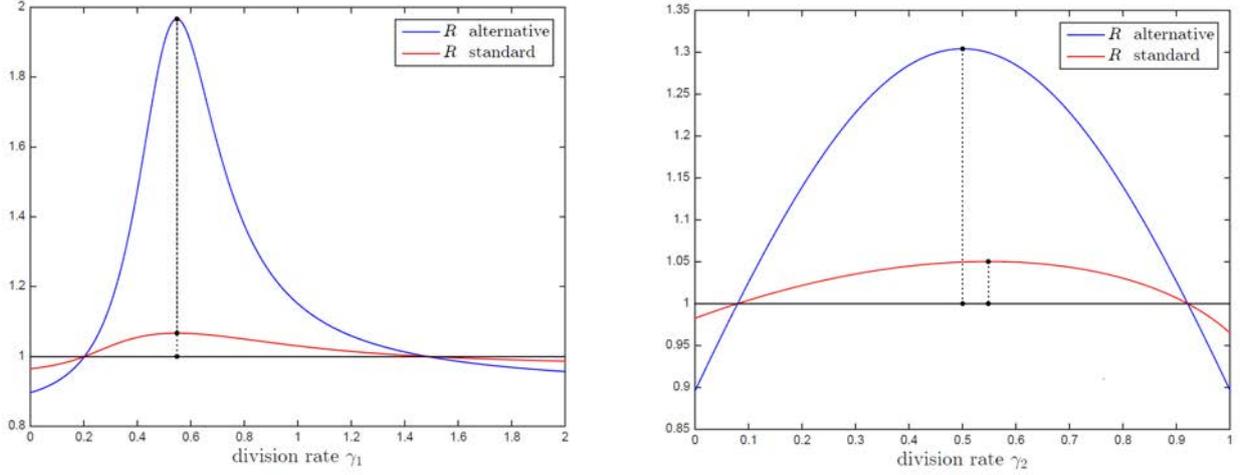


Figure 3.1: Standard (\mathcal{R}) and alternative ($\tilde{\mathcal{R}}$) reproduction numbers of system (3.1.1). In the left panel a trade-off is imposed between the growth rate of attached bacteria (γ_1) and their detachment rate (δ) through the function $\delta(\gamma_1) = 0.3 + \gamma_1^2$. The other parameters satisfy $\mu/\rho = 4$, $l/c = 1.5$, $\gamma_2 = 1$ and $\alpha = 0.05$. In the right panel a trade-off is imposed between the growth rate of luminal bacteria (γ_2) and their attachment rate (α) through the function $\alpha(\gamma_2) = 1 - \gamma_2^2$. The other parameters satisfy $\mu/\rho = 4$, $l/c = 1.5$, $\gamma_1 = 0.5$ and $\delta = 1$.

3.6 Suggestions for an experimental computation of $\tilde{\mathcal{R}}$

In this section we determine the alternative reproduction number $\tilde{\mathcal{R}}$ from a biological perspective instead of applying the systematic generational framework as in the previous section. Beyond the mathematical relevance that the methodology presented below can have by itself, it also motivates experimental procedures to obtain $\tilde{\mathcal{R}}$ empirically in the field. We follow two different strategies that lead to the same result. From our point of view the redundancy in the results is outweighed by the biological details they provide separately. Specifically, we introduce two additional systems which are slight modifications of the original gut microbiota model. In the first modified system we assume that the bacteria leaving the intestine are not allowed to reinfect the host any more, whereas in the second one, we assume that the bacteria leaving the intestine are also removed from the system but there is an extra supply of bacteria to the external medium.

3.6.1 Following one infection event

Let us recall that $\tilde{\mathcal{R}}$ corresponds to the expected number of bacteria that leave the intestine and descend from a bacterium originally in the external media. It is important to point out that the offspring of the mother cell are the microbes that return to the environment for the first time, so that $\tilde{\mathcal{R}}$ only counts the bacteria leaving the intestine in the first cycle of infection

and not the descenders of environmental bacteria that descend from the founder mother.

In order to compute this quantity first notice that the factor $\rho/(\rho + \mu)$ gives the probability that the founder bacterium eventually enters the intestine. Hence, $\tilde{\mathcal{R}}$ should be this probability times the expected total number of bacteria leaving the intestine for the first time given that there is a single one at the beginning of the intestine. The latter can be computed solving the following initial value problem with an initial condition that reduces to a Dirac measure centred at the point $x = 0$:

$$\begin{cases} \partial_t u(x, t) = \gamma_1 u(x, t) + \alpha v(x, t) - \delta u(x, t) \\ \partial_t v(x, t) = -c \partial_x v(x, t) + \gamma_2 v(x, t) - \alpha v(x, t) + \delta u(x, t) \\ b'(t) = cv(l, t) \\ cv(0, t) = 0 \\ v(x, 0) = \delta_0(x), u(x, 0) \equiv 0, b(0) = 0 \end{cases} \quad (3.6.1)$$

Indeed, we then have that

$$\tilde{\mathcal{R}} = \frac{\rho}{\rho + \mu} \lim_{t \rightarrow \infty} b(t) = \frac{\rho}{\rho + \mu} \int_0^\infty b'(t) dt = \frac{\rho}{\rho + \mu} \int_0^\infty cv(l, t) dt. \quad (3.6.2)$$

Notice that here the equation for $b(t)$ is uncoupled and can be suppressed without affecting the argument.

Thanks to the paper by Barbara Boldin [11], we have an explicit expression for the solution of the previous problem. In order to apply the result in [11] we make a change of variables which transforms (3.6.1), without the equation for $b(t)$, to exactly the system that is considered in that paper. Defining $\xi = x/l$, $\tau = ct/l$ and

$$\tilde{u}(\xi, \tau) = u\left(l\xi, \frac{l\tau}{c}\right), \quad \tilde{v}(\xi, \tau) = v\left(l\xi, \frac{l\tau}{c}\right),$$

(3.6.1) becomes to

$$\begin{cases} \tilde{u}_\tau(\xi, \tau) = \frac{l(\gamma_1 - \delta)}{c} \tilde{u}(\xi, \tau) + \frac{l\alpha}{c} \tilde{v}(\xi, \tau) \\ \tilde{v}_\tau(\xi, \tau) = -\tilde{v}_\xi(\xi, \tau) + \frac{l\delta}{c} \tilde{u}(\xi, \tau) + \frac{l(\gamma_2 - \alpha)}{c} \tilde{v}(\xi, \tau) \\ \tilde{v}(0, \tau) = 0 \\ \tilde{v}(\xi, 0) = \delta_0(l\xi) = \frac{1}{l} \delta_0(\xi) \end{cases}$$

or equivalently

$$\begin{cases} \tilde{u}_\tau(\xi, \tau) = \alpha_{11} \tilde{u}(\xi, \tau) + \alpha_{12} \tilde{v}(\xi, \tau) \\ \tilde{v}_\tau(\xi, \tau) = -\tilde{v}_\xi(\xi, \tau) + \alpha_{21} \tilde{u}(\xi, \tau) + \alpha_{22} \tilde{v}(\xi, \tau) \\ \tilde{v}(0, \tau) = \frac{1}{l} \delta_0(\tau) \\ \tilde{v}(\xi, 0) = 0 \end{cases}.$$

with $\alpha_{11} = l(\gamma_1 - \delta)/c$, $\alpha_{12} = l\alpha/c$, $\alpha_{21} = l\delta/c$ and $\alpha_{22} = l(\gamma_2 - \alpha)/c$. Therefore, from (3.6.2) we have that

$$\tilde{\mathcal{R}} = \frac{\rho}{\rho + \mu} \int_0^\infty c\tilde{v}\left(1, \frac{tc}{l}\right) dt = \frac{l\rho}{\rho + \mu} \int_0^\infty \tilde{v}(1, \tau) d\tau.$$

In [11] an explicit solution of the system is obtained. In particular it turns out that,

$$\tilde{v}(\xi, \tau) = \frac{e^{\alpha_{22}\xi}}{l} \delta_0(\tau - \xi) + \frac{e^{(\alpha_{22}-\alpha_{11})\xi}}{l} e^{\alpha_{11}\tau} \sqrt{\frac{\alpha_{12}\alpha_{21}\xi}{\tau - \xi}} I_1 \left(2\sqrt{\alpha_{12}\alpha_{21}\xi(\tau - \xi)} \right) H(\tau - \xi) \quad (3.6.3)$$

where I_1 is one of the so-called modified Bessel functions of the first kind and H is the Heaviside function. So we obtain

$$\int_0^\infty \tilde{v}(1, \tau) d\tau = \frac{1}{l} e^{\alpha_{22}} + \frac{1}{l} e^{(\alpha_{22}-\alpha_{11})} \int_1^\infty e^{\alpha_{11}\tau} \sqrt{\frac{\alpha_{12}\alpha_{21}}{\tau - 1}} I_1 \left(2\sqrt{\alpha_{12}\alpha_{21}(\tau - 1)} \right) d\tau.$$

This leads to the equality

$$\tilde{\mathcal{R}} = \frac{\rho}{\rho + \mu} e^{\alpha_{22}} \left(1 + \int_1^\infty e^{\alpha_{11}(\tau-1)} \sqrt{\frac{\alpha_{12}\alpha_{21}}{\tau - 1}} I_1 \left(2\sqrt{\alpha_{12}\alpha_{21}(\tau - 1)} \right) d\tau \right). \quad (3.6.4)$$

If $\gamma_1 \geq \delta$ (i.e. if the population growth rate of the attached bacteria is larger than or equal to their detachment rate), the improper integral in the previous equation does not converge, meaning that in this case the expected total number of bacteria leaving the intestine is infinite, i.e., $\tilde{\mathcal{R}} = \infty$.

Next we compute the right hand side of (3.6.4), assuming $\gamma_1 < \delta$. The change of variables $2\sqrt{\alpha_{12}\alpha_{21}(\tau - 1)} = y$ leads to write the integral in (3.6.4) as $\int_0^\infty e^{-ay^2} I_1(y) dy$, where $a := \frac{-\alpha_{11}}{4\alpha_{12}\alpha_{21}} > 0$. For this we have, using the series expansion for the modified Bessel function and the Lebesgue's monotone convergence theorem,

$$\int_0^\infty e^{-ay^2} I_1(y) dy = \sum_{k=0}^\infty \frac{\int_0^\infty y^{2k+1} e^{-ay^2} dy}{2^{2k+1} k! (k+1)!} = \sum_{k=0}^\infty \frac{1/(4a)^{k+1}}{(k+1)!} = e^{\frac{1}{4a}} - 1 \quad (3.6.5)$$

So, the right hand side of (3.6.4) reduces to

$$\frac{\rho}{\rho + \mu} e^{\alpha_{22}} e^{\frac{1}{4a}} = \frac{\rho}{\rho + \mu} e^{\frac{\alpha_{11}\alpha_{22} - \alpha_{12}\alpha_{21}}{\alpha_{11}}} = \frac{\rho}{\rho + \mu} e^{\left(\frac{\alpha\gamma_1}{\delta - \gamma_1} + \gamma_2\right) \frac{l}{c}}, \quad (3.6.6)$$

which means that, if $\gamma_1 < \delta$, then $\tilde{\mathcal{R}} = \frac{\rho}{\rho + \mu} e^{\left(\frac{\alpha\gamma_1}{\delta - \gamma_1} + \gamma_2\right) \frac{l}{c}}$.

Notice, on the one hand, that the initial condition in system (3.6.1) reflects an experimental procedure consisting in giving an initial bacterial dose to the animal under study. On the other hand, the bacteria that leave the intestine of such an animal corresponds to the variable $b(t)$ in (3.6.1) as t goes to infinity. Therefore by computing the ratio between the recollected bacteria and the given dose the field researcher could obtain the amount of bacteria released to the environment per bacteria initially inoculated to the animal. If in addition one knows the probability that an external bacterium is ingested by the animal, then the reproduction number $\tilde{\mathcal{R}}$ can be determined in this way.

3.6.2 Bacteria released per bacteria supplied

Instead of giving a single dose to the animal and counting all the bacteria that it releases, one can also supply bacteria to the environment at a constant rate and compute the ratio between the released bacteria and the supplied ones. By this means the probability that a bacterium is ingested by the host before dying is implicitly incorporated into the experimental system. To model this situation, we modify System (3.1.1) in such a way that the bacteria leaving the intestine are lost (i.e., they do not return to the environment), while we assume a constant influx of bacteria to the external medium (the supplied bacteria), denoted by the constant β . Thus,

$$\begin{cases} \partial_t u(x, t) = \gamma_1 u(x, t) + \alpha v(x, t) - \delta u(x, t) \\ \partial_t v(x, t) = -c \partial_x v(x, t) + \gamma_2 v(x, t) - \alpha v(x, t) + \delta u(x, t) \\ b'(t) = -\rho b(t) - \mu b(t) + \beta \\ cv(0, t) = \rho b(t) \end{cases} \quad (3.6.7)$$

Assuming that initially there are no bacteria in the system, we postulate that the expected number of bacteria that leave the intestine per bacterium supplied to the external medium equals $\tilde{\mathcal{R}}$. Specifically, we are going to show that

$$\tilde{\mathcal{R}} = \lim_{t \uparrow \infty} \frac{b_s(t)}{b_e(t)}, \quad (3.6.8)$$

where $b_s(t)$ is the expected number of bacteria that leave the intestine during the time interval $[0, t]$ and $b_e(t)$ is the number of bacteria supplied during the same time. In fact, one has

$$b_s(t) = \int_0^t cv(l, s) ds \quad \text{and} \quad b_e(t) = \beta t.$$

It can be checked that, if $\gamma_1 > \delta$, then the solutions of system (3.6.7) diverge exponentially fast at a rate $\gamma_1 - \delta > 0$. In particular, for large values of t , $b_s(t)$ is of the order $e^{t(\gamma_1 - \delta)}$. Thus, the limit in (3.6.8) becomes infinite and the equality $\tilde{\mathcal{R}} = \infty$ holds as desired. This is also true when $\gamma_1 = \delta$, but in this case $b_s(t)$ is of the order t^2 .

Alternatively, if $\gamma_1 < \delta$, the solutions of system (3.6.7) tend to the steady state $(\hat{u}, \hat{v}, \hat{b})$ given by the solution of

$$\begin{cases} u(x) = \alpha v(x) / (\delta - \gamma_1) \\ cv_x(x) = \gamma_2 v(x) - \alpha v(x) + \delta u(x) \\ b = \beta / (\rho + \mu) \\ cv(0) = \rho b \end{cases}, \quad (3.6.9)$$

which in particular satisfies the formula

$$c\hat{v}(x) = \frac{\beta\rho}{\rho + \mu} e^{\left(\frac{\alpha\gamma_1}{\delta - \gamma_1} + \gamma_2\right)\frac{x}{c}}.$$

In fact, one can even say that the component v of the solutions converge to \hat{v} not only in the L^1 norm but in the supremum norm. A way of showing this is as follows. Notice that if (u, v, b) is a solution of system (3.6.7), then $(u - \hat{u}, v - \hat{v}, b - \hat{b})$ solves (3.6.7) with $\beta = 0$. The right hand side of this last system generates a positive strongly continuous semigroup $S(t)$ on $L^1(0, l) \times L^1(0, l) \times \mathbb{R}$ with spectral bound $\max(\gamma_1 - \delta, -\rho - \mu) < 0$, and hence with negative growth bound. Since the initial condition for (u, v, b) is the origin, the initial condition for $(u - \hat{u}, v - \hat{v}, b - \hat{b})$ is $-(\hat{u}, \hat{v}, \hat{b})$ which belongs to the domain D of the generator. The semigroup $S(t)$ restricted to the Banach space defined by the domain D endowed with the graph norm (which here is equivalent to the $W^{1,1}$ -norm) is also a strongly continuous semigroup with the same growth bound as $S(t)$ (see [34], Chap. II.2.c). By the Sobolev embedding theorem ($W^{1,1}(0, l)$ continuously embedded in $C^0(0, l)$), it turns out that $(u - \hat{u}, v - \hat{v}, b - \hat{b})$ tends to 0 exponentially in the supremum norm.

Therefore, we can write,

$$\lim_{t \uparrow \infty} \frac{b_s(t)}{b_\varepsilon(t)} = \lim_{t \uparrow \infty} \frac{\int_0^t cv(l, s) - c\hat{v}(l)ds}{\beta t} + \lim_{t \uparrow \infty} \frac{\int_0^t c\hat{v}(l)ds}{\beta t} \stackrel{*}{=} \frac{c\hat{v}(l)}{\beta} = \frac{\rho}{\rho + \mu} e^{\left(\frac{\alpha\gamma_1}{\delta - \gamma_1} + \gamma_2\right)\frac{l}{c}} = \tilde{\mathcal{R}},$$

which results in equation (3.6.8). Notice that in $\stackrel{*}{=}$ we have used for the first limit that, if $f(s) \in L^1(0, \infty)$ and $f(s) \rightarrow 0$ uniformly as s tends to infinity (i.e., if f tends to 0 in the supremum norm), then

$$\int_0^t f(s) \in o(t) \quad \text{when } t \uparrow \infty.$$

Indeed, given $\varepsilon > 0$, there exists T_ε such that if $s > T_\varepsilon$ then $|f(s)| \leq \varepsilon$. Hence,

$$\lim_{t \uparrow \infty} \left| \frac{1}{t} \int_0^t f(s) ds \right| \leq \lim_{t \uparrow \infty} \frac{1}{t} \int_0^{T_\varepsilon} |f(s)| ds + \lim_{t \uparrow \infty} \frac{1}{t} \int_{T_\varepsilon}^t \varepsilon ds = \lim_{t \uparrow \infty} \frac{\varepsilon(t - T_\varepsilon)}{t} = \varepsilon,$$

which implies $\lim_{t \uparrow \infty} \frac{1}{t} \int_0^t f(s) ds = 0$.

3.7 Discussion

The reproduction number was rigorously introduced in a 1925 paper by Dublin and Lotka [32] (see also [43] and references therein). They realised that the ratio of total births between successive generations was easy to obtain from empirical data, namely the age tables of fecundity and mortality, and that it could be used to infer changes in the growth rate of a certain population. Among the reasons that made this possible was the fact that they worked with an age structured model, in which all individuals were assumed to be born at the same state, i.e., at age zero. If this is not the case, giving the reproduction number in terms of measurable parameters could be unworkable. However, other meaningful quantities may exist with a natural derivation from the biological system. The work presented here is a clear example of that in a model of continuously structured populations, in the line of the simpler examples given in [25], see also e.g. [16]. Indeed, bacteria can divide (i.e. be born) along the whole

intestine, so that there is an infinite number of states-at-birth. This is why the standard reproduction number \mathcal{R} given by (3.3.5) and (3.3.4) has such a complicate expression. If instead one focuses on the environmental bacteria and considers the intestine as a kind of biological reactor, then the states-at-birth reduce dramatically to just one: all bacteria are “born” in the environment as they leave the intestine. Notice that strictly speaking no bacteria is born in the external media, since they divide only within the intestine. However, by reinterpreting the life history of bacteria in such a way, useful biological quantities pop up. Indeed, the value $\tilde{\mathcal{R}}$ defined in (3.4.1) has a simpler expression than \mathcal{R} and, more importantly, it can be empirically obtained by conducting the experimental designs represented by the systems introduced in section 3.6. In many other occasions the researcher may gain a better comprehension of the system by identifying suitable artificial generations characterized by two properties. On the one hand, individuals recently generated must present small differences, i.e., they must share similar physiological and physical conditions. On the other hand, the generation events have to be accessible by the observer. Then, the ratio of total individuals produced between such generations, which is not necessarily the standard reproduction number but a generalization of it, could give clearer information of the population dynamics.

Conclusions

The problem treated in this thesis was originally motivated by some experiments performed by Montserrat Llagostera and her team from the Universitat Autònoma de Barcelona. Among other research lines, they design and evaluate different phage therapies to treat *Salmonella* in chicks [22, 21] and, in this sense, they are specially interested in determining how *Salmonella* propagates and persists in a given population and how bacteriophages could affect these processes. Although several empirical studies exist about important dynamical properties of both viruses and bacteria, most of them are performed in vitro, so that it is unclear to what extent they can be used to explain what happens in vivo: many different microorganisms and organic substances found in the guts of animals could dramatically modify some of the rates observed in vitro. We realised that the biological information was too limited to write a quantitative model in accordance with Llagostera's experiments, hence we decided to focus on more conceptual models that could improve our understanding of the gut ecosystem. To this end, the models presented in [7] and [11] have been, in some aspects, generalised into a dynamical system that links the external environment with the gut environment, so that questions about the interrelation between them could be addressed.

The class of models proposed in this thesis can be used to study dynamical properties in a precise way through their semilinear formulation. This fact has been illustrated in the second chapter, in which issues such as identifying stationary points and determining their stability in terms of certain parameters have been successfully addressed for a specific example. In addition, the biological meaning of the model makes possible to study the dynamics from a generational point of view, which is useful in cases where data are acquired discretely according to certain intrinsic rhythm of the individuals. For instance, in the third chapter we have computed the expected number of bacterial cells that leave the intestine after a primary infection, a quantity that seems easier to obtain experimentally than the mean division rate of bacteria in the system.

Arguably, the example we have examined in this work is exceptional in the sense that it is possible to perform many computations explicitly. Notice that neither the size of the host population nor its heterogeneity makes the computations more difficult. This is because, on the one hand, what happens inside each host is independent of what happens in the guts of the other hosts, and, on the other hand, although the pool of environmental bacteria depends dynamically on all the hosts, its complexity as a variable is always the same (a scalar quantity if only one microbial type is modelled, a two dimensional vector if two microbial types are modelled, etc). However, if instead of increasing the number of hosts we increase the number of bacterial strains, then the analysis of the system becomes much more complex and the results

necessarily rely on numerical simulations.

I would like to finish this thesis by mentioning a couple of open questions we faced, unsuccessfully, during the course of this research. The first question is about Biology, and it focuses on clarifying to what extent the microbiome can affect the mating preferences of individuals and, ultimately, participate in the evolution of new species. As mentioned in the introduction, this idea was proposed some years ago as a possible mechanism of speciation [13, 71, 74]. Here, by speciation we refer to the process by which a population composed by individuals of a single species splits into two or more reproductive isolated sub-populations. Despite the broad agreement in the mechanisms that shape the evolution of a single species (mutations, genetic drift, natural selection and gene flow), understanding the origin of new species is still a controversial topic in the field of evolutionary biology [14]. There are multiple ways by which reproductive barriers can develop, but it is unclear whether some of them have a major impact than others. In fact, an old debate exists about the importance of geographical barriers. Whereas some scientists defend that geographic isolation of populations is a fundamental step in the course of a speciation event, others argue that strong reproductive barriers may arise as a consequence of several ecological mechanisms taking place in a single habitat. Could the microbial community act as one of these mechanisms? Analysing this question either empirically or theoretically is challenging, although it may be worth doing it if we take into account the recent studies showing how microorganisms can affect the behaviour of their hosts [36, 1].

The second question is about Mathematics. Recall that in the first chapter we proved that a certain semigroup was eventually norm continuous. This property implied the Spectral Mapping Theorem, which essentially gives a one to one relation between the spectrum of the semigroup evaluated at t and the spectrum of its generator. The proof, however, relied on the particular structure of the system we considered and, from our point of view, this was not optimal. By studying alternative ways to treat the problem, we realised that the kind of semigroup we were analysing was obtained by perturbing an eventually continuous semigroup by a bounded operator (in fact, the bounded operator was atypical in the sense that it was defined from the base space X to $X^{\odot T^*}$, with T being the unperturbed semigroup, but let us set aside this particularity now). A natural question at this point is if the perturbation of an eventually continuous semigroup by a bounded perturbation is also eventually norm continuous. As Nagel and Engel show in their book, this is not true in general (see Example III.1.15 in [33], in which the unperturbed semigroup is even nilpotent), although if the bounded perturbation is also compact, then the perturbed semigroup does inherit the eventual continuity of the unperturbed semigroup (see Theorem 1.2.22). Since in our case the compactness of the perturbation was not something we could assume, deducing the eventual continuity of the perturbed semigroup by means of general results seemed unfeasible. However, our final goal was not to show that the perturbed semigroup was eventually continuous, we wanted to prove the Spectral Mapping Theorem for the perturbed semigroup, which is something weaker. In this sense, we need a general result as the following.

Conjecture 1. *Let X be a Banach space. Let T be an eventually norm continuous semigroup on X generated by A . Let B be a bounded operator on X . Then the Spectral Mapping Theorem*

holds for the semigroup S generated by $A + B$, i.e.

$$\sigma(S(t)) \setminus \{0\} = e^{t\sigma(A+B)}$$

holds for all $t \geq 0$

Our attempts to prove or disprove the above conjecture were unfruitful, but since we have not found any reference to this problem in the specialised literature [33, 66], we present it here for those with more expertise. Similarly, a weaker version of the above conjecture that, if proved to be true, would also imply Theorem 1.3.6 as a corollary is the following.

Conjecture 2. *Let X be a Banach space. Let T be an eventually norm continuous semigroup on X generated by A . Let B be a bounded operator on X . Then the growth bound of the semigroup S generated by $A + B$ is equal to the spectral bound of the operator $A + B$, i.e.*

$$\omega_0(S) = s(A + B).$$

We finish, therefore, with two questions stemming from the same work and yet quite different from one another. One hardly could justify that they are related in any way. Is this strange? I doubt it. In my opinion this feature is found from time to time by those working on Mathematical Biology. A mystery from the living world turns into a mystery in the world of immutable truths. The paths diverge. Choosing is no easy job.

Appendix A

The standard semilinear formulation

The main purpose of this appendix is to introduce the theory of operator semigroups to the unfamiliar reader. To this end, the text below is based on a series of examples, definitions and results that culminate with the semilinear formulation developed by Amon Pazy [68], the framework over which this thesis builds on (through the generalisation carried out by Clement and collaborators [18, 19]). The reader interested in a more complete introduction to the theory of operator semigroups is referred to the textbooks [33], [68] and [10].

Strongly continuous semigroups

Let $(X, \|\cdot\|)$ be a Banach space (whose elements can be thought as possible states/configurations of a physical system). Let T be a family of continuous operators from X to X parametrized by $t \in [0, \infty)$, that is, for each $t \geq 0$ the operator $T(t) : X \rightarrow X$ is defined on all X and is continuous. Given a point x of X , the set $\{T(t)x, t \in [0, \infty)\}$ can be interpreted as the orbit into the future of state x : that is, the image of x by $T(t)$ is associated to the state t units of time into the future of a system originally at x . The following definition characterises the families T defining continuous orbits into the future.

Definition A.0.1. *The family T is said to be **strongly continuous** if, $\forall t \geq 0$,*

$$\lim_{h \rightarrow 0} \|T(t+h)x - T(t)x\| = 0 \quad \forall x \in X,$$

the limit being only from the right when $t = 0$.

Similarly, the following definition characterizes the families T representing deterministic dynamical systems, in the sense that the future states are determined by the current state.

Definition A.0.2. *The family T is said to be a **semigroup of operators** if*

$$\begin{aligned} T(0) &= Id, \\ T(t+s) &= T(t)T(s) \quad \forall t, s > 0. \end{aligned}$$

Notice that, by taking $x \in X$ as the current state of the system, the first condition above means that the state the system has 0 units of time into the future is nothing but x , whereas the second condition means that the state of the system $t + s$ units of time into the future, i.e. $T(t + s)x$, can be obtained by computing first the state of the system s units of time into the future, i.e. $T(s)x$, and, secondly, the state t units of time into the future starting from $T(s)x$, i.e. $T(t)T(s)x$. Now we are ready to combine the above two definitions, emphasising the fact that the operators of the family T are not necessarily linear.

Definition A.0.3. *The family T is said to be a **nonlinear strongly continuous semigroup** if T is a semigroup of operators and T is strongly continuous. The simpler term **strongly continuous semigroup** is reserved to the cases in which the operators of T are linear.*

Unless otherwise stated, now T refers to a family of linear operators. Thanks to the semigroup property, proving that a semigroup of linear operators is strongly continuous is easier than it might seem a priori. Specifically, if T is a semigroup of linear operators, then T is strongly continuous if and only if

$$\lim_{h \downarrow 0} \|T(h)x - x\| = 0 \quad \forall x \in X.$$

This is seen by computing

$$\lim_{h \downarrow 0} \|T(t+h)x - T(t)x\| = \lim_{h \downarrow 0} \|T(t)(T(h)x - x)\| \leq \lim_{h \downarrow 0} \|T(t)\| \|T(h)x - x\| = 0,$$

where $\|T(t)\|$, which denotes the operator norm of $T(t)$, is finite because $T(t)$ is a continuous operator. The limit as $h \uparrow 0$ when $t > 0$ requires the use of the Uniform Boundedness Principle to justify that the operators $T(s)$ are uniformly bounded for all $s \in [0, t]$, so that

$$\lim_{h \uparrow 0} \|T(t+h)x - T(t)x\| = \lim_{h \uparrow 0} \|T(t+h)(x - T(-h)x)\| \leq \lim_{h \uparrow 0} \|T(t-h)\| \|T(h)x - x\| = 0.$$

In fact, the Uniform Boundedness Principles can be used to prove that for each strongly continuous semigroup T , there exist constants M and ω such that

$$\|T(t)\| \leq Me^{\omega t}. \tag{A.0.1}$$

Since the trajectories of strongly continuous semigroups are continuous, it makes sense to ask if they are also differentiable so that a link between strongly continuous semigroups and differential equations can be drawn.

Definition A.0.4. *The **infinitesimal generator** (or simply **generator**) of a strongly continuous semigroup T is a linear operator from X to X with domain*

$$D(A) = \{x \in X \text{ such that the limit } \lim_{h \downarrow 0} \frac{T(h)x - x}{h} \text{ exists in } X\}$$

and images $Ax = \lim_{h \downarrow 0} \frac{T(h)x - x}{h}$.

It can be proved that the generator is a closed operator with a dense domain. This is important because it somehow implies that the generator stores much of the information of the semigroup. In fact, the name generator comes from the fact that any strongly continuous semigroup can be recovered from its generator. That is, if two strongly continuous semigroups T and S have the same generator A , then necessarily $T = S$.

From the definition above it is clear that the generator can be used to compute the right derivative of the trajectory $T(\cdot)x$ at any point t . Indeed, if $T(\cdot)x$ is differentiable at t , then its derivative, which coincides with its right derivative, satisfies

$$\lim_{h \downarrow 0} \frac{T(t+h)x - T(t)x}{h} = \lim_{h \downarrow 0} \frac{T(h)T(t)x - T(t)x}{h} = AT(t)x,$$

or in other words, the trajectory of $u := T(\cdot)x$ is a solution of the system

$$\begin{cases} u'(t) = Au(t) \\ u(0) = x \end{cases}. \quad (\text{A.0.2})$$

It can be shown that $T(\cdot)x$ is the only solution of the above system. Indeed, if $v(\cdot)$ were another solution, then for fixed $t > 0$ and $0 < s < t$,

$$\begin{aligned} \frac{d}{ds}(T(t-s)v(s)) &= \lim_{h \rightarrow 0} \frac{T(t-s-h)v(s+h) - T(t-s)v(s)}{h} = \\ &= \lim_{h \rightarrow 0} \frac{T(t-s-h)v(s+h) - T(t-s-h)v(s)}{h} + \lim_{h \rightarrow 0} \frac{T(t-s-h)v(s) - T(t-s)v(s)}{h} = \\ &= T(t-s)v'(s) - T(t-s)Av(s) = 0, \end{aligned}$$

where in the last equation we used that v is a solution of the system, so that $v'(s) = Av(s)$. Integrating from 0 to t both sides of

$$\frac{d}{ds}(T(t-s)v(s)) = 0$$

we finally conclude $v(t) = T(t)v(0) = T(t)x = u(t)$ for any $t \geq 0$.

As we pointed before, saying that $u = T(\cdot)x$ is a solution of system (A.0.2) is clear if u is differentiable for all $t \geq 0$ (which implies that $u(t) \in D(A)$ for all $t \geq 0$). Thanks to the semigroup property, u is differentiable for all t provided it is differentiable at 0, i.e. if $x \in D(A)$. In these cases we refer to u as a classic solution. If $x \notin D(A)$, then function u is said to be a generalised solution of (A.0.2). It is generalised in the sense that, for any sequence of initial conditions $\{x_n\}_{n \in \mathbb{N}} \subset D(A)$ converging to x (which exist because $D(A)$ is dense in X), the associated sequence of orbits $\{u_n\}_{n \in \mathbb{N}}$ converges to u uniformly on compact intervals (the orbit u_n is the solution of $u'_n(t) = Au_n(t)$ with $u_n(0) = x_n$).

Definition A.0.3 shows how the generator can be obtained in terms of the semigroup. However, in most applications the situation is the opposite: one knows the generator A and needs some information on the semigroup T . The methodology to accomplish this is one of the main

problems that has motivated the development of the theory of strongly continuous semigroups. The philosophy to address the problem is based on the expression

$$“T(t) = e^{At}” \tag{A.0.3}$$

which, at least formally, implies

$$\frac{d}{dt}T(t)x = \frac{d}{dt}e^{At}x = Ae^{At}x = AT(t)x.$$

In fact, equation (A.0.3) makes sense if A is a bounded operator (which is always the case if X is finite dimensional) through the series

$$e^{At} = \sum_{n=0}^{\infty} \frac{t^n A^n}{n!}. \tag{A.0.4}$$

If A is an unbounded operator the above series does not converge and other meaningful formulas for e^{At} have to be used, such as, for instance,

$$e^{At} = \lim_{n \uparrow \infty} \left(1 - \frac{t}{n}A\right)^{-n}$$

or

$$e^{At} = \lim_{h \downarrow 0} e^{\frac{T(h)-Id}{h}t}.$$

A good example to illustrate the above concepts is given by the translation semigroup. Let $C = C([0, 1], \mathbb{R})$ be the space of real continuous functions defined on $[0, 1]$, and let $\|\cdot\|$ be the supreme norm, i.e. $\|f\| = \sup\{f(a) \mid a \in [0, 1]\}$ for all $f \in C$. Let T be a semigroup of operators on C given by

$$(T(t)f)(a) = \begin{cases} 0 & a < t \\ f(a-t) & a \geq t \end{cases} \quad \forall t \geq 0,$$

with $a \in [0, 1]$. It turns out that the semigroup T is not strongly continuous. To check that it is enough to take a constant function in $[0, 1]$, for instance $f \equiv 1$, and realise that

$$\|T(h)f - f\| = \|\mathbf{1}_{[0,h]}(\cdot)\| = 1$$

so that the limit of $\|T(h)f - f\|$ as h decreases towards 0 is 1. The lack of continuity in the trajectories can be fixed by choosing those f in C whose orbit is continuous, which results in the subspace of C given by

$$C_0 = \{f \in C \mid f(0) = 0\}.$$

Finally, since formally

$$\lim_{h \downarrow 0} \frac{T(h)f - f}{h} = \lim_{h \downarrow 0} \frac{f(\cdot - h) - f(\cdot)}{h} = -f'(\cdot),$$

it follows that the generator of T on C_0 is the operator with domain

$$D(A) = \{f \in C_0 \mid f' \in C_0\}$$

and images $Af = -f'$. Notice that if f is analytic, then $T(t)f$ can be recovered from A using the exponential series:

$$(T(t)f)(a) = \sum_{n=0}^{\infty} \left(\frac{t^n A^n}{n!} f \right) (a) = \sum_{n=0}^{\infty} \frac{(-t)^n f^{(n)}(a)}{n!} = f(a - t),$$

where f is assumed to be extended into the negative values by 0, i.e. by defining $f(a) = 0$ for $a < 0$.

Lipschitz Perturbations of strongly continuous semigroups

Let $(X, \|\cdot\|)$ be a Banach space and T be a strongly continuous semigroup on X generated by A . Given a function $f : [0, \infty) \rightarrow X$, we wonder if the inhomogeneous initial value problem

$$\begin{cases} u'(t) = Au(t) + f(t) \\ u(0) = x \in X \end{cases} \quad (\text{A.0.5})$$

has any solution. Let us assume that f is integrable on bounded intervals, i.e. $f \in L^1((0, k), X)$ for all $k > 0$. If system (A.0.5) had a solution u , it would be differentiable and $u(t)$ would belong to $D(A)$ for all $t \in [0, \infty)$. In this case, for each $t > 0$ we could define the X valued function $g(s) = T(t-s)u(s)$ on $s \in [0, t]$, which would be differentiable and would satisfy

$$g'(s) = -AT(t-s)u(s) + T(t-s)u'(s) = T(t-s)f(s),$$

where in the second equality we have used $u'(s) = Au(s) + f(s)$. Then, by integrating from 0 to t both sides of the above equation, it would finally follow

$$u(t) = T(t)x + \int_0^t T(t-s)f(s)ds. \quad (\text{A.0.6})$$

Thus, we conclude that, if f is integrable, then system (A.0.5) has at most one solution, and in case it has, it is given explicitly in terms of x , T and f by the formula (A.0.6), referred as the variation of constants formula. This somehow motivates the following definition.

Definition A.0.5. *Let f be integrable on bounded intervals. Then u given by (A.0.6) is a mild solution of problem (A.0.5).*

Notice that, by definition, system (A.0.5) has always a mild solution. However, as occurred with the homogeneous equation, the concept of mild solution is more fundamental than that of an arbitrary definition. Indeed, by taking sequences $\{x_n\}_{n \in \mathbb{N}} \subset D(A)$ and $\{f_n\}_{n \in \mathbb{N}} \subset$

$C^1([0, \infty), X)$ converging to x (with the X norm) and f (with the $L^1((0, \infty), \mathbb{R})$) respectively, then u is the uniform limit (on bounded intervals) of $\{u_n\}_{n \in \mathbb{N}}$ defined as

$$u_n(t) = T(t)x_n + \int_0^t T(t-s)f_n(s)ds,$$

and, due to the regularity of f_n , each u_n is the solutions of

$$\begin{cases} u'(t) = Au(t) + f_n(t) \\ u(0) = x_n \end{cases}.$$

In other words, the mild solution u of (A.0.5) can be arbitrarily approximated by the regular solution of an initial value problem close enough to (A.0.5).

The inhomogeneous term f in the differential equation of system (A.0.5) represents an external “force”, i.e. something that modulates the dynamics independently of the current state of the system. In many situations, however, is precisely the state of the system what underlies such a modulation. In these cases the perturbation is given by a function of the state of the system, that is, instead of $f : [0, \infty) \rightarrow X$ we must take a function \mathcal{F} defined from X to X . The dynamics of a system initially at state x is then represented by the semilinear initial value problem

$$\begin{cases} u'(t) = Au(t) + \mathcal{F}(u(t)) \\ u(0) = x \end{cases}. \quad (\text{A.0.7})$$

Let us assume that \mathcal{F} is continuous, so that, if u is a solution of (A.0.7), then the composition $\mathcal{F} \circ u$ is a continuous function of time, and, consequently, it is also integrable. Thus, in this case we can interpret $\mathcal{F} \circ u$ as a given inhomogeneous term and follow the same steps as before in order to conclude that, if u is a solution of (A.0.7) defined on $[0, \hat{t}]$, then u satisfies the integral equation

$$u(t) = T(t)x + \int_0^t T(t-s)\mathcal{F}(u(s))ds \quad (\text{A.0.8})$$

for all $t \in [0, \hat{t}]$, the equation being referred as the variation of constants equation. This observation motivates the following definition.

Definition A.0.6. *Let \mathcal{F} be continuous. A continuous function $u : [0, \hat{t}] \rightarrow X$ is a mild solution of problem (A.0.7) on $[0, \hat{t}]$ if it is a solution of (A.0.8) for all $t \in [0, \hat{t}]$.*

We end this appendix by giving an important result about the mild solutions of system (A.0.7). The methodology to prove it relies on the Banach fixed-point theorem in a similar way as it is done in the theory of ordinary differential equations. One starts considering the space of continuous functions from $[0, \hat{t}]$ to X with the supreme norm, which is a Banach space, and the mapping

$$V : C([0, \hat{t}], X) \rightarrow C([0, \hat{t}], X)$$

defined as

$$(Vu)(t) = T(t)x + \int_0^t T(t-s)\mathcal{F}(u(s))ds \quad \forall t \in [0, \hat{t}].$$

Since, by construction, any fixed point of V is a mild solution of (A.0.7) on $[0, \hat{t}]$ (and vice versa), system (A.0.7) has one and only one mild solution provided V^n is a contraction for some $n \in \mathbb{N}$, i.e. if

$$\|V^n u_1 - V^n u_2\| < \|u_1 - u_2\| \quad \forall u_1, u_2 \in C([0, \hat{t}], X),$$

where V^n means composing V with itself n times. This condition holds if \mathcal{F} is uniformly Lipschitz in $[0, \hat{t}]$, which means that a constant L exists such that

$$\|\mathcal{F}(x_1) - \mathcal{F}(x_2)\|_X \leq L \|x_1 - x_2\|_X,$$

since then one can compute, inductively,

$$\|Vu_1(t) - Vu_2(t)\|_X \leq \int_0^t \|\mathcal{F}(u_1(s)) - \mathcal{F}(u_2(s))\|_X \leq Lt \|u_1 - u_2\|,$$

$$\|V^2 u_1(t) - V^2 u_2(t)\|_X \leq \int_0^t \|\mathcal{F}(Vu_1(s)) - \mathcal{F}(Vu_2(s))\|_X \leq L^2 \frac{t^2}{2} \|u_1 - u_2\|$$

⋮

$$\|V^n u_1(t) - V^n u_2(t)\|_X \leq \int_0^t \|\mathcal{F}(V^{n-1} u_1(s)) - \mathcal{F}(V^{n-1} u_2(s))\|_X \leq L^n \frac{t^n}{n!} \|u_1 - u_2\|,$$

and conclude that, for n large enough,

$$\|V^n u_1 - V^n u_2\| \leq \sup_{t \in [0, \hat{t}]} \|V^n u_1(t) - V^n u_2(t)\|_X \leq L^n \frac{\hat{t}^n}{n!} \|u_1 - u_2\| < \|u_1 - u_2\|.$$

In fact, the Banach fixed-point Theorem also states that the fixed point u of V is the limit of any sequence $\{u_n\}_{n \in \mathbb{N}}$ with u_1 arbitrary and $u_n = Vu_{n-1}$ for $n > 1$, so that the mild solution of (A.0.7) can be approximated in an explicit way.

Appendix B

In this appendix we give a detailed proof of Proposition 1.3.1 in chapter 1. We restrict to the simpler case in which $m = 1$, $k = 1$ and $\Lambda = 1$, so that

$$C_b = \{(v, r) \in C([0, 1], \mathbb{R}) \times \mathbb{R} \mid v(0) = r\}$$

and

$$T_2(t) \begin{pmatrix} v \\ r \end{pmatrix} = \begin{pmatrix} r\mathbf{1}_-(\varphi(-t, \cdot)) + v(\varphi(-t, \cdot))\mathbf{1}_+(\varphi(-t, \cdot)) \\ r \end{pmatrix}. \quad (\text{B.0.1})$$

The generator A_{T_2} of T_2 is given by

$$A_{T_2} \begin{pmatrix} v \\ r \end{pmatrix} = \begin{pmatrix} -cv' \\ 0 \end{pmatrix} \quad (\text{B.0.2})$$

with domain

$$D(A_{T_2}) = \{(v, r) \in C_b \mid (cv', 0) \in C_b\},$$

Recall that c is a bounded function satisfying $c(x) \geq 1$ and that $\partial_1 \varphi(t, x) = c(\varphi(t, x))$. This simplification facilitates the exposition of the arguments, which could be extended without new ideas to deal with Proposition 1.3.1. In order to simplify the notation, from now on we use T instead of T_2 and A instead of A_{T_2} . Before showing that

$$L_\infty \times \mathbb{R} \cong C_b^{\odot T^*} \quad \text{and} \quad C_b \cong C_b^{\odot T}, \quad (\text{B.0.3})$$

we introduce some terminology and results about functions of bounded variation.

Borel measures and bounded variation functions

Let $f : [a, b] \rightarrow \mathbb{R}$ be a given function. The *total variation function* $\text{TV}(f)$ is defined as

$$\text{TV}(f)(s) = \sup_{P(a,s)} \sum_{j=1}^N |f(\sigma_j) - f(\sigma_{j-1})|,$$

where $P(a, s)$ denotes a finite partition $a = \sigma_0 < \sigma_1 < \dots < \sigma_N = s$ of $[a, s]$ (where N is the size of the partition and depends on P).

When $\text{TV}(f)(b)$ is bounded it is said that f is of *bounded variation*. If, in addition, $f(0) = 0$ and f is right continuous at every point of $(a, b]$ (i.e. right continuity can only fail at point a), then f is said to be a *normalised bounded variation* function and in this case we write $f \in \text{NBV}([a, b])$. It turns out that $\text{NBV}([a, b])$ is a Banach space with the norm $\|f\| = \text{TV}(f)(b)$.

Functions of normalised bounded variation are useful because they are in a one-to-one correspondence with Borel measures. Specifically, let $\mathcal{M}([a, b])$ denote the space of Borel measures on $[a, b]$ with the norm

$$\|\mu\| = |\mu|([0, 1])$$

where the function $|\mu| : \mathcal{B}([a, b]) \rightarrow [0, \infty)$ is defined as

$$|\mu|(\omega) = \sup_{P(\omega)} \sum_{j=1}^N |\mu(\omega_j)|, \quad \forall \omega \in \mathcal{B}([0, 1]),$$

with P denoting a partition $\{\omega_1, \omega_2, \dots, \omega_N\}$ of ω . Then, the normed spaces $\text{NBV}([a, b])$ and $\mathcal{M}([a, b])$ are isometrically isomorphic. The natural isometric isomorphism between the two spaces is $\phi : \mathcal{M}([a, b]) \rightarrow \text{NBV}([a, b])$ given by

$$\phi(\mu) = \eta_\mu \quad \text{such that} \quad \eta_\mu(s) = \begin{cases} 0 & \text{if } s = a \\ \mu[a, s] & \text{if } s \in (a, b] \end{cases}. \quad (\text{B.0.4})$$

As a consequence, since the Riesz representation theorem states that $\mathcal{M}([a, b])$ is a representation of the dual space of $C([a, b], \mathbb{R})$, it follows that $\text{NBV}([a, b])$ is also a representation of $C([a, b], \mathbb{R})^*$. The pairing between $\eta \in \text{NBV}([a, b])$ and $v \in C([a, b], \mathbb{R})$ is given by

$$\langle \eta, v \rangle = \int_a^b v d\eta := \lim_{d(P) \downarrow 0} \sum_{j=1}^N v(\tau_j)(\eta(\sigma_j) - \eta(\sigma_{j-1})), \quad (\text{B.0.5})$$

with P a partition $a = \sigma_0 < \sigma_1 < \dots < \sigma_N = b$ of $[a, b]$ with $|\sigma_j - \sigma_{j-1}| < d(P)$ for all j and τ_j an arbitrary point in $[\sigma_{j-1}, \sigma_j]$. This limit always exists because of the continuity of v (see Theorem AI.1.7 in [28]). This pairing is called the Riemann-Stieltjes integral of v with respect to η . Some important properties about these integrals are the integration by parts formula, that is

$$\int_a^b v d\eta = v(b)\eta(b) - v(a)\eta(a) - \int_a^b \eta dv,$$

and the relation

$$\int_a^b \eta dv = \int_a^b \eta(s)v'(s)ds$$

for functions $v \in C^1[a, b]$. In addition, the Riemann-Stieltjes integrals can be seen as a particular case of Lebesgue integral by considering

$$\int_a^b v d\eta = \int_a^b v d\mu_\eta,$$

where μ_η is the associated Borel measure defined by the ϕ isomorphism ($\mu_\eta = \phi^{-1}(\eta)$). This makes possible to apply results from integration theory such as the dominated convergence theorem when dealing with Riemann-Stieltjes integrals.

Once introduced the space of normalised bounded variation functions we are ready to prove the relations in (B.0.3).

Determining C_b^* , $D(A^*)$ and $C_b^{\odot T}$

Let us start showing that $C_b^* \cong \mathcal{M}_b \times \mathbb{R}$, with

$$\mathcal{M}_b = \{\mu \in \mathcal{M}([0, 1]) \mid \mu(0) = 0\}.$$

This follows from the Riesz representation theorem $C([0, 1], \mathbb{R})^* \cong \mathcal{M}([0, 1])$ and the fact that C_b is a subspace of $C([0, 1], \mathbb{R}) \times \mathbb{R}$ of co-dimension one:

$$C([0, 1], \mathbb{R}) \times \mathbb{R} = C_b \oplus \langle(0, 1)\rangle$$

where $\langle(0, 1)\rangle$ is the space generated by the pair $(0, 1) \in C([0, 1], \mathbb{R}) \times \mathbb{R}$. These two conditions imply that C_b^* can be represented by any subspace of $\mathcal{M}([0, 1]) \times \mathbb{R}$ of co-dimension one. In particular, the space $\mathcal{M}_b \times \mathbb{R}$ has co-dimension one:

$$\mathcal{M}([0, 1]) \times \mathbb{R} = \mathcal{M}_b \times \mathbb{R} \oplus \langle(\delta_0, 0)\rangle$$

with $\delta_0(\omega) = 1$ if $0 \in \omega$ and 0 otherwise.

We use the isomorphism (B.0.4) between $\mathcal{M}([0, 1])$ and $\text{NBV}([0, 1])$ in order to obtain the representation $C_b^* \cong \text{NBV}_b \times \mathbb{R}$ with

$$\text{NBV}_b = \phi(\mathcal{M}_b) = \{\eta \in \text{NBV}([0, 1]) \mid \lim_{s \downarrow 0} \eta(s) = 0\}$$

and the pairing $\langle(\eta, q), (v, r)\rangle = \langle\eta, v\rangle + q \cdot r$ and

$$\langle\eta, v\rangle = \int_0^1 v d\eta$$

as defined in (B.0.5). From now on we make an abuse of notation by identifying C_b^* with $\text{NBV}_b \times \mathbb{R}$.

Next we prove that $C_b^{\odot T} \cong L^1(0, 1) \times \mathbb{R}$ with the norm

$$\|(\nu, q)\| = \|\nu\|_{L^1_c} + |q| := \int_0^1 \left| \frac{\nu(s)}{c(s)} \right| ds + |q| \quad (\text{B.0.6})$$

and the pairing

$$\left\langle \begin{pmatrix} \nu \\ q \end{pmatrix}, \begin{pmatrix} v \\ r \end{pmatrix} \right\rangle = \int_0^1 v(s) \frac{\nu(s)}{c(s)} ds + rq.$$

This is shown by means of the identity $C_b^{\circ r} = \overline{D(A^*)}$, where A^* is the adjoin of the generator of T (see (B.0.1) and (B.0.2)). In order to apply this relation we first characterise the domain of A^* . Before entering into details observe that $(v, r) \in D(A)$ if and only if

$$v(s) = r + \int_0^s \frac{g(\sigma)}{c(\sigma)} d\sigma \quad \text{for some } g \in C([0, 1], \mathbb{R}).$$

Indeed, $(v, r) \in D(A)$ if $cv' = g \in C([0, 1], \mathbb{R})$ and $c(0)v'(0) = g(0) = 0$, so that $v(s) - v(0) = \int_0^s g(\sigma)/c(\sigma) d\sigma$ and $v(0) = r$ because $(v, r) \in C_b$.

By definition, $(\eta, q) \in D(A^*) \subset \text{NBV}_b \times \mathbb{R}$ if $\exists(\nu, p) \in \text{NBV}_b \times \mathbb{R}$ such that

$$\langle(\eta, q), A(v, r)\rangle = \langle(\nu, p), (v, r)\rangle \quad \forall(v, r) \in D(A). \quad (\text{B.0.7})$$

Since $A(v, r) = (cv', 0)$, it follows that $(\eta, q) \in D(A^*)$ if and only if

$$\exists \nu \in \text{NBV}_b \quad \text{such that} \quad \langle \eta, -cv' \rangle = \langle \nu, v \rangle \quad \forall(v, r) \in D(A). \quad (\text{B.0.8})$$

Indeed, if (B.0.8) holds then $(\nu, 0)$ satisfies (B.0.7). The following proposition gives a characterization of $D(A^*)$ by determining the subspace of NBV_b in which condition (B.0.8) is satisfied.

Proposition B.0.1. *$(\eta, q) \in D(A^*)$ if and only if $q \in \mathbb{R}$ and*

$$\eta(s) = \int_0^s \frac{\nu(\sigma)}{c(\sigma)} d\sigma \quad \forall s \in [0, 1], \quad (\text{B.0.9})$$

where $\nu \in \text{NBV}_b$ and satisfies $\nu(1) = 0$.

Proof. Let $(\eta, q) \in D(A^*)$ and $\nu \in \text{NBV}_b$ such that

$$\langle \eta, -cv' \rangle = \langle \nu, v \rangle \quad \forall(v, r) \in D(A).$$

Developing these expressions we get (recall $\nu(0) = 0$ because $\nu \in \text{NBV}_b$)

$$\langle \eta, -cv' \rangle = \langle \nu, v \rangle = \int_0^1 v d\nu = v(1)\nu(1) - \int_0^1 \nu(\sigma)v'(\sigma) d\sigma.$$

For any $s \in (0, 1)$ take $\{(v_n, 0)\}_n \subset D(A)$ such that $cv'_n \rightarrow \mathbf{1}_{(0, x]}$ and $|cv'_n| < 1$. Then, by the dominated convergence theorem, we have

$$\lim_{n \rightarrow \infty} \langle \eta, -cv'_n \rangle = - \int_0^1 \mathbf{1}_{(0, s]} d\eta = -\eta(s) + \eta(0^+) = -\eta(s)$$

for one side (where $\eta(0^+)$ means the limit of η at 0 from the right, which is 0 because $\eta \in \text{NBV}_b$), and

$$\lim_{n \rightarrow \infty} - \int_0^1 \nu(\sigma)v'_n(\sigma) d\sigma = - \int_0^s \frac{\nu(\sigma)}{c(\sigma)} d\sigma$$

for the other. Then we obtain

$$\eta(s) = \int_0^s \frac{\nu(\sigma)}{c(\sigma)} d\sigma.$$

Similarly, for the case $s = 1$ we take $\{(v_n, 0)\}_n \subset D(A)$ such that $cv'_n \rightarrow \mathbb{1}_{(0,1]}$, $|cv'_n| < 1$ and $v_n(1) = k$ arbitrary. Then it follows

$$\eta(1) = -\nu(1)k + \int_0^1 \frac{\nu(\sigma)}{c(\sigma)} d\sigma,$$

and due to the fact that $\eta(1)$ is fixed and cannot depend on k we conclude $\nu(1) = 0$.

It remains showing that if η satisfies (B.0.9) then $\langle \eta, -cv' \rangle = \langle \nu, v \rangle$ holds for all $(v, r) \in D(A)$. Indeed, it is clear from (B.0.9) that, for all $v \in C([0, 1])$,

$$\int_0^1 v d\eta = \lim_{d(P) \downarrow 0} \sum_{j=1}^{|P|} v(\tau_j) \int_{\theta_{j-1}}^{\theta_j} \frac{\nu(s)}{c(s)} ds = \lim_{d(P) \downarrow 0} \sum_{j=1}^{|P|} \int_{\theta_{j-1}}^{\theta_j} v(s) \frac{\nu(s)}{c(s)} ds = \int_0^1 v(s) \frac{\nu(s)}{c(s)} ds.$$

Finally, because of the properties of the Riemann-Stieltjes integral, we get

$$\begin{aligned} \langle \eta, -cv' \rangle &= -\int_0^1 cv' d\eta = -\int_0^1 c(s)v'(s) \frac{\nu(s)}{c(s)} ds = -\int_0^1 v'(s)\nu(s) ds \\ &= \int_0^1 v d\nu - v(1)\nu(1) + v(0)\nu(0) = \int_0^1 v d\nu = \langle \nu, v \rangle \quad . \end{aligned}$$

for all $(v, r) \in D(A)$. □

To complete the determination of C_b^\circledast we must compute the closure of $D(A^*)$. Let Y be the projection of $D(A^*)$ in NBV_b , so that $D(A^*) = Y \times \mathbb{R}$. Since $\overline{Y \times \mathbb{R}} = \overline{Y} \times \mathbb{R}$, we only need to study the closure of Y . Consider the sequence $\{\eta_n\}_n \subset Y$ such that $\eta_n \rightarrow \eta \in \text{NBV}_b$ and η_n determined by ν_n through (B.0.9). The completeness of NBV_b , together with the relations

$$\sup_P \sum_{j=1}^{|P|} \left| \int_{\theta_{j-1}}^{\theta_j} \nu_n(s) - \nu_m(s) ds \right| = \sup_P \sum_{j=1}^{|P|} \int_{\theta_{j-1}}^{\theta_j} |\nu_n(s) - \nu_m(s)| ds = \int_0^1 |\nu_n(s) - \nu_m(s)| ds,$$

imply

$$0 = \lim_{n,m \rightarrow \infty} \|\eta_n - \eta_m\|_{\text{TV}} = \lim_{n,m \rightarrow \infty} \|\nu_n - \nu_m\|_{L^1(0,1)}.$$

Hence, because of the completeness of $L^1(0, 1)$, there is $\nu \in L^1(0, 1)$ such that $\nu_n \xrightarrow{L^1} \nu$. Moreover, η is determined by ν as one would expect, that is,

$$\eta(s) = \int_0^s \frac{\nu(\sigma)}{c(\sigma)} d\sigma \quad \forall s \in [0, 1],$$

as one can deduce by considering

$$\|\eta(\cdot) - \int_0^\cdot \frac{\nu(\sigma)}{c(\sigma)} d\sigma\|_{\text{TV}} \leq \lim_{m \rightarrow \infty} \|\eta - \eta_m\|_{\text{TV}} + \|\nu - \nu_m\|_{L_c^1} = 0.$$

As a result, we have obtained

$$\bar{Y} \subset \left\{ \eta \in \text{NBV}_b \mid \eta(s) = \int_0^s \frac{\nu(\sigma)}{c(\sigma)} d\sigma \quad \text{for some } \nu \in L^1(0, 1) \right\}.$$

Reciprocally, for all $\nu \in L^1(0, 1)$ there exists $\{\nu_n\}_n \subset \text{NBV}_b$ such that $\nu_n(1) = 0$ and $\nu_n \rightarrow \nu$ in $L^1(0, 1)$. If we denote as η and η_n the functions determined by ν and ν_n , then, by the same equalities as before it follows that $\eta_n \rightarrow \eta$ in NBV_b , so that

$$\bar{Y} \supset \left\{ \eta \in \text{NBV}_b \mid \eta(s) = \int_0^s \frac{\nu(\sigma)}{c(\sigma)} d\sigma \quad \text{for some } \nu \in L^1(0, 1) \right\}.$$

Furthermore, \bar{Y} is isometrically isomorphic to $L^1(0, 1)$ with the norm $\|\cdot\|_{L_c^1}$ as it is shown using the natural isomorphism from $L^1(0, 1)$ to \bar{Y} given by

$$\eta(s) = \int_0^s \frac{\nu(\sigma)}{c(\sigma)} d\sigma \in \bar{Y} \quad \forall \nu \in L^1(0, 1).$$

Now we can summarize the characterizations of $C_b^{\odot T}$.

Theorem B.0.2. *Let L_c^1 be the space $(L^1(1, 0), \|\cdot\|_{L_c^1})$. Then the following isometric isomorphism*

$$C_b^{\odot T} = \overline{D(A^*)} = \left\{ \eta \in \text{NBV}_b \mid \eta(s) = \int_0^s \frac{\nu(\sigma)}{c(\sigma)} d\sigma \quad \text{for some } \nu \in L^1(0, 1) \right\} \times \mathbb{R} \cong L_c^1 \times \mathbb{R}$$

holds, with the pairing between $L_c^1 \times \mathbb{R}$ and C_b given by

$$\left\langle \begin{pmatrix} \nu \\ q \end{pmatrix}, \begin{pmatrix} v \\ r \end{pmatrix} \right\rangle = \int_0^1 v(s) \frac{\nu(s)}{c(s)} ds + rq.$$

Determining $C_b^{\odot T^*}$, $A_{T^\odot}^*$ and $C_b^{\odot \odot T}$

Since $C_b^{\odot T}$ is isomorphic to $L_c^1 \times \mathbb{R}$, from now we represent $C_b^{\odot T}$ with the space $L_c^1 \times \mathbb{R}$. This allows us to determine easily

$$C_b^{\odot *} = (L_c^1 \times \mathbb{R})^* \cong L^\infty(0, 1) \times \mathbb{R} =: L^\infty \times \mathbb{R},$$

with the pairing between $L^\infty \times \mathbb{R}$ and $L_c^1 \times \mathbb{R}$ given by

$$\left\langle \begin{pmatrix} v \\ r \end{pmatrix}, \begin{pmatrix} \nu \\ q \end{pmatrix} \right\rangle = \int_0^1 \frac{v(s)}{c(s)} \nu(s) ds + rq.$$

The norm of L^∞ is the standard one since, as an element of the dual space, one has

$$\left| \begin{pmatrix} v \\ r \end{pmatrix} \right| = \sup_{\|(\nu, q)\| \leq 1} \left\langle \begin{pmatrix} v \\ r \end{pmatrix}, \begin{pmatrix} \nu \\ q \end{pmatrix} \right\rangle = \sup_{s \in [0, 1]} |v(s)| + |r|.$$

Next we prove the sun-reflexivity property of C_b with respect T , that is $C_b \cong C_b^{\odot \odot T}$. To determine $C_b^{\odot \odot T}$ we need T^\odot . This can be done in an standard way.

Proposition B.0.3. $T^\odot(t) : L_c^1 \times \mathbb{R} \rightarrow L_c^1 \times \mathbb{R}$ is given for $t \geq 0$ by

$$T^\odot(t) \begin{pmatrix} \nu \\ q \end{pmatrix} = \begin{pmatrix} c(\cdot) \frac{\nu(\varphi(t, \cdot))}{c(\varphi(t, \cdot))} \partial_2 \varphi(t; \cdot) \mathbb{1}_+(\varphi(-t, 1) - \cdot) \\ \int_0^1 \mathbb{1}_-(\varphi(-t; s)) \frac{\nu(s)}{c(s)} ds + q \end{pmatrix}$$

Proof. Let $(\nu, q) \in L_c^1 \times \mathbb{R}$, then for all $(v, r) \in C_b$

$$\begin{aligned} \left\langle \begin{pmatrix} \nu \\ q \end{pmatrix}, T(t) \begin{pmatrix} v \\ r \end{pmatrix} \right\rangle &= \left\langle \begin{pmatrix} \nu \\ q \end{pmatrix}, \begin{pmatrix} r \mathbb{1}_-(\varphi(-t; \cdot)) + v(\varphi(-t; \cdot)) \mathbb{1}_+(\varphi(-t; \cdot)) \\ r \end{pmatrix} \right\rangle = \\ &= \int_0^1 r \mathbb{1}_-(\varphi(-t; s)) \frac{\nu(s)}{c(s)} ds + \int_0^1 v(\varphi(-t; s)) \mathbb{1}_+(\varphi(-t; s)) \frac{\nu(s)}{c(s)} ds + qr = \\ &= \left(\int_0^1 \mathbb{1}_-(\varphi(-t; s)) \frac{\nu(s)}{c(s)} ds + q \right) r + \int_{\varphi(-t, 0)}^{\varphi(-t, 1)} v(\sigma) \mathbb{1}_+(\sigma) \frac{\nu(\varphi(t, \sigma))}{c(\varphi(t, \sigma))} \partial_2 \varphi(-t; \varphi(t; \sigma))^{-1} d\sigma \\ &= \left(\int_0^1 \mathbb{1}_-(\varphi(-t; s)) \nu(s) ds + q \right) r + \int_0^1 v(\sigma) \mathbb{1}_+(\varphi(-t, 1) - \sigma) \frac{\nu(\varphi(t, \sigma))}{c(\varphi(t, \sigma))} \partial_2 \varphi(t; \sigma) d\sigma \\ &= \left\langle T^\odot(t) \begin{pmatrix} \nu \\ q \end{pmatrix}, \begin{pmatrix} v \\ r \end{pmatrix} \right\rangle. \end{aligned}$$

□

Similarly, by reversing the reorganizations and the changes of variables in the previous prove one obtains the semigroup $T^{\odot*}$ defined on $L^\infty \times \mathbb{R}$.

Proposition B.0.4. $T^{\odot*}(t) : L^\infty \times \mathbb{R} \rightarrow L^\infty \times \mathbb{R}$ is given for $t \geq 0$ by

$$T^{\odot*}(t) \begin{pmatrix} v \\ r \end{pmatrix} = \begin{pmatrix} r\mathbb{1}_-(\varphi(-t; \sigma)) + v(\varphi(-t, \sigma)) \\ r \end{pmatrix}$$

As one would expect, $T^{\odot*}$ is just the extension of $T(t) : C_b \rightarrow C_b$ in $L^\infty \times \mathbb{R}$. The point is that $T^{\odot*}(t)$ is not strongly continuous on $L^\infty \times \mathbb{R}$. In order to determine $C_b^{\odot \circ T}$ we determine first the generator of T^\odot on $L_c^1 \times \mathbb{R}$.

Proposition B.0.5. The generator of T^\odot is given by

$$D(A_{T^\odot}) = \{(\nu, q) \in L_c^1 \times \mathbb{R} \mid \nu \text{ is absolutely continuous and } \nu(1) = 0\}$$

and $A_{T^\odot}(\nu, q) = (c\nu', \nu(0))$.

The prove consists in computing the limit $\frac{(T^\odot(h)-Id)}{h}(\nu, q)$ and noticing that the limit exists in $L_c^1 \times \mathbb{R}$ if and only if the condition in the proposition holds. Observe that if $(\nu, q) \in D(A_{T^\odot})$ then $c\nu'$ always belongs to L_c^1 because c is bounded. Once we have a formula for A_{T^\odot} we compute $A_{T^\odot}^*$.

Proposition B.0.6. The adjoin of A_{T^\odot} is given by

$$D(A_{T^\odot}^*) = \{(v, r) \in L^\infty \times \mathbb{R} \mid v \text{ is Lipschitz and } v(0) = r\}$$

and $A_{T^\odot}^*(v, r) = (-cv', 0)$.

Proof. Let $(v, r) \in D(A_{T^\odot}^*)$ and let $A_{T^\odot}^*(v, r) = (w, p)$. Then, for all $(\nu, q) \in D(A_{T^\odot})$ one has, on the one hand,

$$\left\langle A_{T^\odot}^* \begin{pmatrix} v \\ r \end{pmatrix}, \begin{pmatrix} \nu \\ q \end{pmatrix} \right\rangle = \left\langle \begin{pmatrix} v \\ r \end{pmatrix}, A_{T^\odot} \begin{pmatrix} \nu \\ q \end{pmatrix} \right\rangle = \int_0^1 \frac{v(s)}{c(s)} c(s) \nu'(s) ds + r\nu(0),$$

and, on the other hand,

$$\left\langle A_{T^\odot}^* \begin{pmatrix} v \\ r \end{pmatrix}, \begin{pmatrix} \nu \\ q \end{pmatrix} \right\rangle = \left\langle \begin{pmatrix} w \\ p \end{pmatrix}, \begin{pmatrix} \nu \\ q \end{pmatrix} \right\rangle = \int_0^1 \frac{w(s)}{c(s)} \nu(s) ds + pq$$

that, using integration by parts, can be written as

$$\nu(1) \left(\alpha + \int_0^1 \frac{w(\sigma)}{c(\sigma)} d\sigma \right) - \nu(0)\alpha - \int_0^1 \left(\alpha + \int_0^s \frac{w(\sigma)}{c(\sigma)} d\sigma \right) \nu'(s) ds + pq$$

for some α . Then, since both expressions are the same and $\nu(1) = 0$, one necessarily has $\alpha = -r$, $p = 0$ and

$$v(s) = - \left(\alpha + \int_0^s \frac{w(\sigma)}{c(\sigma)} d\sigma \right) = r - \int_0^s \frac{w(\sigma)}{c(\sigma)} d\sigma.$$

This means that $A_{T^\circ}^*(v, r) = (-cv', 0)$ and $v(0) = r$. Moreover, since w belongs to L^∞ (so does w/c), it also follows that v is Lipschitz.

Reciprocally, let $r \in \mathbb{R}$ and v be a Lipschitz function satisfying $v(0) = r$. This implies that v can be written as

$$v(s) = r + \int_0^1 \tilde{w}(\sigma) d\sigma$$

for some $\tilde{w} \in L^\infty$. Thus, defining $w(\sigma) := \tilde{w}(\sigma)c(\sigma)$ we can proceed as above to show

$$\left\langle \begin{pmatrix} v \\ r \end{pmatrix}, A_{T^\circ} \begin{pmatrix} \nu \\ q \end{pmatrix} \right\rangle = r\nu(0) - \int_0^1 \frac{w(s)}{c(s)} \nu(s) ds + \left(r + \int_0^1 \frac{w(\sigma)}{c(\sigma)} d\sigma \right) \nu(1) - r\nu(0)$$

Since $\nu(1) = 0$ and $v' = w/c$, we have

$$\left\langle \begin{pmatrix} v \\ r \end{pmatrix}, A_{T^\circ} \begin{pmatrix} \nu \\ q \end{pmatrix} \right\rangle = \left\langle \begin{pmatrix} -cv' \\ 0 \end{pmatrix}, \begin{pmatrix} \nu \\ q \end{pmatrix} \right\rangle,$$

which means that $(v, r) \in D(A_{T^\circ}^*)$ and $A_{T^\circ}^*(v, r) = (-cv', 0)$. □

Finally, we can compute $C_b^{\circ\circ T}$ by taking the closure of $D(A_{T^\circ}^*)$. When doing so we lose the Lipschitz condition on v but the continuity remains. Therefore,

$$C_b^{\circ\circ T} \cong \{(v, r) \in C([0, 1], \mathbb{R}) \times \mathbb{R} \mid v(0) = r\} = C_b,$$

as desired.

Bibliography

- [1] Elizabeth A. Archie and Kevin R. Theis. Animal behaviour meets microbial ecology. *Animal Behaviour*, 82(3):425–436, September 2011.
- [2] R. J. Atterbury, M. A. P. Van Bergen, F. Ortiz, M. A. Lovell, J. A. Harris, A. De Boer, J. A. Wagenaar, V. M. Allen, and P. A. Barrow. Bacteriophage Therapy To Reduce Salmonella Colonization of Broiler Chickens. *Applied and Environmental Microbiology*, 73(14):4543–4549, July 2007.
- [3] Nicolas Bacaër. *A Short History of Mathematical Population Dynamics*. Springer-Verlag, London, 2011.
- [4] Nicolas Bacaër and Souad Guernaoui. The epidemic threshold of vector-borne diseases with seasonality. *Journal of Mathematical Biology*, 53(3):421–436, September 2006.
- [5] Johan S. Bakken. Fecal bacteriotherapy for recurrent *Clostridium difficile* infection. *Anaerobe*, 15(6):285–289, December 2009.
- [6] M. M. Ballyk, D. A. Jones, and H. L. Smith. Microbial Competition in Reactors with Wall Attachment. *Microbial Ecology*, 41(3):210–221, April 2001.
- [7] Mary Ballyk and Hal Smith. A model of microbial growth in a plug flow reactor with wall attachment. *Mathematical Biosciences*, 158(2):95–126, May 1999.
- [8] Carles Barril and Àngel Calsina. Stability analysis of an enteropathogen population growing within a heterogeneous group of animals. *Discrete and Continuous Dynamical Systems - Series B*, 22(4):1231–1252, February 2017.
- [9] Carles Barril, Àngel Calsina, and Jordi Ripoll. On the Reproduction Number of a Gut Microbiota Model. *Bulletin of Mathematical Biology*, 79(11):2727–2746, November 2017.
- [10] A. Belleni-Morante and A. C. McBride. *Applied Nonlinear Semigroups: An Introduction*. Wiley, Chichester ; New York, 1 edition edition, November 1998.
- [11] Barbara Boldin. Persistence and Spread of Gastro-Intestinal Infections: the Case of Enterotoxigenic *Escherichia coli* in Piglets. *Bulletin of Mathematical Biology*, 70(7):2077, October 2008.

- [12] Fred Brauer. Mathematical epidemiology is not an oxymoron. *BMC Public Health*, 9(1):S2, November 2009.
- [13] Robert M. Brucker and Seth R. Bordenstein. The Hologenomic Basis of Speciation: Gut Bacteria Cause Hybrid Lethality in the Genus *Nasonia*. *Science*, page 1240659, July 2013.
- [14] Roger Butlin, Allan Debelle, Claudius Kerth, Rhonda R Snook, Leo W Beukeboom, RF Cajas Castillo, Wenwen Diao, Martine E Maan, Silvia Paolucci, Franz J Weissing, et al. What do we need to know about speciation? *Trends in Ecology & Evolution*, 27(1):27–39, 2012.
- [15] À. Calsina and J. J. Rivaud. A size structured model for bacteria–phages interaction. *Nonlinear Analysis: Real World Applications*, 15(Supplement C):100–117, January 2014.
- [16] Àngel Calsina, Josep M. Palmada, and Jordi Ripoll. Optimal latent period in a bacteriophage population model structured by infection-age. *Mathematical Models and Methods in Applied Sciences*, 21(04):693–718, April 2011.
- [17] S.-N. Chow and J. K. Hale. *Methods of Bifurcation Theory*. Springer, 1982.
- [18] Ph Clément, O. Diekmann, M. Gyllenberg, H. J. a. M. Heijmans, and H. R. Thieme. Perturbation theory for dual semigroups. *Mathematische Annalen*, 277(4):709–725, August 1987.
- [19] Philippe Clément, Odo Diekmann, M. Gyllenberg, Henk Heijmans, and H. R. Thieme. Perturbation theory for dual semigroups. III. Nonlinear Lipschitz continuous perturbations in the sun-reflexive case. January 1989.
- [20] M. E. Coleman, D. W. Dreesen, and R. G. Wiegert. A simulation of microbial competition in the human colonic ecosystem. *Applied and Environmental Microbiology*, 62(10):3632–3639, January 1996.
- [21] Joan Colom, Mary Cano-Sarabia, Jennifer Otero, Javier Aríñez-Soriano, Pilar Cortés, Daniel Maspoeh, and Montserrat Llagostera. Microencapsulation with alginate/CaCO₃: A strategy for improved phage therapy. *Scientific Reports*, 7:41441, January 2017.
- [22] Joan Colom, Mary Cano-Sarabia, Jennifer Otero, Pilar Cortés, Daniel Maspoeh, and Montserrat Llagostera. Liposome-Encapsulated Bacteriophages for Enhanced Oral Phage Therapy against *Salmonella* spp. *Applied and Environmental Microbiology*, 81(14):4841–4849, July 2015.
- [23] The Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. *Nature*, 486(7402):207–214, June 2012.
- [24] Michael H. Cortez. When does pathogen evolution maximize the basic reproductive number in well-mixed host–pathogen systems? *Journal of Mathematical Biology*, 67(6-7):1533–1585, December 2013.

- [25] J. M. Cushing and Odo Diekmann. The many guises of R_0 (a didactic note). *Journal of Theoretical Biology*, 404(Supplement C):295–302, September 2016.
- [26] O. Diekmann, P. Getto, and M. Gyllenberg. Stability and Bifurcation Analysis of Volterra Functional Equations in the Light of Suns and Stars. *SIAM Journal on Mathematical Analysis*, 39(4):1023–1069, October 2007.
- [27] O. Diekmann, J. a. P. Heesterbeek, and J. a. J. Metz. On the definition and the computation of the basic reproduction ratio R_0 in models for infectious diseases in heterogeneous populations. *Journal of Mathematical Biology*, 28(4):365–382, June 1990.
- [28] Odo Diekmann, Stephan A. van Gils, Sjoerd M. V. Lunel, and Hans-Otto Walther. *Delay Equations: Functional-, Complex-, and Nonlinear Analysis*. Springer-Verlag, 1995.
- [29] Odo Diekmann and Mats Gyllenberg. Equations with infinite delay: Blending the abstract and the concrete. *Journal of Differential Equations*, 252(2):819–851, January 2012.
- [30] Odo Diekmann and Karolina Korvasova. Linearization of solution operators for state-dependent delay equations: a simple example. *Discrete Contin Dyn Syst A*, 36(1):137–149, 2016.
- [31] Diane M. B. Dodd. Reproductive Isolation as a Consequence of Adaptive Divergence in *Drosophila Pseudoobscura*. *Evolution*, 43(6):1308–1311, September 1989.
- [32] Loomis I. Dublin and Alfred J. Lotka. On the True Rate of Natural Increase: As Exemplified by the Population of the United States, 1920. *Journal of the American Statistical Association*, 20(151):305–339, September 1925.
- [33] Klaus-Jochen Engel and Rainer Nagel. *One-Parameter Semigroups for Linear Evolution Equations*. Springer-Verlag, 2000.
- [34] Klaus-Jochen Engel and Rainer Nagel. *A Short Course on Operator Semigroups*. Springer Science & Business Media, 2006.
- [35] Leonhard Euler. A general investigation into the mortality and multiplication of the human species (Translated by N. and B. Keyfitz and republished 1970). *Theoretical Population Biology*, 1(3):307–314, 1760. (reprint of the original 1760).
- [36] Vanessa O. Ezenwa, Nicole M. Gerardo, David W. Inouye, Mónica Medina, and Joao B. Xavier. Animal Behavior and the Microbiome. *Science*, 338(6104):198–199, October 2012.
- [37] R. A. Fisher. The Wave of Advance of Advantageous Genes. *Annals of Eugenics*, 7(4):355–369, June 1937.
- [38] Rolf Freter. In *Human Intestinal Microflora in Health and Disease*. Academic Press, 1983.

- [39] Francesca Gaggia, Paola Mattarelli, and Bruno Biavati. Probiotics and prebiotics in animal feeding for safe food production. *International Journal of Food Microbiology*, 141(Supplement):S15–S28, July 2010.
- [40] S. A. H. Geritz, E. Kisdi, G. Meszéna, and J. A. J. Metz. Evolutionarily singular strategies and the adaptive growth and branching of the evolutionary tree. *Evolutionary Ecology*, 12(1):35–57, January 1998.
- [41] Morton E. Gurtin and Richard C. Maccamy. Non-linear age-dependent population dynamics. *Archive for Rational Mechanics and Analysis*, 54(3):281–300, September 1974.
- [42] Ilkka Hanski and Michael Gilpin. Metapopulation dynamics: brief history and conceptual domain. In *Metapopulation Dynamics: Empirical and Theoretical Investigations*, pages 3–16. Academic Press, 1991.
- [43] J. A. P. Heesterbeek. A Brief History of R_0 and a Recipe for its Calculation. *Acta Biotheoretica*, 50(3):189–204, September 2002.
- [44] Daniel Henry. *Geometric Theory of Semilinear Parabolic Equations*. Springer-Verlag, 1981.
- [45] H. Hethcote. The Mathematics of Infectious Diseases. *SIAM Review*, 42(4):599–653, January 2000.
- [46] Herbert W. Hethcote and James W. Van Ark. Epidemiological models for heterogeneous populations: proportionate mixing, parameter estimation, and immunization programs. *Mathematical Biosciences*, 84(1):85–118, May 1987.
- [47] Hisashi Inaba. On a new perspective of the basic reproduction number in heterogeneous environments. *Journal of Mathematical Biology*, 65(2):309–348, August 2012.
- [48] D. Jones, D. Le, H. Smith, and H. Kojouharov. Bacterial Wall Attachment in a Flow Reactor. *SIAM Journal on Applied Mathematics*, 62(5):1728–1771, January 2002.
- [49] D. Jones and H. Smith. Microbial Competition for Nutrient and Wall Sites in Plug Flow. *SIAM Journal on Applied Mathematics*, 60(5):1576–1600, January 2000.
- [50] Tosio Kato. *Perturbation theory for linear operators*. Springer-Verlag, 1995.
- [51] A.N. Kolmogorov, I. G Petrovskii, and N. S. Piskunov. A Study of the Diffusion Equation with Increase in the Amount of Substance, and its Application to a Biological Problem. In *Selected Works of A. N. Kolmogorov*, Mathematics and Its Applications (Soviet Series), pages 242–270. Springer, Dordrecht, 1991.
- [52] M. A. Krasnoselskii, P. P. Zabreyko, and E. I. Pustyl'nik. *Integral operators in spaces of summable functions*. Springer, edición: softcover reprint of the original 1st ed. 1976 edition, 1976.

- [53] M. Lichtner. Variation of Constants Formula for Hyperbolic Systems. *Journal of Applied Analysis*, 15(1):79–100, 2010.
- [54] Alfred J. Lotka. Relation Between Birth Rates and Death Rates. *Science*, 26(653):21–22, July 1907.
- [55] Alfred J. Lotka. Relation Between Birth Rates and Death Rates. In *Mathematical Demography*, Biomathematics, pages 93–95. Springer, Berlin, Heidelberg, 1977.
- [56] Catherine A. Lozupone, Jesse I. Stombaugh, Jeffrey I. Gordon, Janet K. Jansson, and Rob Knight. Diversity, stability and resilience of the human gut microbiota. *Nature*, 489(7415):220–230, September 2012.
- [57] Frithjof Lutscher and Gunog Seo. The effect of temporal variability on persistence conditions in rivers. *Journal of Theoretical Biology*, 283(1):53–59, August 2011.
- [58] Thomas Robert Malthus. *An Essay on the Principle of Population*. Cosimo, Inc., 1798.
- [59] Lynn Margulis and Dorion Sagan. *Captando genomas : una teoría sobre el origen de las especies*. Editorial Kairós Sa, Barcelona, 1 edición edition, 2003.
- [60] Bonnie M. Marshall and Stuart B. Levy. Food Animals and Antimicrobials: Impacts on Human Health. *Clinical Microbiology Reviews*, 24(4):718–733, January 2011.
- [61] Margaret McFall-Ngai, Michael G. Hadfield, Thomas C. G. Bosch, Hannah V. Carey, Tomislav Domazet-Lošo, Angela E. Douglas, Nicole Dubilier, Gerard Eberl, Tadashi Fukami, Scott F. Gilbert, Ute Hentschel, Nicole King, Staffan Kjelleberg, Andrew H. Knoll, Natacha Kremer, Sarkis K. Mazmanian, Jessica L. Metcalf, Kenneth Nealon, Naomi E. Pierce, John F. Rawls, Ann Reid, Edward G. Ruby, Mary Rumpho, Jon G. Sanders, Diethard Tautz, and Jennifer J. Wernegreen. Animals in a bacterial world, a new imperative for the life sciences. *Proceedings of the National Academy of Sciences*, 110(9):3229–3236, February 2013.
- [62] Sharon L. Messenger, Ian J. Molineux, and J. J. Bull. Virulence evolution in a virus obeys a trade off. *Proceedings of the Royal Society of London B: Biological Sciences*, 266(1417):397–404, February 1999.
- [63] Johan A. Metz and Odo Diekmann. *The Dynamics of Physiologically Structured Populations*. Springer, 1986.
- [64] Richard K. Miller and Anthony N. Michel. *Ordinary Differential Equations*. Academic Press, 1982.
- [65] Isao Miyadera. *Nonlinear Semigroups*. American Mathematical Soc., 1977.
- [66] Jan van Neerven. *The Asymptotic Behaviour of Semigroups of Linear Operators*. Birkhäuser, 1996.

- [67] E. Pachepsky, F. Lutscher, R. M. Nisbet, and M. A. Lewis. Persistence, spread and the drift paradox. *Theoretical Population Biology*, 67(1):61–73, February 2005.
- [68] Amnon Pazy. *Semigroups of Linear Operators and Applications to Partial Differential Equations*. Springer-Verlag, 1983.
- [69] Kathryn J. Pflughoeft and James Versalovic. Human Microbiome in Health and Disease. *Annual Review of Pathology: Mechanisms of Disease*, 7(1):99–122, 2012.
- [70] Andrea Pugliese. On the evolutionary coexistence of parasite strains. *Mathematical Biosciences*, 177-178(Supplement C):355–375, May 2002.
- [71] Eugene Rosenberg and Ilana Zilber-Rosenberg. Microbes Drive Evolution of Animals and Plants: the Hologenome Concept. *mBio*, 7(2):e01395–15, April 2016.
- [72] Helmut H. Schaefer. *Banach lattices and positive operators*. 1974. Published: Die Grundlehren der mathematischen Wissenschaften. Band 215. Berlin-Heidelberg-New York: Springer-Verlag. XI, 376 p. DM 98.00; \$ 40.00 (1974).
- [73] Gil Sharon, Daniel Segal, John M. Ringo, Abraham Hefetz, Ilana Zilber-Rosenberg, and Eugene Rosenberg. Commensal bacteria play a role in mating preference of *Drosophila melanogaster*. *Proceedings of the National Academy of Sciences*, 107(46):20051–20056, November 2010.
- [74] J. Dylan Shropshire and Seth R. Bordenstein. Speciation by Symbiosis: the Microbiome and Behavior. *mBio*, 7(2):e01785–15, April 2016.
- [75] H. Smith. Models of Virulent Phage Growth with Application to Phage Therapy. *SIAM Journal on Applied Mathematics*, 68(6):1717–1737, January 2008.
- [76] Hal Smith. A semilinear hyperbolic system. In *Proceedings Of The Mathematics Conference*. 2000.
- [77] Hal Smith and Xiao-Qiang Zhao. Microbial Growth in a Plug Flow Reactor with Wall Adherence and Cell Motility. *Journal of Mathematical Analysis and Applications*, 241(1):134–155, January 2000.
- [78] O. Soave and C. D. Brand. Coprophagy in animals: a review. *The Cornell veterinarian*, 81(4):357–364, October 1991.
- [79] Douglas C. Speirs and William S. C. Gurney. Population Persistence in Rivers and Estuaries. *Ecology*, 82(5):1219–1237, May 2001.
- [80] H. Thieme. Spectral Bound and Reproduction Number for Infinite-Dimensional Population Structure and Time Heterogeneity. *SIAM Journal on Applied Mathematics*, 70(1):188–211, January 2009.

- [81] Horst R. Thieme and Hal L. Smith. Chemostats and epidemics: Competition for nutrients/hosts. *Mathematical Biosciences and Engineering*, 10(5/6):1635–1650, August 2013.
- [82] P. van den Driessche and James Watmough. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Mathematical Biosciences*, 180(1):29–48, November 2002.
- [83] Antoni van Leeuwenhoek. *Alle de brieven*, volume 2. N. V. Swets & Zeitlinger, Amsterdam, 1941. In Letter 26 from 1676, translated by B. Cohen.
- [84] Pierre F. Verhulst. Notice sur la loi que la population suit dans son accroissement. In *Correspondance mathématique et physique*. Impr. d’H. Vandekerckhove, 1838.
- [85] Jürgen Voigt. On the convex compactness property for the strong operator topology. *Note di Matematica*, 12(1):259–269, January 1992.
- [86] Wendi Wang and Xiao-Qiang Zhao. Threshold Dynamics for Compartmental Epidemic Models in Periodic Environments. *Journal of Dynamics and Differential Equations*, 20(3):699–717, September 2008.
- [87] G. F. Webb. *Theory of nonlinear age-dependent population dynamics*. 1985.
- [88] Xiao Yu and Xiao-Qiang Zhao. A periodic reaction–advection–diffusion model for a stream population. *Journal of Differential Equations*, 258(9):3037–3062, May 2015.