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Transport equations and plasmid-induced cellular heterogeneity

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Abstract

Autonomously replicating extra-chromosomal elements called plasmids can cause cellular heterogeneity by varying plasmid copy numbers. The present thesis deals with the long-time distribution of plasmids in a bacterial population. Firstly, vertical gene transfer in a bacterial population structured by the number of plasmids is modeled. The resulting model equations are hyperbolic transport equations with an integral term. Secondly, the associated eigenproblems are analyzed using theory of semigroups of operators, theory of positive operators, and the Laplace transform. Spectral analysis and the Generalized Relative Entropy method are used to obtain stability results. Numerically constructed eigensolutions visualize the long-time distribution of plasmids in the vertical gene transfer models. Finally, horizontal gene transfer of plasmids is included into the model.

Zusammenfassung

Extra-chromosomale Elemente, die sich selbstständig replizieren und als Plasmide bezeichnet werden, können durch unterschiedliche Plasmidzahlen zelluläre Heterogenität verursachen. In der vorliegenden Arbeit wird die langfristige Verteilung von Plasmiden in einer Bakterienpopulation untersucht. Zuerst wird vertikaler Gentransfer in einer Bakterienpopulation, die nach der Anzahl der Plasmide strukturiert ist, modelliert. Die Modellgleichungen sind hyperbolische Transportgleichungen mit einem Integralterm. Die entsprechenden Eigenprobleme werden mithilfe der Halbgruppentheorie von Operatoren, der Theorie positiver Operatoren und der Laplace Transformation analysiert. Spektralanalyse und die Verallgemeinerte Relative Entropie Methode liefern Stabilitätsergebnisse. Numerisch konstruierte Eigenlösungen visualisieren die Langzeitverteilung von Plasmiden in den vertikalen Gentransfermodellen. Zuletzt wird dem Modell horizontaler Gentransfer von Plasmiden hinzugefügt.

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Contents

1 Introduction

Bacterial populations can be heterogeneous even if they are grown from a single bacterium [2]. For example, regarding the number of plasmids, which are autonomously replicating extra-chromosomal genetic elements, bacteria may vary from being plasmid-free to containing several hundred plasmids [21]. Plasmids can carry genes that are beneficial to bacteria like, for example, resistance or metabolic properties, but they also are a metabolic burden to the host bacterium [45]. As bacteria reproduce asexually, plasmids are essential for the genetic variability, adaptation, and evolution of bacterial populations [45, 79]. They can be transferred vertically, i.e., from one generation to the next, or horizontally, i.e., between two individuals that are not necessarily related. In particular, the spread of antibiotic resistance genes via plasmids and their use as vectors in biotechnology make plasmids interesting objects of study.

Plasmids are very diverse and can be classified in many ways [98]. For example, one can distinguish plasmids with only few copies per cell and plasmids with many copies per cell. The former are referred to as low-copy plasmids and the latter as high-copy plasmids [95]. As plasmids are genetic elements, they reproduce by replication [98]. The replication of low-copy plasmids is usually strongly regulated and coupled to the cell division cycle of the host. For high-copy plasmids, this is typically not the case. They replicate throughout the cell division cycle until they reach their characteristic copy number [56, 95].

For biotechnological use, the genes for the production of a protein are inserted into the plasmid genome so that plasmid-bearing bacteria produce this protein. The first hormone produced this way and made available for clinical use was insulin [22]. Today there is a wide range of substances produced with this method like antibodies or blood clotting factors [22]. In order to increase protein production, high-copy plasmids are commonly used in biotechnology [22]. If there are more copies of the gene in the cell, then the cell also produces more protein. However, with the plasmid copy number also the metabolic burden of the bacterium increases, possibly to the point that the bacterium becomes inactive and it does not produce the target protein anymore, or cell division ceases [77]. Thus, for stable production, it has to be ensured on the one hand that the plasmid is not lost and on the other hand that it does not accumulate. By inserting not only the DNA of the target protein but also antibiotic resistance genes and adding antibiotics to the growth medium of the bacteria, one can assure that only plasmid-bearing and therefore producing bacteria survive. However, this procedure is costly as antibiotics are expensive [22]. Moreover, the accumulation of plasmids cannot be prevented in this manner. Therefore, it is of interest to study the mechanisms that may lead to either plasmid loss or accumulation.

Bacterial populations, structured populations, and also plasmids have been extensively studied. Mathematical models for plasmids often distinguish only between plasmid-free and plasmid-bearing cells [55,57,61,62,97]. However, there are also models that take into account the number of plasmids [14, 38, 74]. Plasmids have been modeled using both deterministic [62,74,92,97] and stochastic models [55,73,99]. Plasmid-induced antibiotic resistance has been studied due to its great importance for clinical applications [25, 62]. Also other aspects have been modeled and studied, for example, the copy number of plasmids [5, 14, 81], the time to plasmid half-elimination in the bacterial population [38], or the molecular mechanisms of plasmid replication [6, 59]. Both vertical [38, 74] and horizontal [25, 55, 57, 61, 92, 97] plasmid transfer have been studied.

Besides mathematical models for plasmids, also structured populations [18,24,43,64, 68] and physiologically structured cellular populations [4, 10, 29, 83] have been studied. Models for a population structured by a continuous variable are often characterized as growth-fragmentation models or growth-fragmentation-death models [9, 19, 29, 72]. For the analysis of models of cellular or bacterial populations structured by some variable representing, e.g., age, size or protein-content it is sometimes assumed that cell division only occurs if the structuring variable exceeds a certain threshold [4, 19]. This threshold is, in general, positive as there is, e.g., a minimal size, age, or protein-content necessary for cell division. However, in the models for bacteria structured by the number of plasmids this is not the case: bacteria do not need a minimal amount of plasmids for cell-division. In order to incorporate both the possibility of plasmid loss and reproduction of plasmid-free bacteria there is no such threshold in models for bacteria and plasmids.

The mathematical methods used in the analysis of physiologically structured population models or plasmid models include the theory of semigroups of operators [50, 72, 103], theory of positive operators [19, 29], and the Laplace transform [48]. Arino [4] gives an overview of mathematical models for cell population dynamics and the methods used for their analysis. For hyperbolic equations, the method of characteristics can be used to obtain existence of solutions [29]. The stability of solutions can be studied using spectral analysis [48, 72] or the Generalized Relative Entropy method [70, 83].

In the present thesis, we study the distribution of high-copy plasmids as these plasmids are commonly used in biotechnology in order to increase the yield. We are in particular interested in the long-time distribution of plasmids in a bacterial population.

As with an increasing number of plasmids bacteria become inactive and both cell and plasmid reproduction ceases, it makes sense to assume that there is a maximal number of plasmids a bacterium can carry. This behavior can, for example, be modeled by logistic plasmid reproduction. Furthermore, the behavior of bacteria changes with the number of plasmids and therefore both cell division and death rate, in general, depend on the number of plasmids. At cell division, plasmids are distributed to the two daughter cells. The plasmid segregation kernel models how plasmids are segregated, i.e., whether there is random segregation, a unimodal, or a bimodal distribution of plasmids. There are no existence and stability results for the eigenproblem associated with the model of a bacterial population structured by the continuous plasmid load with logistic plasmid reproduction, non-constant cell division and death rate, and a general plasmid segregation kernel.

We consider a hyperbolic transport equation with an integral term that models a bacterial population structured by the number of plasmids. The model includes the growth of bacteria with respect to (w.r.t.) the structuring variable, i.e., the number of plasmids increases by plasmid reproduction. It also includes fragmentation of plasmids at cell division and death of bacteria. Thus, it is a growth-fragmentation-death equation. Since we are interested in the long-term distribution of plasmids in the bacterial population, we consider the associated eigenproblem and analyze the stability of the eigensolution using spectral analysis and the Generalized Relative Entropy method. We extend existence and stability results for growth-fragmentation-death equations.

This thesis is structured as follows: firstly, in Chapter 2, we give biological background information about plasmids, Vertical Gene Transfer (VGT) of plasmids, and the most important mechanisms of Horizontal Gene Transfer (HGT) of plasmids. Secondly, Section 2.2 contains definitions, lemmas, and theorems that are used in this thesis.

In Chapter 3, we study VGT of plasmids. To this end, we derive a model for a bacterial population structured by the discrete number of plasmids. We consider two different cases for plasmid segregation in bacteria with only few bacteria. For each case, we obtain a VGT model. Since we are interested in high-copy plasmids, we take the continuum limit and obtain two models consisting of hyperbolic integro-partial differential equations. These models are referred to as regular and singular VGT model, respectively. The regular VGT model is analyzed in Section 3.2 and the singular VGT model in Section 3.3. The long-time distribution of plasmids in the bacterial population is studied by considering the associated eigenproblems and showing existence of eigensolutions for each of these models. For the stability analysis of the eigensolution, we use spectral analysis and the Generalized Relative Entropy method. Finally, we construct eigenfunctions numerically for these models and thereby visualize the expected long-time behavior.

We include HGT by conjugation in Chapter 4. As conjugative plasmids are typically single-copy plasmids, we analyze the distribution of a mobilizable high-copy plasmid in a bacterial population where we have a subpopulation of bacteria containing a conjugative plasmid and a subpopulation that does not carry the conjugative plasmid. In the same way as in the VGT models we derive a model consisting of integro-partial differential equations by first creating a model for the bacterial population structured by the discrete number of mobilizable plasmids and then passing to the continuum limit. We analyze the model by considering the long-time development of the proportion of bacteria without the conjugative plasmid.

In Chapter 5, we summarize the results and conclude.

At the end of this thesis, a list of abbreviations and notations and an index is included for the convenience of the reader.

Parts of this thesis have been published, submitted, or are in preparation for submission. The derivation of the singular model is as in the submitted publication [74]. The derivation of the regular VGT model, its analysis, and the numerical construction of the eigenfunction were published [96]. A publication of the analysis of the singular VGT model is in preparation [75]. There is also one further submitted paper that is not a part of this thesis [94].

2 Background

2.1 Biological Background

2.1.1 Plasmids

Plasmids are extrachromosomal genetic elements in prokaryotes[1] [37] which replicate independently of the chromosome(s) [11]. The term plasmid was introduced by J. Lederberg in 1952 as a generic term for hereditary extra-chromosomal elements [58]. There is great diversity among plasmids, they can vary in shape, size, copy number per cell, and host-organism. For example, very rarely plasmids can even be found in organelles of eukaryotes[2] [11] and in yeast cells [37]. Most plasmids have a circular form but there are also linear plasmids [98]. Their size can vary from about 1 kb, i.e., 1,000 base pairs, up to several hundred kbs [37]. The steady-state number of plasmids in a host bacterium is called the *copy number* of plasmids and may vary from 1 or 2 copies to several hundred [21]. Depending on their copy number plasmids are often referred to as single-copy, low-copy, medium-copy, or high-copy plasmids. We will use the terms *low-copy* for plasmids with only few copies per cell and *high-copy* for plasmids with up to several hundreds of copies per cell. Another way to distinguish plasmids is by whether or not plasmid reproduction is coupled with chromosome reproduction. The plasmid is accordingly classified as having either *stringent* or *relaxed plasmid reproduction control* [80, 95]. Typically, high-copy plasmids have relaxed plasmid reproduction control and low-copy plasmids have stringent plasmid reproduction control [95]. When we use the term high-copy plasmid we mean a plasmid with high copy number and relaxed plasmid reproduction but for simplicity just call it *high-copy plasmid*.

Often bacteria have a selective advantage through plasmids [11]. However, plasmids usually do not contain genes necessary for survival [37] and the advantage for the host is limited to specific and often atypical environments [98]. Some of the various properties plasmids can bestow on their host are:

- Resistance properties: e.g., antibiotic resistance, heavy metal resistance, resistance to toxic anions [98]. Such plasmids are often referred to as *resistance* or *R plasmids* [49].
- Metabolic properties: e.g., bacteriocin/colicin production, metabolism of simple carbohydrates or proteins, pigmentation [98].
- Toxin production, virulence (many human- and animal-pathogenic bacteria produce plasmid-coded toxins [37]), capsule production, sensitivity to bacteriocins, chemotaxis [98], and tumor induction in plants [37].

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[1] Single-celled organisms without membrane-bound nucleus or organelle like bacteria [37].

[2] Eukaryotic cells have membrane-bound nucleus and organelles, e.g., plant and animal cells [37].

If these properties are advantageous for the host, then plasmids can increase the fitness of their host bacterium. Otherwise, they can also decrease their host's fitness due to the metabolic burden associated with the harboring of plasmids [13, 98]. This additional metabolic burden can have a detrimental effect on the growth rate of the host. However, plasmids can ensure or at least increase the probability of their persistence, even if they have a negative effect on the fitness of the host, using, e.g., an active partitioning system or toxin-antitoxin-systems [98].

Plasmids are also used in biotechnology as so-called vectors [11]. When removed from their host cell the plasmid genome can be changed by adding, changing, or removing genes [22]. These artificial plasmids are called *recombinant plasmids*. They can be inserted into host organisms like bacteria or eukaryotic cells that express the recombinant plasmid genes [22]. This method can be used for gene cloning [11] and for production of recombinant proteins [22]. For example, insulin and blood clotting factors for medical usage are produced in this way [22].

For their biotechnological usage, it is important to control the copy number of plasmids. If the recombinant plasmid is lost then the recombinant genes are not expressed and there is no protein production. In order to avoid this problem, one can include antibiotic resistance genes into the recombinant plasmid genome and add antibiotics to the growth medium of bacteria such that only bacteria containing the recombinant plasmid can survive [22]. However, not only the loss of plasmids but also the accumulation of plasmids in cells, i.e., a very high copy number of plasmids, is detrimental. With increasing copy number the metabolic burden increases, it can even increase to a level that renders bacteria unproductive [13].

2.1.2 Vertical gene transfer of plasmids

Genes are passed on from one generation to the next. At cell division every daughter cell may inherit genes from the mother cell. This gene transfer by inheritance is referred to as *Vertical Gene Transfer (VGT)* [21].

Low-copy plasmids have an active partitioning system to ensure that at cell division each daughter cell receives a copy of the plasmid [21, 37]. Additionally, some low-copy plasmids secure their remaining in the population by toxin-antitoxin-systems, i.e., the bacteria carrying such a plasmid produce a toxin that kills all bacteria in the population except those who also have the plasmid and therefore also produce the antitoxin [21, 37, 46].

High-copy plasmids lack genes for active partitioning systems [71]. Therefore, it is usually assumed that there is no partitioning system for high-copy plasmids and they are distributed randomly between the daughter cells at cell division [98]. However, there is also evidence that high-copy plasmids are not distributed randomly [71, 84]. It was proposed that a partitioning system exists which moves high-copy plasmids to the cell poles[3] at cell division [71]. Furthermore, it appears that high-copy plasmids are clustered and do not diffuse freely in the cell [77, 84, 88]. This clustering may also affect segregation of high-copy plasmids to the daughter cells.

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[3] The cell poles are the respective ends of rod-shaped cells. One can distinguish the poles, e.g., by their age or by the ability of the bacteria to grow from one pole ("growth pole") but not from the other [1].

If a plasmid is distributed in such a way that at cell division each daughter cell receives at least one copy of this plasmid then it is said to be *segregationally stable*. Otherwise, i.e., if plasmid-free bacteria arise after cell division, the plasmid is called *segregationally unstable* [98]. Segregational instability and the loss of plasmids depends amongst others on the plasmid copy number, variance in the copy number, the host, and plasmid design [85, 98].

2.1.3 Horizontal gene transfer of plasmids

Horizontal Gene Transfer (HGT) is the exchange of genes between two organisms where one organism is not the offspring of one other [11, 37]. These organisms need not be related, they can even belong to different species [11]. For example, there can be HGT between prokaryotes and eukaryotes [37].

HGT is important for the dynamics of bacterial genes and the adaptation of bacteria to different environments [37, 79]. However, it appears that exchange of genes via HGT only occurs rarely in nature [11], e.g., in the gut it is barely detectable [36].

The major mechanisms of HGT of plasmids in bacteria are *conjugation*, *transduction*, and *transformation* [11, 98]. They are described in more detail below.

Conjugation

Conjugation is the transfer of genes from the donor to the recipient via a cell-to-cell connection [11, 101]. It is probably the most important mechanism of HGT of plasmids between bacteria [11, 93, 101]. Conjugation occurs in the soil, in animal intestines, on leaves, and in water [11]. By conjugation, genes can even be transferred across biological domains, e.g., from bacteria into yeast or plant cells [11, 37].

A plasmid that contains all genes necessary for its transfer via conjugation is called a *conjugative* or *self-transmissible* plasmid [101]. There is more than one mechanism for conjugation [37]. Gram-negative[4] bacteria with a conjugative plasmid (the donors) build a protein structure called *pilus* in order to establish a cell-to-cell connection with a bacterium that does not contain a conjugative plasmid (the recipient) [11, 37]. After the connection between donor and recipient is established a copy of the conjugative plasmid is transferred from donor to recipient. The donor does not lose the conjugative plasmid in the process. A scheme of conjugation in Gram-negative bacteria is displayed in Figure 2.1.

In general, conjugation in Gram-positive bacteria is not yet as well understood as in Gram-negative bacteria [37, 101]. Pheromone-induced plasmid transfer in Gram-positive bacteria, however, is well-studied [101]. Plasmid-free cells of some species secret pheromones or clumping-inducing agents which stimulate cell clumping [37, 98]. The clumping of donors and recipients fosters the creation of cell-to-cell connections and thereby increases the rate of conjugation [37].

A plasmid that can be transferred to another host organism by conjugation but does not have all genes necessary for conjugation is called *mobilizable*. Therefore, a mobilizable plasmid can only be transmitted if the donor also contains a conjugative

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[4] Bacteria are often classified as either Gram-positive or Gram-negative depending on how they can be stained with cell-wall specific stains [101].

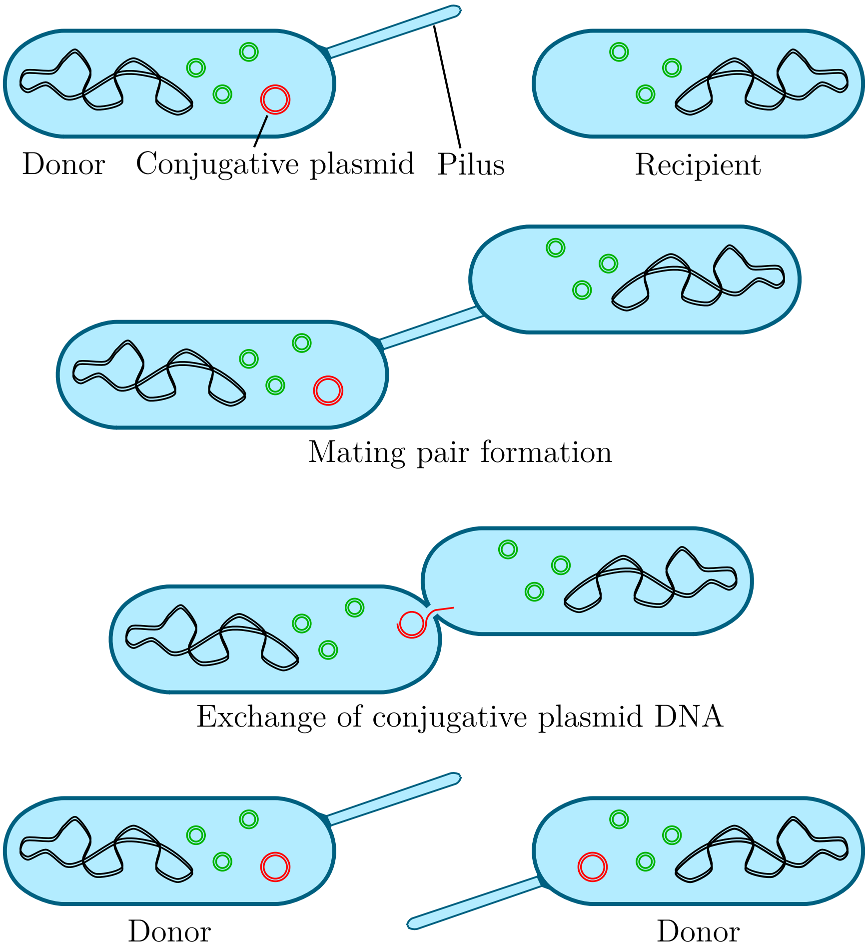


Figure 2.1: Scheme of HGT by conjugation in Gram-negative bacteria.

plasmid [39]. This conjugative plasmid is then called a *mobilizer* [11]. In general, conjugative plasmids are low-copy plasmids and mobilizable plasmids are high-copy plasmids [39]. A *transconjugant* is a recipient cell that has incorporated DNA from a donor cell via conjugation [91].

There are mechanisms to ensure conjugation takes place only between a donor with a conjugative plasmid and a recipient that does not yet carry a conjugative plasmid, i.e., there is no conjugation between two bacteria that both carry a conjugative plasmid [37].

Transduction

Viruses that infect bacteria, so-called *phages*, can also transfer cellular DNA from one cell to another [11, 37]. If a phage integrates its genome into the host bacterium's genome, e.g., by forming a plasmid or by inserting the phage DNA into the chromosome, it is called *lysogenic* or *temperate* [37]. The transfer of cellular DNA from one cell to another by lysogenic phages is called *transduction* [11].

The DNA of lysogenic phages can remain in bacteria for many generations [11]. After a trigger, e.g., a stress signal like hunger, the phages become *lytic*. This means that the phage DNA is excised from the host's chromosome and replicated while the host bacterium's DNA is destroyed. The host cell then produces virus shells and packs phage DNA into the heads of the virus shells and thereby produces phages. These phages are released from the host bacterium [11, 37, 98]. In some cases the phages are released from the host bacterium by lysis, i.e., the cell wall dissolves and the host dies [37]. During the packing of the virus shells, host DNA can be packed into the empty virus heads either instead of or together with phage DNA [11, 98]. Thereby, a plasmid can be transferred within a phage to another bacterium. See Figure 2.2 for a scheme of plasmid gene transfer via transduction.

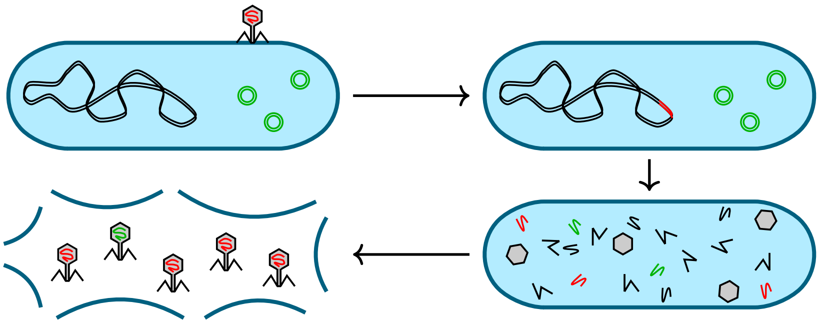


Figure 2.2: Scheme of HGT of a plasmid (green) via transduction. The phage with the plasmid DNA can infect a bacterium and thereby transfer the plasmid from one bacterium to another.

The size of the virus head limits the length of DNA packaged into a virus shell, the DNA may neither be too short nor too long, i.e., plasmids that are similar in DNA length to the length of the phage DNA are more efficiently transferred by transduction [98].

Phages usually have restricted host range [11, 98]. Therefore, transduction between unrelated species is in general unlikely to occur. On the other hand, packaged DNA is protected from degradation and diffuses faster than free DNA [11]. As a cell-to-cell connection is not necessary for transduction, genes can be transported over considerable distances by transduction [11]. Transduction has been observed to occur in marine water, soil, and on the surface of leaves [11, 98].

Transformation

Some bacteria can directly take up free extracellular DNA and include it into their genome by recombination [11]. This process is called *transformation*. The DNA sequence that is taken up in this way usually replaces another partly similar sequence [11].

A cell that has incorporated extracellular DNA via transformation is called *transformed* and cells that are capable of transformation are called *competent* [98]. In order to be capable of transformation, cells have to be in a physiological state called *competence* [37, 100]. Many different bacteria are naturally competent [11]. Competence can also be induced, for example, by a limited amount of nutrients [37]. In this case between 10% and up to almost 100% of bacteria can become competent [37]. Other factors that can induce competence are the accumulation of proteins called *competence factors* in the local environment, a change of growth rate, nutrient access, and cell density [98, 100]. Competence induced in this manner is usually time-limited [100]. The exact mechanisms and inducing factors of competence vary between bacterial species and strains [100]. It is estimated that approximately 1% of bacteria are naturally competent [100]. However, the prevalence of natural transformation might be underestimated as special conditions for the induction of competence could just be a laboratory artifact [98]. For example, soil bacteria are capable of natural transformation when grown under soil conditions [101].

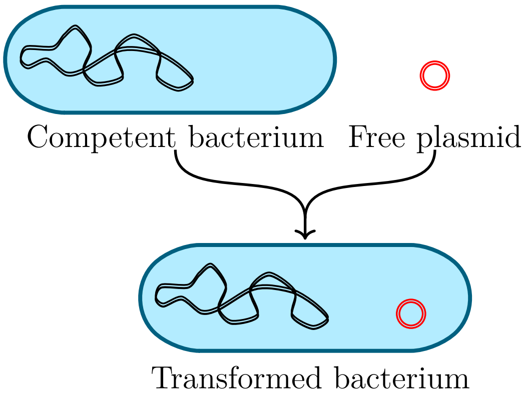


Figure 2.3: A scheme of transformation of bacteria, i.e., uptake of a free plasmid by a competent bacterium.

Transformation is only possible if there is free extracellular DNA present. This is the case in soil and marine water amongst others [11]. Free DNA fragments originate from the decomposition of dead organisms, from viruses, or from active excretion from living cells [11,100]. They are usually small and short-lived but can survive for months if they are absorbed, e.g., by soil particles [11]. Some bacteria prefer to take up DNA fragments from closely related species, while other bacteria seem to make no difference between DNA from related species or other species [98].

For transformation, cell-to-cell contact is not required, therefore it can occur over substantial distances [11]. Transformation is also one mechanism by which antibiotic resistance genes can spread [11]. Interestingly, out of the three main mechanisms of VGT, viz. conjugation, transformation, and transduction, transformation is the only one that is controlled by the bacterium rather than a conjugative plasmid or a phage [45].

2.2 Mathematical Background

In this chapter, we state the definitions, lemmas, and theorems that we use later. The purpose of this section is to clarify the terms and notations used in this thesis and to collect important results that are already known. Therefore, proofs are omitted (in most cases, they can be found in the given reference).

Let X denote a Banach space with norm $\|\cdot\|_X$ and I the identity operator on X.

2.2.1 General

Definition 2.1. A closed set $K \subseteq X$ is called a *cone* if $0 \in K$, u, $v \in K$ implies that $\alpha u + \beta v \in K$ for all α, $\beta \geq 0$, and $v \in K$ and $-v \in K$ implies that $v = 0$ [26, p. 188].

If the cone K satisfies $X = K - K$, then it is called a *reproducing cone* [26, p. 188].

Definition 2.2. The real Banach space $(X, \|\cdot\|_X)$ is called a *Banach lattice* if X is a *Riesz space*, i.e., if there is a partial order "$\leq$" on X with

(i) $f \leq g$ implies that $f + h \leq g + h$ for every $h \in X$,

(ii) $f \geq 0$ implies $\alpha f \geq 0$ for every $\alpha \in \mathbb{R}_{\geq 0}$,

(iii) $f \vee g := \sup\{f, g\}$ and $f \wedge g := \inf\{f, g\}$ exist for all f, $g \in X$, and $f \vee g \in X$, $f \wedge g \in X$,

and if $|f| \leq |g|$ implies that $\|f\|_X \leq \|g\|_X$, where $|f| := f \vee (-f)$ [105, p. 85].

Example 2.3. Consider the Banach space $L^p((a, b))$, i.e., the space of functions such that the p-th power of the function is Lebesgue integrable, with $a < b$, $1 \leq p < \infty$, and the norm $\|f\|_{L^p((a,b))} := \Big(\int\limits_a^b |f(x)|^p \; dx\Big)^{\frac{1}{p}}$ and let $f \leq g$ if and only if $f(x) \leq g(x)$ for almost every (a.e.) $x \in (a, b)$. Then, $\Big(L^p((a, b)), \|\cdot\|_{L^p((a,b))}\Big)$ is a Banach lattice.

Definition 2.4. A function is said to have the *Luzin N-property* if it maps every set of measure zero to a set of measure zero [15, Definition 3.6.8].

Example 2.5. Every absolutely continuous function and therefore in particular every continuously differentiable function has the Luzin N-property [47, p. 53].

Definition 2.6. Let f and g be continuous functions and a be in the domain of both f and g. We say that f *behaves like* g *at* a and write $f \sim g$ at a if

$$\lim_{x \to a} \frac{f(x)}{g(x)} = C \in (0, \infty).$$

Lemma 2.7. ***Grönwall-Bellman inequality***
Let $y(t)$ be a positive and monotonously increasing function and $x(t) \geq 0$, $z(t) \geq 0$, then

$$x(t) \leq y(t) + \int\limits_a^t x(s)\, z(s)\, ds \quad \textit{implies that} \quad x(t) \leq y(t)\, e^{\int_a^t z(s)\, ds}$$

[12, p. 266].

Lemma 2.7 is also know as Grönwall's inequality or Grönwall's lemma.

Definition 2.8. (a) We call an operator A *positive*, if it leaves the cone K invariant, i.e., if $A(K) \subseteq K$ [26, p. 188].

(b) Let the cone K have non-empty interior, i.e., $K^\circ \neq \emptyset$. A positive operator A is called *strictly positive*, if $A(x) \in K^\circ$ for all $x \in K \setminus \{0\}$ [26, p. 188].

Definition 2.9. Let A be a bounded linear operator that maps the real Banach space X into itself, $K \subset X$ a cone, and $K^* \subset X^*$ a cone in the dual space X^* of X. The operator A is called *semi-non-supporting in X w.r.t. K* if A is positive and for all $x \in K \setminus \{0\}$ and all $f \in K^* \setminus \{0\}$ there exist a number $n = n(x, f) \in \mathbb{N}$ such that $f(A^n[x]) > 0$ [90, Definition 1].

Note that we use the term "semi-non-supporting" (which seems to be more commonly used [48,66]) rather than the term "semi-non-support" as Sawashima [90]. The property semi-non-supporting is connected to irreducibility of the operator A.

Definition 2.10. A bounded linear operator $T : X \to Y$, where X and Y are Banach spaces, is called *compact* if $T[B_1(X)]$ with $B_1(X) := \{f \in X : \|f\|_X \leq 1\}$ has compact closure in Y (in the strong topology) [17, p. 157].

It is often very useful to have compactness results for the operators under consideration. There are two well-known and commonly used theorems to show compactness of operators of continuous and L^p-functions, respectively.

Theorem 2.11. ***Theorem of Arzelà-Ascoli***
Let K be a compact metric space with metric d and $\mathcal{H}$ a bounded subset of $\mathcal{C}^0(K)$. If $\mathcal{H}$ is uniformly equicontinuous, *i.e., for all $\varepsilon > 0$ there exists a $\delta > 0$ such that*

$$d(x_1, x_2) < \delta \text{ implies that } |f(x_1) - f(x_2)| < \varepsilon \quad \text{for all } f \in \mathcal{H},$$

then the closure of $\mathcal{H}$ in $\mathcal{C}^0(K)$ is compact [17, Theorem 4.25].

Theorem 2.12. ***Kolmogorov-Riesz-Fréchet Theorem***
Let $n \in \mathbb{N}$, $\mathcal{F}$ a bounded set in $L^p(\mathbb{R}^n)$ where $1 \leq p < \infty$, and denote with τ_h the shift operator, i.e., $(\tau_h f)(x) = f(x + h)$ for all $f \in L^p(\mathbb{R}^n)$ and $x, h \in \mathbb{R}^n$. If

$$\lim_{|h| \to 0} \|\tau_h f - f\|_{L^p(\mathbb{R}^n)} = 0 \quad \text{uniformly in } f \in \mathcal{F},$$

then the closure of $\mathcal{F}|_\Omega$ in $L^p(\Omega)$ is compact for every measurable set $\Omega \subsetneq \mathbb{R}^n$ with finite measure [17, Theorem 4.26].

2.2.2 The Laplace transform

Definition 2.13. The *Laplace transform* of a function $f : \mathbb{R} \to \mathbb{R}$ is given by

$$\hat{f}(s) = \mathcal{L}\{f\}(s) = \int_0^\infty e^{-st} f(t)\, dt,$$

for $s \in \mathbb{C}$, provided that the integral exists [40, p. 1].

The *inverse Laplace transform* maps $\hat{f}$ to f and is denoted by $\mathcal{L}^{-1}\{\cdot\}$.

Definition 2.14. A function f is said to be of *bounded exponential growth* if there are constants $c \in \mathbb{R}$, $a > 0$, and $M > 0$ such that

$$|f(t)| < M\, e^{ct}$$

for all $t > a$ [40, p. 3].

If f is a Lebesgue-measurable function of bounded exponential growth with exponent $c \in \mathbb{R}$ and

$$\int\limits_0^a |f(t)| \; dt \quad \text{exists and is finite,}$$

then $\hat{f}(s)$ exists for $s \in \mathbb{C}$ with $\Re(s) > c$, where $\Re(s)$ denotes the real part of $s \in \mathbb{C}$ (and we denote by $\Im(s)$ the imaginary part of $s \in \mathbb{C}$).

Lemma 2.15. *Let $f : \mathbb{R} \to \mathbb{R}$ be some function and $\hat{f}$ its Laplace transform.*

(a) If the Laplace transform of f', the derivative of f, exists, then

$$\mathcal{L}\{f'\}(s) = s\hat{f}(s) - \lim_{x \to 0^+} f(x).$$

(b) For every $a \in \mathbb{C}$ it holds that

$$\mathcal{L}\Big\{e^{at} f(t)\Big\}(s) = \hat{f}(s - a).$$

(c) If f is of bounded exponential growth, then

$$\frac{d^n}{ds^n} \hat{f}(s) = \mathcal{L}\{(-t)^n f(t)\}$$

exists for all $n \in \mathbb{N}$ and therefore $\hat{f} \in \mathcal{C}^\infty((c, \infty))$.

(d) If $\mathcal{L}\{f\} = \hat{f}$ and $\mathcal{L}\{g\} = \hat{g}$ exist, then

$$\mathcal{L}\{f * g\}(s) = \hat{f}(s) \cdot \hat{g}(s),$$

where $f * g$ denotes the convolution of f and g.

(See, e.g., [40].)

In particular property (d) is very useful. It can, for example, be used to solve equations containing convolutions by applying the Laplace transform, solving the convolution-free equation, and applying the inverse Laplace transform to the solution.

Theorem 2.16. *If $\lim\limits_{t \to 0^+} f(t)$ exists and $\hat{f}$ has a half-plane of convergence, i.e., the Laplace transform $\hat{f}$ of f exists for all $s \in \mathbb{C}$ with $\Re(s) > C$ for some $C \in \mathbb{R}$, then*

$$\lim_{t \to 0^+} f(t) = \lim_{s \to \infty} s\, \hat{f}(s)$$

[28, Theorem 33.5].

Theorem 2.17. *Let* $\hat{f} = \mathcal{L}\{f\}$*. If there are* $s \in \mathbb{R}_{>0}$ *and* $z \in \mathbb{C}$ *such that* $\hat{f}(z)$ *exists and*

$$\hat{f}(z + n\,s) = 0 \quad \textit{for all } n \in \mathbb{N},$$

i.e., the Laplace transform of f *vanishes on an infinite sequence of equidistant points on a line parallel to the real axis, then* $f = 0$ *almost everywhere (a.e.) [28, Theorem 5.3].*

Theorem 2.18. *If the Laplace transforms* $\hat{f}$ *and* $\hat{g}$ *of two functions* f *and* g *are equal on an infinite sequence of equidistant points on a line parallel to the real axis, then* $f = g$ *a.e. [28, Theorem 5.4].*

Lemma 2.19. *If the function* $\hat{f}$ *satisfies*

$$\lim_{s\to\infty} \hat{f}(s) = 0 \quad \textit{and} \quad \lim_{s\to\infty} s\,\hat{f}(s) < \infty,$$

then the inverse Laplace transform of $\hat{f}$ *exists [34, p. 135].*

2.2.3 Spectral theory

We consider a bounded linear operator $A : X \to X$ and first recall the basic definitions in spectral theory.

Definition 2.20. The *resolvent set* $\rho(A)$ of A is defined by

$$\rho(A) := \{\lambda \in \mathbb{C} : \ (\lambda I - A) \text{ is bijective from } X \text{ onto } X\}\,.$$

For $\lambda \in \rho(A)$, the *resolvent* of A is the operator $R(\lambda, A) := (\lambda I - A)^{-1}$, $R(\lambda, A)$ maps X to X.

We call the complement of the resolvent set the *spectrum* of A and denote it by $\sigma(A) := \mathbb{C} \setminus \rho(A)$. The *point spectrum* $\sigma_P(A)$ is the set of $\lambda \in \mathbb{C}$ for which there is a $x \in X \setminus \{0\}$ such that $A[x] = \lambda x$. The elements of $\sigma_P(A)$ are called *eigenvalues* and $x \in X \setminus \{0\}$ with $A[x] = \lambda x$ is called the corresponding *eigenvector* or *eigenfunction.* If $\lambda \in \sigma_P(A)$, then the dimension of the null space of $\lambda I - A$, $\dim(N(\lambda I - A))$, is called the *(geometric) multiplicity* of λ. An eigenvalue with multiplicity one is called a *simple* eigenvalue.

The *spectral radius* $r(A)$ of A is defined by

$$r(A) := \sup_{\lambda \in \sigma(A)} |\lambda|\,.$$

An eigenvalue λ_d of A is called *dominant* if $\Re(\lambda) < \Re(\lambda_d)$ for all $\lambda \in \sigma(A) \setminus \{\lambda_d\}$. (See, e.g., [17, 32, 33, 102].)

If the operator A is compact, then we know more about what its spectrum $\sigma(A)$ looks like.

Theorem 2.21. *If A is a compact operator, then $\sigma(A)$ is a countable set with no accumulation point other than zero. Each $\lambda \in \sigma(A) \setminus \{0\}$ is an eigenvalue of A with finite multiplicity [51, Theorem III-6.26].*

Theorem 2.22. *Every eigenvalue $\lambda \in \sigma_p(A)$ of a compact operator A is also a pole of the resolvent of A [23, Corollary VII.7.8].*

The following theorem is very useful to show existence of an eigenvalue with a corresponding positive eigenfunction.

Theorem 2.23. ***Krein-Rutman Theorem (strong form)***
Let K be a reproducing cone with non-empty interior, i.e., $K^\circ \neq \emptyset$, and let A be a strictly positive compact operator on K. Then $r(A)$ is a simple eigenvalue of A and there is a unique corresponding eigenvector in K° with norm = 1 [26, Theorem VIII-1].

There are cases where the positive cone does not have non-empty interior like $L^1_+(\mathbb{R}_{>0})$. In these cases the following form of the Krein-Rutman Theorem that is sometimes called "weak form" can be used.

Theorem 2.24. ***Krein-Rutman Theorem (weak form)***
Let A be a linear, positive, and compact operator on a reproducing cone K in the Banach space X. If $r(A) \neq 0$, then there is a $x \in K \setminus \{0\}$ with $A[x] = r(A)x$ [26, Theorem VIII-2].

Alternatively, also the following result by Sawashima [90] is useful in the case that the cone under consideration does not have non-empty interior.

Theorem 2.25. *If the operator A is semi-non-supporting and the resolvent $R(\lambda, A)$ has a pole at $\lambda = r(A)$, then the eigenspace corresponding to the eigenvalue $r(A)$ has dimension one [90, Theorem 2].*

2.2.4 Theory of semigroups of operators

For results about theory of semigroups see, e.g., [78, 82] and for a semigroup approach to population equations see, e.g., [68, 102, 103].

Definition 2.26. (a) We call a one parameter family $T(t)$, $t \geq 0$, of bounded linear operators from X to X a *semigroup of bounded linear operators on X* if it satisfies
  (i) $T(0) = I$ and
  (ii) the semigroup property: $T(t+s) = T(t)\,T(s)$ for every t, $s \geq 0$.

(b) A semigroup of bounded linear operators $T(t)$, $t \geq 0$, is *uniformly continuous* if

$$\lim_{t \to 0^+} \|T(t) - I\|_{\mathrm{op}} = 0,$$

where $\|\cdot\|_{\mathrm{op}}$ denotes the operator norm.

(c) A semigroup $T(t)$, $t \geq 0$, of bounded linear operators on X is a *strongly continuous* semigroup of bounded linear operators or short a $\mathcal{C}^0$*-semigroup* if

$$\lim_{t \to 0^+} T(t)x = x \quad \text{for every } x \in X.$$

(d) The *infinitesimal generator* of the semigroup $T(t)$ or shorter just *generator* of $T(t)$ is the linear operator A defined by

$$A[x] := \lim_{t \to 0^+} \frac{T(t)x - x}{t} = \left. \frac{d^+ T(t)x}{dt} \right|_{t=0} \qquad \text{for } x \in D(A),$$

where

$$D(A) := \left\{ x \in X : \lim_{t \to 0^+} \frac{T(t)x - x}{t} \text{ exists} \right\}$$

is the domain of A.
[82, Definitions 1.1.1 and 1.2.1]

The following theorem gives sufficient and necessary conditions for an operator A to be the infinitesimal generator of a uniformly continuous semigroup or a $\mathcal{C}^0$-semigroup.

Theorem 2.27. *(a) The operator A is the inifinitesimal generator of a uniformly continuous semigroup if and only if A is a bounded linear operator [82, Theorem 1.1.2].*

(b) The linear operator A is the infinitesimal generator of a $\mathcal{C}^0$-semigroup that satisfies $\|T(t)\|_{op} \leq e^{\omega t}$ if and only if A is closed, $\overline{D(A)} = X$, and the resolvent set $\rho(A)$ of A contains the ray $\{\lambda \in \mathbb{C} : \Im(\lambda) = 0,\ \lambda > \omega\}$ and for all λ on this ray it holds that $\|R(\lambda, A)\|_{op} \leq \frac{1}{\lambda - \omega}$ [82, Corollary 1.3.8].

(c) If A is the infinitesimal generator of a $\mathcal{C}^0$-semigroup, then $D(A)$ is dense in X and A is a closed linear operator [82, Corollary 1.2.5].

Definition 2.28. (a) The *growth bound* of the linear semigroup $T(t)$, $t \geq 0$, is the real number given by

$$\omega := \inf \left\{ w \in \mathbb{R} : \exists M \in \mathbb{R}_{>0} \text{ such that } \|T(t)\|_{\mathrm{op}} \leq M e^{wt} \text{ for all } t \geq 0 \right\}$$

[65, p. 228].

(b) A $\mathcal{C}^0$-semigroup $T(t)$, $t \geq 0$, on a Banach lattice X is called *positive* if $T(t)$ is a positive operator for each $t \geq 0$, i.e., for all $t \geq 0$

$$f \in X \text{ with } f \geq 0 \quad \text{implies that} \quad T(t)f \geq 0$$

[32, Definition IV.1.7].

Theorem 2.29. *For every $\mathcal{C}^0$-semigroup $T(t)$, $t \geq 0$, there exist constants $M \geq 1$ and $\omega \geq 0$ such that $\|T(t)\|_{op} \leq Me^{t\omega}$ for $t \in [0, \infty)$ [82, Theorem 1.2.2].*

Consider a semigroup $T(t)$ with infinitesimal generator A. Then, for $x \in D(A)$, $T(t)x$ is the solution of the initial value problem

$$\frac{du}{dt} = A[u], \quad u(0) = x \tag{2.1}$$

(see, e.g., [82]). For this reason, the theory of semigroups can be useful to study solutions to differential equations.

Theorem 2.30. *Let A be a densely defined linear operator with $\rho(A) \neq \emptyset$. The initial value problem* (2.1) *has a unique continuously differentiable solution $u(t)$ for every initial value $x \in D(A)$ if and only if A is the infinitesimal generator of a $\mathcal{C}^0$-semigroup $T(t)$. Furthermore, the unique solution is given by $T(t)x$ [82, Theorem 4.1.3].*

If $x \in X \setminus D(A)$, then $T(t)x$ is not necessarily continuously differentiable and therefore it need not be a solution to (2.1) in the classical sense. However, we can still consider it to be a generalized solution. We call a solution of this type a *mild* solution.

Definition 2.31. Let A be the infinitesimal generator of the semigroup $T(t)$, $t \geq 0$, on X. For every $x \in X$, even $x \in X \setminus D(A)$, we call $T(t)x$ a *mild solution* to the initial value problem (2.1) [82, p. 105].

Theorem 2.32. *Let A be the infinitesimal generator of a $\mathcal{C}^0$-semigroup $T(t)$ on X with $\|T(t)\|_{op} \leq Me^{\omega t}$. If B is a bounded linear operator on X, then $A+B$ is the infinitesimal generator of a $\mathcal{C}^0$-semigroup $S(t)$ on X with $\|S(t)\| \leq Me^{(\omega + M\|B\|)t}$. Furthermore, $S(t)$, $t \geq 0$, is the unique solution to the following variation of constants equation:*

$$S(t)x = T(t)x + \int_0^t T(t-s)B[S(s)x]\,ds \qquad \text{for } x \in D(A)$$

[82, Theorem 3.1.1, Proposition 3.1.2].

3 Vertical gene transfer of plasmids

3.1 Derivation of the models

This section is based on [74, 96].

We want to derive a model for vertical gene transfer (VGT) of plasmids in a bacterial population. To be more exact, we aim at a model for bacteria structured by the number of plasmids as we are in particular interested in describing and understanding the loss and accumulation of high-copy plasmids in bacteria.

We consider two VGT models of plasmids that contain different assumptions on how plasmids at distributed to the daughter cells at cell division if the mother cell carries only few plasmids. In the first model, we make no specific assumption on the segregation of plasmids. In the second model, we assume that one daughter receives all of the mother's plasmids. This assumption makes the model more realistic as a mother cell with only one plasmid can only give all its plasmids to one daughter cell. Moreover, it simplifies the analysis of the model.

Following [74, 96], we start with developing models for bacteria structured by the discrete number of plasmids. These models incorporate cell death and division, plasmid reproduction, and the distribution of plasmids to the daughter cells at cell division. As we want to consider high-copy plasmids that can have up to several hundred copies per cell we proceed to the continuum limit. In this way, we derive from the discrete models the continuous models.

3.1.1 Discrete models

First model

We consider a bacterial population structured by the number plasmids. A scheme of the discrete model with plasmid reproduction, cell division, and plasmid segregation is shown in Figure 3.1.

Let $u_i(t)$ denote the density of bacteria carrying $i \in \mathbb{N}_0$ plasmids at time $t \geq 0$. Plasmids reproduce, i.e., bacteria "move" from lower to higher plasmid numbers, according to the plasmid reproduction rate $\tilde{b}(i)$. Since plasmids cannot reproduce if there is no plasmid in the cell we require the plasmid reproduction rate to satisfy $\tilde{b}(0) = 0$ and $\tilde{b}(-1) = 0$. Therefore,

$$\frac{d}{dt} u_i(t) = -\tilde{b}(i)\, u_i(t) + \tilde{b}(i-1)\, u_{i-1}(t).$$

Bacteria die at rate $\tilde{\mu}(i)$ depending on the number of plasmids i in the cell,

$$\frac{d}{dt} u_i(t) = -\tilde{b}(i)\, u_i(t) + \tilde{b}(i-1)\, u_{i-1}(t) - \tilde{\mu}(i)\, u_i(t).$$

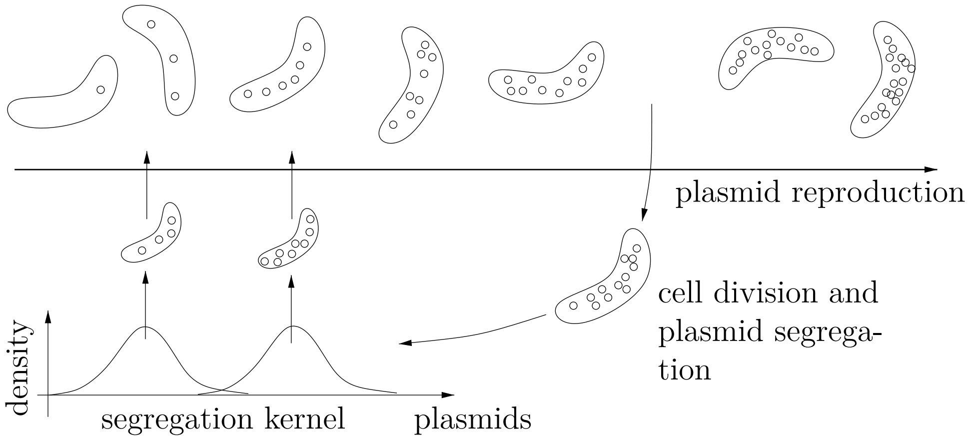


Figure 3.1: Scheme of the first discrete model for VGT: plasmids reproduce, cells divide, and plasmids are distributed to the daughter cells at cell division. The segregation kernel models how the plasmids are distributed to the daughter cells. (Picture from [76].)

Cell division of bacteria occurs at rate $\tilde{\beta}(i)$. When a bacterium divides into two cells the plasmids are divided amongst the two daughter cells. First, we add only the cell division to the model:

$$\frac{d}{dt}u_i(t) = -\tilde{b}(i)\,u_i(t) + \tilde{b}(i-1)\,u_{i-1}(t) - \tilde{\mu}(i)\,u_i(t) - \tilde{\beta}(i)\,u_i(t).$$

Now, we also add the segregation of plasmids to the model. The two daughter cells can be distinguished from each other as only one can inherit the mother's older cell pole (we distinguish the cell poles by their age). We call the daughter cell inheriting the mother's older pole the *first daughter* and the other one the *second daughter*. If the bacteria under consideration are not rod-shaped and the two daughter cells cannot be distinguished from one another by their cell poles or otherwise, then one can randomly choose a daughter cell and call it the first daughter and the other the second daughter. Segregation of plasmids is modeled by the probability $p(i,j)$ that the first daughter receives i plasmids from a mother with j plasmids. The second daughter receives the remaining $j-i$ plasmids. Therefore, for a mother with j plasmids the average number of daughters with i plasmids is given by $p(i,j)+p(j-i,j)$. Including plasmid segregation into the model, we obtain the following discrete model for VGT of plasmids:

$$\begin{aligned}\frac{d}{dt}u_i(t) = &-\tilde{b}(i)\,u_i(t) + \tilde{b}(i-1)\,u_{i-1}(t) - \tilde{\mu}(i)\,u_i(t) - \tilde{\beta}(i)\,u_i(t)\\ &+\sum_{j=i}^{\infty}\tilde{\beta}(j)\,[p(i,j)+p(j-i,j)]\,u_j(t).\end{aligned} \tag{3.1}$$

For consistency, we require that $p(i,j) = 0$ if $i < 0$, $j < 0$, or $i > j$ as a daughter cannot have more plasmids than the mother. By definition of $p(i,j)$ it holds that $\sum_{i=0}^{j} p(i,j) = 1$. We have two more consistency conditions on p. Firstly, for every $j \geq 0$

it holds that

$$\sum_{i=0}^{j} p(i,j) + p(j-i,j) = 2.$$

This condition models that bacteria always divide into two daughter cells. Secondly, as we have mass conservation of plasmids at cell division, the two daughter cells contain as many plasmids as the mother cell, meaning for every $j \geq 0$ it holds that

$$\sum_{i=0}^{j} i\,[p(i,j) + p(j-i,j)] = j.$$

As we will see later in the continuous models, plasmid segregation at low plasmid numbers is central for the properties of the model equation and also for the analysis of the model. For this reason, we will also consider a second slightly altered model.

The first discrete model was numerically simulated using a forward Euler scheme and the software MATLAB [67]. The numerical solution was normalized, i.e.,

$$\tilde{u}_i(t) := \frac{u_i(t)}{\sum\limits_{i=0}^{N} u_i(t)},$$

in order to visualize the development of the distribution of plasmids rather than the growth of bacteria. We denote by N the maximal number of plasmids in a bacterium.

For constant cell division and death rate $\tilde{\beta}$ and $\tilde{\mu}$, the plasmid-free bacteria outgrow the plasmid-bearing bacteria and the plasmid is lost in the long run (see Figure 3.2). If the cell death rate of plasmid-free bacteria is increased, e.g., by adding antibiotics to the growth medium such that bacteria without the plasmid die, then the plasmid-free bacteria cannot outgrow the plasmid-bearing bacteria (see Figure 3.3b). Besides the different number of plasmid-free bacteria and the different growth rate of the bacteria, the distribution of plasmids in the case of constant cell death rate and increased cell death rate for plasmid-free bacteria agree well (see Figure 3.4).

The bacterial population grows exponentially (see Figure 3.2c). For constant cell death and division the numerical estimate for the growth rate is $0.299/h$. If the cell division and death rate are constant, then the exact growth rate of the bacterial population is given by $\tilde{\beta} - \tilde{\mu} = 0.3/h$ (the growth rate of the total bacterial population can be computed by summing (3.1) for all $i \geq 0$, interchanging the order of summation in the last term, and using the above consistency condition on p). In the case of increased cell death rate for plasmid-free bacteria, the numerical estimate for the growth rate is $0.241/h$. As expected, the bacterial population grows slower in this case.

Next, we include a metabolic burden for plasmid-bearing bacteria in form of a linearly decreasing cell division $\tilde{\beta}(i) = 0.4\left(1 - \frac{i}{N}\right)/h$. In this case, there are more bacteria with a high number of plasmids (see Figure 3.3c and Figure 3.4). The bacterial population grows similarly to before, the numerical estimate for the growth rate is $0.248/h$.

For different initial conditions the same distribution of plasmids was obtained. Thus, the numerical simulations indicate that the initial distribution does not influence the distribution of plasmids in the long run.

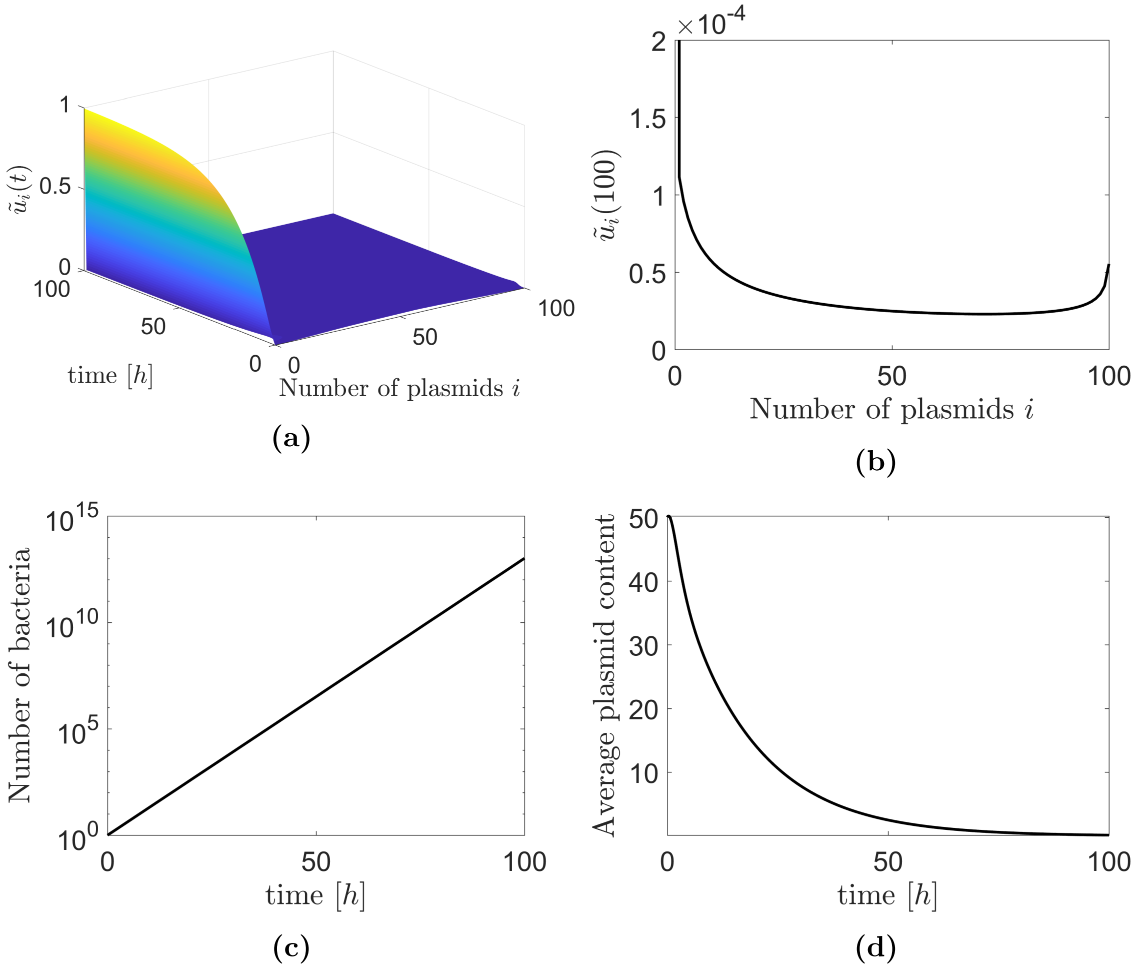
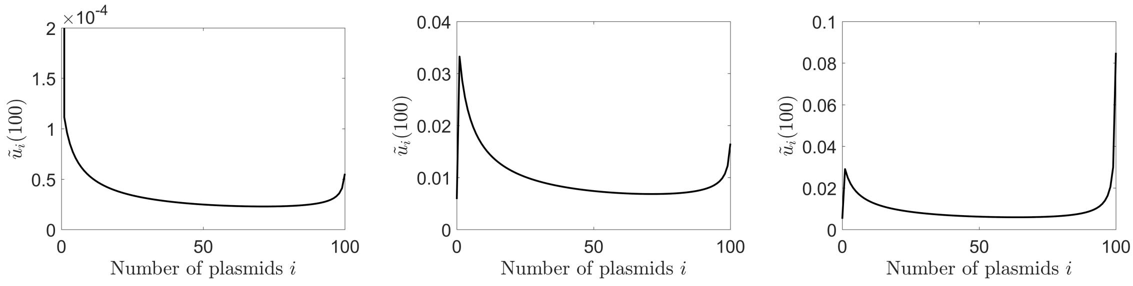


Figure 3.2: Numerical simulation of the normalized solution to the first discrete VGT model (3.1). The parameter values used for the numerical simulations were $\tilde{\beta} = 0.4/h$, $\tilde{\mu} = 0.1/h$, $N = 100$, $\tilde{b}(i) = \frac{i}{N}(N-i)/h$, and uniform plasmid segregation, i.e., $p(i,j) = \frac{1}{j+1}$ for all $0 \leq i \leq j$ and $0 \leq j \leq N$. The initial condition was $u_i(0) = i^2\,(N-i)^2$. We used a forward Euler scheme with $\Delta t = 0.01$. **(a)** Numerical simulation of $\tilde{u}_i(t)$ for $t \in [0, 100]$ and $i \in \{0, 1, \ldots, N\}$. **(b)** Numerical simulation of $\tilde{u}_i(100)$. **(c)** Growth of the bacterial population against time. **(d)** Average plasmid content of bacteria against time.



(a) **(b)** **(c)**

Figure 3.3: Numerical simulation of the normalized solution to the first discrete VGT model (3.1) for different cell division and death rate. The parameter values used for the numerical simulations were $N = 100$, $\tilde{b}(i) = \frac{i}{N}(N-i)/h$, and uniform plasmid segregation, i.e., $p(i,j) = \frac{1}{j+1}$ for all $0 \le i \le j$ and $0 \le j \le N$. The initial condition was $u_i(0) = i^2\,(N-i)^2$. We used a forward Euler scheme with $\Delta t = 0.01$. **(a)** Constant cell division and death rate $\tilde{\beta} = 0.4/h$, $\tilde{\mu} = 0.1/h$. **(b)** Constant cell division rate $\tilde{\beta} = 0.4/h$ and cell death rate $\tilde{\mu}(i) = 0.1/h$ for all $i > 0$, $\tilde{\mu}(0) = 10/h$. **(c)** Linearly decreasing cell division rate $\tilde{\beta}(i) = 0.4\left(1 - \frac{i}{N}\right)/h$ and cell death rate $\tilde{\mu}(i) = 0.1/h$ for all $i > 0$, $\tilde{\mu}(0) = 10/h$.

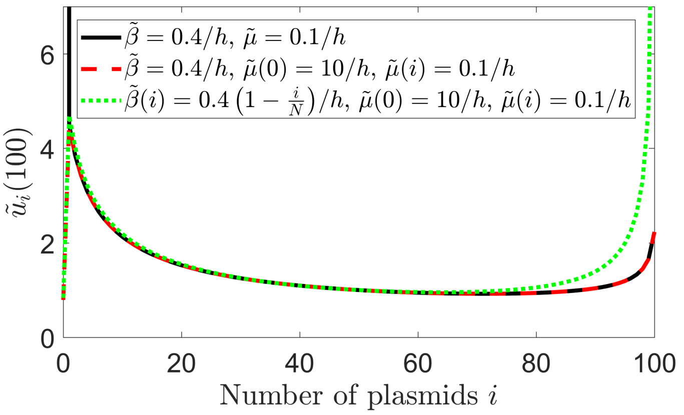


Figure 3.4: Comparison of the numerical solutions for different cell division and death rate. The solutions are compared for constant cell division and death rate (blue solid line), for constant cell division rate and increased cell death rate for plasmid-free bacteria (red dashed line), and for decreasing cell division rate and increased cell death rate for plasmid-free bacteria (green dotted line). In order to be able to better compare the distribution of plasmids for these three cases, the solutions were scaled such that $\tilde{u}_{50}(100) = 1$.

Second model

If a bacterium has only one plasmid, then it can give this plasmid only to one daughter at cell division and the other daughter does not receive a plasmid. This observation is generalized in the following hypothesis for the second model:

> There is a number $n \in \mathbb{N}$ of plasmids such that bacteria with fewer than n plasmids give all plasmids to one daughter at cell division.

In order to incorporate this hypothesis into the discrete model, we distinguish between bacteria with fewer than n plasmids, denoted by $v_i(t)$ for $i \in \mathbb{N}_0$ with $i < n$, and bacteria with at least n plasmids, denoted by $w_i(t)$ for $i \in \mathbb{N}$ with $i \geq n$. The notation and requirements for plasmid reproduction rate, cell death and division rate, and plasmid segregation probability are the same as in the previous model.

In the subpopulation with few plasmids, v_i, one daughter always receives all plasmids and the other daughter receives none, i.e., $p(0,j) + p(j,j) = 1$ for $0 < j < n$. Furthermore, $p(0,0) = 1$ as plasmid-free bacteria can only have plasmid-free daughters. Plasmid reproduction and cell division and death are exactly as in the first model. Therefore, we obtain the following model equations for plasmid-free bacteria, v_0, and bacteria with fewer than n plasmids, v_i with $i \in \mathbb{N}$ and $i < n$:

$$\frac{d}{dt} v_0(t) = \left(\tilde{\beta}(0) - \tilde{\mu}(0)\right) v_0(t) + \sum_{j=1}^{n-1} \tilde{\beta}(j)\, v_j(t) + \sum_{j=n}^{\infty} \tilde{\beta}(j)\, [p(0,j) + p(j,j)]\, w_j(t), \tag{3.2}$$

$$\begin{aligned} \frac{d}{dt} v_i(t) = &-\tilde{b}(i)\, v_i(t) + \tilde{b}(i-1)\, v_{i-1}(t) - \tilde{\mu}(i)\, v_i(t) \\ &+ \sum_{j=n}^{\infty} \tilde{\beta}(j)\, [p(i,j) + p(j-i,j)]\, w_j(t). \end{aligned} \tag{3.3}$$

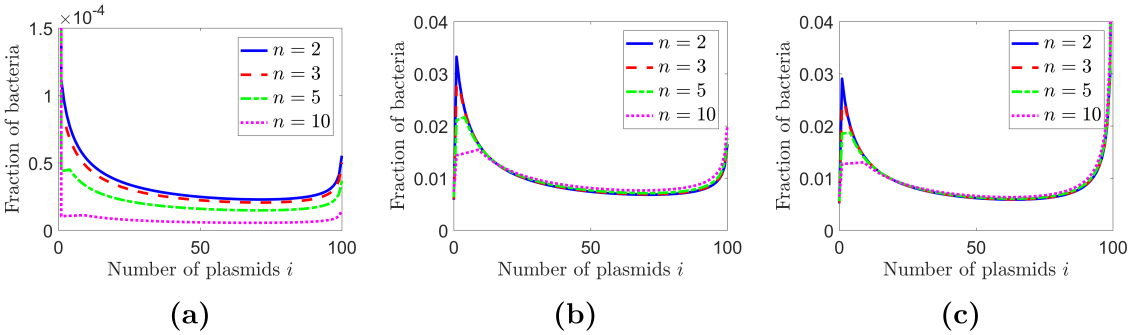
In the equation for v_i, there is no term for cell division of bacteria with fewer than n plasmids. This is due to the assumption that at cell division one daughter cell receives all plasmids and the other none. We distinguish bacteria only by the number of plasmids they carry, meaning if a bacterium with i, where $0 < i < n$, plasmids divides, then it produces a plasmid-free daughter cell and another daughter cell carrying i plasmids. This daughter cell then replaces the mother cell and the number of bacteria with i plasmids does not change due to cell division.

The bacteria with at least n plasmids behave as the bacteria in the previous model, i.e.,

$$\begin{aligned} \frac{d}{dt} w_i(t) = &-\tilde{b}(i)\, w_i(t) + \tilde{b}(i-1)\, w_{i-1}(t) - \left(\tilde{\beta}(i) + \tilde{\mu}(i)\right) w_i(t) \\ &+ \sum_{j=i}^{\infty} \tilde{\beta}(j)\, [p(i,j) + p(j-i,j)]\, w_j(t), \end{aligned} \tag{3.4}$$

where $w_{n-1} := v_{n-1}$. The second discrete model consists of equations (3.2), (3.3), and (3.4).

The second discrete model was also numerically simulated with different thresholds n. For $n = 2$, the first and the second discrete VGT model agree. If the plasmid-free bacteria outgrow the plasmid-bearing bacteria, then a threshold $n > 2$ has only very little effect on the distribution on plasmids (see Figure 3.5a and note the scale). If plasmid-free bacteria do not outgrow the plasmid-bearing bacteria, then the threshold $n > 2$ decreases the number of bacteria with fewer than n plasmids (see Figure 3.5b and Figure 3.5c).



(a) **(b)** **(c)**

Figure 3.5: Comparison of the numerical solution to the second discrete VGT model (3.2) to (3.4) at time $t = 100h$ for the thresholds $n = 2$ (blue solid line), $n = 3$ (red dashed line), $n = 5$ (green dotdashed line), and $n = 10$ (magenta dotted line), and for different cell division and death rate. **(a)** Constant cell division and death rate $\tilde{\beta} = 0.4/h$, $\tilde{\mu} = 0.1/h$. **(b)** Constant cell division rate $\tilde{\beta} = 0.4/h$ and cell death rate $\tilde{\mu}(i) = 0.1/h$ for all $i > 0$, $\tilde{\mu}(0) = 10/h$. **(c)** Linearly decreasing cell division rate $\tilde{\beta}(i) = 0.4\left(1 - \frac{i}{N}\right)/h$ and cell death rate $\tilde{\mu}(i) = 0.1/h$ for all $i > 0$, $\tilde{\mu}(0) = 10/h$.

3.1.2 Continuous models

As we consider high-copy plasmids which can have several hundred copies per bacterium, we proceed to the continuum limit to obtain models for the plasmid load which is modeled by a continuous variable. This continuous variable can be interpreted, e.g., as the relative plasmid number i/N, where N is the maximal plasmid copy number in a single cell [38]. Another interpretation is that the continuous plasmid load measures a plasmid-induced property of the bacterium like the fluorescence level (the plasmid copy number can be estimated by using a fluorescent protein as a plasmid marker and measuring the level of fluorescence [77]).

First model

We proceed to the continuum limit in order to obtain continuous models from the discrete models (see, e.g., [24, 74]). To this end, we approximate $u_i(t)$ by a smooth function $u(z,t)$ where now $z \in \mathbb{R}_{\geq 0}$ models the plasmid content of a cell, i.e., for some $h > 0$ small,

$$u_i(t) \approx \int_{ih-\frac{h}{2}}^{ih+\frac{h}{2}} u(z,t)\,dz \approx u(ih,t)\,h.$$

Likewise, we approximate:

- $\tilde{b}(i) \approx b(ih)\frac{1}{h}$ for $i \in \mathbb{N}_0$.

- $\tilde{\beta}(i) \approx \beta(ih)$ and $\tilde{\mu}(i) \approx \mu(ih)$ for $i \in \mathbb{N}_0$.
- $p(i,j) + p(j-i,j) \approx k(ih, jh)h$ for $i \in \mathbb{N}_0$, $j \in \mathbb{N}$ with $i < j$.

We drop the tilde in the continuous model to distinguish between the rates in the discrete and the continuous model. Substituting these approximations into the first discrete model (3.1), we obtain

$$\begin{aligned}\partial_t u(ih,t)\,h = {}& -b(ih)\,\frac{1}{h}\,u(ih,t)\,h + b(ih-h)\,\frac{1}{h}\,u(ih-h,t)\,h - \beta(ih)\,u(ih,t)\,h \\ & - \mu(ih)\,u(ih,t)\,h + \sum_{j=i}^{\infty} \beta(jh)\,k(ih,jh)\,h\,u(jh,t)\,h.\end{aligned}$$

Next, we divide by h and define $jh =: z'$ and $ih =: z$,

$$\begin{aligned}\partial_t u(z,t)\,h = {}& -\frac{b(z)\,u(z,t) - b(z-h)\,u(z-h,t)}{h} - (\beta(z)+\mu(z))\,u(z,t) \\ & + \sum_{j=i}^{\infty} \beta(jh)\,k(ih,jh)\,h\,u(jh,t).\end{aligned}$$

Finally, we take the limit $h \to 0$ and arrive at

$$\partial_t u(z,t) = -\partial_z\left(b(z)\,u(z,t)\right) - (\beta(z)+\mu(z))\,u(z,t) + \int_z^{\infty} \beta(z')\,k(z,z')\,u(z',t)\,dz'.$$

In this model there is no HGT and therefore no influx of bacteria at $z = 0$. The first continuous VGT model is the above Partial Differential Equation (PDE) together with a zero-flux boundary condition at $z = 0$ and an initial condition:

$$\begin{cases} \partial_t u(z,t) + \partial_z\left(b(z)\,u(z,t)\right) = -\left(\beta(z)+\mu(z)\right)u(z,t) + \displaystyle\int_z^{\infty} \beta(z')\,k(z,z')\,u(z',t)\,dz', \\ b(0)\,u(0,t) = 0 \quad \text{for all } t \geq 0, \quad u(z,0) = \varphi(z) \quad \text{for all } z \geq 0. \end{cases} \tag{3.5}$$

We assume that the parameters of the model satisfy: $b(0) = 0$, $b \geq 0$, $\beta \geq 0$, $\mu \geq 0$, $k \geq 0$. Furthermore, we require for consistency that the plasmid segregation kernel k satisfies:

- $\int_0^{z'} k(z,z')\,dz = 2$ for all $z' > 0$.
- $k(z,z') = 0$ if $z > z'$, $z < 0$, or $z' < 0$.
- $k(z,z') = k(z'-z,z')$ for all z, $z' \geq 0$.
- $\int_0^{z'} z\,k(z,z')\,dz = z'$ for all $z' \geq 0$.

These requirements are a direct consequence of the approximation $k(ih, jh)\, h \approx p(i, j) + p(j-i, j)$, the properties of p, and consistency conditions on p. The first requirement models that each bacterium divides into two daughter bacteria at cell division (see, e.g., [30, 69]). The second requirement models that a daughter cannot have more plasmids than the mother and bacteria cannot have negative plasmid content. The third requirement models that if one daughter receives z plasmids from a mother with z' plasmids, then the other daughter receives the remaining $z' - z$ plasmids and therefore there are as many bacteria receiving z plasmids as there are bacteria receiving the remaining $z' - z$ plasmids. The last requirement on k takes into account that plasmids are not lost during cell division meaning the daughter cells have as many plasmids as the mother had. It is therefore a mass conservation condition (see, e.g., [83]).

Example 3.1. The above conditions on the kernel k are satisfied if there is a function $\Phi : [0, 1] \to \mathbb{R}_{\geq 0}$ such that for all $z' > 0$

$$k(z, z') = \frac{2}{z'}\, \Phi\Big(\frac{z}{z'}\Big)\, \chi_\Omega(z, z'),$$

where $\Omega := \{z,\, z' \in \mathbb{R}_{\geq 0} :\ z \leq z'\}$ and Φ satisfies $\int_0^1 \Phi(\xi)\, d\xi = 1$, $\Phi(\xi) = \Phi(1-\xi)$ for all $\xi \in [0, 1]$, and $\int_0^1 \xi\, \Phi(\xi)\, d\xi = \frac{1}{2}$. Note that the last condition follows directly from the first and second condition and can therefore be omitted.

A kernel of this form models that bacteria always distribute their plasmids in the same way independent of the number of plasmids the bacterium contains at cell division. The way the plasmids are distributed is modeled by the function Φ. For example, if Φ is centered around 0.2 and 0.8, then bacteria give approximately 20% of the plasmids to one daughter cell and the remaining approximately 80% to the other daughter cell (see the plasmid segregation kernel in Figure 3.6).

Example 3.1 motivates the following definition (see [74]).

Definition 3.2. If there exists a function $\Phi : [0, 1] \to \mathbb{R}_{\geq 0}$ such that for $z' > 0$

$$k(z, z') = \frac{2}{z'}\, \Phi\Big(\frac{z}{z'}\Big)\, \chi_\Omega(z, z'),$$

then we call the kernel k *scalable.*

A scalable kernel has the advantage that one can assume the function Φ to be bounded. In this way, it is possible to separate the plasmid segregation modeled by Φ and the pole in the kernel k from one another and simplify computations. It is sometimes assumed in growth-fragmentation equations that the kernel is scalable (see, e.g., [8, 19, 20, 74]) even though these kernels are not usually referred to as scalable.

Second model

We proceed similarly for the second discrete model by first approximating both the subpopulation with fewer than n plasmids and the subpopulation with at least n plasmids

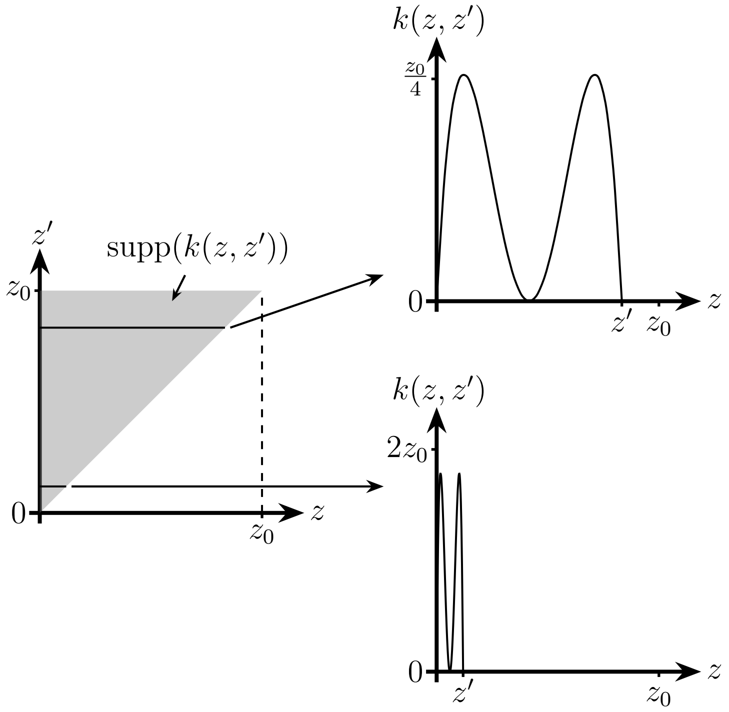


Figure 3.6: Example of a scalable kernel with $\Phi(\xi) = 120\,\xi\left(\frac{1}{2}-\xi\right)^2(1-\xi)$ and maximal plasmid content $z_0 > 0$.

by smooth functions:

$$v_i(t) \approx \int_{ih-\frac{h}{2}}^{ih+\frac{h}{2}} v(z,t)\,dz \approx v(ih,t)\,h \quad \text{and} \quad w_i(t) \approx \int_{ih-\frac{h}{2}}^{ih+\frac{h}{2}} w(z,t)\,dz \approx w(ih,t)\,h.$$

The parameters $\tilde{b}$, $\tilde{\beta}$, and $\tilde{\mu}$ are approximated as before for the first model. However, since in the second discrete model we consider the class of plasmid-free bacteria separately we approximate the segregation kernel differently. For $h > 0$ small:

- For $i \in \mathbb{N}$, $j \in \mathbb{N}$ with $i < j$ and $j \geq n$: $p(i,j) + p(j-i,j) \approx k(ih, jh)\,h$.
- For $j \in \mathbb{N}$ with $j \geq n$: $p(0,j) + p(j,j) \approx k_0(jh)$.

Substituting these approximations into the second discrete model, dividing by h, defining $jh =: z'$, $ih =: z$, and $nh =: m$, and taking the limit $h \to 0$, we obtain the equations

$$\frac{d}{dt}v_0(t) = (\beta(0) - \mu(0))\,v_0(t) + \int_0^m \beta(z')\,v(z',t)\,dz' + \int_m^\infty \beta(z')\,k_0(z')\,w(z',t)\,dz', \quad (3.6)$$

for $z \in (0,m)$

$$\partial_t v(z,t) + \partial_z\left(b(z)\,v(z,t)\right) = -\mu(z)\,v(z,t) + \int_m^\infty \beta(z')\,k(z,z')\,w(z',t)\,dz', \quad (3.7)$$

and for $z \geq m$

$$\begin{aligned}
&\partial_t w(z,t) + \partial_z \left(b(z)\, w(z,t)\right) = \\
&\quad = -\left(\beta(z) + \mu(z)\right) w(z,t) + \beta(z)\, k_0(z)\, w(z,t) + \int_z^\infty \beta(z')\, k(z,z')\, w(z',t)\, dz' \\
&\quad = -\Big(\beta(z)\,(1-k_0(z)) + \mu(z)\Big)\, w(z,t) + \int_z^\infty \beta(z')\, k(z,z')\, w(z',t)\, dz'. \qquad (3.8)
\end{aligned}$$

We assume again that $b(0) = 0$, $b \geq 0$, $\beta \geq 0$, $\mu \geq 0$, $k \geq 0$, and $k_0 \geq 0$. Some of the consistency conditions on the plasmid segregation kernel are now slightly different to before:

- $2\,k_0(z') + \int_0^{z'} k(z,z')\, dz = 2$ for all $z' \geq m$.
- $k_0(z) \in [0,1]$ for all $z \geq m$ and $k_0(z) = 0$ for $z \in (0,m)$.
- $k(z,z') = 0$ if $z \geq z'$, $z < 0$, $z' < m$.
- $k(z,z') = k(z'-z,z')$ for all $z > 0$, $z' \geq m$.
- $z'\,k_0(z') + \int_0^{z'} z\, k(z,z')\, dz = z'$ for all $z' \geq m$.

These conditions model as in the first model that a mother always divides into two daughters, a daughter cannot have more plasmids as its mother, there is no negative plasmid load, if one daughter receives z plasmids from a mother with z' plasmids, then the other daughter receives $z'-z$ plasmids, and we have mass conservation of plasmids at cell division. The function $k_0(z)$ models the fraction of bacteria with $z \geq m$ plasmids that distribute their plasmids such that one daughter cell receives all plasmids and the other none.

As in the first model, we require boundary and initial conditions. We do not have HGT in our model therefore plasmid-free bacteria stay plasmid-free and we have again a zero-flux boundary condition at $z = 0$. Furthermore, if plasmids reproduce in bacteria with less than m plasmids there will eventually be more than m plasmids in the bacteria. In other words, at $z = m$ the outflow of bacteria from the class v equals the inflow into the class w. Overall, we have the boundary conditions

$$\lim_{z\to 0^+} b(z)\, v(z,t) = 0 \quad \text{and} \quad \lim_{z\to m^-} b(z)\, v(z,t) = \lim_{z\to m^+} b(z)\, w(z,t) \quad \text{for all } t \geq 0$$

and the initial conditions

$$v_0(0) = \varphi_0, \quad v(z,0) = \varphi_v(z), \quad \text{and} \quad w(z,0) = \varphi_w(z).$$

The second model consists of equations (3.6) to (3.8) with the above boundary and initial conditions.

We want to simplify this model. If we have solutions for equations (3.7) and (3.8), then we can find a solution to (3.6) by variation of parameters. For this reason we drop in the following equation (3.6) and only analyze the remaining two equations. For the renewal equation, i.e., the case that bacteria always give all plasmids to one daughter at cell division, it is known that there is a discontinuity at $z = 0$ [83]. Since we assume in the second model that bacteria give all plasmids to one daughter if they contain fewer than $m > 0$ plasmids (respectively, fewer than n plasmids in the discrete model), we do not expect to have continuity at $z = 0$.

Remark 3.3. We are interested in the long-term distribution of plasmids in the bacterial population. Therefore, we need to be careful when dropping equation (3.6) since we are then basically ignoring plasmid-free bacteria. If the plasmid-free bacteria can outgrow the plasmid-bearing bacteria in the population, then in the long-run the plasmid will be lost in the bacterial population. If, however, the plasmid-free bacteria grow slower than the plasmid-bearing bacteria, then it is justified to ignore the plasmid-free bacteria as they do not influence the long-term distribution of plasmids.

By adding antibiotics to the growth medium of bacteria, the mortality of plasmid-free bacteria is increased compared to the mortality of plasmid-bearing bacteria. This is typically done in biotechnology to counteract the emergence of plasmid-free bacteria [22]. Thus, in this scenario, we expect the plasmid-free bacteria to grow slower than plasmid-bearing bacteria due to their increased mortality. Thus, it is reasonable to consider only the plasmid-bearing population to find the long-term distribution of plasmids in the population.

Next, we consider the total population (excluding the plasmid-free bacteria v_0). We denote the total population by $u(z,t)$ and formally define it by

$$u(z,t) := v(z,t)\,\chi_{(0,m)}(z) + w(z,t)\,\chi_{[m,\infty)}(z),$$

where χ denotes the characteristic function, i.e., $\chi_A(x) = 1$ if $x \in A$ and $\chi_A(x) = 0$ if $x \notin A$ for some set A. Then, by equations (3.7) and (3.8), $u(z,t)$ satisfies for $z > 0$ the following equation:

$$\begin{aligned}\partial_t u(z,t) + \partial_z\left(b(z)\,u(z,t)\right) = &-\Big(\beta(z)\ (1-k_0(z))\ \chi_{[m,\infty)}(z) + \mu(z)\Big)\,u(z,t)\\ &+ \int\limits_{\max\{m,\,z\}}^{\infty} \beta(z')\,k(z,z')\,u(z',t)\,dz'.\end{aligned}$$

We define $\beta_m(z) := \beta(z)\,\chi_{[m,\infty)}(z)$ and simplify the equation for u to

$$\begin{aligned}\partial_t u(z,t) + \partial_z\left(b(z)\,u(z,t)\right) = &-\Big(\beta_m(z)\ (1-k_0(z)) + \mu(z)\Big)\,u(z,t)\\ &+ \int\limits_{z}^{\infty} \beta_m(z')\,k(z,z')\,u(z',t)\,dz'.\end{aligned}$$

Together with the zero-flux boundary condition $\lim\limits_{z\to 0^+} b(z)\,u(z,t) = 0$ for all $t \geq 0$ and an initial condition, the second continuous VGT model is

$$\begin{cases}\partial_t u(z,t) + \partial_z\left(b(z)\,u(z,t)\right) = -\Big(\beta_m(z)\ (1-k_0(z)) + \mu(z)\Big)\,u(z,t)\\ \qquad\qquad\qquad\qquad\qquad\qquad + \displaystyle\int\limits_{z}^{\infty} \beta_m(z')\,k(z,z')\,u(z',t)\,dz',\\ \lim\limits_{z\to 0^+} b(z)\,u(z,t) = 0 \quad \text{for all } t \geq 0, \quad u(z,0) = \varphi(z) \quad \text{for all } z > 0.\end{cases} \tag{3.9}$$

Comparison of the two models

Both model equations are hyperbolic transport equations with an integral term. They also both contain a non-local term as bacteria with many plasmids can divide in such a way that one of their daughters has only few plasmids.

However, the first and the second model differ from one another in the integral kernel. In the first model, the integral kernel is $\beta(z')\,k(z,z')$. Due to the condition $\int_0^{z'} k(z,z')\,dz = 2$ for all $z' > 0$, it holds that

$$\lim_{z'\to 0^+} \sup_{z\in[0,z']} \beta(z')\,k(z,z') = \infty,$$

if $\beta(z') > c > 0$ in a neighborhood of $z' = 0$. For example, if the kernel k is scalable, then k has a singularity at $z' = 0$.

In the second model the integral kernel satisfies

$$\beta_m(z')\,k(z,z') = \beta(z')\,\chi_{[m,\infty)}(z')\,k(z,z') = 0 \quad \text{for all } 0 < z' < m.$$

Therefore, we can assume the integral kernel is bounded for all $(z,z') \in \mathbb{R}_{>0} \times \mathbb{R}_{>0}$. This assumptions simplifies the analysis of the model. For example, we can show compactness and existence of a real dominant eigenvalue for the eigenproblem associated with the second model (see Section 3.2.2). In the first model this is not possible and we have to use another method to show stability of the eigensolution, viz. the Generalized Relative Entropy method (see Section 3.3.4).

In the following, we refer to the first model as the "singular" VGT model and the second as the "regular" VGT model owing to the singularity or regularity of the integral kernel in the two models.

3.2 Analysis of the regular vertical gene transfer model

This section is based on [96].

We consider model (3.9), the regular model for VGT of plasmids, i.e.,

$$\begin{cases} \partial_t u(z,t) + \partial_z \left(b(z)\,u(z,t)\right) = -\Big(\beta_m(z)\ (1-k_0(z)) + \mu(z)\Big)\,u(z,t) \\ \qquad\qquad\qquad\qquad\qquad\qquad + \displaystyle\int_z^{\infty} \beta_m(z')\,k(z,z')\,u(z',t)\,dz', \\ \displaystyle\lim_{z\to 0^+} b(z)\,u(z,t) = 0 \quad \text{for all } t \ge 0, \quad u(z,0) = \varphi(z) \quad \text{for all } z > 0. \end{cases}$$

The aim of this section is to analyze the long-term behavior of the regular VGT model. First, we state the assumptions on the parameters which we assume to hold throughout this section. Then, we study existence of a solution to the eigenproblem associated with the regular VGT model in Section 3.2.1 and the stability of the eigensolution using spectral analysis in Section 3.2.2.

We make the following assumptions on the parameters of the model:

(A1) There is a $z_0 > m$ such that $b(0) = b(z_0) = 0$, $b(z) > 0$ for all $z \in (0, z_0)$, and $b \in \mathcal{C}^1([0,z_0])$.

(A2) $\beta \in \mathcal{C}^0([0,z_0])$ and $0 < \underline{\beta}_m \leq \beta(z) \leq \overline{\beta}_m$ for all $z \in [m, z_0]$.

(A3) $\mu \in \mathcal{C}^0([0,z_0])$ and $0 \leq \underline{\mu} \leq \mu(z) \leq \overline{\mu}$ for all $z \in [0, z_0]$.

(A4) $k_0 \in \mathcal{C}^0([m,z_0])$, $k_0(z) = 0$ for $z < m$, and $k_0(z) \in [0,1]$ for all $z \in [m, z_0]$.

(A5) k is supported on the set $\Omega := \{z, z' \in [0,z_0] : z \leq z' \text{ and } z' \geq m\}$, k is Lipschitz-continuous in the first variable, i.e., there is a Lipschitz-constant $L > 0$ such that $|k(z_1,z') - k(z_2,z')| \leq L\,|z_1 - z_2|$ for all $z' \in [m, z_0]$ and all z_1, $z_2 \in [0, z']$, $k \geq 0$, k is symmetric in the sense that $k(z,z') = k(z'-z,z')$ for all $(z,z') \in \Omega$, $2k_0(z') + \int_0^{z'} k(z,z')\,dz = 2$ for all $z' \in [m,z_0]$, and $z'\,k_0(z') + \int_0^{z'} z\,k(z,z')\,dz = z'$ for all $z' \in [m, z_0]$.

These assumptions are regularity and non-negativity assumptions on the parameters together with the consistency conditions on the plasmid segregation kernel k and k_0. The integral conditions on k and k_0 model that bacteria always divide in two daughter cells and we have mass conservation of plasmids at cell division (see Section 3.1.2 for more details).

By Assumption **(A1)**, there is a number of plasmids $z_0 > 0$ such that there is no more plasmid reproduction in bacteria with z_0 plasmids. If we start with a bacterial population where no bacterium contains more than z_0 plasmids, i.e., $\varphi(z) = 0$ if $z > z_0$, then the number of plasmids in a bacterium never grows above z_0 due to Assumption **(A1)**. With an increasing number of plasmids the metabolic burden of the host bacterium also increases and the reproduction rate of plasmids decreases. It is possible that the metabolic burden increases so far that a bacterium becomes inactive [13]. For this reason we assume that there is a maximal number of plasmids z_0 and we only consider bacteria with at most z_0 plasmids, i.e., $z \leq z_0$.

For the remainder of this section we always assume that Assumptions **(A1)** to **(A5)** hold. Incorporating these assumptions into the regular VGT model, we obtain the following model equation

$$\begin{cases} \partial_t u(z,t) + \partial_z\left(b(z)\,u(z,t)\right) = -\Big(\beta_m(z)\ \left(1 - k_0(z)\right) + \mu(z)\Big)\,u(z,t) \\ \qquad\qquad\qquad\qquad\qquad\qquad + \displaystyle\int_z^{z_0} \beta_m(z')\,k(z,z')\,u(z',t)\,dz', \\ \lim\limits_{z\to 0^+} b(z)\,u(z,t) = 0 \quad \text{for all } t \geq 0, \quad u(z,0) = \varphi(z) \quad \text{for all } z \in (0, z_0]. \end{cases} \tag{3.10}$$

In the following, we analyze the long-time behavior of solutions to (3.10).

3.2.1 Existence of eigensolutions

This section is based on [96] and extends it to the case that $k_0(z)$ can be positive for $z \in [m, z_0]$. As the long-time behavior is characterized by eigenfunctions (see, e.g., [30, 69, 83]) and we want to study the long-time distribution of plasmids in a bacterial population, we consider the eigenproblem associated with the regular VGT model (3.10):

$$\begin{cases} \dfrac{d}{dz}\Big(b(z)\mathcal{U}(z)\Big) = -\Big(\beta_m(z)\,(1-k_0(z)) + \mu(z) + \lambda\Big)\mathcal{U}(z) + \displaystyle\int_z^{z_0} \beta_m(z')\,k(z,z')\,\mathcal{U}(z')\,dz', \\ \displaystyle\lim_{z\to 0^+} b(z)\mathcal{U}(z) = 0, \quad \mathcal{U}(z) \geq 0 \text{ for all } z \in (0,z_0), \quad \int_0^{z_0} \mathcal{U}(z)\,dz = 1. \end{cases} \tag{3.11}$$

The aim of this section is to show existence of a solution $(\lambda, \mathcal{U})$ to the eigenproblem (3.11).

The increase in the number of plasmids by reproduction is modeled by the flow $Z(t,z)$ that is given by

$$\begin{cases} \dfrac{d}{dt}Z(t,z) = b(Z(t,z)), \quad \text{for all } t \geq 0,\ z \in [0,z_0], \\ Z(0,z) = z, \quad \text{for all } z \in [0,z_0]. \end{cases} \tag{3.12}$$

The Picard-Lindelöf Theorem [3, Theorem 1.10] gives existence and uniqueness of the flow $Z(t,z)$ for $z \in (0,z_0)$ because $b \in \mathcal{C}^1([0,z_0])$ by **(A1)** and thus b is Lipschitz-continuous with Lipschitz constant $\mathrm{Lip}(b) = \max\limits_{z\in[0,z_0]} |b'(z)| < \infty$.

With the flow $Z(t,z)$ we can state the result of this section, the existence of an eigensolution to the regular VGT model.

Theorem 3.4. *Under Assumptions **(A1)** to **(A5)**, and the additional assumption*

(A6) $\int\limits_0^\infty \int\limits_0^{z_0} e^{-\int_0^t \underline{\mu}-\overline{\mu}+\beta_m(Z(s,z'))(1-k_0(Z(s,z')))\,ds}\, dz'dt < \infty,$

there exists a solution $(\lambda, \mathcal{U})$ *to the eigenproblem* (3.11) *such that* $\mathcal{U} \in \mathcal{C}^1((0,z_0))$ *and* $\lambda \in [-\overline{\mu}, 2\overline{\beta}_m + 2 - \underline{\mu}]$.

Remark 3.5. (a) Note that if μ is constant and $k_0 \equiv 0$, then Assumption **(A6)** coincides with Assumption 3-4 of [19] and can therefore be interpreted in the same way: the flow $Z(t,z)$ has to move away from 0 or to be more exact out of the interval $[0,m]$ sufficiently fast (see [19, Remark 7]).

(b) If there is $0 < M < z_0$ such that $\inf_{z\in[M,z_0]} \underline{\mu} - \overline{\mu} + \beta_m(z)\,(1-k_0(z)) > 0$ and there exist $\varepsilon \in (0,1)$, $a > 0$ such that $b(z) \geq a z^{1+\varepsilon}$ in a neighborhood of 0, then Assumption **(A6)** holds (this can be shown as in [19, Proposition 7]).

(c) By change of variables $z := Z(t,z')$, it holds that

$$\int\limits_0^\infty \int\limits_0^{z_0} e^{-\int_0^t \underline{\mu}-\overline{\mu}+\beta_m(Z(s,z'))(1-k_0(Z(s,z')))\,ds} dz'\,dt =$$

$$= \int\limits_0^{z_0} \int\limits_{z'}^{z_0} e^{-\int_{z'}^{z} (\underline{\mu}-\overline{\mu}+\beta_m(y)(1-k_0(y)))/b(y)\,dy} \frac{1}{b(z)}\,dz\,dz'.$$

Therefore, Assumption **(A6)** is equivalent to

$$\int_0^{z_0}\int_{z'}^{z_0} e^{-\int_{z'}^{z}(\underline{\mu}-\overline{\mu}+\beta_m(y)(1-k_0(y)))/b(y)\,dy}\,\frac{1}{b(z)}\,dz\,dz' < \infty.$$

The proof of Theorem 3.4 follows Doumic [29] and Campillo et al. [19]. Doumic [29] shows existence of an eigensolution for a model for a cell population structured by age and molecular content using the method of characteristics, a regularization, and theory of positive operators. Regularization and approximation techniques are very useful and widely used (see, e.g., [53, 69]). Campillo et al. [19] use a similar method as Doumic [29] to show existence of an eigensolution for a growth-fragmentation-death equation for a mass-structured population. They include a constant death rate and assume the segregation kernel is scalable. The following proof extends the approach used by Doumic [29] and Campillo et al. [19] to the case of non-constant cell death rate and general, i.e., not necessarily scalable, plasmid segregation kernel.

Proof. The proof follows [29] and [19]. We do the proof in five steps. First, we regularize the problem and define the operator G_λ^ε that we use later to obtain an eigensolution. This operator was derived by Doumic [29] using the method of characteristics. Due to the regularization, the operator G_λ^ε is strictly positive. In Step 2 we show compactness of G_λ^ε and in Step 3 we use the Krein-Rutman Theorem to show that the spectral radius is an eigenvalue of G_λ^ε. We show that the unregularized operator G_λ^0 has a fixed point in Step 4 and conclude in Step 5 by defining the eigenfunction $\mathcal{U}$ in terms of the fixed point of G_λ^0.

Step 1: Regularization
Firstly, we introduce the regularization parameter $\varepsilon \geq 0$ and define for $z \in [0, z_0]$ and $z' \in [m, z_0]$ the functions

$$B_\varepsilon(z) := \beta_m(z)\,(1-k_0(z)) + \mu(z) + \varepsilon \quad \text{and} \quad \kappa_\varepsilon(z, z') := \beta_m(z')k(z, z') + \frac{2\varepsilon}{z_0}.$$

We consider the Banach space $\mathcal{C}^0([0, z_0])$ of continuous functions endowed with the supremum norm $\|\cdot\|_\infty$. Let

$$\underline{\lambda}_\varepsilon := \inf\left\{\lambda \in \mathbb{R} : \int_0^\infty\int_0^{z_0} e^{-\int_0^t \lambda + B_\varepsilon(Z(s,z'))\,ds}\,dz'\,dt < \infty\right\}.$$

Since $\lambda + B_\varepsilon(Z(s, z')) \leq \lambda + \overline{\beta}_m + \overline{\mu} + \varepsilon$ for all $z' \in [0, z_0]$, $s \in [0, \infty)$,

$$\int_0^\infty\int_0^{z_0} e^{-t(\lambda+\overline{\beta}_m+\overline{\mu}+\varepsilon)}\,dz'\,dt \leq \int_0^\infty\int_0^{z_0} e^{-\int_0^t \lambda + B_\varepsilon(Z(s,z'))\,ds}\,dz'\,dt.$$

For $\lambda < -(\overline{\beta}_m + \overline{\mu} + \varepsilon)$ the integral on the left-hand side diverges, therefore we know that $\underline{\lambda}_\varepsilon \geq -(\overline{\beta}_m + \overline{\mu} + \varepsilon)$.

Since $\lambda + B_\varepsilon(Z(s,z')) \geq \underline{\mu} - \overline{\mu} + \beta_m(Z(s,z'))\,(1 - k_0(Z(s,z')))$ for all $\lambda > -\overline{\mu}$ and $z' \in [0, z_0]$, $s \in [0, \infty)$, by Assumption **(A6)**,

$$\int\limits_0^\infty \int\limits_0^{z_0} e^{-\int_0^t \lambda + B_\varepsilon(Z(s,z'))\,ds}\,dz'\,dt \leq \int\limits_0^\infty \int\limits_0^{z_0} e^{-\int_0^t \underline{\mu} - \overline{\mu} + \beta_m(Z(s,z'))(1-k_0(Z(s,z')))\,ds}\,dz'\,dt < \infty.$$

Therefore, $\underline{\lambda}_\varepsilon \in [-(\overline{\beta}_m + \overline{\mu} + \varepsilon), -\overline{\mu}]$.

Let $\varepsilon \geq 0$ and $\lambda > \underline{\lambda}_\varepsilon$ for the remainder of this proof. For $f \in \mathcal{C}^0([0, z_0])$ define the operator G^ε_λ by

$$G^\varepsilon_\lambda[f](z) := \int\limits_0^\infty \int\limits_0^{z_0} \kappa_\varepsilon(z, Z(t,z'))f(z')e^{-\int_0^t \lambda + B_\varepsilon(Z(s,z'))\,ds}\,dz'\,dt.$$

G^ε_λ is well-defined for $\lambda > \underline{\lambda}_\varepsilon$, therefore in particular also for $\lambda > -\overline{\mu}$.

The operator G^ε_λ maps continuous functions to continuous functions as $\beta_m(z')k(z,z')$ is continuous in z for a fixed $z' \in [0, z_0]$. Due to the regularization, the operator G^ε_λ is strictly positive in the sense that for every $f \in \mathcal{C}^0([0, z_0])$ with $f \geq 0$ and $f \neq 0$, $G^\varepsilon_\lambda[f](z) > 0$ for all $z \in [0, z_0]$ and for all $\varepsilon > 0$.

Step 2: Compactness of G^ε_λ

Next, we consider the unit ball of functions $f \in \mathcal{C}^0([0, z_0])$ with $\|f\|_\infty \leq 1$ and show that $G^\varepsilon_\lambda[f]$ is uniformly bounded and equicontinuous. The Theorem of Arzelà-Ascoli (see Theorem 2.11) then implies that the operator G^ε_λ is compact.

It holds for all $f \in \mathcal{C}^0([0, z_0])$ with $\|f\|_\infty \leq 1$ that

$$\|G^\varepsilon_\lambda[f]\|_\infty \leq \left(\overline{\beta}_m \|k\|_\infty + \frac{2\varepsilon}{z_0}\right) \|f\|_\infty \int\limits_0^\infty \int\limits_0^{z_0} e^{-\int_0^t \lambda + B_\varepsilon(Z(s,z'))\,ds}\,dz'\,dt,$$

where $\|k\|_\infty = \|\,k|_\Omega\|_\infty < \infty$ and the last factor is finite because $\lambda > \underline{\lambda}_\varepsilon$. Therefore, $G^\varepsilon_\lambda[f]$ is uniformly bounded.

Let $f \in \mathcal{C}^0([0, z_0])$ with $\|f\|_\infty \leq 1$ and z_1, $z_2 \in [0, z_0]$, then

$$|G^\varepsilon_\lambda[f](z_1) - G^\varepsilon_\lambda[f](z_2)| \leq \overline{\beta}_m\, L\, |z_1 - z_2|\, \|f\|_\infty \int\limits_0^\infty \int\limits_0^{z_0} e^{-\int_0^t \lambda + B_\varepsilon(Z(s,z'))\,ds}\,dz'dt.$$

Therefore, $G^\varepsilon_\lambda[f]$ is equicontinuous and by the Theorem of Arzelà-Ascoli, the operator $G^\varepsilon_\lambda : \mathcal{C}^0([0, z_0]) \to \mathcal{C}^0([0, z_0])$ is compact for every $\varepsilon \geq 0$ and $\lambda > \underline{\lambda}_\varepsilon$.

Step 3: Eigenelements

As G^ε_λ is compact and strictly positive for $\varepsilon > 0$ and $\lambda > \underline{\lambda}_\varepsilon$, by the Krein-Rutman Theorem (see Theorem 2.23), the spectral radius $r(G^\varepsilon_\lambda) > 0$ is a simple eigenvalue of G^ε_λ and there is a unique positive eigenfunction $\Psi^\varepsilon_\lambda \in \mathcal{C}^0([0, z_0])$ with $\|\Psi^\varepsilon_\lambda\|_\infty = 1$.

The map $\lambda \mapsto r(G^\varepsilon_\lambda)$ is continuous (see, e.g., [19]).

Step 4: Fixed point of G^0_λ

Now, we use the continuity of the map $\lambda \mapsto r(G^\varepsilon_\lambda)$ and the fact that a fixed point is an eigenfunction corresponding to the eigenvalue 1 in order to show that there is a fixed point for the operator G^ε_λ.

First, we show that the spectral radius takes values ≤ 1. For $f \in \mathcal{C}^0([0,z_0])$ integrate w.r.t. z, for $\lambda > -\underline{\mu}$,

$$\begin{aligned}\int_0^{z_0} G_\lambda^\varepsilon[f](z)\,dz &= \int_0^\infty \int_0^{z_0} \Big(2\beta_m(Z(t,z')) + 2\varepsilon\Big)\, f(z')\, e^{-\int_0^t \lambda + B_\varepsilon(Z(s,z'))\,ds}\, dz'\, dt \\ &\leq \Big(2\overline{\beta}_m + 2\varepsilon\Big) \int_0^\infty \int_0^{z_0} f(z') e^{-t(\lambda+\underline{\mu})}\, dz'\, dt \\ &\leq \frac{2\overline{\beta}_m + 2\varepsilon}{\lambda + \underline{\mu}} \int_0^{z_0} f(z')\, dz'.\end{aligned}$$

Let $f = \Psi_\lambda^\varepsilon$, then

$$r(G_\lambda^\varepsilon) \int_0^{z_0} \Psi_\lambda^\varepsilon(z)\,dz \leq \frac{2\overline{\beta}_m + 2\varepsilon}{\lambda + \underline{\mu}} \int_0^{z_0} \Psi_\lambda^\varepsilon(z')\,dz'.$$

Therefore, $r(G_\lambda^\varepsilon) \leq 1$ for $\lambda \geq 2\overline{\beta}_m + 2\varepsilon - \underline{\mu}$.

In a similar way, we obtain a lower bound for $r(G_\lambda^\varepsilon)$. Integration w.r.t. z over $[0,z_0]$ yields

$$\begin{aligned}\int_0^{z_0} G_\lambda^\varepsilon[f](z)\,dz &= \int_0^\infty \int_0^{z_0} \Big(2\beta_m(Z(t,z'))(1-k_0(Z(t,z'))) + 2\varepsilon\Big) f(z') e^{-\int_0^t \lambda + B_\varepsilon(Z(s,z'))\,ds}\, dz' dt \\ &\geq 2 \int_0^\infty \int_0^{z_0} e^{-t(\lambda+\overline{\mu})} f(z')\, \partial_t \Big(-e^{-\int_0^t \beta_m(Z(s,z'))(1-k_0(Z(s,z')))+\varepsilon\,ds} \Big)\, dz'\, dt.\end{aligned}$$

Recall that we assume $\lambda > -\overline{\mu}$. Integration by parts yields

$$\begin{aligned}\int_0^{z_0} G_\lambda^\varepsilon[f](z)\,dz \geq{}& 2 \int_0^{z_0} f(z')\,dz' \\ &- 2 \int_0^\infty \int_0^{z_0} f(z')\,(\lambda + \overline{\mu})\, e^{-\int_0^t \lambda + \overline{\mu} + \beta_m(Z(s,z'))(1-k_0(Z(s,z')))+\varepsilon\,ds}\, dz'\, dt.\end{aligned}$$

With $f = \Psi_\lambda^\varepsilon$, we obtain

$$\begin{aligned}r(G_\lambda^\varepsilon) \int_0^{z_0} \Psi_\lambda^\varepsilon(z)\,dz &\geq 2 \int_0^{z_0} \Psi_\lambda^\varepsilon(z')\,dz' \\ &\quad - 2\,(\lambda + \overline{\mu}) \int_0^\infty \int_0^{z_0} \Psi_\lambda^\varepsilon(z')\, e^{-\int_0^t \lambda + \overline{\mu} + \beta_m(Z(s,z'))(1-k_0(Z(s,z')))+\varepsilon\,ds}\, dz'\, dt \\ &\geq 2 \int_0^{z_0} \Psi_\lambda^\varepsilon(z')\,dz' - 2(\lambda+\overline{\mu}) \int_0^\infty \int_0^{z_0} \Psi_\lambda^\varepsilon(z')\, e^{-\int_0^t \lambda + B_\varepsilon(Z(s,z'))\,ds}\, dz' dt.\end{aligned}$$

Hence, $\lim\limits_{\lambda \to -\overline{\mu}^+} r(G_\lambda^\varepsilon) \geq 2$. Due to continuity of the map $\lambda \mapsto r(G_\lambda^\varepsilon)$, for every $\varepsilon > 0$ there exists a $\lambda_\varepsilon \in [-\overline{\mu}, 2\overline{\beta}_m + 2\varepsilon - \underline{\mu}]$ such that $r(G_{\lambda_\varepsilon}^\varepsilon) = 1$. For brevity, denote the associated eigenfunction by $\Psi_\varepsilon =: \Psi_{\lambda_\varepsilon}^\varepsilon$.

For every $\varepsilon \in (0,1]$ the operator $G^{\varepsilon}_{\lambda_\varepsilon}$ has the fixed point $\Psi_\varepsilon \in \mathcal{C}^0([0,z_0])$ with $\Psi_\varepsilon > 0$, $\|\Psi_\varepsilon\|_\infty = 1$, and $\lambda_\varepsilon \in [-\overline{\mu}, 2\overline{\beta}_m + 2 - \underline{\mu}]$. The family $(\Psi_\varepsilon)_{0<\varepsilon\le 1}$ is uniformly bounded by 1. Let z_1, $z_2 \in [0,z_0]$, we use $\Psi_\varepsilon = G^{\varepsilon}_{\lambda_\varepsilon}[\Psi_\varepsilon]$ and the same estimates as in the Step 2 to obtain

$$\begin{aligned} |\Psi_\varepsilon(z_1) - \Psi_\varepsilon(z_2)| &\le \overline{\beta}_m\, L\, |z_1 - z_2| \int_0^\infty \int_0^{z_0} e^{-\int_0^t \lambda_\varepsilon + B_\varepsilon(Z(s,z'))\, ds}\, dz'dt \\ &\le \overline{\beta}_m\, L\, |z_1 - z_2| \int_0^\infty \int_0^{z_0} e^{-\int_0^t \underline{\mu} - \overline{\mu} + \beta_m(Z(s,z'))(1-k_0(Z(s,z')))\, ds}\, dz'dt, \end{aligned}$$

where the last factor is bounded by Assumption **(A6)**. Thus, the family $(\Psi_\varepsilon)_{0<\varepsilon\le 1}$ is compact by the Theorem of Arzelà-Ascoli. Hence, we can extract a subsequence of $(\lambda_\varepsilon, \Psi_\varepsilon)_{0<\varepsilon\le 1}$ which converges for $\varepsilon \to 0$ to $(\lambda, \Psi) \in [-\overline{\mu}, 2\overline{\beta}_m + 2 - \underline{\mu}] \times \mathcal{C}^0([0,z_0])$ with $\Psi \ge 0$ and $\|\Psi\|_\infty = 1$. By Assumption **(A6)** and dominated convergence, the function Ψ satisfies the following equation:

$$\Psi(z) = \int_0^\infty \int_0^{z_0} \beta_m(Z(t,z'))\, k(z, Z(t,z'))\, \Psi(z')\, e^{-\int_0^t \lambda + \beta_m(Z(s,z'))(1-k_0(Z(s,z'))) + \mu(Z(s,z'))\, ds}\, dz'dt.$$

Step 5: Conclusion
We conclude by defining for every $z \in (0, z_0)$

$$\mathcal{U}(z) := \frac{1}{b(z)} \int_0^z \Psi(y)\, e^{-\int_y^z \frac{\lambda + \beta_m(s)(1-k_0(s)) + \mu(s)}{b(s)}\, ds}\, dy \tag{3.13}$$

and showing that $\mathcal{U}$ is an eigenfunction corresponding to the eigenvalue λ.

For all $z \in (0,z_0)$, $\mathcal{U}(z) \ge 0$ and $\mathcal{U} \in \mathcal{C}^1((0,z_0))$. Moreover,

$$(b(z)\mathcal{U}(z))_z = -\Big(\lambda + \beta_m(z)(1-k_0(z)) + \mu(z)\Big)\mathcal{U}(z) + \Psi(z).$$

With change of variables $Z(t,z') \to y$ and $Z(s,z') \to w$, we obtain

$$\begin{aligned} \Psi(z) &= \int_0^\infty \int_0^{z_0} \beta_m(Z(t,z'))k(z,Z(t,z'))\Psi(z')e^{-\int_0^t \lambda + \beta_m(Z(s,z'))(1-k_0(Z(s,z'))) + \mu(Z(s,z'))\, ds}\, dz'dt \\ &= \int_0^{z_0} \int_{z'}^{z_0} \beta_m(y)\, k(z,y)\, \Psi(z')\, e^{-\int_{z'}^y \frac{\lambda + \beta_m(w)(1-k_0(w)) + \mu(w)}{b(w)}\, dw}\, \frac{1}{b(y)}\, dy\, dz' \\ &= \int_0^{z_0} \beta_m(y)\, k(z,y)\, \frac{1}{b(y)} \int_0^y \Psi(z')\, e^{-\int_{z'}^y \frac{\lambda + \beta_m(w)(1-k_0(w)) + \mu(w)}{b(w)}\, dw}\, dz'\, dy \\ &= \int_z^{z_0} \beta_m(y)\, k(z,y)\, \mathcal{U}(y)\, dy. \end{aligned}$$

Therefore, $\mathcal{U}$ defined by (3.13) is a solution to the PDE in (3.11).

Since it follows directly from the definition of $\mathcal{U}$ that the zero-flux boundary condition and the non-negativity condition are satisfied, it remains to show that the integrability condition also holds which we do now. Using again change of variables, $\|\Psi\|_\infty = 1$, $\lambda \in [-\overline{\mu}, 2\overline{\beta}_m + 2 - \underline{\mu}]$, and Assumption **(A6)**,

$$\begin{aligned}
\int_0^{z_0} \mathcal{U}(z)\, dz &= \int_0^{z_0} \frac{1}{b(z)} \int_0^{z} \Psi(y)\, e^{-\int_y^z \frac{\lambda+\beta_m(s)+\mu(s)}{b(s)}\, ds}\, dy\, dz \\
&\leq \|\Psi\|_\infty \int_0^{z_0} \int_y^{z_0} e^{-\int_y^z (\lambda+\beta_m(s)+\mu(s))\, \frac{ds}{b(s)}}\, \frac{dz}{b(z)}\, dy \\
&= \int_0^{z_0} \int_0^{\infty} e^{-\int_0^t \lambda+\beta_m(Z(w,y))+\mu(Z(w,y))\, dw}\, dt\, dy \\
&\leq \int_0^{z_0} \int_0^{\infty} e^{-\int_0^t \underline{\mu}-\overline{\mu}+\beta_m(Z(w,y))\, dw}\, dt\, dy < \infty.
\end{aligned}$$

Therefore, $\tilde{\mathcal{U}}(z) = \frac{\mathcal{U}(z)}{\int_0^{z_0} \mathcal{U}(z')\, dz'}$ is a solution to (3.11). □

3.2.2 Spectral analysis

This section is based on [96]. We are interested in the stability of the eigenfunction and the long-time distribution of plasmids in a bacterial population and therefore we perform a spectral analysis of the operator A that is defined such that the model equation (3.10) is given by $\partial_t u(z,t) = A[u(\cdot,t)](z)$. The operator A maps a function $U \in \mathcal{W} := \{f \in L^1((0,z_0)) :\ (b\,f)' \in L^1((0,z_0))\}$ to

$$\begin{aligned}
A[U](z) := &-\frac{d}{dz}\Big(b(z)\,U(z)\Big) - \Big(\beta_m(z)\,(1-k_0(z)) + \mu(z)\Big)\,U(z) \\
&+ \int_z^{z_0} \beta_m(z')\,k(z,z')\,U(z')\,dz'.
\end{aligned}$$

Hence, A maps $\mathcal{W}$ to $L^1((0,z_0))$.

The aim of this section is to show that the operator A has a simple real dominant eigenvalue. In order to show that it is a simple eigenvalue, we need to make an additional assumption on the plasmid segregation kernel k, viz. that k is a.e. strictly positive. We assume the following assumption to hold for the remainder of this section:

(A7) $k(z,z') > 0$ for a.e. $z \in (0,z')$, $z' \in (m,z_0)$.

Assumption **(A7)** holds for example for a scalable kernel with $\Phi(\xi) > 0$ for a.e. $\xi \in (0,1)$.

Instead of directly analyzing the spectrum of the integro-differential operator A, we relate the spectrum of A to the spectrum of an integral operator T_λ and analyze its spectrum.

Let $I : \mathcal{W} \to L^1((0,z_0))$ be the embedding of $\mathcal{W} \subseteq L^1((0,z_0))$ into $L^1((0,z_0))$. For $\lambda \in \mathbb{C}$ define the operator $R_\lambda : \mathcal{W} \to L^1((0,z_0))$ by $R_\lambda := (\lambda I - A)$. The operator R_λ

is invertible if and only if for every $f \in L^1((0,z_0))$ there is a unique $U \in \mathcal{W}$ such that

$$\frac{d}{dz}\Big(b(z)\,U(z)\Big)+\Big(\lambda+\beta_m(z)(1-k_0(z))+\mu(z)\Big)U(z)-\int\limits_z^{z_0}\beta_m(z')k(z,z')U(z')\,dz'=f(z). \tag{3.14}$$

We use the transform $v(z) := b(z)\,U(z)$. If $U \in \mathcal{W}$, then

$$v \in \mathcal{W}_v := \left\{ f \in L^1\left((0,z_0), \frac{dz}{b(z)}\right) :\ f' \in L^1((0,z_0))\right\}.$$

Moreover, the function v is a solution to the integro-differential equation

$$v'(z)+\frac{\lambda+\beta_m(z)(1-k_0(z))+\mu(z)}{b(z)}\,v(z)-\int\limits_z^{z_0}\frac{\beta_m(z')\,k(z,z')}{b(z')}\,v(z')\,dz'=f(z). \tag{3.15}$$

For the sake of brevity we define

$$\alpha(\lambda,z) := \frac{\lambda+\beta_m(z)(1-k_0(z))+\mu(z)}{b(z)} \quad \text{and} \quad L^1_w := L^1\left((0,z_0), \frac{dz}{b(z)}\right).$$

The weighted L^1-space L^1_w is a Banach space with the norm

$$\|f\|_{L^1_w} := \int\limits_0^{z_0} |f(z)|\,\frac{dz}{b(z)}.$$

We can reformulate equation (3.15) using variation of parameters. In this way, we obtain an integral equation for v that does not contain the derivative of v. Variation of parameters and $\lim\limits_{z\to 0^+} v(z) = 0$ (as $\lim\limits_{z\to 0^+} b(z)u(z,t) = 0$ for all $t \geq 0$ for every solution u to (3.10)) yields

$$v(z)=\int\limits_0^z\int\limits_x^{z_0}\frac{\beta_m(z')k(x,z')}{b(z')}v(z')\,dz'\,e^{-\int_x^z \alpha(\lambda,y)\,dy}\,dx+\int\limits_0^z f(x)e^{-\int_x^z \alpha(\lambda,\,y)\,dy}\,dx. \tag{3.16}$$

For $v \in L^1_w$ we define the first summand on the right-hand side in (3.16) as the operator T_λ, i.e.,

$$T_\lambda[v](z) := \int\limits_0^z\int\limits_x^{z_0}\frac{\beta_m(z')\,k(x,z')}{b(z')}\,v(z')\,dz'\,e^{-\int_x^z \alpha(\lambda,\,y)\,dy}\,dx.$$

Note that we have the index λ in T_λ as α depends on λ.

In the next lemma, we show some basic properties of the operator T_λ before relating the spectrum of T_λ to the spectrum of A in Lemma 3.7.

Lemma 3.6. *Let $\Re(\lambda) > -\underline{\mu}$. The operator T_λ is a bounded operator that maps L^1_w to L^1_w and the operator norm of T_λ satisfies*

$$\|T_\lambda\|_{op} \leq \frac{2\overline{\beta}_m}{\Re(\lambda)+\underline{\mu}}.$$

Proof. Note that $\Re(\alpha(\lambda, z)) = \alpha(\Re(\lambda), z)$ as b, β_m, μ, and k_0 are real. Let $v \in L^1_w$, then

$$\|T_\lambda[v]\|_{L^1_w} \le \int_0^{z_0} \frac{1}{b(z)} \int_0^{z} \int_x^{z_0} \frac{\beta_m(z')\,k(z,z')}{b(z')}\,|v(z')|\,dz'\,e^{-\int_x^z \alpha(\Re(\lambda),\,y)\,dy}\,dx\,dz$$
$$= \int_0^{z_0} \int_x^{z_0} \int_x^{z_0} \frac{1}{b(z)}\,e^{-\int_x^z \alpha(\Re(\lambda),\,y)\,dy}\,dz\,\frac{\beta_m(z')\,k(z,z')}{b(z')}\,|v(z')|\,dz'\,dx.$$

With

$$\frac{d}{dz}\left(e^{-\int_x^z \alpha(\Re(\lambda),\,y)\,dy}\right) = -\alpha(\Re(\lambda), z)\,e^{-\int_x^z \alpha(\Re(\lambda),\,y)\,dy}$$
$$= -\frac{\Re(\lambda) + \beta_m(z) + \mu(z)}{b(z)}\,e^{-\int_x^z \alpha(\Re(\lambda),\,y)\,dy},$$

we obtain that for $\Re(\lambda) > -\underline{\mu}$,

$$\frac{1}{b(z)}\,e^{-\int_x^z \alpha(\Re(\lambda),\,y)\,dy} \le -\frac{d}{dz}\left(e^{-\int_x^z \alpha(\Re(\lambda),\,y)\,dy}\right)(\Re(\lambda) + \underline{\mu})^{-1}.$$

Thus,

$$\|T_\lambda[v]\|_{L^1_w} \le (\Re(\lambda) + \underline{\mu})^{-1} \int_0^{z_0} \int_x^{z_0} \frac{\beta_m(z')\,k(z,z')}{b(z')}\,|v(z')|\,dz'\,dx$$
$$\le \frac{\overline{\beta}_m}{\Re(\lambda) + \underline{\mu}} \int_0^{z_0} \int_0^{z'} k(x,z')\,dx\,\frac{|v(z')|}{b(z')}\,dz' \le \frac{2\overline{\beta}_m}{\Re(\lambda) + \underline{\mu}}\,\|v\|_{L^1_w}.$$

Therefore, $\|T_\lambda[v]\|_{L^1_w} < \infty$ for $\Re(\lambda) > -\underline{\mu}$ and $T_\lambda[v] \in L^1_w$. □

Next, we study the connection between the spectra of A and T_λ.

Lemma 3.7. *The spectrum of A and the spectrum of T_λ are connected in the following way:*

(a) If $1 \in \rho(T_\lambda)$, then $\lambda \in \rho(A)$, where $\rho(\cdot)$ denotes the resolvent set.

(b) If $\lambda \in \sigma(A)$, then $1 \in \sigma(T_\lambda)$, where $\sigma(\cdot)$ denotes the spectrum.

(c) $\lambda \in \sigma_P(A)$ if and only if $1 \in \sigma_P(T_\lambda)$, where $\sigma_P(\cdot)$ denotes the point spectrum.

Proof. (a) Let I denote the identity operator. If $1 \in \rho(T_\lambda)$, then the operator $I - T_\lambda$ is invertible, i.e., for every $f \in L^1((0, z_0))$ there exists a unique solution v to (3.16). This function v is the unique solution to (3.15) and $U(z) := \frac{v(z)}{b(z)}$ is the unique solution to (3.14). This means that the operator $R_\lambda := (\lambda I - A)$ is invertible and therefore $\lambda \in \rho(A)$.

(b) This is a direct consequence of (a) because the spectrum is the complement of the resolvent set.

(c) $\lambda \in \sigma_P(A)$ if and only if there is an eigenfunction $U \in \mathcal{W}$ that satisfies (3.14) with $f = 0$. With the definition $v(z) := b(z)\,U(z)$ we see that this holds if and only if there is a function $v \in \mathcal{W}_v$ satisfying (3.15) with $f = 0$. By variation of parameters, this is equivalent to the existence of a solution v to (3.16). This means, by the definition of T_λ that v satisfies $T_\lambda[v] = v$ and therefore v is an eigenfunction of the operator T_λ to the eigenvalue 1, i.e., $1 \in \sigma_P(T_\lambda)$.

□

This lemma allows us to analyze the spectrum of the integral operator T_λ and then draw conclusions about the spectrum of the integro-differential operator A. By combining Lemma 3.6 and Lemma 3.7, we obtain a first result about the spectrum of A.

Lemma 3.8. *If $\lambda \in \mathbb{C}$ with $\Re(\lambda) > 2\overline{\beta}_m - \underline{\mu}$, then $\lambda \in \rho(A)$.*

Proof. By Lemma 3.6,

$$\|T_\lambda\|_{\mathrm{op}} \le \frac{2\overline{\beta}_m}{\Re(\lambda) + \underline{\mu}},$$

where $\|T_\lambda\|_{\mathrm{op}}$ denotes the operator norm of the operator $T_\lambda : L^1_w \to L^1_w$.

For $\Re(\lambda) > 2\overline{\beta}_m - \underline{\mu}$, $\|T_\lambda\|_{\mathrm{op}} < 1$. If $\|T_\lambda\|_{\mathrm{op}} < 1$, then $1 \in \rho(T_\lambda)$ and therefore $\lambda \in \rho(A)$ by Lemma 3.7(a). □

Similarly, we use Lemma 3.7 in the following by first analyzing the operator T_λ and its spectrum in the next three lemmas and then returning to the operator A.

Lemma 3.9. *Let $\Re(\lambda) > -\underline{\mu}$, then the operator T_λ is compact.*

Proof. We apply the Kolmogorov-Riesz-Fréchet Theorem (see Theorem 2.12) to prove compactness of T_λ in L^1_w. To this end, we extend β_m, μ, k, and b by 0 to $\mathbb{R}$ respectively for k to $\mathbb{R}^2$.

The operator T_λ is a bounded linear operator for $\Re(\lambda) > -\underline{\mu}$ (see Lemma 3.6). Let $v \in L^1_w$, $\|v\|_{L^1_w} \le 1$, and $h > 0$ (the case $h < 0$ is analogous), then

$$\begin{aligned}
\|T_\lambda[v](\cdot + h) - T_\lambda[v](\cdot)\|_{L^1_w} = \int_0^{z_0} \frac{1}{b(z)} \Bigg| \int_0^{z+h} \int_x^{z_0} \frac{\beta_m(z')\,k(x,z')}{b(z')}\, v(z')\,dz'\, e^{-\int_x^{z+h} \alpha(\lambda,\,y)\,dy}\,dx \\
- \int_0^{z} \int_x^{z_0} \frac{\beta_m(z')\,k(x,z')}{b(z')}\, v(z')\,dz'\, e^{-\int_x^{z} \alpha(\lambda,\,y)\,dy}\,dx \Bigg|\,dz \\
\le \int_0^{z_0} \frac{1}{b(z)} \Bigg(\int_0^{z} \int_x^{z_0} \frac{\beta_m(z')\,k(x,z')}{b(z')}\, |v(z')|\,dz' \left| e^{-\int_x^{z+h} \alpha(\lambda,\,y)\,dy} - e^{-\int_x^{z} \alpha(\lambda,\,y)\,dy} \right| dx
\end{aligned}$$

$$
\begin{aligned}
&+ \int_z^{z+h} \int_x^{z_0} \frac{\beta_m(z')\,k(x,z')}{b(z')}\,|v(z')|\,dz' \left| e^{-\int_x^{z+h} \alpha(\lambda,\,y)\,dy} \right| dx \Bigg) dz \\
&\le \overline{\beta}_m\,\|k\|_\infty \Bigg(\int_0^{z_0} \int_0^{z} \frac{1}{b(z)} e^{-\int_x^{z} \alpha(\Re(\lambda),\,y)\,dy} \left| e^{-\int_z^{z+h} \alpha(\lambda,\,y)\,dy} - 1 \right| dx\,dz \\
&\quad + \int_0^{z_0} \int_z^{z+h} \frac{1}{b(z)} e^{-\int_x^{z+h} \alpha(\Re(\lambda),\,y)\,dy}\,dx\,dz \Bigg) \\
&\xrightarrow{h\to 0^+} 0,
\end{aligned}
$$

uniformly in $v \in L^1_w$ with $\|v\|_{L^1_w} \le 1$ because the first summand is bounded for every $h > 0$ due to

$$
\begin{aligned}
&\int_0^{z_0} \int_0^{z} \frac{1}{b(z)} e^{-\int_x^{z} \alpha(\Re(\lambda),\,y)\,dy} \left| e^{-\int_z^{z+h} \alpha(\lambda,\,y)\,dy} - 1 \right| dx\,dz \\
&\qquad \le \frac{2}{\Re(\lambda) + \underline{\mu}} \int_0^{z_0} \int_x^{z_0} -\frac{d}{dz}\Big(e^{-\int_x^{z} \alpha(\lambda,\,y)\,dy} \Big)\,dx\,dz \le \frac{2\,z_0}{\Re(\lambda) + \underline{\mu}} < \infty
\end{aligned}
$$

for $\Re(\lambda) > -\underline{\mu}$.

With $\|v\|_{L^1(\mathbb{R})} = \|v\|_{L^1((0,z_0))} \le \bar{b}\,\|v\|_{L^1_w} \le \bar{b}$ where $\bar{b} := \max_{z\in[0,z_0]} b(z)$, the above calculation, and the Kolmogorov-Riesz-Fréchet Theorem (see Theorem 2.12) we see that $\frac{1}{b(z)} T_\lambda[v]$ is relatively compact in $L^1((0,z_0))$.

Let $(v_n)_{n\in\mathbb{N}}$ be a sequence in L^1_w with $\|v_n\|_{L^1_w} \le 1$, then there is a subsequence $(v_m)_{m\in\mathbb{N}}$ such that $\frac{1}{b(z)} T_\lambda[v_m]$ converges in $L^1((0,z_0))$. Since $\frac{1}{b(z)} T_\lambda[v_m]$ is a Cauchy sequence in $L^1((0,z_0))$, $T_\lambda[v_m]$ is a Cauchy sequence in L^1_w and hence converges. Therefore, T_λ is a compact operator in L^1_w. ☐

Lemma 3.10. *Let $\lambda \in \mathbb{R}$ with $\lambda > -\underline{\mu}$, then $r(T_\lambda) \in \sigma(T_\lambda)$ and if $r(T_\lambda) > 0$, then it is an eigenvalue of T_λ with a corresponding non-negative eigenfunction.*

Proof. For the first part of the lemma we use a Theorem by Bonsall [16, Theorem 1, p. 148]. L^1_w is a partially ordered Banach space with the relation $f \le g$ if and only if $f(z) \le g(z)$ for a.e. $z \in (0,z_0)$ and $L^{1\,+}_w := \{f \in L^1_w : f \ge 0 \text{ a.e.}\}$ is a normal cone as it is a non-empty closed set and $\|f+g\|_{L^1_w} \ge \|f\|_{L^1_w}$ for all $f,\,g \in L^{1\,+}_w$. It holds that $L^1_w = L^{1\,+}_w - L^{1\,+}_w$. T_λ is a bounded linear operator and for $v \in L^1_w$ with $v \ge 0$ a.e.,

$$
T_\lambda[v](z) = \int_0^{z} \int_x^{z_0} \frac{\beta_m(z')\,k(x,z')}{b(z')}\,v(z')\,dz'\,e^{-\int_x^{z} \alpha(\lambda,\,y)\,dy}\,dx \ge 0 \text{ for a.e. } z \in (0,z_0).
$$

Therefore, $T_\lambda : L^1_w \to L^1_w$ is a endormorphism (in the sense of [16]) and $r(T_\lambda) \in \sigma(T_\lambda)$ by [16, Theorem 1, p. 148].

By Lemma 3.9, T_λ is a compact operator. Since T_λ is a positive operator and $L^1_w = L^{1\,+}_w - L^{1\,+}_w$ the second part of the Lemma follows directly from the weak form of the Krein-Rutman Theorem (see Theorem 2.24). ☐

In the next lemma, we use the positivity assumption on k, Assumption **(A7)**, to show that the spectral radius of T_λ is a simple eigenvalue of T_λ.

Usually, one uses the Krein-Rutman Theorem in its strong form (see Theorem 2.23) or the theory of non-supporting operators developed by Sawashima [90] to show that the spectral radius is a simple eigenvalue [48]. However, the operator T_λ is neither strictly positive nor non-supporting as it maps a function with essential support in $[0,m]$ to zero. Therefore, in the following lemma we consider the operator T_λ only on the interval (m,z_0) and then use the weak form of the Krein-Rutman Theorem and a result on semi-non-supporting operators (Theorem 2.25) on the truncated operator in order to show that the spectral radius is a simple eigenvalue of the truncated operator. Then, we conclude that the spectral radius of T_λ is also a simple eigenvalue of T_λ.

Lemma 3.11. *Let $\lambda \in \mathbb{R}$ with $\lambda > -\underline{\mu}$. If $r(T_\lambda) > 0$, then $r(T_\lambda)$ is a simple eigenvalue of T_λ, i.e., there is a unique non-negative eigenfunction for $r(T_\lambda)$.*

Proof. We define the weighted L^1-space $\tilde{L}^1_w := L^1\left((m,z_0), \frac{dz}{b(z)}\right)$ and the extension operator $E : \tilde{L}^1_w \to L^1_w$ that extends a function $\tilde{v} \in \tilde{L}^1_w$ by zero to a function in L^1_w. The inverse operator of E is the restriction operator, i.e., $E[\tilde{v}]|_{(m,z_0)} = \tilde{v}$ for every $\tilde{v} \in \tilde{L}^1_w$ and for every $v \in L^1_w$ it holds that $E[v|_{(m,z_0)}] = v\,\chi_{(m,z_0)}$.

Now, we define the operator $\tilde{T}_\lambda[\tilde{v}] := T_\lambda[E[\tilde{v}]]|_{(m,z_0)}$ that maps $\tilde{L}^1_w$ to $\tilde{L}^1_w$. We show Lemma 3.11 in steps. Firstly, we show that the spectral radius of $\tilde{T}_\lambda$ is an eigenvalue of $\tilde{T}_\lambda$. Secondly, we show that it is a simple eigenvalue. In Steps 3 and 4, we study the connection between the spectra of $\tilde{T}_\lambda$ and T_λ. Finally, we conclude in Step 5 that the spectral radius is a simple eigenvalue of T_λ.

Step 1: $r(\tilde{T}_\lambda)$ is an eigenvalue of $\tilde{T}_\lambda$

The operator $\tilde{T}_\lambda$ is compact if $\Re(\lambda) > -\underline{\mu}$ (this can be shown as compactness of T_λ in Lemma 3.9). Let $\lambda \in \mathbb{R}$ and $\tilde{v} \in \tilde{L}^1_w$ with $\tilde{v} \geq 0$ and $\tilde{v} \neq 0$, then by assumption **(A7)** for a.e. $x < m$

$$\int_x^{z_0} \frac{\beta_m(z')\,k(x,z')}{b(z')}\,E[\tilde{v}](z')\,dz' > 0.$$

Therefore, for all $z \in (m,z_0)$

$$\tilde{T}_\lambda[\tilde{v}](z) = \int_0^z \int_x^{z_0} \frac{\beta_m(z')\,k(x,z')}{b(z')}\,E[\tilde{v}](z')\,dz'\,e^{-\int_x^z \alpha(\lambda,y)\,dy}\,dx\Bigg|_{(m,z_0)} > 0$$

and $\tilde{T}_\lambda$ is a strictly positive operator for $\lambda \in \mathbb{R}$. By the weak form of the Krein-Rutman Theorem (see Theorem 2.24) $\tilde{r} := r(\tilde{T}_\lambda)$ is an eigenvalue of $\tilde{T}_\lambda$.

Step 2: $\tilde{r} = r(\tilde{T}_\lambda)$ is a simple eigenvalue of $\tilde{T}_\lambda$

We use Theorem 2.25 in order to show that $\tilde{r} = r(\tilde{T}_\lambda)$ is a simple eigenvalue, i.e., we show that $\tilde{T}_\lambda$ is semi-non-supporting and that the resolvent of $\tilde{T}_\lambda$ has a pole at $\tilde{r}$ and directly obtain that $\tilde{r}$ is a simple eigenvalue. As every eigenvalue of a compact operator is a pole of the resolvent (see Theorem 2.22) it just remains to show that $\tilde{T}_\lambda$ is semi-non-supporting in $\tilde{L}^1_w$ w.r.t. the positive cone.

The operator $\tilde{T}_\lambda$ is a bounded, linear, compact, and strictly positive operator mapping $\tilde{L}^1_w$ to $\tilde{L}^1_w$. The positive cone in $\tilde{L}^1_w$ is given by

$$K := \left\{ f \in \tilde{L}^1_w : \; f(z) \geq 0 \text{ for a.e. } z \in (m, z_0) \right\},$$

the dual space of $\tilde{L}^1_w$ is the weighted-L^∞ space

$$\tilde{L}^\infty_w := \left\{ f \in L^\infty((m, z_0)) : \; \left\| \frac{f(z)}{b(z)} \right\|_\infty < \infty \right\},$$

and the positive cone in the dual space is given by

$$K^* := \left\{ f \in \tilde{L}^\infty_w : \; f(z) \geq 0 \text{ for a.e. } z \in (0, z_0) \right\}.$$

For every $\tilde{v} \in K \setminus \{0\}$, $\tilde{T}_\lambda[\tilde{v}] > 0$ as $\tilde{T}_\lambda$ is a strictly positive operator. For every $f \in K^* \setminus \{0\}$ there exists a set of positive measure such that $f > 0$ a.e. on this set. Therefore, $\int_m^{z_0} f(z)\, \tilde{T}_\lambda[\tilde{v}](z)\, dz > 0$ for every $\tilde{v} \in K \setminus \{0\}$ and every $f \in K^* \setminus \{0\}$ and the operator $\tilde{T}_\lambda$ is semi-non-supporting in $\tilde{L}^1_w$ w.r.t. K.

Step 3: $\xi \in \mathbb{C} \setminus \{0\}$ is an eigenvalue of $\tilde{T}_\lambda$ if and only if ξ is an eigenvalue of T_λ
Note that because of $\beta_m(z) = 0$ for all $z \in (0, m)$ it holds for all u, $v \in L^1_w$ that

$$u|_{(m,z_0)} = v|_{(m,z_0)} \quad \text{implies that} \quad T_\lambda[u] = T_\lambda[v].$$

Let $\xi \in \mathbb{C} \setminus \{0\}$ be an eigenvalue of T_λ with eigenfunction $v \in L^1_w$, then

$$\tilde{T}_\lambda[v|_{(m,z_0)}] = T_\lambda[v\, \chi_{(m,z_0)}]\Big|_{(m,z_0)} = T_\lambda[v]|_{(m,z_0)} = \xi\, v|_{(m,z_0)}.$$

Therefore, the function $\tilde{v} := v|_{(m,z_0)} \in \tilde{L}^1_w$ is an eigenfunction of $\tilde{T}_\lambda$ with eigenvalue $\xi \in \mathbb{C} \setminus \{0\}$.
Let $\xi \in \mathbb{C} \setminus \{0\}$ be an eigenvalue of $\tilde{T}_\lambda$ with eigenfunction $\tilde{v} \in \tilde{L}^1_w$. We define the function $v := \frac{1}{\xi}\, T_\lambda[E[\tilde{v}]]$, then $v \in L^1_w$ and it holds that

$$v|_{(m,z_0)} = \frac{1}{\xi}\, T_\lambda[E[\tilde{v}]]\Bigg|_{(m,z_0)} = \frac{1}{\xi}\, \tilde{T}_\lambda[\tilde{v}] = \frac{1}{\xi}\, \xi\, \tilde{v} = \tilde{v},$$

and

$$T_\lambda[v] = T_\lambda[v\, \chi_{(m,z_0)}] = T_\lambda[E[\tilde{v}]] = \xi\, v.$$

Therefore, v is an eigenfunction of T_λ with eigenvalue ξ.

Step 4: A simple non-zero eigenvalue of $\tilde{T}_\lambda$ is also a simple eigenvalue of T_λ
Let $\xi \in \mathbb{C} \setminus \{0\}$ be a simple eigenvalue of $\tilde{T}_\lambda$ with unique eigenfunction. From the previous step we already know that ξ is also an eigenvalue of T_λ. Assume there are two different eigenfunctions v_1, $v_2 \in L^1_w$ for the eigenvalue ξ. Then $v_1|_{(m,z_0)}$ and $v_2|_{(m,z_0)}$ are eigenfunctions of $\tilde{T}_\lambda$ for ξ by Step 3. As ξ is a simple eigenvalue of the operator $\tilde{T}_\lambda$ it holds that $v_1|_{(m,z_0)} = c\, v_2|_{(m,z_0)}$ for some $c \in \mathbb{C} \setminus \{0\}$. W.l.o.g. $c = 1$. Hence,

$$\xi v_1 = T_\lambda[v_1] = T_\lambda[v_1|_{(m,z_0)}] = T_\lambda[v_2|_{(m,z_0)}] = T_\lambda[v_2] = \xi v_2.$$

Therefore, $v_1 = v_2$ which is a contradiction to v_1 and v_2 being different eigenfunctions.

Step 5: Conclusion

By Step 3 and compactness of both T_λ and $\tilde{T}_\lambda$ we know that $\sigma(T_\lambda) \setminus \{0\} = \sigma(\tilde{T}_\lambda) \setminus \{0\}$. Therefore, $\tilde{r} = r(T_\lambda)$ and by Steps 1 and 3 it follows that $r(T_\lambda)$ is a simple eigenvalue of T_λ. The non-negativity of the eigenfunction follows from Lemma 3.10. □

Now we return to the operator A.

Lemma 3.12. *The largest real eigenvalue λ_d of A is a simple eigenvalue and an isolated point of $\sigma(A) \cap \mathbb{R}$.*

Proof. For $\lambda \in \mathbb{R}$ the map $\lambda \mapsto r(T_\lambda)$ is continuous as T_λ is compact for $\lambda > -\underline{\mu}$ (see, e.g., [27, Theorem 2.1, p. 104]) and strictly decreasing as T_λ is strictly decreasing in λ.

For $\lambda > 2\overline{\beta}_m - \underline{\mu}$, $r(T_\lambda) \leq \|T_\lambda\|_{\mathrm{op}} < 1$ and by Theorem 3.4 there is an eigensolution $(\lambda^*, \mathcal{U})$ to (3.11). This means that there is a $\lambda^* \in [-\underline{\mu}, 2\overline{\beta}_m - \underline{\mu}]$ (note that due to Lemma 3.8 we have a better upper estimate here than in Theorem 3.4) such that $\lambda^* \in \sigma_P(A)$ thus $1 \in \sigma_P(T_{\lambda^*})$ by Lemma 3.7 (c) and $r(T_{\lambda^*}) \geq 1$. Since $\lambda \mapsto r(T_\lambda)$ is continuous and strictly decreasing there is a unique $\hat{\lambda} \in [-\underline{\mu}, 2\overline{\beta}_m - \underline{\mu}]$ such that $r(T_{\hat{\lambda}}) = 1$, i.e., $\hat{\lambda} \in \sigma(A)$.

For $\lambda > \hat{\lambda}$, $r(T_\lambda) < 1$, i.e., $1 \in \rho(T_\lambda)$ and hence $\lambda \in \rho(A)$ by Lemma 3.7 (a). As $r(T_{\hat{\lambda}}) = 1$ is a positive eigenvalue of a compact operator, it is an isolated point in the spectrum, i.e., there is $\varepsilon > 0$ such that $[1-\varepsilon, 1+\varepsilon] \cap \sigma(T_{\hat{\lambda}}) = \{1\}$. By continuity and monotonicity of the map $\lambda \mapsto r(T_\lambda)$ there is therefore an $\varepsilon > 0$ such that for $\lambda \in [\hat{\lambda} - \varepsilon, \hat{\lambda})$, $1 \notin \sigma(T_\lambda)$, i.e., $\lambda \notin \sigma(A)$ and $\hat{\lambda}$ is an isolated point in the real spectrum of A.

It remains to show that $\hat{\lambda}$ is a simple eigenvalue of A. Denote the unique (up to a constant) eigenfunction corresponding to $1 = r(T_{\hat{\lambda}})$ by $\hat{v} \in L^1_w$ ($\hat{v}$ is unique by Lemma 3.11). Then, $\tilde{v}$ is the unique solution to $\hat{v} = T_{\hat{\lambda}}[\hat{v}]$ and therefore $\hat{v}$ is the unique solution to

$$\hat{v}'(z) + \frac{\hat{\lambda} + \beta_m(z)\,(1 - k_0(z)) + \mu(z)}{b(z)}\,\hat{v}(z) - \int_z^{z_0} \frac{\beta_m(z')\,k(z,z')}{b(z')}\,\hat{v}(z')\,dz' = 0.$$

Define for $z \in (0, z_0)$, $\hat{u}(z) := \frac{\hat{v}(z)}{b(z)}$, then $\hat{u} \in L^1((0, z_0))$ and since $\hat{v}$ satisfies $\hat{v} = T_{\hat{\lambda}}[\hat{v}]$ it holds that $\hat{v} \in \mathcal{W}_v$ and thus $\hat{u} \in \mathcal{W}$. Furthermore, $(\hat{\lambda} I - A)[\hat{u}] = 0$, i.e., $\hat{u}$ is the unique eigenfunction for the simple eigenvalue $\hat{\lambda}$ of A and $\lambda_d := \hat{\lambda}$. □

Finally, we use the previous lemma to show the main result of this section, viz. that the operator A has a real simple dominant eigenvalue.

Theorem 3.13. *The eigenvalue largest real eigenvalue of A, denoted by λ_d, is a dominant eigenvalue, i.e., if $\lambda \in \sigma(A) \setminus \{\lambda_d\}$, then $\Re(\lambda) < \lambda_d$.*

Proof. The proof follows the proof of Theorem 6.13 in [48]. We use the connection between the spectra of T_λ and A that we have shown in Lemma 3.7, the previous lemma, and the same method as Heijmans [48] in order to show that λ_d is a dominant eigenvalue.

Let $\lambda \in \sigma(A)$ with $\Re(\lambda) > -\underline{\mu}$ and denote with λ_d the largest real eigenvalue of A. As $\lambda \in \sigma(A)$, $1 \in \sigma(T_\lambda)$ by Lemma 3.7 (b) and therefore, by compactness of T_λ, 1 is an eigenvalue of T_λ. Denote the corresponding eigenfunction by $f \in L^1_w \setminus \{0\}$. Then,

$$\begin{aligned} |f| = |T_\lambda[f]| &= \left| \int\limits_0^z \int\limits_x^{z_0} \frac{\beta_m(z')\, k(x,z')}{b(z')}\, f(z')\, dz'\, e^{-\int_x^z \alpha(\lambda,y)\, dy}\, dx \right| \\ &\le \int\limits_0^z \int\limits_x^{z_0} \frac{\beta_m(z')\, k(x,z')}{b(z')}\, |f|(z')\, dz'\, e^{-\int_x^z \Re(\alpha(\lambda,y))\, dy}\, dx \\ &= T_{\Re(\lambda)}[|f|]. \end{aligned}$$

As $r(T_{\Re(\lambda)}) \neq 0$ is an eigenvalue of $T_{\Re(\lambda)}$ and $T_{\Re(\lambda)}$ is compact, $r(T_{\Re(\lambda)})$ is also a eigenvalue of the dual operator $T^*_{\Re(\lambda)}$ (see, e.g., [104, Theorem 2, p. 284]). Denote the corresponding eigenfunction by $f^* \in L^\infty_w := \left\{ f \in L^\infty((0,z_0)) : \frac{f(z)}{b(z)} \in L^\infty((0,z_0)) \right\}$. Let f^* be normalized s.t. $\langle f^*, f \rangle = 1$. Taking duality pairings in $|f| \le T_{\Re(\lambda)}[|f|]$ yields

$$r(T_{\Re(\lambda)})\, \langle f^*, f \rangle \ge \langle f^*, f \rangle\,,$$

therefore $r(T_{\Re(\lambda)}) \ge 1$. As $\lambda \mapsto r(T_\lambda)$ is decreasing for $\lambda \in \mathbb{R}$ and $r(T_{\lambda_d}) = 1$ (see the proof of Lemma 3.12) this implies that $\Re(\lambda) \le \lambda_d$.

Suppose that $\lambda = \lambda_d + i\eta \in \sigma(A)$. We show now that this implies that $\eta = 0$, i.e., there no element in the spectrum of A with real part λ_d but λ_d itself. As $\Re(\lambda) = \lambda_d$ we obtain $T_{\lambda_d}[|f|] \ge |f|$. Assume that $T_{\lambda_d}[|f|] > |f|$, then taking duality pairings again, $\langle f, f^* \rangle > \langle f, f^* \rangle$ which is a contradiction. Therefore, $T_{\lambda_d}[|f|] = |f|$.

Let f_d be the non-negative eigenfunction of T_{λ_d} for the simple eigenvalue 1 (by Lemma 3.12). Therefore, $|f| = c\, f_d$ for some constant $c \in \mathbb{R}$, i.e., $f(z) = c\, f_d(z)\, e^{ig(z)}$ for some real valued function $g(z)$. W.l.o.g. $c = 1$. Substituting this into $T_{\lambda_d}[f_d] = |T_\lambda[f]|$ yields

$$\begin{aligned} &\int\limits_0^z \int\limits_x^{z_0} \frac{\beta_m(z')\, k(x,z')}{b(z')}\, f_d(z')\, dz'\, e^{-\int_x^z \frac{\lambda_d + \beta_m(y)\,(1-k_0(y)) + \mu(y)}{b(y)}\, dy}\, dx = \\ &\quad = \left| \int\limits_0^z \int\limits_x^{z_0} \frac{\beta_m(z')\, k(x,z')}{b(z')}\, f_d(z')\, e^{ig(z')}\, dz'\, e^{-\int_x^z \frac{\lambda_d + i\eta + \beta_m(y)\,(1-k_0(y)) + \mu(y)}{b(y)}\, dy}\, dx \right|. \end{aligned}$$

By [89, Theorem 1.39, p. 30], there exists $a \in \mathbb{C}$ with $|a| = 1$ such that

$$f_d(z) = \left| f_d(z)\, e^{i\left(g(z') - \eta \int_x^z \frac{1}{b(y)}\, dy\right)} \right| = a\, f_d(z)\, e^{i\left(g(z') - \eta \int_x^z \frac{1}{b(y)}\, dy\right)}.$$

Let $\varphi \in \mathbb{R}$ such that $a = e^{i\varphi}$, then

$$g(z') - \eta \int_x^z \frac{1}{b(y)}\, dy + \varphi = 0. \tag{3.17}$$

We substitute $f(z') = f_d(z')\, e^{ig(z')} = f_d(z')\, e^{i\left(\eta \int_x^z \frac{1}{b(y)}\, dy - \varphi\right)}$ into $T_\lambda[f] = f$ and obtain

$$\begin{aligned} f_d(z)\, e^{ig(z)} &= \int\limits_0^z \int\limits_x^{z_0} \frac{\beta_m(z')\, k(x,z')}{b(z')}\, f_d(z')\, e^{i\left(\eta \int_x^z \frac{1}{b(y)}\, dy - \varphi\right)}\, dz'\, e^{-\int_x^z \frac{\lambda_d + i\eta + \beta_m(y) + \mu(y)}{b(y)}\, dy}\, dx \\ &= e^{-i\varphi}\, T_{\lambda_d}[f_d](z) = e^{-i\varphi}\, f_d(z). \end{aligned}$$

Therefore, $g(z) + \varphi = 2\pi\, k$, $k \in \mathbb{Z}$, and with (3.17) we obtain for $k \in \mathbb{Z}$,

$$\eta \int\limits_x^z \frac{1}{b(y)}\, dy = 2\pi\, k.$$

As this is in particular independent of x and z, we have $\eta = 0$. Thus, we have now shown that if $\lambda = \lambda_d + i\eta \in \sigma(A)$ then $\eta = 0$, i.e., $\lambda = \lambda_d$. Overall, if $\lambda \in \sigma(A)$ and $\lambda \neq \lambda_d$ then $\Re(\lambda) < \lambda_d$. □

In this section, we have shown that the operator A has a real simple dominant eigenvalue that is isolated in the real spectrum.

3.3 Analysis of the singular vertical gene transfer model

A publication about this section is in preparation [75].

Now, we consider equation (3.5), the singular VGT model,

$$\begin{cases} \partial_t u(z,t) + \partial_z \left(b(z) u(z,t)\right) = -\left(\beta(z) + \mu(z)\right)\, u(z,t) + \int\limits_z^\infty \beta(z') k(z,z') u(z',t)\, dz', \\ b(0) u(0,t) = 0 \quad \text{for all } t \geq 0, \quad u(z,0) = \varphi(z) \quad \text{for all } z \geq 0. \end{cases}$$

As for the regular VGT model, we aim at analyzing the long-term behavior of solutions to the singular model. Due to the differences between the two model we take another approach here than we did for the regular model. Firstly, we again state assumptions on the parameters of the model. Then, we show existence of a unique mild solution to the initial value problem in Section 3.3.1 and existence of a solution to the eigenproblem in Section 3.3.2. In the singular VGT case, we cannot show that there is a simple real dominating eigenvalue as in the regular case. Therefore, we do a spectral analysis in Section 3.3.3 and study the stability of the eigensolution using another method, viz. the Generalized Relative Entropy method, in Section 3.3.4.

Similar to the regular VGT model, we make the following assumptions on the parameters of the model:

(A1') There is a $z_0 > 0$ such that $b(0) = b(z_0) = 0$, $b(z) > 0$ for all $z \in (0, z_0)$, and $b \in \mathcal{C}^1([0, z_0])$.

(A2') $\beta \in \mathcal{C}^0([0, z_0])$ and $0 < \underline{\beta} \leq \beta(z) \leq \overline{\beta}$ for all $z \in [0, z_0]$.

(A3') $\mu \in \mathcal{C}^0([0, z_0])$ and $0 \leq \underline{\mu} \leq \mu(z) \leq \overline{\mu}$ for all $z \in [0, z_0]$.

(A4') k is measurable, $\operatorname{supp}(k) \subseteq \Omega := \{z,\ z' \in [0, z_0] :\ z \leq z'\}$, $k \geq 0$, k is symmetric in the sense that $k(z, z') = k(z' - z, z')$ for all $(z, z') \in \Omega$, $\int_0^{z'} k(z, z')\, dz = 2$ for all $z' \in (0, z_0]$, and $\int_0^{z'} z\, k(z, z')\, dz = z'$ for all $z' \in (0, z_0]$.

These are regularity and non-negativity assumptions on the parameter and consistency conditions on the plasmid segregation kernel k. The two integral conditions on k model that bacteria always divide in two daughter cells (see, e.g., [69]) and that we have mass conservation of plasmids at cell division (for more details see the derivation of the model in Section 3.1.2).

Due to Assumption **(A1')** it suffices to consider bacteria with no more than z_0 plasmids, i.e., $z \in [0, z_0]$ (see Section 3.2). Under Assumptions **(A1')** to **(A4')**, the singular VGT model is given by

$$\begin{cases} \partial_t u(z,t) + \partial_z \left(b(z)\, u(z,t)\right) = -\left(\beta(z) + \mu(z)\right) u(z,t) + \displaystyle\int_z^{z_0} \beta(z')\, k(z,z')\, u(z',t)\, dz', \\ b(0)\, u(0,t) = 0 \quad \text{for all } t \geq 0, \quad u(z,0) = \varphi(z) \quad \text{for all } z \in [0, z_0]. \end{cases} \tag{3.18}$$

First, we show existence of mild solutions to the initial value problem (3.18). Next, we show existence of eigensolutions as we are in particular interested in the long-time distribution of plasmids. To this end, we make more restrictive assumptions on the model parameters and use a different approach as in the case of the regular VGT model due to the singular kernel k. Finally, we analyze the stability of the eigensolution by means of spectral analysis and the Generalized Relative Entropy method.

3.3.1 Existence of a unique mild solution to the initial value problem

In this section, we show existence of a mild solution, in the sense of Definition 2.31, to the initial value problem (3.18) using theory of semigroups (see Section 2.2.4). We follow [31, 103].

Throughout this section, we assume that Assumptions **(A1')** to **(A4')** hold. As a direct consequence of Assumption **(A1')**, we obtain the following lemma (see [31, Lemma 3.1]).

Lemma 3.14. *If b satisfies Assumption **(A1')**, then for every $z \in (0, z_0)$ it holds that*

$$\lim_{y \to 0^+} \int_y^z \frac{1}{b(x)}\, dx = \infty \quad \textit{and} \quad \lim_{y \to z_0^-} \int_z^y \frac{1}{b(x)}\, dx = \infty.$$

This lemma has a biological interpretation. Define for $0 < s < z < z_0$

$$g(s,z) := \int_s^z \frac{1}{b(x)}\, dx.$$

Then, $g(s, z)$ is the time it takes an individual with s plasmids to increase the number of plasmids to z (see, e.g., [103]). Hence, Lemma 3.14 means that bacteria do not

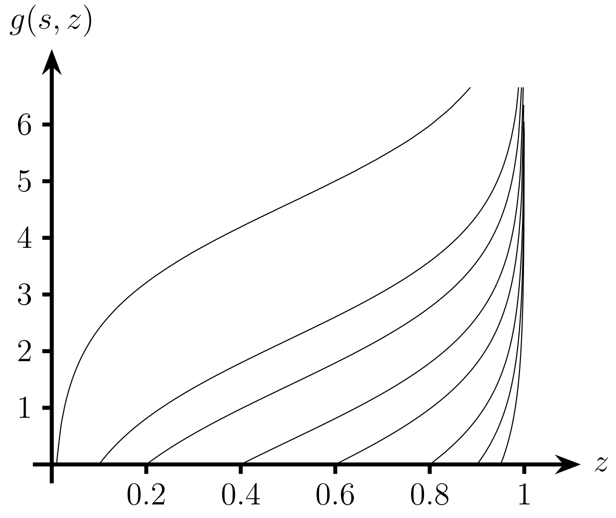


Figure 3.7: Plot of the function $g(s, z)$ that models the growth of plasmids in a bacterium for logistic plasmid reproduction $b(z) = z\,(1 - z)$ and $s = 0.01$, 0.1, 0.2, 0.4, 0.6, 0.8, 0.9, and 0.95.

"move" from zero plasmids to $z > 0$ plasmids in a finite time and also they do not reach the maximal number of plasmids z_0 in finite time.

Example 3.15. In the case of logistic plasmid reproduction $b(z) = \frac{b_0}{z_0}\, z\,(z_0 - z)$ for some $b_0 > 0$, g is given by:

$$g(s, z) = \frac{1}{b_0} \int_s^z \frac{z_0}{x\,(z_0 - x)}\, dx = \frac{1}{b_0} \int_s^z \frac{1}{x} + \frac{1}{z_0 - x}\, dx = \frac{1}{b_0} \log\left(\frac{z\,(z_0 - s)}{s\,(z_0 - z)} \right).$$

See Figure 3.7 for a plot of $g(s, z)$ for different initial plasmid numbers s and $b_0 = 1$, $z_0 = 1$.

For every fixed $s \in (0, z_0)$ the function $g(s, \cdot)$ is strictly increasing as $b(z) > 0$ for $z \in (0, z_0)$. Therefore, for a fixed $s \in (0, z_0)$ the inverse of $g(s, \cdot)$ exists and we denote it with $g^{-1}(s, t)$. The function $g^{-1}(s, t)$ can then be interpreted as mapping the time t to the amount of plasmids a bacterium contains after time t if it had s plasmids initially. For $s \in (0, z_0)$ the function g^{-1} satisfies

$$\frac{d}{dt} g^{-1}(s, t) = b(g^{-1}(s, t)), \qquad g^{-1}(s, 0) = s.$$

Hence, we find that $g^{-1}(s, t)$ is identical with the flow $Z(t, s)$ defined in (3.12).

With these definitions, we now show Lemma 3.14.

Proof of Lemma 3.14. This proof follows [31, Proof of Lemma 3.1].

For all $z \in (0, z_0)$ and $t \in \mathbb{R}$ it holds that

$$1 = \frac{b(g^{-1}(z, t))}{b(g^{-1}(z, t))} = \frac{\frac{d}{dt} g^{-1}(z, t)}{b(g^{-1}(z, t))}.$$

Integration then yields

$$t = \int_0^t \frac{1}{b(g^{-1}(z,\tau))} \frac{dg^{-1}(s,\tau)}{d\tau}\, d\tau = \int_z^{g^{-1}(z,t)} \frac{1}{b(x)}\, dx. \tag{3.19}$$

Due to Assumption **(A1')** it holds that

$$\lim_{t\to\infty} g^{-1}(s,t) = z_0 \quad \text{and} \quad \lim_{t\to-\infty} g^{-1}(s,t) = 0.$$

Using this in (3.19), we obtain for all $z \in (0, z_0)$

$$\lim_{y\to z_0^-} \int_z^y \frac{1}{b(x)}\, dx = \infty \quad \text{and} \quad \lim_{y\to 0^+} \int_y^z \frac{1}{b(x)}\, dx = \infty.$$

This finishes the proof. ☐

Now, we show existence of a mild solution to (3.18). We do this by considering the equation term by term: first, we consider only cell division and cell death. Then, we include plasmid reproduction, i.e., equation (3.18) without the integral term and zero-flux boundary condition, and show existence of solutions to this equation. Finally, we include the integral term and show existence of a solution to (3.18).

We first consider equation (3.18) without the integral term, i.e.,

$$\begin{cases} \partial_t u(z,t) + \partial_z (b(z)\, u(z,t)) = -\,(\beta(z) + \mu(z))\, u(z,t), \\ u(z,0) = \varphi(z). \end{cases} \tag{3.20}$$

Define the operator $A : L^1((0,z_0)) \to L^1((0,z_0))$ by

$$A[\varphi](z) := -(\beta(z) + \mu(z))\, \varphi(z).$$

We show existence of a mild solution to (3.20) by first showing in the next lemma that A is the infinitesimal generator of a $\mathcal{C}^0$-semigroup.

Lemma 3.16. *The operator A is the infinitesimal generator of a linear positive uniformly continuous $\mathcal{C}^0$-semigroup $T(t)$, $t \geq 0$, on $L^1((0,z_0))$.*

Proof. Both β and μ are bounded functions. Therefore, A is a bounded and linear operator and the infinitesimal generator of a uniformly continuous semigroup $T(t)$, $t \geq 0$, by Theorem 2.27(a). As every uniformly continuous semigroup is in particular also a $\mathcal{C}^0$-semigroup, $T(t)$ is a uniformly continuous $\mathcal{C}^0$-semigroup.

The operator $T(t)$, $t \geq 0$ is the solution operator for the linear initial value problem

$$\frac{d}{dt} u(z,t) = A[u(\cdot,t)](z) = -\,(\beta(z) + \mu(z))\, u(z,t) \qquad \text{and} \qquad u(z,0) = \varphi(z).$$

Therefore, $T(t)\varphi(z) = e^{-t\,(\beta(z)+\mu(z))}\,\varphi(z)$ and $T(t) = e^{-t\,(\beta(z)+\mu(z))}$. It follows directly from the definition of $T(t)$, $t \geq 0$, that it is a linear and positive $\mathcal{C}^0$-semigroup. ☐

Next, we include plasmid reproduction. Using the method of characteristics, we show that there is a unique mild solution to (3.20).

Theorem 3.17. *Let* $\varphi \in L^1((0,z_0))$, $t \geq 0$, *and define*

$$S(t)\varphi(z) := \frac{b(g^{-1}(z,-t))}{b(z)} T(t)\varphi(g^{-1}(z,-t)), \qquad \text{for all } z \in (0,z_0). \tag{3.21}$$

Then, $S(t)$, $t \geq 0$, *is a* $\mathcal{C}^0$*-semigroup of bounded linear operators on* $L^1((0,z_0))$. *It holds that:*

(a) There are $M \geq 1$ *and* $\omega \geq 0$ *such that* $\|S(t)\varphi\|_{L^1((0,z_0))} \leq Me^{\omega t}\|\varphi\|_{L^1((0,z_0))}$ *for every* $\varphi \in L^1((0,z_0))$ *and* $t \geq 0$.

(b) $S(t)$, $t \geq 0$, *is a positive semigroup on* $L^1((0,z_0))$.

(c) $S(t)\varphi(z)$ *is the unique mild solution to* (3.20).

Proof. We follow again [103] and show the theorem in steps. In Step 1, we show that $S(t)$ is a bounded operator and (a), then we show that $S(t)$ is a linear semigroup of operators in Step 2 and that $S(t)$ is a $\mathcal{C}^0$-semigroup in Step 3. In Step 4, we show positivity and we conclude in Step 5 with the uniqueness of the mild solution $S(t)\varphi(z)$. In Step 5, we use the method of characteristics to show that every solution to (3.18) can be written as $S(t)\varphi(z)$. Therefore, the definition of the semigroup $S(t)$ in (3.21) is motivated by the method of characteristics.

Step 1: $S(t)$ is a bounded linear operator for every $t \geq 0$

Let $\varphi \in L^1((0,z_0))$ and fix some $t \geq 0$. We define $s := g^{-1}(z,-t)$, then by definition of g^{-1} it holds that $g(z,s) = -t$, i.e., $\int_z^s \frac{1}{b(x)}\,dx = -t$. Due to the Leibniz integral rule it holds that

$$-\frac{dt}{dz} = \frac{1}{b(s)}\frac{ds}{dz} - \frac{1}{b(z)}$$

and because t does not depend on z,

$$\frac{ds}{dz} = \frac{b(s)}{b(z)} = \frac{b(g^{-1}(z,-t))}{b(z)}.$$

With change of variables $g^{-1}(z,-t) = s$ and $\frac{ds}{dz} = \frac{b(g^{-1}(z,-t))}{b(z)}$, we obtain that there are constants $M \geq 1$ and $\omega \geq 0$ such that

$$\begin{aligned}\|S(t)\varphi\|_{L^1((0,z_0))} &= \int_0^{z_0} |S(t)\varphi(z)|\,dz = \int_0^{z_0} \frac{b(g^{-1}(z,-t))}{b(z)}\left|T(t)\varphi(g^{-1}(z,-t))\right|\,dz \\ &= \int_0^{z_0} |T(t)\varphi(s)|\,ds = \|T(t)\varphi\|_{L^1((0,z_0))} \\ &\leq Me^{\omega t}\|\varphi\|_{L^1((0,z_0))}.\end{aligned}$$

In the last step we have used that since $T(t)$ is a $\mathcal{C}^0$-semigroup by Lemma 3.16 there are constants $M \geq 1$ and $\omega \geq 0$ such that $\|T(t)\|_{\mathrm{op}} \leq Me^{\omega t}$ for $t \geq 0$ (see Theorem 2.29) where $\|\cdot\|_{\mathrm{op}}$ denotes the operator norm. Therefore, $S(t) : L^1((0, z_0)) \to L^1((0, z_0))$ is bounded for every $t \geq 0$ and we have already shown (a).

Step 2: $S(t)$, $t \geq 0$, is a linear semigroup
Linearity of $S(t)$ follows directly from linearity of $T(t)$, $t \geq 0$. It therefore remains to show that $S(t)$ is a semigroup of operators.

Let $\varphi \in L^1((0, z_0))$ and $z \in (0, z_0)$ then

$$S(0)\varphi(z) = \frac{b(g^{-1}(z, 0))}{b(z)} T(0)\varphi(g^{-1}(z, 0)) = \frac{b(z)}{b(z)} T(0)\varphi(z) = \varphi(z).$$

Hence, $S(0) = I$. Furthermore, for all t_1, $t_2 > 0$, $\varphi \in L^1((0, z_0))$, and $z \in (0, z_0)$,

$$\begin{aligned} S(t_1)S(t_2)\varphi(z) &= S(t_1)\left(\frac{b(g^{-1}(z, -t_2))}{b(z)} T(t_2)\varphi(g^{-1}(z, -t_2))\right) = \\ &= \frac{b(g^{-1}(g^{-1}(z, -t_2), -t_1))}{b(g^{-1}(z, -t_2))} \frac{b(g^{-1}(z, -t_2))}{b(z)} T(t_1)T(t_2)\varphi(g^{-1}(g^{-1}(z, -t_2), -t_1)). \end{aligned}$$

With $g^{-1}(g^{-1}(z, -t_2), -t_1) = g^{-1}(z, -(t_1 + t_2))$ (this follows from the fact that g is a flow, see [103]) and using that $T(t)$, $t \geq 0$, is a semigroup, we obtain

$$\begin{aligned} S(t_1)S(t_2)\varphi(z) &= \frac{b(g^{-1}(z, -(t_1 + t_2))}{b(z)} T(t_1 + t_2)\varphi(g^{-1}(z, -(t_1 + t_2))) \\ &= S(t_1 + t_2)\varphi(z). \end{aligned}$$

Thus, $S(t)$, $t \geq 0$, is a linear semigroup of operators.

Step 3: $S(t)$, $t \geq 0$, is a $\mathcal{C}^0$-semigroup
In order to show that $S(t)$ is a $\mathcal{C}^0$-semigroup, we show that $\lim_{t \to 0^+} S(t)\varphi = \varphi$ for all $\varphi \in L^1((0, z_0))$. First, we consider $S(t)$ on the set of continuous functions. Let $X := \mathcal{C}^0([0, z_0])$, X is dense in $L^1((0, z_0))$. Let $\varphi \in X$ and $t \geq 0$ then

$$\begin{aligned} \|S(t)\varphi - \varphi\|_{L^1((0,z_0))} &= \int_0^{z_0} |S(t)\varphi(z) - \varphi(z)| \, dz \\ &\leq \int_0^{z_0} \left| \frac{b(g^{-1}(z, -t))}{b(z)} \Big[T(t)\varphi(g^{-1}(z, -t)) - \varphi(g^{-1}(z, -t))\Big] \right| dz \\ &\quad + \int_0^{z_0} \left| \left(\frac{b(g^{-1}(z, -t))}{b(z)} - 1 \right) \varphi(g^{-1}(z, -t)) \right| dz \\ &\quad + \int_0^{z_0} \Big| \varphi(g^{-1}(z, -t)) - \varphi(z) \Big| \, dz \\ &=: I + II + III. \end{aligned}$$

Change of variables $g^{-1}(z, -t) = s$, $\frac{ds}{dz} = \frac{b(g^{-1}(z, -t))}{b(z)}$ (see Step 1), and using that $g^{-1}(z, -t) = s$ implies that

$$-t = g(z, s) = -g(s, z), \quad \text{thus} \quad t = g(s, z) \quad \text{and} \quad z = g^{-1}(s, t)$$

in I and II, we obtain

$$I = \int_0^{z_0} |T(t)\varphi(s) - \varphi(s)| \; ds \qquad \text{and}$$

$$II = \int_0^{z_0} \left| \left(\frac{b(s)}{b(z)} - 1 \right) \varphi(s) \right| \frac{b(z)}{b(s)} \; ds = \int_0^{z_0} \left| 1 - \frac{b(g^{-1}(s,t))}{b(s)} \right| |\varphi(s)| \; ds.$$

Since $g^{-1}(s,t) \xrightarrow{t \to 0} s$ uniformly for $s \in \operatorname{supp}(\varphi) \subseteq [0, z_0]$, $T(t)$, $t \geq 0$, is a uniformly continuous $\mathcal{C}^0$-semigroup, φ is continuous, and the range of φ on $\operatorname{supp}(\varphi)$ has compact closure in $\mathbb{R}$, we know that $S(t)$, $t \geq 0$, is a $\mathcal{C}^0$-semigroup on X.

With Step 1 and since X is dense in $L^1((0, z_0))$ it follows that $S(t)$, $t \geq 0$ is a $\mathcal{C}^0$-semigroup on $L^1((0, z_0))$ (by extension of $S(t)$ from X to $L^1((0, z_0))$).

Step 4: $S(t)$, $t \geq 0$, is a positive semigroup

Let $\varphi \in L^1_+((0, z_0))$, i.e., $\varphi(z) \geq 0$ for a.e. $z \in (0, z_0)$, then $T(t)\varphi(g^{-1}(z, -t)) \in L^1_+((0, z_0))$ as $T(t)$ is a positive semigroup. Therefore, together with $b(z) > 0$ for all $z \in (0, z_0)$ we obtain that $S(t)\varphi(z) \geq 0$ for a.e. $z \in (0, z_0)$, i.e., $S(t)\varphi \in L^1_+((0, z_0))$ and $S(t)$, $t \geq 0$, is a positive semigroup.

Step 5: Uniqueness of the mild solution $S(t)\varphi(z)$

We use the method of characteristics to show that every solution $u(z,t)$ to (3.20) satisfies $u(z,t) = S(t)\varphi(z)$.

Let $u(z,t)$ be a solution to (3.20) with $u(z, 0) = \varphi(z)$ and let $\tau(v,t) := v - t$ for $v \geq t$, $\tau^{-1}(x,t) = x + t$. Then,

$$\frac{d}{dx}\tau^{-1}(x,t) = 1, \qquad \tau^{-1}(0,t) = t \qquad \text{for all } t \geq 0.$$

Fix $z \in (0, z_0)$ and $t > 0$. We define $w(x) := u(g^{-1}(z,x), \tau^{-1}(x,t))$. The function $w(x)$ can be interpreted as the density of bacteria at time $t + x$ that had z plasmids at time t, i.e., in particular $w(0) = u(z,t)$ (for a plot of the function g for logistic plasmid reproduction see Figure 3.7).

Using that u is a solution to (3.20) we obtain

$$\begin{aligned}
\frac{d}{dx}w(x) &= \frac{d}{dx}u(g^{-1}(z,x), \tau^{-1}(x,t)) \\
&= \partial_z u(g^{-1}(z,x), \tau^{-1}(x,t)) \, \partial_x g^{-1}(z,x) + \partial_t u(g^{-1}(z,x), \tau^{-1}(x,t)) \, \partial_x \tau^{-1}(x,t) \\
&= \partial_z u(g^{-1}(z,x), \tau^{-1}(x,t)) \, b(g^{-1}(z,x)) \\
&\quad - \partial_z \Big(b(g^{-1}(z,x)) \, u(g^{-1}(z,x), \tau^{-1}(x,t)) \Big) + Au(g^{-1}(z,x), \tau^{-1}(x,t)) \\
&= -\partial_z b(g^{-1}(z,x)) \, u(g^{-1}(z,x), \tau^{-1}(x,t)) + Au(g^{-1}(z,x), \tau^{-1}(x,t)) \\
&= -\partial_z b(g^{-1}(z,x)) \, w(x) + Aw(x).
\end{aligned}$$

Define $\hat{w}(x) := w(x - t)$, then we can interpret $\hat{w}$ similar to w: $\hat{w}(x)$ is the density of bacteria at time x for bacteria that have z plasmids at time t, i.e., $\hat{w}(t) = u(z,t)$ and $\hat{w}(0) = u(g^{-1}(z, -t), 0)$.

We use the method of characteristics: the function $\hat{w}$ is our characteristic curve along which the PDE becomes an Ordinary Differential Equation (ODE). We can solve this

ODE and thereby obtain a solution to (3.20). It holds that

$$\begin{aligned}\frac{d}{dx}\hat{w}(x) &= \frac{d}{dx}w(x-t) = -\partial_z b(g^{-1}(z,x-t))\,w(x-t) + Aw(x-t)\\ &= -\partial_z b(g^{-1}(z,x-t))\,\hat{w}(x) + A\hat{w}(x) = \Big(-\partial_z b(g^{-1}(z,x-t)) + A\Big)\,\hat{w}(x).\end{aligned}$$

We can solve this equation for $\hat{w}$. With change of variables $g^{-1}(z,y) = \tilde{y}$ and $dy = \frac{1}{b(\tilde{y})}d\tilde{y}$ with dropping the tilde again, we obtain

$$\begin{aligned}\hat{w}(x) &= \exp\left[\int_0^x -\partial_z b(g^{-1}(z,y-t))\,dy\right]T(x)\hat{w}(0)\\ &= \exp\left[-\int_{-t}^{x-t} \partial_z b(g^{-1}(z,y))\,dy\right]T(x)\hat{w}(0) = \exp\left[-\int_{g^{-1}(z,-t)}^{g^{-1}(z,x-t)} \frac{b'(y)}{b(y)}\,dy\right]T(x)\hat{w}(0)\\ &= \exp\left[\log\left(\frac{b(g^{-1}(z,-t))}{b(g^{-1}(z,x-t))}\right)\right]T(x)\hat{w}(0) = \frac{b(g^{-1}(z,-t))}{b(g^{-1}(z,x-t))}\,T(x)\hat{w}(0).\end{aligned}$$

It holds that $g^{-1}(z,-t) \in (0,z_0)$ for every $t \in \mathbb{R}$, $z \in (0,z_0)$ due to Lemma 3.14. Hence,

$$\begin{aligned}u(z,t) &= u(g^{-1}(z,0),\tau^{-1}(0,t)) = w(0) = \hat{w}(t) = \frac{b(g^{-1}(z,-t))}{b(g^{-1}(z,0))}\,T(t)\hat{w}(0)\\ &= \frac{b(g^{-1}(z,-t))}{b(z)}\,T(t)w(-t) = \frac{b(g^{-1}(z,-t))}{b(z)}\,T(t)u(g^{-1}(z,-t),\tau^{-1}(-t,t))\\ &= \frac{b(g^{-1}(z,-t))}{b(z)}\,T(t)u(g^{-1}(z,-t),0) = \frac{b(g^{-1}(z,-t))}{b(z)}\,T(t)\varphi(g^{-1}(z,-t))\\ &= S(t)\varphi(z).\end{aligned}$$

Therefore, every solution $u(z,t)$ to (3.20) with $u(z,0) = \varphi(z)$ satisfies $u(z,t) = S(t)\varphi(z)$ and the solution $S(t)\varphi(z)$ is the unique mild solution to (3.20). ☐

We have shown existence of a unique mild solution to (3.20) and now we add the integral term and the zero-flux boundary condition, i.e., we consider the full model (3.18). To this end we define for $u \in L^1((0,z_0))$ the integral operator

$$F[u](z) := \int_z^{z_0} \beta(z')\,k(z,z')\,u(z')\,dz'.$$

In the next lemma we gather some properties of the operator F before we move on to showing existence and uniqueness of a mild solution to (3.18).

Lemma 3.18. *The operator F is linear and bounded. It maps $L^1((0,z_0))$ to $L^1((0,z_0))$, its operator norm satisfies $\|F\|_{op} \leq 2\overline{\beta}$, and it is Lipschitz continuous with Lipschitz constant Lip$(F) = 2\overline{\beta}$.*

Proof. The linearity of F follows directly from linearity of the integral.

Let $u \in L^1((0, z_0))$, then

$$\begin{aligned}
\|F[u]\|_{L^1((0,z_0))} &= \int_0^{z_0} |F[u](z)| \; dz \leq \int_0^{z_0} \int_z^{z_0} \beta(z')\, k(z,z')\, |u(z')| \; dz'dz \\
&\leq \overline{\beta} \int_0^{z_0} \int_0^{z'} k(z,z') \; dz \; |u(z')| \; dz' = 2\overline{\beta} \int_0^{z_0} |u(z')| \; dz' \\
&= 2\overline{\beta} \; \|u\|_{L^1((0,z_0))} \, .
\end{aligned}$$

Therefore, F is a bounded operator, it maps $L^1((0, z_0))$ to $L^1((0, z_0))$, and $\|F\|_{\mathrm{op}} \leq 2\overline{\beta}$.

It only remains to show that F is Lipschitz-continuous with Lipschitz constant $\mathrm{Lip}(F) = 2\overline{\beta}$. To this end, take arbitrary functions u_1 and $u_2 \in L^1((0, z_0))$, then

$$\begin{aligned}
&\|F[u_1] - F[u_2]\|_{L^1((0,z_0))} = \\
&= \int_0^{z_0} \left| \int_z^{z_0} \beta(z')\, k(z,z')\, u_1(z') \; dz' \, dz - \int_z^{z_0} \beta(z')\, k(z,z')\, u_2(z') \; dz' \right| dz \\
&\leq \int_0^{z_0} \int_z^{z_0} \beta(z')\, k(z,z')\, |u_1(z') - u_2(z)| \; dz' \, dz \\
&\leq \overline{\beta} \int_0^{z_0} \int_0^{z'} k(z,z') \; dz' \; |u_1(z') - u_2(z')| \; dz \\
&= 2\overline{\beta} \, \|u_1 - u_2\|_{L^1((0,z_0))} \, .
\end{aligned}$$

Therefore, F is Lipschitz continuous with Lipschitz constant $\mathrm{Lip}(F) = 2\overline{\beta}$. ☐

We combine now Lemma 3.18 and Theorem 3.17 via variation of constants in order to obtain a mild solution for the singular VGT model (3.18).

Theorem 3.19. *Let $S(t)$, $t \geq 0$, be the positive $\mathcal{C}^0$-semigroup from Theorem 3.17 and let $\varphi \in L^1((0, z_0))$. Then, there is a unique solution $U(t)\varphi$ for the integral equation*

$$U(t)\varphi = S(t)\varphi + \int_0^t S(t-s)F[U(s)\varphi] \, ds, \qquad t \geq 0.$$

Furthermore, it holds that

(a) $U(t)$, $t \geq 0$, is a positive $\mathcal{C}^0$-semigroup,

(b) there are $M \geq 1$ and $\omega \geq 0$ such that it holds for all $t \geq 0$, φ_1, $\varphi_2 \in L^1((0, z_0))$ that $\|U(t)\varphi_1 - U(t)\varphi_2\|_{L^1((0,z_0))} \leq M e^{(2\overline{\beta} M + \omega)t} \|\varphi_1 - \varphi_2\|_{L^1((0,z_0))}$, and

(c) $U(t)\varphi(z)$ is the unique mild solution to (3.18).

Proof. By Theorem 3.17, we know that $S(t)$, $t \geq 0$, is a $\mathcal{C}^0$-semigroup on $L^1((0, z_0))$ and there are $M \geq 1$ and $\omega \geq 0$ such that $\|S(t)\|_{\text{op}} \leq Me^{\omega t}$. We denote the infinitesimal generator of $S(t)$, $t \geq 0$, by A_S. By Lemma 3.18, we know that F is a bounded linear operator.

All conditions of Theorem 2.32 are satisfied and therefore $A_S + F$ is the infinitesimal generator of a $\mathcal{C}^0$-semigroup $U(t)$, $t \geq 0$, on $L^1((0, z_0))$ that is the unique solution to

$$U(t)\varphi = S(t)\varphi + \int_0^t S(t-s)F[U(s)\varphi]\,ds$$

for $t \geq 0$ and $\varphi \in L^1((0, z_0))$. Furthermore, it follows that $\|U(t)\|_{\text{op}} \leq Me^{(\omega + M\|F\|_{\text{op}})t}$. With $\|F\|_{\text{op}} = 2\overline{\beta}$, (b) directly follows.

By Theorem 2.27(c), we know that $A_S + F$ is densely defined. We also know that the resolvent of $A_S + F$ is not empty (as $[2\overline{\beta} - \underline{\beta} - \underline{\mu}, \infty) \subset \rho(A_S + F)$, this can be show analogously to Lemma 3.8). Therefore, by Theorem 2.30, $U(t)\varphi(z)$ is the unique solution to (3.18).

Finally, positivity follows from positivity of $S(t)$ and the proof of Proposition 3.1.2 in [82]. The zero-flux boundary condition is satisfied due to the integrability of $U(t)\varphi(z)$ and Lemma 3.14. □

Thus, we have shown that there exists a unique non-negative mild solution to the singular VGT model for every initial condition $\varphi \in L^1_+((0, z_0))$.

If φ is in the domain of the generator of the semigroup U that we denote by A_U, then the solution is continuously differentiable w.r.t. time and a weak solution (or a solution in the classical sense if it is also continuously differentiable w.r.t. z).

Following [31], we can state $D(A_U)$. First, we fix some $s \in (0, z_0)$ and define

$$\theta : (0, z_0) \to \mathbb{R}, \quad \theta(z) := g(s, z).$$

and

$$\Theta : L^1(\mathbb{R}) \to L^1((0, z_0)), \quad \Theta[\varphi](z) := \varphi(\theta(z))\,\theta'(z) = \frac{\varphi(\theta(z))}{b(z)}.$$

Then, the domain of A_U is given by $D(A_U) = \Theta[W^{1,1}(\mathbb{R})]$ [31].

3.3.2 Existence of solutions to the eigenproblem

We are again interested in the long-time distribution of plasmids in the bacterial population. Therefore, we consider the eigenproblem associated with the singular VGT model (3.18).

In the regular model, we could adapt the approach by Doumic [29] and Campillo et al. [19] to show existence of a solution to the eigenproblem. However, in the case of the singular model this is not possible (see Remark 3.20). Therefore, we use a different approach.

Remark 3.20. Recall the comparison of the two VGT models at the end of Section 3.1.2: in the singular model the integral kernel $\beta(z')\,k(z,z')$ is unbounded for $z' \to 0$ while in the regular model we have the integral kernel $\beta_m(z')\,k(z,z')$ with $\beta_m(z')\,k(z,z') = 0$ for all $z' < m$. For this reason, we cannot show compactness of the operator G_λ^ε using the Theorem of Arzelà-Ascoli as we did in the proof of Theorem 3.4 because we estimated the kernel by its supremum norm which is not possible for an unbounded kernel (see the computation below).

Let $\varepsilon > 0$ and $f \in \mathcal{C}^0([0,z_0])$, consider the operator $G_\lambda^\varepsilon[f]$ defined, as in the proof of Theorem 3.4, by

$$G_\lambda^\varepsilon[f](z) := \int_0^\infty \int_0^{z_0} \Big(\beta(Z(t,z'))\,k(z,Z(t,z')) + \frac{2\varepsilon}{z_0}\Big)\,f(z')\,e^{-\int_0^t \lambda+\beta(Z(s,z'))+\mu(Z(s,z'))\,ds}\,dz'\,dt.$$

Let $f \in \mathcal{C}^0([0,z_0])$ with $\|f\|_\infty \le 1$, then

$$\begin{aligned}\|G_\lambda^\varepsilon[f]\|_\infty \le \overline{\beta} \sup_{z\in[0,z_0]} &\int_0^\infty \int_0^{z_0} k(z,Z(s,z'))\,e^{-\int_0^t \lambda+\beta(Z(s,z'))+\mu(Z(s,z'))\,ds}\,dz'\,dt \\ &+ \frac{2\varepsilon}{z_0}\int_0^\infty \int_0^{z_0} e^{-\int_0^t \lambda+\beta(Z(s,z'))+\mu(Z(s,z'))\,ds}\,dz'\,dt.\end{aligned}$$

Now, we consider only the first summand on the right-hand side and assume the kernel k is scalable, i.e., $k(z,z') = \frac{2}{z'}\,\Phi\big(\frac{z}{z'}\big)$ with $\|\Phi\|_\infty < \infty$, then

$$\begin{aligned}&\overline{\beta} \sup_{z\in[0,z_0]} \int_0^\infty \int_0^{z_0} k(z,Z(s,z'))\,e^{-\int_0^t \lambda+\beta(Z(s,z'))+\mu(Z(s,z'))\,ds}\,dz'\,dt \\ &\le 2\overline{\beta}\,\|\Phi\|_\infty \int_0^\infty \int_0^{z_0} \frac{1}{z'}\,e^{-\int_0^t \lambda+\beta(Z(s,z'))+\mu(Z(s,z'))\,ds}\,dz'\,dt.\end{aligned}$$

We have the following lower bound for the second factor in the integral:

$$e^{-\int_0^t \lambda+\beta(Z(s,z'))+\mu(Z(s,z'))\,ds} \ge e^{-t\left(\lambda+\overline{\beta}+\overline{\mu}\right)} > 0$$

for all $t \ge 0$. Therefore, we do not even have boundedness of the operator G_λ^ε in general.

In this section, we consider the specific example of logistic plasmid reproduction rate, constant cell division and death rate, and a scalable segregation kernel. Therefore, we replace Assumptions **(A1')** to **(A4')** with the following:

(A5') $b(z) = \frac{b_0}{z_0} z(z_0 - z)$ for $z_0 > 0$, $b_0 > 0$.

(A6') β is constant with $0 < \beta < \infty$.

(A7') μ is constant with $0 \le \mu < \infty$.

(A8') The kernel k is scalable and the function Φ satisfies: $\Phi(\xi) = \Phi(1-\xi)$ for all $\xi \in [0,1]$, $\Phi \in L^\infty([0,1])$, and $\int_0^1 \Phi(\xi)\,d\xi = 1$.

Under these assumptions, the eigenproblem associated with the singular VGT model (3.18) is given by:

$$\begin{cases} \left(b(z)\,\mathcal{U}(z)\right)_z = -\left(\beta+\mu+\lambda\right)\mathcal{U}(z) + 2\beta \displaystyle\int_z^{z_0} \frac{1}{z'}\,\Phi\Big(\frac{z}{z'}\Big)\,\mathcal{U}(z')\,dz', \\ \displaystyle\lim_{z\to 0^+} b(z)\,\mathcal{U}(z) = 0, \quad \mathcal{U}(z)\geq 0 \text{ for all } z\in(0,z_0), \quad \int_0^{z_0}\mathcal{U}(z)\,dz = 1. \end{cases} \tag{3.22}$$

In the special case of constant cell division and death rate, we can give the eigenvalue explicitly (see [74, Corollary 3.3]).

Lemma 3.21. *In the case of constant cell division and death rate, i.e., β and μ are constant, there is an integrable solution to the eigenproblem associated with* (3.18) *only if $\lambda = \beta - \mu$.*

Proof. The proof follows the proof of [74, Corollary 3.3].

Consider equation (3.18) with β and μ constant, i.e.,

$$\partial_t u(z,t) + \partial_z\left(b(z)\,u(z,t)\right) = -(\beta+\mu)u(z,t) + \beta\int_z^{z_0} k(z,z')\,u(z',t)\,dz', \tag{3.23}$$

and assume there is a function $\mathcal{U}\in L^1((0,z_0))$ and a $\lambda\in\mathbb{C}$ such that $u(z,t) = e^{\lambda t}\mathcal{U}(z)$. Then, $(\lambda,\mathcal{U})$ is a solution to the eigenproblem associated with (3.18).

Note that here we do not make any assumptions on the kernel k except for the consistency condition that we always assume to hold (see the derivation of the model, section 3.1.2). In particular, k need not be a scalable kernel.

Since $\mathcal{U}\in L^1((0,z_0))$, $u(z,t)$ is integrable over z for all finite t. Therefore, we can integrate (3.23) over z from 0 to z_0. We obtain

$$\frac{d}{dt}\int_0^{z_0} u(z,t)\,dz = -(\beta+\mu)\int_0^{z_0} u(z,t)\,dz + \beta\int_0^{z_0}\int_z^{z_0} k(z,z')\,u(z',t)\,dz'dz.$$

Interchanging the order of integration in the last term, we obtain

$$\beta\int_0^{z_0}\int_z^{z_0} k(z,z')\,u(z',t)\,dz'dz = \beta\int_0^{z_0}\int_0^{z'} k(z,z')\,dz\,u(z',t)\,dz = 2\beta\int_0^{z_0} u(z',t)\,dt.$$

Overall,

$$\frac{d}{dt}\int_0^{z_0} u(z,t)\,dz = -(\beta+\mu)\int_0^{z_0} u(z,t)\,dz + 2\beta\int_0^{z_0} u(z',t)\,dt = (\beta-\mu)\int_0^{z_0} u(z,t)\,dz.$$

Hence, every solution of the form $u(z,t) = e^{\lambda t}\mathcal{U}(z)$ with $\mathcal{U}\in L^1((0,z_0))$ satisfies $\lambda = \beta-\mu$. ☐

Remark 3.22. For constant β and μ we know λ but for non-constant β and μ we do not. In general, it is non-trivial to determine λ. Furthermore, we do not (yet) know if there is a solution $\mathcal{U}$ to the eigenproblem (3.22). We aim at showing existence of an eigenfunction and ideally would like our approach to be extendable to the case of non-constant β and μ. Therefore, we do not use the fact that we already know λ in the following. Moreover, we hope to gain a better understanding of the model in this way.

Similarly to the spectral analysis of the regular VGT model (see Section 3.2.2), we rescale the eigensolution $\mathcal{U}$.

Lemma 3.23. *There is a solution* $(\lambda, \mathcal{U})$ *with* $\mathcal{U} \in \mathcal{C}^1((0, z_0))$ *to the eigenproblem* (3.22) *if and only if there is a solution* (λ, v) *with* $v \in \mathcal{C}^1((0, z_0))$ *to*

$$\begin{cases} v'(z) + \dfrac{\lambda+\beta+\mu}{b_0}\, z_0\, \dfrac{v(z)}{z(z_0 - z)} = \dfrac{2\beta z_0}{b_0} \displaystyle\int_z^{z_0} \dfrac{\Phi\left(\frac{z}{z'}\right) v(z')}{(z')^2\,(z_0 - z')}\, dz', \\ \displaystyle\lim_{z\to 0^+} v(z) = 0, \quad v(z) \geq 0 \text{ for all } z \in (0, z_0), \quad \int_0^{z_0} \frac{v(z)}{b(z)}\, dz = 1. \end{cases} \tag{3.24}$$

Proof. If $(\lambda, \mathcal{U})$ with $\mathcal{U} \in \mathcal{C}^1((0, z_0))$ is a solution to (3.22), then (λ, v) with $v(z) := b(z)\mathcal{U}(z) \in \mathcal{C}^1((0, z_0))$ is a solution to (3.24).

Likewise, if (λ, v) is a solution to (3.24), then define $\mathcal{U}(z) := \frac{v(z)}{b(z)}$. $\mathcal{U}$ is well-defined for $z \in (0, z_0)$ as $b(z) \neq 0$ for $z \in (0, z_0)$, $\mathcal{U} \in \mathcal{C}^1((0, z_0))$, and $(\lambda, \mathcal{U})$ is a solution to (3.22). ☐

For the sake of brevity, we define

$$\alpha = \alpha(\lambda) := \frac{\lambda+\beta+\mu}{b_0} \quad \text{and} \quad \alpha_0 := \frac{2\beta}{b_0}.$$

Note that α corresponds to $\alpha(\lambda, z)$ that we defined for spectral analysis in the case of the regular VGT model. If $\lambda = \beta - \mu$, then $\alpha = \alpha_0$.

Example 3.24. In the case $\Phi(\xi) = 1$ for all $\xi \in [0, 1]$, i.e., uniform plasmid segregation, one can explicitly compute that $\mathcal{U}(z) = Cz^{-\alpha}(z_0 - z)^{\alpha-1}$ with $C > 0$, $\lambda = \beta - \mu$, and $\alpha = \alpha_0$ is a solution to (3.22) [74]. Therefore, by Lemma 3.23, $v(z) = b(z)\mathcal{U}(z) = C\, \frac{b_0}{z_0}\, z^{1-\alpha}\,(z_0 - z)^{\alpha}$ is a solution to (3.24).

This example motivates another rescaling of the solution v to (3.24).

Lemma 3.25. *If there is a solution* (α, g) *with* $g \in \mathcal{C}^0((0, z_0]) \cap \mathcal{C}^1((0, z_0))$ *to*

$$\begin{cases} g'(z) + \dfrac{\alpha}{z}\, g(z) = \dfrac{\alpha_0\, z_0}{(z_0 - z)^{\alpha}} \displaystyle\int_z^{z_0} \Phi\left(\frac{z}{z'}\right) (z')^{-2}\, (z_0 - z')^{\alpha-1}\, g(z')\, dz', \\ g(z_0) = 1, \ \displaystyle\lim_{z\to 0^+} g(z) = 0, \ g(z) \geq 0 \text{ for all } z \in (0, z_0), \ \int_0^{z_0} \frac{(z_0 - z)^{\alpha}\, g(z)}{b(z)}\, dz < \infty, \end{cases} \tag{3.25}$$

then (λ, v) *with* $\lambda := \alpha\, b_0 - \beta - \mu$ *and* $v(z) := C\,(z_0 - z)^\alpha\, g(z)$ *for some* $C > 0$ *is a solution to* (3.24) *with* $v \in \mathcal{C}^1((0, z_0))$.

Remark 3.26. In Lemma 3.25 we do not have equivalence as there can only be a function g with $v(z) = C\,(z_0 - z)^\alpha\, g(z)$ and $g(z_0) = 1$ if $v(z) \sim (z_0 - z)^\alpha$ at z_0, i.e., if v behaves like $(z_0 - z)^\alpha$ at z_0 (see Definition 2.6). Otherwise, it holds that either $g(z_0) = 0$ or $\lim\limits_{z \to z_0^-} g(z) = \infty$.

In Lemma 3.23, we had equivalence because we can simply rescale the solution $\mathcal{U}$ to (3.22) to obtain a solution v to (3.24) and vice versa. However, in Lemma 3.25, we do not just rescale but we assume that the solution v satisfies $v(z) \sim (z_0 - z)^\alpha$ at z_0, i.e., v behaves like $(z_0 - z)^\alpha$ near z_0, and then obtain a solution g to (3.25). If the function v does not satisfy this assumption, then it is not possible to find a solution g to (3.25) that satisfies $g(z_0) = 1$ and therefore we do not have equivalence.

By Example 3.24 we know that at least for $\Phi \equiv 1$, $v(z) \sim (z_0 - z)^\alpha$ at z_0.

Proof. Define $v(z) := (z_0 - z)^\alpha g(z)$. As g is a solution to (3.25),

$$\begin{aligned}
v'(z) &= g'(z)\,(z_0 - z)^\alpha + g(z)\,\alpha\,(z_0 - z)^{\alpha-1}\,(-1) \\
&= (z_0 - z)^\alpha \left(-\frac{\alpha}{z}\, g(z) + \frac{\alpha_0\, z_0}{(z_0 - z)^\alpha} \int_z^{z_0} \Phi\Big(\frac{z}{z'}\Big)\,(z')^{-2}\,(z_0 - z')^{\alpha-1}\, g(z')\, dz' \right) \\
&\quad - \frac{\alpha}{z_0 - z}\, v(z) \\
&= -\frac{\alpha\, z_0}{z\,(z_0 - z)} v(z) + \alpha_0\, z_0 \int_z^{z_0} \frac{\Phi\big(\frac{z}{z'}\big)\, v(z')}{(z')^2\,(z_0 - z')}\, dz'.
\end{aligned}$$

Therefore, v is a solution to the PDE in (3.24). It is straightforward to check that v satisfies all conditions in (3.24), therefore (λ, v) with $\lambda = \alpha b_0 - \beta - \mu$ is a solution to (3.24). ☐

For now, we consider the integro-differential equation for g in (3.25) together with $g(z_0) = 1$, i.e., we omit the conditions $\lim\limits_{z \to 0^+} g(z) = 0$, $g(z) \geq 0$ for all $z \in (0, z_0)$, and the integral condition:

$$\begin{cases}
g'(z) + \dfrac{\alpha}{z}\, g(z) = \dfrac{\alpha_0\, z_0}{(z_0 - z)^\alpha} \displaystyle\int_z^{z_0} \Phi\Big(\frac{z}{z'}\Big)\,(z')^{-2}\,(z_0 - z')^{\alpha-1}\, g(z')\, dz' \\
g(z_0) = 1.
\end{cases} \tag{3.26}$$

In the following lemma we show existence of a solution g to (3.26). We use this lemma later both in the proof of existence of a solution to the eigenproblem (3.22) and for the numerical construction of the eigensolution (see Section 3.4).

Lemma 3.27. *For every* $\alpha > 0$ *there exists a unique solution* $g \in \mathcal{C}^0((0, z_0]) \cap \mathcal{C}^1((0, z_0))$ *to* (3.26).

Proof. Let $\alpha > 0$. Variation of parameters yields for $x \in (0, z_0]$ the solution

$$\begin{aligned} g(x) &= e^{-\int_{z_0}^{x} \frac{\alpha}{\tau}\, d\tau} \left[\int\limits_{z_0}^{x} \frac{\alpha_0\, z_0}{(z_0 - z)^{\alpha}} \int\limits_{z}^{z_0} \Phi\Big(\frac{z}{z'}\Big)\, (z')^{-2}\, (z_0 - z')^{\alpha - 1}\, g(z')\, dz' e^{\int_{z_0}^{z} \frac{\alpha}{\tau}\, d\tau}\, dz + 1 \right] \\ &= \frac{\alpha_0\, z_0}{x^{\alpha}} \int\limits_{z_0}^{x} \Big(\frac{z}{z_0 - z}\Big)^{\alpha} \int\limits_{z}^{z_0} \Phi\Big(\frac{z}{z'}\Big)\, (z')^{-2}\, (z_0 - z')^{\alpha - 1}\, g(z')\, dz' dz + \Big(\frac{z_0}{x}\Big)^{\alpha}. \end{aligned}$$

Let $I_1 := (z_0/x)^{\alpha}$ and consider for $a \in (0, z_0)$ the operator $T : \mathcal{C}^0([a, z_0]) \to \mathcal{C}^0([a, z_0])$ defined by

$$T[g](x) := \frac{\alpha_0\, z_0}{x^{\alpha}} \int\limits_{z_0}^{x} \Big(\frac{z}{z_0 - z}\Big)^{\alpha} \int\limits_{z}^{z_0} \Phi\Big(\frac{z}{z'}\Big)\, (z')^{-2}\, (z_0 - z')^{\alpha - 1}\, g(z')\, dz' dz.$$

Hence, $g(x) = T[g](x) + I_1(x)$. On $[a, z_0]$ for $a \in (0, z_0)$ and for $\alpha \neq 1$, T is a bounded operator as

$$\begin{aligned} \|T[g]\|_{\infty} &\leq \alpha_0\, z_0\, \|\Phi\|_{L^{\infty}([0,1])} \sup_{x \in [a, z_0]} x^{-\alpha} \left| \int\limits_{z_0}^{x} \Big(\frac{z}{z_0 - z}\Big)^{\alpha} \frac{1}{z^2} \int\limits_{z}^{z_0} (z_0 - z')^{\alpha - 1}\, dz'\, dz \right| \|g\|_{\infty} \\ &= \frac{\alpha_0\, z_0}{\alpha} \|\Phi\|_{L^{\infty}([0,1])} \sup_{x \in [a, z_0]} x^{-\alpha} \left| \int\limits_{z_0}^{x} z^{\alpha - 2}\, dz \right| \|g\|_{\infty} \\ &= \frac{\alpha_0\, z_0}{\alpha\, |\alpha - 1|} \|\Phi\|_{L^{\infty}([0,1])} \sup_{x \in [a, z_0]} x^{-\alpha} \left| x^{\alpha - 1} - z_0^{\alpha - 1} \right| \|g\|_{\infty} \\ &= \frac{\alpha_0}{\alpha\, |\alpha - 1|} \|\Phi\|_{L^{\infty}([0,1])} \left| \frac{z_0}{a} - \Big(\frac{z_0}{a}\Big)^{\alpha} \right| \|g\|_{\infty}. \end{aligned}$$

It holds that

$$\lim_{a \to z_0^-} \left| \frac{z_0}{a} - \Big(\frac{z_0}{a}\Big)^{\alpha} \right| = 0.$$

Therefore, there exists some $\varepsilon \in (0, z_0)$ such that T is a contraction on $[z_0 - \varepsilon, z_0]$. Furthermore, I_1 is bounded on $[z_0 - \varepsilon, z_0]$. Hence, by the Banach Fixed Point Theorem, there is a unique continuous solution $g : [z_0 - \varepsilon, z_0] \to \mathbb{R}$ of (3.26). The case $\alpha = 1$ can be handled analogously.

We construct a continuously differentiable solution iteratively: assume we already have a unique continuous solution $g : [a, z_0] \to \mathbb{R}$ on $[a, z_0]$ for some $a \in (0, z_0)$. By variation of parameters, for $x \in (0, a]$,

$$\begin{aligned} g(x) &= e^{-\int_{a}^{x} \frac{\alpha}{\tau}\, d\tau} \left[\int\limits_{a}^{x} \frac{\alpha_0\, z_0}{(z_0 - z)^{\alpha}} \int\limits_{z}^{z_0} \Phi\Big(\frac{z}{z'}\Big)\, (z')^{-2}\, (z_0 - z')^{\alpha - 1}\, g(z')\, dz'\, e^{\int_{a}^{z} \frac{\alpha}{\tau}\, d\tau}\, dz + g(a) \right] \\ &= \frac{\alpha_0\, z_0}{x^{\alpha}} \int\limits_{a}^{x} \Big(\frac{z}{z_0 - z}\Big)^{\alpha} \int\limits_{z}^{a} \Phi\Big(\frac{z}{z'}\Big)\, (z')^{-2}\, (z_0 - z')^{\alpha - 1}\, g(z')\, dz'\, dz \end{aligned}$$

$$+\frac{\alpha_0\, z_0}{x^\alpha} \int_a^x \left(\frac{z}{z_0 - z}\right)^\alpha \int_a^{z_0} \Phi\Big(\frac{z}{z'}\Big)\, (z')^{-2}\, (z_0 - z')^{\alpha-1}\, g(z')\, dz'\, dz + \left(\frac{a}{x}\right)^\alpha g(a).$$

Denote the second summand by $I_2(x)$ and the third summand by $I_3(x)$. We consider for some $\delta \in (0, a)$ the operator $T_a : \mathcal{C}^1([a-\delta, a]) \to \mathcal{C}^1([a-\delta, a])$ given by

$$T_a[g](x) := \frac{\alpha_0\, z_0}{x^\alpha} \int_a^x \left(\frac{z}{z_0 - z}\right)^\alpha \int_z^{a} \Phi\Big(\frac{z}{z'}\Big)\, (z')^{-2}\, (z_0 - z')^{\alpha-1}\, g(z')\, dz'\, dz,$$

such that $g(x) = T_a[g](x) + I_2(x) + I_3(x)$ for $x \le a$. Analogously to before, for $x \in [a-\delta, a]$ and $\alpha \neq 1$,

$$\begin{aligned}
\|T_a[g]\|_\infty &\le \alpha_0\, z_0\, \|\Phi\|_{L^\infty([0,1])} \sup_{x\in[a-\delta,a]} x^{-\alpha} \left| \int_a^x \left(\frac{z}{z_0 - z}\right)^\alpha \frac{1}{z^2} \int_z^a (z_0 - z')^{\alpha-1}\, dz'\, dz \right| \\
&\qquad \left\| g|_{[a-\delta,a]} \right\|_\infty \\
&\le \frac{\alpha_0\, z_0}{\alpha}\, \|\Phi\|_{L^\infty([0,1])} \sup_{x\in[a-\delta,a]} x^{-\alpha} \left| \int_x^a z^{\alpha-2}\, dz \right| \left\| g|_{[a-\delta,a]} \right\|_\infty \\
&\le \frac{\alpha_0\, z_0}{\alpha\, |\alpha - 1|\, a}\, \|\Phi\|_{L^\infty([0,1])} \sup_{x\in[a-\delta,a]} \left| \left(\frac{a}{x}\right)^\alpha - \frac{a}{x} \right| \left\| g|_{[a-\delta,a]} \right\|_\infty \\
&\le \frac{\alpha_0\, z_0}{\alpha\, |\alpha - 1|\, a}\, \|\Phi\|_{L^\infty([0,1])} \left| \left(\frac{a}{a-\delta}\right)^\alpha - \frac{a}{a-\delta} \right| \left\| g|_{[a-\delta,a]} \right\|_\infty.
\end{aligned}$$

Furthermore,

$$\begin{aligned}
\frac{d}{dx} T_a[g](x) &= \left(-\frac{\alpha}{x}\right) T_a[g](x) + \frac{\alpha_0\, z_0}{x^\alpha} \left(\frac{x}{z_0 - x}\right)^\alpha \int_x^a \Phi\Big(\frac{x}{z'}\Big)\, (z')^{-2}\, (z_0 - z')^{\alpha-1}\, g(z')\, dz' \\
&= \left(-\frac{\alpha}{x}\right) T_a[g](x) + \frac{\alpha_0\, z_0}{(z_0 - x)^\alpha} \int_x^a \Phi\Big(\frac{x}{z'}\Big)\, (z')^{-2}\, (z_0 - z')^{\alpha-1}\, g(z')\, dz',
\end{aligned}$$

and for $x \in [a-\delta, a]$,

$$\begin{aligned}
\left\| \frac{d}{dx} T_a[g] \right\|_\infty &\le \frac{\alpha}{a-\delta}\, \|T_a[g]\|_\infty + \alpha_0\, z_0\, \|\Phi\|_{L^\infty([0,1])} \left\| g|_{[a-\delta,a]} \right\|_\infty \\
&\qquad \max_{x\in[a-\delta,a]} \frac{1}{(z_0 - x)^\alpha} \int_x^a (z')^{-2}\, (z_0 - z')^{\alpha-1}\, dz'.
\end{aligned}$$

Because of

$$\begin{aligned}
&\max_{x\in[a-\delta,a]} \frac{1}{(z_0 - x)^\alpha} \int_x^a (z')^{-2}\, (z_0 - z')^{\alpha-1}\, dz' \\
&\quad \le \frac{1}{(a-\delta)^2}\, \frac{1}{(z_0 - a)^\alpha} \max_{x\in[a-\delta,a]} \int_x^a (z_0 - z')^{\alpha-1}\, dz' \\
&\quad = \frac{1}{(a-\delta)^2}\, \frac{1}{(z_0 - a)^\alpha}\, \frac{1}{\alpha} \max_{x\in[a-\delta,a]} \Big((z_0 - x)^\alpha - (z_0 - a)^\alpha \Big)
\end{aligned}$$

$$= \frac{1}{(a-\delta)^2} \frac{1}{(z_0-a)^\alpha} \frac{1}{\alpha}\Big((z_0-(a-\delta))^\alpha - (z_0-a)^\alpha\Big),$$

and $a \in (0, z_0)$ it holds that for $\delta \in (0, a)$ sufficiently small

$$\|T_a[g]\|_{\mathcal{C}^1([a-\delta,a])} = \max\left\{\|T_a[g]\|_\infty, \left\|\frac{d}{dx}T_a[g]\right\|_\infty\right\} < \|g\|_{\mathcal{C}^1([a-\delta,a])}.$$

Hence, T_a is a contraction on $[a-\delta, a]$. The inhomogeneities I_2 and I_3 are bounded on $[a-\delta, a]$, as $a-\delta > 0$ and

$$\|I_2\|_\infty \leq \frac{\alpha_0\, z_0}{\alpha\,|\alpha-1|\,a}\, \|\Phi\|_{L^\infty([0,1])} \left\|g|_{[a,z_0]}\right\|_\infty \left|\frac{a}{a-\delta} - \left(\frac{a}{a-\delta}\right)^\alpha\right| < \infty.$$

By Banach's Fixed Point Theorem, there is a unique solution $g_1 \in \mathcal{C}^1([a-\delta, a])$ with $g_1(a) = g(a)$ and hence there is a solution $g \in \mathcal{C}^0([a-\delta, z_0]) \cap \mathcal{C}^1([a-\delta, a])$ of (3.26). The case $\alpha = 1$ is again analogous to the case $\alpha \neq 1$.

Proceeding iteratively, we can construct a unique solution $g \in \mathcal{C}^0((0, z_0]) \cap \mathcal{C}^1((0, a])$ of (3.26) for every $\alpha > 0$ and since $a \in (0, z_0)$ arbitrary, $g \in \mathcal{C}^0((0, z_0]) \cap \mathcal{C}^1((0, z_0))$ for every $\alpha > 0$. ☐

The proof of Lemma 3.27 gives a method to iteratively construct a solution to (3.26). This solution can then be rescaled to obtain a solution for the eigenproblem (3.22) (see Section 3.4).

Note that Lemma 3.27 gives existence of a solution for $\alpha > 0$, i.e., for $\lambda > -(\beta+\mu)$. We expect that there is a unique $\lambda > -(\beta+\mu)$ and therefore a unique $\alpha > 0$ for which the function $g(z)$ satisfies the previously omitted conditions $\lim\limits_{z\to 0^+} g(z) = 0$ and $g(z) \geq 0$.

If $\alpha \leq 0$, then $\lambda \leq -(\beta+\mu) < 0$ and the bacterial population goes extinct. We are interested in finding a non-trivial asymptotic solution, therefore in the following, we consider only the case $\alpha > 0$.

Now we add again the conditions to equation (3.26) that we have omitted in the previous lemma and give necessary and sufficient conditions on the parameters of the model for existence and uniqueness of a solution to (3.25).

Theorem 3.28. *There is a unique solution $g \in \mathcal{C}^0((0, z_0]) \cap \mathcal{C}^1((0, z_0))$ with $g(z) > 0$ for $z \in (0, z_0]$ for (3.25) if and only if*

$$\alpha = \alpha_0, \ \text{and } \alpha_0 < -\frac{1}{\tilde{\Phi}'(0)},$$

where $\tilde{\Phi}(s) := \int_0^1 u^s\, \Phi(u)\, du$.

In the proof of Theorem 3.28, we use the following notation (see for example [7]).

Definition 3.29. The *convolution* of two L^1-functions f, $g : [0,\infty) \to \mathbb{R}$ is defined by

$$(f * g)(t) := \int_0^t f(\tau)\, g(t-\tau)\, d\tau.$$

For $n \in \mathbb{N}$, we define the *n-fold convolution* of f with g by

$$\left(f^{*n} * g\right)(t) := \Big(f * \Big(f^{*(n-1)} * g\Big)\Big)(t), \quad \text{where } \Big(f^{*0} * g\Big)(t) := g(t).$$

We prove Theorem 3.28 in steps. Firstly, we derive the conditions on the parameters given existence of the solution g to (3.25). By rescaling the solution g, we obtain a function q that satisfies an equation containing n-fold convolutions. This equation can be simplified with the Laplace transform as the Laplace transform of a convolution is the product of the Laplace transforms. Then, the boundedness of the Laplace transform yields a first condition on the parameters. The remaining conditions follow from positivity and boundedness of the Laplace transform.

Secondly, we show that the conditions on the parameters imply the existence of the unique solution g to (3.25). By Lemma 3.27, we know that there is a unique solution g to the integro-differential equation in (3.25). It thus remains to show that g satisfies the integrability condition in (3.25) and is a positive function. To this end, we use the assumptions on the parameters, the same rescaling as in the first part of the proof, and the Laplace transform to obtain an iteration formula for the Laplace transform of q. This iteration formula can be used to extend the Laplace transform. Finally, we show that the integral condition on g holds using the uniqueness (a.e.) of the inverse Laplace transform. The positivity condition on g follows via a proof by contradiction.

We now start by assuming that there is a solution g to (3.25) and showing that the rescaled solution q satisfies an equation containing n-fold convolutions.

Proposition 3.30. *If there is a solution $g \in \mathcal{C}^0((0,z_0]) \cap \mathcal{C}^1((0,z_0))$ to (3.25), then the function $q : \mathbb{R}_{\geq 0} \to \mathbb{R}_{\geq 0}$ defined by*

$$q(t) := \left(1 - e^{-t}\right)^{\alpha} g(z_0 e^{-t})$$

satisfies $q(0) = 0$, $\lim_{t\to\infty} q(t) = 0$, $q(t) \geq 0$ for all $t \geq 0$, $q \in \mathcal{C}^0([0,\infty)) \cap \mathcal{C}^1((0,\infty))$, there exist $M > 0$ and $a > 0$ such that $q(t) \leq M e^{-at}\left(1-e^{-t}\right)^{\alpha}$ for all $t \geq 0$, and with $\check{\Phi}(t) := \Phi(e^{-t})\, e^{-t}$ the following equation holds for every $n \in \mathbb{N}$:

$$\begin{aligned}\alpha\, q(t) = \left(1 - e^{-t}\right) \sum_{k=0}^{n} \left(\frac{\alpha_0}{\alpha}\right)^k \left(\check{\Phi}^{*k} * (q'(s))\right)(t) \\ + \left(1 - e^{-t}\right)\left(\frac{\alpha_0}{\alpha}\right)^{n+1} \left(\check{\Phi}^{*(n+1)} * \left(\frac{\alpha\, q(s)}{1-e^{-s}}\right)\right)(t).\end{aligned} \tag{3.27}$$

Proof. We rescale g to derive the equation for q.

Assume there is a solution g for (3.25) and let $g\left(z_0 e^{-t}\right) = e^{\alpha t}\, h(t)$ or equivalently $g(z) = \left(\frac{z_0}{z}\right)^{\alpha} h(-\log(\frac{z}{z_0}))$. Then h satisfies

$$h(0) = 1, \quad \lim_{t\to\infty} e^{\alpha t}\, h(t) = 0, \quad h(t) \geq 0 \text{ for all } t \geq 0, \quad h \in \mathcal{C}^0([0,\infty)) \cap \mathcal{C}^1((0,\infty)),$$

$$\int_0^{z_0} \frac{(z_0-z)^\alpha\, z^{-\alpha}\, h(-\log(z/z_0))}{b(z)}\, dz < \infty.$$

The integrability condition on g in (3.25) is

$$\int_0^{z_0} \frac{(z_0-z)^\alpha\, g(z)}{z\,(z_0-z)}\, dz = \int_0^{z_0} (z_0-z)^{\alpha-1}\, z^{-1}\, g(z)\, dz < \infty.$$

The integrand is integrable in a neighborhood of zero if and only if[5] there exist $\varepsilon > 0$, $C > 0$, and $a > 0$ such that for all $0 < z < \varepsilon$ it holds that

$$g(z) \leq C\, z^a.$$

Therefore, with the transformation to h and since $h \in \mathcal{C}^0([0,\infty))$ it holds for h that

$$\text{there exist } M > 0,\ a > 0 \text{ such that } h(t) \leq M e^{-(a+\alpha)t} \text{ for all } t \geq 0.$$

With $\check{\Phi}(t) := \Phi(e^{-t})\, e^{-t}$ and the transform $\sigma = -\log(z'/z_0)$, we obtain

$$\begin{aligned} h'(t) &= \left(e^{-\alpha t} g(z_0 e^{-t})\right)' = -\alpha e^{-\alpha t} g(z_0 e^{-t}) + e^{-\alpha t} g'(z_0 e^{-t})\,(-z_0 e^{-t}) \\ &= -\alpha e^{-\alpha t} g(z_0 e^{-t}) - z_0 e^{-(\alpha+1)t} \Bigg[-\frac{\alpha}{z_0 e^{-t}} g(z_0 e^{-t}) \\ &\quad + \frac{\alpha_0 z_0}{(z_0 - z_0 e^{-t})^\alpha} \int_{z_0 e^{-t}}^{z_0} \Phi\left(\frac{z_0 e^{-t}}{z'}\right) (z')^{-2} (z_0 - z')^{\alpha-1} g(z')\, dz' \Bigg] \\ &= -\frac{\alpha_0}{(e^t-1)^\alpha} \int_0^t \check{\Phi}(t-\sigma)\, h(\sigma)\, e^{\alpha\sigma}\, (1-e^{-\sigma})^{\alpha-1}\, d\sigma \\ &= -\frac{\alpha_0}{\alpha(e^t-1)^\alpha} \int_0^t \check{\Phi}(t-\sigma)\, h(\sigma)\, \frac{d}{d\sigma}(e^\sigma - 1)^\alpha\, d\sigma. \end{aligned}$$

Therefore,

$$\left(e^t - 1\right)^\alpha h'(t) = -\frac{\alpha_0}{\alpha} \int_0^t \check{\Phi}(t-\sigma)\, h(\sigma)\, \frac{d}{d\sigma}\left(e^\sigma - 1\right)^\alpha\, d\sigma.$$

We use n-fold convolutions and the notation from Definition 3.29 to rewrite the equation for h as

$$\left(e^t - 1\right)^\alpha h'(t) = -\frac{\alpha_0}{\alpha} \left(\check{\Phi}^{*1} * \left(h(s)\, \frac{d}{ds}\left(e^s - 1\right)^\alpha\right)\right)(t).$$

---

[5] It holds that $\int_0^\varepsilon \frac{1}{z}\, g(z)\, dz < \infty$ for all $\varepsilon \in (0, z_0)$. Let $\varepsilon \in (0, \min\{z_0, 1\})$, $C > 0$, and assume that for all $a > 0$ it holds that $g(z) > C z^a$ on $(0,\varepsilon)$, then $g(z) \geq \lim_{a \to 0^+} C z^a = C \operatorname{sgn}(z)$, where sgn denotes the sign function, i.e., $\operatorname{sgn}(z) = 1$ for $z > 0$, $\operatorname{sgn}(0) = 0$, and $\operatorname{sgn}(z) = -1$ for $z < 0$. Therefore, $\int_0^\varepsilon \frac{1}{z}\, g(z)\, dz \geq C \int_0^\varepsilon \frac{1}{z}\, dz = \infty$ which is a contradiction to the integrability of $\frac{1}{z}\, g(z)$. Hence, there exist $a > 0$ and $C > 0$ such that $g(z) \leq C\, z^a$ for all $z \in (0,\varepsilon)$.

Thus, we obtain

$$
\begin{aligned}
h(t)\,\frac{d}{dt}\Big(e^t-1\Big)^\alpha &= \frac{d}{dt}\Big[\Big(e^t-1\Big)^\alpha h(t)\Big] - \Big(e^t-1\Big)^\alpha \frac{d}{dt}h(t)\\
&= \frac{d}{dt}\Big[\Big(e^t-1\Big)^\alpha h(t)\Big] + \frac{\alpha_0}{\alpha}\left(\check{\Phi}^{*1} * \left(h(s)\,\frac{d}{ds}(e^s-1)^\alpha\right)\right)(t)\\
&= \left(\frac{\alpha_0}{\alpha}\right)^0\left(\check{\Phi}^{*0} * \left(\frac{d}{ds}\Big[\,(e^s-1)^\alpha\,h(s)\Big]\right)\right)(t) + \frac{\alpha_0}{\alpha}\left(\check{\Phi}^{*1} * \left(\frac{d}{ds}\Big[\,(e^s-1)^\alpha\,h(s)\Big]\right)\right)(t)\\
&\quad - \frac{\alpha_0}{\alpha}\left(\check{\Phi}^{*1} * \left((e^s-1)^\alpha\,\frac{d}{ds}h(s)\right)\right)(t)\\
&= \left(\frac{\alpha_0}{\alpha}\right)^0\left(\check{\Phi}^{*0} * \left(\frac{d}{ds}\Big[\,(e^s-1)^\alpha\,h(s)\Big]\right)\right)(t) + \frac{\alpha_0}{\alpha}\left(\check{\Phi}^{*1} * \left(\frac{d}{ds}\Big[\,(e^s-1)^\alpha\,h(s)\Big]\right)\right)(t)\\
&\quad + \left(\frac{\alpha_0}{\alpha}\right)^2\left(\check{\Phi}^{*2} * \left(h(s)\,\frac{d}{ds}(e^s-1)^\alpha\right)\right)(t).
\end{aligned}
$$

Proceeding recursively, we obtain for every $n \in \mathbb{N}$

$$
\begin{aligned}
h(t)\,\frac{d}{dt}\Big(e^t-1\Big)^\alpha = \sum_{k=0}^{n}\left(\frac{\alpha_0}{\alpha}\right)^k\left(\check{\Phi}^{*k} * \left(\frac{d}{ds}\Big[\,(e^s-1)^\alpha\,h(s)\Big]\right)\right)(t)\\
+ \left(\frac{\alpha_0}{\alpha}\right)^{n+1}\left(\check{\Phi}^{*(n+1)} * \left(h(s)\,\frac{d}{ds}(e^s-1)^\alpha\right)\right)(t).
\end{aligned}
$$

Therefore,

$$
\begin{aligned}
\alpha\,h(t)\,\Big(e^t-1\Big)^\alpha = \Big(1-e^{-t}\Big)\sum_{k=0}^{n}\left(\frac{\alpha_0}{\alpha}\right)^k\left(\check{\Phi}^{*k} * \left(\frac{d}{ds}\left[(e^s-1)^\alpha\,h(s)\right]\right)\right)(t)\\
+ \Big(1-e^{-t}\Big)\left(\frac{\alpha_0}{\alpha}\right)^{n+1}\left(\check{\Phi}^{*(n+1)} * \left(h(s)\,\frac{d}{ds}\,(e^s-1)^\alpha\right)\right)(t).
\end{aligned}
\tag{3.28}
$$

Now let $q(t) := h(t)\,(e^t-1)^\alpha$, then q satisfies

$$
\begin{gathered}
q(0)=0, \quad \lim_{t\to\infty} q(t)=0, \quad q(t)\geq 0 \text{ for all } t\geq 0, \quad q\in\mathcal{C}^0([0,\infty))\cap\mathcal{C}^1((0,\infty)),\\
\text{there exist } M>0 \text{ and } a>0 \text{ such that } q(t)\leq Me^{-at}\Big(1-e^{-t}\Big)^\alpha \text{ for all } t\geq 0.
\end{gathered}
$$

By (3.28), q satisfies

$$
\begin{aligned}
\alpha\,q(t) = \Big(1-e^{-t}\Big)\sum_{k=0}^{n}\left(\frac{\alpha_0}{\alpha}\right)^k\Big(\check{\Phi}^{*k} * (q'(s))\Big)(t)\\
+ \Big(1-e^{-t}\Big)\left(\frac{\alpha_0}{\alpha}\right)^{n+1}\left(\check{\Phi}^{*(n+1)} * \left(\frac{\alpha\,q(s)}{1-e^{-s}}\right)\right)(t).
\end{aligned}
$$

This finishes the proof. □

The function q satisfies equation (3.27) which contains n-fold convolutions. As a convolution is transformed into a multiplication under the Laplace transform (see Lemma 2.15(d)), we simplify (3.27) by taking the Laplace transform.

Proposition 3.31. *Assume there is a solution* $g \in \mathcal{C}^0\left((0,z_0]\right) \cap \mathcal{C}^1\left((0,z_0)\right)$ *to* (3.25), *define the function* q *as in Proposition 3.30, and denote its Laplace transform by* $\hat{q}$. *Then,* $\hat{q} : \mathbb{R} \to \mathbb{R}$ *satisfies*

$$\hat{q}(s) > 0 \text{ for all } s \geq 0, \quad \hat{q} \in \mathcal{C}^\infty([0,\infty)),$$

and for every $n \in \mathbb{N}$ *and* $s > 0$,

$$\hat{q}(s+n) = \hat{q}(s)\,\frac{\alpha - \alpha_0\,\tilde{\Phi}(s+n)}{\alpha - \alpha_0\,\tilde{\Phi}(s)} \prod_{k=1}^{n} \frac{(s+k-1) - \alpha + \alpha_0\,\tilde{\Phi}(s+k-1)}{s+k}, \tag{3.29}$$

where $\tilde{\Phi}(s) := \int_0^1 u^s\,\Phi(u)\,du$.

Furthermore, it holds that $\alpha_0 \leq \alpha$.

Proof. The Laplace transforms $\mathcal{L}\{q(t)\}(s)$ and $\mathcal{L}\Big\{\frac{\alpha\,q(t)}{1-e^{-t}}\Big\}(s)$ exist for $\Re(s) \geq 0$ as there are $M > 0$ and $a > 0$ such that $q(t) \leq M\,e^{-at}\,(1-e^{-t})^\alpha$ for all $t \geq 0$ by Proposition 3.30.

We ultimately aim at proving Theorem 3.28. To do so, it suffices to consider the Laplace transforms only on the real axis. Therefore, for the remainder of this proof we let $s \in \mathbb{R}$.

Denote by $\hat{q}(s)$ the Laplace transform of $q(t)$ and

$$\begin{aligned}\tilde{\Phi}(s) &:= \mathcal{L}\Big\{\check{\Phi}(t)\Big\}(s) = \int_0^\infty e^{-st}\,\Phi\Big(e^{-t}\Big)\,e^{-t}\,dt = \int_0^1 u^s\,\Phi(u)\,du,\\ \mathcal{L}\{q'(t)\}(s) &= s\hat{q}(s) - \lim_{x\to 0^+} q(x) = s\hat{q}(s),\end{aligned}$$

for $s > 0$. Note that $\tilde{\Phi}$ has the following properties

$$\tilde{\Phi}(0) = 1, \quad \tilde{\Phi}(1) = \frac{1}{2}, \quad \tilde{\Phi}'(s) < 0 \ \forall s \geq 0, \quad \lim_{s\to\infty} \tilde{\Phi}(s) = 0, \quad \tilde{\Phi}(s) \in (0,1) \ \forall s \in (0,\infty).$$

These properties are a direct consequence of the properties of Φ. Taking the Laplace transform of equation (3.27) yields for $s > 0$,

$$\begin{aligned}\alpha\,\hat{q}(s) &= \sum_{k=0}^{n} \left(\frac{\alpha_0}{\alpha}\right)^k \tilde{\Phi}^k(s)\,s\,\hat{q}(s) - \sum_{k=0}^{n} \left(\frac{\alpha_0}{\alpha}\right)^k \tilde{\Phi}^k(s+1)\,(s+1)\,\hat{q}(s+1)\\ &\quad + \left(\frac{\alpha_0}{\alpha}\,\tilde{\Phi}(s)\right)^{n+1} \mathcal{L}\left\{\frac{\alpha\,q(t)}{1-e^{-t}}\right\}(s) - \left(\frac{\alpha_0}{\alpha}\,\tilde{\Phi}(s+1)\right)^{n+1} \mathcal{L}\left\{\frac{\alpha q(t)}{1-e^{-t}}\right\}(s+1)\\ &= \frac{\left(\frac{\alpha_0}{\alpha}\,\tilde{\Phi}(s)\right)^{n+1} - 1}{\frac{\alpha_0}{\alpha}\,\tilde{\Phi}(s) - 1}\,s\,\hat{q}(s) - \frac{\left(\frac{\alpha_0}{\alpha}\,\tilde{\Phi}(s+1)\right)^{n+1} - 1}{\frac{\alpha_0}{\alpha}\,\tilde{\Phi}(s+1) - 1}\,(s+1)\,\hat{q}(s+1)\\ &\quad + \left(\frac{\alpha_0}{\alpha}\,\tilde{\Phi}(s)\right)^{n+1} \mathcal{L}\left\{\frac{\alpha\,q(t)}{1-e^{-t}}\right\}(s) - \left(\frac{\alpha_0}{\alpha}\,\tilde{\Phi}(s+1)\right)^{n+1} \mathcal{L}\left\{\frac{\alpha\,q(t)}{1-e^{-t}}\right\}(s+1).\end{aligned} \tag{3.30}$$

As the functions q and $\frac{\alpha\,q(t)}{1-e^{-t}}$ are integrable (for $\alpha > 0$) and non-negative, their Laplace transforms $\hat{q}(s)$ and $\mathcal{L}\Big\{\frac{\alpha\,q(t)}{1-e^{-t}}\Big\}(s)$ are bounded and positive for $s \geq 0$. Moreover,

$\tilde{\Phi}(0) = 1$ and $\tilde{\Phi}(s) < 1$ for $s > 0$ and therefore the inequality $\alpha_0 \leq \alpha$ follows by contradiction:
Assume $\alpha_0 > \alpha$, then there are $0 < \underline{s} < \overline{s}$ such that $\frac{\alpha_0}{\alpha}\tilde{\Phi}(s) > 1$ and $\frac{\alpha_0}{\alpha}\tilde{\Phi}(s+1) < 1$ for all $s \in [\underline{s}, \overline{s}]$. Hence, for $s \in [\underline{s}, \overline{s}]$ the first and third summand in (3.30) are increasing in $n \in \mathbb{N}$ and tending to infinity for $n \to \infty$, while the second and fourth summand remain bounded for all $n \in \mathbb{N}$. This is a contradiction to the boundedness of $\hat{q}(s)$ for all $s \geq 0$ and all $n \in \mathbb{N}$ (which follows directly from g being a solution to (3.25) and the definitions of q and $\hat{q}$ respectively), therefore, $\alpha_0 \leq \alpha$.

Taking the limit $n \to \infty$ in (3.30) yields, because of $\alpha_0 \leq \alpha$ and $\tilde{\Phi}(s) < 1$ for $s > 0$,

$$\alpha\, \hat{q}(s) = \frac{s\, \hat{q}(s)}{1 - \alpha_0\, \tilde{\Phi}(s)/\alpha} - \frac{(s+1)\, \hat{q}(s+1)}{1 - \alpha_0\, \tilde{\Phi}(s+1)/\alpha}. \tag{3.31}$$

We rearrange the terms in equation (3.31) to obtain

$$\begin{aligned}
\hat{q}(s+1) &= \hat{q}(s)\, \frac{1 - \alpha_0\, \tilde{\Phi}(s+1)/\alpha}{s+1} \left(\frac{s}{1 - \alpha_0\, \tilde{\Phi}(s)/\alpha} - \alpha \right) \\
&= \hat{q}(s)\, \frac{\left(1 - \alpha_0\, \tilde{\Phi}(s+1)/\alpha\right)\left(s - \alpha + \alpha_0\, \tilde{\Phi}(s)\right)}{(s+1)\left(1 - \alpha_0\, \tilde{\Phi}(s)/\alpha\right)} \\
&= \hat{q}(s)\, \frac{\left(\alpha - \alpha_0\, \tilde{\Phi}(s+1)\right)\left(s - \alpha + \alpha_0\, \tilde{\Phi}(s)\right)}{(s+1)\left(\alpha - \alpha_0\, \tilde{\Phi}(s)\right)}.
\end{aligned}$$

By iteration, we obtain equation (3.29), i.e., for $n \in \mathbb{N}$, $s > 0$, and $\alpha_0 \leq \alpha$,

$$\hat{q}(s+n) = \hat{q}(s)\, \frac{\alpha - \alpha_0\, \tilde{\Phi}(s+n)}{\alpha - \alpha_0\, \tilde{\Phi}(s)} \prod_{k=1}^{n} \frac{(s+k-1) - \alpha + \alpha_0\, \tilde{\Phi}(s+k-1)}{s+k}.$$

As $q \geq 0$, $\hat{q}(s) > 0$ for all $s \geq 0$ and $\hat{q} \in \mathcal{C}^\infty([0,\infty))$ as q is of bounded exponential growth (see Lemma 2.15(c)). ☐

We can now finish the first part of the proof of Theorem 3.28 by deriving the remaining conditions on α, α_0, and the plasmid segregation kernel Φ in the following proposition.

Proposition 3.32. *If* $\alpha_0 \leq \alpha$ *and there is a positive function* $\hat{q} \in \mathcal{C}^\infty([0,\infty))$ *which satisfies* (3.29)*, then*

$$\alpha = \alpha_0 \textit{ and } \alpha_0 < -\frac{1}{\tilde{\Phi}'(0)}.$$

Proof. The function $\hat{q}$ is determined by $\hat{q}|_{(0,1]}$ and (3.29) with $s \in (0,1]$ and $n \in \mathbb{N}$.

By positivity of $\hat{q}$, $\hat{q}|_{(0,1]} > 0$ and all factors on the right-hand side of (3.29) are positive. As $\alpha_0 \leq \alpha$ and $\tilde{\Phi}(s) < 1$ for $s > 0$, we obtain for the second factor on the right-hand side of (3.29) and for $s > 0$

$$0 < \frac{\alpha - \alpha_0 \tilde{\Phi}(s+n)}{\alpha - \alpha_0 \tilde{\Phi}(s)} < \infty \quad \text{for all } s \in (0,1] \text{ and } n \in \mathbb{N}.$$

By positivity of the denominator of the third term on the right-hand side of (3.29), we obtain the following condition for the numerator: for all $k \in \mathbb{N}$ and $s \in (0,1]$

$$\begin{aligned} &(s+k-1) - \alpha + \alpha_0\, \tilde{\Phi}(s+k-1) > 0 \\ \Leftrightarrow\, &\alpha < s+k-1+\alpha_0\tilde{\Phi}(s+k-1) =: f(s+k-1). \end{aligned}$$

This inequality can only hold if $f(x) > f(0) = \alpha_0$ for all $x > 0$, because otherwise it would contradict $\alpha \geq \alpha_0$. Therefore, we need $f'(0) \geq 0$.

$$f'(x) = 1 + \alpha_0\tilde{\Phi}'(x) \qquad \text{and} \qquad f''(x) = \alpha_0\tilde{\Phi}''(x),$$

where

$$\tilde{\Phi}'(x) = \int_0^1 \log(u)\, u^x\, \Phi(u)\, du < 0 \qquad \text{and} \qquad \tilde{\Phi}''(x) = \int_0^1 (\log(u))^2\, u^x\, \Phi(u)\, du > 0.$$

If $f'(0) \geq 0$, then it follows because of $f''(x) > 0$ for all $x \geq 0$ that $f'(x) > 0$ for all $x > 0$.

$$f'(0) \geq 0 \quad \text{if and only if} \quad \alpha_0 \leq -\frac{1}{\tilde{\Phi}'(0)}.$$

Therefore, $-\alpha + \alpha_0\tilde{\Phi}(s+k-1) + s + k - 1 > 0$ holds for all $k \in \mathbb{N}$ and $s \in (0,1]$ if $\alpha \leq \alpha_0 \leq -\left(\tilde{\Phi}'(0)\right)^{-1}$ since $\alpha < f(x)$ for all $x > 0$ and, in particular, due to continuity of f we have that $\alpha \leq f(0) = \alpha_0$. Together with the condition $\alpha_0 \leq \alpha$, we have the following necessary conditions for positivity:

$$\alpha = \alpha_0 \quad \text{and} \quad \alpha_0 \leq -\left(\tilde{\Phi}'(0)\right)^{-1}.$$

In the following we use $\alpha = \alpha_0$.

It remains show that $\alpha_0 < -\left(\tilde{\Phi}'(0)\right)^{-1}$.

The function $\hat{q}$ is continuous. In particular, $\hat{q}|_{[0,1]}$ is continuous and $\hat{q}(n)$ is continuous at $n \in \mathbb{N}$, i.e.,

$$\hat{q}(n) = \lim_{s \to 0^+} \hat{q}(n+s) \qquad \text{for all } n \in \mathbb{N}.$$

Using (3.29) and continuity of $\tilde{\Phi}$, yields for $n = 1$,

$$\begin{aligned} \lim_{s \to 0^+} \hat{q}(s+1) &= \lim_{s \to 0^+} \hat{q}(s) \frac{1-\tilde{\Phi}(s+1)}{1-\tilde{\Phi}(s)}\, \frac{-\alpha_0 + \alpha_0\tilde{\Phi}(s) + s}{s+1} \\ &= \hat{q}(0)\left(1-\tilde{\Phi}(1)\right) \lim_{s \to 0^+} \frac{-\alpha_0 + \alpha_0\tilde{\Phi}(s) + s}{1-\tilde{\Phi}(s)}. \end{aligned}$$

With L'Hôpital's rule,

$$\lim_{s \to 0^+} \frac{-\alpha_0 + \alpha_0\tilde{\Phi}(s) + s}{1-\tilde{\Phi}(s)} = \lim_{s \to 0^+} (-\alpha_0)\frac{1-\tilde{\Phi}(s)}{1-\tilde{\Phi}(s)} + \frac{s}{1-\tilde{\Phi}(s)} = -\alpha_0 + \frac{1}{-\tilde{\Phi}'(0)}.$$

Therefore,

$$\hat{q}(1) = \hat{q}(0)\,\frac{1}{2}\left(-\alpha_0 - \frac{1}{\tilde{\Phi}'(0)}\right),$$

i.e., $\hat{q}(1)$ is positive if and only if

$$\alpha_0 < -\frac{1}{\tilde{\Phi}'(0)}.$$

This finishes the proof. □

We have now finished the first part of the proof. Thus, we proceed to the second part, i.e., we show that the conditions on the parameters imply existence and uniqueness of a positive solution g to (3.25). To this end, we use the same rescalings and transformations as in the previous propositions.

Proposition 3.33. *Let $\alpha = \alpha_0$ and $\alpha_0 < -\left(\tilde{\Phi}'(0)\right)^{-1}$. Then, there exists a unique solution $g \in \mathcal{C}^0((0, z_0]) \cap \mathcal{C}^1((0, z_0))$ to (3.26). There is a $C > 0$ such that the function $\hat{q}$ defined as in Propositions 3.30 and 3.31 is holomorphic for $s \in \mathbb{C}$ with $\Re(s) > C$ and satisfies for all $n \in \mathbb{N}$ and $s \in \mathbb{C}$ with $\Re(s) > C$,*

$$\hat{q}(s+n) = \hat{q}(s)\,\frac{1-\tilde{\Phi}(s+n)}{1-\tilde{\Phi}(s)}\prod_{k=1}^{n}\frac{(s+k-1)-\alpha+\alpha\,\tilde{\Phi}(s+k-1)}{s+k}. \tag{3.32}$$

Furthermore, for all $s \in \mathbb{C}$ with $\Re(s) > C$ and all $n \in \mathbb{N}$ it holds that $\hat{q}(s) \neq 0$, $1 - \tilde{\Phi}(s+n) \neq 0$, and $f(s) := s - \alpha + \alpha\,\tilde{\Phi}(s) \neq 0$.

Proof. Let $\alpha = \alpha_0$ and $\alpha_0 < -\left(\tilde{\Phi}'(0)\right)^{-1}$. By Lemma 3.27, we know that a unique solution $g \in \mathcal{C}^0((0, z_0]) \cap \mathcal{C}^1((0, z_0))$ for (3.26) exists. Using the same rescaling as in the proof of Proposition 3.30, i.e., $g(z) = \left(\frac{z_0}{z}\right)^{\alpha} h\left(-\log(\frac{z}{z_0})\right)$ and $h(t) = e^{-\alpha t}\, g(z_0\, e^{-t})$, we obtain a solution $h \in \mathcal{C}^0([0,\infty)) \cap \mathcal{C}^1((0,\infty))$ for

$$h'(t) = -\int_0^t \check{\Phi}(t-\sigma)\,h(\sigma)\,\frac{\frac{d}{d\sigma}(e^{\sigma}-1)^{\alpha}}{(e^t-1)^{\alpha}}\,d\sigma \quad \text{and} \quad h(0) = 1, \tag{3.33}$$

where $\check{\Phi}(t) := \Phi(e^{-t})\,e^{-t}$. We want to apply the Laplace transform to the function q that again defined as in the proof of Proposition 3.30 by $q(t) = h(t)\,(e^t-1)^{\alpha}$. Therefore, we show that the Laplace transforms of $q(t)$ and $\frac{\alpha\, q(t)}{1-e^{-t}}$ exist by applying the Grönwall-Bellman inequality (see Lemma 2.7) to the function $|h|$.

Renaming t to τ and integrating (3.33) over τ from 0 to t yields

$$h(t) - h(0) = -\int_0^t \int_0^{\tau} \check{\Phi}(\tau-\sigma)\,h(\sigma)\,\frac{\frac{d}{d\sigma}(e^{\sigma}-1)^{\alpha}}{(e^{\tau}-1)^{\alpha}}\,d\sigma d\tau,$$

$$h(t) = 1 - \int_0^t \int_0^\tau \check{\Phi}(\tau - \sigma)\, h(\sigma)\, \frac{\frac{d}{d\sigma}(e^\sigma - 1)^\alpha}{(e^\tau - 1)^\alpha}\, d\sigma d\tau.$$

We take the absolute value and interchange the order of the integration,

$$|h(t)| \leq 1 + \int_0^t \int_0^\tau \check{\Phi}(\tau - \sigma)\ |h(\sigma)|\ \frac{\frac{d}{d\sigma}(e^\sigma - 1)^\alpha}{(e^\tau - 1)^\alpha}\, d\sigma d\tau,$$

$$|h(t)| \leq 1 + \int_0^t \int_\sigma^t \check{\Phi}(\tau - \sigma)\ (e^\tau - 1)^{-\alpha}\ d\tau\, \frac{d}{d\sigma}(e^\sigma - 1)^\alpha\ |h(\sigma)|\ d\sigma.$$

Define $B(\sigma, t) := \int_\sigma^t \check{\Phi}(\tau-\sigma)\,(e^\tau - 1)^{-\alpha}\ d\tau\, \frac{d}{d\sigma}(e^\sigma - 1)^\alpha$. In order to apply the Grönwall-Bellman inequality, B must not depend on t. As B is increasing in t, we estimate

$$\begin{aligned} B(\sigma, t) &\leq \int_\sigma^\infty \check{\Phi}(\tau - \sigma)\,(e^\tau - 1)^{-\alpha}\ d\tau\, \frac{d}{d\sigma}(e^\sigma - 1)^\alpha \\ &\leq \|\Phi\|_{L^\infty([0,1])} \int_\sigma^\infty \frac{e^{-\tau}}{(e^\tau - 1)^\alpha}\, d\tau\, e^\sigma\, \alpha\, e^\sigma\, (e^\sigma - 1)^{\alpha - 1}. \end{aligned}$$

We want this upper bound for B to be integrable as otherwise the Grönwall-Bellman inequality gives the estimate $|h(t)| \leq \infty$, i.e., we want the following integral to be finite

$$\begin{aligned} \int_0^t \int_\sigma^\infty \frac{e^{-\tau}}{(e^\tau - 1)^\alpha}\, d\tau\, \alpha\, e^{2\sigma}\, (e^\sigma - 1)^{\alpha-1}\ d\sigma &= \int_0^t \int_0^\tau \alpha\, e^{2\sigma}\, (e^\sigma - 1)^{\alpha-1}\ d\sigma\, \frac{e^{-\tau}}{(e^\tau - 1)^\alpha}\, d\tau \\ &\quad + \int_t^\infty \int_0^t \alpha\, e^{2\sigma}\, (e^\sigma - 1)^{\alpha-1}\ d\sigma\, \frac{e^{-\tau}}{(e^\tau - 1)^\alpha}\, d\tau. \end{aligned} \tag{3.34}$$

Using that with the transformation $x = e^\sigma$ yields

$$\begin{aligned} \int_0^t \alpha\, e^{2\sigma}\, (e^\sigma - 1)^{\alpha-1}\ d\sigma = \int_1^{e^t} \alpha\, x\, (x-1)^{\alpha-1}\, dx &= \left[\frac{(x-1)^\alpha\,(\alpha\, x + 1)}{\alpha + 1}\right]_{x=1}^{x=e^t} \\ &= \frac{1}{\alpha+1}\left(e^t - 1\right)^\alpha \left(\alpha e^t + 1\right). \end{aligned}$$

Thus, we obtain for (3.34),

$$\begin{aligned} &\int_0^t \int_\sigma^\infty \frac{e^{-\tau}}{(e^\tau - 1)^\alpha}\, d\tau\, \alpha\, e^{2\sigma}\, (e^\sigma - 1)^{\alpha-1}\ d\sigma \\ &= \frac{1}{\alpha+1} \int_0^t \alpha + e^{-\tau}\ d\tau + \frac{1}{\alpha+1}\left(e^t - 1\right)^\alpha \left(\alpha\, e^t + 1\right) \int_t^\infty \frac{e^{-\tau}}{(e^\tau - 1)^\alpha}\, d\tau \\ &\leq \frac{\alpha\, t}{\alpha+1} + \frac{1}{\alpha+1}\left[-e^{-\tau}\right]_{\tau=0}^{\tau=t} + \frac{1}{\alpha+1}\left(e^t + 1\right)^\alpha \left(\alpha\, e^t + 1\right)\left(e^t - 1\right)^{-\alpha} \int_t^\infty e^{-\tau}\, d\tau \end{aligned}$$

$$= \frac{\alpha\, t + 1 - e^{-t}}{\alpha + 1} + \frac{\alpha + e^{-t}}{\alpha + 1} = \frac{\alpha t + \alpha + 1}{\alpha + 1}.$$

We estimate

$$|h(t)| \leq 1 + \int\limits_0^t \|\Phi\|_{L^\infty([0,1])} \int\limits_\sigma^\infty \frac{e^{-\tau}}{(e^\tau - 1)^\alpha}\, d\tau\, \alpha\, e^{2\sigma}\, (e^\sigma - 1)^{\alpha - 1}\, |h(\sigma)|\, d\sigma$$

and therefore the Grönwall-Bellman inequality yields for $t \geq 0$

$$|h(t)| \leq e^{\int_0^t \|\Phi\|_{L^\infty([0,1])} \int_\sigma^\infty \frac{e^{-\tau}}{(e^\tau - 1)^\alpha}\, d\tau\, \alpha\, e^{2\sigma} (e^\sigma - 1)^{\alpha - 1}\, d\sigma} \leq e^{\|\Phi\|_{L^\infty([0,1])} \frac{\alpha t + \alpha + 1}{\alpha + 1}} = C e^{s_0\, t},$$

where $C := e^{\|\Phi\|_{L^\infty([0,1])}} > 0$ and $s_0 := \alpha\, \|\Phi\|_{L^\infty([0,1])} / (\alpha + 1) > 0$.

With the transformation $q(t) = h(t)\, (e^t - 1)^\alpha$, we obtain for all $t \geq 0$ that

$$|q(t)| \left(e^t - 1\right)^{-\alpha} \leq C e^{s_0 t}.$$

Therefore,

$$|q(t)| \leq C e^{s_0 t} \left(e^t - 1\right)^\alpha = C e^{(s_0 + \alpha) t} \left(1 - e^{-t}\right)^\alpha \leq C e^{(s_0 + \alpha) t}$$

and it follows that both the Laplace transform $\hat{q}(s)$ of $q(t)$ and the Laplace transform of $\frac{\alpha\, q(t)}{1 - e^{-t}}$ exist for $\Re(s) > s_0 + \alpha$. Furthermore, q satisfies equation (3.27).

Now, we can take the Laplace transform of equation (3.27) and obtain for all $s \in \mathbb{C}$ with $\Re(s) > s_0 + \alpha$,

$$\begin{aligned} \alpha\, \hat{q}(s) = {} & \frac{1 - \tilde{\Phi}^{n+1}(s)}{1 - \tilde{\Phi}(s)}\, s\, \hat{q}(s) - \frac{1 - \tilde{\Phi}^{n+1}(s + 1)}{1 - \tilde{\Phi}(s + 1)}\, (s + 1)\, \hat{q}(s + 1) \\ & + \tilde{\Phi}^{n+1}(s)\, \mathcal{L}\left\{\frac{\alpha\, q(t)}{1 - e^{-t}}\right\}(s) - \tilde{\Phi}^{n+1}(s + 1)\, \mathcal{L}\left\{\frac{\alpha q(t)}{1 - e^{-t}}\right\}(s + 1). \end{aligned}$$

As in the proof of Proposition 3.31, we can now take the limit $n \to \infty$ because we know that $\left|\tilde{\Phi}(s)\right| \leq \tilde{\Phi}(\Re(s)) < 1$ for $\Re(s) > s_0 + \alpha > 0$. Recursively, we obtain (3.32), i.e., for all $n \in \mathbb{N}$ and $s \in \mathbb{C}$ with $\Re(s) > s_0 + \alpha$,

$$\hat{q}(s + n) = \hat{q}(s)\, \frac{1 - \tilde{\Phi}(s + n)}{1 - \tilde{\Phi}(s)} \prod_{k=1}^{n} \frac{(s + k - 1) - \alpha + \alpha\, \tilde{\Phi}(s + k - 1)}{s + k}.$$

The Laplace transform $\hat{q}$ of q is analytic, i.e., holomorphic, on $\Re(s) > s_0 + \alpha$. We know by Lemma 3.27 that $g(z_0) = 1$ and $g \in \mathcal{C}^0((0, z_0]) \cap \mathcal{C}^1((0, z_0))$. Therefore, there is a set of positive measure where q is strictly positive.

If there is a $s \in \mathbb{C}$ with $\Re(s) > s_0 + \alpha$ and $\hat{q}(s) = 0$, then $\hat{q}(s + n) = 0$ for all $n \in \mathbb{N}$ by (3.32). Hence, $\hat{q}$ vanishes on a sequence of equidistant points along a line parallel to the real axis, therefore $q = 0$ a.e. by Theorem 2.17. This is a contradiction to $q > 0$ on a set of positive measure. Therefore, $\hat{q}(s) \neq 0$ for $s \in \mathbb{C}$ with $\Re(s) > s_0 + \alpha$.

In particular, due to (3.32) it also follows that for all $s \in \mathbb{C}$ with $\Re(s) > s_0 + \alpha$ and for all $n \in \mathbb{N}$ that $1 - \tilde{\Phi}(s + n) \neq 0$, and $f(s) := s - \alpha + \alpha\tilde{\Phi}(s) \neq 0$. $\square$

We use now the iteration formula (3.32) to extend the function $\hat{q}$.

Proposition 3.34. *If $\alpha = \alpha_0$ and $\alpha_0 < -\left(\tilde{\Phi}'(0)\right)^{-1}$, then there exists an $\varepsilon > 0$ such that the function $\hat{q}$ defined in Propositions 3.30 and 3.31 can be extended to a holomorphic function $\hat{q}^*$ on the half-plane $\Re(s) \geq -\varepsilon$.*

Proof. By Proposition 3.33, there is a $C > 0$ such that for all $s \in \mathbb{C}$ with $\Re(s) > C$ the function $\hat{q}(s)$ is holomorphic, $\hat{q}$ satisfies (3.32) for all $n \in \mathbb{N}$, $\hat{q}(s) \neq 0$, $1 - \tilde{\Phi}(s+n) \neq 0$ for all $n \in \mathbb{N}$, and $f(s) := s - \alpha + \alpha\, \tilde{\Phi}(s) \neq 0$.

As $\hat{q}(s) \neq 0$ for $s \in \mathbb{C}$ with $\Re(s) > C$, we can write equivalently to (3.32) for $\Re(s) > C$

$$\hat{q}(s) = \hat{q}(s+n)\, \frac{1 - \tilde{\Phi}(s)}{1 - \tilde{\Phi}(s+n)} \prod_{k=1}^{n} \frac{s+k}{(s+k-1) - \alpha + \alpha\, \tilde{\Phi}(s+k-1)}. \tag{3.35}$$

We use (3.35) to construct an extension of $\hat{q}$ to $s \in \mathbb{C}$ with $\Re(s) > -\varepsilon$ for some $\varepsilon > 0$.

Let $m \geq \lceil C+2 \rceil$, where $\lceil x \rceil$ denotes the ceiling function that maps x to the least integer greater than or equal to x. First, we show that the right-hand side of (3.35) is well-defined, i.e., that $1-\tilde{\Phi}(s+n) \neq 0$ and $f(s+k-1) := (s+k-1)-\alpha+\alpha\, \tilde{\Phi}(s+k-1) \neq 0$ for all $s \in \mathbb{C}$ with $\Re(s) > -\varepsilon$, $k \in \mathbb{N}$, for some $\varepsilon > 0$, and for $n = m$.

By the choice of m we already know that $1 - \tilde{\Phi}(s+m) \neq 0$ for all $s \in \mathbb{C}$ with $\Re(s) > -1$. It remains to show that $f(z) \neq 0$ for $\Re(z) > -\varepsilon$. With $z = a + ib$ for $a > -1$ and $b \in \mathbb{R}$,

$$\begin{aligned} f(z) = z - \alpha + \alpha\tilde{\Phi}(z) &= a + ib - \alpha + \alpha \int_0^1 u^{a+ib}\Phi(u)\, du \\ &= a - \alpha + ib + \alpha \int_0^1 u^a(\cos(b\log(u)) + i\sin(b\log(u)))\Phi(u)\, du \\ &= a - \alpha + \alpha \int_0^1 u^a \cos(b\log(u))\Phi(u)\, du + i\left(b + \alpha \int_0^1 u^a \sin(b\log(u))\Phi(u)\, du\right). \end{aligned}$$

As $f(z) = 0$ if and only if $\Re(f(z)) = 0$ and $\Im(f(z)) = 0$ we are searching for a, $b \in \mathbb{R}$ satisfying both

$$\begin{aligned} f_1(a,b) &:= \int_0^1 u^a \cos(b\log(u))\Phi(u)\, du + \frac{a}{\alpha} \overset{!}{=} 1 \quad \text{and} \\ f_2(a,b) &:= \int_0^1 u^a \sin(b\log(u))\Phi(u)\, du + \frac{b}{\alpha} \overset{!}{=} 0. \end{aligned}$$

We see that (a,b) is a solution to $f_1(a,b) = 1$ and $f_2(a,b) = 0$ if and only if $(a,-b)$ is a solution. Therefore, it suffices to consider $b \geq 0$.

For $b = 0$, it holds that $f_2(a, 0) = 0$ for all $a \in \mathbb{R}$. The partial derivative of f_2 w.r.t. b is

$$\begin{aligned}\partial_b f_2(a, b) &= \int_0^1 u^a \cos(b \log(u)) \, \log(u) \, \Phi(u) \, du + \frac{1}{\alpha}, \\ \partial_b f_2(a, 0) &= \int_0^1 u^a \log(u) \, \Phi(u) \, du + \frac{1}{\alpha} = \tilde{\Phi}'(a) + \frac{1}{\alpha}.\end{aligned}$$

The function $\tilde{\Phi}'$ is negative and strictly increasing (this follows directly from the properties of Φ, see proofs of Propositions 3.31 and 3.32). As $0 < \alpha < -1/\tilde{\Phi}'(0)$ there is an $l < 0$ such that $\alpha = -1/\tilde{\Phi}'(l)$ by continuity of $\tilde{\Phi}'$. Hence,

$$\partial_b f_2(a, 0) = \tilde{\Phi}'(a) - \tilde{\Phi}'(l) > 0$$

if and only if $a > l$. For $b > 0$,

$$\begin{aligned}\partial_b f_2(a, b) &= \int_0^1 u^a \cos(b \log(u)) \, \log(u) \, \Phi(u) \, du - \tilde{\Phi}'(l) \\ &= \int_0^1 \log(u) \, \Phi(u) \left(u^a \cos(b \log(u)) - u^l \right) \, du.\end{aligned}$$

For $u \in (0, 1)$, $\log(u) < 0$, $\Phi(u) \geq 0$, and

$$u^a \cos(b \log(u)) - u^l \leq u^a - u^l \leq 0$$

if $a > l$. Therefore, for $a > l$, $\partial_b f_2(a, b) \geq 0$ for all $b > 0$ and $\partial_b f_2(a, 0) > 0$, i.e., there cannot be a solution to $f_2(a, b) = 0$ other than $b = 0$. If $b = 0$, then we are looking for a real solution to $f(s) = s - \alpha + \alpha \, \tilde{\Phi}(s) = 0$. In this case we know that $s = 0$ is a solution. Moreover, $f'(s) > 0$ for $s \geq 0$, $f'(s) = 1 + \alpha \, \tilde{\Phi}'(s) = 0$ if and only if $s = l$ by definition of l, and $f''(s) > 0$ for all $s \in \mathbb{R}$. Therefore, $f(s) < 0$ for $s \in (l, 0)$ and the only solution to $f(s) = 0$ in (l, ∞) is $s = 0$.

Define $\varepsilon := \min\{-l, 1\}/2$, then $f(z) = 0$ only for $z = 0$ and $f(z) \neq 0$ for all $z \in \mathbb{C}$ with $z \neq 0$ and $\Re(z) \geq -\varepsilon$.

We rewrite (3.35) with $n = m$, where $m \geq \lceil C + 2 \rceil$,

$$\hat{q}(s) = \frac{\hat{q}(s + m) \, (s + 1)}{1 - \tilde{\Phi}(s + m)} \, \frac{1 - \tilde{\Phi}(s)}{s - \alpha + \alpha \, \tilde{\Phi}(s)} \prod_{k=2}^{m} \frac{s + k}{(s + k - 1) - \alpha + \alpha \, \tilde{\Phi}(s + k - 1)}. \tag{3.36}$$

For $s \in \mathbb{C} \setminus \{0\}$ with $\Re(s) \geq -\varepsilon$ the expression on the right-hand side is holomorphic as a product of holomorphic functions. The function $\hat{q}$ is holomorphic as it is the Laplace transform of q and the fact that $\tilde{\Phi}$ is holomorphic is easily checked using the definition of $\tilde{\Phi}$. With L'Hôpital's rule for analytic functions of a complex variable (see, e.g., [106, Theorem 3.3]),

$$\lim_{z \to 0} \frac{1 - \tilde{\Phi}(z)}{z - \alpha + \alpha \, \tilde{\Phi}(z)} = \lim_{z \to 0} \frac{-\tilde{\Phi}'(z)}{1 + \alpha \, \tilde{\Phi}'(z)} = \frac{-\tilde{\Phi}'(0)}{1 + \alpha \, \tilde{\Phi}'(0)},$$

which is finite by the assumption $\alpha > -1/\tilde{\Phi}'(0)$. Therefore, the right-hand side of (3.36) is holomorphically extendable to $z = 0$ by the Riemann removable singularities theorem (see, e.g., [42, Theorem 4.1.1]) and the following extension of $\hat{q}$ is holomorphic, for $s \in \mathbb{C}$ with $\Re(s) \geq -\varepsilon$,

$$\hat{q}^*(s) = \begin{cases} \frac{\hat{q}(s+m)(s+1)}{1-\tilde{\Phi}(s+m)} \frac{1-\tilde{\Phi}(s)}{s-\alpha+\alpha\tilde{\Phi}(s)} \prod\limits_{k=2}^{m} \frac{s+k}{(s+k-1)-\alpha+\alpha\tilde{\Phi}(s+k-1)}, & \text{for } \Re(s) \in [-\varepsilon, m] \text{ and } s \neq 0, \\ \frac{\hat{q}(m)}{1-\tilde{\Phi}(m)} \frac{-\tilde{\Phi}'(0)}{1+\alpha\tilde{\Phi}'(0)} \prod\limits_{k=2}^{m} \frac{k}{(k-1)-\alpha+\alpha\tilde{\Phi}(k-1)}, & \text{for } s = 0, \\ \hat{q}(s), & \text{for } \Re(s) > m. \end{cases}$$

□

We are now ready to gather the results of Propositions 3.30 to 3.34 and finish the proof of Theorem 3.28.

Proof of Theorem 3.28.

Step 1: From the solution g to the conditions on the parameters.
Assume there is a solution $g \in \mathcal{C}^0((0, z_0]) \cap \mathcal{C}^1((0, z_0))$ for (3.25), then Propositions 3.30 to 3.32 directly give the conditions on α and α_0.

Step 2: From the conditions on the parameters to the unique solution g.
Lemma 3.27 gives existence of a unique solution $g \in \mathcal{C}^0((0, z_0]) \cap \mathcal{C}^1((0, z_0))$ to (3.26). It remains show that the solution g to (3.26) is also a solution to (3.25), i.e., that g satisfies

$$\lim_{z \to 0^+} g(z) = 0, \quad g(z) \geq 0 \text{ for all } z \in (0, z_0), \quad \text{and} \quad \int_0^{z_0} \frac{(z_0 - z)^{\alpha} g(z)}{b(z)} \, dz < \infty.$$

In the following, we use Propositions 3.33 and 3.34, take the inverse Laplace transform of $\hat{q}^*$, $\mathcal{L}^{-1}\{\hat{q}^*(s)\}(t) =: q^*(t)$, and show that $q(t) = q^*(t)$ for a.e. $t \geq 0$.

If

$$\lim_{s \to \infty} \hat{q}^*(s) = 0 \quad \text{and} \quad \lim_{s \to \infty} s\,\hat{q}^*(s) < \infty,$$

then the inverse Laplace transform q^* of $\hat{q}^*$ exists (see Lemma 2.19). We know that

$$0 = \lim_{t \to 0^+} q(t) = \lim_{s \to \infty} s\,\hat{q}(s),$$

by Theorem 2.16, and for $s \in \mathbb{C}$ with $\Re(s) \geq -\varepsilon$ and $|s| > \delta > 0$ and for $m := \lceil C + 2 \rceil$,

$$\hat{q}^*(s) = \hat{q}(s+m) \frac{1 - \tilde{\Phi}(s)}{1 - \tilde{\Phi}(s+m)} \prod_{k=1}^{m} \frac{s+k}{(s+k-1) - \alpha + \alpha\,\tilde{\Phi}(s+k-1)}.$$

Since

$$\left|\tilde{\Phi}(s)\right| \leq \tilde{\Phi}(\Re(s)) \leq \tilde{\Phi}(-\varepsilon) < \infty$$

and for all $k \in \mathbb{N}$, $k \leq m$, and all $|s| > \delta > 0$

$$\frac{s+k}{s+k-1-\alpha+\alpha\,\tilde{\Phi}(s+k-1)} = \frac{1+\frac{k}{s}}{1+\frac{k-1-\alpha}{s}+\frac{\alpha\,\tilde{\Phi}(s+k-1)}{s}} < \infty,$$

it holds that $\hat{q}^*(s) = h(s)\,\hat{q}(s+m)$ for some function h that is bounded for all $s \in \mathbb{C}$ with $\Re(s) \geq -\varepsilon$ and $|s| > \delta > 0$. Therefore,

$$\lim_{s\to\infty} s\,\hat{q}^*(s) = 0$$

and the inverse Laplace transformation q^* of $\hat{q}^*$ exists.

Due to uniqueness of the inverse Laplace transform (see Theorem 2.18), q^* and q are a.e. equal. In particular, with $q(t) = g(z_0 e^{-t})\,(1-e^{-t})^\alpha$ and the change of variables $z = z_0 e^{-t}$,

$$\begin{aligned}\hat{q}^*(0) &= \int_0^\infty q^*(t)\,dt = \int_0^\infty q(t)\,dt = \int_0^{z_0} g(z)\left(1-\frac{z}{z_0}\right)^\alpha \frac{1}{z}\,dz \\ &= z_0^{-\alpha}\int_0^{z_0} \frac{g(z)\,(z_0-z)^\alpha}{z}\,dz < \infty.\end{aligned}$$

Therefore, $g(z)/z$ is integrable at $z=0$. As $g \in \mathcal{C}^0((0,z_0])$ with $g(z_0)=1$ there are $\delta > 0$ and a $c > 0$ such that

$$\frac{g(z)\,(z_0-z)^\alpha}{z\,(z_0-z)} \leq c\,\frac{(z_0-z)^\alpha}{z_0-z} \quad \text{for all } z \in [z_0-\delta, z_0],$$

it holds that $\frac{g(z)\,(z_0-z)^\alpha}{z\,(z_0-z)}$ is integrable at $z = z_0$. Hence,

$$\lim_{z\to 0^+} g(z) = 0 \quad \text{and} \quad \int_0^{z_0} \frac{g(z)(z_0-z)^\alpha}{b(z)}\,dz < \infty.$$

Step 3: Positivity of the solution g.

The function $v(z) := C(z_0-z)^\alpha g(z)$ for some $C > 0$ is a solution to (3.24) by Lemma 3.25 and $v \geq 0$ if and only if $g \geq 0$ on $(0,z_0)$. We know that $\lim_{z\to 0^+} v(z) = 0$, $v(z_0) = 0$, and v is positive in a neighborhood of z_0 as $g(z_0) = 1$ and g is continuous in $(0,z_0]$. With $\alpha = \alpha_0$, integrating (3.24) from z to z_0 yields

$$v(z_0) - v(z) = -\alpha\,z_0 \int_z^{z_0} \frac{v(z')}{z'(z_0-z')}\,dz' + \alpha\,z_0 \int_z^{z_0}\int_y^{z_0} \frac{\Phi\left(\frac{y}{z'}\right) v(z')}{(z')^2(z_0-z')}\,dz'dy.$$

By change of variables $\xi = \frac{y}{z'}$, we obtain

$$v(z) = \alpha\,z_0 \left(\int_z^{z_0} \frac{v(z')}{z'(z_0-z')}\,dz' - \int_z^{z_0}\int_{z/z'}^{1} \Phi(\xi)\,d\xi\,\frac{v(z')}{z'(z_0-z')}\,dz'\right)$$

$$= \alpha\, z_0 \int_z^{z_0} \int_0^{z/z'} \Phi(\xi)\, d\xi\, \frac{v(z')}{z'(z_0 - z')}\, dz'.$$

Due to continuity of v, v can only be negative if there is a $z \in (0, z_0)$ such that $v(z) = 0$. Let $z^* \in (0, z_0)$ be the largest $z \in (0, z_0)$ such that $v(z) = 0$, i.e., $v(z) > 0$ for all $z \in (z^*, z_0)$. Therefore,

$$v(z^*) = \alpha\, z_0 \int_{z^*}^{z_0} \int_0^{z^*/z'} \Phi(\xi)\, d\xi\, \frac{v(z')}{z'(z_0 - z')}\, dz'.$$

By definition of z^*, it holds that

$$\frac{v(z')}{z'(z_0 - z')} > 0 \quad \text{for all } z \in (z^*, z_0).$$

Moreover, there is an $\varepsilon > 0$ such that for all $z' \in (z^*, z^* + \varepsilon)$

$$\int_0^{z^*/z'} \Phi(\xi)\, d\xi > 0.$$

Therefore, $v(z^*) > 0$ which is a contradiction to the definition of z^*, $v(z^*) = 0$, therefore there is no such z^* and $v(z) > 0$ for $z \in (0, z_0)$. Hence, $g \geq 0$ and $g(z) > 0$ for all $z \in (0, z_0]$.

Overall, we have shown that the unique solution $g \in \mathcal{C}^0((0, z_0]) \cap \mathcal{C}^1((0, z_0))$ to (3.26) is also a solution to (3.25) in Step 2. Since every solution to (3.25) is also a solution to (3.26) the function g is the unique solution to (3.25). Moreover, because of $v(z) > 0$ for $z \in (0, z_0)$, $v(z) = C\,(z_0 - z)^{\alpha} g(z)$ with $C > 0$, and $g(z_0) = 1$ it follows that $g(z) > 0$ for $z \in (0, z_0]$. ☐

So far, we have shown existence and uniqueness of a solution g to (3.25) but we are interested in a solution to the singular VGT eigenproblem (3.22). Therefore, we rescale the solution g to obtain an eigensolution $\mathcal{U}$ and the following result.

Theorem 3.35. *If $\alpha = \alpha_0$ and $\alpha_0 < -\left(\tilde{\Phi}'(0)\right)^{-1}$ or equivalently if*

$$\lambda = \beta - \mu \quad \textit{and} \quad \frac{2\beta}{b_0} < -\frac{1}{\tilde{\Phi}'(0)},$$

then there exists a solution $\mathcal{U} \in \mathcal{C}^1((0, z_0))$ to (3.22) with $\mathcal{U}(z) > 0$ for all $z \in (0, z_0)$. Moreover, $\mathcal{U}$ is the unique solution to (3.22) with $\mathcal{U}(z) \sim (z_0 - z)^{\alpha - 1}$ at z_0.

Proof. Theorem 3.35 follows directly from Theorem 3.28 using Lemmas 3.23 and 3.25 and Remark 3.26. ☐

We have shown existence of a solution $\mathcal{U}$ to (3.22) and that $\mathcal{U}(z) \sim (z_0 - z)^{\alpha-1}$ at z_0. Thus, we know the behavior of the eigensolution at z_0 (if it exists) and we have the following corollary that agrees with the known behavior of eigensolutions at z_0 (see [74, Corollary 4.19]).

Corollary 3.36. *Let the assumptions of Theorem 3.35 hold, then the eigensolution* $\mathcal{U}$ *to* (3.22) *satisfies:*

(a) If $\tilde{\Phi}'(0) \leq -1$, *then* $\alpha < 1$, *i.e.,* $2\beta < b_0$, *and* $\lim\limits_{z \to z_0^-} \mathcal{U}(z) = \infty$.

(b) If $\tilde{\Phi}'(0) > -1$ *and* $\alpha = 1$, *i.e.,* $2\beta = b_0$, *then there exists a constant* $C \in (0, \infty)$ *such that* $\lim\limits_{z \to z_0^-} \mathcal{U}(z) = C$.

(c) If $\tilde{\Phi}'(0) > -1$ *and* $1 < \alpha < -\left(\tilde{\Phi}'(0)\right)^{-1}$, *i.e., in particular* $2\beta > b_0$, *then* $\lim\limits_{z \to z_0^-} \mathcal{U}(z) = 0$.

Example 3.37. The condition $\alpha < -\left(\tilde{\Phi}'(0)\right)^{-1}$ in Theorem 3.28, Theorem 3.35, and Corollary 3.36 gives for different Φ the following conditions on α:

(a) For $\Phi(\xi) = 1$ for all $\xi \in [0, 1]$, $\tilde{\Phi}'(0) = -1$, hence $\alpha < 1$.
Note that in this case we know that the explicit solution is given by $\mathcal{U}(z) = C\, z^{-\alpha}\, (z_0 - z)^{\alpha-1}$ (see Example 3.24). This solution is integrable over $[0, z_0]$ if and only if $\alpha \in (0, 1)$ which agrees with the assumption that $\alpha > 0$ and the condition that $\alpha < -\left(\tilde{\Phi}'(0)\right)^{-1} = 1$.

(b) For $\Phi(\xi) = 6\xi(1 - \xi)$, $\tilde{\Phi}'(0) = -\frac{5}{6}$, hence $\alpha < \frac{6}{5}$.
Therefore, depending on the parameters β and b_0, the eigensolution can satisfy either $\lim\limits_{z \to z_0^-} \mathcal{U}(z) = 0$, $\lim\limits_{z \to z_0^-} \mathcal{U}(z) = C \in (0, \infty)$, or $\lim\limits_{z \to z_0^-} \mathcal{U}(z) = \infty$ (see Figure 3.10 in Section 3.4 for the numerical construction of eigenfunctions with different behavior at z_0).

(c) For $\Phi(\xi) = 120\xi\left(\frac{1}{2} - \xi\right)^2 (1 - \xi)$, $\tilde{\Phi}'(0) = -\frac{31}{30}$, hence $\alpha < \frac{30}{31}$.
Thus, all eigenfunctions $\mathcal{U}$ (defined as in Theorem 3.35) satisfy $\lim\limits_{z \to z_0^-} \mathcal{U}(z) = \infty$.

We have shown that if $\lambda = \beta - \mu$ and $\frac{2\beta}{b_0} < -\left(\tilde{\Phi}'(0)\right)^{-1}$, then an eigensolution to the singular VGT model exsits and given examples for the second condition for different plasmid segregation kernels. We now try to interpret the second condition.

The reproduction of bacteria (modeled by the constant cell division rate β) may not be too fast compared to the reproduction of plasmids (modeled by $b(z) = \frac{b_0}{z_0}\, z\, (z_0 - z)$) as we expect otherwise that bacteria lose the plasmid in the long-run. If the plasmid is lost, then the density $u(z, t)$ converges to a delta distribution at $z = 0$ and we cannot find a continuously differentiable eigenfunction. Thus, $\frac{2\beta}{b_0}$ should be bounded.

For the interpretation of the second part of the condition, note that by the definition of $\tilde{\Phi}$ it holds that

$$-\frac{1}{\tilde{\Phi}'(0)} = \left(\int_0^1 (-\log(x))\,\Phi(x)\,dx\right)^{-1},$$

i.e., it is the inverse of the weighted plasmid segregation kernel. The weight integrates to one and gives more weight to plasmid segregation kernels where one daughter cell is plasmid-free or receives only very few plasmids from the mother cell. Due to symmetry of the plasmid segregation kernel Φ, this means that a plasmid distribution where one daughter cell receives much more plasmids than the other, i.e., an unequal plasmid distribution, is weighted higher than an "equal" distribution of plasmids where both daughters receive approximately the same fraction of plasmids. Therefore, $-\left(\tilde{\Phi}'(0)\right)^{-1}$ can be interpreted as a measure of how equally the plasmids are distributed to the daughter cells. For uniform plasmid segregation we obtained the value 1, for a unimodal distribution, i.e., a distribution where daughters are more likely to receive about half of the mother's plasmids, we obtained a value larger than 1, and for a bimodal distribution, i.e., an unequal plasmid distribution, we obtained a value smaller than 1 (see Example 3.37).

It still remains to interpret the connection between the cell reproduction compared to the plasmid reproduction and the plasmid distribution. If the plasmid distribution is unequal, then there are more daughter cells with only few plasmids and plasmid reproduction needs to be large compared to cell reproduction in order for the plasmid not to be lost. In other words, we need $\frac{2\beta}{b_0}$ to be small. If, however, plasmid distribution is equal, then there are fewer daughters with few plasmids (compared to an unequal plasmid distribution). In this case, the condition on the connection between cell reproduction and plasmid reproduction can be relaxed a bit.

This is one possible interpretation of the condition on the parameters. We note that with this interpretation we have not accounted for the possibility of plasmid accumulation. If plasmids reproduce much faster than bacteria, then we would expect that the density $u(z,t)$ converges to a delta distribution at $z = z_0$ and we cannot find an eigenfunction $\mathcal{U} \in \mathcal{C}^1((0,z_0))$. However, we have no condition saying that $\frac{2\beta}{b_0}$ needs to be bounded below for existence of an eigensolution.

In a sense, this suggests that in our model plasmids will not accumulate in the population and there is no convergence to a delta distribution. This may be due to the fact that we show existence of an eigensolution $\mathcal{U}(z) \sim (z_0 - z)^{\alpha-1}$ at z_0, i.e., an eigensolution with a prescribed behavior at z_0. It may also be due to the assumptions of the model. By Assumptions **(A5')** to **(A8')**, the plasmid reproduction rate is small in a neighborhood of z_0 regardless of whether b_0 is small or large but the cell division and death rates are the same for all bacteria. If a plasmid-free bacterium divides, then its daughters are also plasmid-free but if a bacterium with z_0 plasmids divides, then at most one of its daughters also contains z_0 plasmids. For this reason, we expect that in our model plasmid-free bacteria grow faster than bacteria with z_0 plasmids, i.e., if plasmid-free bacteria do not outgrow plasmid-carrying bacteria, then also bacteria with z_0 plasmids do not outgrow plasmid-bearing bacteria. Thus, under these assumptions we expect that it suffices to control the behavior of the bacteria at $z = 0$.

3.3.3 Spectral analysis

We consider the eigenproblem for the singular VGT model with constant cell division and death rate, scalable plasmid segregation kernel, and logistic plasmid reproduction as in the previous section, i.e., equation (3.22) with Assumptions **(A5')** to **(A8')**.

As for the regular VGT model (see Section 3.2.2), we let

$$U \in \mathcal{W} := \Big\{ f \in L^1((0,z_0)) : \ (b\,f)' \in L^1((0,z_0)) \Big\}$$

and consider the operator $A : \mathcal{W} \to L^1\left((0,z_0)\right)$ defined by

$$A[U](z) = -\frac{d}{dz}(b(z)\,U(z)) - (\beta+\mu)\,U(z) + 2\beta \int\limits_z^{z_0} \frac{1}{z'}\,\Phi\Big(\frac{z}{z'}\Big)\,U(z')\,dz'.$$

Let I be the identity operator. We define for $\lambda \in \mathbb{C}$ and $U \in \mathcal{W}$ the operator $R_\lambda : \mathcal{W} \to L^1((0,z_0))$ by

$$\begin{aligned} R_\lambda[U](z) &:= (\lambda I - A)\,[U](z) \\ &= \frac{d}{dz}(b(z)\,U(z)) + (\lambda+\beta+\mu)\,U(z) - 2\beta \int\limits_z^{z_0} \frac{1}{z'}\,\Phi\Big(\frac{z}{z'}\Big)\,U(z')\,dz'. \end{aligned}$$

We want to determine the resolvent set $\rho(A)$ of A, meaning the set of $\lambda \in \mathbb{C}$ for which R_λ is invertible. Let $f \in L^1((0,z_0))$ and $U \in \mathcal{W}$, then $R_\lambda[U](z) = f(z)$ if and only if

$$\frac{d}{dz}(b(z)\,U(z)) + (\lambda+\beta+\mu)\,U(z) - 2\beta \int\limits_z^{z_0} \frac{1}{z'}\,\Phi\Big(\frac{z}{z'}\Big)\,U(z')\,dz' = f(z). \tag{3.37}$$

For λ real and large enough, the operator R_λ is invertible by the following lemma.

Lemma 3.38. *If $\lambda \in \mathbb{R}$ and $\lambda > \beta - \mu$, then $\lambda \in \rho(A)$.*

Proof. We use the same definitions we used before, i.e., $v(z) = b(z)\mathcal{U}(z)$, $\alpha_0 = \frac{2\beta}{b_0}$, and

$$\alpha := \alpha(\lambda) = \frac{\lambda+\beta+\mu}{b_0}.$$

There is a solution $U \in \mathcal{W}$ to (3.37) if and only if there is a solution v to

$$v'(z) + \alpha z_0 \frac{v(z)}{z(z_0-z)} - \alpha_0 z_0 \int\limits_z^{z_0} \frac{\Phi\big(\frac{z}{z'}\big)\,v(z')}{(z')^2\,(z_0-z')}\,dz' = f(z). \tag{3.38}$$

with $v \in \mathcal{W}_v := \Big\{ f \in L^1\Big((0,z_0), \frac{dz}{z(z_0-z)}\Big) : \ f' \in L^1((0,z_0)) \Big\}$. With variation of parameters and $v(0)=0$ (because of $\lim\limits_{z\to 0^+} b(z)\,U(z) = 0$), we obtain

$$\begin{aligned} v(z) &= \alpha_0 z_0 \Big(\frac{z_0-z}{z}\Big)^{\alpha} \int\limits_0^z \Big(\frac{x}{z_0-x}\Big)^{\alpha} \int\limits_x^{z_0} \frac{\Phi\big(\frac{x}{z'}\big)\,v(z')}{(z')^2\,(z_0-z')}\,dz'dx \\ &\quad + \Big(\frac{z_0-z}{z}\Big)^{\alpha} \int\limits_0^z f(x) \Big(\frac{x}{z_0-x}\Big)^{\alpha}\,dx. \end{aligned} \tag{3.39}$$

Define the first summand in (3.39) as $T : L^1\Big((0,z_0), \frac{dz}{z(z_0-z)}\Big) \to L^1\Big((0,z_0), \frac{dz}{z(z_0-z)}\Big)$,

$$T[v](z) := \alpha_0 z_0 \Big(\frac{z_0-z}{z}\Big)^{\alpha} \int\limits_0^{z} \Big(\frac{x}{z_0-x}\Big)^{\alpha} \int\limits_x^{z_0} \frac{\Phi\Big(\frac{x}{z'}\Big)\, v(z')}{(z')^2\,(z_0-z')}\, dz' dx.$$

We aim at showing that T is a contraction and thus we estimate,

$$\begin{aligned}
\|T[v]\|_{L^1((0,z_0),\frac{dz}{z(z_0-z)})} &\le \alpha_0 z_0 \int\limits_0^{z_0} \frac{(z_0-z)^{\alpha-1}}{z^{\alpha+1}} \int\limits_0^{z} \Big(\frac{x}{z_0-x}\Big)^{\alpha} \int\limits_x^{z_0} \frac{\Phi\Big(\frac{x}{z'}\Big)\, |v(z')|}{(z')^2\,(z_0-z')}\, dz' dx dz \\
&= \alpha_0 z_0 \int\limits_0^{z_0} \int\limits_x^{z_0} \int\limits_x^{z_0} \frac{(z_0-z)^{\alpha-1}}{z^{\alpha+1}}\, dz\, \Big(\frac{x}{z_0-x}\Big)^{\alpha} \frac{\Phi\Big(\frac{x}{z'}\Big)\, |v(z')|}{(z')^2\,(z_0-z')}\, dz' dx \\
&= \frac{\alpha_0}{\alpha} \int\limits_0^{z_0} \int\limits_0^{z'} \frac{1}{z'}\, \Phi\Big(\frac{x}{z'}\Big)\, dx\, \frac{|v(z')|}{z'\,(z_0-z')}\, dz' \\
&= \frac{\alpha_0}{\alpha}\, \|v\|_{L^1((0,z_0),\frac{dz}{z(z_0-z)})}\,,
\end{aligned}$$

where we have used

$$\int\limits_x^{z_0} \frac{(z_0-z)^{\alpha-1}}{z^{\alpha+1}}\, dz = \Big[-\frac{1}{\alpha z_0}\Big(\frac{z_0-z}{z}\Big)^{\alpha}\Big]_{z=x}^{z=z_0} = \frac{1}{\alpha z_0}\Big(\frac{z_0-x}{x}\Big)^{\alpha}.$$

Hence, T is a contraction for $\alpha > \alpha_0$, i.e., for $\lambda > \beta - \mu$.

We estimate the $L^1\Big((0,z_0), \frac{dz}{z(z_0-z)}\Big)$-norm of the second summand on the right-hand side of (3.39) by

$$\begin{aligned}
&\int\limits_0^{z_0} \left| \Big(\frac{z_0-z}{z}\Big)^{\alpha} \int\limits_0^{z} f(x) \Big(\frac{x}{z_0-x}\Big)^{\alpha} dx \right| \frac{1}{z\,(z_0-z)}\, dz \\
&\le \int\limits_0^{z_0} \int\limits_0^{z} |f(x)| \Big(\frac{x}{z_0-x}\Big)^{\alpha} \frac{(z_0-z)^{\alpha-1}}{z^{\alpha+1}}\, dx dz \\
&= \int\limits_0^{z_0} \int\limits_x^{z_0} \frac{(z_0-z)^{\alpha-1}}{z^{\alpha+1}}\, dz\; |f(x)| \Big(\frac{x}{z_0-x}\Big)^{\alpha} dx \\
&= \frac{1}{\alpha\, z_0}\, \|f\|_{L^1((0,z_0))}\,.
\end{aligned}$$

Therefore, by the Banach Fixed Point Theorem, there is a unique solution v for (3.39) with $v \in L^1\Big((0,z_0), \frac{dz}{z(z_0-z)}\Big)$. Furthermore, as the solution v satisfies (3.39) v is differentiable with v' given by (3.38). Hence,

$$\begin{aligned}
\|v'\|_{L^1((0,z_0))} &= \int\limits_0^{z_0} \left| -\alpha\, z_0\, \frac{v(z)}{z\,(z_0-z)} + \alpha_0\, z_0 \int\limits_z^{z_0} \frac{\Phi\Big(\frac{z}{z'}\Big)\, v(z')}{(z')^2\,(z_0-z')}\, dz' + f(z) \right| dz \\
&\le \alpha\, z_0\, \|v\|_{L^1((0,z_0),\frac{dz}{z(z_0-z)})} + \alpha_0\, z_0 \int\limits_0^{z_0} \int\limits_0^{z'} \frac{1}{z'}\, \Phi\Big(\frac{z}{z'}\Big)\, dz'\, \frac{|v(z')|}{z'\,(z_0-z')}\, dz
\end{aligned}$$

$$
\begin{aligned}
&+ \|f\|_{L^1((0,z_0))} \\
&= (\alpha + \alpha_0)\, z_0\, \|v\|_{L^1((0,z_0),\frac{dz}{z(z_0-z)})} + \|f\|_{L^1((0,z_0))} < \infty,
\end{aligned}
$$

this means that $v' \in L^1((0,z_0))$ and therefore $v \in \mathcal{W}_v$.

Thus, if $\lambda \in \mathbb{R}$ with $\lambda > \beta - \mu$ then for every $f \in L^1((0,z_0))$ there is a unique solution $v \in \mathcal{W}_v$ to (3.24), i.e., there is a unique solution $U \in \mathcal{W}$ to (3.37). Hence, R_λ^{-1} exists and is everywhere defined in $L^1((0,z_0))$, linear, and bounded. Therefore, $\lambda \in \rho(A)$. ☐

Next, we generalize the result of Lemma 3.38 to the case of complex λ.

Lemma 3.39. *If $\lambda \in \mathbb{C}$ with $\Re(\lambda) > 0$ and $\Re(\lambda) > \beta - \mu$, then $\lambda \in \rho(A)$.*

Proof. Let $\lambda \in \mathbb{C}$ with $\Re(\lambda) > 0$ and $\mathcal{U} \in \mathcal{W}$ a function which can take complex values. Define as before $v(z) := b(z)\, U(z)$, $\alpha = \frac{\lambda+\beta+\mu}{b_0} \in \mathbb{C}$, and $\alpha_0 = \frac{2\beta}{b_0} \in \mathbb{R}$. Note that we still consider $z \in [0, z_0]$, i.e., $z \in \mathbb{R}$. Then, as in the case of real λ,

$$
v'(z) + \alpha\, z_0 \frac{v(z)}{z\,(z_0 - z)} - \alpha_0\, z_0 \int_z^{z_0} \frac{\Phi\left(\frac{z}{z'}\right) v(z')}{(z')^2\,(z_0 - z')}\, dz' = f(z). \tag{3.40}
$$

For the sake of brevity, we denote the real part of v, f, and α by v_R, f_R, and α_R, respectively, and the imaginary part by v_I, f_I, and α_I, respectively. We use $v(z) = v_R(z) + i v_I(z)$ and $\alpha = \alpha_R + i\alpha_I$ in (3.40),

$$
\begin{aligned}
v_R'(z) + i v_I'(z) = &-(\alpha_R + i\alpha_I)\, z_0 \frac{v_R(z) + i v_I(z)}{z\,(z_0 - z)} + \alpha_0\, z_0 \int_z^{z_0} \frac{\Phi\left(\frac{z}{z'}\right) (v_R(z') + i v_I(z'))}{(z')^2\,(z_0 - z')}\, dz' \\
&+ f_R(z) + i f_I(z).
\end{aligned}
$$

Next, we separate real and imaginary part and obtain the following equation

$$
\begin{aligned}
\frac{d}{dz} \begin{pmatrix} v_R(z) \\ v_I(z) \end{pmatrix} = &- \frac{z_0}{z\,(z_0 - z)} \begin{pmatrix} \alpha_R & -\alpha_I \\ \alpha_I & \alpha_R \end{pmatrix} \begin{pmatrix} v_R(z) \\ v_I(z) \end{pmatrix} \\
&+ \begin{pmatrix} \alpha_0 z_0 \int_z^{z_0} \frac{\Phi\left(\frac{z}{z'}\right) v_R(z')}{(z')^2\,(z_0 - z')}\, dz' + f_R(z) \\ \alpha_0 z_0 \int_z^{z_0} \frac{\Phi\left(\frac{z}{z'}\right) v_I(z')}{(z')^2\,(z_0 - z')}\, dz' + f_I(z) \end{pmatrix}.
\end{aligned}
$$

For the sake of brevity, define

$$
B(z) := -\frac{z_0}{z\,(z_0 - z)} \begin{pmatrix} \alpha_R & -\alpha_I \\ \alpha_I & \alpha_R \end{pmatrix} \quad \text{and} \quad J(z) := \begin{pmatrix} \alpha_0 z_0 \int_z^{z_0} \frac{\Phi\left(\frac{z}{z'}\right) v_R(z')}{(z')^2\,(z_0 - z')}\, dz' + f_R(z) \\ \alpha_0 z_0 \int_z^{z_0} \frac{\Phi\left(\frac{z}{z'}\right) v_I(z')}{(z')^2\,(z_0 - z')}\, dz' + f_I(z) \end{pmatrix}.
$$

Therefore, we can solve (3.40) using variation of parameters (see, e.g., [35, p. 131]), using $v(0) = 0$, i.e., $v_R(0) = 0$ and $v_I(0) = 0$,

$$\begin{aligned}\begin{pmatrix} v_R(z) \\ v_I(z) \end{pmatrix} &= \exp\left(\int_0^z B(s)\,ds\right) \int_0^z \left(\exp\left(\int_0^x B(s)\,ds\right)\right)^{-1} J(x)\,dx \\ &= \int_0^z \exp\left(\int_x^z B(s)\,ds\right) J(x)\,dx. \\ &= \int_0^z \exp\left(\int_z^x \frac{z_0}{s\,(z_0 - s)}\,ds \begin{pmatrix} \alpha_R & -\alpha_I \\ \alpha_I & \alpha_R \end{pmatrix}\right) J(x)\,dx.\end{aligned}$$

With

$$\int_z^x \frac{z_0}{s\,(z_0 - s)}\,ds = \int_z^x \frac{1}{s}\,ds + \int_z^x \frac{1}{z_0 - s}\,ds = \log\left(\frac{x}{z}\right) + \log\left(\frac{z_0 - z}{z_0 - x}\right) = \log\left(\frac{x(z_0 - z)}{z(z_0 - x)}\right),$$

and

$$\begin{pmatrix} \alpha_R & -\alpha_I \\ \alpha_I & \alpha_R \end{pmatrix} = \begin{pmatrix} -i & i \\ 1 & 1 \end{pmatrix} \begin{pmatrix} \overline{\alpha} & 0 \\ 0 & \alpha \end{pmatrix} \begin{pmatrix} \frac{i}{2} & \frac{1}{2} \\ -\frac{i}{2} & \frac{1}{2} \end{pmatrix},$$

we obtain

$$\begin{aligned}&\exp\left(\int_z^x \frac{z_0}{s\,(z_0 - s)}\,ds \begin{pmatrix} \alpha_R & -\alpha_I \\ \alpha_I & \alpha_R \end{pmatrix}\right) \\ &\quad= \begin{pmatrix} -i & i \\ 1 & 1 \end{pmatrix} \begin{pmatrix} \left(\frac{x(z_0-z)}{z(z_0-x)}\right)^{\overline{\alpha}} & 0 \\ 0 & \left(\frac{x(z_0-z)}{z(z_0-x)}\right)^{\alpha} \end{pmatrix} \begin{pmatrix} \frac{i}{2} & \frac{1}{2} \\ -\frac{i}{2} & \frac{1}{2} \end{pmatrix} \\ &\quad= \begin{pmatrix} \frac{1}{2}\left(\frac{x(z_0-z)}{z(z_0-x)}\right)^{\overline{\alpha}} + \frac{1}{2}\left(\frac{x(z_0-z)}{z(z_0-x)}\right)^{\alpha} & -\frac{i}{2}\left(\frac{x(z_0-z)}{z(z_0-x)}\right)^{\overline{\alpha}} + \frac{i}{2}\left(\frac{x(z_0-z)}{z(z_0-x)}\right)^{\alpha} \\ \frac{i}{2}\left(\frac{x(z_0-z)}{z(z_0-x)}\right)^{\overline{\alpha}} - \frac{i}{2}\left(\frac{x(z_0-z)}{z(z_0-x)}\right)^{\alpha} & \frac{1}{2}\left(\frac{x(z_0-z)}{z(z_0-x)}\right)^{\overline{\alpha}} + \frac{1}{2}\left(\frac{x(z_0-z)}{z(z_0-x)}\right)^{\alpha} \end{pmatrix}.\end{aligned}$$

The solution by variation of parameter is then given by

$$\begin{aligned}v_R(z) = \int_0^z \frac{1}{2}&\left(\left(\frac{x(z_0 - z)}{z(z_0 - x)}\right)^{\overline{\alpha}} + \left(\frac{x(z_0 - z)}{z(z_0 - x)}\right)^{\alpha}\right)\left(\alpha_0 z_0 \int_x^{z_0} \frac{\Phi\left(\frac{x}{z'}\right) v_R(z')}{(z')^2\,(z_0 - z')}\,dz' + f_R(z)\right) \\ &+ \frac{i}{2}\left(\left(\frac{x(z_0 - z)}{z(z_0 - x)}\right)^{\alpha} - \left(\frac{x(z_0 - z)}{z(z_0 - x)}\right)^{\overline{\alpha}}\right)\left(\alpha_0 z_0 \int_x^{z_0} \frac{\Phi\left(\frac{x}{z'}\right) v_I(z')}{(z')^2\,(z_0 - z')}\,dz' + f_I(z)\right) dx \\ = \frac{\alpha_0 z_0}{2}&\left(\frac{z_0 - z}{z}\right)^{\overline{\alpha}} \int_0^z \left(\frac{x}{z_0 - x}\right)^{\overline{\alpha}} \int_x^{z_0} \frac{\Phi\left(\frac{x}{z'}\right) \overline{v(z')}}{(z')^2\,(z_0 - z')}\,dz'dx \\ &+ \frac{\alpha_0 z_0}{2}\left(\frac{z_0 - z}{z}\right)^{\alpha} \int_0^z \left(\frac{x}{z_0 - x}\right)^{\alpha} \int_x^{z_0} \frac{\Phi\left(\frac{x}{z'}\right) v(z')}{(z')^2\,(z_0 - z')}\,dz'dx\end{aligned}$$

$$+\frac{1}{2}\Big(\frac{z_0-z}{z}\Big)^{\overline{\alpha}}\int\limits_0^z\Big(\frac{x}{z_0-x}\Big)^{\overline{\alpha}}\overline{f(x)}\,dx+\frac{1}{2}\Big(\frac{z_0-z}{z}\Big)^{\alpha}\int\limits_0^z\Big(\frac{x}{z_0-x}\Big)^{\alpha}f(x)\,dx,$$

and, analogously,

$$\begin{aligned}iv_I(z)=&-\frac{\alpha_0 z_0}{2}\Big(\frac{z_0-z}{z}\Big)^{\overline{\alpha}}\int\limits_0^z\Big(\frac{x}{z_0-x}\Big)^{\overline{\alpha}}\int\limits_x^{z_0}\frac{\Phi\Big(\frac{x}{z'}\Big)\overline{v(z')}}{(z')^2\,(z_0-z')}\,dz'dx\\&+\frac{\alpha_0 z_0}{2}\Big(\frac{z_0-z}{z}\Big)^{\alpha}\int\limits_0^z\Big(\frac{x}{z_0-x}\Big)^{\alpha}\int\limits_x^{z_0}\frac{\Phi\Big(\frac{x}{z'}\Big)v(z')}{(z')^2\,(z_0-z')}\,dz'dx\\&-\frac{1}{2}\Big(\frac{z_0-z}{z}\Big)^{\overline{\alpha}}\int\limits_0^z\Big(\frac{x}{z_0-x}\Big)^{\overline{\alpha}}\overline{f(x)}\,dx+\frac{1}{2}\Big(\frac{z_0-z}{z}\Big)^{\alpha}\int\limits_0^z\Big(\frac{x}{z_0-x}\Big)^{\alpha}f(x)\,dx.\end{aligned}$$

Therefore, variation of parameter yields

$$\begin{aligned}v(z)=v_R(z)+iv_I(z)=\alpha_0 z_0\left(\frac{z_0-z}{z}\right)^{\alpha}\int\limits_0^z\left(\frac{x}{z_0-x}\right)^{\alpha}\int\limits_x^{z_0}\frac{\Phi\Big(\frac{x}{z'}\Big)v(z')}{(z')^2\,(z_0-z')}\,dz'dx\\+\left(\frac{z_0-z}{z}\right)^{\alpha}\int\limits_0^z\left(\frac{x}{z_0-x}\right)^{\alpha}f(x)\,dx.\end{aligned}$$

This is the same formula as in the case of real λ and α but here $\alpha\in\mathbb{C}$.

We define the operator $T: L^1\Big((0,z_0),\frac{dz}{z(z_0-z)}\Big)\to L^1\Big((0,z_0),\frac{dz}{z(z_0-z)}\Big)$ by

$$T[v](z):=\alpha_0 z_0\left(\frac{z_0-z}{z}\right)^{\alpha}\int\limits_0^z\left(\frac{x}{z_0-x}\right)^{\alpha}\int\limits_x^{z_0}\frac{\Phi\Big(\frac{x}{z'}\Big)v(z')}{(z')^2\,(z_0-z')}\,dz'dx.$$

Using that

$$\left|x^{a+ib}\right|=\left|x^a\right|\left|x^{ib}\right|=|x|^a\left|e^{ib\log(x)}\right|=x^a,$$

for $x\in\mathbb{R}_{\geq 0}$ and a, $b\in\mathbb{R}$, and the previous calculation for the real case (in the proof of Lemma 3.38),

$$\begin{aligned}\|T[v]\|_{L^1((0,z_0),\frac{dz}{z(z_0-z)})}&\leq\alpha_0 z_0\int\limits_0^{z_0}\frac{(z_0-z)^{\alpha_R-1}}{z^{\alpha_R+1}}\int\limits_0^z\left(\frac{x}{z_0-x}\right)^{\alpha_R}\int\limits_x^{z_0}\frac{\Phi\Big(\frac{x}{z'}\Big)|v(z')|}{(z')^2\,(z_0-z')}\,dz'dxdz\\&\leq\frac{\alpha_0}{\alpha_R}\|v\|_{L^1((0,z_0),\frac{dz}{z(z_0-z)})}.\end{aligned}$$

The operator T is a contraction if $\alpha_R>\alpha_0$. By the Banach Fixed Point Theorem, there is for every $f\in L^1((0,z_0))$ a unique solution $v\in\mathcal{W}_v$ to (3.40) and hence also a unique solution $\mathcal{U}\in\mathcal{W}$ to (3.37) if $\alpha_R>\alpha_0$. We finish the proof in the same way as the proof of Lemma 3.38 and find that if $\lambda_R=\Re(\lambda)>\beta-\mu$, then $\lambda\in\rho(A)$. □

From Lemma 3.39 we know that if $\lambda\in\sigma(A)$, then $\Re(\lambda)\leq\beta-\mu$.

We would like to proceed as in the case of the regular VGT model (see Section 3.2.2), i.e., we would like to consider the rescaled function $v(z) := b(z)\,U(z)$, show that the operator $T_\lambda : L^1\Big((0,z_0), \frac{dz}{z(z_0-z)}\Big) \to L^1\Big((0,z_0), \frac{dz}{z(z_0-z)}\Big)$ defined by

$$T_\lambda[v](z) := \alpha_0\, z_0 \left(\frac{z_0 - z}{z}\right)^{\alpha} \int\limits_0^z \left(\frac{x}{z_0 - x}\right)^{\alpha} \int\limits_x^{z_0} \frac{\Phi\big(\frac{x}{z'}\big)\, v(z')}{(z')^2\,(z_0 - z)}\, dz' dx$$

is compact, and use this property to show that $\lambda = \beta - \mu$ is a dominant eigenvalue. However, we cannot show compactness of T_λ as before using the Kolmogorov-Riesz-Fréchet Theorem because we do not have an upper estimate for the plasmid segregation kernel as in the regular case.

Another idea would be to use that the operator T_λ maps $L^1_w := L^1\Big((0,z_0), \frac{dz}{z(z_0-z)}\Big)$ to $\mathcal{W}_v := L^1_w \cap W^{1,1}((0,z_0))$ and to show that $\mathcal{W}_v \subset\subset L^1_w$, meaning that $\mathcal{W}_v$ is compactly embedded in L^1_w. However, this is not the case as the following example illustrates.

Example 3.40. Let $X := W^{1,1}((0,z_0)) \cap L^1((0,1), \frac{dx}{x})$ and define the norms

$$\|f\|_{L^1((0,1),\frac{dx}{x})} := \int\limits_0^1 |f(x)|\, \frac{1}{x}\, dx \quad \text{and} \quad \|f\|_X := \|f'\|_{L^1((0,z_0))} + \|f\|_{L^1((0,1),\frac{dz}{z})}\,.$$

Let $(f_n)_{n\in\mathbb{N}}$ be a uniformly bounded sequence in X, then there is a subsequence (still denoted by $(f_n)_{n\in\mathbb{N}}$) that converges in $L^1((0,z_0))$ because $W^{1,1}((0,z_0)) \subset\subset L^1((0,z_0))$. Denote the limit of f_n by $\tilde{f} \in L^1((0,z_0))$. Because $(f_n)_{n\in\mathbb{N}}$ is uniformly bounded in $L^1((0,1), \frac{dz}{z})$ it holds that $\tilde{f} \in L^1((0,1), \frac{dx}{x})$. However, we do not necessarily have that $f_n \xrightarrow{n\to\infty} \tilde{f}$ in $L^1((0,1), \frac{dx}{x})$.

For example, consider for $n \in \mathbb{N}$ with $n \geq 2$

$$f_n(x) := \begin{cases} nx, & \text{if } 0 < x < \frac{1}{n}, \\ n\left(\frac{2}{n} - x\right), & \text{if } \frac{1}{n} < x < \frac{2}{n}, \\ 0 & \text{if } \frac{2}{n} < x. \end{cases}$$

Then, f_n is a uniformly bounded sequence in X as

$$\|f_n'\|_{L^1((0,z_0))} = 2 \quad \text{and} \quad \|f_n\|_{L^1((0,1),\frac{dx}{x})} = 2\log(2) \quad \text{for all } n \geq 2.$$

Moreover, $f_n \xrightarrow{n\to\infty} \tilde{f} = 0$ in $L^1((0,z_0))$. Because of $\|f_n\|_{L^1((0,1),\frac{dx}{x})} = 2\log(2)$ for all $n \geq 2$ and $\big\|\tilde{f}\big\|_{L^1((0,1),\frac{dx}{x})} = 0$ the sequence f_n cannot converge to $\tilde{f}$ in $L^1((0,1), \frac{dx}{x})$.

This example can be extended to show that $\mathcal{W}_v$ is not compactly embedded in L^1_w. Therefore, in the next section we use another approach to obtain stability results for the singular VGT model.

3.3.4 Stability analysis with the Generalized Relative Entropy method

The aim of this section is to show stability of the eigensolution to the singular VGT model (3.18) using the Generalized Relative Entropy (GRE) method. We follow [70,83] and assume that the parameters of the model satisfy **(A1')** – **(A4')**.

We consider eigensolutions $(\lambda,\, \mathcal{U},\, \Psi)$, where $(\lambda,\, \mathcal{U})$ is a solution to the eigenproblem associated with (3.18),

$$\begin{cases} \dfrac{d}{dz}(b(z)\mathcal{U}(z)) = -\,(\beta(z)+\mu(z)+\lambda)\mathcal{U}(z) + \displaystyle\int_z^{z_0} \beta(z')\, k(z,z')\mathcal{U}(z')\, dz', \\ \lim\limits_{z\to 0^+} b(z)\mathcal{U}(z) = 0, \quad \mathcal{U}(z) > 0 \text{ for all } z \in (0,z_0), \quad \displaystyle\int_0^{z_0} \mathcal{U}(z)\, dz = 1 \end{cases} \tag{3.41}$$

and $(\lambda,\, \Psi)$ is a solution to the dual eigenproblem

$$\begin{cases} -\, b(z)\dfrac{d}{dz}\Psi(z) = -\,(\beta(z)+\mu(z)+\lambda)\,\Psi(z) + \beta(z)\displaystyle\int_0^{z} k(z',z)\,\Psi(z')\, dz', \\ \Psi(z) \geq 0 \text{ for all } z \in (0,z_0), \quad \displaystyle\int_0^{z_0} \Psi(z)\mathcal{U}(z)\, dz = 1. \end{cases} \tag{3.42}$$

So far, we know that there is an eigensolution $(\lambda, \mathcal{U})$ to (3.41) with $\lambda = \beta - \mu$ and $\mathcal{U}(z) > 0$ for all $z \in (0, z_0)$ in the case that β and μ are constant, b is logistic, and k is scalable (see Section 3.3.2). For the eigensolution $(\lambda,\, \Psi)$ to the dual eigenproblem (3.42) we have the following existence result.

Lemma 3.41. *Let β and μ be constant and $(\lambda,\, \mathcal{U})$ a solution to* (3.41)*, then $\Psi \equiv 1$ is a solution to the dual eigenproblem* (3.42)*.*

Proof. The proof is a straightforward computation using $\lambda = \beta - \mu$ and the consistency condition $\int_0^z k(z,z')\, dz = 2$. □

In this section, we aim at showing the stability of the eigenfunction $\mathcal{U}$, thus we assume that there is a unique eigensolution $(\lambda,\, \mathcal{U},\, \Psi)$ throughout this section:

(A9') There is a unique eigensolution $(\lambda,\, \mathcal{U},\, \Psi)$ such that $(\lambda,\, \mathcal{U})$ is a solution to (3.41) with $\lambda \in \mathbb{R}$ and $\mathcal{U}(z) > 0$ for all $z \in (0, z_0)$ and $(\lambda,\, \Psi)$ is a solution to (3.42). Moreover, there is no other solution $(\lambda^*,\, \mathcal{U}^*)$ to (3.41) with $\Re(\lambda^*) > \lambda$.

We rescale the solution $u(z,t)$ to (3.18) by defining $\tilde{u}(z,t) := e^{-\lambda t}\, u(z,t)$. Then, the function $\tilde{u}$ is a solution to

$$\begin{cases} \partial_t \tilde{u}(z,t) + \partial_z(b(z)\tilde{u}(z,t)) = -\,(\beta(z)+\mu(z)+\lambda)\,\tilde{u}(z,t) + \displaystyle\int_z^{z_0} \beta(z')k(z,z')\tilde{u}(z',t)\, dz', \\ b(0)\tilde{u}(0,t) = 0 \quad \text{for all } t \geq 0, \qquad \tilde{u}(z,0) = u_0(z) \quad \text{for all } z \in [0,z_0]. \end{cases} \tag{3.43}$$

The idea behind the GRE method is to obtain a Lyapunov functional for solutions to (3.43) in order to determine the long-time asymptotics. The following theorem is the first step towards a Lyapunov functional.

Theorem 3.42. *Let $\tilde{u}(z,t)$ be a solution to* (3.43) *and $(\lambda, \mathcal{U}, \Psi)$ be an eigensolution in the sense of* ***(A9')***. *For every absolutely continuous function $H : \mathbb{R} \to \mathbb{R}$, it holds that*

$$\begin{aligned}
&\partial_t \left[\Psi(z) \mathcal{U}(z)\, H\!\left(\frac{\tilde{u}(z,t)}{\mathcal{U}(z)} \right) \right] + \partial_z \left[b(z)\, \Psi(z) \mathcal{U}(z)\, H\!\left(\frac{\tilde{u}(z,t)}{\mathcal{U}(z)} \right) \right] \\
&+ \int\limits_0^{z_0} \beta(z)\, k(z',z)\, \Psi(z') \mathcal{U}(z)\, H\!\left(\frac{\tilde{u}(z,t)}{\mathcal{U}(z)} \right) - \beta(z')\, k(z,z')\, \Psi(z) \mathcal{U}(z')\, H\!\left(\frac{\tilde{u}(z',t)}{\mathcal{U}(z')} \right) dz' \\
&= \int\limits_0^{z_0} \beta(z')\, k(z,z')\, \Psi(z) \mathcal{U}(z') \left[H\!\left(\frac{\tilde{u}(z,t)}{\mathcal{U}(z)} \right) - H\!\left(\frac{\tilde{u}(z',t)}{\mathcal{U}(z')} \right) \right. \\
&\qquad \left. + H'\!\left(\frac{\tilde{u}(z,t)}{\mathcal{U}(z)} \right) \left[\frac{\tilde{u}(z',t)}{\mathcal{U}(z')} - \frac{\tilde{u}(z,t)}{\mathcal{U}(z)} \right] \right] dz'.
\end{aligned}$$

Proof. The proof is lengthy but consists of straightforward computations.

We define $U(z,t) := e^{\lambda t} \mathcal{U}(z)$. Then, $U(z) > 0$ for all $z \in (0, z_0)$ and U is a solution to (3.18). Furthermore, we define $\psi(z,t) := e^{-\lambda t} \Psi(z)$. Then ψ is a solution to the dual equation of (3.18), i.e., it is a solution to

$$\begin{cases}
-\partial_t \psi(z,t) - b(z) \partial_z \psi(z,t) = -\left(\beta(z) + \mu(z) \right) \psi(z,t) + \beta(z) \displaystyle\int\limits_0^{z} k(z',z) \psi(z',t)\, dz', \\
\psi(z,t) \geq 0 \text{ for all } z \in (0, z_0) \text{ and } t \geq 0, \quad \displaystyle\int\limits_0^{z_0} \psi(z,t)\, U(z,t)\, dz = 1.
\end{cases} \tag{3.44}$$

With these definitions, we obtain

$$\begin{aligned}
\Psi(z) \mathcal{U}(z)\, H\!\left(\frac{\tilde{u}(z,t)}{\mathcal{U}(z)} \right) &= \Psi(z)\, e^{-\lambda t} e^{\lambda t} \mathcal{U}(z)\, H\!\left(\frac{\tilde{u}(z,t)\, e^{\lambda t}}{\mathcal{U}(z)\, e^{\lambda t}} \right) \\
&= \psi(z,t)\, U(z,t)\, H\!\left(\frac{u(z,t)}{U(z,t)} \right).
\end{aligned}$$

Recall that as H is absolutely continuous, it is differentiable a.e. and the derivative H' is Lebesgue-integrable. For the sake of brevity, we omit the arguments of ψ, U, and u everywhere except in the integrals. It holds that

$$\begin{aligned}
&\partial_t \left[\psi\, U\, H\!\left(\frac{u}{U} \right) \right] + \partial_z \left[b(z)\, \psi\, U\, H\!\left(\frac{u}{U} \right) \right] \\
&= (\partial_t \psi)\; U\; H\!\left(\frac{u}{U} \right) + \psi\; (\partial_t U)\; H\!\left(\frac{u}{U} \right) \\
&\quad + \psi\, U\, H'\left(\frac{u}{U} \right)\; \partial_t \left(\frac{u}{U} \right) + (\partial_z \psi)\; b(z)\, U\, H\!\left(\frac{u}{U} \right) + \psi\, \partial_z (b(z)\, U)\, H\!\left(\frac{u}{U} \right) \\
&\quad + \psi\, b(z)\, U\, H'\left(\frac{u}{U} \right)\; \partial_z \left(\frac{u}{U} \right) \\
&= U\, H\!\left(\frac{u}{U} \right) \left[\partial_t \psi + b(z)\, \partial_z \psi \right] + \psi\, H\!\left(\frac{u}{U} \right) \left[\partial_t U + \partial_z (b(z)\, U) \right]
\end{aligned}$$

$$+\,\psi\, U\, H'\Big(\frac{u}{U}\Big)\,\Big[\partial_t\Big(\frac{u}{U}\Big) + b(z)\,\partial_z\Big(\frac{u}{U}\Big)\Big].$$

Now, we use the fact that ψ is a solution to (3.44) and U is a solution to (3.18):

$$\begin{aligned}
&\partial_t\left[\psi U H\Big(\frac{u}{U}\Big)\right] + \partial_z\left[b(z)\psi U H\Big(\frac{u}{U}\Big)\right]\\
&= U H\Big(\frac{u}{U}\Big)\left[(\beta(z)+\mu(z))\,\psi - \beta(z)\int\limits_0^z k(z',z)\psi(z',t)\,dz'\right]\\
&\quad + \psi\, H\Big(\frac{u}{U}\Big)\left[-\,(\beta(z)+\mu(z))\,U + \int\limits_z^{z_0}\beta(z')\,k(z,z')\,U(z',t)\,dz'\right]\\
&\quad + \psi\, U\, H'\Big(\frac{u}{U}\Big)\left[\partial_t\Big(\frac{u}{U}\Big) + b(z)\,\partial_z\Big(\frac{u}{U}\Big)\right]\\
&= -\int\limits_0^{z_0}\beta(z)\,k(z',z)\,\psi(z',t)\,U(z,t)\,H\left(\frac{u(z,t)}{U(z,t)}\right)dz'\\
&\quad + \int\limits_0^{z_0}\beta(z')\,k(z,z')\,\psi(z,t)\,U(z',t)\,H\left(\frac{u(z,t)}{U(z,t)}\right)dz'\\
&\quad + \psi\, U\, H'\Big(\frac{u}{U}\Big)\left[\partial_t\Big(\frac{u}{U}\Big) + b(z)\,\partial_z\Big(\frac{u}{U}\Big)\right].
\end{aligned}$$

We compute that

$$\begin{aligned}
&\partial_t\Big(\frac{u}{U}\Big) + b(z)\,\partial_z\Big(\frac{u}{U}\Big) = \frac{\partial_t u}{U} - \frac{u\,\partial_t U}{U^2} + b(z)\left(\frac{\partial_z u}{U} - \frac{u\,\partial_z U}{U^2}\right)\\
&= \frac{1}{U}\left[-\partial_z(b(z)u) - (\beta(z)+\mu(z))\,u + \int\limits_z^{z_0}\beta(z')\,k(z,z')\,u(z',t)\,dz' + b(z)\,\partial_z u\right]\\
&\quad - \frac{u}{U^2}\left[-\partial_z(b(z)U) - (\beta(z)+\mu(z))\,U + \int\limits_z^{z_0}\beta(z')\,k(z,z')\,U(z',t)\,dz' + b(z)\,\partial_z U\right]\\
&= \int\limits_0^{z_0}\beta(z')\,k(z,z')\left(\frac{u(z',t)}{U(z,t)} - \frac{U(z',t)\,u(z,t)}{U^2(z,t)}\right)\,dz'\\
&\quad + \frac{1}{U}\left[-\partial_z(b(z)u) + b(z)\,\partial_z u - \frac{u}{U}\,(-\partial_z(b(z)U) + b(z)\,\partial_z U)\right]\\
&= \int\limits_0^{z_0}\beta(z')\,k(z,z')\,\frac{U(z',t)}{U(z,t)}\left(\frac{u(z',t)}{U(z',t)} - \frac{u(z,t)}{U(z,t)}\right)\,dz' + \frac{1}{U}\left[-b'(z)\,u - \frac{u}{U}\,(-b'(z)\,U)\right],
\end{aligned}$$

then the last summand is zero. Therefore, we obtain

$$\begin{aligned}
&\partial_t\Big[\psi\, U\, H\Big(\frac{u}{U}\Big)\Big] + \partial_z\Big[b(z)\,\psi\, U\, H\Big(\frac{u}{U}\Big)\Big] = -\int\limits_0^{z_0}\Bigg\{\beta(z)\,k(z',z)\,\psi(z',t)\,U(z,t)\,H\left(\frac{u(z,t)}{U(z,t)}\right)\\
&\quad - \beta(z')\,k(z,z')\,\psi(z,t)\,U(z',t)\,H\left(\frac{u(z',t)}{U(z',t)}\right)\Bigg\}\,dz'
\end{aligned}$$

$$
\begin{aligned}
&+\int_0^{z_0} \beta(z')\,k(z,z')\,\psi(z,t)\,U(z',t)\left[H\left(\frac{u(z,t)}{U(z,t)}\right)-H\left(\frac{u(z',t)}{U(z',t)}\right)\right]dz'\\
&+\psi\,U\,H'\left(\frac{u}{U}\right)\int_0^{z_0}\beta(z')\,k(z,z')\,\frac{U(z',t)}{U(z,t)}\left(\frac{u(z',t)}{U(z',t)}-\frac{u(z,t)}{U(z,t)}\right)dz'\\
=&-\int_0^{z_0}\Bigg\{\beta(z)\,k(z',z)\,\psi(z',t)\,U(z,t)\,H\left(\frac{u(z,t)}{U(z,t)}\right)\\
&-\beta(z')\,k(z,z')\,\psi(z,t)\,U(z',t)\,H\left(\frac{u(z',t)}{U(z',t)}\right)\Bigg\}\,dz'\\
&+\int_0^{z_0}\beta(z')\,k(z,z')\,\psi(z,t)\,U(z',t)\left[H\left(\frac{u(z,t)}{U(z,t)}\right)-H\left(\frac{u(z',t)}{U(z',t)}\right)\right]dz'\\
&+\int_0^{z_0}\beta(z')\,k(z,z')\,\psi(z,t)\,U(z',t)\,H'\left(\frac{u(z,t)}{U(z,t)}\right)\left(\frac{u(z',t)}{U(z',t)}-\frac{u(z,t)}{U(z,t)}\right)dz'.
\end{aligned}
$$

Together with

$$\psi(z,t)\,U(z,t)=\Psi(z)\mathcal{U}(z)\quad\text{and}\quad\frac{u(z,t)}{U(z,t)}=\frac{\tilde u(z,t)}{\mathcal{U}(z)}$$

this finishes the proof. □

Theorem 3.42 is the central theorem of this section, the following lemmas are basically consequences of the equation in Theorem 3.42. If we choose the function H in Theorem 3.42 to be convex, then the next lemma shows that we have a Lyapunov functional for solutions $\tilde u$ to (3.43).

Lemma 3.43. *Let $H:\mathbb{R}\to\mathbb{R}_{\geq 0}$ be a convex and absolutely continuous function, $\tilde u(z,t)$ a solution to* (3.43)*, and $(\lambda,\mathcal{U},\Psi)$ an eigensolution as in* ***(A9')****. Then,*

$$t\mapsto\mathcal{H}_\Psi(\tilde u|\mathcal{U}):=\int_0^{z_0}\Psi(z)\mathcal{U}(z)\,H\left(\frac{\tilde u(z,t)}{\mathcal{U}(z)}\right)dz$$

is decreasing and

$$
\begin{aligned}
\frac{d}{dt}\mathcal{H}_\Psi(\tilde u|\mathcal{U})=\int_0^{z_0}\int_0^{z_0}&\beta(z')\,k(z,z')\,\Psi(z)\mathcal{U}(z')\left[H\left(\frac{\tilde u(z,t)}{\mathcal{U}(z)}\right)-H\left(\frac{\tilde u(z',t)}{\mathcal{U}(z')}\right)\right.\\
&\left.+H'\left(\frac{\tilde u(z,t)}{\mathcal{U}(z)}\right)\left[\frac{\tilde u(z',t)}{\mathcal{U}(z')}-\frac{\tilde u(z,t)}{\mathcal{U}(z)}\right]\right]dz'dz=:-\mathcal{D}_\Psi(\tilde u|\mathcal{U})\leq 0.
\end{aligned}
$$

Proof. Following [70], we start with the formula in Theorem 3.42 and integrate it w.r.t. z from 0 to z_0. Then, the second summand on the left-hand side is

$$b(z)\,\Psi(z)\mathcal{U}(z)\,H\left(\frac{\tilde u(z,t)}{\mathcal{U}(z)}\right)\Bigg|_{z=0}^{z=z_0}=0,$$

as $\int_0^{z_0} \Psi(z)\mathcal{U}(z)\, dz = 1$, by Assumption **(A1')** and Lemma 3.14, because of

$$\lim_{z\to 0^+} \frac{\tilde{u}(z,t)}{\mathcal{U}(z)} = \lim_{z\to 0^+} \frac{u(z,t)}{\mathcal{U}(z)\, e^{\lambda t}} < \infty$$

which implies that $\lim\limits_{z\to 0^+} H\Big(\frac{\tilde{u}(z,t)}{\mathcal{U}(z)}\Big) < \infty$, and analogously $\lim\limits_{z\to z_0^-} H\Big(\frac{\tilde{u}(z,t)}{\mathcal{U}(z)}\Big) < \infty$. The last two assertions hold as there is no eigenvalue with real part larger than λ by Assumption **(A9')** and thus no solution grows faster than $\mathcal{U}(z)\, e^{\lambda t}$. Therefore, $H\Big(\frac{\tilde{u}(z,t)}{\mathcal{U}(z)}\Big)$ is bounded for $z \to 0^+$ and $z \to z_0^-$.

The third summand on the left-hand side is

$$\begin{aligned}&\int_0^{z_0}\int_0^{z_0} \beta(z)\, k(z,z')\, \Psi(z')\mathcal{U}(z)\, H\bigg(\frac{\tilde{u}(z,t)}{\mathcal{U}(z)}\bigg)\, dz'dz\\ &- \int_0^{z_0}\int_0^{z_0} \beta(z')\, k(z,z')\, \Psi(z)\mathcal{U}(z')\, H\bigg(\frac{\tilde{u}(z',t)}{\mathcal{U}(z')}\bigg)\, dzdz' = 0.\end{aligned}$$

Therefore,

$$\begin{aligned}\frac{d}{dt}\int_0^{z_0} \Psi(z)\mathcal{U}(z)\, H\bigg(\frac{\tilde{u}(z,t)}{\mathcal{U}(z)}\bigg)\, dz = \int_0^{z_0}\int_0^{z_0} \beta(z')\, k(z,z')\, \Psi(z)\mathcal{U}(z')\, \Bigg[H\bigg(\frac{\tilde{u}(z,t)}{\mathcal{U}(z)}\bigg)\\ -H\bigg(\frac{\tilde{u}(z',t)}{\mathcal{U}(z')}\bigg) + H'\bigg(\frac{\tilde{u}(z,t)}{\mathcal{U}(z)}\bigg)\left[\frac{\tilde{u}(z',t)}{\mathcal{U}(z')} - \frac{\tilde{u}(z,t)}{\mathcal{U}(z)}\right]\Bigg]\, dz'dz,\end{aligned}$$

which shows the second part of the lemma.

Since H is convex and a.e. differentiable it holds for almost all x, $y \in \mathbb{R}$ that $H(x) \geq H(y) + H'(y)(x-y)$ or equivalently $H'(y)(x-y) \leq H(x) - H(y)$. Hence,

$$H\bigg(\frac{\tilde{u}(z,t)}{\mathcal{U}(z)}\bigg) - H\bigg(\frac{\tilde{u}(z',t)}{\mathcal{U}(z')}\bigg) + H'\bigg(\frac{\tilde{u}(z,t)}{\mathcal{U}(z)}\bigg)\left[\frac{\tilde{u}(z',t)}{\mathcal{U}(z')} - \frac{\tilde{u}(z,t)}{\mathcal{U}(z)}\right] \leq 0$$

and

$$\frac{d}{dt}\mathcal{H}_\Psi(\tilde{u}|\mathcal{U}) \leq 0,$$

i.e., the map $t \mapsto \mathcal{H}_\Psi(\tilde{u}|\mathcal{U})$ is decreasing. ☐

Now, we can use the previous Lemma 3.43 to obtain a priori estimates for solutions to (3.43).

Lemma 3.44. *Under the assumptions of Lemma 3.43, we have*

(i) Conversation of mass*:* $\int_0^{z_0} \tilde{u}(z,t)\, \Psi(z)\, dz = \int_0^{z_0} \tilde{u}(z,0)\, \Psi(z)\, dz =: m$ *for all* $t \geq 0$.

(ii) Contraction principle*:* $\int_0^{z_0} |\tilde{u}(z,t)|\ \Psi(z)\, dz \leq \int_0^{z_0} |\tilde{u}(z,0)|\ \Psi(z)\, dz$ *for all* $t \geq 0$.

Proof. The proof uses the formula for $\frac{d}{dt}\mathcal{H}_\Psi(\tilde{u}|\mathcal{U})$ in Lemma 3.43.

(i) We choose $H(h) = h$, then

$$\begin{aligned}&\frac{d}{dt}\mathcal{H}_\Psi(\tilde{u}|\mathcal{U}) =\\ &= \int_0^{z_0}\int_0^{z_0} \beta(z')\,k(z,z')\,\Psi(z)\,\mathcal{U}(z')\left[\frac{\tilde{u}(z,t)}{\mathcal{U}(z)} - \frac{\tilde{u}(z',t)}{\mathcal{U}(z')} + \left[\frac{\tilde{u}(z',t)}{\mathcal{U}(z')} - \frac{\tilde{u}(z,t)}{\mathcal{U}(z)}\right]\right] dzdz'\\ &= 0.\end{aligned}$$

Therefore, $\mathcal{H}_\Psi(\tilde{u}|\mathcal{U})$ is constant in time and $\mathcal{H}_\Psi(\tilde{u}|\mathcal{U}) = \int_0^{z_0} \Psi(z)\,\tilde{u}(z,t)\,dz$.

(ii) With $H(h) = |h|$, we obtain from Lemma 3.43 that

$$\frac{d}{dt}\mathcal{H}_\Psi(\tilde{u}|\mathcal{U}) = \frac{d}{dt}\int_0^{z_0} |\tilde{u}(z,t)|\;\Psi(z)\,dz \leq 0.$$

Thus, (ii) follows.

□

In the next lemma, we show further a priori estimates for solutions to (3.43).

Lemma 3.45. *Under the conditions of Lemma 3.43,* $\Psi > 0$*, and the following conditions on the initial condition* u_0 *of a solution* $\tilde{u}$ *to* (3.43) *and the eigenfunction* $\mathcal{U}$*: there exists a* $C > 0$ *such that for all* $z \in [0, z_0]$

$$|u_0(z)| \leq C\mathcal{U}(z), \quad \frac{d}{dz}(b(z)\mathcal{U}(z)) \in L^1((0,z_0),\Psi(z)dz), \text{ and}$$
$$\frac{d}{dz}((b(z)\,u_0(z)) \in L^1((0,z_0),\Psi(z)dz),$$

it holds that

(i) $|\tilde{u}(z,t)| \leq C\mathcal{U}(z)$ *for a.e.* $z \in [0,z_0]$ *and for all* $t \geq 0$*,*

(ii) $\int_0^{z_0} |\partial_t\tilde{u}(z,t)|\,\Psi(z)\,dz \leq C_1(u_0)$ *for all* $t \geq 0$*, where* $C_1(u_0)$ *is a constant depending on* u_0*, and*

(iii) $\int_0^{z_0} |\partial_z(b(z)\,\tilde{u}(z,t))|\,\Psi(z)\,dz \leq C_2(u_0)$ *for all* $t \geq 0$*.*

Proof. This proof follows the proof of [83, Theorem 4.5].

(i) We choose $H(h) = (|h| - C)_+$, where $(\cdot)_+$ denotes the positive part. Therefore, by Lemma 3.43,

$$\begin{aligned}\frac{d}{dt}\mathcal{H}_\Psi(\tilde{u}|\mathcal{U}) &= \frac{d}{dt}\int_0^{z_0} \Psi(z)\mathcal{U}(z)\left(\frac{|\tilde{u}(z,t)|}{\mathcal{U}(z)} - C\right)_+ dz\\ &= \frac{d}{dt}\int_0^{z_0} \Psi(z)\, \left(|\tilde{u}(z,t)| - C\mathcal{U}(z)\right)_+ dz \le 0.\end{aligned}$$

Hence,

$$0 \le \int_0^{z_0} \Psi(z)\, \left(|\tilde{u}(z,t)| - C\mathcal{U}(z)\right)_+ dz \le \int_0^{z_0} \Psi(z) \left(|\tilde{u}(z,0)| - C\mathcal{U}(z)\right)_+ dz = 0$$

and because $\Psi > 0$ a.e., we have $\left(|\tilde{u}(z,t)| - C\mathcal{U}(z)\right)_+ = 0$ for a.e. z. Therefore, $|\tilde{u}(z,t)| \le C\mathcal{U}(z)$ for a.e. $z \in [0, z_0]$ and for every $t \ge 0$.

(ii) Recall that $\tilde{u}$ is a solution to

$$\begin{aligned}&\partial_t\tilde{u}(z,t) + \partial_z(b(z)\,\tilde{u}(z,t)) =\\ &\qquad = -\left(\beta(z) + \mu(z) + \lambda\right)\tilde{u}(z,t) + \int_z^{z_0} \beta(z')\, k(z,z')\, \tilde{u}(z',t)\, dz'.\end{aligned}$$

By differentiation in time t, we obtain that $q(z,t) := \partial_t\tilde{u}(z,t)$ also satisfies this equation. Therefore, we can apply the contraction principle from Lemma 3.44 to the solution q to conclude

$$\int_0^{z_0} |q(z,t)|\, \Psi(z)\, dz \le \int_0^{z_0} |q(z,0)|\, \Psi(z)\, dz.$$

By the definition of q we have

$$\begin{aligned}q(z,0) &= \partial_t\tilde{u}(z,0)\\ &= -\partial_z(b(z)\,u_0(z)) - \left(\beta(z) + \mu(z) + \lambda\right)u_0(z) + \int_z^{z_0} \beta(z')\, k(z,z')\, u_0(z')\, dz.\end{aligned}$$

Next, we use the assumption on u_0 to estimate the right hand side and the fact that $\mathcal{U}$ is a solution to (3.41) to obtain

$$\begin{aligned}|q(z,0)| &\le \left|\frac{d}{dz}(b(z)\,u_0(z))\right| + |\beta(z) + \mu(z) + \lambda|\, C\,\mathcal{U}(z) + \int_z^{z_0} \beta(z')k(z,z')C\,\mathcal{U}(z')\, dz\\ &\le \left|\frac{d}{dz}(b(z)\,u_0(z))\right| + 2\,|\beta(z) + \mu(z) + \lambda|\, C\,\mathcal{U}(z) + C\left|\frac{d}{dz}\,(b(z)\mathcal{U}(z))\right|.\end{aligned}$$

Therefore,

$$\int_0^{z_0} |q(z,0)|\, \Psi(z)\, dz \le \int_0^{z_0} \left[\left|\frac{d}{dz}(b(z)\,u_0(z))\right| + C\left|\frac{d}{dz}(b(z)\mathcal{U}(z))\right|\right] \Psi(z)\, dz$$

$$
\begin{aligned}
&+ 2C\Big(\overline{\beta} + \overline{\mu} + |\lambda|\Big) \\
&\leq C_1(u_0) < \infty,
\end{aligned}
$$

where $C_1(u_0) > 0$ is some constant depending on the initial condition u_0. In the last step we have used that $\frac{d}{dz}(b(z)u_0(z))$ and $\frac{d}{dz}(b(z)\,\mathcal{U}(z)) \in L^1((0,z_0),\Psi(z)\,dz)$, by assumption. Overall, we have

$$
\int_0^{z_0} |\partial_t \tilde{u}(z,t)|\,\Psi(z)\,dz = \int_0^{z_0} |q(z,t)|\,\Psi(z)\,dz \leq \int_0^{z_0} |q(z,0)|\,\Psi(z)\,dz \leq C_1(u_0).
$$

(iii) Since $\tilde{u}$ is a solution to (3.43), we have that

$$
\begin{aligned}
\partial_z(b(z)\,\tilde{u}(z,t)) = &-\partial_t \tilde{u}(z,t) - (\beta(z) + \mu(z) + \lambda)\,\tilde{u}(z,t) \\
&+ \int_0^{z_0} \beta(z')\,k(z,z')\,\tilde{u}(z',t)\,dz'.
\end{aligned}
$$

We take the absolute value, multiply with Ψ, and integrate over z from 0 to z_0 and obtain with (i) and (ii) similar to the above calculation

$$
\begin{aligned}
\int_0^{z_0} \left|\frac{d}{dz}(b(z)\,\tilde{u}(z,t))\right| \Psi(z)\,dz &\leq \int_0^{z_0} |\partial_t \tilde{u}(z,t)|\,\Psi(z)\,dz + 2C\left(\overline{\beta} + \overline{\mu} + |\lambda|\right) \\
&\quad + C\int_0^{z_0} \left|\frac{d}{dz}(b(z)\,\mathcal{U}(z))\right| \Psi(z)\,dz \\
&\leq C_2(u_0).
\end{aligned}
$$

This finishes the proof. ☐

Finally, we can show the main theorem of this section on convergence of any solution to the eigensolution $\mathcal{U}$.

Theorem 3.46. *If the conditions of Lemma 3.45 hold and there exists a continuously differentiable function* $\Gamma : [0,z_0] \to [0,\infty)$ *such that* $\Gamma(I) = [0,z_0]$ *for some interval* $I = [0,a] \subseteq [0,z_0]$*,*

$$
\{(z,\Gamma(z)),\ z \in I\} \subseteq \operatorname*{supp}_{[0,z_0]\times[0,z_0]} k(z,z'), \text{ and } b(z)\,\Gamma'(z) \neq b(\Gamma(z)) \text{ for a.e. } z \in I, \tag{3.45}
$$

hold, then solutions to (3.18) *tend to a steady state as with* $m := \int_0^{z_0} u_0(z)\,\Psi(z)\,dz$ *it holds that*

$$
\lim_{t\to\infty} \int_0^{z_0} \Big|u(z,t)\,e^{-\lambda t} - m\,\mathcal{U}(z)\Big|\,b(z)\,\Psi(z)\,dz = 0.
$$

Remark 3.47. Condition (3.45) in Theorem 3.46 is a non-degeneracy condition on the support of the plasmid segregation kernel k. It holds, for example, for logistic plasmid segregation and a scalable kernel, where $\Phi : [0,1] \to \mathbb{R}_{\geq 0}$ satisfies:

$$\text{there are constants } 0 < \delta_1 < \delta_2 < 1 \text{ and } c > 0 \text{ such that } \Phi(x) \geq c \text{ for all } x \in [\delta_1, \delta_2]$$

(see [70, Remark 4.4]) because then there is some $a > 1$ such that $\Gamma(z) = az$ satisfies $\Gamma([0, \frac{z_0}{a}]) = [0, z_0]$, the graph of $\Gamma(z)$ for $z \in I = [0, \frac{z_0}{a}]$ is a subset of the support of k, and $\Gamma'(z) = a > \frac{a(z_0 - az)}{z_0 - z} = \frac{b(\Gamma(z))}{b(z)}$ for all $z \in I$.

Proof. This proof is based on the proofs of [83, Theorem 4.7] and [70, Theorems 3.2, 4.3]. The proof consists of four steps. In the first and second step, we show convergence results. In Step 3, we show that the limit obtained in Step 2 can be written as $m\, b(z) \mathcal{U}(z)$. Finally, we combine Steps 1 to 3 to finish the proof.

Step 1: Convergence of $b(z)\, \tilde{u}_n(z,t)$

If $u(z,t)$ is a solution to (3.18), then $\tilde{u}(z,t) := u(z,t)\, e^{-\lambda t}$ is a solution to (3.43). We introduce the sequence $\tilde{u}_n(z,t) := \tilde{u}(z, t + t_n)$ where $(t_n)_{n \in \mathbb{N}}$ is a sequence with $t_n \geq 0$ and $t_n \xrightarrow{n \to \infty} \infty$.

We define $\tilde{v}_n(z,t) := b(z)\, \tilde{u}_n(z,t)$ for every $n \in \mathbb{N}$. Then, $\tilde{v}_n(z,t)$ is a solution to

$$\begin{cases} \partial_t \tilde{v}(z,t) + b(z) \partial_z \tilde{v}(z,t) = -(\beta(z) + \mu(z) + \lambda) \tilde{v}(z,t) + b(z) \int\limits_z^{z_0} \beta(z') k(z,z') \dfrac{\tilde{v}(z',t)}{b(z')}\, dz', \\ \tilde{v}(0,t) = 0 \quad \text{for all } t \geq 0, \qquad \tilde{v}(z,0) = b(z)\, u_0(z) \quad \text{for all } z \in (0, z_0). \end{cases} \tag{3.46}$$

By Lemma 3.45, it holds that

$$|\tilde{v}_n(z,t)| = |b(z)\, \tilde{u}_n(z,t)| \leq \|b\|_\infty |\tilde{u}(z, t + t_n)| \leq \|b\|_\infty\, C \mathcal{U}(z)$$

for all $t \geq 0$ and $n \in \mathbb{N}$,

$$\begin{aligned} \int\limits_0^{z_0} |\partial_t \tilde{v}_n(z,t)|\, \Psi(z)\, dz = \int\limits_0^{z_0} |\partial_t \left(b(z)\, \tilde{u}_n(z,t) \right)| \, \Psi(z)\, dz &\leq \|b\|_\infty \int\limits_0^{z_0} |\partial_t \tilde{u}_n(z,t)|\, \Psi(z)\, dz \\ &\leq \|b\|_\infty\, C_1(u_0) < \infty, \end{aligned}$$

and

$$\int\limits_0^{z_0} |\partial_z \tilde{v}_n(z,t)|\, \Psi(z)\, dz = \int\limits_0^{z_0} |\partial_z \left(b(z)\, \tilde{u}_n(z,t) \right)| \, \Psi(z)\, dz \leq C_2(u_0) < \infty.$$

This means that we have bounded variation regularity of the solution $\tilde{v}_n$ to (3.46) which gives local strong compactness of families of solutions to (3.46) (see [83, p. 91]). Therefore, there is a subsequence that we still denote by $\tilde{v}_n$ such that for all $T > 0$

$$\tilde{v}_n(z,t) \xrightarrow{n \to \infty} h(z,t) \quad \text{strongly in } L^1((0, z_0) \times [0, T]).$$

Then, $h(z,t)$ is also a solution to (3.46), and it holds that $|h(z,t)| \leq C \mathcal{U}(z)$ for some $C > 0$ due to $|\tilde{v}_n(z,t)| \leq \|b\|_\infty\, C \mathcal{U}(z)$ for all $t \geq 0$.

Step 2: Convergence of $\mathcal{H}_{\tilde\Psi}(g|\,\mathcal{V})(t)$ and $\tilde{\mathcal{D}}_{\tilde\Psi}(g|\,\mathcal{V})(t)$
With $v(z,t)=b(z)\,u(z,t)$, $\mathcal{V}(z)=b(z)\mathcal{U}(z)$, $\tilde\Psi(z)=\frac{\Psi(z)}{b(z)}$, and $\tilde v(z,t)=b(z)\,\tilde u(z,t)$ we can show exactly as before (see Theorem 3.42 and Lemma 3.43) that

$$\frac{d}{dt}\mathcal{H}_{\tilde\Psi}(\tilde v|\,\mathcal{V})(t)=\frac{d}{dt}\int_0^{z_0}\tilde\Psi(z)\,\mathcal{V}(z)\,H\left(\frac{\tilde v(z,t)}{\mathcal{V}(z)}\right)dz=-\tilde{\mathcal{D}}_{\tilde\Psi}(\tilde v|\,\mathcal{V})(t)\le 0,$$

where

$$\begin{aligned}\tilde{\mathcal{D}}_{\tilde\Psi}(\tilde v|\,\mathcal{V})(t):=\int_0^{z_0}\int_0^{z_0}\frac{b(z)}{b(z')}\,\beta(z')\,k(z,z')\,\tilde\Psi(z)\,\mathcal{V}(z')\Bigg[&H\left(\frac{\tilde v(z',t)}{\mathcal{V}(z')}\right)-H\left(\frac{\tilde v(z,t)}{\mathcal{V}(z)}\right)\\&+H'\left(\frac{\tilde v(z,t)}{\mathcal{V}(z)}\right)\left[\frac{\tilde v(z,t)}{\mathcal{V}(z)}-\frac{\tilde v(z',t)}{\mathcal{V}(z')}\right]\Bigg]dz'\,dz.\end{aligned}$$

Thus, for every solution g to (3.46) and every non-negative, convex, and a.e. differentiable function H, the function $\mathcal{H}_{\tilde\Psi}(g|\,\mathcal{V})(t)$ is monotonously decreasing and bounded below by 0 (as $\tilde\Psi$, $\mathcal{V}$, and H are non-negative). Therefore, $\mathcal{H}_{\tilde\Psi}(g|\,\mathcal{V})(t)$ converges to some $L\ge 0$ for $t\to\infty$ and $\tilde{\mathcal{D}}_{\tilde\Psi}(g|\,\mathcal{V})(t)=-\frac{d}{dt}\mathcal{H}_{\tilde\Psi}(g|\,\mathcal{V})(t)\xrightarrow{t\to\infty}0$.

Step 3: Solutions g to (3.46) *with $\int_0^\infty\tilde{\mathcal{D}}_{\tilde\Psi}(g|\,\mathcal{V})(t)\,dt=0$ satisfy $g(z,t)=m\,b(z)\mathcal{U}(z)$*
Next, we want to characterize solutions g to (3.46) with $\int_0^\infty\tilde{\mathcal{D}}_{\tilde\Psi}(g|\,\mathcal{V})(t)\,dt=0$. With the choice $H(s)=s^2$ (for the remainder of this proof we always make this choice for H) and the definition of $\tilde{\mathcal{D}}_{\tilde\Psi}(g|\,\mathcal{V})(t)$, we obtain that

$$\begin{aligned}0&=\int_0^\infty\tilde{\mathcal{D}}_{\tilde\Psi}(g|\,\mathcal{V})(t)\,dt\\&=\int_0^\infty\int_0^{z_0}\int_0^{z_0}\frac{b(z)}{b(z')}\,\beta(z')\,k(z,z')\,\tilde\Psi(z)\,\mathcal{V}(z')\left[\frac{g(z,t)}{\mathcal{V}(z)}-\frac{g(z',t)}{\mathcal{V}(z')}\right]^2dz'dzdt.\end{aligned}$$

Recall that $\underline{\beta}>0$, $\Psi>0$, $\mathcal{U}>0$, and for all z, $z'\in(0,z_0)$ it holds that $\frac{b(z)}{b(z')}>0$. Therefore, for a.e. $t>0$ and $(z,z')\in\operatorname{supp}(k)$ it holds that

$$\frac{g(z,t)}{\mathcal{V}(z)}=\frac{g(z',t)}{\mathcal{V}(z')}.\tag{3.47}$$

If we define $\psi(z,t):=\frac{g(z,t)}{\mathcal{V}(z)}$, then for a.e. $t>0$, $z\in(0,z_0)$

$$\psi(z,t)=\psi(\Gamma(z),t).$$

As in the proof of Theorem 3.42, it is straightforward to show that for a.e. $t>0$ and $z\in(0,z_0)$

$$\partial_t\psi(z,t)+b(z)\,\partial_z\psi(z,t)=0,\tag{3.48}$$

where we use (3.47) and the same rescaling as before.

We aim at showing that $\psi(z,t)$ is constant and therefore use that

$$\left(\partial_t\psi\right)(z,t)=\left(\partial_t\psi\right)(\Gamma(z),t)\quad\text{and}\quad\left(\partial_z\psi\right)(z,t)=\Gamma'(z)\left(\partial_z\psi\right)(\Gamma(z),t).$$

Hence, for a.e. $t > 0$ and $z \in (0, z_0)$

$$(\partial_t \psi)(\Gamma(z), t) + b(z)\, \Gamma'(z)\; (\partial_z \psi)(\Gamma(z), t) = 0$$

and

$$(\partial_t \psi)(\Gamma(z), t) + b(\Gamma(z))\, (\partial_z \psi)(\Gamma(z), t) = 0.$$

Overall, it holds that

$$\Big(\Gamma'(z)\, b(z) - b(\Gamma(z))\Big)\, (\partial_z \psi)(\Gamma(z), t) = 0.$$

As by assumption $b(z)\, \Gamma'(z) \neq b(\Gamma(z))$ for a.e. $z \in I$, it holds for a.e. $t > 0$ and $z \in I$ that

$$(\partial_z \psi)(\Gamma(z), t) = 0.$$

Since Γ is a continuously differentiable function it has the Luzin N-property which means it maps sets of measure zero to sets of measure zero (see Definition 2.4 and Example 2.5). Therefore, $(\partial_z \psi)(z, t) = 0$ for a.e. $z \in (0, z_0)$ and ψ is constant for a.e. $z \in (0, z_0)$. Equation (3.48) implies that ψ is also constant for a.e. $t > 0$.

By definition of ψ it follows that there is some constant $c > 0$ such that a solution g to (3.46) with $\int_0^\infty \tilde{\mathcal{D}}_{\tilde{\Psi}}(g|\, \mathcal{V})(t)\, dt = 0$ satisfies $g(z,t) = c\, \mathcal{V}(z) = c\, b(z) \mathcal{U}(z)$ for a.e. $t > 0$ and $z \in (0, z_0)$. Multiplying $g(z,t) = c\, \mathcal{V}(z)$ with $\tilde{\Psi}(z)$, integrating over z, and once again rescaling yields

$$\begin{aligned} c = c \int_0^{z_0} \mathcal{U}(z)\, \Psi(z)\, dz &= c \int_0^{z_0} \frac{\mathcal{V}(z)}{b(z)}\, b(z)\, \tilde{\Psi}(z)\, dz = \int_0^{z_0} c\, \mathcal{V}(z)\, \tilde{\Psi}(z)\, dz = \int_0^{z_0} g(z,t)\, \tilde{\Psi}(z)\, dz \\ &= \int_0^{z_0} b(z)\, \tilde{u}(z,t)\, \frac{\Psi(z)}{b(z)}\, dz = \int_0^{z_0} \tilde{u}(z,t)\, \Psi(z)\, dz = m. \end{aligned}$$

Therefore, a solution g to (3.46) with $\int_0^\infty \tilde{\mathcal{D}}_{\tilde{\Psi}}(g|\, \mathcal{V})(t)\, dt = 0$ it holds that $g(z,t) = m\, \mathcal{V}(z) = m\, b(z) \mathcal{U}(z)$ for a.e. $t > 0$ and $z \in (0, z_0)$.

Step 4: Conclusion

Finally, we want to combine Steps 1, 2, and 3. Consider the sequence $\tilde{v}_n(z,t)$ from Step 1 and define the function $f : \mathbb{N} \times \mathbb{R}_{>0} \to \mathbb{R}$,

$$f(n, T) := \int_0^T \tilde{\mathcal{D}}_{\tilde{\Psi}}(\tilde{v}_n|\, \mathcal{V})(t)\, dt.$$

For every $T > 0$, by Step 1, it holds that

$$\lim_{n\to\infty} f(n, T) = \int_0^T \tilde{\mathcal{D}}_{\tilde{\Psi}}(h|\, \mathcal{V})(t)\, dt < \infty$$

and for every $n \in \mathbb{N}$ it holds that

$$\lim_{T\to\infty} f(n, T) = \int_0^\infty \tilde{\mathcal{D}}_{\tilde{\Psi}}(\tilde{v}_n|\, \mathcal{V})(t)\, dt =: \tilde{g}(n) < \infty,$$

since with $\frac{d}{dt}\mathcal{H}_{\tilde{\Psi}}(\tilde{v}_n|\,\mathcal{V})(t) = -\tilde{\mathcal{D}}_{\tilde{\Psi}}(\tilde{v}_n|\,\mathcal{V})(t)$,

$$\int_0^\infty \tilde{\mathcal{D}}_{\tilde{\Psi}}(\tilde{v}_n|\,\mathcal{V})(t)\,dt = \mathcal{H}_{\tilde{\Psi}}(\tilde{v}_n|\,\mathcal{V})(0) - \lim_{t\to\infty}\mathcal{H}_{\tilde{\Psi}}(\tilde{v}_n|\,\mathcal{V})(t) = \mathcal{H}_{\tilde{\Psi}}(\tilde{v}_n|\,\mathcal{V})(0) - L < \infty,$$

for every solution $\tilde{v}_n$ to (3.46) by Step 2. Furthermore, it holds that

$$\begin{aligned}
\lim_{T\to\infty}\sup_{n\in\mathbb{N}}|f(n,T)-\tilde{g}(n)| &= \lim_{T\to\infty}\sup_{n\in\mathbb{N}}\left|\int_0^T \tilde{\mathcal{D}}_{\tilde{\Psi}}(\tilde{v}_n|\,\mathcal{V})(t)\,dt - \int_0^\infty \tilde{\mathcal{D}}_{\tilde{\Psi}}(\tilde{v}_n|\,\mathcal{V})(t)\,dt\right| \\
&= \lim_{T\to\infty}\sup_{n\in\mathbb{N}}\left|\int_0^T \tilde{\mathcal{D}}_{\tilde{\Psi}}(\tilde{v}|\,\mathcal{V})(t+t_n)\,dt - \int_0^\infty \tilde{\mathcal{D}}_{\tilde{\Psi}}(\tilde{v}|\,\mathcal{V})(t+t_n)\,dt\right| \\
&= \lim_{T\to\infty}\sup_{n\in\mathbb{N}}\left|\int_{t_n}^{T+t_n} \tilde{\mathcal{D}}_{\tilde{\Psi}}(\tilde{v}|\,\mathcal{V})(t)\,dt - \int_{t_n}^\infty \tilde{\mathcal{D}}_{\tilde{\Psi}}(\tilde{v}|\,\mathcal{V})(t)\,dt\right| \\
&= \lim_{T\to\infty}\sup_{n\in\mathbb{N}}\left|\int_{T+t_n}^{\infty} \tilde{\mathcal{D}}_{\tilde{\Psi}}(\tilde{v}|\,\mathcal{V})(t)\,dt\right| \\
&= \lim_{T\to\infty}\int_{T+\inf_{n\in\mathbb{N}} t_n}^{\infty} \tilde{\mathcal{D}}_{\tilde{\Psi}}(\tilde{v}|\,\mathcal{V})(t)\,dt = 0.
\end{aligned}$$

Therefore, $f(n,T) \xrightarrow{T\to\infty} \tilde{g}(n)$ uniformly on $\mathbb{N}$ and by the Moore-Osgood Theorem (see, e.g., [41, p. 100]) it holds that $\lim\limits_{n\to\infty}\lim\limits_{T\to\infty} f(n,T) = \lim\limits_{T\to\infty}\lim\limits_{n\to\infty} f(n,T)$, i.e.,

$$\int_0^\infty \tilde{\mathcal{D}}_{\tilde{\Psi}}(\tilde{v}_n|\,\mathcal{V})(t)\,dt \xrightarrow{n\to\infty} \int_0^\infty \tilde{\mathcal{D}}_{\tilde{\Psi}}(h|\,\mathcal{V})(t)\,dt.$$

On the other hand, it also holds that

$$\int_0^\infty \tilde{\mathcal{D}}_{\tilde{\Psi}}(\tilde{v}_n|\,\mathcal{V})(t)\,dt = \int_0^\infty \tilde{\mathcal{D}}_{\tilde{\Psi}}(\tilde{v}|\,\mathcal{V})(t+t_n)\,dt = \int_{t_n}^\infty \tilde{\mathcal{D}}_{\tilde{\Psi}}(\tilde{v}|\,\mathcal{V})(t)\,dt \xrightarrow{n\to\infty} 0.$$

Since the limit is unique, we have that h is a solution to (3.46) and it satisfies $\int_0^\infty \tilde{\mathcal{D}}_{\tilde{\Psi}}(h|\,\mathcal{V})(t)\,dt = 0$. Then, due to Step 3, it follows that $h(t,z) = m\,b(z)\,\mathcal{U}(z)$ a.e. and therefore

$$b(z)\,\tilde{u}(z,t) = \tilde{v}(z,t) \xrightarrow{t\to\infty} m\,b(z)\,\mathcal{U}(z) \quad \text{in } L^1((0,z_0),\,\Psi(z)\,dz)$$

or equivalently

$$\tilde{u}(z,t) \xrightarrow{t\to\infty} m\,\mathcal{U}(z) \quad \text{in } L^1((0,z_0),\,b(z)\,\Psi(z)\,dz).$$

This finishes the proof. □

Overall, we have shown that the eigensolution $\mathcal{U}$ is asymptotically stable if there are unique solutions to the eigenproblem (3.41) and the dual eigenproblem satisfying Assumption **(A9')** and the assumptions in Theorem 3.46 on the initial condition u_0, the eigenfunction $\mathcal{U}$, the dual eigenfunction Ψ, and the support of k are satisfied. However, we do not know that these assumptions are indeed satisfied. We only know that a strictly positive eigenfunction $\mathcal{U}$ exists in the special case of constant β and μ and logistic plasmid reproduction b (see Section 3.3.3) and that there is a dual eigenfunction Ψ for constant β and μ (see Lemma 3.41).

3.4 Numerical construction of the eigensolution

3.4.1 Constant cell division and death rate

This section is based on [96].

We can numerically construct the eigensolution $\mathcal{U}$ for the singular VGT model with constant cell division and death rate, logistic plasmid reproduction, and scalable plasmid segregation kernel with the same method that we have used in the proof of Lemma 3.27. In the proof, we have used Banach's Fixed Point Theorem to show existence of a unique solution $g \in \mathcal{C}^0((0, z_0]) \cap \mathcal{C}^1((0, z_0))$ to (3.26) for every $\alpha > 0$. We also use that we know due to Theorem 3.28 and Lemma 3.21 that $\lambda = \beta - \mu$ and therefore $\alpha = \alpha_0 = \frac{2\beta}{b_0}$.

We have used the software R [87] for the numerical construction of the function g. Following the proof of Lemma 3.27, the solution g to (3.26) was simulated iteratively: in each step, we simulated g on the interval $[a-\delta, a]$ where a is given from the previous step (in the first step $a = z_0$) and we chose $\delta > 0$ such that the operators T and T_a in the proof of Lemma 3.27 are contractions on $\mathcal{C}^0([a-\delta, a])$, i.e.,

$$\delta = \begin{cases} \underset{y\in(0,a)}{\arg\min} \left| \frac{z_0}{|\alpha_0-1|a} \left\|\Phi\right\|_\infty \left| \frac{a}{a-y} - \left(\frac{a}{a-y}\right)^{\alpha_0} \right| - 1 \right| + 10^{-5}, & \text{if } \alpha_0 \neq 1, \\ \underset{y\in(0,a)}{\arg\min} \left| z_0 \left\|\Phi\right\|_\infty \log\left(\frac{a}{a-y}\right) \frac{1}{a-y} - 1 \right| + 10^{-5}, & \text{if } \alpha_0 = 1. \end{cases}$$

For all points x, which were chosen equidistant between $a-\delta$ and a, we set $g_0(x) := g(a)$, where $g(a)$ is known from the previous step ($g(a) = g(z_0) = 1$ in the first step). For $n \in \mathbb{N}_0$, the iteration

$$\begin{aligned} g_{n+1}(x) := &\frac{\alpha_0 z_0}{x^{\alpha_0}} \int_a^x \left(\frac{z}{z_0 - z}\right)^{\alpha_0} \int_z^a \Phi\left(\frac{z}{z'}\right) (z')^{-2} (z_0 - z')^{\alpha_0 - 1} g_n(z')\, dz' dz + \left(\frac{a}{x}\right)^{\alpha_0} g(a) \\ &+ \frac{\alpha_0 z_0}{x^{\alpha_0}} \int_a^x \left(\frac{z}{z_0 - z}\right)^{\alpha_0} \int_a^{z_0} \Phi\left(\frac{z}{z'}\right) (z')^{-2} (z_0 - z')^{\alpha_0 - 1} g_n(z')\, dz' dz, \end{aligned}$$

where the last summand was omitted for the first step where $a = z_0$. For the integration we used the R function `integrate`.

The choice of δ guarantees that this iteration converges on $[a-\delta, a]$ as T_a (defined as in the proof of Lemma 3.27, i.e., $T_a[g_n]$ is the first summand in the above iteration) is a contraction. The function g_n is updated until either

$$\max_{x\in[a-\delta,a]} |g_n(x) - g_{n-1}(x)| < 10^{-6}$$

or $n = 100$. Then, we define $g(x) := g_n(x)$ for $x \in [a - \delta, a]$.

We repeated the same procedure for the next steps, with $a := a - \delta$ until either $a - \delta < 0.005$ or we have reached the maximal number of iterations, viz. 1000. In this way, we numerically constructed a solution $g \in \mathcal{C}^0([m, z_0])$ for some $m > 0$. The function g was rescaled to obtain the eigenfunction $\mathcal{U}$ using

$$\mathcal{U}(z) = \frac{v(z)}{b(z)} = \frac{(z_0 - z)^{\alpha_0} g(z)}{b(z)}.$$

We normalized $\mathcal{U}$ such that $\int_{0.005}^{z_0} \mathcal{U}(z)\, dz = 1$, where we numerically determined the integral using again the function `integrate`.

So far, we have only considered the case of the singular VGT model for the numerical construction of the eigenfunction. However, we can use the very same method to construct a solution $\mathcal{U}$ to the regular VGT model with $k_0 \equiv 0$ on the interval $[m, z_0]$ (see [96, Section 5]).

In Figure 3.8, numerically constructed eigenfunctions $\mathcal{U}$ for different plasmid segregation kernels, i.e., different Φ, are shown. In the case $\Phi \equiv 1$ we know the exact solution (see Example 3.24) and therefore plotted the exact solution for comparison. The exact solution and the numerically constructed eigenfunction agree well (see Figure 3.8, upper right figure).

For each of the three different plasmid segregation modes, viz. uniform, unimodal, and bimodal plasmid segregation, the corresponding eigenfunction $\mathcal{U}$ has the same shape (see Figure 3.9 for a comparison of the eigenfunctions). It has two poles, one at zero and the other at z_0, the maximal number of plasmids in a bacterium (this pole is of lower order than the pole at zero), between these two poles the eigenfunction is almost constant. In Table 3.1 the percentage of bacteria that contain a certain fraction of the maximal plasmid load is shown.

	$\Phi(\xi) = 1$	$\Phi(\xi) = 30\,\xi^2\,(1-\xi)^2$	$\Phi(\xi) = 120\,\xi\,(\frac{1}{2}-\xi)^2\,(1-\xi)$
$0 < z < \frac{1}{3}z_0$	64.56%	51.10%	68.39%
$\frac{1}{3}z_0 < z < \frac{2}{3}z_0$	18.93%	28.37%	15.79%
$\frac{2}{3}z_0 < z < z_0$	16.51%	20.53%	15.82%

Table 3.1: The percentage of bacteria with less than a third of the maximal plasmid load, between one and two thirds of the maximal plasmid load, and with at least two thirds of the maximal plasmid load, respectively, for three different scalable plasmid reproduction kernels, viz. $\Phi(\xi) = 1$, $\Phi(\xi) = 30\,\xi^2\,(1-\xi)^2$, and $\Phi(\xi) = 120\,\xi\,(\frac{1}{2}-\xi)^2\,(1-\xi)$. The fractions are calculated from the numerically constructed eigenfunction shown in Figure 3.8.

These numerically constructed eigenfunctions indicate that in the long run the plasmid segregation does not influence the distribution of plasmids in a bacterial population. Therefore, we would expect that in the long run a large proportion of bacteria will

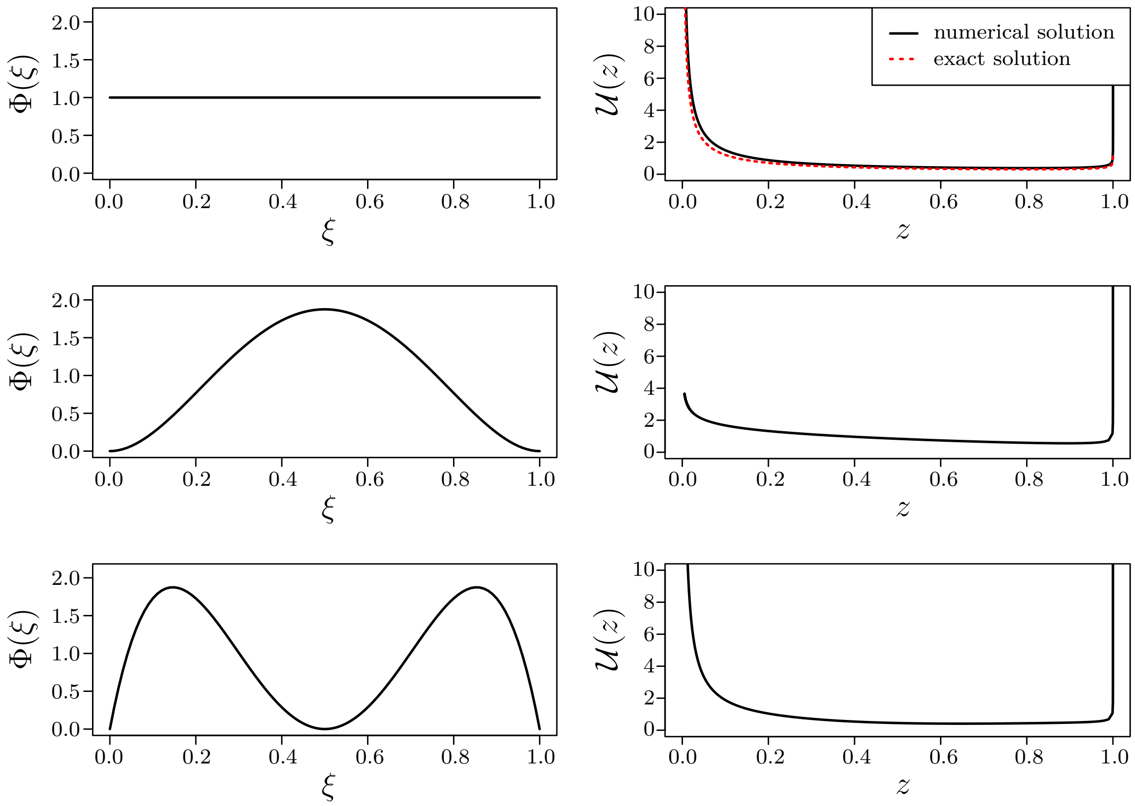


Figure 3.8: Numerical constructions of the eigenfunction $\mathcal{U}$ for $\beta = 0.4/h$, $\mu = 0.1/h$, $b(z) = z(1-z)/h$, $\alpha = 0.8$, and different Φ. *Left:* Different plasmid segregation kernels Φ, from top to bottom: $\Phi(\xi) = 1$, $\Phi(\xi) = 30\,\xi^2\,(1-\xi)^2$, and $\Phi(\xi) = 120\,\xi\,(\frac{1}{2}-\xi)^2\,(1-\xi)$. *Right:* The eigenfunction $\mathcal{U}$ corresponding to the function Φ on the left-hand side. For $\Phi \equiv 1$, the exact solution to $\mathcal{U}$ is plotted red (dotted line) for comparison.

have either no or only very few plasmids independently of how plasmids are distributed at cell division.

Eigensolutions were also numerically constructed for different β but same Φ, μ, and b (see Figure 3.10 and Table 3.2). In this case, the numerical eigenfunctions indicate that with increasing cell division rate the fraction of bacteria losing the plasmid or having only few plasmids increases. This is plausible as we would expect that if bacteria divide faster but plasmids reproduce at the same rate, then more bacteria will lose plasmids in the long run. Furthermore, we find that the eigenfunction $\mathcal{U}$ behaves differently at the maximal plasmid load z_0 for different β. The eigenfunctions we constructed here satisfy $\mathcal{U}(z) \sim (z_0 - z)^{\alpha-1}$ at z_0 (see Theorem 3.35 and Corollary 3.36). Hence, it follows that:

- If $\alpha < 1$, then $\lim\limits_{z \to z_0^-} \mathcal{U}(z) = \infty$.
- If $\alpha = 1$, then $\lim\limits_{z \to z_0^-} \mathcal{U}(z) = C \in (0, \infty)$.
- If $\alpha > 1$, then $\lim\limits_{z \to z_0^-} \mathcal{U}(z) = 0$.

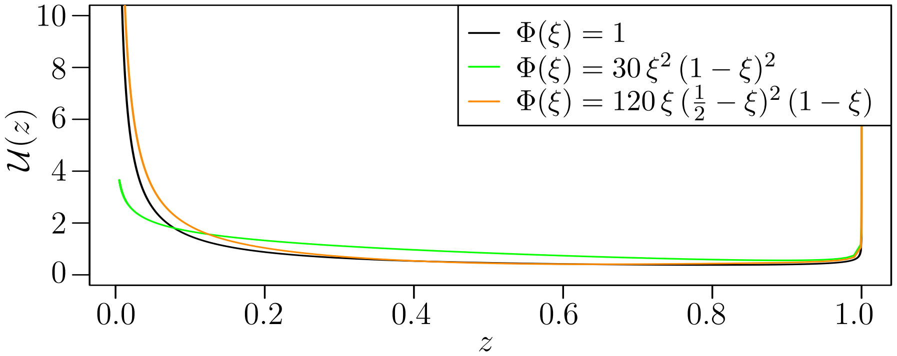


Figure 3.9: Comparison of the numerically constructed eigenfunctions for $\beta = 0.4/h$, $\mu = 0.1/h$, $b(z) = z\,(1-z)/h$, $\alpha = 0.8$, and different kernels Φ: $\Phi(\xi) = 1$ (black), $\Phi(\xi) = 30\,\xi\,(1-\xi)$ (green), and $\Phi(\xi) = 120\,\xi\,(\frac{1}{2}-\xi)^2\,(1-\xi)$ (orange).

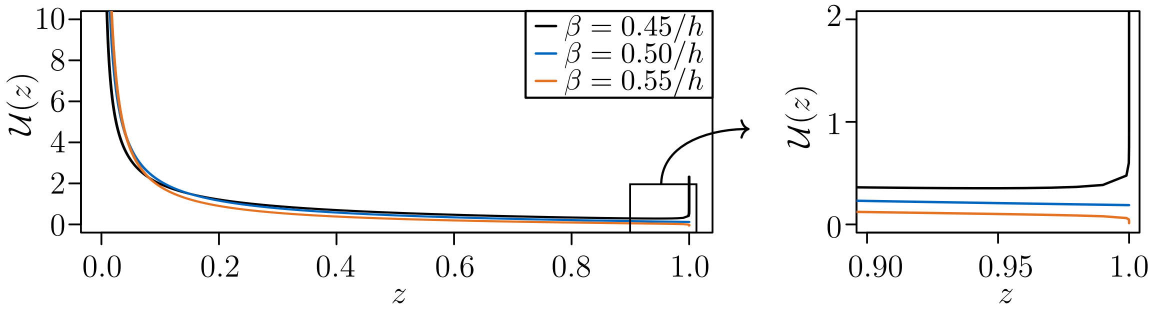


Figure 3.10: Numerically constructed eigenfunctions for $\Phi(\xi) = 6\xi(1-\xi)$, $\mu = 0.1/h$, $b(z) = z(1-z_0)/h$, and different β, viz. $\beta = 0.45/h$ (black), $0.5/h$ (blue), and $0.55/h$ (orange). The different cell division rates lead to different behavior of the eigenfunction $\mathcal{U}(z)$ at the maximal plasmid number z_0.

The numerically constructed eigenfunctions also show this behavior (see Figure 3.10 right-hand side). For $\beta < 0.5/h$ it holds that $\alpha = \frac{2\beta}{b_0} < 1$ and the eigenfunction hat a pole at z_0, for $\beta = 0.5/h$ the eigenfunction is constant at z_0, and for $\beta > 0.5/h$ it tends to zero for $z \to z_0^-$. This is in accordance with the Threshold Theorem for the distribution of plasmids at the maximal plasmid load obtained in [74].

Changing μ, the death rate of bacteria, affects the growth of the bacterial population as it grows exponentially with exponent $\lambda = \beta - \mu$. Moreover, numerically constructed eigensolutions are the same for different μ indicating that μ only influences the growth rate of bacteria but not the plasmid distribution.

3.4.2 General cell division and death rate

The above method for numerically constructing the eigenfunction $\mathcal{U}$ for the case of constant cell division and death rate can be extended to non-constant cell division and death rate. In this section, we aim at deriving a numerical scheme to numerically construct the eigenfunction $\mathcal{U}$ for the singular VGT model for more general cell division and death rate.

	$\beta = 0.45/h$	$\beta = 0.5/h$	$\beta = 0.55/h$
$0 < z < \frac{1}{3}z_0$	65.15%	73.72%	80.92%
$\frac{1}{3}z_0 < z < \frac{2}{3}z_0$	21.52%	13.47%	11.77%
$\frac{2}{3}z_0 < z < z_0$	13.33%	8.82%	5.61%

Table 3.2: The percentage of bacteria with less than a third of the maximal plasmid load, between one and two thirds of the maximal plasmid load, and with at least two thirds of the maximal plasmid load, respectively, for three cell division rates, viz. $\beta = 0.45/h$, $\beta = 0.5/h$, and $\beta = 0.55/h$. The fractions are calculated from the numerically constructed eigenfunction shown in Figure 3.10.

We consider the eigenproblem associated with the singular VGT model, i.e.,

$$\begin{cases} \dfrac{d}{dz}(b(z)\mathcal{U}(z)) = -\,(\beta(z)+\mu(z)+\lambda)\mathcal{U}(z) + \displaystyle\int_z^{z_0} \beta(z')\,k(z,z')\mathcal{U}(z')\,dz', \\ \lim\limits_{z\to 0^+} b(z)\mathcal{U}(z) = 0, \quad \mathcal{U}(z) > 0 \text{ for all } z \in (0,z_0), \quad \displaystyle\int_0^{z_0} \mathcal{U}(z)\,dz = 1. \end{cases} \tag{3.49}$$

Throughout this section, we make the following assumptions on the parameters: β and μ are continuous, i.e., **(A2')** and **(A3')** hold, the plasmid segregation kernel satisfies the consistency conditions **(A4')**, b is logistic **(A5')**, and

(A10') $-\,\partial^-(\beta(z)+\mu(z))|_{z=z_0} < \infty$.

(A11') There exists a $C > 0$ such that $k(z,z') \le \frac{C}{z'}$ for all $z \in (0,z')$, $z' \in (0,z_0]$.

Here, ∂^- denotes the left-sided partial derivative.

In this case, we do not know the eigenvalue λ as we did in the case of constant cell division and death rate (see Lemma 3.21). However, we have not used that we know λ in Section 3.3.2. Thus, we can at least derive a numerical scheme for the approximation of the eigenfunction in an analogous way. First, we rescale the eigenfunction.

Lemma 3.48. *There is a solution $(\lambda, \mathcal{U})$ with $\mathcal{U} \in \mathcal{C}^1((0,z_0))$ to the eigenproblem (3.49) if and only if there is a solution (λ, v) with $v \in \mathcal{C}^1((0,z_0))$ to*

$$\begin{cases} v'(z) = -\dfrac{\lambda+\beta(z)+\mu(z)}{b(z)}\,v(z) + \displaystyle\int_z^{z_0} \dfrac{\beta(z')\,k(z,z')}{b(z')}\,v(z')\,dz', \\ \lim\limits_{z\to 0^+} v(z) = 0, \quad v(z) \ge 0 \textit{ for all } z \in (0,z_0), \quad \displaystyle\int_0^{z_0} \dfrac{v(z)}{b(z)}\,dz = 1. \end{cases} \tag{3.50}$$

Proof. If $(\lambda, \mathcal{U})$ is a solution to (3.49), then (λ, v) with $v(z) := b(z)\mathcal{U}(z)$ is a solution to (3.50). Likewise, if (λ, v) is a solution to (3.50), then $(\lambda, \mathcal{U})$ with $\mathcal{U}(z) := \frac{v(z)}{b(z)}$ is a solution to (3.49). ☐

In Section 3.3.2, we used an explicit solution for another rescaling of the solution v to (3.50). Here, we do not have an explicit solution but we rescale nonetheless.

Lemma 3.49. *Let $c > 0$. If there is a solution (λ, g) with $g \in \mathcal{C}^1((0, z_0)) \cap \mathcal{C}^0([0, z_0])$ to*

$$\begin{cases} g'(z) = \left(c\,(z_0 - z)^{-1} - \dfrac{\lambda + \beta(z) + \mu(z)}{b(z)}\right) g(z) \\ \qquad\qquad + (z_0 - z)^{-c} \displaystyle\int_z^{z_0} \frac{\beta(z')\,k(z, z')}{b(z)}\,(z_0 - z')^c\, g(z')\,dz', \\ g(z_0) = 1,\ \lim\limits_{z \to 0^+} g(z) = 0,\ g(z) \geq 0 \text{ for all } z \in (0, z_0),\ \displaystyle\int_0^{z_0} \frac{(z_0 - z)^c g(z)}{b(z)} dz < \infty, \end{cases} \tag{3.51}$$

then (λ, v) with $v(z) := C\,(z_0 - z)^c\, g(z)$ for some $C > 0$ is a solution to (3.50) and $v \in \mathcal{C}^1((0, z_0))$.

Proof. It is a straightforward computation to show that if there is a solution g to (3.51), then $v(z) := C\,(z_0 - z)^c\, g(z)$ is a solution to (3.50). ☐

For the sake of brevity, we define

$$\alpha(\lambda, z) := -c\,(z_0 - z)^{-1} + \frac{\lambda + \beta(z) + \mu(z)}{b(z)} = -\frac{b_0\, c\, z - z_0\,(\lambda + \beta(z) + \mu(z))}{b_0\, z\,(z_0 - z)}.$$

We consider again the integro-differential equation for g together with the boundary condition $g(z_0) = 1$, i.e.,

$$\begin{cases} g'(z) = -\alpha(\lambda, z)\, g(z) + (z_0 - z)^{-c} \displaystyle\int_z^{z_0} \frac{\beta(z')\,k(z, z')}{b(z)}\,(z_0 - z')^c\, g(z')\,dz', \\ g(z_0) = 1. \end{cases} \tag{3.52}$$

Lemma 3.50. *Let $c = \frac{1}{b_0}\,(\lambda + \beta(z_0) + \mu(z_0))$. Then, for every $\lambda > -\big(\beta(z_0) + \mu(z_0)\big)$ there exists a unique solution $g \in \mathcal{C}^1((0, z_0)) \cap \mathcal{C}^0((0, z_0])$ to (3.52).*

Proof. Variation of parameters together with $g(z_0) = 1$ yields for $z \in (0, z_0]$

$$g(z) = \frac{z_0}{b_0} \int_{z_0}^{z} (z_0 - x)^{-c} \int_x^{z_0} \frac{\beta(z')\,k(x, z')}{z'}\,(z_0 - z')^{c-1} g(z')\,dz'\, e^{\int_z^x \alpha(\lambda, y)\,dy}\,dx + e^{\int_z^{z_0} \alpha(\lambda, y)\,dy}. \tag{3.53}$$

As $g(z_0) = 1$, it holds that $e^{\int_z^{z_0} \alpha(y)\,dy} < \infty$ for all $z \in (0, z_0)$ and therefore $\alpha(z)$ needs to be integrable at z_0. We have that

$$c = \frac{1}{b_0}(\lambda + \beta(z_0) + \mu(z_0)),$$

i.e. $c > 0$ if and only if $\lambda > -(\beta(z_0) + \mu(z_0))$. Therefore,

$$\begin{aligned}
\lim_{z \to z_0^-} \alpha(\lambda, z) &= \lim_{z \to z_0^-} -\frac{z(\lambda + \beta(z_0) + \mu(z_0)) - z_0(\lambda + \beta(z) + \mu(z))}{b_0 z(z_0 - z)} \\
&= \lim_{h \to 0^+} \frac{\lambda}{b_0(z_0 - h)} + \frac{z_0(\beta(z_0 - h) + \mu(z_0 - h)) - (z_0 - h)(\beta(z_0) + \mu(z_0))}{b_0(z_0 - h)h} \\
&= \frac{\lambda}{b_0 z_0} + \lim_{h \to 0^+} -\frac{z_0(\beta(z_0) - \beta(z_0 - h) + \mu(z_0) - \mu(z_0 - h))}{b_0(z_0 - h)h} \\
&\quad + \frac{\beta(z_0) + \mu(z_0)}{b_0 z_0} \\
&= \frac{\lambda + \beta(z_0) + \mu(z_0)}{b_0 z_0} - \frac{1}{b_0}\, \partial^-\left(\beta(z) + \mu(z)\right)\Big|_{z=z_0} < \infty,
\end{aligned}$$

as $-\,\partial^-\left(\beta(z) + \mu(z)\right)\big|_{z=z_0} < \infty$ by Assumption **(A10')**. Thus, $\alpha(\lambda, z)$ is bounded at z_0.

Let $a \in (0, z_0)$, $g \in \mathcal{C}^0([a, z_0])$ and define the operator $G : \mathcal{C}^0([a, z_0]) \to \mathcal{C}^0([a, z_0])$ by

$$G[g](z) := \frac{z_0}{b_0} \int_{z_0}^{z} (z_0 - x)^{-c} \int_{x}^{z_0} \frac{\beta(z')\, k(x, z')}{z'} \, (z_0 - z')^{c-1}\, g(z')\, dz'\, e^{\int_z^x \alpha(\lambda, y)\, dy}\, dx.$$

Using Assumption **(A11')** and

$$\alpha(\lambda, z) = \frac{1}{z}\, \frac{z_0\,(\lambda + \beta(z) + \mu(z)) - b_0\, c\, z}{b_0\,(z_0 - z)} \leq \frac{\tilde{c}}{z}$$

for all $z \in [0, z_0]$ and some $\tilde{c} > 0$, we estimate the supremum norm of $G[g](z)$ by

$$\begin{aligned}
\|G[g]\|_\infty &\leq \frac{z_0}{b_0}\, \|g\|_\infty\, \overline{\beta}\, C \sup_{z \in [a, z_0]} \left| \int_z^{z_0} (z_0 - x)^{-c}\, \frac{1}{x^2} \int_x^{z_0} (z_0 - z')^{c-1}\, dz'\, e^{\int_z^x \alpha(\lambda, y)\, dy}\, dx \right| \\
&\leq \frac{z_0\, \overline{\beta}\, C}{b_0\, c} \left(\frac{z_0}{a}\right)^{\tilde{c}} \|g\|_\infty \sup_{z \in [a, z_0]} \left(\int_z^{z_0} \frac{1}{x^2}\, dx \right) \\
&\leq \frac{z_0\, \overline{\beta}\, C}{b_0\, c} \left(\frac{z_0}{a}\right)^{\tilde{c}} \|g\|_\infty \sup_{z \in [a, z_0]} \left(\frac{1}{z} - \frac{1}{z_0} \right) \xrightarrow{a \to z_0^-} 0.
\end{aligned}$$

Therefore, G is a contraction on $\mathcal{C}^0([a, z_0])$ for $a \in (0, z_0)$ sufficiently large. By the Banach Fixed Point Theorem, the operator G has a unique fixed point in $\mathcal{C}^0([a, z_0])$. As the second term in (3.53) is bounded for $z \in [a, z_0]$, there is a unique solution $g \in \mathcal{C}^0([a, z_0])$ to (3.53).

We construct the solution to (3.52) iteratively. Let $a \in (0, z_0)$ such that there is a solution $g \in \mathcal{C}^0([a, z_0])$ to (3.52). Variation of parameters yields for $z \in (0, a]$

$$\begin{aligned}
g(z) = {} & \frac{z_0}{b_0} \int_a^z (z_0 - x)^{-c} \int_x^{z_0} \frac{\beta(z')\, k(x, z')}{z'}\, (z_0 - z')^{c-1}\, g(z')\, dz'\, e^{\int_z^x \alpha(\lambda, y)\, dy}\, dx \\
& + g(a)\, e^{\int_z^a \alpha(\lambda, y)\, dy}
\end{aligned}$$

$$
\begin{aligned}
&= \frac{z_0}{b_0}\int_a^z (z_0-x)^{-c}\int_x^a \frac{\beta(z')\,k(x,z')}{z'}\,(z_0-z')^{c-1}\,g(z')\,dz'\,e^{\int_z^x \alpha(\lambda,\,y)\,dy}\,dx \\
&\quad + \frac{z_0}{b_0}\int_a^z (z_0-x)^{-c}\int_a^{z_0} \frac{\beta(z')\,k(x,z')}{z'}\,(z_0-z')^{c-1}\,g(z')\,dz'\,e^{\int_z^x \alpha(\lambda,\,y)\,dy}\,dx \\
&\quad + g(a)\,e^{\int_z^a \alpha(\lambda,\,y)\,dy}.
\end{aligned} \tag{3.54}
$$

For $\delta \in (0,a)$ and $g \in \mathcal{C}^1([a-\delta,a])$ define the operator $G_a : \mathcal{C}^1([a-\delta,a]) \to \mathcal{C}^1([a-\delta,a])$ by

$$
G_a[g](z) := \frac{z_0}{b_0}\int_a^z (z_0-x)^{-c}\int_x^a \frac{\beta(z')\,k(x,z')}{z'}\,(z_0-z')^{c-1}\,g(z')\,dz'\,e^{\int_z^x \alpha(\lambda,\,y)\,dy}\,dx.
$$

We estimate the supremum norm as before by

$$
\begin{aligned}
\|G_a[g]\|_\infty &\le \frac{z_0\,\overline{\beta}\,C}{b_0\,c}\left(\frac{a}{a-\delta}\right)^{\tilde{c}} \left\| g|_{[a-\delta,a]}\right\|_\infty \sup_{z\in[a-\delta,a]}\left|\int_z^a (z_0-z')^{-c}\frac{1}{x^2}\int_x^a (z_0-z')^{c-1}\,dz'\,dx\right| \\
&\le \frac{z_0\,\overline{\beta}\,C}{b_0\,c}\left(\frac{a}{a-\delta}\right)^{\tilde{c}} \left\| g|_{[a-\delta,a]}\right\|_\infty \sup_{z\in[a-\delta,a]}\left(\frac{1}{z}-\frac{1}{a}\right) \xrightarrow{\delta\to 0^+} 0.
\end{aligned}
$$

Furthermore,

$$
\frac{d}{dz}G_a[g](z) = -\alpha(\lambda,z)\,G_a[g](z) + \frac{z_0}{b_0}\,(z_0-z)^{-c}\int_z^a \frac{\beta(z')\,k(x,z')}{z'}\,(z_0-z')^{c-1}\,g(z')\,dz'
$$

and therefore

$$
\begin{aligned}
\left\|\frac{d}{dz}G_a[g]\right\|_\infty &\le C_1\,\frac{1}{a-\delta}\,\left\| g|_{[a-\delta,a]}\right\|_\infty \sup_{z\in[a-\delta,a]}\left(\frac{1}{z}-\frac{1}{a}\right) \\
&\quad + C_2\,\left\| g|_{[a-\delta,a]}\right\|_\infty \sup_{z\in[a-\delta,a]}(z_0-z)^{-c}\int_z^a \left(\frac{1}{z'}\right)^2 (z_0-z')^{c-1}\,dz' \\
&\le \frac{C_1}{a-\delta}\,\left\| g|_{[a-\delta,a]}\right\|_\infty \sup_{z\in[a-\delta,a]}\left(\frac{1}{z}-\frac{1}{a}\right) \\
&\quad + \frac{C_2}{z_0-a}\,\left\| g|_{[a-\delta,a]}\right\|_\infty \sup_{z\in[a-\delta,a]}\left(\frac{1}{z}-\frac{1}{a}\right) \xrightarrow{\delta\to 0^+} 0.
\end{aligned}
$$

Thus, for $\delta \in (0,a)$ sufficiently small there is a $C < 1$ such that

$$
\|G_a[g]\|_{\mathcal{C}^1([a-\delta,a])} := \max\left\{\|G_a[g]\|_\infty,\ \left\|\frac{d}{dz}G_a[g]\right\|_\infty\right\} < C\,\left\| g|_{[a-\delta,a]}\right\|_\infty .
$$

Therefore, G_a is a contraction for $\delta \in (0,a)$ sufficiently small. The second and third summand in (3.54) are bounded (w.r.t. the norm $\|\cdot\|_{\mathcal{C}^1([a-\delta,a])}$). By the Banach Fixed Point Theorem there is a unique solution $g \in \mathcal{C}^1([a-\delta,a])$ for (3.54).

Iteratively, we find a unique solution $g \in \mathcal{C}^1((0,z_0)) \cap \mathcal{C}^0((0,z_0])$ to (3.52) for every $\lambda > -\big(\beta(z_0)+\mu(z_0)\big)$. □

Remark 3.51. Lemma 3.50 gives existence of a solution g to (3.52). Thus, by Lemmas 3.49 and 3.48, we know that

$$\mathcal{U}(z) := \frac{v(z)}{b(z)} = \frac{(z_0 - z)^{\alpha_0} g(z)}{b(z)}$$

is a solution to the integro-differential equation in (3.49). However, it is not clear under which conditions there exists a $\lambda > -\big(\beta(z_0) + \mu(z_0)\big)$ such that the corresponding eigenfunction $\mathcal{U}$ also satisfies the non-negativity and integrability condition in (3.49).

We can construct the solution g as in the case of constant β and μ by using the proof of Lemma 3.50. First, we choose a $\lambda > -\big(\beta(z_0) + \mu(z_0)\big)$. In each step, g was simulated on the interval $[a - \delta, a]$ where a is given from the previous step ($a = z_0$ in the first step) and we chose δ such that the operators G and G_a in the proof of Lemma 3.50 are contractions on $\mathcal{C}^0([a - \delta, a])$, i.e.,

$$\delta = \operatorname*{arg\,min}_{y \in (0,a)} \left| \frac{z_0 \, \overline{\beta} \, C}{b_0 \, c} \left(\frac{a}{a - y} \right)^{\tilde{c}} \left(\frac{1}{a - y} - \frac{1}{a} \right) - 1 \right| + 10^{-5}.$$

We choose again equidistant points in $[a - \delta, a]$ and set $g_0(z) := g(a)$. Then, we use for $n \in \mathbb{N}_0$ the iteration

$$\begin{aligned} g_{n+1}(z) := {} & \frac{z_0}{b_0} \int_a^z (z_0 - x)^{-c} \int_x^a \frac{\beta(z') \, k(x, z')}{z'} \, (z_0 - z')^{c-1} \, g_n(z') \, dz' \, e^{\int_z^x \alpha(\lambda, y) \, dy} \, dx \\ & + \frac{z_0}{b_0} \int_a^z (z_0 - x)^{-c} \int_a^{z_0} \frac{\beta(z') \, k(x, z')}{z'} \, (z_0 - z')^{c-1} \, g_n(z') \, dz' \, e^{\int_z^x \alpha(\lambda, y) \, dy} \, dx \\ & + g(a) \, e^{\int_z^a \alpha(\lambda, y) \, dy}, \end{aligned}$$

where we omit the second summand in the first step where $a = z_0$. We iterate g_n until either

$$\max_{z \in [a - \delta, a]} |g_n(z) - g_{n-1}(z)| < 10^{-6}$$

or $n = 100$. Then, we define $g(z) := g_n(z)$ for $z \in [a - \delta, a]$.

We repeated the same procedure for the next intervals, where $a := a - \delta$, until either $a - \delta < 0.01$ or we have reached the maximal number of iterations, viz. 1000. In this way, we numerically constructed a solution $g \in \mathcal{C}^0([m, z_0])$ for some $m > 0$. The function g was rescaled to obtain the eigenfunction $\mathcal{U}$ using

$$\mathcal{U}(z) = \frac{v(z)}{b(z)} = \frac{(z_0 - z)^{\alpha_0} g(z)}{b(z)}.$$

We normalized $\mathcal{U}$ such that $\int_m^{z_0} \mathcal{U}(z) \, dz = 1$, where we numerically determined the integral using again the function `integrate`.

In this way, we obtain numerically constructed eigensolutions $\mathcal{U}$ for different λ (see Figure 3.11). For the numerical construction of the eigenfunction, we chose the cell

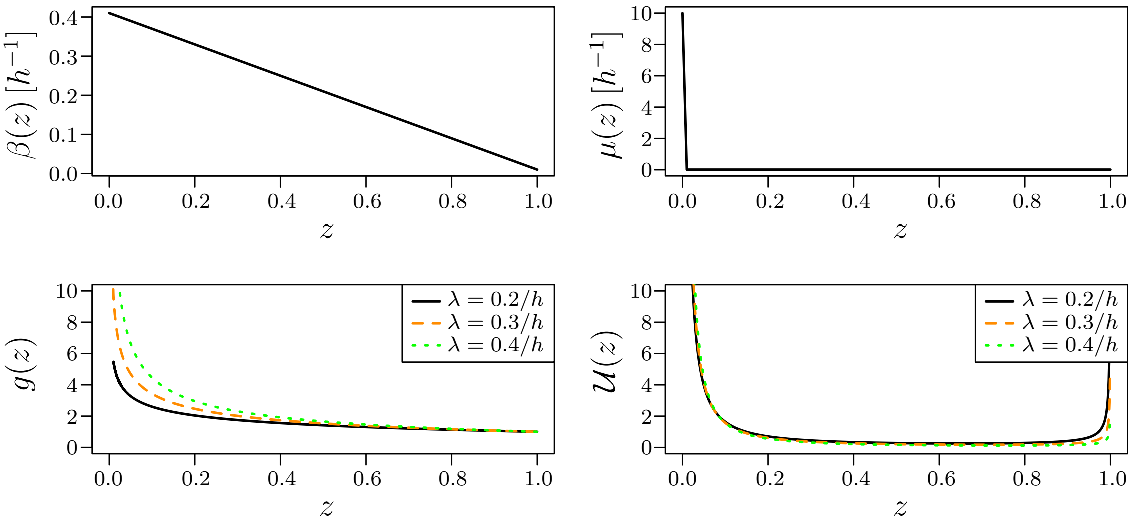


Figure 3.11: Numerical construction of the eigenfunction for the singular VGT model with cell division rate $\beta(z) = \big(0.4\,(1-z)+0.01\big)/h$, cell death rate $\mu(z) = (10-999z)/h$ for $z \in [0, 0.01)$, $\mu(z) = 0.01/h$ for $z \in (0.01, 1]$, and $\Phi(\xi) = 1$. *Upper row:* Plots of β and μ, respectively. *Bottom row:* Plots of the solution g and $\mathcal{U}$ for different λ.

death rate $\mu(z) = (10 - 999z)/h$ for $z \in [0, 0.01)$ and $\mu(z) = 0.01/h$ for $z \in (0.01, 1]$ to model that plasmid-free bacteria have a highly increased cell death rate compared to plasmid-bearing bacteria (e.g., due to antibiotics usage that kills plasmid-free bacteria). For the cell division rate we chose $\beta(z) = \big(0.4(1 - z) + 0.01\big)/h$ in order to model the metabolic burden associated with the harboring of plasmids. With these parameters, there is a unique solution g to (3.52) for all $\lambda > 0$ by Lemma 3.50.

The eigenfunctions $\mathcal{U}$ satisfy the integro-differential equation in (3.49), but we do not know that whether there is an eigenfunction that also satisfies the remaining conditions. The integrability condition on the eigenfunction $\mathcal{U}$ can only hold if $\lim\limits_{z\to 0^+} g(z) = 0$. The numerically constructed functions indicate that $g(z)$ is increasing in λ and that for $\lim\limits_{z\to 0^+} g(z) > 1$ for $\lambda \geq 0.2/h$. Thus, we expect that there is a unique $\lambda < 0.2/h$ such that the conditions hold.

Furthermore, the numerically constructed eigenfunctions indicate that for non-constant cell division and death rate the distribution of plasmids has the same shape as for constant cell division and death rate in the long run (at least for this choice of parameters).

4 Vertical and horizontal gene transfer of plasmids

4.1 Derivation of a model including conjugation

In this chapter, we include HGT into the model. The aim of this chapter is to develop a model for the distribution of plasmids including both VGT and HGT of plasmids via conjugation and to explore the effects of HGT on the distribution of plasmids.

We consider a population of bacteria with two kinds of plasmids, a conjugative and a mobilizable plasmid. The conjugative plasmid enables the plasmid-carrying bacteria to transfer both a copy of the mobilizable and a copy of the conjugative plasmid to bacteria without a conjugative plasmid. We make the following model assumption:

- A bacterium can have either no or one conjugative plasmid, the populations are denoted by u and v, respectively.
- The conjugative plasmid is segregationally stable, meaning that at cell division each daughter receives a copy of the plasmid, it is not lost during cell division.
- There is no conjugation between two bacteria which both carry the conjugative plasmid.
- A bacterium which has received a conjugative plasmid is immediately capable of conjugation.
- The population dynamics are the same for conjugative plasmid-carrying bacteria and non-carrying bacteria (later we will add a metabolic burden for the bacteria with the conjugative plasmid).
- The mobilizable plasmid is a high copy plasmid and the populations of bacteria with and without the conjugative plasmid are structured by the number $i \in \mathbb{N}_0$ of mobilizable plasmids.

In this chapter, we consider the case that cell division and death rate are constant in order to first get an idea of the effects of HGT in a toy model. In Section 4.2.2, we include a metabolic burden for the bacteria with the conjugative plasmid.

Bacteria have mechanisms to ensure that they do not take up a second conjugative plasmid. Thus, there are is no conjugation between two bacteria both carrying a conjugative plasmid [37]. A mobilizable plasmid may be transferred if the recipient already carries a copy of the same plasmid or it may not be transferred. For this reason, we consider two different models, one for each of the two cases of transfer of mobilizable plasmids.

1. If the donor has at least one mobilizable plasmid, the recipient receives one copy of the mobilizable plasmid regardless of the number of mobilizable plasmids of the recipient.
2. The recipient can receive a mobilizable plasmid from the donor only if it does not already carry a mobilizable plasmid.

A scheme of the model of transfer of mobilizable plasmids in Model 1 and Model 2 can be found in Figures 4.1 and 4.4, respectively. We proceed as we did for the VGT models (see Section 3.1). First, we derive two models for the bacterial population structured by the discrete number of mobilizable plasmids, one for each of the above two cases. Secondly, we derive continuous models from the discrete models using a continuum limit.

4.1.1 Discrete models

In the discrete models, we denote by $u_i(t)$ the population size at time t of bacteria with $i \in \mathbb{N}_0$ mobilizable with no conjugative plasmid and by $v_i(t)$ the population size of bacteria with $i \in \mathbb{N}_0$ mobilizable and one conjugative plasmid. The reproduction rate of mobilizable plasmids is denoted by $\tilde{b}(i)$, β and μ are cell division and death rate, θ is the conjugation rate, and $p(i, j)$ is the probability that the first daughter receives i plasmids at cell division if the mother had j plasmids. We assume that conjugation is proportional to the fraction of bacteria carrying a conjugative plasmid [60].

First model

First, we consider the discrete model for the case that a donor bacterium with at least one mobilizable plasmids always transmits a mobilizable plasmid at conjugation regardless of whether the recipient already carries a mobilizable plasmid or not. A scheme of the gene transfer of mobilizable plasmids in this model can be found in Figure 4.1.

We denote the total population size of bacteria at time t by $\tilde{N}(t)$, i.e.,

$$\tilde{N}(t) = \sum_{j=0}^{\infty} \left[u_j(t) + v_j(t) \right].$$

We derive the model equations for the HGT model analogously to the VGT model (see Section 3.1) and then add terms for HGT by conjugation. The rate of conjugation is given by θ and the fraction of bacteria that contain a conjugative plasmid and either no or at least one mobilizable plasmid, i.e.,

$$\frac{v_0}{\tilde{N}} \qquad \text{and} \qquad \frac{\sum\limits_{i=1}^{\infty} v_i}{\tilde{N}},$$

respectively.

We require again, as in the VGT models (see Section 3.1), that $\tilde{b}(0) = 0$, $\tilde{b}(-1) = 0$, and that p satisfies the following two consistency conditions: the condition modeling

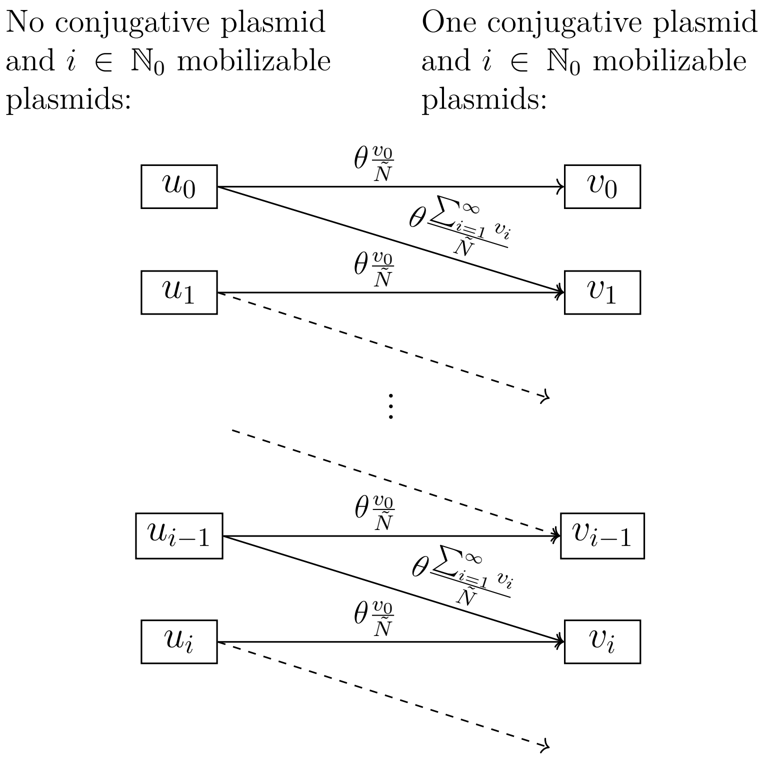


Figure 4.1: Scheme of gene transfer by conjugation in the first discrete HGT model. Conjugation occurs only between bacteria with a conjugative plasmid (donors, denoted by v_i) and bacteria without a conjugative plasmid (recipients, denoted by u_i). The rate of conjugation is proportional to the fraction of bacteria with the conjugative plasmid ($\tilde{N}$ denotes the total bacterial population and θ the conjugation rate). At conjugation, the recipient receives a conjugative plasmid, i.e., it moves from the subpopulation without conjugative plasmid to the subpopulation with the conjugative plasmid. If the donor carries at least one mobilizable plasmid, then the recipient also receives a mobilizable plasmid.

that bacteria always divide into two daughter cells, i.e.,

$$\sum_{i=0}^{j} \left[p(i,j) + p(j-i,j)\right] = 2 \qquad \text{for all } j \in \mathbb{N}_0, \tag{4.1}$$

and the condition on mass conservation of plasmids at cell division

$$\sum_{i=0}^{j} i \left[p(i,j) + p(j-i,j)\right] = j \qquad \text{for all } j \geq 0. \tag{4.2}$$

Therefore, we obtain the following ODE model for HGT via conjugation:

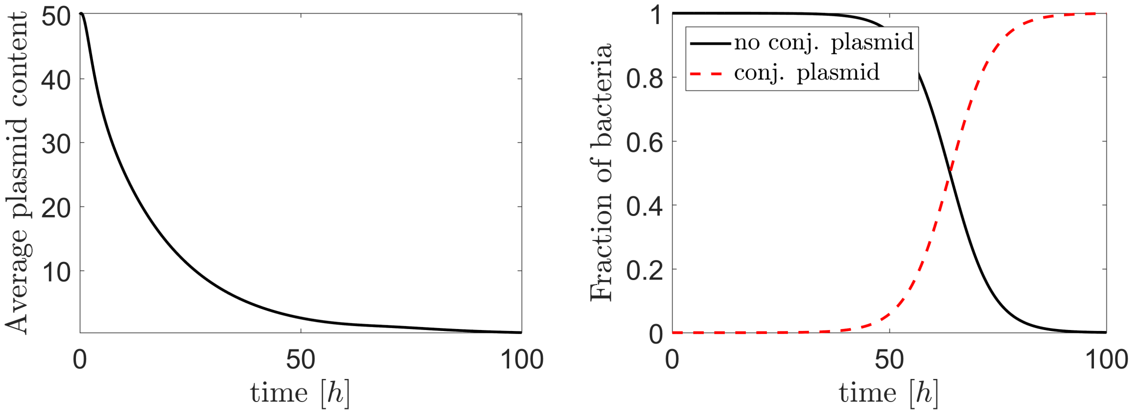
$$\dot{u}_0 = (\beta - \mu)\, u_0 + \beta \sum_{j=1}^{\infty} \left[p(0,j) + p(j,j)\right] u_j - \theta\, u_0\, \frac{\sum_{j=0}^{\infty} v_j}{\tilde{N}} \tag{4.3}$$

$$\dot{u}_i = -(\beta+\mu)\,u_i + \beta\sum_{j=i}^{\infty}\left[p(i,j)+p(j-i,j)\right]u_j + \tilde{b}(i-1)\,u_{i-1} - \tilde{b}(i)\,u_i \\ \quad - \theta\,u_i\,\frac{\sum_{j=0}^{\infty} v_j}{\tilde{N}} \tag{4.4}$$

$$\dot{v}_0 = (\beta-\mu)\,v_0 + \beta\sum_{j=1}^{\infty}\left[p(0,j)+p(j,j)\right]v_j + \theta\,u_0\,\frac{v_0}{\tilde{N}} \tag{4.5}$$

$$\dot{v}_i = -(\beta+\mu)\,v_i + \beta\sum_{j=i}^{\infty}\left[p(i,j)+p(j-i,j)\right]v_j + \tilde{b}(i-1)\,v_{i-1} - \tilde{b}(i)\,v_i \\ \quad + \theta\left(u_i\,\frac{v_0}{\tilde{N}} + u_{i-1}\,\frac{\sum_{j=1}^{\infty} v_j}{\tilde{N}}\right). \tag{4.6}$$

The first discrete HGT model was numerically simulated using a forward Euler scheme and the software MATLAB [67]. For constant cell division and death rate, the mobilizable plasmid is lost in the long run (as in the discrete VGT models) and the conjugative plasmid takes over the population (see Figure 4.2).



(a) **(b)**

Figure 4.2: Numerical simulation of the plasmid distribution in the first discrete HGT model against time. The parameter values used for the numerical simulations where $\beta = 0.4/h$, $\mu = 0.1/h$, the maximal number of mobilizable plasmids $N = 100$, $\tilde{b}(i) = \frac{i}{N}(N-i)$, and uniform plasmid segregation, i.e., $p(0,0) = 1$, $p(i,j) = \frac{1}{j}$ for all $0 \le i \le j$, $0 < j \le N$. The initial conditions were $u_i(0) = i^2\,(N-i)^2/1000$ and $v_1(0) = 1$, $v_i(0) = 0$ for $i \ne 1$, i.e., initally there is one bacterium carrying the conjugative plasmid (and one mobilizable plasmid). We used a forward Euler scheme with $\Delta t = 0.01$. **(a)** Average plasmid content of the mobilizable plasmid in the total population against time. **(b)** Fraction of bacteria that carry the conjugative plasmid (red dashed line) and fraction of bacteria without the conjugative plasmid (black solid line) against time.

For the numerical simulations, we consider again, as for the discrete VGT model, the case that the cell death rate is increased for plasmid-free bacteria, meaning bacteria without the mobilizable plasmid. In this case, the mobilizable plasmid is necessary for the survival of the bacteria as can be the case, e.g., if the mobilizable plasmid carries antibiotic resistance genes or other resistance genes. We find that in this case the mobilizable plasmid can persist and the conjugative plasmid spreads throughout the population (see Figure 4.3).

Second model

Now we consider the second case, i.e., that mobilizable plasmids are transmitted at conjugation only if the recipient does not yet carry a mobilizable plasmid. A scheme of HGT of mobilizable plasmids in this model is shown in Figure 4.4.

Analogously to the first model, we obtain the following model equations:

$$\dot{u}_0 = (\beta - \mu)\, u_0 + \beta \sum_{j=1}^{\infty} [p(0,j) + p(j,j)]\, u_j - \theta\, u_0\, \frac{\sum_{j=0}^{\infty} v_j}{\tilde{N}} \tag{4.7}$$

$$\begin{aligned} \dot{u}_i = & - (\beta + \mu)\, u_i + \beta \sum_{j=1}^{\infty} [p(i,j) + p(j-i,j)]\, u_j + \tilde{b}(i-1)\, u_{i-1} - \tilde{b}(i)\, u_i \\ & - \theta\, u_i\, \frac{\sum_{j=0}^{\infty} v_j}{\tilde{N}} \end{aligned} \tag{4.8}$$

$$\dot{v}_0 = (\beta - \mu)\, v_0 + \beta \sum_{j=1}^{\infty} [p(0,j) + p(j,j)]\, v_j + \theta\, u_0\, \frac{v_0}{\tilde{N}} \tag{4.9}$$

$$\begin{aligned} \dot{v}_1 = & - (\beta + \mu)\, v_1 + \beta \sum_{j=1}^{\infty} [p(1,j) + p(j-1,j)]\, v_j - \tilde{b}(1)\, v_1 \\ & + \theta \left(u_0\, \frac{\sum_{j=1}^{\infty} v_j}{\tilde{N}} + u_1\, \frac{\sum_{j=0}^{\infty} v_j}{\tilde{N}} \right) \end{aligned} \tag{4.10}$$

$$\begin{aligned} \dot{v}_i = & - (\beta + \mu)\, v_i + \beta \sum_{j=i}^{\infty} [p(i,j) + p(j-i,j)]\, v_j + \tilde{b}(i-1)\, v_{i-1} - \tilde{b}(i)\, v_i \\ & + \theta\, u_i \frac{\sum_{j=0}^{\infty} v_j}{\tilde{N}}. \end{aligned} \tag{4.11}$$

The numerical simulations of the second model yielded the same long-term plasmid distribution as in the first discrete HGT model.

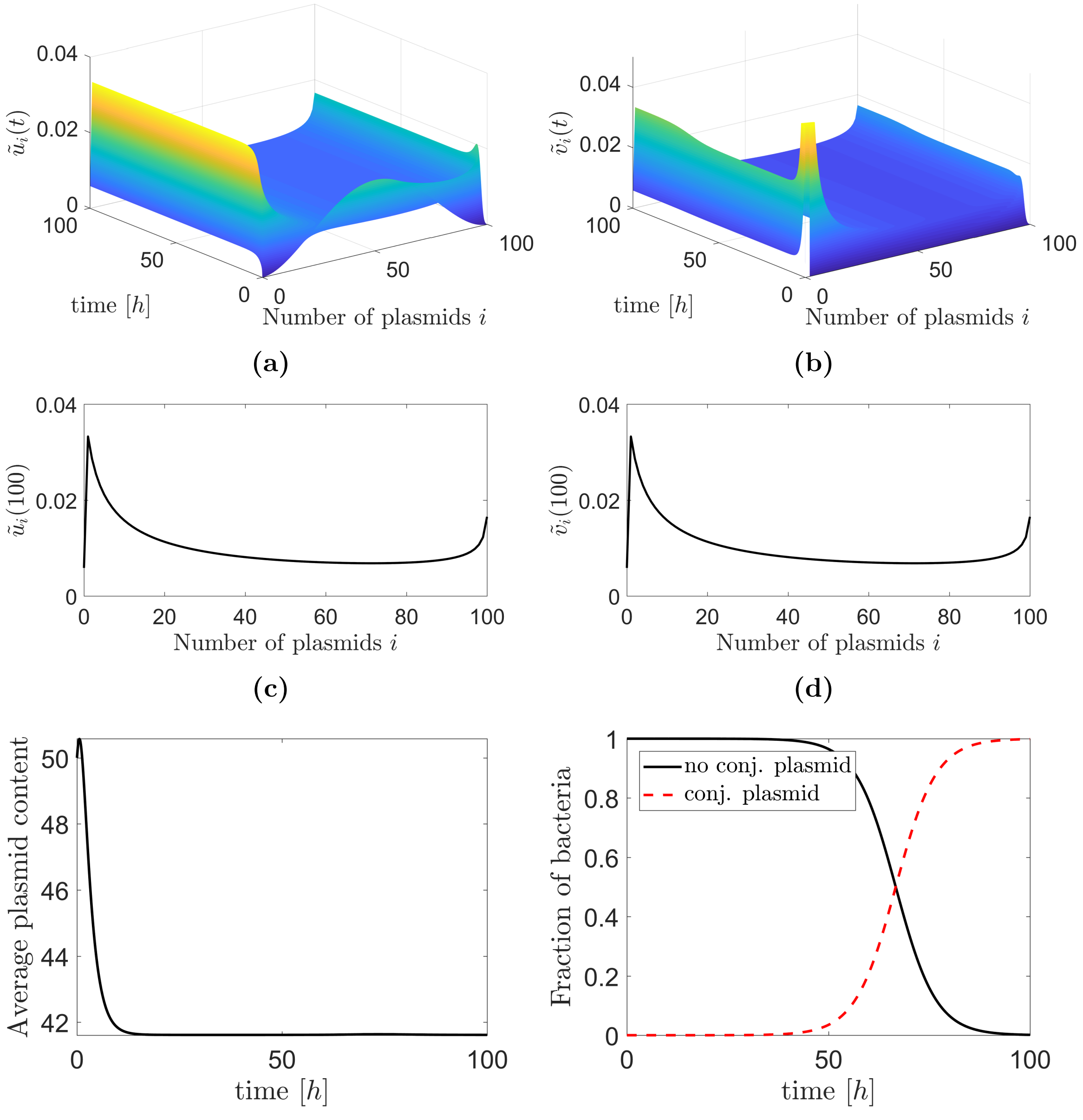
4.1.2 Continuous models

We assume that the mobilizable plasmid is a high-copy plasmid and proceed to the continuum limit in order to obtain continuous models for HGT by conjugation. We approximate $u_i(t)$ by a smooth function $u(z,t)$, i.e., for $h > 0$ small we have

$$u_i(t) \approx \int_{ih-\frac{h}{2}}^{ih+\frac{h}{2}} u(z,t)\, dz \approx u(ih,t)\, h.$$

Likewise, we approximate

- $\dot{u}_i(t) \approx \partial_t u(ih,t)\, h$ for $i \in \mathbb{N}$,
- $v_i(t) \approx v(t,ih)\, h$ and $\dot{v}_i(t) \approx \partial_t v(t,ih)\, h$ for $i \in \mathbb{N}$,



(a) **(b)**

(c) **(d)**

(e) **(f)**

Figure 4.3: Numerical simulation of the plasmid distribution in the first discrete HGT model against time. The parameter values used for the numerical simulations where $\beta = 0.4/h$, $\mu(i) = 0.1/h$ for $i \neq 0$ and $\mu(0) = 10/h$, maximal number of mobilizable plasmids $N = 100$, $\tilde{b}(i) = \frac{i}{N}(N-i)$, and uniform plasmid segregation kernel. The initial conditions were $u_i(0) = i^2\,(N-i)^2/1000$ and $v_1(0) = 1$, $v_i(0) = 0$ for $i \neq 1$. The solutions were computed using a forward Euler scheme with $\Delta t = 0.01$. **(a)** The normalized solution u_i to the first discrete HGT model against time. **(b)** The normalized solution v_i against time. **(c)** Numerical simluation of $\tilde{u}_i(100)$. **(d)** Numerical simulation of $\tilde{v}_i(100)$. **(e)** Average plasmid content of the mobilizable plasmid in the total population against time. **(f)** Fraction of bacteria that carry the conjugative plasmid (red dashed line) and fraction of bacteria without the conjugative plasmid (black solid line) against time.

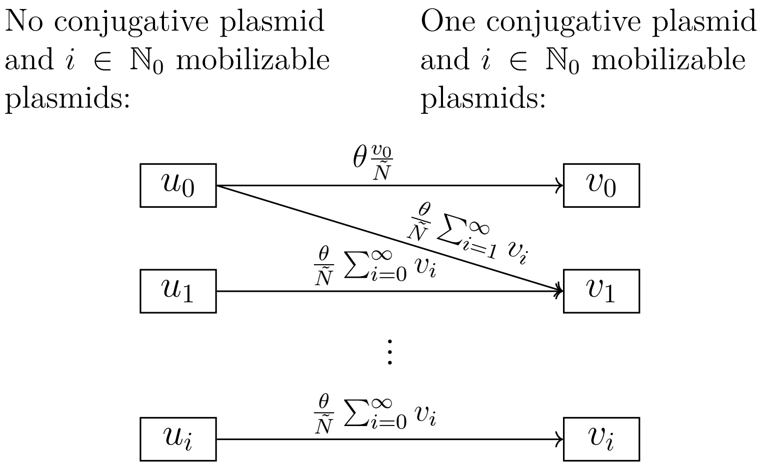


Figure 4.4: Scheme of gene transfer by conjugation in the second discrete HGT model. Conjugation happens at rate θ and is proportional to the fraction of bacteria with the conjugative plasmid ($\tilde{N}$ denotes the total bacterial population). At conjugation, the recipient receives a conjugative plasmid, i.e., it moves from the subpopulation without conjugative plasmid to the subpopulation with the conjugative plasmid. There is no conjugation between two bacteria that both carry the conjugative plasmid. The mobilizable plasmid is only transferred if the recipient does not already carry a mobilizable plasmid.

- $\tilde{b}(i) = b(ih)\,\frac{1}{h}$ for $i \in \mathbb{N}$,
- $p(0,j) + p(j,j) = k_0(jh)$ for $j \in \mathbb{N}_0$, and
- $p(i,j) + p(j-i,j) = k(ih,jh)\,h$ for $i \in \mathbb{N}$, $j \in \mathbb{N}$.

As before, we drop the tilde above the discrete parameters for the parameters in the continuous models.

The function $k_0(z)$ models the fraction of bacteria that divide plasmids at cell division such that one daughter cell receives all plasmids and the other none. Due to the definition of p (see also (4.1)), it holds that

$$k_0(0) = p(0,0) + p(0,0) = 2.$$

Thus, it holds that $k_0(z) \in [0,1]$ for all $z > 0$ and $k_0(0) = 2$. Furthermore,

$$2k_0(jh) + \sum_{i=1}^{j-1} k(ih,jh)h = 2 \qquad \text{for all } j \in \mathbb{N}$$

implies that

$$2k_0(z') + \int_0^{z'} k(z,z')\,dz = 2 \qquad \text{for all } z' > 0,$$

where $z := ih$, $z' := jh$, and we took the limit $h \to 0$. This condition models that every bacterium always divides into two daughter cells (see e.g. [30,69]). Moreover, the definition of k implies symmetry in the sense of

$$k(z, z') = k(z' - z, z') \quad \text{for all } z,\ z' \in \mathbb{R}_{>0}.$$

The condition on mass conservation of plasmids at cell division (4.2) yields

$$z'\, k_0(z') + \int\limits_0^{z'} z\, k(z, z')\, dz = z' \quad \text{for all } z' \geq 0.$$

We assume for the remainder of this chapter that all of the above consistency conditions on k_0 and k are satisfied.

Let $N(t)$ be the total population size at time t in the continuous model,

$$N(t) := u_0(t) + v_0(t) + \int\limits_0^{\infty} u(z, t) + v(z, t)\, dz.$$

First model

With the continuum limit approximation, equation (4.3) is given by

$$\dot{u}_0 = (\beta - \mu)\, u_0 + \beta \sum_{j=1}^{\infty} k_0(jh)\, u(jh, t)\, h - \theta\, u_0\, \frac{v_0 + \sum_{j=1}^{\infty} v(t, jh)\, h}{u_0 + v_0 + \sum_{j=1}^{\infty} [u(jh, t)\, h + v(t, jh)\, h]}.$$

With $jh =: z'$ and in the limit $h \to 0$, we obtain

$$\dot{u}_0(t) = (\beta - \mu)\, u_0(t) + \beta \int\limits_0^{\infty} k_0(z')\, u(z', t)\, dz' - \frac{\theta}{N(t)}\, u_0(t) \left(v_0(t) + \int\limits_0^{\infty} v(z', t)\, dz' \right).$$

In the same way, we obtain for (4.4) the following equation

$$\begin{aligned} \partial_t u(ih, t)\, h = &- (\beta + \mu)\, u(ih, t)\, h + \beta\, k_0(ih)\, u(ih, t)\, h + \beta \sum_{j=i+1}^{\infty} k(ih, jh)\, h\, u(ih, t)\, h \\ &+ \frac{1}{h}\, b(ih - h)\, u(t, ih - h)\, h - \frac{1}{h}\, b(ih)\, u(ih, t)\, h \\ &- \theta\, u(ih, t)\, h\, \frac{v_0 + \sum_{j=1}^{\infty} v(t, jh)\, h}{u_0 + v_0 + \sum_{j=1}^{\infty} [u(jh, t)\, h + v(t, jh)\, h]}. \end{aligned}$$

Dividing by h, defining $z := ih$, $z' := jh$, and passing to the limit $h \to 0$, yields

$$\begin{aligned} \partial_t u(z, t) + \partial_z \left(b(z)\, u(z, t) \right) = &- (\beta + \mu)\, u(z, t) + \beta\, k_0(z)\, u(z, t) + \beta \int\limits_z^{\infty} k(z, z')\, u(z', t)\, dz' \\ &- \frac{\theta}{N(t)}\, u(z, t) \left(v_0(t) + \int\limits_0^{\infty} v(z', t)\, dz' \right). \end{aligned}$$

Analogously, the continuous equations for v can be derived from (4.5) and (4.6) for $i \in \mathbb{N} \setminus \{1\}$.

Equation (4.6) for $i = 1$ will give a boundary condition:

$$\dot{v}_1 = -(\beta + \mu)\, v_1 + \beta\, [p(1,1) + p(0,1)]\, v_1 + \beta \sum_{j=2}^{\infty} [p(1,j) + p(j-1,j)]\, v_j - \tilde{b}(1)\, v_1 \\ + \theta \left(u_1 \frac{v_0}{\tilde{N}} + u_0 \frac{\sum_{j=1}^{\infty} v_j}{\tilde{N}} \right).$$

With the continuum limit approximations for $v_i(t)$, $\tilde{b}$, and p and $i = 1$, equation (4.6) reads

$$\partial_t v(t,h)\, h = -(\beta + \mu)\, v(t,h)\, h + \beta\, k_0(h)\, v(t,h)\, h + \beta \sum_{j=2}^{\infty} k(h, jh)\, h\, v(t, jh)\, h \\ - \frac{1}{h}\, b(h)\, v(t,h)\, h + \theta \left(u(t,h)\, h\, \frac{v_0}{\tilde{N}} + u_0\, \frac{\sum_{j=1}^{\infty} v(t,h) h}{\tilde{N}} \right).$$

Defining again $z' := jh$ and letting $h \to 0$, we obtain the boundary condition

$$b(0)\, v(t,0) = \frac{\theta}{N(t)}\, u_0(t) \int_0^{\infty} v(z',t)\, dz'.$$

Therefore, we have an influx caused by conjugation events between bacteria with both conjugative and mobilizable plasmids ($v(z,t)$) and bacteria without conjugative or mobilizable plasmids (u_0).

Overall, the first continuous model is given by:

$$\dot{u}_0(t) = (\beta - \mu)\, u_0(t) + \beta \int_0^{\infty} k_0(z')\, u(z',t)\, dz' - \frac{\theta}{N(t)}\, u_0(t) \left(v_0(t) + \int_0^{\infty} v(z',t)\, dz' \right), \tag{4.12}$$

$$\partial_t u(z,t) + \partial_z \left(b(z)\, u(z,t) \right) = -(\beta + \mu)\, u(z,t) + \beta\, k_0(z)\, u(z,t) \\ + \beta \int_z^{\infty} k(z,z')\, u(z',t)\, dz' - \frac{\theta}{N(t)}\, u(z,t) \left(v_0(t) + \int_0^{\infty} v(z',t)\, dz' \right), \tag{4.13}$$

$$\dot{v}_0(t) = (\beta - \mu)\, v_0(t) + \beta \int_0^{\infty} k_0(z')\, v(z',t)\, dz' + \frac{\theta}{N(t)}\, u_0(t)\, v_0(t), \tag{4.14}$$

$$\partial_t v(z,t) + \partial_z \left(b(z)\, v(z,t) \right) = -(\beta + \mu)\, v(z,t) + \beta\, k_0(z)\, v(z,t) \\ + \beta \int_z^{\infty} k(z,z')\, v(z',t)\, dz' + \frac{\theta}{N(t)}\, u(z,t) \left(v_0(t) + \int_0^{\infty} v(z',t)\, dz' \right), \tag{4.15}$$

$$b(0)\, v(0,t) = \frac{\theta}{N(t)}\, u_0(t) \int_0^{\infty} v(z',t)\, dz'. \tag{4.16}$$

For the population without a conjugative plasmid we impose a zero flux boundary condition as in the VGT model (as can be seen from the scheme of the first HGT model in Figure 4.1 there is no influx into $u(z,t)$ caused by conjugation):

$$b(0)\, u(0,t) = 0. \tag{4.17}$$

The first HGT model is then given by equations (4.12) to (4.17).

Second model

The second continuous model can be derived analogously to the equations for the first model. One obtains the exact same equations as for the first continuous model, i.e., equations (4.12) to (4.16) with boundary condition (4.17) for u.

We obtain the same continuous model for HGT via conjugation for the two different cases of transmission of a mobilizable plasmid, viz. either the donor always transmits the mobilizable plasmid or it does so only if the recipient does not contain a mobilizable plasmid. The difference between these two cases is that a recipient receives either one additional mobilizable plasmid or none. When taking the continuum limit the compartments of the discrete model move closer together and the difference of one mobilizable plasmid becomes negligible. Therefore, we obtain the same dynamics in both cases.

Remark 4.1. If in this model either all or no bacteria contain a conjugative plasmid, then there is no conjugation anymore. If the conjugative plasmid is lost, then there cannot be any conjugation and if all bacteria have the conjugative plasmid, then there is no conjugation because conjugation takes place only between bacteria with the conjugative plasmid and bacteria without it. The model is thus reduced to the model for VGT of plasmids that we have studied in Chapter 3.

Remark 4.2. Plasmids can be interpreted as parasites with bacteria as their host. Thus, we expect the model to be similar to epidemic models for parasite load per individual [44, 54, 86]. Epidemic models can be classified as prevalence or density models where the former classify the host by states such as "susceptible" or "infected" and the latter take into account the explicit number of parasites [44]. We have two different types of parasites in our model, the conjugative plasmid and the mobilizable plasmid, and we take into account only the explicit number of the mobilizable plasmid but not of the conjugative plasmid. For this reason, our model is a combination of the VGT model with a prevalence model such as the SIR model [52] rather than a density model.

4.2 Analysis of the model including conjugation

For the model without conjugation, existence of solutions can be shown using the theory of semigroups of operators (see Section 3.3.1). We expect that existence results can be extended to the model with conjugation using perturbation theory (see, e.g., [51, 82] and [50, 63]).

4.2.1 Model without metabolic burden

In this section, we analyze the long-time development of a solution to the continuous model given by equations (4.12) to (4.17). We do so by considering the proportion of bacteria that contain the conjugative plasmid and consider the long-time development of this proportion. If all bacteria either lose the conjugative plasmid or carry it, then by Remark 4.1, we know that the long-time behavior of the bacterial population is as in the VGT model.

Recall that the total population size of the bacterial population $N(t)$ is given by

$$N(t) := u_0(t) + \int_0^\infty u(z,t)\,dz + v_0(t) + \int_0^\infty v(z,t)\,dz$$

and satisfies the equation

$$\dot{N}(t) = (\beta - \mu)\,N(t).$$

Therefore,

$$N(t) = N(0)\,e^{(\beta-\mu)t}.$$

We project the continuous model by defining

$$\tilde{u}_0(t) := \frac{u_0(t)}{N(t)}, \quad \tilde{u}(z,t) := \frac{u(z,t)}{N(t)}, \quad \tilde{v}_0(t) := \frac{v_0(t)}{N(t)}, \quad \text{and} \quad \tilde{v}(z,t) := \frac{v(z,t)}{N(t)},$$

i.e., we consider the proportions of bacteria with neither the conjugative nor mobilizable plasmids, without the conjugative but with mobilizable plasmids, with the conjugative but without mobilizable plasmids, and with both the conjugative and mobilizable plasmids, respectively. It holds that

$$\dot{\tilde{u}}_0(t) = \frac{\dot{u}_0(t)}{N(t)} - \frac{u_0(t)}{N(t)}\,\frac{\dot{N}(t)}{N(t)} = \frac{\dot{u}_0(t)}{N(t)} - (\beta-\mu)\tilde{u}_0(t),$$

analogously for $\tilde{u}(z,t)$, $\tilde{v}_0$, and $\tilde{v}(z,t)$. Therefore, we obtain the following rescaled equations

$$\dot{\tilde{u}}_0(t) = \beta \int_0^\infty k_0(z')\,\tilde{u}(z',t)\,dz' - \theta\,\tilde{u}_0(t)\left(\tilde{v}_0(t) + \int_0^\infty \tilde{v}(z',t)\,dz'\right), \tag{4.18}$$

$$\begin{aligned}\partial_t\tilde{u}(z,t) + \partial_z(b(z)\,\tilde{u}(z,t)) &= -2\beta\tilde{u}(z,t) + \beta k_0(z)\,\tilde{u}(z,t)\\ &\quad + \beta\int_z^\infty k(z,z')\,\tilde{u}(z',t)\,dz' - \theta\,\tilde{u}(z,t)\left(\tilde{v}_0(t) + \int_0^\infty \tilde{v}(z',t)\,dz'\right),\end{aligned} \tag{4.19}$$

$$\dot{\tilde{v}}_0(t) = \beta\int_0^\infty k_0(z')\,\tilde{v}(z',t)\,dz' + \theta\,\tilde{u}_0(t)\,\tilde{v}_0(t), \tag{4.20}$$

$$\begin{aligned}\partial_t\tilde{v}(z,t) + \partial_z(b(z)\,\tilde{v}(z,t)) &= -2\beta\tilde{v}(z,t) + \beta\,k_0(z)\,\tilde{v}(z,t)\\ &\quad + \beta\int_z^\infty k(z,z')\,\tilde{v}(z',t)\,dz' + \theta\,\tilde{u}(z,t)\left(\tilde{v}_0(t) + \int_0^\infty \tilde{v}(z',t)\,dz'\right),\end{aligned} \tag{4.21}$$

with boundary conditions

$$b(0)\,\tilde{v}(0,t) = \theta\,\tilde{u}_0(t)\int_0^\infty \tilde{v}(z',t)\,dz' \quad \text{and} \quad b(0)\,\tilde{u}(0,t) = 0 \quad \text{for all } t \geq 0.$$

The proportions of cells without and with the conjugative plasmid are given by

$$U(t) := \tilde{u}_0(t) + \int_0^\infty \tilde{u}(z,t)\,dz \quad \text{and} \quad V(t) := \tilde{v}_0(t) + \int_0^\infty \tilde{v}(z,t)\,dz,$$

respectively.

We can now solve the differential equation for $U(t)$ and give the solution explicitly.

Lemma 4.3. *The proportion of cells without the conjugative plasmid $U(t)$ is given by*

$$U(t) = \frac{1}{e^{\theta t}\left(\frac{1}{U_0} - 1\right) + 1},$$

where $U_0 := U(0)$. Therefore, $\lim\limits_{t\to\infty} U(t) = 0$ for every $U_0 \in (0,1)$.

Proof. With equations (4.18) to (4.21), we find that the functions $U(t)$ and $V(t)$ satisfy the following equations:

$$U'(t) = -\theta\, U(t)\, V(t), \quad \text{and} \quad V'(t) = \theta\, U(t)\, V(t),$$

where the initial values are $U_0 = U(0)$ and $V_0 = V(0)$, U_0, $V_0 \in (0,1)$. As $U(t)$ and $V(t)$ are defined as the fraction of bacteria without the conjugative plasmid and with the conjugative plasmid, respectively, it holds for all $t \geq 0$ that $V(t) + U(t) = 1$. We use separation of variables and $V(t) = 1 - U(t)$ to compute the explicit solution

$$U(t) = \frac{1}{e^{\theta t}\left(\frac{1}{U_0} - 1\right) + 1}$$

and analogously

$$V(t) = \frac{e^{\theta t}}{e^{\theta t} + \frac{1}{V_0} - 1}.$$

The limit of $U(t)$ for $t \to \infty$ follows immediately and the proof is finished. □

In Figure 4.5 the development of the proportion of bacteria without the conjugative plasmid over time is plotted for different initial values U_0. We see that in the long run almost all cells will contain a conjugative plasmids as $\lim\limits_{t\to\infty} U(t) = 0$ for all $U_0 \in (0,1)$. This is to be expected as in our model there is no disadvantage for bacteria containing the conjugative plasmid like a decreased cell division rate and bacteria cannot refuse to accept the conjugative plasmid.

In the long run, all bacteria will have a conjugative plasmid, the population will then behave as the bacteria without HGT. This is due to the fact that we have included in our model that there is no HGT between cells containing a conjugative plasmid (see Remark 4.1).

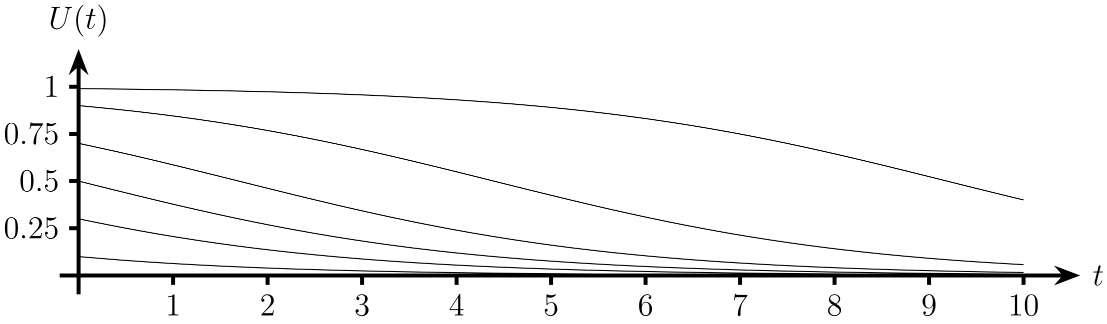


Figure 4.5: The proportion of bacteria without conjugative plasmid $U(t)$ over time t for $\theta = 0.5$ and initial values $U_0 = 0.99$, 0.9, 0.7, 0.5, 0.3, and 0.1.

4.2.2 Model including metabolic burden for the conjugative plasmid

We analyze again the long-term behavior of the subpopulation without conjugative plasmid, but now we also include a metabolic burden for bacteria carrying the conjugative plasmid.

The metabolic burden is modeled by the parameter $\delta \in [0,1]$ where for $\delta = 1$ there is no metabolic burden and for $\delta = 0$ the metabolic burden for cells with the conjugative plasmid is so high that they become inactive, meaning there is no plasmid reproduction or no cell division. Hence, δ is the factor by which plasmid and cell reproduction are reduced due to metabolic burden. The continuous model with metabolic burden is

$$\dot{u}_0(t) = (\beta - \mu)\, u_0(t) + \beta \int_0^\infty k_0(z')\, u(z',t)\, dz' - \frac{\theta}{N(t)}\, u_0(t) \left(v_0(t) + \int_0^\infty v(z',t)\, dz' \right), \tag{4.22}$$

$$\begin{aligned} \partial_t u(z,t) + \partial_z \left(b(z)\, u(z,t) \right) = &- (\beta + \mu)\, u(z,t) + \beta\, k_0(z)\, u(z,t) \\ &+ \beta \int_z^\infty k(z,z')\, u(z',t)\, dz' - \frac{\theta}{N(t)}\, u(z,t) \left(v_0(t) + \int_0^\infty v(z',t)\, dz' \right), \end{aligned} \tag{4.23}$$

$$\dot{v}_0(t) = (\delta\, \beta - \mu)\, v_0(t) + \delta\, \beta \int_0^\infty k_0(z')\, v(z',t)\, dz' + \frac{\theta}{N(t)}\, u_0(t)\, v_0(t), \tag{4.24}$$

$$\begin{aligned} \partial_t v(z,t) + \partial_z \left(\delta\, b(z)\, v(z,t) \right) = &- (\delta\, \beta + \mu)\, v(z,t) + \delta\, \beta\, k_0(z)\, v(z,t) \\ &+ \delta\, \beta \int_z^\infty k(z,z')\, v(z',t)\, dz' + \frac{\theta}{N(t)}\, u(z,t) \left(v_0(t) + \int_0^\infty v(z',t)\, dz' \right), \end{aligned} \tag{4.25}$$

$$\delta\, b(0)\, v(0,t) = \frac{\theta}{N(t)}\, u_0(t) \int_0^\infty v(z',t)\, dz', \quad b(0)\, u(0,t) = 0 \quad \text{for all } t \geq 0. \tag{4.26}$$

We use the same notation as before , i.e.,

$$N(t) := u_0(t) + \int_0^\infty u(z,t)\, dz + v_0(t) + \int_0^\infty v(z,t)\, dz,$$

$$U(t) := \frac{u_0(t)}{N(t)} + \int_0^\infty \frac{u(z,t)}{N(t)}\,dz, \quad \text{and} \quad V(t) := \frac{v_0(t)}{N(t)} + \int_0^\infty \frac{v(z,t)}{N(t)}\,dz.$$

Therefore,

$$\dot{N}(t) = (\beta - \mu)\left(u_0(t) + \int_0^\infty u(z,t)\,dz\right) + (\delta\beta - \mu)\left(v_0(t) + \int_0^\infty v(z,t)\,dz\right)$$

and

$$\frac{\dot{N}(t)}{N(t)} = (\beta - \mu)\,U(t) + (\delta\,\beta - \mu)\,V(t).$$

As in the case without metabolic burden, we can give the function $U(t)$ explicitly and compute the limit for $t \to \infty$.

Lemma 4.4. *The proportion of cells without conjugative plasmid $U(t)$ in the model with metabolic burden for cells with the conjugative plasmid given by equations* (4.12) *to* (4.26) *satisfies*

$$U(t) = \frac{1}{e^{(\theta - \beta\,(1-\delta))\,t}\left(\frac{1}{U_0} - 1\right) + 1},$$

where $U(0) = U_0 \in (0,1)$. Therefore, it holds that

(i) if $\theta - \beta(1-\delta) < 0$, then $\lim_{t\to\infty} U(t) = 1$,

(ii) if $\theta - \beta(1-\delta) = 0$, then $U(t) = U_0$, and

(iii) if $\theta - \beta(1-\delta) > 0$, then $\lim_{t\to\infty} U(t) = 0$.

Proof. Note that by definition of $U(t)$ and $V(t)$, $U(t) + V(t) = 1$. Therefore,

$$\begin{aligned}
\dot{U}(t) &= \frac{\dot{u}_0(t)}{N(t)} - \frac{u_0(t)}{N(t)} \cdot \frac{\dot{N}(t)}{N(t)} + \int_0^\infty \frac{\partial_t u(z,t)}{N(t)} - \frac{\dot{N}(t)}{N(t)} \cdot \frac{u(z,t)}{N(t)}\,dz \\
&= (\beta - \mu)\,U(t) - (\beta - \mu)\,U^2(t) - (\theta + \delta\beta - \mu)\,U(t)\,V(t) \\
&= (\beta - \mu)\,U(t) - (\beta - \mu)\,U^2(t) - (\theta + \delta\,\beta - \mu)\,U(t)\,(1 - U(t)) \\
&= (\beta - \delta\,\beta - \theta)\,U(t) - (\beta - \delta\,\beta - \theta)\,U^2(t) \\
&= -(\theta - \beta\,(1-\delta))\,U(t)\,(1 - U(t)).
\end{aligned}$$

We use again separation of variables to find the explicit solution

$$U(t) = \frac{1}{e^{(\theta - \beta\,(1-\delta))\,t}\left(\frac{1}{U_0} - 1\right) + 1}.$$

The rest of the lemma then directly follows. □

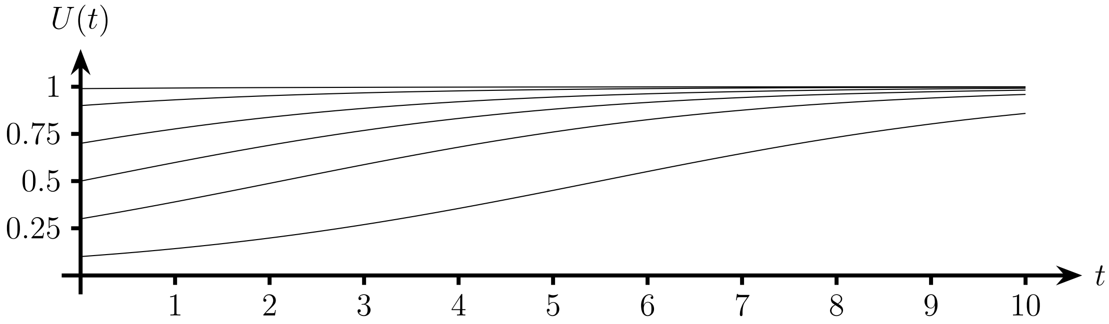


Figure 4.6: The proportion of bacteria without conjugative plasmid $U(t)$ in the model with metabolic burden over time t for $\theta = 0.5$, $\delta = 0.1$, $\beta = 1$ and initial values $U_0 = 0.99$, 0.9, 0.7, 0.5, 0.3, and 0.1.

Therefore, for $\theta \neq \beta(1-\delta)$ in the long run either all bacteria will have the conjugative plasmid or no bacteria will have the conjugative plasmid depending on the sign of $\theta-\beta(1-\delta)$, i.e., depending on whether the cell division rate in bacteria with metabolic burden is high compared to the conjugation rate. Either way, we again end up in the long run with a population without HGT by conjugation.

In this model, we considered the case that the population dynamics are the same for bacteria that carry the conjugative plasmid and bacteria that do not carry a conjugative plasmid. Moreover, we considered the cell division rate β to be constant. We expect that for suitable non-constant β and different population dynamics (caused, e.g., by the metabolic burden of the conjugative and mobilizable plasmid to the host bacterium) there is an equilibrium such that there are both bacteria with the conjugative plasmid and bacteria without the conjugative plasmid in the long run.

There are many ways to extend this model. For example, one can consider different population dynamics and non-constant cell division rate. Since conjugation can only take place when a cell-to-cell connection between recipient and donor is established, the spatial structure of bacteria can be included. Also, the inclusion of a nutrient or food source for bacteria is possible as conjugation depends strongly on the physiological state of the bacteria [57]. Other possibilities are including a minimal time between conjugation events, a trade-off between VGT and HGT, or pheromone signaling for conjugation.

5 Conclusion

In this thesis, we considered different models for vertical and horizontal gene transfer of plasmids in a bacterial population. Firstly, we derived two different models for VGT only. These two models differ in the distribution of plasmids at low plasmid numbers resulting in a singular and regular plasmid segregation kernel, respectively. This difference in the kernel gave the two models for VGT their names, singular and regular VGT model, respectively. For each of the two models, we started with a system of ODEs modeling the bacterial population structured by the discrete number of plasmids. By proceeding to the continuum limit, we derived continuous models, so-called growth-fragmentation-death models, for VGT of plasmids.

In Section 3.2, we have shown existence of an eigensolution to the regular VGT eigenproblem using regularization, theory of positive operators, and compactness. We further analyzed the eigenproblem by spectral analysis. With a transformation and variation of parameters, we have related the spectrum of an integro-differential operator to the spectrum of an integral operator. In this way, we could show that there is a real dominant simple eigenvalue using compactness and theory of positive operators again.

In the case of the singular VGT model, in Section 3.3, we do not have compactness and therefore used a different approach. Existence of an eigensolution for constant cell division and death rate, logistic plasmid reproduction, and scalable plasmid segregation kernel was shown using several transforms, including the Laplace transform. Due to lack of compactness, the spectral analysis did not yield existence of a dominant eigenvalue but that there are no elements in the spectrum with larger real part than the eigenvalue $\lambda = \beta - \mu$. Hence, instead of spectral analysis, we used the Generalized Relative Entropy method to show that the eigenfunction is asymptotically stable under assumption on the initial plasmid distribution, the eigenfunction, and the dual eigenfunction.

The proof of existence of an eigensolution for the singular VGT model was constructive and resulted in a method to construct the eigensolution to both VGT models numerically. The method used was fixed point iterations on subintervals of the domain that converge by the Banach Fixed Point Theorem. The eigensolutions for both the regular and the singular model were constructed numerically in this way for visualization. The numerical construction of the eigenfunction indicates that in the long-run the plasmid segregation mode, uniform, unimodal, or bimodal, does not influence the plasmid distribution. In each case, a large proportion of bacteria has no or only few plasmids. The fraction of bacteria with few plasmids increases monotonously with the constant cell division rate, as would be expected, and a change of the constant cell death rate does not influence the distribution of plasmids but only the growth of the bacterial population.

In the fourth chapter, we modeled vertical and horizontal gene transfer by conjugation. We considered two different cases of transmission of mobilizable plasmids, viz.

that they are only transferred if the recipient does not have a mobilizable or that they are transferred regardless of whether the recipient carries a copy of the mobilizable plasmid. In the continuum limit, one obtains the same continuous model in both cases. The proportion of bacteria without the conjugative plasmid grows to 1 in the long-run, i.e., all bacteria will carry the conjugative plasmid in the long-run in this model. If the metabolic burden for the conjugative plasmid is too high, then it is lost.

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Bibliography

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List of Abbreviations and Notation

Abbreviations:

a.e.	almost every(where)
GRE	Generalized Relative Entropy
HGT	Horizontal Gene Transfer
ODE	Ordinary Differential Equation
PDE	Partial Differential Equation
VGT	Vertical Gene Transfer
w.r.t.	with respect to

Notation used in the models:

$u(z,t)$	density of bacteria structured by plasmid number z and time t
$b(z)$	plasmid reproduction rate
$\beta(z)$	cell division rate
$\beta_m(z) = \beta(z)\,\chi_{[m,z_0]}$	
$\mu(z)$	cell death rate
$k(z,z')$	plasmid segregation kernel
$\Phi(\xi)$	plasmid segregation for a scalable kernel
m	threshold for plasmid segregation, i.e., bacteria with fewer than m plasmids give all plasmids to one daughter cell at cell division
z_0	maximal plasmid number
$\mathcal{U}(z)$	eigenfunction for the VGT model
$\Psi(z)$	dual eigenfunction for the VGT model
θ	conjugation rate
$v(z,t)$	density of bacteria with a conjugative plasmid, structured by the number of mobilizable plasmids z and time t

Mathematical symbols and notation:

$\mathbb{N} = \{1,2,3,\ldots\}$

$\mathbb{N}_0 = \{0,1,2,\ldots\}$

$\mathbb{R}$	real numbers

$\mathbb{R}_{>0}$	positive real numbers
$\mathbb{R}_{\geq 0}$	non-negative real numbers
$\mathbb{C}$	complex numbers
$L^1((a,b))$	Lebesgue integrable functions on (a,b)
$L^1_+((a,b))$	Lebesgue integrable functions on (a,b) that are non-negative a.e.
$L^p((a,b))$	functions on (a,b) whose p-th power is Lebesgue integrable
$L^\infty((a,b))$	measurable functions on (a,b) that are bounded a.e.
$W^{k,p}((a,b))$	Sobolev space of k times weakly differentiable functions in $L^p((a,b))$
$\mathcal{C}^0([a,b])$	continuous functions on the interval $[a,b]$
$\mathcal{C}^n([a,b])$	functions on $[a,b]$ with continuous derivative up to order $n \in \mathbb{N}$
K°	interior of the set K
$\overline{K}$	closure of the set K
X^*	dual space of X
$X \subset\subset Y$	X is compactly embedded in Y
$B_1(X)$	closed unit ball in the Banach space X
$D(A)$	domain of the operator A
I	identity operator
$\lVert\cdot\rVert_{\mathrm{op}}$	operator norm
$\lVert\cdot\rVert_\infty$	supremum norm
$\mathrm{Lip}(\cdot)$	Lipschitz constant
$\Re(z)$	real part of $z \in \mathbb{C}$
$\Im(z)$	imaginary part of $z \in \mathbb{C}$
$\chi_A(x)$	characteristic function
$\lceil\cdot\rceil$	ceiling function
$(\cdot)_+$	positive part
$\mathrm{sgn}(\cdot)$	sign function
$\log(\cdot)$	natural logarithm
$\hat{f} = \mathcal{L}\{f\}$	Laplace transform of the function f
$\mathcal{L}^{-1}\{f\}$	inverse Laplace transform of the function f
$f \sim g$ at a	$\lim\limits_{x\to a} \frac{f(x)}{g(x)} = C \in (0,\infty)$
$f * g$	convolution of the functions f and g
$f^{*n} * g$	n-fold convolution of f with g
$\lim\limits_{x\to a^+}, \lim\limits_{x\to a^-}$	right-, left-sided limit
$\frac{d^+}{dt}, \frac{d^-}{dt}$	right-, left-sided derivative
∂^+, ∂^-	right-, left-sided partial derivative

$\dot{u}(t)$	derivative w.r.t. time of $u(t)$
$R(\lambda, A)$	resolvent of the operator A
$\sigma(A)$	spectrum of the operator A
$\sigma_P(A)$	point spectrum of the operator A
$\rho(A)$	resolvent set of A
$r(A)$	spectral radius of the operator A

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