Mathematics of Cell Growth

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Abstract

We present a model that describes growth, division and death of cells structured by size. Here, size can be interpreted as DNA content or physical size. The model is an extension of that studied by Hall and Wake [24] and incorporates the symmetric as well as the asymmetric division of cells.

We first consider the case of symmetric cell division. This leads to an initial boundary value problem that involves a first-order linear PDE with a functional term. We study the separable solution to this problem which plays an important role in the long term behaviour of solutions. We also derive a solution to the problem for arbitrary initial cell distributions. The method employed exploits the hyperbolic character of the underlying differential operator, and the advanced nature of the functional argument to reduce the problem to a sequence of simple Cauchy problems. The existence of solutions for arbitrary initial distributions is established along with uniqueness. The asymptotic relationship with the separable solution is established, and because the solution is known explicitly, higher order terms in the asymptotics can be obtained. Adding variability to the growth rate of cells leads to a modified Fokker-Planck equation with a functional term. We find the steady size distribution solution to this equation. We also obtain a constructive existence and uniqueness theorem for this equation with an arbitrary initial size-distribution and with a no-flux condition.

We then proceed to study the binary asymmetric division of cells. This leads to an initial boundary value problem that involves a first-order linear PDE with two functional terms. We find and prove the unimodality of the steady size distribution solution to this equation. The existence of higher eigenfunctions is also discussed. Adding stochasticity to the growth rate of cells yields a second-order functional differential equation with two non-local terms.

These problems, being a particular kind of functional differential equations exhibit unusual characteristics. Although the associated boundary value problems are well-posed, the spectral problems that arise by separating the variables, cannot be easily shown to have a complete set of eigenfunctions or the usual orthogonality properties.

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Published work

The following publications are based on the research work done during the course of this thesis:

1. **Ali A. Zaidi**, B. van-Brunt, G. C. Wake, A model for asymmetrical cell division, *Mathematical Biosciences and Engineering*, accepted November 2014.

2. Graeme Wake, **Ali A. Zaidi** and Bruce van-Brunt, Tumour Cell Biology and some New Non-local Calculus. *The Impact of Applications on Mathematics -Proceedings of Forum "Math-for-Industry" 2013*, Springer 2014.

3. **Ali A. Zaidi**, B. van-Brunt, G. C. Wake, Solutions to an advanced functional partial differential equation of the pantograph-type, submitted December 2014.

Oral Presentations

The following oral presentations and talks were given, based on the research work done during the course of this thesis:

1. Presented and won **first** prize for my talk on "Solutions to an advanced functional partial differential equation of the pantograph-type" at the second INMS Postgradaute Student Conference 2014.

2. Presented and won **second** prize for my talk on "A size structured cell growth model" at the first INMS Postgradaute Student Conference 2013.

3. Presented a talk on "Asymmetric cell division arising in stem cells and cancer" at the ANZIAM Conference 2013.

4. Presented a talk on "Solutions to an advanced functional partial differential equation of the pantograph-type" at the NZ Math and Stat Postgraduate Student Conference 2014.

5. Presented a talk on "A size structured cell growth model" at the NZ Math Colloquium 2013.

6. Presented a talk on "A size structured cell growth model" at the NZ Math and Stat Postgraduate Student Conference 2013.

7. Presented a talk on "Multiple delay differential equations and a nonlinear eigenvalue problem" at the NZ Math Colloquium 2012.

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Chapter 1

Introduction

1.1 Cell Biology

A cell is usually considered a basic "structural" and "functional" unit of a living organism. A "large" number of individual cells constitutes a "cell population". Individual cells within a cell population increase their numbers by means of cell growth and division, a property referred to as the "cell proliferation". In this thesis, we use cell growth in the context of an increase in the "physical" size of a cell. This size could be the mass, radius or volume of a cell. More generally, DNA content can also be used as a proxy for size. The measurement of the DNA content in a cell is usually done through a scientific process known as "flow cytometry" [5, 41, 65, 66, 67].

It was generally believed that cells divide in a symmetrical way, i.e., one mother cell divides to give two daughter cells of equal sizes. However, it has been observed over the years that many cell divisions are asymmetric [49, 10, 22]. An asymmetric cell division generally means the following:

1. A mother cell divides into two daughter cells of different sizes.
2. Cellular constituents are preferentially segregated into only one of the two daughter cells.
3. The two daughter cells are endowed with different potentials to differentiate into a particular cell type.

[49, 30]. Neumüller and Knoblich [49], Chant [11], Thorpe *et al.* [69] observed that the division of yeast is highly asymmetric. Gromley *et al.* [23] and

Neumüller and Knoblich [49] noted that even in cultured cells, only one of the daughter cells often inherits the midbody. Piel *et al.* [54], Spradling and Zheng [64], Neumüller and Knoblich [49] mentioned that the protein composition of the two centrosomes may be different. Rando [56], found that the chromatin in the two daughter cells could be different. In the nematode *C. elegans* and the fruitfly *Drosophila*, cell division is asymmetric.

Morrison and Kimble [48], Gönczy [22] discuss an example of symmetric and asymmetric cell division and the coordination of these division mechanisms in stem cells. These stem cells can divide asymmetrically and give rise to one stem cell (a property referred to as "self renewal") and another daughter cell that can differentiate into a more specialized cell. Stem cells can also divide symmetrically giving rise to either two stem cells or to two daughter cells that can differentiate into more specialized cells. Most stem cells switch between these two modes of division according to the needs of the body. For instance, stem cells increase in number during development [48, 35], or after an injury [48, 83] by virtue of symmetric cell division.

A connection between the sizes of the daughter cells and their fates was discussed by Gönczy [22]. This paper suggests that in animal cells, when the anaphase [1] spindle is positioned asymmetrically in the mother cell, daughter cells differ not only in fate but also in cell size. This asymmetric division can be observed in *C. elegans* and the *Drosophila*. Similarly, It has been observed that in animal cells, the size of the two daughter cells depends upon the the position of the mitotic spindle [49, 21]. A centrally located mitotic spindle will result in two daughter cells of the same size, whereas any displacement of the spindle toward one pole will generate one larger and one smaller daughter cell [49]. For a detailed account on the asymmetric cell division in the *C. elegans* and the *Drosophila*, see Neumüller and Knoblich [49], Gönczy [22].

In this thesis, we use asymmetric cell division in the context of a mother cell dividing into two daughter cells of different sizes. This asymmetric cell division conserves mass.

Asymmetry is extreme in case of certain diploid cells. Diploid cells have two homologous copies of each chromosome and certain diploid cells divide so unevenly that most of the cytoplasm is inherited by one of the two daughter cells called egg, and the other daughter cell called a polar body inherits much less and dies. In somatic divisions, asymmetry is mild and rarely one

[1] anaphase: One of the stages of mitosis or meiosis in which chromosomes divide and move towards opposite poles of a cell.

daughter cell is more than double the size of the other [49].

A cell passes through four phases in order to divide and reproduce. These are the G_1, S, G_2 and M phases. These four phases are preceded by the G_0 phase (also referred to as the quiescent/senescent phase) which is a resting phase and cells stop dividing in G_0. Spencer *et al.* [63] noted that in metazoans, cells decide at the end of mitosis to either start the next cycle immediately or to enter G_0. Begg [5] observed that a cell may remain in the G_0 phase for years before returning to the cell division cycle. A single-compartment model does not distinguish between the various phases of the cell cycle whereas a multi-compartment model has a separate cell growth model for each of the cell cycle phase. Begg [5] suggested that if DNA is considered as the measure of the cell size, then a multi-compartment model is more appropriate. On the other hand, single-compartment model is more suited to modeling the actual physical size of a cell since physical size changes in the G_1, G_2 and the S phase. Begg [5] also noted that the mathematical ideas used in the study of single-compartment models may be useful in the study of multi-compartment models. In this thesis, we deal only with single-compartment models.

Tzur *et al.* [73] studied intrinsic mechanisms for coordinating growth and cell cycle in metazoan cells. They examined cell size distributions in populations of lymphoblasts and showed that the growth rate is size dependent through out the cell cycle. This motivates us to write the growth rate g of a cell as a function of its size x i.e., $g = g(x)$. In our general cell growth model (chapter 4), we have used $g(x)$ to denote the growth rate of a cell of size x, however, in subsequent analysis (except chapter 9, section 9.2) we have taken the growth rate g to be a constant for simplicity.

Rouzaire-Dubois *et al.* [57] studied the connection between cell size and division in rat glioma cells and found that the rate of cell proliferation changed with cell volume in a bell shaped manner, so that it is optimal within a cell volume window and is controlled by low and high cell size checkpoints. They observed that glioma cell proliferation is controlled predominantly but not exclusively by cell size-dependent mechanisms. This provides us with a rationale for making the frequency of division b size dependent. In our generic model (chapter 4), we have used the frequency of division, or the rate of cell division b as $b(x)$, where x is the size of a cell. However, in subsequent analysis (except chapter 9, section 9.2) again we have taken the splitting rate of cells b as a constant for simplicity.

1.2 Outline of thesis

Chapter 2

In this chapter we review the mathematical literature and the work done previously in this subject area. We introduce some basic size-structured cell growth models used and formulated hitherto by various mathematicians. These models usually involve functional differential equations. We note the paucity, and the development, of solution techniques to solve these functional differential equations.

Chapter 3

Chapter 3 deals with some of the basic concepts, definitions and notations we use through out the thesis. These provide the basic building blocks to the subsequent development of theory and analysis. We define the concepts of cell number density and the steady size distributions. We also introduce notations for the growth rates and the splitting rates of cells and discuss their nature.

Chapter 4

Here we present a model that describes the growth, division and death of a cell population structured by size. The model is an extension of that studied by Hall and Wake [24] and incorporates the asymmetric division of cells. Initially, we consider deterministic growth and splitting rates. We then extend this cell growth model to include stochasticity in the growth rate of cells. This extension results in a “dispersion-like” model and yields a second order partial integro-differential equation.

Chapter 5

In this chapter we study the symmetric cell division problem with deterministic growth rate and focus on separable solutions to the cell growth equation. The motivation for the study of such solutions came from experimental results for certain plant cells that suggested solutions of this type, at least as a long term approximation [27]. We find "the steady size distribution" (SSD) and show that it is unique. We discuss the existence and uniqueness of higher eigenfunctions. The question of whether the set of the eigenfunctions we obtain are complete is still open.

Chapter 6

Here we study the symmetric division of cells. A model for cells structured by size undergoing growth and division leads to an initial boundary value problem that involves a first-order linear partial differential equation with a functional term. Here, size can be interpreted as DNA content or physical size. The separable solution to this problem has been studied extensively and plays an important role in the long term behaviour of solutions. It has been observed experimentally and shown analytically that solutions for arbitrary initial cell distributions are asymptotic to the separable solution as time goes to infinity. The solution to the problem for arbitrary initial distributions, however, is elusive owing to the presence of the functional term and the paucity of solution techniques for such problems.

In this chapter we derive a solution to the problem for arbitrary initial cell distributions. The method employed exploits the hyperbolic character of the underlying differential operator, and the advanced nature of the functional argument to reduce the problem to a sequence of simple Cauchy problems. The existence of solutions for arbitrary initial distributions is established along with uniqueness. The asymptotic relationship with the separable solution is established, and because the solution is known explicitly, higher order terms in the asymptotics can be readily obtained.

Chapter 7

In this chapter, we study a cell growth equation with dispersion. This involves a second order functional partial differential equation. We obtain steady size distributions corresponding to the separable solutions of the functional equation and establish the existence and uniqueness of higher eigenfunctions y_m for $m \geq 2$. It remains elusive to determine the eigenvalue λ_1 owing to the indeterminate nature of the value of the eigenfunction at the origin. This value of λ_1 leads to a non-linear functional differential equation. We expose the problem. It is still an open question as to whether or not the solutions obtained by separation of variables form a complete spanning set

We then obtain a constructive existence theorem for the linear, non-local dispersion growth equation with an arbitrary initial size distribution and with a no-flux boundary condition. We show that this solution is unique.

Chapter 8

Here, we study the case of binary asymmetrical splitting in which a cell of size ξ divides into two daughter cells of different sizes and find the steady size distribution (SSD) solution to the non-local differential equation. We then discuss the shape of the SSD solution and show that it is unimodal. The existence and uniqueness of higher eigenfunctions is also discussed.

Chapter 9

In chapter 9 we consider the case of binary asymmetrical splitting and variable cell growth. We investigate the cell growth equation with dispersion, first for the constant coefficients case (Section 9.1) and then for a certain choice of non constant coefficients that correspond to dispersion, growth and splitting rates (Section 9.2).

For the constant coefficients case, we find the steady size distribution (SSD) solution to the cell growth equation with dispersion and show that the solution is unique and positive. We then discuss the shape of the SSD solution and establish that the SSD solution is unimodal.

Our choice of non-constant coefficients corresponding to the dispersion, growth and splitting rates leads to a Bessel type operator, and it is shown that there is a unique probability distribution function that solves the equation. The solution is constructed using the Mellin transform and is given in terms of an infinite series of modified Bessel functions.

Chapter 2

Literature review

Mathematical models use mathematical concepts and language to describe and analyze information about a natural, biological, social or any other phenomena. Population models are those mathematical models which deal with populations. These models have long been used to analyze various biological and physical processes. Population models can be classified as either structured or unstructured. The first to appear were the unstructured population models. Such models are based on the total number of individuals in a population. This means that individuals within a population cannot be distinguished on the basis of either their age, size or any other property. The human population growth was analyzed by Malthus in 1798 ([40]) through an unstructured population model which can be written as

$$\frac{dN}{dt} = \beta N - \mu N = \gamma N,$$

where N is the number of individuals in a population, β is the per capita birth rate, μ is the per capita death rate and $\gamma = \beta - \mu$ is called the Malthusian parameter or the intrinsic rate of natural increase. The model, however, ignores many relevant facts, including the age of individuals. For instance, a newborn individual cannot reproduce. This shortcoming lead to the use of structured population models, which are useful when individuals within a population could be distinguished from one another on the basis of some attribute. For instance, Mckendrick [43] in 1926 structured cell population models on age. Age structured population models were also used and discussed by various mathematicians including Bailey [2], Lewis [38], Leslie [37], Lotka [39], Sharpe and Lotka [60], Feller [19], Scherbaum and Rasch [59], von

Foerster [79], Oster [51], Trucco [70, 71] and Rubinow [58]. The book by Metz and Diekmann [44] and Hall's PhD thesis [25] provide detailed accounts on age structured population models.

Living cell populations which simultaneously grow and divide are usually structured on size. This requires us to focus our attention to the size structured cell population models. In this case, cells with in a population are distinguishable on the basis of their size, where the size could be the mass, volume, DNA content or any other attribute that quantifies the physical dimension of a cell. The measurement of the DNA content is done through a scientific process.

Various researchers structured cell populations on size during the 1960s. These include Collins and Richmond [12] who described a method to determine the growth rate of "*Bacillus cereus*" at any given length; Koch and Schaechter [34] who proposed a model for statistics of the cell division process; Powell [55] who discussed the consequences of the hypothesis given by Koch and Schaechter; and Painter and Marr [52] who studied microbial populations. In 1971, Sinko and Streifer [62] formulated a deterministic, size structured model for the dynamics of single species populations of organisms reproducing by fission. They discussed the case of planarian worms in which the original organism breaks into a parent organism and an offspring. This gives the evolution equation as

$$\frac{\partial \rho(t,m)}{\partial t} + \frac{\partial [g(t,m)\rho(t,m)]}{\partial m} = -b(t,m)\rho(t,m) +$$
$$\frac{1}{1-H} b\left[t, \frac{m}{(1-H)}\right] \rho\left[t, \frac{m}{(1-H)}\right] + \frac{1}{hH} b\left[t-\tau, \frac{m}{(hH)}\right] \rho\left[t-\tau, \frac{m}{(hH)}\right]$$

where $\rho(t,m)$ is the mass density function which depends on mass m and time t. The mass of the offspring just after fission is denoted by Hm, where H is a parameter, and so the mass retained by the parent organism just after fission is $(1-H)m$. Here, the time required by the offspring after fission to attain the capability of growth is denoted by τ after which the mass of the offspring is given by hHm, where h is the fraction of the mass retained after τ. The function $b(t,m)$ is defined as "the rate at which an organism of mass m at time t divides" and $g(t,m)$ is the "average rate of growth for an organism of mass m at time t". The left hand side of the above continuity equation accounts for the continuous changes in mass. Sinko and Streifer noted that "the first term on the right hand side accounts for animals of mass m which give birth and fall to a lower mass, the second term for animals of higher mass which give birth and fall to mass m, and the last term accounts for the number of neonates (offspring which have just developed into viable individuals) of mass m.

O. Diekmann *et al.* [18] analyzed a related linear problem during the 1980s. Heijmans [29] formulated a nonlinear size structured model to describe the dynamics of cell populations in which cells divide asymmetrically (into two unequal parts) by fission. Heijmans [29] also observed that cell size is generally accepted by cell biologists as one of the most decisive parameters and that it is attractive to structure cell population models on size because cell size can be measured with relative ease and precision. Following Sinko and Streifer [62], O. Diekmann *et al.* [18] and others, Hall and Wake [24] formulated a size structured cell population model and considered the case where a cell of size x divides into α daughter cells of the same size $\frac{x}{\alpha}$. This leads to an advanced first order functional partial differential equation of the form

$$\frac{\partial}{\partial t}(n(x,t)) + \frac{\partial}{\partial x}(g(x)n(x,t)) = -b(x)n(x,t) + \alpha^2 b(\alpha x,t)n(\alpha x,t). \tag{2.1}$$

where $n(x,t)$ denotes the number of cells of size x at time t, $g(x) > 0$ is the growth rate of these cells, and $b(x) > 0$ is the rate at which cells of size x divide to create α daughter cells. Here $\alpha > 1$ is a constant (in applications it is usually 2). The first term on the left hand side of equation (2.1) accounts for the net rate of change while the second term accounts for the growth rate in size. The first term on the right hand side of equation (2.1) denotes the loss of cells through division while the second term on the right hand side gives the cells from division at size αx. Hall and Wake [24] noted the interest of biologists in the steady size distributions (SSDs) which can arise in an exponentially increasing population with proportion of any given size of cells remaining constant. This interest is also observed in Collins and Richmond [12] and Tyson and Diekmann [72]. An SSD solution to equation (2.1) corresponds to a separable solution,

$$n(x,t) = N(t)y(x), \tag{2.2}$$

where y is a probability density function (pdf). Assuming that the growth and division rates are functions of size alone and substituting the solution form (2.2) into equation (2.1) yields

$$\frac{1}{N(t)}\frac{d}{dt}N(t) = \frac{1}{y(x)}\left(-\frac{d}{dx}(g(x)y(x)) - b(x)y(x) + \alpha^2 b(\alpha x)y(\alpha x)\right) = \Lambda, \tag{2.3}$$

where Λ is a constant of separation. Equation (2.3) gives

$$N(t) = Ae^{\Lambda t},$$

for some constant A, and the functional differential equation

$$\frac{\partial}{\partial x}(g(x)y(x)) + (b(x) + \Lambda)y(x) = \alpha^2 b(\alpha x)y(\alpha x). \tag{2.4}$$

The boundary conditions for this problem are

$$y(0) = 0, \quad \lim_{x\to\infty} y(x) = 0, \tag{2.5}$$

and since y must be a pdf, it is required that $y \in L^1[0,\infty)$, $y(x) \geq 0$ for all $x \geq 0$, and

$$\int_0^\infty y(x)dx = 1. \tag{2.6}$$

The constant Λ is elusive except in certain cases. Integrating equation (2.1) from 0 to ∞, using the boundary conditions (2.5) along with the normalizing condition (2.6), yields

$$\Lambda = (\alpha - 1)\int_0^\infty b(x)y(x)dx. \tag{2.7}$$

Here, it is assumed that $b(x)y(x) \in L^1[0,\infty)$. The first case studied by Hall and Wake [24] concerned constant growth and division rates. Let $g(x) = g$ and $b(x) = b$, where g and b are positive constants. Equation (2.7) and condition (2.6) imply

$$\Lambda = (\alpha - 1)b. \tag{2.8}$$

For this case, equation (2.4) reduces to the pantograph equation

$$gy'(x) + b\alpha y(x) = b\alpha^2 y(\alpha x). \tag{2.9}$$

The pantograph equation, as van-Brunt and Wake [75] observe, appears in many applications such as light absorption in the Milky Way [1], a ruin problem [20], and the collection of current in an electric train [50]. A detailed analysis of the equation is given by Kato and McLeod [32] (see also [31]). The cell growth application differs, however, because it is a boundary value problem involving an eigenvalue. In this sense the problem can be regarded as a singular "Sturm Liouville" problem. Indeed, one can find higher eigenvalues, but the corresponding eigenfunctions are not pdfs (see [77] and [78]). Hall and Wake [24] showed that there exists a unique pdf solution to equation (2.9). It is of interest to note that they did not need to impose a positivity condition on y. It turns out that the eigenvalue Λ corresponds to the first eigenvalue for the "Sturm-Liouville" problem and the corresponding eigenfunction y has no positive zeros (cf. [77]).

In some applications such as the aforementioned light absorption problem [1], a ruin problem [20] and a cell growth model [24], equation (2.9) is advanced and the solution is required to be a probability density function (pdf). The strong connection with problems in probability, in hindsight, is not surprising given that it can be derived as a consequence of a first order Markov process. The relationship has been explored by Derfel [15].

Another relation for Λ can be gleaned by multiplying both sides of equation (2.4) by x and then integrating from 0 to ∞. Assuming $g(x)y(x)$ and $xy(x)$ are in $L^1[0, \infty)$, this approach yields

$$\Lambda = \frac{\int\limits_0^\infty g(x)y(x)dx}{\int\limits_0^\infty xy(x)dx}. \tag{2.10}$$

In particular, if $g(x) = gx$, where g is a constant, then $\Lambda = g$. This case was explored by Hall and Wake [26] for $b(x) = bx^n$, where n is a positive number and b is a constant. They showed that there is a unique pdf solution to the boundary-value problem (2.4) subject to condition (2.5). Van-Brunt and Vlieg-Hulstman [77] then showed that this boundary value problem leads to a family of eigenvalues and corresponding eigenfunctions with the first eigenfunction being the probability density function. The existence of such eigenvalues and eigenfunctions was established through the use of Mellin transforms. The Mellin transform of a function $h(x)$ is given by

$$M[h,s] = \int_0^\infty x^{s-1} h(x)dx. \tag{2.11}$$

The eigenvalues are given by the discrete spectrum

$$\lambda_m = b\alpha^{m(n+1)+1}, \tag{2.12}$$

for $m = 0, 1, 2, \ldots$. The corresponding eigenfunctions are in terms of Dirichlet series of the form

$$y_m(x) = K_m \left(e^{-bx^{n+1}/(n+1)} + \sum_{k=1}^{\infty} p_k(\lambda_m) e^{-b\alpha^{k(n+1)}x^{n+1}/(n+1)} \right), \tag{2.13}$$

where

$$K_m = (n+1)\left(\frac{b}{n+1}\right)^{1/(n+1)} \left(\Gamma\left(\frac{1}{n+1}\right)\right)^{-1} \prod_{k=0}^{\infty}\left(1 - \frac{1}{b\alpha^{(k-m)(n+1)+1}}\right)^{-1}, \tag{2.14}$$

and

$$p_k(\lambda_m) = \frac{(-1)^k \alpha^{km(n+1)}}{\alpha^{(n+1)k(k-1)/2} \prod_{j=1}^{k} (1 - \alpha^{-(n+1)j})}. \tag{2.15}$$

Notice that the pdf solutions obtained by Hall and Wake [24] are recovered when $m = 0$ in equation (2.13). The use of Mellin transforms to solve the problem was a notable feature of van-Brunt and Vlieg-Hulstman's work. It provides a powerful tool for the construction of eigenvalues and eigenfunctions. The question whether these eigenfunctions are complete, i.e., whether they form a basis of some space, is not answered by van-Brunt and Vlieg-Hulstman [77]. In this thesis (see chapter 5), we will use the Mellin transforms to construct eigenfunctions that arise in cell growth models. We also discuss the "completeness" of eigenfunctions.

DaCosta *et al.* [13] revisited the two cases (the constant coefficient case and the variable coefficient case) of equation (2.4) and showed that the distributions must be unimodal. They further showed that, for more general choices of growth and division rates, at least one eigenvalue exists. Note that the case where the growth rate is linear $g(x) = gx$, and the division rate is constant, $b(x) = b$, is special. For this case, equations (2.7) and (2.10) imply

$$\Lambda = (\alpha - 1)b = g,$$

so that the parameters α, b and g cannot be specified independently.

The pantograph equation has been generalized in many ways. For instance, it has been studied in the complex plane by Derfel and Iserles [16]. They considered two generalizations of the pantograph equation to the complex plane, first a "*pantograph equation with involution*", i.e., an equation of the form

$$y'(z) = \sum_{k=0}^{m-1} a_k y(\omega^k z) + \sum_{k=0}^{m-1} b_k y(r\omega^k z) + \sum_{k=0}^{m-1} c_k y'(r\omega^k z), \; z \in \mathbb{C}, \tag{2.16}$$

where $a_k, b_k, c_k \in \mathbb{C}$, $k = 0, 1, \ldots, m-1$, are given, $r \in (0, 1)$, and "ω is the m-th primitive root of unity, i.e., $\omega = e^{2\pi i/m}$". They also considered a "*pantograph equation of the second type*", i.e., an equation of the form

$$y(z) = \sum_{j=0}^{l} \sum_{k=1}^{n} a_{j,k} y^{(k)}(\omega_j z), \quad z \in \mathbb{C},$$

where $a_{j,k}, \omega_j \in \mathbb{C}$, together with appropriate initial conditions at the origin. Another generalization of the pantograph equation has been to replace the simple functional argument with a nonlinear argument (Heard [28], van-Brunt *et al.* [74]). Second order versions have been studied in relation to a cell-growth model by Basse *et al.* [4], Wake *et al.* [80], as a singular "Sturm Liouville" problem by van-Brunt *et al.* [76], and in the context of complex dynamics by Marshall *et al.* [42]. Matrix versions, among numerous other variations, have also been considered by Carr and Dyson [7].

Hall and Wake's model [24] was used by Basse *et al.* [4], Begg *et al.* [6] and Hall *et al.* [27] to describe cell growth in plants. Basse *et al.* [3] used the same model for tumor cell growth. Suebcharoen *et al.* [68] extended the model to include the asymmetric division of cells where a cell of size $\beta_i x$

divides into $\beta_i > 1$ daughter cells of different sizes at a rate a_i for $i = 1, 2$. The resulting model is a first order partial integro-differential equation

$$\frac{\partial n(x,t)}{\partial t} = -g\frac{\partial n(x,t)}{\partial x} - B(x)n(x,t) + \int_x^\infty W(x,\xi)n(\xi,t)d\xi - \mu n(x,t), \tag{2.17}$$

where $B(x)$ is the rate at which cells of size x divide. Also, $n(x,t)$, $g > 0$ and $\mu \geq 0$ are the number density, growth rate and mortality of cells respectively. The integral term denotes the increase in cell number of size x due to the division of cells of size greater than x and $W(\xi, x)$ is the "rate at which cells of size x further subdivide into cells of size $\frac{x}{\beta_i}$". Mathematically, $W(\xi, x)$ is given by

$$W(\xi,x) = a_1\beta_1\delta\left(\xi - \frac{x}{\beta_1}\right) + a_2\beta_2\delta\left(\xi - \frac{x}{\beta_2}\right).$$

Equation (2.17) is supplemented with an arbitrary initial condition

$$n(x,0) = n_0(x), \ x \geq 0, \tag{2.18}$$

the boundary condition

$$n(0,t) = 0, \ t \geq 0, \tag{2.19}$$

and the condition

$$\lim_{x\to\infty} n(x,t) = 0. \tag{2.20}$$

Suebcharoen *at al.* [68] noted the occurrence of such an asymmetric division in the embryos of *C. elegans* (worms) and *Drosophila* (flies). They considered an SSD solution of the form

$$n(x,t) = N(t)y(x),$$

where $y(x)$ is a pdf. This approach yields a functional differential equation with two non-local terms and is given by

$$y'(x) + \left(\frac{a_1\beta_1 + a_2\beta_2}{g(\beta_1+\beta_2)} + \frac{\mu - \Lambda}{g}\right)y(x) = \frac{a_1\beta_1^2}{g}y(\beta_1 x) + \frac{a_2\beta_1^2}{g}y(\beta_2 x), \tag{2.21}$$

where the pdf eigenvalue is

$$\Lambda = \mu - \left(a_1\beta_1 + a_2\beta_2 - \frac{a_1\beta_1 + a_2\beta_2}{\beta_1 + \beta_2} \right), \tag{2.22}$$

which reduces equation (2.21) to

$$y'(x) + Ky(x) = \frac{a_1\beta_1^2}{g} y(\beta_1 x) + \frac{a_2\beta_1^2}{g} y(\beta_2 x). \tag{2.23}$$

The boundary conditions for this problem are

$$y(0) = 0, \quad \lim_{x\to\infty} y(x) = 0, \tag{2.24}$$

where $K = \frac{a_1\beta_1 + a_2\beta_2}{g}$. Suebcharoen *et al.* [68] showed that the solution to equation (2.23) subject to the conditions in (2.24) is in terms of a double Dirichlet series. The uniqueness and positivity of solutions were also shown. However, the proof of the SSD solution being unimodal remained elusive.

Hall and Wake's model [24], however, did not cover the asymmetric division of cells and Suebcharoen *et al.*'s model [68] did not focus on the biological interpretation of the splitting kernel. In this thesis (see chapter 4), we extend Hall and Wake's model to cater for the asymmetric division of cells and establish the model directly from a biological interpretation of the splitting kernel.

The model given by Suebcharoen *et al.* [68] and the model given by Hall and wake [24] were deterministic in nature and there was no randomness in the number density, growth and division of cells. Wake *et al.* [80] extended the model given by Hall and Wake [24] to allow for the number density of cells over a size variable to disperse over size. Their model was, however, for symmetric cell division and considered the scenario of a cell of size αx, where $x > 0$ dividing into α daughter cells of equal sizes x and so $\alpha > 1$. The resulting model was in accordance with the modified Fokker-Plank equation

$$n_t(x,t) = -(gn)_x + (Dn)_{xx} + b\alpha^2 n(\alpha x, t) - bn(x,t), \tag{2.25}$$

where D is the dispersion coefficient for the growth of cells and is given by

$$D = \frac{variance}{2},$$

and $n(x,t)$ is the number density. The model is supplemented with the no flux condition

$$Dn_x(0,t) - gn(0,t) = 0, \tag{2.26}$$

an arbitrary initial condition

$$n(x,0) = n_0(x), \tag{2.27}$$

and the conditions

$$\lim_{x\to\infty} n(x,t) = 0, \ \lim_{x\to\infty} n_x(x,t) = 0. \tag{2.28}$$

Here g is the growth rate and b is the frequency of splitting. Hall and Wake [80] considered growth rate $g(x) = g$ and frequency of division $b(x) = b$. They obtained an SSD solution to equation (2.25) on a pattern similar to that used by Hall and Wake [24] (discussed earlier) for the deterministic case. It is interesting to note that the eigenvalue corresponding to a pdf solution y in both these cases (the deterministic case and the dispersion case) remains the same (given by equation (2.8)). However, the functional differential equation associated with the eigenvalue in the dispersion case involves a second order derivative and is given by

$$\frac{D}{g}y''(x) - y'(x) - \frac{b\alpha}{g}y(x) + \frac{b\alpha}{g}\alpha y(\alpha x) = 0, \tag{2.29}$$

where $\frac{D}{g} > 0$ has dimensions of length and $\frac{b\alpha}{g} > 0$ has dimensions of length^{-1}.The "no-flux" condition given by equation (2.26) becomes

$$\frac{D}{g}y'(0) - y(0) = 0, \tag{2.30}$$

and condition (2.28) gives

$$\lim_{x\to\infty} y(x) = 0. \tag{2.31}$$

The solution to equation (2.29) is in the form of a Dirichlet series.

In this thesis (chapters 7, 9), we also extend 'variability in growth rates of cells' to the case of asymmetric cell division and consider certain choices of growth rates, splitting rates and dispersion coefficients.

Another second order analogue of the pantograph equation is given by a functional differential equation of the form

$$y''(x) - ay'(x) - by(x) + \lambda y(\alpha x) = 0. \tag{2.32}$$

subject to the normalizing condition (2.6), the boundary conditions (2.5) and

$$\lim_{x\to\infty} y'(x) = 0.$$

Here α, a and b are constants such that $\alpha > 1$, $a > 0$, and $b > 0$. This second order analogue was studied by van-Brunt *et al.* [76].

Perthame and Ryzhik [53] discussed a fragmentation equation

$$\begin{aligned}
&\frac{\partial}{\partial t}n(t,x) + \frac{\partial}{\partial x}n(t,x) + b(x)n(t,x) = 4b(2x)n(t,2x),\ t>0,\ x\geq 0,\\
&n(t,x=0) = 0,\ t>0,\\
&n(0,x) = n^0(x) \in L^1(\mathcal{R}^+),
\end{aligned} \tag{2.33}$$

and mentioned its occurrence as a "basic model for size-structured populations". Here $n(t,x)$ denotes the population density of cells of size x at time t. This equation arises when the rate of cell growth is constant and a cell divides into two identical daughter cells at a rate $b(x)$. The same equation also models problems in physics including degradation in polymers and droplets and in internet protocols. For the constant coefficient case i.e., $b(x) = B$, Perthame and Ryzhik [53] obtained the first eigenvalue

$$\lambda = B, \tag{2.34}$$

and the eigenfunction $N(x)$, corresponding to the pdf condition

$$\int_0^\infty N(x)dx = 1, \tag{2.35}$$

in the form of a Dirichlet series.

Michel *et al.* [45] considered the general scattering equation and the age, size and maturity structured population models and showed a common relative entropy structure using the "first eigenelements" of the problem . A binary fragmentation of cell division was considered by Michel *et al.* [46].

Laurençot and Perthame [36] described the growth-fragmentation equation which allowed for cell division into any number of pieces. The rate of convergence of fragmentation equations was studied by Cáceres *et al.* [8, 9].

Withers and Nadarajah [82] extended the results of Hall and Wake [24, 26] and of van-Brunt and Vlieg-Hulstman [77, 78]. They obtained solutions for generalizations of the steady size functional differential equation

$$y'(x) + c(x)y(x) = g(x)^{-1} \sum_{i=1}^{I} p_i b(\alpha_i x) y(\alpha_i x). \tag{2.36}$$

where p_i is the probability of a cell of size x dividing and creating α_i new cells of size $\frac{x}{\alpha_i}$ at the rate $b(x)$. The function $c(x)$ is determined by $b(x)$ and the growth rate of a cell $g(x)$. The solutions for $y(0) \neq 0$ were also considered. Withers and Nadarajah [82] considered the generalization when the daughter cells are given by a discrete valued probability distribution, i.e.,

$$\alpha = \alpha_i \text{ with probability } p_i, \quad i = 1, \dots, I \text{ and } \sum_{i=1}^{I} p_i = 1.$$

This was also analyzed for continuous pdf's by Hall *et al.* [27].

The second order cell growth model was studied by Wake *et al.* [80] and Kim [33] for the case of constant coefficients with one non-local term. A symmetric cell division model for plankton was studied by Basse *et al.* [4]. In their model, the dispersion and growth rates are constant, but $b(x)$ is a generalized function. The second order asymmetric model with non-constant coefficients has received little attention owing primarily to the difficulty in obtaining explicit solutions. Kim [33] studied a simpler related symmetric problem involving a second order pantograph equation with certain choices of non-constant coefficients. The role and placement of the eigenvalue parameter, however, is different. An interpretation of a related boundary-value problem as a singular Sturm Liouville problem is given by van-Brunt *et al.* [76]. In this study, the coefficients are constants and the eigenvalue parameter appears with the functional term.

More recently, van-Brunt and Wake [75] studied the second order symmetric cell growth problem given by

$$(D(x)y(x))'' - (g(x)y(x))' + \alpha^2 B(\alpha x)y(\alpha x) - (B(x) + \Lambda)y(x) = 0, \tag{2.37}$$

where $D = \frac{\sigma^2}{2}$ is the dispersion, σ is the variance, $g(x)$ is the growth rate, B is the frequency of division, α corresponds to the number of daughter cells and Λ is a constant that arises from separation of variables. The second order cell growth functional equation (2.37) is supplemented with a boundary condition

$$\lim_{x\to\infty} y(x) = 0, \tag{2.38}$$

and the zero flux conditions

$$\lim_{x\to\infty} \{(D(x)y(x))' - g(x)y(x)\} = 0, \tag{2.39}$$

$$\lim_{x\to 0^+} \{(D(x)y(x))' - g(x)y(x)\} = 0. \tag{2.40}$$

Van-Brunt and Wake [75] considered the case in which the dispersion is linear, i.e., $D(x) = Dx$ but the growth and the splitting rates are constant, i.e., $g(x) = g$ and $B(x) = B$ respectively. Here D, g and B are positive constants. This reduces the functional differential equation (2.37) to

$$xy''(x) - ay'(x) - by(x) = -b\alpha y(\alpha x), \tag{2.41}$$

where

$$a = \left(\frac{g}{D} - 2\right),$$

and

$$b = \frac{B\alpha}{D}.$$

It was shown that if a solution to the above problem, subject to the normalizing condition $\int_0^\infty y(x)dx = 1$, exists in $L^1[0,\infty)$, then that solution is unique and positive. They further showed that the probability density function (pdf) solutions to the second order cell growth equation (2.37) subject to conditions (2.38)-(2.40) and the normalizing condition $\int_0^\infty y(x)dx = 1$ is in terms of the modified Bessel functions. A key aspect in this study was the use of the Mellin transform to solve the functional equation and study the asymptotics of the solution as $x \to \infty$ and $x \to 0^+$. These techniques can also be exploited if the growth rate is linear, provided the Mellin transform can be determined. In chapter 9, we extend these results for the asymmetric division of cells in which dispersion is quadratic, growth rate is linear and frequency of division is quadratic.

Chapter 3

Basic Concepts, Assumptions and Notations

3.1 The nature of $W(x, \xi)$

The division event of a cell splitting into daughter cells of either equal or different sizes is captured by a function W. Here we define $W(x, \xi)$, where $\xi > x$, as the number density of cells of size x produced when one cell of size ξ divides. The function $W(x, \xi)$ is deterministic in nature and depends not only on the size ξ of the cell which divides (the mother cell) but also on the size x of the daughter cell. If the dimension of W is denoted by $[W]$, then $[W] = M^{-1}$, where M denotes size.

3.2 Rate of cell division $b(\xi)$

The rate at which the cells of a particular size ξ divide at a given time is determined by $b(\xi)$. This frequency depends on the size ξ of the mother cell. Its dimension is $[T^{-1}]$, where T denotes time. In general b could be either probabilistic or deterministic. We, however, restrict ourselves to a deterministic b.

3.3 Number density $n(x,t)$

The concept of number density has been used extensively in structured population models by various mathematicians. We consider a continuous number density $n(x,t)$ such that at time t, the total number of cells $N(t)$ between size a and size b is given by

$$N(t) = \int_a^b n(x,t)dx. \tag{3.1}$$

The dimension of $n(x,t)$ is $[M^{-1}]$, where M denotes size. There are other notations for number density which have been used in the literature. For instance, Sinko and Streifer [62] used $\rho(t,m)$ to denote a mass density function which depends on time t and mass m. In another paper [61], they presented an age-size structure of a population and used $\eta(t,a,m)$ to denote a density function which depends on time t, age a, and size m.

3.4 Growth rate $g(x)$

We use $g(x)$ to denote the growth rate of cells of size x at time t. The dimension of the growth rate g is $[MT^{-1}]$, where M denotes size and T denotes time. Initially, the growth rate is taken to be deterministic i.e., void of any randomness but later in the thesis we consider a probabilistic growth rate. A deterministic growth rate leads to a first order partial inetgro-differential equation while a probabilistic growth rate results in a second order partial integro-differential equation with dispersion i.e., a modified Fokker-Planck equation (as we shall see later).

3.5 Steady Size Distributions (SSDs)

"Steady size-distributions, or SSDs, occur when the size distribution of a cell population retains a constant shape while the overall number of cells in the population may be growing or decaying" (Begg [25]). The evolution of the number density $n(x,t)$ of cells by size x, in an unperturbed situation, is observed experimentally to exhibit the attribute of that of an asymptotic SSD. That is, $n(x,t) \sim$ scaled (by time t) multiple of a constant shape $y(x)$

as $t \to \infty$, and $y(x)$ is then the SSD distribution, with constant shape for large time (see *Figure 3.1*).

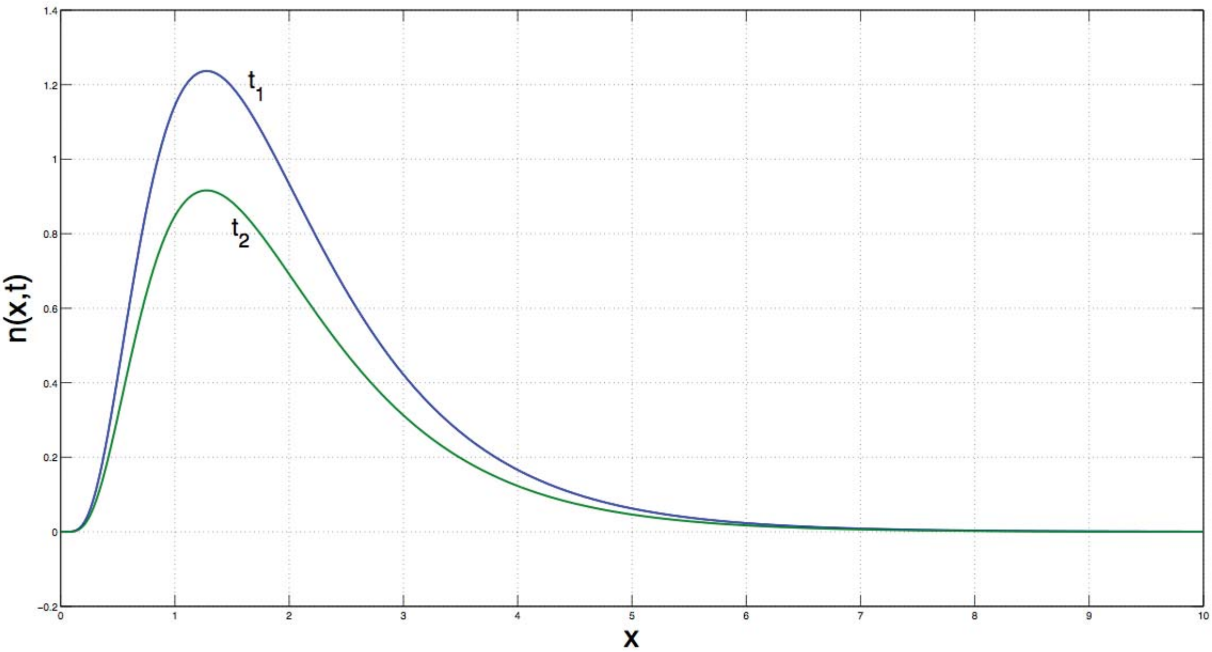

Figure 3.1: A figure showing the SSD behavior for binary symmetric division of cells. This graph plots the number density of cells $n(x,t)$ against the cell size x (with units $[x] = M$, where M is the mass) for large times t_1 and t_2.

Chapter 4

Model derivation

In this chapter, we present a model that describes growth, division and death of cells structured by size. The model is an extension of that studied by Hall and Wake [24] and incorporates the asymmetric division of cells. As discussed in the literature review (chapter 2), Hall and Wake's original model [24] only allowed for the symmetric division of cells and the model given by Suebcharoen *et al.* [68] did not focus on the biological interpretation of the splitting kernel. Here, we extend Hall and Wake's model to cater for the asymmetric division of cells and establish the model directly from a biological interpretation of the splitting kernel. We first assume that the system is deterministic and derive a model for such a system. We then add stochasticity to the growth rate of cells.

Let the horizontal axis represent the size and let $n(x,t)$ be the number density of cells of size x at time t. If the units of x, $[x] = M$ then $[n] = M^{-1}$. Consider the interval $(x, x + dx)$ (as shown in *Figure 4.1*). In the absence of division or death, the rate of change of the cell number density in the size-interval dx equals the rate of the cell number density "convected" into dx minus the rate of the cell number density "convected" out of dx. This gives

$$\frac{\partial n}{\partial t} = -\frac{\partial}{\partial x}(gn), \tag{4.1}$$

where $g(x)$ is the per capita growth rate, $[g] = MT^{-1}$, and $T = [t]$. The incoming rate of change of cell density in the interval $(x, x + dx)$ (because of

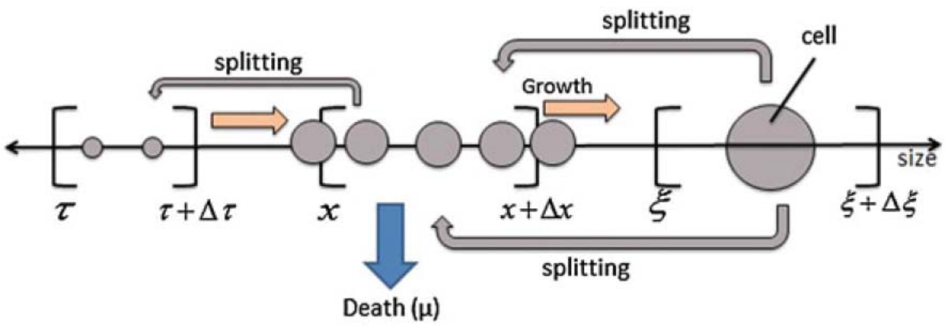

Figure 4.1: Cell growth and division for the cohort

the splitting of cells of larger size) is

$$\int_x^\infty b(\xi)W(x,\xi)n(\xi,t)d\xi, \tag{4.2}$$

where $W(x,\xi)$ is the number density of cells of size x produced when one cell of size ξ divides ($[W] = M^{-1}$) and $b(\xi)$ ($[b] = T^{-1}$) is the frequency at which the cells of size ξ divide to give the cells of size x. The term $\tau W(\tau,x)d\tau$ is the biomass of the cells that arrive in the interval $(\tau, \tau + d\tau)$ when one cell of size x divides. Thus, $\frac{\tau}{x}W(\tau,x)d\tau$ gives the fraction of the cell of size x used to form this biomass. The out going cell density rate due to the splitting of cells of size x is therefore

$$-\left(\int_0^x b(x)\frac{\tau}{x}W(\tau,x)d\tau\right)n(x,t), \tag{4.3}$$

where the minus sign indicates that the cells are leaving the point x. Also, the contribution due to the death rate of cells of size x is $-\mu n(x,t)$ where $\mu(x)$ is the specific death rate ($[\mu] = T^{-1}$). Incorporating the cell division and death, equation (4.1) becomes

$$\frac{\partial n}{\partial t} + \frac{\partial}{\partial x}(gn) = \int\limits_{x}^{\infty} b(\xi) W(x,\xi) n(\xi,t) d\xi$$

$$- \left(\int\limits_{0}^{x} b(x) \frac{\tau}{x} W(\tau,x) d\tau \right) n(x,t) - \mu n(x,t). \tag{4.4}$$

At any time t, it is biologically reasonable to expect the number density of cells of size zero to be zero, i.e., for all $t \geq 0$

$$n(0,t) = 0. \tag{4.5}$$

Although no size limit is placed on cells in this model, it is also reasonable to impose the condition

$$\lim_{x \to \infty} n(x,t) = 0, \tag{4.6}$$

for all $t \geq 0$. The cell population model is studied from an initial number density distribution,

$$n(x,0) = n_0(x), \tag{4.7}$$

where n_0 is a given non-negative function satisfying equations (4.5)-(4.6). The problem is thus an initial-boundary value problem that consists of solving the integro-differential equation (4.4) subject to conditions (4.5)-(4.7). As noted the size x of a cell can be volume, mass, DNA content etc. Here, we shall make the choice that the size corresponds to a quantity that is conserved during the division, e.g. DNA content or biomass. We simply refer to this as "biomass". Since $\tau W(\tau, x) d\tau$ is the biomass of the cells that arrive in the interval $(\tau, \tau + d\tau)$ when one cell of size x divides, the mass balance requires the equation

$$x = \int\limits_{0}^{x} \tau W(\tau,x) d\tau, \tag{4.8}$$

which is a Volterra integral equation with many solutions. Further, for binary division (two daughter cells) we need

$$\int\limits_{0}^{\xi} W(x,\xi) dx = 2. \tag{4.9}$$

Equations (4.8) and (4.9) together provide restrictions on the admissible functions possible for W. We introduce the most feasible W in the next section. Using the mass balance equation (4.8), equation (4.4) then simplifies to

$$\frac{\partial n}{\partial t} + \frac{\partial}{\partial x}(gn) = \int_x^\infty b(\xi)W(x,\xi)n(\xi,t)d\xi - (b(x)+\mu)n(x,t), \tag{4.10}$$

This, together with appropriate boundary and initial conditions is a problem to be addressed in chapters 5, 6 and 8.

The deterministic cell growth model (4.4)-(4.7) can be refined to include stochasticity in the growth rate of cells. As Hall [25] notes that there may be an "experimental evidence showing significant variation in the growth rates of individuals all with the same measured properties". In such a scenario, the deterministic cell growth model discussed above would be inappropriate. To cater for this, we add stochasticity to the growth rate of cells, i.e.,

$$dx = gdt + \sigma dS,$$

where S is a Wiener process with $dS^2 = dt$. This leads to a (modified) Fokker-Planck equation. For a detailed derivation of such an equation, see the book by Cox and Miller [14] and Hall's thesis [25]. The resulting modified Fokker-Planck equation is a partial integro-differential equation of the form

$$\begin{aligned}\frac{\partial}{\partial t}n(x,t) + \frac{\partial}{\partial x}(g(x)n(x,t)) &= \frac{\partial^2}{\partial x^2}(D(x)n(x,t)) \\ &+ \int_x^\infty b(\xi)W(x,\xi)n(\xi,t)d\xi - \left(\int_0^x b(x)\frac{\tau}{x}W(\tau,x)d\tau\right)n(x,t) - \mu n(x,t),\end{aligned} \tag{4.11}$$

where $D(x) = \frac{\sigma^2}{2} \geq 0$ is the dispersion coefficient (the units are $[D] = M^2T^{-1}$ and σ is the standard deviation. The partial integro-differential equation (4.11) is supplemented with the no-flux condition

$$\left.\frac{\partial}{\partial x}(D(x)n(x,t)) - g(x)n(x,t)\right|_{x=0} = 0, \tag{4.12}$$

together with an initial number density distribution

$$n(x,0) = n_0(x). \tag{4.13}$$

We also impose the conditions

$$\lim_{x\to\infty} n(x,t) = 0, \tag{4.14}$$

and

$$\lim_{x\to\infty} \frac{\partial}{\partial x} n(x,t) = 0. \tag{4.15}$$

The mass balance equation (4.8) remains valid in this case and simplifies equation (4.11) to

$$\begin{aligned}\frac{\partial}{\partial t} n(x,t) + \frac{\partial}{\partial x}(g(x)n(x,t)) = {} & \frac{\partial^2}{\partial x^2}(D(x)n(x,t)) \\ & + \int_x^\infty b(\xi)W(x,\xi)n(\xi,t)d\xi - (b(x)+\mu)n(x,t).\end{aligned} \tag{4.16}$$

This, together with appropriate boundary and initial conditions is also a problem to be addressed in chapters 7 and 9.

Chapter 5

Symmetrical cell division and steady size distributions

Symmetric cell division occurs when a cell divides into daughter cells of equal sizes. Here, we study the case in which a cell of size $\xi = \alpha x$ divides into $\alpha > 1$ daughter cells each of size x. The biology compels α to be identically equal to 2, since a mother cell divides exactly into two daughter cells. Although $\alpha \neq 2$ is biologically unrealistic, it may be of mathematical interest. The model we have developed is generic and allows values of α to be different from 2. Since a cell divides only when it is a multiple of α, $W(x, \xi)$ in this case becomes

$$W(x, \xi) = \alpha\delta\left(\frac{\xi}{\alpha} - x\right), \tag{5.1}$$

where δ denotes the Dirac delta function. A straightforward calculation shows that $W(x, \xi)$ given by equation (5.1) satisfies the mass balance equation (4.8) as well as equation (4.9) (for $\alpha = 2$). The above choice of W and the mass balance equation simplify equation (4.4) to

$$\underbrace{n_t(x,t)}_{\text{net rate of change}} + \underbrace{gn_x(x,t)}_{\text{growth rate in size}} = \underbrace{\alpha^2 bn(\alpha x,t)}_{\substack{\text{cells from division}\\ \text{at size } \alpha x}} - \underbrace{bn(x,t)}_{\substack{\text{loss of cells}\\ \text{through division}}} - \underbrace{\mu n(x,t)}_{\text{cell-death}}, \tag{5.2}$$

Here we took for simplicity g and b as specified constants. Equation (5.2) is supplemented by conditions (4.5)-(4.7). This model, without the mortality term, was considered by Hall and Wake [24] as a basic model for size structured cell populations. Here we have derived Hall and Wake's model from our generic model (4.4) that also has mortality incorporated into it. Hall and Wake focused on the solutions to equation (5.2) that correspond to the steady size distribution (SSD) (of constant shape). Perthame and Ryzhik [53] proved the existence of a stable steady distribution (first positive eigenfunction) and exponential convergence of solutions toward such a steady state for large times. Hall and Wake [24] considered separable solutions of the form $n(x,t) = y(x)N(t)$, where $N(t) = \int\limits_0^\infty n(x,t)dx$ is the total population at time t and $y(x)$ (i.e., y is time invariant) is a probability density function with $\int\limits_0^\infty y(x)dx = 1$. They called such solutions "steady size distributions" (SSDs). SSD solutions are thus separable solutions of the form $n(x,t) = N(t)y(x)$ which upon substitution into equation (5.2) gives

$$\begin{aligned}\frac{N'(t)}{N(t)} &= -g\frac{y'(x)}{y(x)} + \frac{\alpha^2 by(\alpha x)}{y(x)} - (b+\mu)\\ &= -\lambda,\end{aligned}$$

where λ is a separation constant (to be found). This leads to solutions of the form

$$n(x,t) = e^{-\lambda t}y(x), \tag{5.3}$$

where y satisfies

$$gy' = \alpha^2 by(\alpha x) - (\mu + b - \lambda)y(x), \tag{5.4}$$

along with the conditions

$$y(0) = 0 = \lim_{x\to\infty} y(x). \tag{5.5}$$

Hall and Wake required $y(x)$ to be greater than or equal to zero for all x greater than or equal to zero. They further required y to be integrable on $[0,\infty)$ and without loss of generality they assumed y to be a probability density function (pdf) so that

$$\int\limits_0^\infty y(x)dx = 1. \tag{5.6}$$

The value of λ can be determined by first integrating equation (5.4) with respect to x from 0 to ∞, i.e.,

$$g\int_0^\infty y'(x)dx = \alpha^2 b\int_0^\infty y(\alpha x)dx - (\mu + b - \lambda)\int_0^\infty y(x)dx,$$

and then using conditions (5.5) and (5.6). This yields

$$\lambda = \mu - b(\alpha - 1).$$

Equation (5.4) thus reduces to

$$gy' = \alpha^2 by(\alpha x) - b\alpha y(x). \tag{5.7}$$

Hall and Wake [24] then solved equation (5.7) along with conditions (5.5) and (5.6) by the use of Laplace transforms. The resulting solution is a Dirichlet series of the form

$$y(x) = \frac{a}{K}\sum_{n=0}^{\infty}\frac{(-1)^n\alpha^n e^{-a\alpha^n x}}{(\alpha-1)(\alpha^2-1)\dots(\alpha^n-1)}, \tag{5.8}$$

where

$$K = \prod_{n=1}^{\infty}(1-\alpha^{-n}), \tag{5.9}$$

and

$$a = \frac{b\alpha}{g}. \tag{5.10}$$

SSD solutions are of central interest in this model since they can be easily matched to data for the size distribution of cells for large time. They are special solutions to the nonlocal partial differential equation (5.2). In particular, given an initial distribution $n(x, 0) = n_0(x)$, the SSD solution does not give the complete solution (unless $n_0(x) = y(x)$) and this prompts one to consider other techniques to solve the more general problem.

This means that there is a set of solutions to equation (5.4) with homogeneous boundary conditions, that is, λ has the role of an eigenvalue as discussed by van-Brunt *et al.* [76]. It may be possible that a class of solutions y_m for $m = 0, 1, \ldots,$ can be obtained using an eigenfunction expansion. Specifically, we can use the conditions given by the successive moments (that is, the Mellin transform),

$$\int_0^\infty x^{m-1} y_m(x) dx = 0, \quad \int_0^\infty x^m y_m(x) dx \neq 0 \tag{5.11}$$

to calculate some further solutions to equation (5.4). These conditions give rise to a class of eigenfunctions and are sufficient in this respect. At this stage it is not clear whether there are other eigenfunctions. The idea mimics that used by van-Brunt and Vlieg-Hulstman [77]. Equation (5.4) is first multiplied by x and then the resulting equation is integrated with respect to x from 0 to ∞, i.e.,

$$g \int_0^\infty xy'(x)dx = \alpha^2 b \int_0^\infty xy(\alpha x)dx - (\mu + b - \lambda) \int_0^\infty xy(x)dx.$$

This gives,

$$g[xy]|_0^\infty - \int_0^\infty y(x)dx = (b - \mu - b + \lambda) \int_0^\infty xy(x)dx,$$

which by using condition (5.11) with $m = 1$ yields

$$\lambda = \mu. \tag{5.12}$$

Similarly, multiplying equation (5.4) by increasing powers of x and then integrating the resulting equations from 0 to ∞ with respect to x leads to the spectrum (see *Figure 5.1*),

$$\lambda_m = \mu + b - b\alpha^{-(m-1)}, \tag{5.13}$$

for $m = 0, 1, 2, \ldots$. These eigenvalues lead to equations of the form

$$gy_m'(x) = \alpha^2 b y_m(\alpha x) - b\alpha^{-(m-1)} y_m(x). \tag{5.14}$$

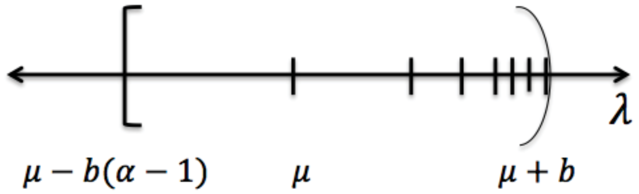

Figure 5.1: Spectrum of Eigenvalues

Of course, there may be other eigenvalues and eigenfunctions. These eigenfunctions y_m are the solutions to equation (5.14) subject to conditions given by (5.11) and

$$y_m(0) = 0 = \lim_{x\to\infty} y_m(x), \tag{5.15}$$

The first eigenfunction is the pdf solution y_0 given by equation (5.8). The higher eigenfunctions can be found by following the procedure used by van-Brunt and Vlieg-Hulstman [77], who considered an equation of the form

$$y'(x) + bx^n y(x) = \lambda\alpha^n x^n y(\alpha x). \tag{5.16}$$

subject to conditions (5.5) and (5.6). Here, we solve equation (5.14) subject to condition (5.15) using the same technique. Let $M(s)$ denote the Mellin transform of y. Applying the Mellin transform to equation (5.14), i.e.,

$$g\int_0^\infty x^{s-1}y_m'(x)dx = \alpha^2 b\int_0^\infty x^{s-1}y_m(\alpha x)dx - b\alpha^{-(m-1)}\int_0^\infty x^{s-1}y_m(x)dx,$$

where $m = 0, 1, 2, \ldots$, gives

$$-(s-1)gM(s-1) + b\alpha^{-(m-1)}M(s) = \frac{b\alpha^2}{\alpha^s}M(s), \tag{5.17}$$

where $M(s)$ is the Mellin transform of $y_m(x)$ and is given by

$$M(s) = \int_0^\infty x^{s-1}y_m(x)dx.$$

The homogeneous equation associated with (5.14) is

$$gy'_m(x) + b\alpha^{-(m-1)}y_m(x) = 0. \tag{5.18}$$

Applying the Mellin transform to the homogeneous equation (5.18), i.e.,

$$g\int_0^\infty x^{s-1}y'_m(x)dx + b\alpha^{-(m-1)}\int_0^\infty x^{s-1}y_m(x)dx = 0,$$

gives

$$-(s-1)gF(s-1) + b\alpha^{-(m-1)}F(s) = 0. \tag{5.19}$$

where $F(s)$ is the Mellin transform of $y_m(x)$ for the associated homogeneous equation (5.18).

We seek solutions to equation (5.17) of the form

$$M(s) = K_m F(s)Q(s), \tag{5.20}$$

where $K_m \neq 0$ is a normalization constant so that

$$\int_0^\infty x^m y_m dx = 1, \tag{5.21}$$

for $m = 0, 1, 2, \ldots$, and the factor Q contains all the influence of the functional term. Substituting the expression for $M(s)$ from equation (5.20) to equation (5.17) gives

$$-(s-1)gK_mF(s-1)Q(s-1) + b\alpha^{-(m-1)}K_mF(s)Q(s) = \frac{b\alpha^2}{\alpha^s}K_mF(s)Q(s),$$

which by using equation (5.19) yields the recurrence relation

$$Q(s-1) = \left(1 - \alpha^{m-s+1}\right)Q(s),$$

so that

$$Q(s) = \prod_{r=0}^{\infty}(1 - \alpha^{m-s-r}). \tag{5.22}$$

The associated homogeneous equation (5.18) can be solved by elementary means. This gives

$$y_m \sim e^{-\frac{b}{g}\alpha^{-(m-1)}x}. \tag{5.23}$$

The Mellin transform of equation (5.23) is

$$\int_0^\infty x^{s-1} y_m(x)dx = \int_0^\infty x^{s-1} e^{-\frac{b}{g}\alpha-(m-1)x} dx,$$

which can be written as

$$F(s) = \left(\frac{g}{\alpha b}\right)^s \alpha^{sm}\Gamma(s), \tag{5.24}$$

where $\Gamma(s)$ is the gamma function. Equation (5.20) along with equations (5.22) and (5.24) give

$$M(s) = K_m \left(\frac{g}{\alpha b}\right)^s \alpha^{sm}\Gamma(s) \prod_{r=0}^{\infty}(1 - \alpha^{m-s-r}). \tag{5.25}$$

Also, condition (5.11) implies that

$$M(1) = \int_0^\infty y_m(x)dx = \begin{cases} 1 & \text{if } m = 0 \\ 0 & \text{if } m \neq 0. \end{cases} \tag{5.26}$$

The expression for M in equation (5.25) is defined for all $s > 0$. However, the gamma function in equation (5.25) has simple poles at $s = -l$, where l is a non-negative integer. This is balanced by the fact that the Q term (the infinite product) in equation (5.25) has simple zeros at precisely these points and hence $M(s)$ is defined for all $s \leq 0$. The infinite product in equation (5.25) can be converted into an infinite sum by the use of Euler's identity,

$$\prod_{r=0}^{\infty}(1 + zq^r) = 1 + \sum_{r=1}^{\infty} \frac{q^{\frac{r(r-1)}{2}} z^r}{\prod_{j=1}^{r}(1 - q^j)},$$

which is valid for $|q| < 1$ and $z \in \mathbb{C}$. Here, $q = \alpha^{-1}$ and $z = -\alpha^{(m-s)}$, and so

$$Q(s) = \prod_{r=0}^{\infty}(1 + zq^r) = 1 + \sum_{r=1}^{\infty} P_r(\Lambda_m), \tag{5.27}$$

where

$$P_r(\Lambda_m) = \frac{(-1)^r \alpha^{rm}}{\alpha^{\frac{r(r-1)}{2}} \prod_{j=1}^{r}(1 - \alpha^{-j})}. \tag{5.28}$$

The Mellin transform equation (5.25) can thus be written as

$$M(s) = K_m \left(F(s) + \sum_{r=1}^{\infty} \frac{P_r(\Lambda_m) F(s)}{\alpha^{rs}} \right).$$

The use of Euler's identity to convert an infinite product into an infinite sum allows us to find the inverse transform of $M(s)$, i.e., we can find $y_m(x)$. Since the inverse transform of $F(s)$ is $f(x) = e^{-\frac{b}{g}\alpha^{-(m-1)}x}$, so the inverse transform of $F(s)\alpha^{-rs}$ is $e^{-\frac{b}{g}\alpha^{-(m-1)+r}x}$. Thus,

$$y_m(x) = K_m \left(e^{-\frac{b}{g}\alpha^{-(m-1)}x} + \sum_{r=1}^{\infty} P_r(\Lambda_m) e^{-\frac{b}{g}\alpha^{-(m-1)+r}x} \right), \tag{5.29}$$

where $P_r(\Lambda_m)$ is given by equation (5.28) and K_m is given by equation (5.21).

5.1 Uniqueness

It could be shown that the Dirichlet series solutions (5.29) are unique under certain rapid decay conditions. Clearly, the Dirichlet series solutions decay rapidly as $x \to \infty$. We establish the uniqueness of the Dirichlet series solutions by following the analysis used by van-Brunt and Vlieg Hulstman [77]. This approach also allows us to show directly from equation (5.14) that y_0 is a probability density function.

Lemma 5.1.1. *Let v be a differentiable function on $[0, \infty)$ such that $v(x) \to 0$ as $x \to \infty$, and*

$$v'(x) = \frac{\alpha b}{g}(v(\alpha x) - v(x)). \tag{5.30}$$

If $v'(x_0) = 0$ for some $x_0 \in (0, \infty)$, then $v(x) = 0$, for all $x \in [0, \infty)$.

Proof. We first show that v cannot have an extremum in $(0, \infty)$. Suppose that v has a positive local maximum in $(0, \infty)$, then v will have a positive global maximum at $P_1 \in (0, \infty)$. Equation (5.30) then implies that

$$v(\alpha P_1) = v(P_1),$$

and since $v(x) \to 0$ as $x \to \infty$ there must exist another global maximum at point $P_2 = \alpha P_1$ at which $v(P_2) = v(P_1)$. This argument can be repeated *ad infinitum* to show that there must be a sequence of global maxima $\{P_j\} = \{\alpha^j P_1\}$ such that $P_j \to \infty$ as $j \to \infty$ and for all $j \in \mathbb{N}$,

$$v(P_j) = v(P_1) > 0.$$

This contradicts the assumption that $v(x) \to 0$ as $x \to \infty$ and so v cannot have a positive global maximum. A similar argument applied to $-v$ shows that v cannot have a negative global minimum. If v has a negative global maximum then the condition $v(x) \to 0$ as $x \to \infty$ implies that v must have a negative global minimum. Similarly, if v has a positive global minimum, v must have a positive global maximum. So,we conclude that v cannot have extrema in $(0, \infty)$.

Suppose that $v'(x_0) = 0$ for some $x_0 \in (0, \infty)$. Then equation (5.30) implies that $v(x_0) = v(\alpha x_0)$, and since v cannot have an extrema it follows that $v(x) = v(x_0)$ for all $x \in [x_0, \alpha x_0]$. Therefore $v'(x) = 0$ for all $x \in [x_0, \alpha x_0]$. Repeating this argument ad infinitum yields $v'(x) = 0$ for all $x \in [x_0, \infty)$. Since $v(x) \to 0$ as $x \to \infty$, $v(x) = 0$ for all $x \in [x_0, \infty)$ and equation (5.30) implies that

$$v'(x) + \frac{\alpha b}{g} v(x) = 0 \ \text{ for } x \in \left[\frac{x_0}{\alpha}, \infty\right),$$

which is an ordinary differential equation for v. This equation must satisfy the initial condition $v(x_0) = 0$. Picard's theorem guarantees a unique trivial solution to this equation. Hence $v(x) = 0$ for all $x \in \left[\frac{x_0}{\alpha}, \infty\right)$. This argument can be repeated any number of times and so $v(x) = 0$ for all $x > 0$. The continuity of v shows that $v(0) = 0$. □

Theorem 5.1.2 (*The first eigenfunction*)**.** *The function y_0 defined by equation* (5.29) *is a solution to the boundary value problem with $\lambda = \mu - b(\alpha - 1)$. This solution is unique among functions y such that*

$$\int_0^\infty x^n y(x) dx < \infty \tag{5.31}$$

Moreover, $y_0(x) > 0$ for all $x > 0$.

Proof. We have already established that y_0 is a solution to the boundary value problem. Suppose y and w satisfy condition (5.31) and are solutions to the boundary value problem, and let $z = y - w$. Then z satisfies condition (5.31), the equation

$$gz' = \alpha^2 bz(\alpha x) - b\alpha z(x), \tag{5.32}$$

and also the relation

$$\int_0^\infty z(x) dx = 0. \tag{5.33}$$

Since z satisfies condition (5.31), the function

$$\delta(x) = \int_x^\infty z(\xi) d\xi. \tag{5.34}$$

is defined for all $x \geq 0$. Integrating equation (5.32) from x to ∞ yields

$$-gz(x) = \alpha b \left(\delta(\alpha x) - \delta(x)\right), \tag{5.35}$$

and since differentiating equation (5.34) yields

$$\delta'(x) = -z(x), \tag{5.36}$$

we thus have

$$\delta'(x) = \frac{\alpha b}{g}(\delta(\alpha x) - \delta(x)).$$

Equation (5.33) implies that either $z \equiv 0$ or z changes sign in $(0, \infty)$. Consequently, there is an $x_0 \in (0, \infty)$ such that $z(x_0) = 0$. Equation (5.36) implies that $\delta'(x_0) = 0$ and from Lemma 5.1.1 $\delta(x) = 0$ and thus $\delta'(x) = 0$ for all $x \geq 0$. Equation (5.36) shows that $z(x) = 0$ for all $x \geq 0$ and so the solution y_0 is unique.

The above argument can also be used to show that y_0 is positive. We can replace z with y_0 in the above arguments. Condition (5.6) does not require y_0 to change sign. Indeed, the above arguments show that if y_0 did change sign, then y_0 would be identically zero. Condition (5.6) shows that y_0 must be positive somewhere in $(0, \infty)$, and since y_0 cannot change sign we conclude that $y_0(x) > 0$ for all $x > 0$. □

To establish the uniqueness of higher eigenfunctions we define a sequence $\{\delta_j\}$ of operators by

$$\begin{aligned} \delta_0 y(x) &= y(x), \quad \text{that is } \delta_0 \text{ is identity, and} \\ \delta_j y(x) &= \int_x^\infty \delta_{j-1} y(\xi) d\xi, \end{aligned} \tag{5.37}$$

where $j \in \mathbb{N}$. Let R_j denote the set of functions $y \in C^0[0, \infty)$ such that

$$\lim_{x \to \infty} x^n \delta_k y(x) = 0. \tag{5.38}$$

and

$$\delta_k y(0) < \infty \tag{5.39}$$

where $k = 1, 2, ..., j$. The Dirichlet series solutions $\{y_m\}$ are evidently in R_j for any $j \in \mathbb{N}$. Theorem 5.1.2 shows that y_0 is the unique solution to the boundary value problem in R_1.

Lemma 5.1.3. *Let $z_m \in R_{m+1}$ be a solution to* (5.14) *with $\lambda = \lambda_m$. Then for $j = 0, 1, ..., m$*

$$\delta'_{j+1}(x) = \frac{\alpha^{(1-j)} b}{g} \delta_{j+1}(\alpha x) - \frac{\alpha^{-(m-1)} b}{g} \delta_{j+1}(x), \tag{5.40}$$

where $\delta_j(x) = \delta_j z_m(x)$.

Proof. Equation (5.14) implies that

$$gz'_m = \alpha^2 b z_m(\alpha x) - b\alpha^{-(m-1)} z_m(x),$$

and integrating the above equation from x to ∞ gives

$$-z_m(x) = \frac{b}{g}\left(\alpha(\delta_1(\alpha x) - \alpha^{-(m-1)}\delta_1(x)\right). \tag{5.41}$$

For any $0 \leq j \leq m$, equation (5.37) gives

$$\delta'_{j+1}(x) = -\delta_j(x), \tag{5.42}$$

and hence,

$$\delta'_1(x) = \frac{\alpha b}{g}\delta_1(\alpha x) - \frac{\alpha^{-(m-1)} b}{g}\delta_1(x).$$

Given that $z_m \in R_{m+1}$, the functions δ_j are well defined and $x^n \delta_j(x) \to \infty$ as $x \to \infty$ for $0 \leq j \leq m+1$. Repeating the argument m-times gives equation (5.40). □

Theorem 5.1.4 (*Higher eigenfunctions*)**.** *The function y_m defined by equation* (5.29) *is a solution to the boundary value problem with $\lambda = \lambda_m$. This solution is unique among functions in R_{m+1}.*

Proof. Let $w_m \in R_{m+1}$ be another solution to the boundary value problem with $\lambda = \lambda_m$ and let $z_m = y_m - w_m$. Then $z_m \in R_{m+1}$, z_m satisfies (5.4) and

$$\int_0^\infty z_m(x)dx = 0. \tag{5.43}$$

The function z_m satisfies the conditions of Lemma 5.1.3 and therefore

$$\delta'_{m+1}(x) = \frac{\alpha^{(1-m)} b}{g}\delta_{m+1}(\alpha x) - \frac{b\alpha^{-(m-1)}}{g}\delta_{m+1}(x), \tag{5.44}$$

We show that $\delta'_{m+1}(x_0) = 0$ for some $x_0 > 0$ and apply Lemma 5.1.1 to equation (5.44). From equation (5.41) we have

$$-\int_0^\infty z_m(x)dx = \frac{b}{g}(1 - \alpha^{-(m-1)})\int_0^\infty \delta_1(x)dx;$$

which by using equation (5.43)

$$0 = (1 - \alpha^{-(m-1)}) \int_0^\infty \delta_1(x)dx.$$

Since $\alpha > 1$, the above equation implies that

$$\int_0^\infty \delta_1(x)dx = 0.$$

Repeating this argument and using equations (5.40) and (5.42) with $j = 1$ gives

$$-\int_0^\infty \delta_1(x)dx = \frac{\alpha^{-1}b}{g} \int_0^\infty \delta_2(\alpha x)\alpha dx - \frac{\alpha^{-(m-1)}b}{g} \int_0^\infty \delta_2(x)dx;$$

hence,

$$0 = \frac{b}{g}(\alpha^{-1} - \alpha^{-(m-1)}) \int_0^\infty \delta_2(x)dx,$$

so that,

$$\int_0^\infty \delta_2(x)dx = 0. \tag{5.45}$$

Repeating the process gives

$$\int_0^\infty \delta_j(x)dx = 0; \quad 0 \leq j \leq m \tag{5.46}$$

For $j = m$, the equation above implies that there is an $x_0 > 0$ such that $\delta_m(x_0) = 0$ and so $\delta'_{m+1}(x_0) = 0$ and by Lemma 5.1.1 we have $\delta_{m+1}(x) = 0$ for all $x \geq 0$. Equation (5.44) gives $\delta'_m(x) = 0$ and since $\delta_m(x_0) = 0$, $\delta_m(x) = 0$ for all $x \geq 0$. Continuing the argument gives $\delta_j(x) = 0$ for $0 \leq j \leq m$ and $x \geq 0$. In particular $z_m(x) = 0$ for all $x \geq 0$. The solution is thus unique in R_{m+1}. $\square$

The unimodality of y_0 can be established on a pattern similar to that used by da Costa *et al.* [13], and by van-Brunt and Vlieg-Hulstman [78].

5.2 Nested Zeros of eigenfunctions

In this section we study the zeros of higher eigenfunctions (see *Figure 5.2*) and follow the analysis used by van-Brunt and Vlieg Hulstman [78].

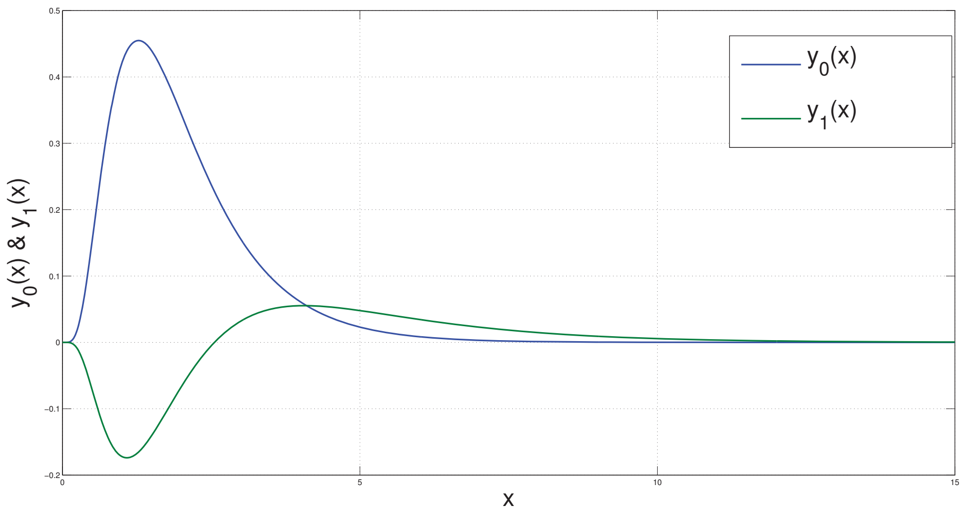

Figure 5.2: Eigenfunctions $y_0(x)$ and $y_1(x)$ given by the Dirichlet series (5.29) for $m = 0, 1,\ g = 2, b = 1, \alpha = 2$.

Lemma 5.2.1. *The equation* $y_1'(x) = 0$ *has a finite number of solutions in* $[z_{1,1}, \infty)$ *where* $z_{1,1}$ *is the zero of* y_1.

Proof. It can be shown (see Appendix A) that

$$y_{m-1}'(x) = A_m y_m(\alpha x),$$

for some constant A_m. This shows that the eigenfunction $y_1(x)$ has only one (non-trivial) zero (since y_0 is unimodal [13, 78]). Let $z_{1,1}$ denote the zero of y_1. Let $y_1(x) < 0$ for $(0, z_{1,1})$ and $y_1(x) > 0$ for $(z_{1,1}, \infty)$. The Dirichlet series that defines $y_1(z)$ is uniformly convergent in any compact subset of the

half plane $\Pi_1 = \{z : Re(z) > z_{1,1}\}$. Weierstrass theorem shows that y_1 is holomorphic in Π_1; consequently y_1' is holomorphic in Π_1. The function y_1 is not a constant function on $(z_{1,1}, \infty)$ otherwise it would be identically zero and this would mean that y_1 has more than one zero. so y_1' is not identically zero in Π_1. The identity theorem implies that the zeros of y_1' must be isolated, so that in particular the zeros of y_1' that occur on $(z_{1,1}, \infty)$ must be isolated.
The above argument does not include $z_{1,1}$ since y_1' need not be holomorphic there. To eliminate the possibilty of $z_{1,1}$ being a limit point of zeros of y_1', we note that $y_1(x) > 0$ for all $x > z_{1,1}$ and $y_1(z_{1,1}) = 0$. The function y_1' is continuous on $[z_{1,1}, \infty)$ and hence there must be a number $x_1 > 0$ such that $y_1'(x) > 0$ for all $x \in (z_{1,1}, x_1)$. All the zeros of y_1' on $[z_{1,1}, \infty)$ must therefore be isolated. Taking the derivative of equation (5.29) (for $m = 1$), we get

$$y_1'(x) = -\frac{b}{g} K_1 \left(e^{-\frac{b}{g}x} + \sum_{r=1}^{\infty} P_r(\Lambda_1) \alpha^r e^{-\frac{b}{g}\alpha^r x} \right), \tag{5.47}$$

where $b > 0$, $g > 0$, and as $x \to \infty$, $y_1'(x) \sim -\frac{b}{g} K_1 e^{-\frac{b}{g}x}$, where $K_1 = \int_0^\infty x y_1(x) dx = 1$. This means that there is a $w > z_{1,1}$ such that $y_1'(x) < 0$ for all $x > w$. The zeros of y_1' must therefore lie in the interval $[z_{1,1}, w]$. There are no limit points for zeros in $[z_{1,1}, w]$. By Bolzano-Weierstrass theorem, the number of zeros must be finite. The function y_1 is smooth and does not change sign on $(z_{1,1}, \infty)$ and condition $y_1(z_{1,1}) = 0 = \lim_{x\to\infty} y_1(x)$ implies that y_1 must have at least one local maximum in this interval. Therefore, there is at least one solution to equation $y_1'(x) = 0$ in $[z_{1,1}, \infty)$. □

Lemma 5.2.2. *Suppose that $y_1'(x) = 0$ has at least two solutions in $(z_{1,1}, \infty)$. Then there is a solution ξ to $y_1'(x) = 0$ such that $\xi > M_1$, where M_1 denotes the smallest value in $(z_{1,1}, \infty)$ at which y_1 has a local maximum.*

Proof. Lemma 5.2.1 shows that solutions to $y_1'(x) = 0$ in $(z_{1,1}, \infty)$ are isolated and y_1 has at least one local maximum. Thus there exists M_1, a smallest value in $(z_{1,1}, \infty)$ at which y_1 has a local maximum. If $x > z_{1,1}$ and $y_1'(x) = 0$, equation (5.14) for $m = 1$ becomes

$$g y_1'(x) = \alpha^2 b y_1(\alpha x) - b y_1(x), \tag{5.48}$$

i.e.,

$$y_1(x) = \alpha^2 y_1(\alpha x). \tag{5.49}$$

Differentiating equation (5.48) gives,

$$gy_1''(x) = \alpha^3 b y_1'(\alpha x) - b y_1'(x),$$

i.e.,

$$y_1''(x) = \frac{\alpha^3 b}{g} y_1'(\alpha x). \tag{5.50}$$

suppose that $y_1'(x)$ has two solutions in $(z_{1,1}, \infty)$. Then there is an $\eta \neq M_1$ such that $y_1'(\eta) = 0$. If $\eta > M_1$, then let $\xi = \eta$. Suppose that $0 < \eta < M_1$. By definition of M_1, there can be no local maximum in $(z_{1,1}, M_1)$. So $y_1''(\eta) = 0$. Equation (5.50) gives $y_1'(\alpha\eta) = 0$. Equation (5.49) then gives $y_1(\eta) > y_1(\alpha\eta)$ since y_1 does not change sign for all $x \in (z_{1,1}, \eta)$. consequently a local maximum exists between η and $\alpha\eta$. Given that $\eta < M_1$, we have $\alpha\eta > M_1$, so that we can choose $\xi = \alpha\eta$. □

Lemma 5.2.3. *Suppose that y_1 has a local maximum at M and that there is a solution ξ to $y_1'(x) = 0$ such that $\xi > M$. Then there is an $m > M$ at which y_1 has a local minimum.*

Proof. We first show that there is a $\tau > M$ such that $y_1'(\tau) = 0$ and $y_1''(\tau) \neq 0$. Suppose that there is no such point. Then $y_1'(\xi) = y_1''(\xi) = 0$ and equation (5.50) implies that $y_1'(\alpha\xi) = 0$. Therefore $y_1'(\alpha\xi) = y_1''(\alpha\xi) = 0$ so that $y_1'(\alpha^2\xi) = 0$. It is clear that this argument can be repeated to establish an infinite sequence $\{\alpha^k \xi\}$ of points that are solutions to $y_1'(x) = 0$. This however contradicts Lemma 5.2.1. So there must be a $\tau > M$ such that $y_0'(\tau) = 0$ and $y_0''(\tau) \neq 0$.
If $y_0''(\tau) > 0$ then we can take $m = \tau$. If $y_0''(\tau) < 0$ then τ corresponds to a local maximum and hence there must be a local minimum at some point m between M and τ. □

Theorem 5.2.4. *There exists a unique solution to $y_1'(x) = 0$ in $(z_{1,1}, \infty)$. In particular y_1 is unimodal in $(z_{1,1}, \infty)$.*

Proof. Suppose that $y_1'(x) = 0$ has at least two solutions in $(z_{1,1}, \infty)$. Lemma 5.2.2 implies that there is an $\xi > M_1$ that solves $y_1'(x) = 0$. Lemma 5.2.3 thus implies that y_1 has a local minimum at some point $m_1 > M_1$. Since y_1 does not change sign and goes to zero as x tends to infinity, there must be another local maximum beyond m_1. Let M_2 denote the closest point beyond m_1 at which y_1 has a local maximum. Then $y_1''(m_1) \geq 0$ and $y_1''(M_2) \leq 0$.

Equation (5.50) implies that $y_1'(\alpha m_1) \geq 0$ and $y_1'(\alpha M_2) \leq 0$. The continuity of y_1' thus indicates that there is a solution ξ_2 to $y_1'(x) = 0$ in the interval $[\alpha m_1, \alpha m_2]$. Equation (5.49) however gives $y_1(m_1) > y_1(\alpha m_1)$ and therefore y_1 must have a local maximum between m_1 and αm_1. The definition of M_2 implies $M_2 < \alpha m_1$ and consequently $\xi_2 > M_2$. Lemma 5.2.3 can now be applied to M_2 and ξ_2 to establish the existence of another local minimum at some point $m_2 > M_2$ and the argument used above can be applied to show that there is another local maximum at some point $M_3 > m_2$ and a point $\xi_3 > M_3$ that solves $y_1'(x) = 0$. It is clear that we can repeat this argument to establish the existence of an infinite sequence $\{\xi_k\}$ of points that are solutions to $y_1'(x) = 0$ such that $\xi_k \to \infty$ as $k \to \infty$. The existence of such a sequence however contradicts Lemma 5.2.1. We thus conclude that $y_1'(x) = 0$ has a unique positive solution. □

Theorem 5.2.5. *There exist precisely two positive solutions to $y_2(x) = 0$. Let $z_{2,1}$ and $z_{2,2}$ denote these solutions with $z_{2,1} < z_{2,2}$. Then $0 < z_{2,1} < \frac{z_{1,1}}{\alpha} < z_{1,1} < z_{2,2}$.*

Proof. We have already shown that $y_1'(x) = 0$ has only one solution in $(z_{1,1}, \infty)$. We now focus on the zeros of $y_1'(x)$ in $(0, z_{1,1})$. Let $\tilde{y}_1(x) = -y_1(x)$ so that $\tilde{y}_1(x) > 0$ for $x \in (0, z_{1,1})$, and $\tilde{y}_1(x) < 0$ for $x \in (z_{1,1}, \infty)$. For simplicity and without loss of generality, we drop the tilde. Since $y_1(0) = 0$, $y_1(z_{1,1}) = 0$ and y is not identically zero on $(0, z_{1,1})$, the function y_1 has at least one local maximum in $(0, z_{1,1})$. Let $M_{1,1}$ be the smallest value in this interval at which y_1 has a local maximum. Suppose that there is a point $w \neq M_{1,1}$ in this interval such that $y_1'(w) = 0$. Since $y_1(w) > 0$, therefore by equation (5.49) $y_1(\alpha w) > 0$. We thus have $\alpha w < z_{1,1}$. The arguments used to establish Lemma 5.2.2 can be used to show that there is an $\xi > M_{1,1}$ such that $y_1'(\xi) = 0$, and the construction in the proof of Lemma 5.2.3 can then be used to establish the existence of a local minimum between $M_{1,1}$ and $z_{1,1}$.

Without loss of generality, we can assume that w corresponds to the largest value in $(0, z_{1,1})$ such that y_1 has a local minimum. Equation (5.49) implies $y_1(w) > y_1(\alpha w) > 0$. Hence there is a local maximum at some point $\sigma \in (w, \alpha w)$. The definition of w implies that σ must correspond to the largest value in $(0, z_{1,1})$ at which y_1 has a local maximum. since w corresponds to a local minimum, equation (5.50) implies that $y_1'(\alpha w) \geq 0$. Similarly $y_1'(\alpha\sigma) \leq 0$ so that y_1' must have a zero at some point $\tau \in (\alpha w, \alpha\sigma)$. There are no local extrema in this interval and therefore $y_1''(\tau) = 0$ so that by equation (5.50) $y_1'(\alpha\tau) = 0$. We can repeat this argument any number of times to get a sequence $\{\alpha^k\tau\}$ such that $y_1'(\alpha^k\tau) = 0$ and $\alpha^k\tau < z_{1,1}$. For k sufficiently large, however $\alpha^k\tau > z_{1,1}$. This contradiction shows that $y_1'(x)$ has only one zero $z_{2,1} = M_{1,1}$ in $(0, z_{1,1})$. Since $\alpha z_{2,1} < z_{1,1}$ we have $z_{2,1} < \frac{z_{1,1}}{\alpha}$. Finally, note that if $y_1'(z_{1,1}) = 0$, then equation (5.48) implies that $y_1(\alpha z_{1,1}) = 0$ which contradicts theorem 5.2.4. □

Theorem 5.2.6. *The function y_m where $m \geq 1$ has precisely m positive zeros. These zeros correspond to local extrema for y_{m-1}. The zeros of two consecutive eigenfunctions are nested: if $z_{m-1,1}, z_{m-1,2}, ..., z_{m-1,m-1}$, and $z_{m,1}, z_{m,2}, ..., z_{m,m}$, denote the zeros of y_{m-1} and y_m respectively, each arranged in ascending magnitude, then $z_{m,1} < z_{m-1,1} < z_{m,2} < z_{m-1,2}, ..., < z_{m,m-1} < z_{m-1,m-1} < z_{m,m}$. Moreover for $j = 1, 2, ..., m-1$, $z_{m,j} < \frac{z_{m-1,j}}{\alpha}$.*

Proof. Theorem 5.2.5 ensures the existence of precisely two zeros, $z_{2,1}$ and $z_{2,2}$, of the eigenfunction y_2. It is clear that the above arguments in Lemmas 5.2.1, 5.2.2, 5.2.3 and Theorems 5.2.4 and 5.2.5 can be modified to show for example, that y_3 has precisely three positive zeros $z_{3,1}, z_{3,2}, z_{3,3}$, and if $z_{3,1} < z_{3,2} < z_{3,3}$, then $z_{3,1} < \frac{z_{2,1}}{\alpha} < z_{2,1} < z_{3,2} < \frac{z_{2,2}}{\alpha} < z_{2,2} < z_{3,3}$, and the pattern continues through the higher eigenfunctions. □

The above theorem shows that the position of the j^{th} zero decreases rapidly as m increases. In particular, for $m > 1$, the position of the first zero of y_m satisfies $z_{m,1} < \frac{z_{1,1}}{\alpha^{m-1}}$.

5.3 Conclusions

In this chapter we studied the symmetrical cell division problem. The focus of our study was on separable solutions to equation (5.2). The motivation for the study of such solutions came from experimental results for certain plant cells that suggested solutions of this type, at least as a long term approximation [27]. We found "the steady size distribution" (SSD) and showed that it was unique. We discussed the existence and uniqueness of higher eigenfunctions. The question of whether the set of the above solutions (eigenfunctions) are complete is still open. Suppose that n is a function of the form

$$n(x,t) = \sum_{m=0}^{\infty} c_m y_m(x) e^{-\lambda_m t}, \tag{5.51}$$

where the above series is uniformly convergent for $x \geq 0$. Then it is straightforward to show that such a function is a solution to equation (5.2). The problem, however, is that in order to satisfy condition (4.7), the coefficients c_m must satisfy

$$n_0(x) = \sum_{m=0}^{\infty} c_m y_m(x), \tag{5.52}$$

and this brings to the fore the crucial question about what function space is spanned by the eigenfunctions. This question and other properties of these eigenfunctions remain to be explored, and this will be the subject of future work.

If, as we conjecture that, equation (5.51) is the full solution to equation (5.2), then clearly $n(x,t) \sim c_0 y_0 e^{-\lambda_0 t}$ for large time, showing the steady size distribution is propotional to $y_0(x)$. This is given in equation (5.29) for $m = 0$ and is shown below in *Figure 5.3* and in *Figure 5.2*. The latter also includes $y_1(x)$, the second eigenfunction.

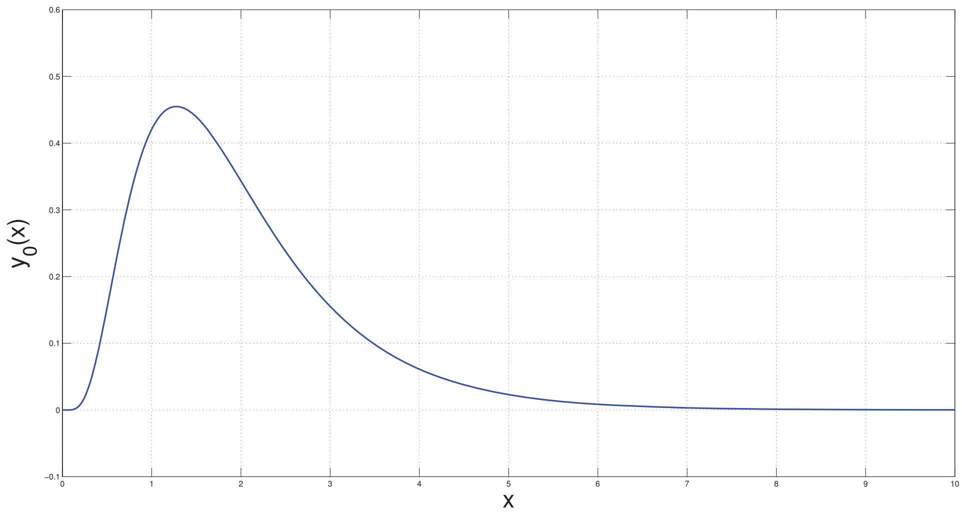

Figure 5.3: Eigenfunction $y_0(x)$ given by the Dirichlet series (5.29) for $m = 0$, $g = 2, b = 1, \alpha = 2$.

Now we have the means, through equation (5.51), to calculate the evolutionary path of the cell population cohort. Although $y_m(x)$ is not monosigned for $m > 0$, we expect that $n(x, t)$ remain positive for all $x, t > 0$ but we have not proved this here. It is to be addressed in a future paper.

Chapter 6

Solutions to an advanced functional partial differential equation of the pantograph-type

6.1 Introduction

In chapter 5 we discussed the cell growth equation

$$\underbrace{n_t(x,t)}_{\text{net rate of change}} + \underbrace{gn_x(x,t)}_{\text{growth rate in size}} = \underbrace{\alpha^2 bn(\alpha x,t)}_{\substack{\text{cells from division}\\ \text{at size } \alpha x}} - \underbrace{bn(x,t)}_{\substack{\text{loss of cells}\\ \text{through division}}} - \underbrace{\mu n(x,t)}_{\text{cell-death}}, \tag{6.1}$$

subject to an initial condition

$$n_0(x,0) = n_0(x), \tag{6.2}$$

and a boundary condition

$$n(0,t) = 0. \tag{6.3}$$

The cell division problem was also studied by Hall and Wake [24]. The focus of their study was on a separable solution to equation (6.1). The motivation for the study of such solutions came from experimental results for certain plant cells that suggested solutions of this type, at least as a long term approximation [27]. They called this solution “the steady size distribution” (SSD) and showed that it was unique.

The separable solution brings to the fore a connection with the well-known pantograph equation. Briefly, let

$$n(x,t) = w(t)y(x),$$

where y is a probability density function. Substituting this solution form into equation (6.1) yields

$$w(t) = ke^{(\lambda-\mu)t},$$

where k is a constant and λ is an eigenvalue arising from the separation of variables. The function y must satisfy

$$gy'(x) + (b+\lambda)y(x) = b\alpha^2 y(\alpha x), \tag{6.4}$$

and the condition

$$\int_0^\infty y(x)\,dx = 1$$

leads to

$$\lambda = b(\alpha - 1).$$

Equation (6.4) is an example of the pantograph equation, which arises in a number of applications including the collection of current in an electric train [50], light absorption in the Milky Way [1] and a ruin problem [20]. A detailed analysis of the equation is given in [32] and [31], and the equation has been studied in the complex plane [16], [42], [74]. We note also that the equation has been studied in the context of probability [15] and the cell growth problem has been interpreted in this framework [17].

The cell division problem has been generalized to include dispersion [80], [4] and this led to the study of second order pantograph equations [76]. The problem has also been studied for certain non constant coefficients [26], [75], and a multi-compartment model has been developed for an application to the treatment of cancer [3].

All the studies focused exclusively on SSD solutions for cases where the eigenvalue can be determined explicitly. In general, the separation constant λ can not be determined explicitly for given functions $b(x)$ and $g(x)$, and this prompts questions concerning the existence of an eigenvalue and corresponding positive eigenfunction. Some results for more general choices of

b and g were obtained by da Costa *et al.* [13] and also by Perthame and Ryzhik [53]. In particular, Perthame and Ryzhik proved the existence of a positive eigenfunction for a class of division rate functions that are positive, bounded, and bounded away from zero. Under suitable decay conditions they also showed that any solution to the cell division problem is asymptotic to this eigenfunction as $t \to \infty$.

Although much is known about SSD solutions to the cell division problem, little is known about the solution to the problem for a given initial distribution, except that it is asymptotic to the SSD solution. In this chapter we develop a solution technique to solve the problem for general initial distributions. We obtain a solution valid for the quadrant $x \geq 0, t \geq 0$. This solution is then used to determine the asymptotic behaviour of the solution explicitly. The general solution allows us to easily get higher order terms in the asymptotic expressions for the number density.

6.2 The existence of a solution for $x \geq gt$

We begin the construction of a general solution to the cell division problem by first constructing a solution that is valid for $x \geq gt \geq 0$. The hyperbolic character of the differential equation and the nature of the initial data prompt the study of solutions in this region, which after a simple transformation is the domain of definition for the data. In the absence of the functional term $n(\alpha x, t)$, equation (6.1) is a classical Cauchy problem that can be solved readily by the method of characteristics. The functional term complicates matters, but since $\alpha > 1$, the domain of definition remains the same. The strategy is to define the solution as a series of functions each of which satisfies a simple Cauchy problem that can be readily solved.

We establish the existence of a non negative solution n to equation (6.1) that satisfies equation (6.2) under moderate conditions for the initial data. Specifically, we assume that n_0 is a bounded probability density function.

Before we embark on constructing the solution we make some simplifications to the differential equation (6.1). Let

$$n(x,t) = e^{-(b+\mu)t}\tilde{n}(x,t).$$

Then,

$$\tilde{n}_t + g\tilde{n}_x = b\alpha^2\tilde{n}(\alpha x, t),$$

and this can be further simplified using the transformation $x = g\hat{x}$, to obtain

$$\hat{n}_t(\hat{x}, t) + \hat{n}_{\hat{x}}(\hat{x}, t) = \alpha^2 b\hat{n}(\alpha\hat{x}, t),$$

where

$$\hat{n}(\hat{x}, t) = \tilde{n}(g\hat{x}, t).$$

Dropping circumflexes and tildes, it is clear that we can reduce the functional differential equation problem to

$$n_t(x, t) + n_x(x, t) = b\alpha^2 n(\alpha x, t), \tag{6.5}$$

and retain the conditions (6.2) and (6.3).

If we restrict our attention to solutions of (6.5) that are integrable with respect to x on $[0, \infty)$ for any fixed $t > 0$, then the transformation

$$m(x, t) = \int_x^\infty n(\xi, t)d\xi, \tag{6.6}$$

yields

$$m_t(x, t) + m_x(x, t) = b\alpha m(\alpha x, t). \tag{6.7}$$

Integrating equation (6.5) from 0 to ∞ w.r.t x and applying condition (6.3) gives

$$m_t(0, t) = b\alpha m(0, t),$$

here, we have assumed that $m \to 0$ as $x \to \infty$ for any $t \geq 0$; hence, for some constant k,

$$m(0, t) = ke^{b\alpha t}.$$

The initial distribution n_0 can be regarded as a probability density function so that $m(0, 0) = 1$; therefore,

$$m(0, t) = e^{b\alpha t}. \tag{6.8}$$

The initial condition for equation (6.7) is

$$m(x,0) = m_0(x) = \int_x^\infty n_0(\xi)d\xi. \tag{6.9}$$

It turns out that it is easier to work with the "cumulative density function" m for the extension to $0 \leq x \leq t$. We construct a solution n and it is clear that the same construction will work for equation (6.7).

Theorem 6.2.1 (*Existence of solution for $x \geq t$*)**.** *Let $W_0 \subseteq \mathcal{R}^2$ denote the set $\{(x,t) : x \geq t \geq 0\}$. There exists a non-negative solution Q to equation* (6.5) *that satisfies condition* (6.2) *and is valid for $(x,t) \in W_0$.*

Proof. We construct a sequence of functions $\{N_k(x,t)\}$, defined by a sequence of partial differential equations such that

$$Q(x,t) = \sum_{k=0}^{\infty} N_k(x,t) \tag{6.10}$$

is a solution to equation (6.5) that satisfies the initial condition (6.2) and is valid for $x \geq t$. The functional differential equation problem can be converted to a sequence of Cauchy problems by defining the following sequence

$$N_0(x,t) = n_0(x-t),$$

and for $k \geq 1$,

$$N_{kt} + N_{kx}(x,t) = b\alpha^2 N_{k-1}(\alpha x, t), \tag{6.11}$$

with

$$N_k(x,0) = 0. \tag{6.12}$$

Note that N_0 satisfies the Cauchy problem

$$n_x(x,t) + n_t(x,t) = 0, \quad n(x,0) = n_0(x),$$

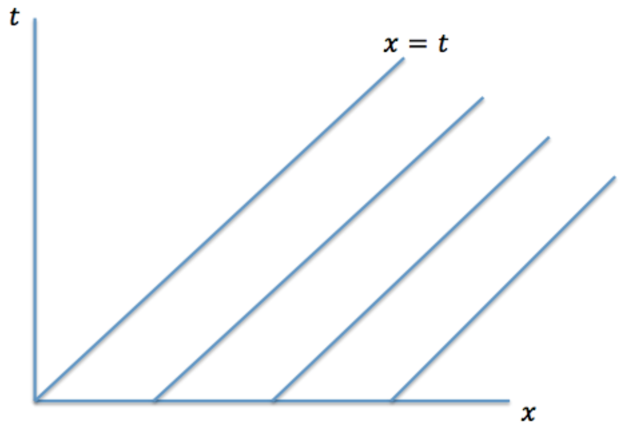

Figure 6.1: Characteristic Projections

and each problem given by equation (6.11) and condition (6.12) is a Cauchy problem that can be solved by the method of characteristics. The characteristic projections (see *Figure* 6.1) ξ and η are given by

$$\begin{aligned}\xi &= t,\\ \eta &= x - t.\end{aligned}$$

In terms of ξ and η, let

$$\begin{aligned}N_k(x,t) &= N_k(\xi+\eta,\xi) = \hat{N}_k(\xi,\eta),\\ N_k(\alpha x,t) &= N_k(\alpha\xi+\alpha\eta,\xi) = \overline{N}_k(\xi,\eta).\end{aligned}$$

For simplicity we drop the circumflex when there is no danger of confusion, but retain the bar to denote an advanced argument. Now,

$$\frac{\partial}{\partial\xi}N_k(\xi,\eta) = N_{k\xi}(\xi,\eta) = b\alpha^2\overline{N}_{k-1}(\xi,\eta),$$

so that the solution to (6.11) that satisfies (6.12) is

$$N_k(\xi,\eta) = b\alpha^2\int_0^\xi \overline{N}_{k-1}(\sigma,\eta)d\sigma. \tag{6.13}$$

To illustrate, we look at the first few terms of the sequence. We have $N_0(x,t) = n_0(\eta)$, and therefore

$$
\begin{aligned}
N_1(\xi,\eta) &= b\alpha^2 \int_0^{\xi} \overline{N}_0(\sigma,\eta)d\sigma \\
&= b\alpha^2 \int_0^{\xi} n_0((\alpha-1)\sigma+\alpha\eta)d\sigma. \\
&= \frac{b\alpha^2}{\alpha-1} \int_{\alpha\eta}^{(\alpha-1)\xi+\alpha\eta} n_0(w)dw. \qquad (6.14)
\end{aligned}
$$

In terms of x and t,

$$
\begin{aligned}
N_1(x,t) &= \frac{b\alpha^2}{(\alpha-1)} \int_{\alpha(x-t)}^{\alpha x-t} n_0(w)dw \\
&= \frac{b\alpha^2}{(\alpha-1)}\{T_1(\alpha x-t) - T_1(\alpha(x-t))\}, \qquad (6.15)
\end{aligned}
$$

where T_1 is an antiderivative of n_0. Similarly,

$$
\begin{aligned}
N_2(x,t) = {} & \frac{(b\alpha^2)^2}{(\alpha-1)(\alpha^2-1)}T_2(\alpha^2 x-t) - \frac{(b\alpha^2)^2}{\alpha(\alpha-1)^2}T_2(\alpha^2 x-\alpha t) \\
& - \left\{\frac{(b\alpha^2)^2}{(\alpha-1)(\alpha^2-1)} - \frac{(b\alpha^2)^2}{\alpha(\alpha-1)^2}\right\} T_2(\alpha^2(x-t))
\end{aligned}
$$

where T_2 is an antiderivative of T_1.

It is straightforward to show that

$$
N_k(x,t) = \sum_{j=0}^{k} d_{k,j} T_k(w_{k,j}(x,t)), \qquad (6.16)
$$

where

$$T_0(w) = n_0(w),$$
$$T'_{k+1}(w) = T_k(w);$$

and $d_{0,0} = 1$,

$$d_{k,j} = \frac{b\alpha^2 d_{k-1,j-1}}{\alpha^{k-j}(\alpha^j - 1)},$$
$$d_{k,0} = -\sum_{j=1}^{k} d_{k,j},$$

Here,

$$w_{k,j}(x,t) = \alpha^{k-j}(\alpha^j x - t),$$

for $k = 1, 2, ...,$ and $j = 1, ..., k$. We also note that

$$\begin{aligned}\overline{w}_{k,j} &= w_{k,j}(\alpha x, t)\\ &= w_{k+1,j+1}(x,t).\end{aligned}$$

We first show that each N_k is non-negative in W_0 and then that the series defining q_0 converges uniformly in any set of W_0 of the form $\{(x,t) \in W_0 : t \leq D\}$, where D is any fixed positive number. Since $n_0(w) \geq 0$, for all $w \geq 0$,

$$\begin{aligned}N_1(x,t) &= \frac{b\alpha^2}{\alpha - 1} \int\limits_{\alpha(x-t)}^{\alpha x - t} n_0(w)dw\\ &\geq 0\end{aligned}$$

for all $(x,t) \in W_0$. If $N_{k-1}(\xi, \eta) \geq 0$, then

$$\begin{aligned}N_k(\xi,\eta) &= b\alpha^2 \int\limits_0^{\xi} \overline{N}_{k-1}(\sigma,\eta)d\sigma\\ &\geq 0,\end{aligned}$$

and hence by induction $N_k(x,t) \geq 0$ in W_0. Let M be an upper bound for n_0. Then $N_0(x,t) \leq M$; hence, equation (6.14) implies,

$$N_1(x,t) \leq \frac{b\alpha^2 M}{\alpha - 1} \int\limits_{\alpha(x-t)}^{\alpha x - t} dw = b\alpha^2 M t,$$

i.e.,
$$N_1(\xi,\eta) \leq b\alpha^2 M \xi.$$

Now,

$$\begin{aligned} N_2(\xi,\eta) &= b\alpha^2 \int\limits_0^{\xi} \overline{N}_1(\sigma,\eta) d\sigma \\ &\leq (b\alpha^2)^2 M \int\limits_0^{\xi} \sigma d\sigma = \frac{M(b\alpha^2)^2 \xi^2}{2}, \end{aligned}$$

so that

$$N_2(x,t) \leq \frac{M(b\alpha^2 t)^2}{2}$$

for all $x \geq t$. We can continue in this fashion to show that

$$N_k(x,t) \leq \frac{M(b\alpha^2 t)^k}{k!}$$

for all $x \geq t$, and this leads to

$$\sum_{k=0}^{\infty} N_k(x,t) \leq M \sum_{k=0}^{\infty} \frac{(b\alpha^2 t)^k}{k!} = M e^{b\alpha^2 t}.$$

The series thus converges uniformly in any set $\{(x,t) \in W_0 : 0 \leq t \leq D\}$. Evidently, $Q(x,t) \geq 0$ for all $(x,t) \in W_0$ and is a solution to equation (6.5) that satisfies condition (6.2). $\square$

Although a solution to equation (6.7) can be gleaned from Q, this equation could also be solved directly using the same approach. In particular, the solution found by integrating Q is also given by a solution to equation (6.7) for $x \geq t$ that satisfies condition (6.9) and is of the form

$$P_0(x,t) = \sum_{k=0}^{\infty} M_k(x,t), \tag{6.17}$$

where

$$M_k(x,t) = \sum_{j=0}^{k} c_{k,j} F_k(w_{k,j}(x,t)).$$

and

$$F_0(w) = m_0(w), \tag{6.18}$$
$$F'_{k+1}(w) = F_k(w). \tag{6.19}$$

Here, the $c_{k,j}$ are given by $c_{0,0} = 1$, and

$$c_{k,j} = \frac{b\alpha c_{k-1,j-1}}{\alpha^{k-j}(\alpha^j - 1)}, \tag{6.20}$$
$$c_{k,0} = -\sum_{j=1}^{k} c_{k,j}, \tag{6.21}$$

where $k = 1, 2, ...,$ and $j = 1, ..., k$.

6.3 Extension of the solution for $0 \leq x < t$

We use the solution constructed to equation (6.7) in section 6.2 to construct a solution that also satisfies condition (6.8) and is valid for all $x \geq 0$, $t \geq 0$. The functional character of equation (6.7) can be exploited to continue the solution (6.17) via a sequence of “wedges”. For $n \geq 1$, let

$$W_n = \{(x,t) : \frac{t}{\alpha^n} \leq x \leq \frac{t}{\alpha^{n-1}}\}$$

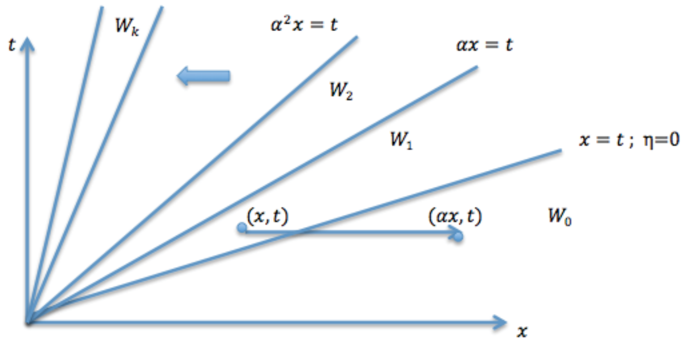

Figure 6.2: Constructing wedges to extend the solution to $0 \leq x < t$

(see *Figure 6.2*). The key here is that equation (6.7) is not functional in W_n if the solution is known in W_{n-1}. In this case the problem reduces to a non-homogeneous first order linear partial differential equation that can be readily solved. It is required that the solution be continuous across the wedge boundaries, and this provides the initial data. The extension to W_1 differs from the other extensions in that the initial data is on the characteristic projection $x = t$. The first extension thus introduces an arbitrary function. Further extensions induce non characteristic data so that there is only one arbitrary function in the construction. In the next section we use condition (6.8) to determine this function.

The solution to equation (6.7) valid in the wedge W_n will be denoted by h_n for $n \geq 1$. In addition, we introduce the notation

$$P_n = \sum_{k=n}^{\infty} \sum_{j=n}^{k} c_{k,j} F_k(w_{k,j}) \tag{6.22}$$

for $n \geq 0$. If $(x, t) \in W_1$ then $(\alpha x, t) \in W_0$. The function h_1 thus satisfies

$$(h_1)_t + (h_1)_x = b\alpha P_0(\alpha x, t).$$

In characteristic coordinates the above partial differential equation is

$$(h_1)_\xi = b\alpha \sum_{k=0}^{\infty} \sum_{j=0}^{k} c_{k,j} F_k(\overline{w}_{k,j}),$$

and using the relation $\overline{w}_{k,j} = w_{k+1,j+1}$ along with equation (6.19) we have

$$h_1(\xi, \eta) = \sum_{k=0}^{\infty} \sum_{j=0}^{k} \frac{b\alpha c_{k,j}}{\alpha^{k-j}(\alpha^j - 1)} F_{k+1}(w_{k+1,j+1}) + G_0(w_{0,0}),$$

where G_0 is an arbitrary function of $w_{0,0} = \eta$. Equation (6.20) thus implies

$$h_1(\xi, \eta) = P_1(\xi, \eta) + G_0(\eta). \tag{6.23}$$

We require the solution to be continuous across the characteristic projection $\eta = 0$ (see *Figure 6.3*), and this condition will not determine G_0 uniquely.

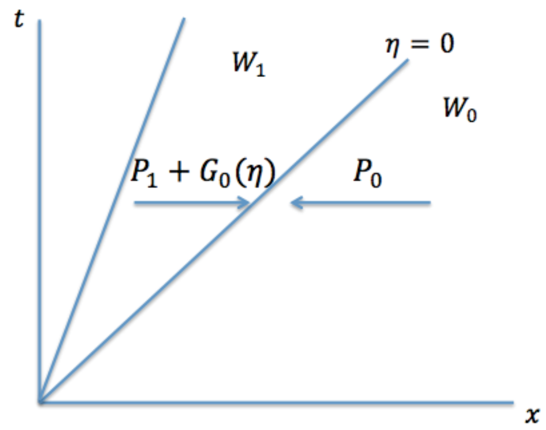

Figure 6.3: Imposing continuity on the line $x = t$ or $\eta = 0$

Now,

$$\lim_{\eta \to 0^-} h_1(\xi, \eta) = P_1(\xi, 0) + G_0(0)$$

and

$$\lim_{\eta \to 0^+} P_0(\xi, \eta) = P_1(\xi, 0) + \lim_{\eta \to 0^+} \sum_{k=0}^{\infty} c_{k,0} F_k(w_{k,0}).$$

The continuity condition and the relation $w_{k,0} = \alpha^k \eta$ thus give

$$G_0(0) = \lim_{\eta \to 0^+} \sum_{k=0}^{\infty} c_{k,0} F_k(0).$$

The function F_{k+1} can be any antiderivative of F_k, since condition (6.21) ensures that condition $M_k(x, 0) = 0$ is satisfied. We can thus choose the F_k such that $F_k(0) = 0$ for $k \geq 1$. Equation (6.18), however, requires that $F_0(0) = 1$. With this choice of F_k we thus have

$$G_0(0) = 1.$$

We now consider the extension of the solution to the wedge W_2 (see *Figure 6.4*) and from this analysis extract a general form for h_n. Proceeding as

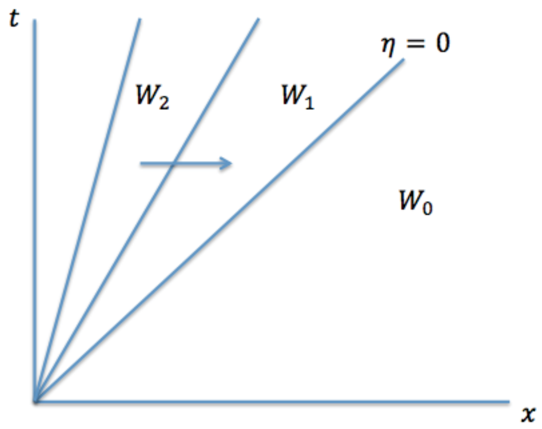

Figure 6.4: Extension of solution to the W_2 wedge

before

$$(h_2)_\xi = b\alpha\overline{h}_1(\xi, \eta),$$

which by using equation (6.23) gives

$$(h_2)_\xi = \overline{P}_1(\xi, \eta) + \overline{G_0}(\eta). \tag{6.24}$$

Integrating equation (6.24) with respect to ξ, using the definition of F_n and the recursion relation (6.20) leads to

$$h_2(\xi, \eta) = P_2(\xi, \eta) + \frac{b\alpha G_1(w_{1,1})}{\alpha - 1} + H(\eta),$$

where H is an arbitrary function and $G_1'(u) = G_0(u)$. (The $\frac{1}{\alpha-1}$ factor comes from $w_{1,1} = (\alpha-1)\xi+\alpha\eta$.) The function G_1 can be any antiderivative of G_0, so we choose G_1 such that $G_1(0) = 0$. To get H, we impose the continuity condition on the line $x = \frac{t}{\alpha}$, i.e., $w_{1,1} = 0$. Thus,

$$\lim_{w_{1,1}\to 0^-} h_2 = \lim_{w_{1,1}\to 0^-} P_2 + \frac{b\alpha G_1(0)}{\alpha-1} + \lim_{w_{1,1}\to 0^-} H(\eta)$$

and

$$\lim_{w_{1,1}\to 0^+} h_1 = \lim_{w_{1,1}\to 0^+} P_2 + \lim_{w_{1,1}\to 0^+} \sum_{k=1}^{\infty} c_{k,1}F_k(w_{k,1}) + \lim_{w_{1,1}\to 0^+} G_0(\eta).$$

Since

$$\begin{aligned} w_{k,1} &= \alpha^{k-1}(\alpha-1)\xi + \alpha^k\eta \\ &= \alpha^{k-1}w_{1,1} \end{aligned}$$

we have

$$\lim_{w_{1,1}\to 0^+} \sum_{k=1}^{\infty} c_{k,1}F_k(w_{k,1}) = \sum_{k=1}^{\infty} c_{k,1}F_k(0) = 0.$$

The continuity of P_2 in $W_2 \cup W_1$ means that

$$\lim_{w_{1,1}\to 0^-} P_2 = \lim_{w_{1,1}\to 0^+} P_2,$$

and the continuity condition

$$\lim_{w_{1,1}\to 0^-} h_2 = \lim_{w_{1,1}\to 0^+} h_1$$

yields

$$\lim_{w_{1,1}\to 0^-} H(\eta) = \lim_{w_{1,1}\to 0^+} G_0(\eta), \tag{6.25}$$

since $G_1(0) = 0$. Now, $w_{1,1} = 0$ implies

$$\eta = -\frac{(\alpha-1)}{\alpha}\xi,$$

and this means condition (6.25) must be satisfied for all ξ on the line $w_{1,1} = 0$, i.e., for all ξ on this line

$$H\left(-\frac{(\alpha-1)}{\alpha}\xi\right) = G_0\left(-\frac{(\alpha-1)}{\alpha}\xi\right).$$

We thus conclude that

$$H(u) = G_0(u),$$

and the solution is thus

$$h_2 = P_2 + \frac{b\alpha}{\alpha-1}G_1(w_{1,1}) + G_0(w_{0,0}).$$

We can determine h_3 in a similar manner to get

$$h_3 = P_3 + \frac{(b\alpha)^2}{(\alpha-1)(\alpha^2-1)}G_2(w_{2,2}) + \frac{b\alpha}{\alpha-1}G_1(w_{1,1}) + G_0(w_{0,0}),$$

where $G_2'(u) = G_1(u)$ and $G_2(0) = 0$. For the general wedge W_n, $n \geq 2$ we find

$$h_n = P_n + G_0(w_{0,0}) + \sum_{k=1}^{n-1} \frac{(b\alpha)^k}{\prod\limits_{m=1}^{k}(\alpha^m - 1)} G_k(w_{k,k}),$$

where, for $k \geq 1$, $G_{k+1}'(u) = G_k(u)$ and

$$G_k(0) = 0.$$

A solution m to equation (6.7) that satisfies the initial condition (6.9) can thus be defined piecewise by the sequence $\{h_n\}$, *viz.*,

$$m(x,t) = \begin{cases} h_0 \equiv P_0, & \text{if } (x,t) \in W_0 \\ h_1 = P_1 + G_0, & \text{if } (x,t) \in W_1 \\ \vdots & \\ h_n = P_n + G_0(w_{0,0}) + \sum_{k=1}^{n-1} \frac{(b\alpha)^k}{\prod_{m=1}^{k}(\alpha^m-1)} G_k(w_{k,k}), & \text{if } (x,t) \in W_n. \\ \vdots & \end{cases} \tag{6.26}$$

By construction the solution is continuous on the wedge boundaries. If the initial data m_0 is smooth, then the construction also shows that m_ξ is smooth for $0 \leq \frac{t}{\alpha^n} \leq x$. The function G_0 in the solution (6.26) is arbitrary. If it is required that m have a continuous derivative with respect to η, then $G_0'(u)$ would have to be continuous but this does not ensure continuity on the line $\eta = 0$. Now,

$$(h_0)_\eta = \sum_{k=0}^{\infty} c_{k,0} F_k'(w_{k,0})\alpha^k + (P_1)_\eta,$$

and

$$\begin{aligned}\lim_{\eta\to 0^+} (h_0)_\eta &= c_{1,0}\alpha F_1'(0) + \lim_{\eta\to 0^+} (P_1)_\eta \\ &= \frac{-b\alpha^2}{\alpha - 1} + \lim_{\eta\to 0^+} (P_1)_\eta,\end{aligned}$$

Here we have used $F_{k+1}'(0) = F_k(0) = 0$ for $k \geq 1$, $F_1'(0) = F_0(0) = m_0(0) = 1$, and $F_0'(0) = m_0'(0) = -n_0(0) = 0$. The continuity condition

$$\lim_{\eta\to 0^+} (h_0)_\eta = \lim_{\eta\to 0^-} (h_1)_\eta$$

thus gives

$$G_0'(0) = -\frac{b\alpha^2}{(\alpha - 1)}. \tag{6.27}$$

Similar calculations on the other wedge boundaries show that (6.27) is in fact the only requirement on G_0 apart from the continuity of G_0'. In the next section we determine G_0 and show that it satisfies this continuity condition and condition (6.27).

6.4 The limiting solution and asymptotics as $t \to \infty$

In this section, we determine G_0 from the boundary condition (6.8) at $x = 0$. To apply this boundary condition it is necessary to look at the limiting function h_n as $n \to \infty$. For a fixed value of t, the limit $x \to 0^+$ corresponds to (x, t) in W_n as $n \to \infty$. We thus consider $\lim\limits_{n\to\infty} h_n(x,t)$.

The series defining P_0 is a convergent; hence, $P_n \to 0$ as $n \to \infty$; and

$$h(0,t) = \lim_{n\to\infty} h_n = G_0(-t) + \sum_{k=1}^{\infty} \frac{(b\alpha)^k}{\prod\limits_{m=1}^{k}(\alpha^m - 1)} G_k(-t).$$

Now $h(0,t) = m(0,t) = e^{b\alpha t}$ by condition (6.8), and therefore

$$e^{-b\alpha u} = G_0(u) + \sum_{k=1}^{\infty} \frac{(b\alpha)^k}{\prod\limits_{m=1}^{k}(\alpha^m - 1)} G_k(u), \tag{6.28}$$

where $u = -t$. Taking the Laplace transform of both sides of equation (6.28) gives

$$\frac{1}{s + b\alpha} = f(s)\left(1 + \sum_{k=1}^{\infty} \frac{(\frac{b\alpha}{s})^k}{\prod\limits_{m=1}^{k}(\alpha^m - 1)}\right), \tag{6.29}$$

where $f(s)$ is the Laplace transform of G_0. The infinite series in (6.29) can be converted into an infinite product by use of the Euler's identity

$$\prod_{k=0}^{\infty}(1 + zq^k) = 1 + \sum_{k=1}^{\infty} \frac{z^k q^{\frac{k(k-1)}{2}}}{\prod\limits_{m=1}^{k}(1 - q^m)},$$

for $|q| < 1$. Now,

$$\begin{aligned}
1 + \sum_{k=1}^{\infty} \frac{(\frac{b\alpha}{s})^k}{\prod\limits_{m=1}^{k}(\alpha^m - 1)} &= 1 + \sum_{k=1}^{\infty} \frac{(\frac{b\alpha}{s})^k}{\alpha^{\frac{k(k+1)}{2}} \prod\limits_{m=1}^{k}\left(1 - \frac{1}{\alpha^m}\right)} \\
&= 1 + \sum_{k=1}^{\infty} \frac{(\frac{b}{s})^k q^{\frac{k(k-1)}{2}}}{\prod\limits_{m=1}^{k}(1 - q^m)},
\end{aligned}$$

where $q = \frac{1}{\alpha}$, We apply the Euler's identity with $z = \frac{b}{s}$ to get

$$\frac{1}{s + b\alpha} = f(s) \prod_{k=0}^{\infty} \left(1 + \frac{b}{\alpha^k s}\right),$$

so that

$$f(s) = \frac{1}{s(1 + \frac{b\alpha}{s})(1 + \frac{b}{s})(1 + \frac{b}{\alpha s})(1 + \frac{b}{\alpha^2 s})...}.$$

It is clear that f has simple poles at $s = -b\alpha^{-k}$, for $k = -1, 0, 1, 2, \dots$, the Mittag-Leffler theorem implies that $f(s)$ can be represented in the form

$$f(s) = \frac{a_{-1}}{s + b\alpha} + \frac{a_0}{s + b} + \frac{a_1}{s + \frac{b}{\alpha}} + ... + r(s),$$

where r is an entire function. The inverse transform of f is therefore

$$\begin{aligned} G_0(u) &= a_{-1}e^{-b\alpha u} + a_0 e^{-bu} + a_1 e^{-\frac{bu}{\alpha}} + ... \\ &= \sum_{n=-1}^{\infty} a_n e^{-b\alpha^{-n} u}, \end{aligned}$$

where

$$a_n = \operatorname*{Res}_{s=-\frac{b}{\alpha^n}} f(s).$$

Now,

$$\begin{aligned} a_{-1} &= \lim_{s \to -b\alpha} \frac{(s + b\alpha)}{(s + b\alpha)(1 + \frac{b}{s})(1 + \frac{b}{\alpha s})(1 + \frac{b}{\alpha^2 s})...} = \frac{1}{\prod_{k=1}^{\infty} \left(1 - \frac{1}{\alpha^k}\right)} = R(\alpha), \\ a_0 &= \lim_{s \to -b} \frac{(s + b)}{s(1 + \frac{b\alpha}{s})(1 + \frac{b}{s})...} = \frac{1}{(1 - \alpha)} R(\alpha), \\ a_1 &= \lim_{s \to -\frac{b}{\alpha}} \frac{s(1 + \frac{b\alpha}{s})}{s(1 + \frac{b\alpha}{s})(1 + \frac{b}{s})(1 + \frac{b}{\alpha s})(1 + \frac{b}{\alpha^2 s})...} = \frac{1}{(1 - \alpha^2)(1 - \alpha)} R(\alpha), \end{aligned}$$

and in general

$$a_k = \frac{(-1)^{k+1}}{\prod\limits_{m=1}^{k+1}(\alpha^m - 1)} R(\alpha);$$

hence,

$$G_0(u) = R(\alpha)\left\{ e^{-b\alpha u} + \sum_{n=1}^{\infty} \frac{(-1)^n e^{-b\alpha \frac{u}{\alpha^n}}}{\prod\limits_{m=1}^{n}(\alpha^m - 1)} \right\}. \tag{6.30}$$

The function G_1 is the antiderivative of G_0, such that $G_1(0) = 0$. Integrating equation (6.30) yields the antiderivative

$$G_1(u) = -\frac{R(\alpha)}{b\alpha}\left\{ e^{-b\alpha u} + \sum_{n=1}^{\infty} \frac{(-1)^n \alpha^n e^{-b\alpha \frac{u}{\alpha^n}}}{\prod\limits_{m=1}^{n}(\alpha^m - 1)} \right\},$$

and it can be confirmed directly from the Euler's identity that $G_1(0) = 0$. In general, for $n \geq 0$, it can be shown that

$$G_n(u) = \frac{(-1)^n R(\alpha)}{(b\alpha)^n}\left\{ e^{-b\alpha u} + \sum_{k=1}^{\infty} \frac{(-1)^k \alpha^{kn} e^{-b\alpha \frac{u}{\alpha^k}}}{\prod\limits_{m=1}^{k}(\alpha^m - 1)} \right\}, \tag{6.31}$$

and that $G_n(0) = 0$ for $n \geq 1$. Substituting $u = w_{n,n} = \alpha^n x - t$ into equation (6.31) yields

$$G_n(\alpha^n x - t) = \frac{(-1)^n R(\alpha)}{(b\alpha)^n}\left\{ e^{-b\alpha\alpha^n x + b\alpha t} + \sum_{k=1}^{\infty} \frac{(-1)^k \alpha^{kn} e^{-b\alpha\alpha^{n-k} x} e^{\frac{b\alpha t}{\alpha^k}}}{\prod\limits_{m=1}^{k}(\alpha^m - 1)} \right\},$$

and the limiting function is therefore

$$h(x,t) = R(\alpha)\{ \left(e^{-b\alpha x + b\alpha t} \sum_{k=1}^{\infty} \frac{(-1)^k e^{\frac{-b\alpha x}{\alpha^k}} e^{\frac{b\alpha t}{\alpha^k}}}{\prod_{m=1}^{k} (\alpha^m - 1)} \right)$$

$$+ \frac{b\alpha}{\alpha - 1} \{ \frac{-1}{b\alpha} \left(e^{-b\alpha\alpha x + b\alpha t} + \sum_{k=1}^{\infty} \frac{(-1)^k \alpha^k e^{-b\alpha\alpha^{1-k} x} e^{\frac{b\alpha t}{\alpha^k}}}{\prod_{m=1}^{k} (\alpha^m - 1)} \right) \}$$

$$+$$

$$\vdots$$

$$+ \frac{(b\alpha)^n}{\prod_{j=1}^{n} (\alpha^j - 1)} \{ \frac{(-1)^n}{(b\alpha)^n} \left(e^{-b\alpha\alpha^n x} e^{b\alpha t} + \sum_{k=1}^{\infty} \frac{(-1)^k \alpha^{kn} e^{-b\alpha\alpha^{n-k} x} e^{\frac{b\alpha t}{\alpha^k}}}{\prod_{m=1}^{k} (\alpha^m - 1)} \right) \}$$

$$+ \ldots \}.$$

The above series can be rearranged to collect the factors of $e^{b\alpha t}$, e^{bt}, $e^{\frac{bt}{\alpha}}$, ... In particular, the $e^{b\alpha t}$ term is

$$v_0(x,t) = e^{b\alpha t} \left\{ e^{-b\alpha x} + \sum_{n=1}^{\infty} \frac{(-1)^n e^{-b\alpha(\alpha^n x)}}{\prod_{m=1}^{n} (\alpha^m - 1)} \right\},$$

and the e^{bt} term is

$$v_1(x,t) = -\frac{e^{bt}}{(\alpha - 1)} \left\{ e^{-b\alpha \frac{x}{\alpha}} + \sum_{n=1}^{\infty} \frac{(-1)^n \alpha^n e^{-b\alpha(\alpha^{n-1} x)}}{\prod_{m=1}^{n} (\alpha^m - 1)} \right\}.$$

In general,

$$v_k(x,t) = -\frac{(-1)^k e^{\frac{b\alpha t}{\alpha^k}}}{\prod_{m=1}^{k} (\alpha^m - 1)} \left\{ e^{-b\alpha \frac{x}{\alpha^k}} + \sum_{n=1}^{\infty} \frac{(-1)^n \alpha^n e^{-b\alpha(\alpha^{n-k} x)}}{\prod_{m=1}^{n} (\alpha^m - 1)} \right\},$$

and the limit function can thus be expressed as

$$h(x,t) = R(\alpha)\sum_{k=0}^{\infty} v_k(x,t). \tag{6.32}$$

We note that the constant $R(\alpha)$ can be evaluated or represented a number of ways. Hall and Wake [24] show that Euler's pentagonal number theorem can be invoked to convert this product to an infinite series. They also note a representation of $R(\alpha)$ in terms of a Jacobi elliptic function. More generally, Morgan [47] considers this constant as a special case and shows that it can be represented in terms of a Dedekind eta function or implicitly in terms of a theta function.

Finally, we note that G_0 is a smooth function and

$$G_0'(0) = -b\alpha R(\alpha)\left\{1 + \sum_{n=1}^{\infty}\frac{(-1)^n}{\alpha^n \prod\limits_{m=1}^{n}(\alpha^m - 1)}\right\}.$$

Euler's identity shows that

$$\begin{aligned} 1 + \sum_{n=1}^{\infty}\frac{(-1)^n}{\alpha^n \prod\limits_{m=1}^{n}(\alpha^m - 1)} &= \prod_{k=0}^{\infty}\left(1 - \frac{1}{\alpha^{k+2}}\right) \\ &= \frac{1}{\left(1-\frac{1}{\alpha}\right)R(\alpha)}, \end{aligned}$$

so that equation (6.27) is satisfied. In summary, we have the following result.

Theorem 6.4.1 (*Existence*)**.** *A solution m to equation* (6.7) *that satisfies conditions* (6.8) *and* (6.9) *is given by equation* (6.26)*, where the P_n are defined by* (6.22) *and G_0 is defined by* (6.30)*. The smoothness of this solution is limited only by the smoothness of the initial function m_0.*

It is known (cf. [53]) that any solution to equation (6.1) that satisfies conditions (6.2) and (6.3) also satisfies

$$n(x,t) \sim e^{b\alpha t}y(x)$$

as $t \to \infty$. Here, y is the steady size distribution derived by Hall and Wake [24]. Thus, for any initial probability density function n_0, the "long term" solution approaches asymptotically the same function. We can deduce this asymptotic relationship directly from our general solution.

Fix any $x > 0$. The solution m is given by a function in the sequence $\{h_n\}$, and it is clear that $n \to \infty$ as $t \to \infty$. We are thus drawn to study the limiting solution $h(x,t)$ given by equation (6.32). From this equation we see immediately that

$$m(x,t) \sim R(\alpha)e^{b\alpha t}v_0(x,t)$$

as $t \to \infty$. Relation (6.6) can then be used to show that

$$n(x,t) \sim -R(\alpha)e^{b\alpha t}\frac{\partial}{\partial x}v_0(x,t),$$

which is the SSD solution obtained by Hall and Wake. Note that the limiting solution, however, provides more refined results. For instance, as $t \to \infty$,

$$m(x,t) \sim -R(\alpha)(e^{b\alpha t}v_0(x,t) + e^{bt}v_1(x,t)) + \mathrm{O}(e^{\frac{b}{\alpha}t}).$$

Finally, we note that the Dirichlet series defined by the v_k correspond to the eigenfunctions derived by van-Brunt and Vlieg-Hulstman [77], [78].

6.5 Uniqueness

We show the solution m in Theorem 6.4.1 is unique. Suppose that m_1 and m_2 are distinct solutions to equation (6.7) that satisfy equations (6.8) and (6.9). Let $u(x,t) = m_1(x,t) - m_2(x,t)$. Then u satisfies

$$\begin{aligned}
&u_t + u_x = b\alpha u(\alpha x, t),\\
&u(x,0) = 0,\\
&u(0,t) = 0.
\end{aligned}$$

Let

$$u(x,t) = e^{b\alpha t}p(x,t).$$

Then p satisfies

$$p_t + p_x = b\alpha(p(\alpha x, t) - p(x, t)), \tag{6.33}$$
$$p(x, 0) = 0, \tag{6.34}$$
$$p(0, t) = 0. \tag{6.35}$$

The next lemma shows that the only solution to above problem is $p = 0$.

Lemma 6.5.1. *Let $W = \{(x, t) : x \geq 0$ and $t \geq 0\}$, and suppose that p is a solution to equation* (6.33) *valid in W that satisfies conditions* (6.34) *and* (6.35). *Suppose further that p_t and p_x are continuous in W and that for any $T \geq 0$ and any $\epsilon > 0$ there are positive numbers δ_ϵ and X_ϵ such that*

$$|p(x, t)| < \epsilon \tag{6.36}$$

whenever $t \in [T, T + \delta_\epsilon]$ and $x > X_\epsilon$. Then $p(x, t) = 0$ for all $(x, t) \in W$.

Proof. Suppose there is a point $(x_0, t_0) \in W$ at which $p(x_0, t_0) \neq 0$. Without loss of generality we can assume $p(x_0, t_0) > 0$. Conditions (6.35) and (6.36) imply that $p_0(x) = p(x, t_0)$ must have a global maximum $\gamma_0 > 0$ at some $x \in (0, \infty)$. Condition (6.36) also indicates that there must be a largest value of x, say m_0, at which $p_0(m_0) = \gamma_0$. Let $l_0 > m_0$ and define the set

$$R_0 = \{(x, t) \in W : x \leq l_0, t \leq t_0\}.$$

Now p is continuous on R_0, so there must be a point $(x_1, t_1) \in R_0$ at which p attains its maximum value $\Lambda_0 \geq \gamma_0$. Since m_0 is the position of the "last" global maximum for $p(x, t_0)$, we have $p_x(m_0, t_0) = 0$ and

$$p_t(m_0, t_0) = b\alpha(p(\alpha m_0, t_0) - p(m_0, t_0)) < 0. \tag{6.37}$$

Inequality (6.37) shows that there must be a $t < t_0$ at which $p(m_0, t) > \gamma_0$; hence, Λ_0 cannot be achieved on the line $t = t_0$. Clearly Λ_0 is not attained on the lines $x = 0$ or $t = 0$; thus, it must be attained at either an interior point of R_0 or on the line segment $L_0 = \{(x, t) : x = l_0, 0 < t < t_0\}$. If it occurs on L_0, then $p_t(x_1, t_1) = 0$ and $p_x(x_1, t_1) \geq 0$; hence, $p(\alpha x_1, t_1) \geq p(x_1, t_1) = \Lambda_0$. If Λ_0 is not attained on L_0, then (x_1, t_1) is an interior point; hence, $p_x(x_1, t_2) = p_t(x_1, t_1) = 0$ and consequently

$$p(\alpha x_1, t_1) = p(x_1, t_1) = \Lambda_0.$$

If $(\alpha x_1, t_1)$ is an interior point of R_0, then the above argument can be applied to $(\alpha x_1, t_1)$. Eventually $\alpha^n x_1 > l_0$ for n large, so that in this manner we can assert the existence of a point (x^*, t_1) with $x^* > l_0$ at which $p(x^*, t_1) \geq \Lambda_0 > \gamma_0$.

The function $p_1(x) = p(x, t_1)$ must have a largest value of x, say m_1, at which p_1 achieves its global maximum $\gamma_1 \geq \Lambda_0$. Choose any number l_1 such that $l_1 > max\{m_1, \alpha l_0\}$ and let

$$R_1 = \{(x, t) \in W : x \leq l_1, t \leq t_1\}.$$

We can repeat the arguments used on R_0 to assert the existence of a point $(\tilde{x}, t_2)$, where $l_1 < \tilde{x}$ and $t_2 < t_1$, at which $p(\tilde{x}, t_2) \geq \Lambda_1 > \gamma_1 > \gamma_0$. Here, Λ_1 denotes the maximum of p in R_1. Evidently, we can continue this process *ad infinitum*, and thus construct sequences $\{t_k\}$, $\{m_k\}$ and $\{\gamma_k\}$, where $p_k(x) = p(x, t_k)$ has its last global maximum γ_k at $x = m_k$. All of these sequences are monotonic: in particular, $\{t_n\}$ is monotonic strictly decreasing and bounded below by 0; $\{m_k\}$ is monotonic strictly increasing and satisfies $m_k > \alpha^{k-1} l_0$; and $\{\gamma_k\}$ is monotonic strictly increasing so that specifically $\gamma_k > \gamma_0 > 0$ for all k. Clearly, there must be a $\tau \geq 0$ such that $t_k \to \tau$ as $k \to \infty$; and $m_k \to \infty$ as $k \to \infty$. For each $k \geq 1$, $p(m_k, t_k) > \gamma_0 > 0$, so that if we choose $T = \tau$ and $\epsilon = \gamma_0$, it is clear that there is no $\delta_\epsilon > 0$ that satisfies (6.36). $\square$

Theorem 6.5.2 (Uniqueness)**.** *Let m be defined by equation* (6.26)*. Then for any $\epsilon > 0$ and any $T \geq 0$ there is a $\delta_\epsilon > 0$ and an X_ϵ such that*

$$|m(x, t)| < \epsilon \tag{6.38}$$

whenever $t \in [T, T + \delta_\epsilon]$ and $x > X_\epsilon$. The function defined by equation (6.26) *is unique among functions with continuous partial derivatives that satisfy equations* (6.7)*,* (6.8)*,* (6.9) *and* (6.38)*.*

Proof. Lemma 6.5.1 shows that the solution m of Theorem 6.4.1 is unique provided m satisfies the appropriate decay condition. Let

$$m(x, t) = e^{b\alpha t} p(x, t).$$

We show that p satisfies condition (6.36). Choose $T \geq 0$ and $\epsilon > 0$. For $x > t$, the solution m is given by equation (6.17), and the arguments used to establish the uniform convergence of the series (6.10) can be readily adapted to show that

$$0 \leq m(x, t) \leq e^{b\alpha t} \Lambda(x, t),$$

where

$$\Lambda(x,t) = \sup_{z \geq \alpha(x-t)} m_0(z).$$

Choose any $\delta_\epsilon > 0$. Since $m_0(x) \to 0$ as $x \to \infty$, there is an X_ϵ such that $X_\epsilon > T + \delta_\epsilon$ and $m_0(z) < \epsilon$ for all $z \geq \alpha(X_\epsilon - (T + \delta_\epsilon))$, i.e.,

$$p(x,t) \leq \Lambda(x,t) < \epsilon$$

for all $x > X_\epsilon$ and $t \in [T, T + \delta_\epsilon]$. □

6.6 Conclusions

In this chapter we developed a new method whereby an initial boundary value problem involving a first order linear functional partial differential equation can be solved. The method is not restricted to the functional equation studied in this paper: the same strategy can be employed to deal with more general functional partial differential equations with advanced arguments. For example, if the division rate b is not constant with respect to x, the same approach in principle can be used. The crux, however, is finding the limiting function. Certainly, future work would include such generalizations.

In terms of the cell division model, the general solution developed in this chapter provides more detailed information about how the cell size distribution depends on the initial distribution. It is well known that solutions are asymptotic to the SSD solution as $t \to \infty$, but the analysis underlying this relation does not fully explain or illustrate why the initial data has such a weak influence on the long term solution and how the SSD solution arises. The weak dependence is a result of the hyperbolic character of the differential operator and the advanced argument. We have shown that the SSD solution arises as the leading order term in an expansion for the limiting function, which represents the solution as $t \to \infty$. In contrast, this limiting solution depends strongly on the boundary data. The expansion also provides the higher order terms in the asymptotic expansion, and these terms correspond to eigenfunctions for the pantograph equation.

Chapter 7

Symmetrical cell division with dispersion

In chapters 5 and 6 we studied the cell growth model (4.4)-(4.7) for deterministic growth rates. Also, we observed in chapter 4 that the deterministic cell growth model (4.4)-(4.7) can be refined to include stochasticity in the growth rate of cells. Hall [25] notes that there may be an "experimental evidence showing significant variation in the growth rates of individuals all with the same measured properties". In such a scenario, the deterministic cell growth model would be inappropriate. To cater for this, we added stochasticity to the growth rate of cells and this lead to a dispersion-like model (4.12)-(4.16). Here, we study this model (4.12)-(4.16) for the case of symmetric division of cells.

As seen in Chapter 5, the process in which a cell of size αx divides into α cells each of size x can be modelled by

$$W(x, \xi) = \alpha\delta\left(\frac{\xi}{\alpha} - x\right), \tag{7.1}$$

where δ denotes the Dirac delta function. A straightforward calculation shows that $W(x, \xi)$ given by equation (7.1) satisfies the mass balance equation (4.8) as well as equation (4.9). The above choice of W and the mass balance equation simplify equation (4.16) to

$$n_t(x, t) + gn_x(x, t) + (b + \mu)n(x, t) = Dn_{xx}(x, t) + \alpha^2 bn(\alpha x, t). \tag{7.2}$$

Here, we take for simplicity D, g and b as positive specified constants.

Equation (7.2) is supplemented with an arbitrary initial number density

$$n(x,0) = n_0(x), \tag{7.3}$$

the no-flux condition

$$Dn_x(0,t) - n(0,t) = 0, \tag{7.4}$$

and the condition

$$\lim_{x\to\infty} n(x,t) = 0. \tag{7.5}$$

We follow a procedure similar to that used for the symmetric division of cells with deterministic growth rates (chapter 5) and focus on the solutions of equation (7.2), subject to the conditions given by (4.12)-(4.15), that correspond to the steady size distribution (SSD) (of constant shape). Wake *et al.* [80] studied equation (7.2) without the mortality term and considered separable solutions of the form $n(x,t) = y(x)N(t)$, where $N(t) = \int\limits_0^\infty n(x,t)dx$ is the total population at time t and $y(x)$ (i.e., y is time invariant) is a probability density function with $\int\limits_0^\infty y(x)dx = 1$. These separable solutions correspond to the "steady size distributions" (SSDs). SSD solutions are thus separable solutions of the form $n(x,t) = N(t)y(x)$ which upon substitution into equation (7.2) leads to solutions of the form

$$n(x,t) = e^{-\lambda t}y(x), \tag{7.6}$$

where λ is a separation constant (to be found) and y satisfies

$$Dy''(x) - gy'(x) - (\mu + b - \lambda)y(x) + \alpha^2 by(\alpha x) = 0. \tag{7.7}$$

The "no-flux condition" (4.12) gives

$$Dy'(0) - gy(0) = 0. \tag{7.8}$$

We also impose the condition

$$\lim_{x\to\infty} y(x) = 0, \tag{7.9}$$

and

$$\lim_{x\to\infty} \frac{\partial}{\partial x} n(x,t) = 0.$$

The function $y(x)$ is a probability density function (pdf) so that

$$\int_0^\infty y(x)dx = 1. \tag{7.10}$$

Integrating equation (7.7) with respect to x from 0 to ∞ and using equations (7.10), (7.8) and (7.9) yield

$$\lambda = \mu - b(\alpha - 1). \tag{7.11}$$

The substitution of λ to equation (7.7) yields the functional differential equation

$$cy''(x) - y'(x) + a\alpha y(\alpha x) - ay(x) = 0, \tag{7.12}$$

where $c = \frac{D}{g}$, and $a = \frac{b\alpha}{g}$. Wake *et al.* [80] showed that the solution to equation (7.12) is in terms of a Dirichlet series and is given by

$$y(x) = \sum_{n=0}^{\infty} a_n e^{-\alpha^n r x}, \tag{7.13}$$

where the coefficients a_n are given by

$$a_n = \frac{-a\alpha a_{n-1}}{cr^2\alpha^{2n} + r\alpha^n - cr^2 - r}. \tag{7.14}$$

The parameter r is the positive root of the indicial equation

$$cr^2 + r - a = 0. \tag{7.15}$$

Wake *et al.* [80] also showed that the SSD solution (7.13) is positive and unique.

As discussed in the non-dispersion case (chapter 5), SSD solutions are of central interest in this model since they can be easily matched to data for the size distribution of cells for large time. They are special solutions to the nonlocal partial differential equation (7.2). In particular, given an initial distribution $n(x,0) = n_0(x)$, the SSD solution does not give the complete solution (unless $n_0(x) = y(x)$) and this prompts one to consider other techniques to solve the more general problem.

This means that there is a set of solutions for equation (7.7) with homogeneous boundary conditions, that is, λ has the role of an eigenvalue as discussed in van-Brunt *et al* [76]. We note that the general solution to the partial differential equation at this stage, is not known. It may be possible that a class of solutions y_m for $m = 0, 1, \ldots$ can be obtained using an eigenfunction expansion. Specifically, we can use the conditions given by the successive moments (that is, the Mellin transform),

$$\int_0^\infty x^{m-1} y_m(x)dx = 0, \quad \int_0^\infty x^m y_m(x)dx \neq 0 \tag{7.16}$$

to calculate some further solutions to equation (7.7). These conditions give rise to a class of eigenfunctions and are sufficient in this respect. At this stage it is not clear whether there are other eigenfunctions. The idea mimics that used by van-Brunt and Vlieg-Hulstman [77]. However, in our case, we will see that the first eigenfunction (after the SSD solution) is qualitatively different from the higher eigenfuntions in that the first eigenfunction involves the solution to a non-local, non-linear functional differential equation. Eigenfunctions, other than the first eigenfunction, entail the solution to a linear, non-local functional differential equation. We first discuss the case of eigenfunctions y_m, where $m \geq 2$ and then consider the eigenfunction y_1. For $m \geq 2$, we multiply equation (7.7) by x^m and then integrate the resulting equation with respect to x from 0 to ∞, i.e.,

$$\begin{aligned} D\int_0^\infty x^m y''(x)dx - g\int_0^\infty x^m y'(x)dx - (\mu + b - \lambda)\int_0^\infty x^m y(x)dx \\ + \alpha^2 b\int_0^\infty x^m y(\alpha x)dx = 0, \end{aligned} \tag{7.17}$$

which by using conditions in (7.16) gives

$$\lambda = \mu + b - b\alpha^{-(m-1)}, \tag{7.18}$$

where $m = 2, 3, \ldots$. The functional differential equation (7.7) thus reduces to

$$Dy''(x) - gy'(x) + \alpha^2 by(\alpha x) - b\alpha^{-(m-1)}y(x) = 0. \tag{7.19}$$

The solution to equation (7.19) subject to the no-flux condition (7.8) and the condition (7.9) can be obtained in a way similar to that used by Wake *et al.* [80] for the SSD solution. We suppose that the solution to equation (7.19) is of the form given by equation (7.13), i.e.,

$$y(x) = \sum_{n=0}^{\infty} a_n e^{-\alpha^n rx}, \tag{7.20}$$

where the coefficients a_n and the parameter r are to be determined. Since

$$y'(x) = -r\sum_{n=0}^{\infty} a_n \alpha^n e^{-\alpha^n rx},$$

$$y''(x) = r^2\sum_{n=0}^{\infty} a_n \alpha^{2n} e^{-\alpha^n rx},$$

and

$$y(\alpha x) = \sum_{n=1}^{\infty} a_{n-1} e^{-\alpha^n rx},$$

equation (7.19) gives

$$Dr^2\sum_{n=0}^{\infty} a_n \alpha^{2n} e^{-\alpha^n rx} + gr\sum_{n=0}^{\infty} a_n \alpha^n e^{-\alpha^n rx} + \alpha^2 b\sum_{n=1}^{\infty} a_{n-1} e^{-\alpha^n rx}$$
$$-b\alpha^{-(m-1)}\sum_{n=0}^{\infty} a_n e^{-\alpha^n rx} = 0.$$

Equating coefficients yields the indicial equation

$$Dr^2 + gr - b\alpha^{-(m-1)} = 0, \tag{7.21}$$

and the recurrence relation

$$a_n = \frac{-\alpha^2 ba_{n-1}}{Dr^2\alpha^{2n} + gr\alpha^n - b\alpha^{-(m-1)}}, \tag{7.22}$$

for $n = 1, 2, \ldots$. Since the series (7.20) diverges for $r \leq 0$, we choose r to be the positive root of (7.21). This positive root is given by

$$r = \frac{-g + \sqrt{g^2 + 4b\alpha^{-(m-1)}D}}{2D}.$$

In closed form, the recurrence relation (7.22) can be written as

$$a_n = \frac{(-1)^n(\alpha^2 b)^n a_0}{\prod_{k=1}^{n}(Dr^2\alpha^{2n} + gr\alpha^n - b\alpha^{-(m-1)})}. \tag{7.23}$$

Since $\lim_{n\to\infty}\left|\frac{a_{n+1}}{a_n}\right| < 1$, the series $\sum_{n=0}^{\infty} a_n$ converges by the ratio test and the absolute convergence test; hence the series (7.20) converges by the limit comparison test. The uniqueness of these eigenfunctions can be established by following the analysis used by Wake *et al.* [80].

For the first non-SSD eigenfunction we multiply equation (7.7) with x and then integrate the resulting equation with respect to x from 0 to ∞, i.e.,

$$D\int_0^\infty xy''(x)dx - g\int_0^\infty xy'(x)dx - (\mu + b - \lambda)\int_0^\infty xy(x)dx$$
$$+ \alpha^2 b\int_0^\infty xy(\alpha x)dx = 0,$$

which by using conditions in (7.16) gives

$$\lambda_1 = \mu - Dy_1(0), \tag{7.24}$$

where the subscript "1" of λ and y is used to show that we are considering the first eigenfunction case. The presence of $y_1(0)$ makes λ_1 unknown since the value of y_1 at $x = 0$ is not known. Exploring the nature of $y_1(0)$ has been left for future work and is not included in this thesis. However, we show that if such a λ_1 exists, then we can find the first eigenfunction on a pattern similar to that used for the other eigenfunctions. We proceed by substituting λ from equation (7.24) to equation (7.7). This yields

$$Dy_1''(x) - gy_1'(x) + \alpha^2 by_1(\alpha x) - (b + Dy_1(0))y_1(x) = 0. \tag{7.25}$$

Notice that the presence of $y_1(0)$ in equation (7.25) makes the equation non-linear (and non-local). The solution to equation (7.25) subject to the no-flux condition (7.8) and condition (7.9) can be obtained in a way similar to that used by Wake *et al.* [80] for the SSD solution. We suppose that the solution to equation (7.25) is of the form given by equation (7.13), i.e.,

$$y_1(x) = \sum_{n=0}^{\infty} a_n e^{-\alpha^n r x}, \tag{7.26}$$

where the coefficients a_n and the parameter r are to be determined. Substituting $y_1(x)$ from equation (7.26) to equation (7.25) gives

$$\begin{aligned} &Dr^2 \sum_{n=0}^{\infty} a_n \alpha^{2n} e^{-\alpha^n r x} + gr \sum_{n=0}^{\infty} a_n \alpha^n e^{-\alpha^n r x} + \alpha^2 b \sum_{n=1}^{\infty} a_{n-1} e^{-\alpha^n r x} \\ &-(b + Dy_1(0)) \sum_{n=0}^{\infty} a_n e^{-\alpha^n r x} = 0. \end{aligned}$$

Equating coefficients yields the indicial equation

$$Dr^2 + gr - (b + Dy_1(0)) = 0, \tag{7.27}$$

and the recurrence relation

$$a_n = \frac{-\alpha^2 b a_{n-1}}{Dr^2 \alpha^{2n} + gr\alpha^n - (b + Dy_1(0))}, \tag{7.28}$$

for $n = 1, 2, \ldots$. Since the series (7.26) diverges for $r \leq 0$, we choose r to be the positive root of (7.27). This positive root is given by

$$r = \frac{-g + \sqrt{g^2 + 4D(b + Dy_1(0))}}{2D}.$$

In closed form, the recurrence relation (7.28) can be written as

$$a_n = \frac{(-1)^n (\alpha^2 b)^n a_0}{\prod_{k=1}^{n} (Dr^2 \alpha^{2n} + gr\alpha^n - (b + Dy_1(0))}. \tag{7.29}$$

Since $\lim_{n\to\infty} \left| \frac{a_{n+1}}{a_n} \right| < 1$, the series $\sum_{n=0}^{\infty} a_n$ converges by the ratio test and the absolute convergence test; hence the series (7.26) converges by the limit comparison test. The uniqueness of the first eigenfunction can be established by following the analysis used by Wake *et al.* [80].

Now, we obtain a constructive existence theorem for the linear non-local dispersion-growth equation (7.2) with an arbitrary initial size-distribution (7.3) and with a no-flux boundary condition (7.4). We show that this solution is unique. We will assume that $n_0(x) \geq 0$ for $x \geq 0$, that n_0 is integrable, bounded and continuous on $[0, \infty)$.

Before we embark on establishing a constructive existence theorem we make some simplifications to the partial differential equation (7.2). Let

$$n(x,t) = e^{-(b+\mu)t}\tilde{n}(x,t).$$

Then partial differential equation (7.2) simplifies to

$$\tilde{n}_t + g\tilde{n}_x = D\tilde{n}_{xx} + b\alpha^2\tilde{n}(\alpha x, t),$$

and this can be further simplified using the transformation $x = g\hat{x}$, to get

$$-\hat{D}\hat{n}_{\hat{x}\hat{x}}(\hat{x},t) + \hat{n}_t(\hat{x},t) + \hat{n}_{\hat{x}}(\hat{x},t) = \alpha^2 b\hat{n}(\alpha\hat{x},t),$$

where $\hat{D} = \frac{D}{g^2}$ and $\hat{n}(\hat{x},t) = \tilde{n}(g\hat{x},t)$. Dropping circumflexes and tildes, it is clear that we can reduce the cell growth partial differential equation with dispersion problem to

$$-Dn_{xx}(x,t) + n_t(x,t) + n_x(x,t) = b\alpha^2 n(\alpha x, t), \tag{7.30}$$

and retain conditions (7.3) and (7.4). The initial cell distribution n_0 can be regarded as a probability density function.

If we restrict our attention to solutions of (7.30) that are integrable with respect to x on $[0, \infty)$ for any fixed $t > 0$, then the transformation

$$m(x,t) = \int_x^\infty n(\xi,t)d\xi, \tag{7.31}$$

yields

$$-Dm_{xx}(x,t) + m_x(x,t) + m_t(x,t) = b\alpha m(\alpha x, t). \tag{7.32}$$

Integrating equation (7.30) from 0 to ∞ w.r.t x and applying condition (7.4) gives

$$m_t(0,t) = b\alpha m(0,t),$$

here, we have assumed that $m \to 0$ as $x \to \infty$ for any $t \geq 0$; hence, for constant $k = \frac{1}{g}$, there is the boundary condition

$$m(0,t) = ke^{b\alpha t}, \tag{7.33}$$

and the initial condition for equation (7.32) is

$$m(x,0) = m_0(x) = \int_x^\infty n_0(\xi)d\xi. \tag{7.34}$$

7.1 A Laplace Transform Solution

The problem posed by equation (7.32) with conditions (7.33) and (7.34) is an initial boundary value problem involving a functional equation. In the absence of a functional term, a common strategy is to use the Laplace transform to reduce the problem to a non-homogeneous second order ordinary differential equation, followed by a solution using the appropriate Green's function. We use this strategy here to solve the problem. In contrast, the functional term leads to a singular Fredholm equation that can be solved using a Neumann series. We show that the integral equation has a unique solution and invoke a Paley-Wiener Theorem to assert that the transform has an inverse.

Let $M(x,s)$ denote the Laplace transform of $m(x,t)$ with respect to time t. Applying the Laplace transform to equation (7.32) with respect to time and using condition (7.34) gives

$$-DM_{xx}(x,s) + M_x(x,s) + sM(x,s) = b\alpha M(\alpha x, s) + m_0(x). \tag{7.35}$$

The boundary conditions are

$$\lim_{x\to\infty} M(x,s) = 0, \tag{7.36}$$

and, from equation (7.33),

$$M(0,s) = \frac{k}{s - b\alpha}. \tag{7.37}$$

To obtain the Green's function, we convert the problem to one with homogeneous boundary conditions. Let

$$V(x,s) = \frac{F(x)}{s - b\alpha} - M(x,s). \tag{7.38}$$

To ensure that the boundary conditions for V are homogeneous, we require

$$\lim_{x\to\infty} F(x) = 0, \tag{7.39}$$

and

$$F(0) = k. \tag{7.40}$$

The transformation (7.38) thus converts the partial differential equation (7.35) to

$$\begin{aligned} &- DV_{xx}(x,s) + V_x(x,s) + sV(x,s) - b\alpha V(\alpha x, s) + m_0(x) - F(x) \\ &= \frac{1}{s - b\alpha}\{-DF''(x) + F'(x) + b\alpha F(x) - b\alpha F(\alpha x)\}, \end{aligned} \tag{7.41}$$

where $'$ denotes the derivative with respect to x. We choose an $F(x)$ such that

$$-DF''(x) + F'(x) + b\alpha F(x) = b\alpha F(\alpha x). \tag{7.42}$$

Equation (7.42) is a second order pantograph equation. Wake *et al.* [80] showed that there is a unique solution F to (7.42) that satisfies conditions (7.39) and (7.40). They also showed that $F'(x) < 0$ for all $x > 0$, so that the derivative can be scaled to be a probability density function. A related eigenvalue problem was studied by van-Brunt *et al.* [76]. The solution is given by the Dirichlet series (7.13)-(7.15). With this choice of F, the partial differential equation (7.41) reduces to

$$-DV_{xx}(x,s) + V_x(x,s) + sV(x,s) = b\alpha V(\alpha x, s) + v_0(x), \tag{7.43}$$

where

$$v_0(x) = -m_0(x) + F(x), \tag{7.44}$$

and by construction

$$V(0, s) = 0 = \lim_{x\to\infty} V(x, s). \tag{7.45}$$

Theorem 7.1.1. *Let $L_s{}^{\infty}[0, \infty)$ denote the space of functions $V : [0, \infty) \times \mathbb{C} \to \mathbb{C}$ such that for $s \in \mathbb{C}$, V is bounded in $[0, \infty)$. If $\operatorname{Re} s > b\alpha$, there exists a solution to equation* (7.43) *that satisfies condition* (7.45)*. This solution is unique among functions in $L_s{}^{\infty}[0, \infty)$.*

Proof. We first recast the problem as an integral equation. The causal Green's function $G(x, \xi, s)$ associated with the boundary value problem satisfies

$$-DG'' + G' + sG = \delta(x - \xi), \tag{7.46}$$

where $'$ denotes $\frac{\partial}{\partial x}$ and δ is the Dirac delta function. The Green's function is

$$G(x, \xi, s) = \begin{cases} G_1(x, \xi, s) = \frac{e^{-m_1\xi}}{D(m_1-m_2)}\left(e^{m_1x} - e^{m_2x}\right); & 0 < x < \xi \\ \\ G_2(x, \xi, s) = \frac{e^{m_2x}}{D(m_1-m_2)}\left(e^{-m_2\xi} - e^{-m_1\xi}\right); & \xi < x < \infty \end{cases} \tag{7.47}$$

where m_1 and m_2 are given by

$$\begin{aligned} m_1 &= \frac{1 + \sqrt{1 + 4sD}}{2D}, \\ m_2 &= \frac{1 - \sqrt{1 + 4sD}}{2D}. \end{aligned} \tag{7.48}$$

The solution $V(x, s)$ thus satisfies the integral equation

$$V(x, s) = b\alpha \int_0^{\infty} G(x, \xi, s)V(\alpha\xi, s)d\xi + f(x, s), \tag{7.49}$$

where

$$f(x,s) = \int_0^\infty G(x,\xi,s)v_0(\xi)d\xi. \tag{7.50}$$

Note that equation (7.49) could be written as a singular Fredholm equation of the second kind, *viz.*

$$V(x,s) = b\int_0^\infty G(x,\frac{\xi}{\alpha},s)V(\xi,s)d\xi + f(x,s). \tag{7.51}$$

Let K and T be operators defined by

$$K\phi = b\alpha\int_0^\infty G(x,\xi,s)\phi(\alpha\xi,s)d\xi,$$
$$T\phi = K\phi + f$$

for $\phi \in {L_s}^\infty[0,\infty)$. We show that for $\mathrm{Re}\, s > b\alpha$, T is a contraction mapping on ${L_s}^\infty[0,\infty)$. Suppose that $\phi \in {L_s}^\infty[0,\infty)$. Then there is an $M_s > 0$ such that $|\phi(x,s)| \leq M_s$ for all $x \in [0,\infty)$. For any fixed s, we consider the Banach space $({L_s}^\infty[0,\infty), \|\|_\infty)$ where

$$\|\phi\|_\infty = \sup_{x\in[0,\infty)} |\phi(x,s)|. \tag{7.52}$$

Now,

$$|K\phi| \leq b\alpha\int_0^\infty |G(x,\xi,s)||\phi(\alpha\xi,s)|d\xi,$$
$$\leq b\alpha\|\phi\|_\infty\int_0^\infty |G(x,\xi,s)|d\xi.$$

Thus

$$|K\phi| \leq b\alpha\|\phi\|_\infty\{J_1 + J_2\}, \tag{7.53}$$

where

$$J_1 = \int_0^x |G_2(x,\xi,s)|d\xi, \tag{7.54}$$

and

$$J_2 = \int_x^\infty |G_1(x,\xi,s)|d\xi. \tag{7.55}$$

A straightforward calculation yields

$$|G_1(x,\xi,s)| \leq \frac{1}{D(\gamma_1+\gamma_2)} e^{-\gamma_1\xi}(e^{\gamma_1 x} + e^{-\gamma_2 x}), \tag{7.56}$$

and

$$|G_2(x,\xi,s)| \leq \frac{1}{D(\gamma_1+\gamma_2)} e^{-\gamma_2 x}(e^{\gamma_2\xi} + e^{-\gamma_1 \xi}), \tag{7.57}$$

where

$$\gamma_1 = \operatorname{Re} m_1 > 0, \tag{7.58}$$

and

$$-\gamma_2 = \operatorname{Re} m_2 < 0. \tag{7.59}$$

The integrals (7.54) and (7.55) thus yield

$$J_1 \leq \frac{1}{D\gamma_2(\gamma_1+\gamma_2)}, \tag{7.60}$$

and

$$J_2 \leq \frac{1}{D\gamma_1(\gamma_1+\gamma_2)}; \tag{7.61}$$

hence, inequality (7.53) along with inequalities (7.60) and (7.61) give

$$|K\phi| \leq \frac{b\alpha}{D\gamma_1\gamma_2}\|\phi\|_\infty. \tag{7.62}$$

Let

$$s = \sigma + i\tau, \quad \sigma, \tau \in \mathcal{R}, \tag{7.63}$$

and

$$\sqrt{1+4sD} = u + iv, \quad u, v \in \mathcal{R}. \tag{7.64}$$

Squaring equation (7.64), using equation (7.63) and equating the real parts yield

$$\operatorname{Re}\sqrt{1+4sD} \geq \sqrt{1+4D\sigma}. \tag{7.65}$$

From equations (7.58), (7.59) and (7.65), it is straightforward to show that

$$\frac{1}{\gamma_1\gamma_2} \leq \frac{D}{\operatorname{Re}s}, \tag{7.66}$$

and thus inequality (7.62) implies

$$|K\phi| \leq \frac{b\alpha}{\operatorname{Re}s}\|\phi\|_\infty. \tag{7.67}$$

Inequality (7.67) implies that for $\operatorname{Re}s > 0$, $K\phi \in {L_s}^\infty[0,\infty)$ if $\phi \in {L_s}^\infty[0,\infty)$, so that K maps ${L_s}^\infty[0,\infty)$ into ${L_s}^\infty[0,\infty)$. In particular, we know that the function m_0 and F are bounded so that v_0 must be bounded. Since $f = Kv_0$, this means that $f \in {L_s}^\infty[0,\infty)$ and, consequently, that $T\phi \in {L_s}^\infty[0,\infty)$ whenever $\phi \in {L_s}^\infty[0,\infty)$ and $\operatorname{Re}s > 0$. Now, for any $\phi_1, \phi_2 \in {L_s}^\infty[0,\infty)$,

$$\begin{aligned}\|T\phi_1 - T\phi_2\| &\leq \|K(\phi_1 - \phi_2)\| \\ &\leq \frac{b\alpha}{\operatorname{Re}s}\|\phi_1 - \phi_2\|,\end{aligned}$$

and the theorem thus follows from the contraction mapping principle. □

The solution is given by the Neumann series

$$V = \sum_{j=0}^{\infty} K^j f, , \tag{7.68}$$

where $K^0 f = f$, and for $j \geq 1$

$$K^j f = K^{j-1} f.$$

The function F has derivatives of all orders for $x \geq 0$. The differential equation (7.43) indicates that the smoothness of V with respect to x relies on that of v_0, which in turn relies on that of m_0.

7.2 The solution

Theorem 7.1.1 provides a solution V to the differential equation (7.43), but it does not guarantee a solution to partial differential equation (7.32). It must be established that V has an inverse Laplace transform with respect to s. The Neumann series (7.68) representation of V makes it awkward to establish this directly for an arbitrary cumulative probability density function m_0. In this section we show that the solution V of Theorem 7.1.1 lies in a suitable Hardy space and appeal to a Paley-Wiener theorem to assert the existence of an inverse Laplace transform.

Let $\Pi_q \subseteq \mathbb{C}$ denote the half plane $\{s \in \mathbb{C} : \operatorname{Re} s > q\}$ and $H(\Pi_q)$ denote the space of functions $V : [0, \infty) \times \mathbb{C} \to \mathbb{C}$ such that $V(x, s)$ is holomorphic with respect to s for all $s \in \Pi_q$ and $x \in [0, \infty)$. Define the function $M(\sigma, V)$ and the norm $\|\|$ by

$$M(\sigma, V) = \{ \int_{-\infty}^{\infty} |V(x, \sigma + i\tau)|^2 d\tau \}^{\frac{1}{2}}$$

and

$$\|V\|_2 = \sup_{\sigma > q} M(\sigma, V).$$

We work with the Hardy space $H^2(q) = \{V \in H(\Pi_q) : \|V\|_2 < \infty\}$.

Lemma 7.2.1. *Let* $\operatorname{Re} s > b\alpha$. *Then there exists an* $M > 0$ *such that*

$$|f(x,s)| = \left| \int_0^\infty G(x,\xi,s)v_0(\xi)d\xi \right| \le \frac{M}{|s|}. \tag{7.69}$$

Proof. Let

$$f(x,s) = B_1 + B_2, \tag{7.70}$$

where

$$B_1 = \int_0^x G_2(x,\xi,s)v_0(\xi)d\xi, \tag{7.71}$$

and

$$B_2 = \int_x^\infty G_1(x,\xi,s)v_0(\xi)d\xi. \tag{7.72}$$

The integration by parts gives

$$B_1 = (v_0(\xi)g_1(x,\xi,s))\Big|_{\xi=0}^{\xi=x} - \int_0^x g_1(x,\xi,s)v_0'(\xi)d\xi, \tag{7.73}$$

and

$$B_2 = (v_0(\xi)g_2(x,\xi,s))\Big|_{\xi=x}^{\infty} - \int_x^\infty g_2(x,\xi,s)v_0'(\xi)d\xi, \tag{7.74}$$

where

$$g_1(x,\xi,s) = \int_0^\xi G_2(x,\tau,s)d\tau, \tag{7.75}$$

and

$$g_2(x,\xi,s) = -\int_{\xi}^{\infty} G_1(x,\tau,s)d\tau. \tag{7.76}$$

It is straightforward to show that

$$|g_1(x,\xi,s)| \leq \frac{1}{|Dm_1(m_1m_2)|} + \frac{|m_2|^2+|m_1|^2}{D|m_1(m_1m_2)(m_1-m_2)|},$$

so that there is a constant Λ_1 such that

$$|g_1(x,\xi,s)| \leq \frac{\Lambda_1}{|s|}, \tag{7.77}$$

for $\operatorname{Re} s > b\alpha$. Similarly, there is a constant Λ_2 such that

$$|g_2(x,\xi,s)| \leq \frac{\Lambda_2}{|s|}, \tag{7.78}$$

for $\operatorname{Re} s > b\alpha$. We know that F and m_0 are positive decreasing functions in $[0,\infty)$; hence,

$$|v_0(x)| = |F(x) - m_0(x)| \leq k. \tag{7.79}$$

In addition, since n_0 is bounded and continuous, and $-m_0'(x) = n_0$, there is a $\tilde{k}$ such that

$$|v_0'(x)| = |F'(x) + n_0(x)| \leq n_0(x) \leq \tilde{k}. \tag{7.80}$$

Inequalities (7.77), (7.78), (7.79), (7.80) establish inequality (7.69) with

$$M = \max(\Lambda_1,\Lambda_2)(k+\tilde{k}). \tag{7.81}$$

$\square$

Corollary 7.2.2. *Let V be the solution of Theorem 7.1.1. Then $V \in H^2(q)$ for any $q > b\alpha$.*

Proof. Choose any $q > b\alpha$ and let $s \in \Pi_q$. The functions $K^n f$ in the Neumann series solution (7.68) are holomorphic for $s \in \Pi_q$. Moreover the analysis in the proof of Theorem 7.1.1 shows that the Neumann series is uniformly convergent in Π_q. We thus conclude that $V \in H(\Pi_q)$.

The analysis in the proof of Theorem 7.1.1 and inequality (7.69) also show that

$$|Kf(x,s)| \le \frac{b\alpha}{q}\frac{M}{|s|},$$

and in general,

$$|K^n f(x,s)| \le \mu^n \frac{M}{|s|},$$

where $\mu = \frac{b\alpha}{q} < 1$. Therefore,

$$\begin{aligned} |V(x,s)| &\le |f(x,s)| + \sum_{n=1}^{\infty} |K^n f(x,s)| \\ &= \frac{M}{s}\frac{1}{1-\mu}. \end{aligned}$$

We thus see that $V \in H^2(q)$. $\square$

We now return to equation (7.32) and conditions (7.33) and (7.34). Theorem 7.1.1 shows that there is a unique solution V to equation (7.43) and hence there is a unique solution M to equation (7.35). Corollary 7.2.2 shows that $V \in H^2(q)$ for any $q > b\alpha$, and a Paley-Wiener theorem can be used to assert the existence of an inverse transform $v(x,t)$. Evidently, $\frac{F(x)}{s-b\alpha}$ has an inverse $e^{b\alpha t}F(x)$ and hence we establish the solution

$$m(x,t) = e^{b\alpha t}F(x) - v(x,t),$$

which is unique.

Since $V \in H^2(q)$ for any $q > b\alpha$, it is possible to glean an asymptotic relation as $t \to \infty$. In particular, it can be shown that for any fixed $x \ge 0$,

$$|v(x,t)| \sim \mathrm{o}(e^{qt})$$

as $t \to \infty$ (cf. Widder [81], Chapter 2). In summary we have the following theorem

Theorem 7.2.3. *Let $W = \{(x,t) : x, t \geq 0\}$. Then there exists a unique solution m to equation* (7.32) *that satisfies conditions* (7.33) *and* (7.34) *and is valid for $(x,t) \in W$. Moreover,*

$$|m(x,t)| \sim \mathrm{o}(e^{qt})$$

for any $q > b\alpha$, as $t \to \infty$.

The asymptotic result for m is a weak result. The function $e^{b\alpha t}F(x)$ is the SSD solution for the problem. Although it has not been shown that $|m(x,t)| \sim e^{b\alpha t}F(x)$ as $t \to \infty$, it is conjectured that this relation holds, i.e.,

$$|v(x,t)| \sim \mathrm{o}(e^{b\alpha t}), \tag{7.82}$$

as $t \to \infty$.

7.3 Conclusions

In this chapter, we studied the cell growth equation with dispersion for symmetric division of cells. We discussed the SSD solution and established the existence of higher eigenfunctions y_m for $m \geq 2$. It remained elusive to determine the eigenvalue λ_1 owing to the presence of a $y_1(0)$ term in a non-linear functional differential equation. This problem was exposed. We then obtained a constructive existence theorem for the linear, non-local dispersion-growth equation with an arbitrary initial size distribution and with a no-flux boundary condition. We showed that this solution is unique. It is still an open question as to whether or not the solutions obtained by separation of variables form a complete spanning set.

Chapter 8

Asymmetrical Cell Division and the Steady size distributions

Here, we study the case of binary asymmetrical splitting in which a cell of size ξ divides into two daughter cells of different sizes and find the steady size distribution (SSD) solution to the non-local differential equation. We then discuss the shape of the SSD solution. The existence of higher eigenfunctions is also discussed.

8.1 Qualitative results and SSD solutions

Asymmetric cell division occurs when a cell divides into daughter cells of different sizes. Here, we study the case in which a cell of size ξ divides into two daughter cells of (different) sizes $\frac{\xi}{\alpha}$ and $\frac{\xi}{\beta}$ (the asymmetrical binary splitting), where $\alpha > \beta > 1$. The function $W(x, \xi)$ in this case becomes

$$W(x, \xi) = \delta\left(\frac{\xi}{\alpha} - x\right) + \delta\left(\frac{\xi}{\beta} - x\right), \tag{8.1}$$

where δ denotes the Dirac delta function. A straightforward calculation shows that $W(x, \xi)$ given by equation (8.1) satisfies the mass balance equation (4.8) as well as equation (4.9). The above choice of W and the mass balance equation simplify equation (4.4) to

$$\underbrace{n_t(x,t)}_{\text{net rate of change}} + \underbrace{gn_x(x,t)}_{\text{growth rate in size}} = \underbrace{\alpha bn(\alpha x,t)}_{\substack{\text{cells from division}\\ \text{at size } \alpha x}} + \underbrace{\beta bn(\beta x,t)}_{\substack{\text{cells from division}\\ \text{at size } \beta x}} - \underbrace{bn(x,t)}_{\substack{\text{loss of cells}\\ \text{through division}}} - \underbrace{\mu n(x,t)}_{\text{cell-death}}. \tag{8.2}$$

Here we took for simplicity g and b as specified constants. Moreover, the mass balance equation (4.8) implies

$$\frac{1}{\alpha} + \frac{1}{\beta} = 1, \tag{8.3}$$

i.e.,

$$\beta = \frac{\alpha}{\alpha - 1}. \tag{8.4}$$

Without loss of generality we can assume

$$\alpha \geq \beta > 1.$$

We follow a procedure similar to that used for the symmetrical case (chapter 5) and focus on the solutions to equation (8.2), subject to the conditions given by equations (4.5)-(4.7), that correspond to the steady size distribution (SSD) (of constant shape). Hall and Wake studied the symmetrical case ($\alpha = \beta = 2$) and focused on the solutions that correspond to the steady size distribution (SSD) (of constant shape). Perthame and Ryzhik [53] proved the existence of a stable steady distribution (first positive eigenfunction) and exponential convergence of solutions toward such a steady state for large times. Hall and Wake [24] considered separated solutions of the form $n(x,t) = y(x)N(t)$, where $N(t) = \int\limits_0^\infty n(x,t)dx$ is the total population at time t and $y(x)$ (i.e., y is time invariant) is a probability density function with $\int\limits_0^\infty y(x)dx = 1$. They called such solutions "steady size distributions" (SSDs). SSD solutions are thus separable solutions of the form $n(x,t) = N(t)y(x)$ which upon substitution into equation (8.2) gives

$$\begin{aligned}\frac{N'(t)}{N(t)} &= -g\frac{y'(x)}{y(x)} + \frac{\alpha by(\alpha x)}{y(x)} + \frac{\beta by(\beta x)}{y(x)} - (b+\mu)\\ &= -\lambda,\end{aligned}$$

where λ is a separation constant (to be found). This leads to solutions of the form

$$n(x,t) = e^{-\lambda t} y(x), \tag{8.5}$$

where y satisfies

$$gy' = \alpha b y(\alpha x) + \beta b y(\beta x) - (\mu + b - \lambda) y(x), \tag{8.6}$$

along with the conditions

$$y(0) = 0 = \lim_{x \to \infty} y(x). \tag{8.7}$$

Clearly, we require that $y(x) \geq 0$ for all $x \geq 0$. We further require that y be integrable on $[0,\infty)$ and without loss of generality we can assume that y is a probability density function (pdf) so that

$$\int_0^\infty y(x)dx = 1. \tag{8.8}$$

The value of λ can be determined by integrating equation (8.6) with respect to x from 0 to ∞ and using conditions (8.7) and (8.8). This yields

$$\lambda = \mu - b. \tag{8.9}$$

This value of λ is consistent with the result in the symmetrical case when $\alpha = 2$. Equation (8.6) thus reduces to

$$y' + \frac{2b}{g} y(x) = \frac{b}{g} \left(\alpha y(\alpha x) + \beta y(\beta x) \right). \tag{8.10}$$

The solution to equation (8.10) subject to the conditions (8.7) and (8.8) can be found (see section 8.3.1) by the following a pattern similar to that used by Suebcharoen *et al.* [68]. The resulting solution is a double Dirichlet series of the form

$$y(x) = \sum_{k=0}^{\infty} \sum_{j=0}^{\infty} c_{k,j} e^{-\frac{2b}{g} \alpha^k \beta^j x}, \tag{8.11}$$

where,

$$c_{0,0} = \frac{2b}{g} + \left(\frac{b}{g}\right) \sum_{k=1}^{\infty} \frac{2^k(\alpha^{-k} + \beta^{-k})}{\prod_{s=1}^{k} (2 - \alpha^{-s} - \beta^{-s})}, \tag{8.12}$$

$$c_{k,0} = \frac{(-1)^k \alpha^k}{2^k \prod_{s=1}^{k} (\alpha^s - 1)} c_{0,0}, \tag{8.13}$$

$$c_{0,j} = \frac{(-1)^j \beta^j}{2^j \prod_{s=1}^{j} (\beta^s - 1)} c_{0,0}, \tag{8.14}$$

$$c_{k,j} = \frac{-1}{2(\alpha^k \beta^j - 1)} (\alpha c_{k-1,j} + \beta c_{k,j-1}), \tag{8.15}$$

for $k, j \in \mathbb{N}$. The convergence of equations (8.12)-(8.15) and uniqueness of the double Dirichlet series solution (8.11) along with the positivity of the solution can also be proved in a way similar to that used by Suebcharoen *et al.* [68]. No closed form solution for $c_{k,j}$ has been obtained, but clearly we can obtain the $c_{k,j}$ iteratively.

8.2 Shape of the SSD solution

The shape of the SSD solution is not obvious from the Dirichlet series (8.11). Numerical experiments, however, suggest strongly that the SSD solution is unimodal (see *Figure* 8.1). Rather than use the Dirichlet series directly, we will use the equation (8.10) to show that the function y must be unimodal. As noted in the last section, it can be shown that $y(x) > 0$ for all $x > 0$.

The proof of unimodality for the single nonlocal term, the basic pantograph equation, was established by da Costa *et al.* [13]. The symmetric case $\alpha = \beta = 2$ is covered by this analysis. If $\alpha \neq 2$, then the presence of a second non-local term complicates the analysis and certain arguments valid in the one term case break down for the two term case. To show the unimodality of the pdf solution y analytically, we suppose on the contrary that y is a pdf solution to equation (8.10) that is not unimodal. Without loss of generality

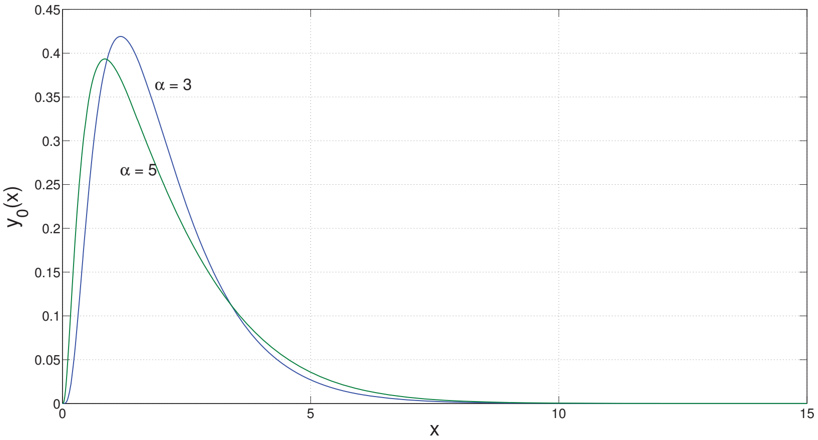

Figure 8.1: The solution $y_0(x)$ given by the Dirichlet series (8.11) for $g = 2$ units, $b = 1$ unit, $\alpha = 3, 5$.

we can assume

$$\alpha > 2 > \beta > 1.$$

Then there exists at least one local minimum. Let $\{m_n\}$ be a strictly increasing sequence of points where y has a local minimum and $\{M_n\}$ be a strictly increasing sequence where y has a local maximum. Since the derivative of y from equation (8.11) can be written as

$$y'(x) = -\frac{2b}{g} c_{0,0} e^{\frac{-2b}{g} x} + \mathrm{O}(e^{-\frac{2b}{g} \beta x}), \tag{8.16}$$

it is clear that $y' = \mathrm{O}(exp(\frac{-2b}{g}x))$ for large x and is negative, and hence y has to be ultimately monotone decreasing (see also Theorem 4 of [13]). Accordingly, neither m_n nor M_n tends to infinity as n tends to infinity. Also, $\{m_n\}$ and $\{M_n\}$ have no limit points since y' is holomorphic in the complex half plane and a limit point of extrema implies $y'(z) = 0$ for all $Re(z) > 0$ which is clearly not true. We thus conclude that the sequences are finite. Note that y cannot be piecewise constant in any interval (a, b), $a < b$ of the positive real axis by the same argument and this means y must be strictly decreasing after the last maximum.

Let m_f and M_f be the locations of the last local minimum and maximum respectively i.e. max $\{m_n\} = m_f$ and max $\{M_n\} = M_f$. Then

$$y(m_f) > 0, y'(m_f) = 0, y''(m_f) \geq 0, \tag{8.17}$$

and equation (8.10) implies

$$2y(m_f) = \alpha y(\alpha m_f) + \beta y(\beta m_f). \tag{8.18}$$

Since $\alpha > 2$ and $y(m_f) > 0$, we have

$$y(m_f) > y(\alpha m_f). \tag{8.19}$$

The last maximum at M_f must occur after the last minimum at m_f, and equation (8.19) implies that

$$m_f < M_f < \alpha m_f. \tag{8.20}$$

In particular, $y'(\alpha m_f)$ cannot be positive as this could induce another local maximum beyond M_f. Also, at the last maximum M_f, equation (8.10) implies

$$2y(M_f) = \alpha y(\alpha M_f) + \beta y(\beta M_f). \tag{8.21}$$

Since

$$2y(m_f) < 2y(M_f), \tag{8.22}$$

Equations (8.18) and (8.21) give

$$\alpha y(\alpha m_f) + \beta y(\beta m_f) < \alpha y(\alpha M_f) + \beta y(\beta M_f). \tag{8.23}$$

The function is decreasing after the last maximum and $\alpha m_f < \alpha M_f$, hence,

$$y(\alpha m_f) > y(\alpha M_f). \tag{8.24}$$

Inequalities (8.23) and (8.24) give,

$$\begin{aligned} \alpha y(\alpha M_f) + \beta y(\beta m_f) &< \alpha y(\alpha m_f) + \beta y(\beta m_f) \\ &< \alpha y(\alpha M_f) + \beta y(\beta M_f), \end{aligned} \tag{8.25}$$

which implies $\beta y(\beta m_f) < \beta y(\beta M_f)$, i.e.,

$$y(\beta m_f) < y(\beta M_f). \tag{8.26}$$

Now $\beta m_f < \beta M_f$ and y is decreasing after the last maximum, consequently,

$$m_f < \beta m_f < M_f < \alpha m_f, \tag{8.27}$$

so that,

$$y(m_f) < y(\beta m_f). \tag{8.28}$$

Equation (8.21) and inequality (8.24) give,

$$\begin{aligned} 2y(M_f) &= \alpha y(\alpha M_f) + \beta y(\beta M_f) \\ &< \alpha y(\alpha m_f) + \beta y(\beta M_f). \end{aligned} \tag{8.29}$$

Adding and subtracting $\beta y(\beta m_f)$ to equation (8.29) gives,

$$2y(M_f) < \alpha y(\alpha m_f) + \beta y(\beta M_f) + \beta y(\beta m_f) - \beta y(\beta m_f),$$

which, using equation (8.18), yields

$$2\left(y(M_f) - y(m_f)\right) < \beta\left(y(\beta M_f) - y(\beta m_f)\right), \tag{8.30}$$

and since $1 < \beta < 2$, Inequalities (8.28) and (8.30) imply,

$$\begin{aligned} y(M_f) - y(m_f) &< y(\beta M_f) - y(\beta m_f) \\ &< y(\beta M_f) - y(m_f). \end{aligned} \tag{8.31}$$

Inequality (8.31) implies,

$$y(M_f) < y(\beta M_f), \tag{8.32}$$

which contradicts the fact that M_f is the last maximum. This proves that y is unimodal for all $\alpha > 2 > \beta > 1$.

8.3 Existence and uniqueness of higher eigenfunctions

SSD solutions are of central interest in this model since they can be easily matched to data for the size distribution of cells for large time. They are special solutions to the nonlocal partial differential equation (8.2). In particular, given an initial distribution $n(x, 0) = n_0(x)$, the SSD solution does not give the complete solution (unless $n_0(x) = y(x)$) and this prompts one to consider other techniques to solve the more general problem.

This means that there is a set of solutions for equation (8.6) with homogeneous boundary conditions, that is, λ has the role of an eigenvalue as discussed in van-Brunt *et al* [76]. We note that even in the single nonlocal term case, the general solution to the partial differential equation is not known. It may be possible that a class of solutions y_m for $m = 0, 1, \ldots$ can be obtained using an eigenfunction expansion. Specifically, we can use the conditions given by the successive moments (that is, the Mellin transform),

$$\int_0^\infty x^{m-1} y_m(x)dx = 0, \quad \int_0^\infty x^m y_m(x)dx \neq 0 \tag{8.33}$$

to calculate some further solutions to equation (8.6). These conditions give rise to a class of eigenfunctions and are sufficient in this respect. At this stage it is not clear whether there are other eigenfunctions. The idea mimics that used by van-Brunt and Vlieg-Hulstman [77], and leads to the spectrum (see *Figure* 8.2)

$$\lambda_m = \mu - b\left(\frac{1}{\alpha^m} + \frac{1}{\beta^m} - 1\right), \tag{8.34}$$

for $m = 0, 1, 2, \ldots$. Here $y = y_m$ is the solution to equation (8.6) when $\lambda = \lambda_m$.

We note that there are a countable number of real eigenvalues in the interval $[\mu - b, \mu + b)$, increasing with m, with point of accumulation $\lambda = \mu + b$. These eigenvalues lead to equations of the form

$$y_m' + \frac{b}{g}(\alpha^{-m} + \beta^{-m})y_m(x) = \frac{b}{g}\left(\alpha y_m(\alpha x) + \beta y_m(\beta x)\right). \tag{8.35}$$

Of course, there may be other eigenvalues and eigenfunctions. These eigen-

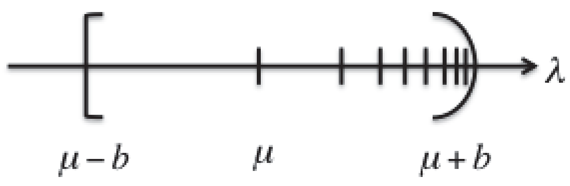

Figure 8.2: Spectrum of Eigenvalues

functions y_m are the solutions to equation (8.35) subject to equation (8.33) and

$$y_m(0) = 0 = \lim_{x\to\infty} y_m(x). \tag{8.36}$$

The first eigenfunction is the pdf solution y_0 given by equation (8.11). The higher eigenfunctions (as shown in *Figure* 8.3) can be found by following the procedure used by Suebcharoen *et al.* [68], as shown in the next section.

8.3.1 A Laplace transform solution

A solution to the boundary value problem can be derived using the Laplace transform. Let $Y(s)$ denote the Laplace transform of y. Applying Laplace transform to equation (8.35) and using equation (8.36) gives

$$\left[s + \frac{b}{g}(\alpha^{-m} + \beta^{-m})\right] Y(s) = \frac{b}{g}\left[Y\left(\frac{s}{\alpha}\right) + Y\left(\frac{s}{\beta}\right)\right]. \tag{8.37}$$

For $m \geq 1$, conditions in (8.33) give $\int\limits_0^\infty y_m(x)dx = 0$, and so

$$Y(0) = 0. \tag{8.38}$$

For $m = 0$, conditions in (8.33) give $\int\limits_0^\infty y_0(x)dx = 1$, and so $Y(0) = 1$. We consider a subset Ω of $\mathbb{C}$ and let $\mathcal{H}(\Omega)$ denote the set of functions holomorphic in Ω. Let $D(a;R)$ denote the disk $s \in \mathbb{C} : |s - a| < R$.

Lemma 8.3.1. *There exists a unique solution to equation* (8.37) *in* $\mathcal{H}\left(D\left(0; \frac{b}{g}\left(\alpha^{-m}+\beta^{-m}\right)\right)\right)$ *that satisfies equation* (8.38).

Proof. Let

$$Y(s) = \sum_{k=0}^{\infty} a_k s^k. \tag{8.39}$$

Equation (8.38) implies that

$$a_0 = 0. \tag{8.40}$$

We show that the radius of convergence is $\frac{b(\alpha^{-m}+\beta^{-m})}{g}$. Substituting the power series into equation (8.37) and balancing powers of s yields

$$\frac{b}{g}(\alpha^{-m} + \beta^{-m} - 1 - 1)a_0 = 0, \tag{8.41}$$

and also the recursion,

$$a_{k-1} + \{\frac{b}{g}(\alpha^{-m} + \beta^{-m}) - \frac{b}{g}(\alpha^{-k} + \beta^{-k})\}a_k = 0, \tag{8.42}$$

for $k \geq 1$ and any fixed $m > k$. Equation (8.41) is satisfied since $a_0 = 0$. Also, equation (8.42) for $k = 1$ and for any fixed $m > k$, yields

$$a_0 + \frac{b}{g}(\alpha^{-m} + \beta^{-m} - (\alpha^{-1} + \beta^{-1}))a_1 = 0, \tag{8.43}$$

and since $\frac{b}{g}(\alpha^{-m} + \beta^{-m} - (\alpha^{-1} + \beta^{-1})) \neq 0$ for any fixed $m > k$, this implies

$$a_1 = 0.$$

The same argument can be repeated for any $k \leq m - 1$. This gives $a_n = 0$ for $n = 0, 1, \ldots, m - 1$. For $k = m$ equation (8.42) implies

$$a_{m-1} + \frac{b}{g}(\alpha^{-m} + \beta^{-m} - (\alpha^{-m} + \beta^{-m}))a_m = 0,$$

which holds true for an arbitrary a_m, since $a_{m-1} = 0$. When $k > m$, the recursive relation (8.42) yields

$$a_{m+k} = \frac{(-1)^k a_m g^k}{b^k \prod_{r=1}^{k} \left(\frac{1}{\alpha^m} + \frac{1}{\beta^m} - \frac{1}{\alpha^{m+r}} - \frac{1}{\beta^{m+r}}\right)}. \tag{8.44}$$

Since,

$$\lim_{k\to\infty} \left| \frac{a_{m+(k+1)}}{a_{m+k}} \right| = \frac{g}{b(\alpha^{-m} + \beta^{-m})},$$

hence by the ratio test the radius of convergence is $\frac{b(\alpha^{-m}+\beta^{-m})}{g}$. □

Lemma 8.3.2. *The holomorphic solution Y of Lemma 8.3.1 can be meromorphically continued beyond $D\left(0; \frac{b}{g}\left(\alpha^{-m} + \beta^{-m}\right)\right)$. The only singularity on the circle is at $s = -\frac{b}{g}\left(\alpha^{-m} + \beta^{-m}\right)$ at which Y has a simple pole.*

Proof. We know from Hadamard's theorem that Y must have at least one singularity on the unit circle. Equation (8.37) can be written as

$$Y(s) = \frac{b}{g\left[s + \frac{b}{g}(\alpha^{-m} + \beta^{-m})\right]} W(s), \tag{8.45}$$

where

$$W(s) = \left[Y\left(\frac{s}{\alpha}\right) + Y\left(\frac{s}{\beta}\right)\right]. \tag{8.46}$$

since $\left[\frac{b}{g}(\alpha^{-m} + \beta^{-m})\right] < \left[\frac{b}{g}(\alpha^{-m} + \beta^{-m})\beta\right] < \left[\frac{b}{g}(\alpha^{-m} + \beta^{-m})\alpha\right]$ and $Y \in H\left(D\left(0; \frac{b}{g}\left(\alpha^{-m} + \beta^{-m}\right)\right)\right)$, so W is holomorphic in $D\left(0; \frac{b}{g}\left(\alpha^{-m} + \beta^{-m}\right)\beta\right)$. In particular W is holomorphic for all s such that $|s| = \frac{b}{g}\left(\alpha^{-m} + \beta^{-m}\right)$ but Y must have a singularity on $D\left(0; \frac{b}{g}\left(\alpha^{-m} + \beta^{-m}\right)\right)$ and consequently it must be at $s = -\frac{b}{g}\left(\alpha^{-m} + \beta^{-m}\right)$. The singularity is a simple pole, and $Y \in \mathcal{H}\left(D\left(0; \frac{b}{g}\beta\left(\alpha^{-m} + \beta^{-m}\right)\right)\right) - \{\frac{b}{g}\left(\alpha^{-m} + \beta^{-m}\right)\}$. □

Lemma 8.3.3. *Let* $S = \{s \in \mathbb{C} : \frac{b}{g}\left(\alpha^{-m} + \beta^{-m}\right)\alpha^k\beta^j; k, j \in \mathbb{N} \cup \{0\}\}$*. The solution of Lemma 8.3.1 can be meromorphically continued in* $\mathbb{C}$*. The unique continuation gives a function* $Y \in \mathcal{H}(\mathbb{C} - S)$*. At each point in* S*,* Y *has a simple pole.*

Proof. We show first that the only singularities of Y must be in the set S. Suppose that σ is a singularity for Y and that $\sigma \notin S$. Without loss of generality, we can assume that σ is the closest such singularity to the origin. Clearly $-\frac{b}{g}\left(\alpha^{-m} + \beta^{-m}\right) \in S$ and therefore $\sigma \neq -\frac{b}{g}\left(\alpha^{-m} + \beta^{-m}\right)$. Equation (8.45) implies that W must be singular at σ and this means that Y is singular at either $\frac{\sigma}{\alpha}$ or $\frac{\sigma}{\beta}$. Since $\sigma \notin S$ neither $\frac{\sigma}{\alpha}$ nor $\frac{\sigma}{\beta}$ are in S. But $\frac{\sigma}{\alpha} < |\sigma|$ and $\frac{\sigma}{\beta} < |\sigma|$ and this contradicts the definition of σ. We thus conclude that the only singularities for Y lie in S.

We now show that each point in S is a simple pole for Y. Suppose that there is a $\sigma \in S$ such that Y does not have a simple pole at σ (e.g., σ is a removable singularity, a higher order pole, or an isolated essential singularity). Without loss of generality we can assume that σ is the closest such singularity to the origin. Now Y has a simple pole at $s = -\frac{b}{g}\left(\alpha^{-m} + \beta^{-m}\right)$. Therefore $\sigma \neq -\frac{b}{g}\left(\alpha^{-m} + \beta^{-m}\right)$. Equation (8.45) implies that W must have the same type of singularity. If $\sigma \in S$, then both $\frac{\sigma}{\alpha}$ and $\frac{\sigma}{\beta}$ are in S. Since σ is the closest singularity that is not a simple pole for Y, we know that Y has a simple pole at both $\frac{\sigma}{\alpha}$ and $\frac{\sigma}{\beta}$. The singularity at σ therefore cannot be a higher order pole or an essential singularity. Since $\alpha \neq \beta$, the singularity cannot be removable. We thus conclude that σ is a simple pole, which contradicts our hypothesis. $\square$

Lemma 8.3.4. *The boundary value problem given by equations* (8.35)*,* (8.36)*,* (8.33) *has a solution of the form*

$$y_m(x) = \sum_{k=0}^{\infty}\sum_{j=0}^{\infty} c_{k,j} e^{-\alpha^k\beta^j \frac{b}{g}\left(\alpha^{-m}+\beta^{-m}\right)x}, \tag{8.47}$$

where,

$$c_{0,0} = (-1)^m \left(\frac{b}{g}(\alpha^{-m} + \beta^{-m})\right)^{m+1} +$$
$$(-1)^m \left(\frac{b}{g}\right)^{m+1} \sum_{k=1}^{\infty} \frac{((\alpha^{-m} + \beta^{-m}))^{k+m} a_m(\alpha^{-(k+m)} + \beta^{-(k+m)})}{\prod_{r=1}^{k}(\alpha^{-m} + \beta^{-m} - \alpha^{-(m+r)} - \beta^{-(m+r)})}, \quad (8.48)$$

$$c_{k,0} = \frac{(-1)^k \alpha^k c_{0,0}}{(\alpha^{-m} + \beta^{-m})^k \prod_{s=1}^{k}(\alpha^s - 1)}, \quad (8.49)$$

$$c_{0,j} = \frac{(-1)^j \beta^j c_{0,0}}{(\alpha^{-m} + \beta^{-m})^j \prod_{s=1}^{j}(\beta^s - 1)}, \quad (8.50)$$

and for $k, j \in \mathbb{N}$

$$c_{k,j} = \frac{-1}{(\alpha^k \beta^j - 1)(\alpha^{-m} + \beta^{-m})}(\alpha c_{k-1,j} + \beta c_{k,j-1}). \quad (8.51)$$

Proof. The function Y has a unique meromorphic continuation in $\mathbb{C}$ and each point of S corresponds to a simple pole for Y. The Mittag-Leffler theorem therefore implies that Y can be represented in the form

$$Y(s) = \sum_{k=0}^{\infty} \sum_{j=0}^{\infty} \left(\frac{c_{k,j}}{s + \frac{b(\alpha^{-m}+\beta^{-m})\alpha^k \beta^j}{g}} - P_{k,j}(s) \right) + h(s), \quad (8.52)$$

where the series is uniformly and absolutely convergent in any compact subset of $\mathbb{C} - S$. Here, the $c_{k,j}$ are the residues of Y at $s = -\frac{b\left(\alpha^{-m}+\beta^{-m}\right)\alpha^k\beta^j}{g}$, the $P_{k,j}$ are polynomials and h is an entire function. We can thus invert the above expression for Y term by term and this yields equation (8.47).

The coefficient $c_{0,0}$ is the residue of Y at $s = -\frac{b\left(\alpha^{-m}+\beta^{-m}\right)}{g}$. Equation (8.45) implies that

$$c_{0,0} = \frac{b}{g}\left(Y\left(\frac{-b(\alpha^{-m} + \beta^{-m})}{g\alpha}\right) + Y\left(\frac{-b(\alpha^{-m} + \beta^{-m})}{g\beta}\right)\right). \quad (8.53)$$

Equations (8.39) and(8.44) give

$$Y(s) = a_m s^m + \sum_{k=1}^{\infty} \frac{(-1)^k a_m g^k s^{k+m}}{b^k \prod_{r=1}^{k} (\frac{1}{\alpha^m} + \frac{1}{\beta^m} - \frac{1}{\alpha^{m+r}} - \frac{1}{\beta^{m+r}})},$$

for all $D\left(0; \frac{b}{g}\left(\alpha^{-m} + \beta^{-m}\right)\right)$. Substituting $s = \left(\frac{-b(\alpha^{-m}+\beta^{-m})}{g\alpha}\right)$ and $s = \left(\frac{-b(\alpha^{-m}+\beta^{-m})}{g\beta}\right)$ in the expression for Y(s) and then using equation (8.53) gives equation (8.48). Let

$$c_k = \frac{\left((\alpha^{-m} + \beta^{-m})\right)^{k+m} a_m(\alpha^{-(k+m)} + \beta^{-(k+m)})}{\prod_{r=1}^{k} (\alpha^{-m} + \beta^{-m} - \alpha^{-(m+r)} - \beta^{-(m+r)})} a_m.$$

Then it is straightforward to show that

$$\lim_{k \to \infty} \frac{c_{k+1}}{c_k} < 1;$$

hence it can be shown directly that the series defining $c_{0,0}$ is convergent. From equation (8.47) we have,

$$y(x) = \sum_{k=0}^{\infty} \sum_{j=0}^{\infty} c_{k,j} e^{-\alpha^k \beta^j \frac{b}{g}(\alpha^{-m}+\beta^{-m})x},$$

and

$$y'(x) = \sum_{k=0}^{\infty} \sum_{j=0}^{\infty} c_{k,j} \left(\frac{-\alpha^k \beta^j b(\alpha^{-m} + \beta^{-m})}{g} \right) e^{-\alpha^k \beta^j \frac{b}{g}(\alpha^{-m}+\beta^{-m})x}.$$

Substituting these equations in equation (8.37) gives,

$$\sum_{k=0}^{\infty} \sum_{j=0}^{\infty} -c_{k,j} A \alpha^k \beta^j e^{-\alpha^k \beta^j Ax} + A \sum_{k=0}^{\infty} \sum_{j=0}^{\infty} c_{k,j} e^{-\alpha^k \beta^j Ax} - \frac{b}{g} \alpha \sum_{k=0}^{\infty} \sum_{j=0}^{\infty} c_{k,j} e^{-\alpha^{k+1} \beta^j Ax}$$
$$- \frac{b}{g} \beta \sum_{k=0}^{\infty} \sum_{j=0}^{\infty} c_{k,j} e^{-\alpha^k \beta^{j+1} Ax} = 0, \tag{8.54}$$

where $A = \frac{b}{g}(\alpha^{-m} + \beta^{-m})$. Balancing the coefficients yields

$$\sum_{j=0}^{\infty} -c_{0,j}A\beta^j e^{-\beta^j Ax} + A\sum_{j=0}^{\infty} c_{0,j}e^{-\beta^j Ax} - \frac{b}{g}\sum_{j=0}^{\infty} c_{0,j}e^{-\beta^{j+1}Ax} = 0, \tag{8.55}$$

$$\sum_{k=1}^{\infty} -c_{k,0}A\alpha^k e^{-\alpha^k Ax} + A\sum_{k=1}^{\infty} c_{k,0}e^{-\alpha^k Ax} - \frac{b}{g}\sum_{k=0}^{\infty} c_{k,0}e^{-\alpha^{k+1}Ax} = 0, \tag{8.56}$$

and

$$\sum_{k=1}^{\infty}\sum_{j=1}^{\infty} -c_{k,j}A\alpha^k\beta^j e^{-\alpha^k\beta^j Ax} + A\sum_{k=1}^{\infty}\sum_{j=1}^{\infty} c_{k,j}e^{-\alpha^k\beta^j Ax} -$$

$$\frac{b}{g}\alpha\sum_{k=0}^{\infty}\sum_{j=1}^{\infty} c_{k,j}e^{-\alpha^{k+1}\beta^j Ax} - \frac{b}{g}\beta\sum_{k=1}^{\infty}\sum_{j=0}^{\infty} c_{k,j}e^{-\alpha^k\beta^{j+1}Ax} = 0. \tag{8.57}$$

Balancing the coefficients in equations (8.55) and (8.56) yields equations (8.50) and (8.49) respectively. Equation (8.57) gives the recursive relation (8.51). In *Figure 8.3*, we have chosen a_m so that $\int\limits_0^{\infty} xy_1(x)dx = 1$.

It can also be shown directly that the double series $\sum\limits_{k=0}^{\infty}\sum\limits_{j=o}^{\infty} c_{k,j}$ converges absolutely. The absolute convergence of this series is established by the recursive relation (8.51) once it is shown that there are M_j and M_k such that $|c_{k,j}| \leq M_j$ for all k and $|c_{k,j}| \leq M_k$ for all j. Consider $\sum\limits_{k=0}^{\infty} |c_{k,0}|$ and $\sum\limits_{j=0}^{\infty} |c_{0,j}|$. Then,

$$\lim_{k\to\infty} |\frac{c_{k+1,0}}{c_{k,0}}| = \lim_{k\to\infty} \frac{\alpha}{(\alpha^{-m} + \beta^{-m})(\alpha^{k+1} - 1)} = 0 < 1,$$

and

$$\lim_{j\to\infty} |\frac{c_{0,j+1}}{c_{0,j}}| = \lim_{j\to\infty} \frac{\beta}{(\alpha^{-m} + \beta^{-m})(\beta^{j+1} - 1)} = 0 < 1.$$

and so $\sum\limits_{k=0}^{\infty} |c_{k,0}|$ and $\sum\limits_{j=0}^{\infty} |c_{0,j}|$ are convergent by the ratio test; hence there are numbers L and N_0 such that $|c_{k,0}| \leq L$ and $|c_{0,j}| \leq N_0$ for all j, k. Let v_1

be the smallest non-negative integer such that $\frac{(\alpha+\beta)}{(\alpha^{-m}+\beta^{-m})(\beta^{v_1}-1)} < 1$ and let $N_1 = max\{|c_{1,0}|, c_{1,1}, ..., |c_1, v_1|, N_0\}$. If $|c_{1,j-1}| \leq N_1$ and $j \geq v_1$,

$$\begin{aligned}
|c_{1,j}| &\leq \frac{1}{(\alpha^{-m}+\beta^{-m})\alpha\beta^j - 1}(\alpha|c_{0,j}| + \beta|c_1, j-1|), \\
&\leq \frac{(\alpha+\beta)N_1}{(\alpha^{-m}+\beta^{-m})(\alpha\beta^j - 1)}, \\
&\leq N_1.
\end{aligned} \tag{8.58}$$

It follows by induction that $|c_{1,j}| \leq N_1$ for all $j \geq v_1$ and hence for all j. This argument can be applied successively to each row. For the n^{th} row we can define v_n as the smallest non-negative integer such that $\frac{(\alpha+\beta)}{(\alpha^{-m}+\beta^{-m})(\alpha^{n-1}\beta^{v_n}-1)} < 1$ and define a new upper bound by let $N_n = max\{|c_{n,0}|, |c_{n,1}|, ..., |c_n, v_n|, N_{n-1}\}$. We can construct a sequence $\{v_n\}$ and $\{N_k\}$ so that $|c_{k,j}| \leq N_n$ for all $k \leq n$ and all j. Let μ be the smallest positive integer such that $\frac{(\alpha+\beta)}{(\alpha^{-m}+\beta^{-m})(\alpha^{\mu-1}-1)} < 1$. Then $v_n = 0$ for all $n \geq \mu$. Now $N_\mu = max\{|c_{\mu,0}|, N_{\mu-1}\}$ and since $|c_{k,0}| \leq L$ and for all k we can use the bound $N = max\{L, N_{\mu-1}\}$. This bound can be applied to all the rows after the μ^{th} row and hence M is an upper bound for $|c_{k,j}|$. $\square$

Remark 1. The solution to the boundary value problem defined by the equations (8.35), (8.36) and (8.33), for $m = 0$, can be deduced from the working above by putting $m = 0$. However the value of the Laplace transform $Y(s)$ at $s = 0$ changes, i.e., $Y(0) = 0$ in the proof of Lemma 8.3.1 changes to $Y(0) = 1$, and this yields $a_0 = 1$. Equation (8.44) and the subsequent working remains valid for $m = 0$.

8.4 Uniqueness

The Dirichlet series solution is based on the assumption that the Laplace transform is holomorphic at the origin. Under this assumption, the meromorphic continuation of Y is unique and the inverse is also unique. The requirement that Y be holomorphic at $s = 0$ places a strong decay condition on y: solutions Y that are holomorphic at the origin correspond to solutions y that decay exponentially. The boundary-value problem makes sense without such strong decay conditions, and it may be that equation (8.37) has solutions that satisfy equation (8.38) but are not holomorphic at $s = 0$. For example, the origin could be a branch point for Y. Rather than chase other Laplace transform solutions, however, we can establish that the Dirichlet series solution is the only solution directly from the boundary value problem. Suebcharoen *et al.* [68] had established the uniqueness of the SSD solution. Here, we modify their proof to establish the uniqueness of the higher eigenfunctions.

Suppose that y is a solution to the boundary value problem (8.35),(8.36),(8.33). Let

$$\delta_0(x) = \int_x^\infty y_m(\xi)d\xi, \tag{8.59}$$

and

$$\delta_j(x) = \int_x^\infty \delta_{j-1}(\xi)d\xi, \tag{8.60}$$

for $j = 1, 2, ..., m$. Integrating the functional differential equation (8.35) from x to ∞ yields

$$g\delta_0'(x) = b\delta_0(\alpha x) + b\delta_0(\beta x) - b(\alpha^{-m} + \beta^{-m})\delta_0(x).$$

Integrating the above equation again from x to ∞ gives

$$g\delta_1'(x) = \frac{b}{\alpha}\delta_1(\alpha x) + \frac{b}{\beta}\delta_1(\beta x) - b(\alpha^{-m} + \beta^{-m})\delta_1(x).$$

Repeating the process $m+1$ times, i.e., integrating equation (8.35) from x to ∞ $m+1$ times yields

$$\delta_m'(x) + \frac{b}{g}(\alpha^{-m} + \beta^{-m})\delta_m(x) = \frac{b}{g\alpha^m}\delta_m(\alpha x) + \frac{b}{g\beta^m}\delta_m(\beta x). \tag{8.61}$$

Also,

$$\delta_m(0) = \int_0^\infty \delta_{m-1}(\xi)d\xi = 1 \neq 0, \tag{8.62}$$

and

$$\lim_{x\to\infty} \delta_m(x) = 0. \tag{8.63}$$

Lemma 8.4.1. *Any solution δ_m to equation* (8.61) *that satisfies equations* (8.62)-(8.63) *cannot have local extrema in* $(0, \infty)$.

Proof. Suppose that δ_m has a positive local maximum at $M_1 > 0$. Then $\delta'_m(M_1) = 0$ and consequently

$$\frac{b}{g}(\alpha^{-m} + \beta^{-m})\delta_m(M_1) = \frac{b}{g\alpha^m}\delta_m(\alpha M_1) + \frac{b}{g\beta^m}\delta_m(\beta M_1), \tag{8.64}$$

which can be written as

$$\delta_m(M_1) = \frac{1}{1 + \frac{\alpha^m}{\beta^m}}\delta_m(\alpha M_1) + \frac{1}{1 + \frac{\beta^m}{\alpha^m}}\delta_m(\beta M_1).$$

Then we can show that either $\delta_m(\alpha M_1) \geq \delta_m(M_1)$ or $\delta_m(\beta M_1) \geq \delta_m(M_1)$. Since $\delta_m(M_1) > 0$ and $\delta_m(x) \to 0$ as $x \to \infty$, there must be another positive local maximum at $M_2 \geq \beta M_1$ at which $\delta_m(M_2) \geq \delta_m(M_1)$. We can repeat this argument on M_2 to show that there is another local maximum at $M_3 \geq \beta^2 M_1$. It is clear by this means we can construct a sequence $\{M_k\}$ where δ_m has positive local maxima such that $\{M_k\} \to \infty$ as $k \to \infty$ and that $\delta_m(M_k) \geq \delta_m(M_1) > 0$. The existence of such a sequence however contradicts equation (8.63) and we thus conclude that δ_m cannot have a local positive maximum in $(0, \infty)$. The above argument can be applied to $-\delta_m$ to show that δ_m cannot have a negative local minimum in $(0, \infty)$. Evidently δ_m cannot have a positive local minimum since this requires a positive local maximum. We thus see that δ_m cannot have any local extrema in $(0, \infty)$. $\square$

Theorem 8.4.2. *Let δ_m be a solution to equation* (8.61) *that satisfies equations* (8.62)-(8.63). *Then $\delta'_m(x) \neq 0$ for all $x \in (0, \infty)$.*

Proof. Suppose that $\delta'_m(\tau) = 0$ for some $\tau > 0$. The proof of Lemma 8.4.1 shows that either $\delta_m(\alpha\tau) \geq \delta_m(\tau) \geq \delta_m(\beta\tau)$ or $\delta_m(\beta\tau) \geq \delta_m(\tau) \geq \delta_m(\alpha\tau)$. Lemma 8.4.1 precludes the existence of an $x > \tau$ such that $\delta_m(x) > \delta_m(\tau)$ since this would require δ_m to have a local maximum. Therefore, $\delta_m(\alpha\tau) = \delta_m(\beta\tau) = \delta_m(\tau)$. But δ_m cannot have a local extrema; consequently $\delta_m(x) = \delta_m(\tau)$ for all $x \in [\tau, \alpha\tau]$. The continuity of δ'_m implies that $\delta'_m(\alpha\tau) = 0$. We can thus repeat the above argument to show that $\delta_m(x) = \delta_m(\tau)$ for all $x \in [\tau, \alpha^2\tau]$. The argument can be repeated any number of times to show that $\delta_m(x) = \delta_m(\tau)$ for all $x \in [\tau, \infty)$. Equation (8.63) therefore implies that

$\delta_m(x) = 0$ for all $x \in [\tau, \infty]$. We now show that $\delta_m(x) = 0$ for all $x \in (0, \tau]$. Since $\delta_m(x) = 0$ for all $x \in [\tau, \infty)$, equation (8.61) reduces to

$$\delta_m'(x) + \frac{b}{g}(\alpha^{-m} + \beta^{-m})\delta_m(x) = 0,$$

for $x \in \left[\frac{\tau}{\alpha}, \tau\right]$. We also know that $\delta(\tau) = 0$. The unique solution to this initial value problem is $\delta_m(x) = 0$. Therefore $\delta_m(x) = 0$ for all $x \in \left[\frac{\tau}{\alpha}, \tau\right]$. We can repeat this argument any number of times and show that $\delta_m(x) = 0$ for all $x \in (0, \tau]$ and hence $\delta_m(x) = 0$ for all $x > 0$. The function δ_m, however, is continuous at $x = 0$ and this implies that $\delta_m(0) = 0$ which contradicts equation (8.62). $\square$

Corollary 8.4.3. *The Dirichlet series* (8.47) *is the unique solution to the boundary value problem* (8.35)*,* (8.36)*,* (8.33)*.*

Proof. Suppose that y_1 and y_2 are solutions to the boundary value problem (8.35),(8.36), (8.33) and let $z = y_1 - y_2$. Redefine δ_m as $\delta_m(x) = \int_x^\infty \int_{\xi_1}^\infty \ldots \int_{\xi_m}^\infty z(s) ds \ldots d\xi_1$. Then δ_m satisfies equations (8.61)-(8.63). The proof of Lemma 8.4.1 is still valid and the proof of theorem 8.4.2 shows that $\delta_m(x) = 0$ for all $x \in [0, \infty)$. Therefore $\delta_m^{(m)} = (-1)^m z(x) = 0$ and consequently $y_1 = y_2$ for all $x \in [0, \infty)$. $\square$

8.5 Conclusions

In this chapter we studied the cell division problem for the case of binary asymmetrical splitting. We extended the results obtained for the symmetrical division of cells (chapter 5). The focus of our study was on separable solutions to equation (5.2). The motivation for the study of such solutions came from experimental results for certain plant cells that suggested solutions of this type, at least as a long term approximation [27]. We found "the steady size distribution" (SSD) and showed that it was unique. The question of whether the set of the above solutions (eigenfunctions) are complete is still open. Suppose that n is a function of the form

$$n(x, t) = \sum_{m=0}^{\infty} c_m y_m(x) e^{-\lambda_m t}, \tag{8.65}$$

where the above series is uniformly convergent for $x \geq 0$. Then it is straightforward to show that such a function is a solution to equation (8.2). The problem, however, is that in order to satisfy condition (4.7), the coefficients c_m must satisfy

$$n_0(x) = \sum_{m=0}^{\infty} c_m y_m(x), \tag{8.66}$$

and this brings to the fore the crucial question about what function space is spanned by the eigenfunctions. This question and other properties of these eigenfunctions remain to be explored, and this will be the subject of future papers.

If, as we conjecture that, equation (8.65) is the full solution to equation (8.2), then clearly $n(x,t) \sim c_0 y_0 e^{-\lambda_0 t}$ for large time, showing the steady size distribution is propotional to $y_0(x)$. This is given in equation (8.47) for $m = 0$ and is shown in *Figure 8.1* and below in *Figure 8.3*. The latter also includes $y_1(x)$, the second eigenfunction.

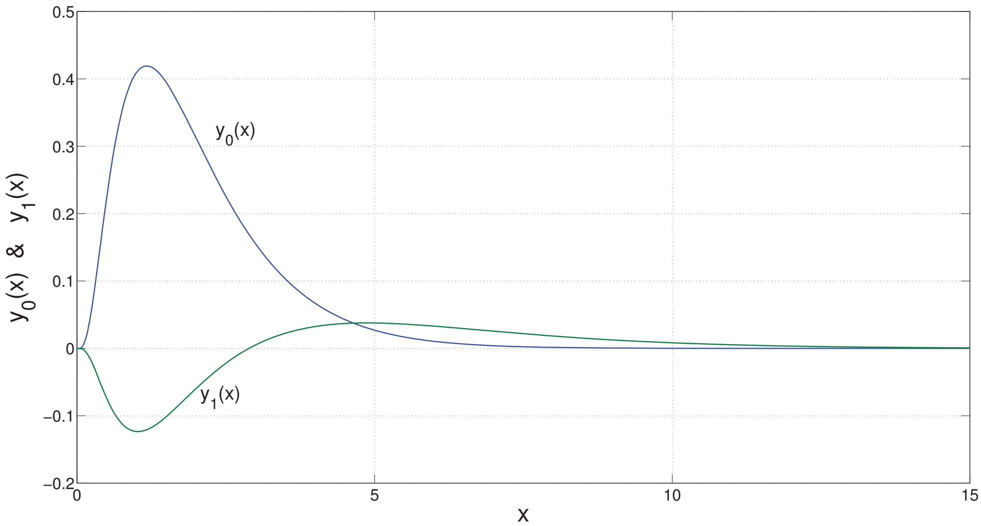

Figure 8.3: The solutions $y_0(x)$ and $y_1(x)$ given by the Dirichlet series (8.47) for $m = 0, 1$, $g = 2$, $b = 1$, $\alpha = 3$, $\beta = \frac{3}{2}$

Now we have the means, through equation (8.65), to calculate the evolutionary path of the cell population cohort. Although $y_m(x)$ is not monosigned for $m > 0$, we expect that $n(x, t)$ remain positive for all $x, t > 0$ but we have not proved this here. It is to be addressed in a future paper.

Chapter 9

Asymmetrical cell division with dispersion

We discussed in chapter 4 that the deterministic cell growth model (4.4)-(4.7) can be refined to include stochasticity in the growth rate of cells. Hall [25] notes that there may be an "experimental evidence showing significant variation in the growth rates of individuals all with the same measured properties". In such a scenario, the deterministic cell growth model would be inappropriate. To cater for this, we added stochasticity to the growth rate of cells and this lead to a dispersion-like model (4.12)-(4.16). In chapter 7, we studied this model (4.12)-(4.16) for the case of symmetric division of cells.

Here, we extend our study to the case of asymmetric division of cells and analyze the cell growth partial integro-differential equation (4.16) subject to conditions (4.12)-(4.15) for binary asymmetrical splitting. The choice of $W(x,\xi)$ in this case becomes

$$W(x,\xi) = \delta\left(\frac{\xi}{\alpha} - x\right) + \delta\left(\frac{\xi}{\beta} - x\right), \tag{9.1}$$

where δ denotes the Dirac delta function. A straightforward calculation shows that $W(x,\xi)$ given by equation (9.1) satisfies the mass balance equation (4.8) as well as equation (4.9). The above choice of W and the mass balance equation simplify equation (4.16) to

$$\begin{aligned}\frac{\partial n(x,t)}{\partial t} + \frac{\partial (g(x)n(x,t))}{\partial x} =& \frac{\partial^2}{\partial x^2}(D(x)n(x,t)) + \alpha b(\alpha x)n(\alpha x,t) + \beta b(\beta x)n(\beta x,t) \\ &- (\mu + b)n(x,t). \end{aligned} \tag{9.2}$$

The numbers α and β are not independent: the mass balance equation (4.8) implies

$$\frac{1}{\alpha} + \frac{1}{\beta} = 1, \tag{9.3}$$

i.e.,

$$\beta = \frac{\alpha}{\alpha - 1}. \tag{9.4}$$

Without loss of generality we can assume

$$\alpha \geq \beta > 1.$$

We follow a procedure similar to that used for the asymmetric division of cells with deterministic growth rates (chapter 8) and focus on the solutions of equation (9.2), subject to the conditions given by equations (4.12)-(4.15), that correspond to the steady size distribution (SSD) (of constant shape). Begg [5] proved the existence of a steady size distribution to the cell growth equation with dispersion (9.2). As discussed earlier that Hall and Wake [80] studied equation (9.2) without the mortality term and considered separated solutions of the form $n(x,t) = y(x)N(t)$, where $N(t) = \int\limits_0^\infty n(x,t)dx$ is the total population at time t and $y(x)$ (i.e., y is time invariant) is a probability density function with $\int\limits_0^\infty y(x)dx = 1$. These separable solutions correspond to the "steady size distributions" (SSDs). SSD solutions are thus separable solutions of the form $n(x,t) = N(t)y(x)$ which upon substitution into equation (9.2) leads to solutions of the form

$$n(x,t) = e^{-\lambda t}y(x), \tag{9.5}$$

where λ is a separation constant (to be found) and y satisfies

$$(D(x)y(x))'' - (g(x)y(x))' + \alpha b(\alpha x)y(\alpha x) + \beta b(\beta x)y(\beta x) - (\mu + b - \lambda)y(x) = 0. \tag{9.6}$$

The no-flux condition (4.12) yields

$$\lim_{x \to 0^+} \{(D(x)y(x))' - g(x)y(x)\} = 0. \tag{9.7}$$

9.1 Constant coefficients case:

In this section, we take for simplicity $D(x) = D$, $g(x) = g$ and $b(x) = b$ as positive specified constants. Clearly, we require that $y(x) \geq 0$ for all $x \geq 0$. We further require that y be integrable on $[0,\infty)$ and without loss of generality we can assume that y is a probability density function (pdf) so that

$$\int_0^\infty y(x)dx = 1. \tag{9.8}$$

Integrating equation (9.6) with respect to x from 0 to ∞ and using conditions (9.7) and (9.8) yield

$$\lambda = \mu - b. \tag{9.9}$$

Equation (9.6) thus reduces to

$$Dy'' - gy' + \alpha by(\alpha x) + \beta by(\beta x) - 2by(x) = 0. \tag{9.10}$$

Equation (9.9) shows that the first eigenvalue remains the same in the dispersion case as in the non-dispersion case. We seek solutions to equation (9.10) subject to conditions (9.7) and (9.8). As seen in chapter 7 that solutions to the functional differential equation (7.7), arising in the case of symmetrical division of cells, are in the form of a Dirichlet series. Also, in the case of asymmetrical division of cells with deterministic growth rate (Chapter 8), functional differential equations such as (9.10) arise with $D = 0$ and have solutions in the form of a Dirichlet series. Motivated by this, we consider a solution to the functional differential equation (9.10) of the form

$$y(x) = \sum_{k=0}^{\infty}\sum_{j=0}^{\infty} c_{k,j}e^{-\alpha^k\beta^j Ax}. \tag{9.11}$$

where the coefficients $c_{k,j}$ and A are to be determined. From equation (9.11) we have,

$$y'(x) = \sum_{k=0}^{\infty}\sum_{j=0}^{\infty}(-\alpha^k\beta^j A)c_{k,j}e^{-\alpha^k\beta^j Ax}, \tag{9.12}$$

and

$$y''(x) = \sum_{k=0}^{\infty}\sum_{j=0}^{\infty}(\alpha^{2k}\beta^{2j}A^2)c_{k,j}e^{-\alpha^k\beta^j Ax}. \tag{9.13}$$

Substituting these to equation (9.10) gives

$$D\sum_{k=0}^{\infty}\sum_{j=0}^{\infty}\alpha^{2k}\beta^{2j}A^2c_{k,j}e^{-\alpha^k\beta^j Ax} - g\sum_{k=0}^{\infty}\sum_{j=0}^{\infty}(-\alpha^k\beta^j A)c_{k,j}e^{-\alpha^k\beta^j Ax}+$$
$$\alpha b\sum_{k=0}^{\infty}\sum_{j=0}^{\infty}c_{k,j}e^{-\alpha^{k+1}\beta^j Ax} + \beta b\sum_{k=0}^{\infty}\sum_{j=0}^{\infty}c_{k,j}e^{-\alpha^k\beta^{j+1}Ax} - 2b\beta\sum_{k=0}^{\infty}\sum_{j=0}^{\infty}c_{k,j}e^{-\alpha^k\beta^j Ax} = 0. \tag{9.14}$$

Equating coefficients of e^{-Ax} yields the indicial equation

$$DA^2 + gA - 2b = 0. \tag{9.15}$$

Since the series (9.11) diverges if $A \leq 0$, we choose A to be the positive root of (9.15). This gives

$$A = \frac{-g + \sqrt{g^2 + 8bD}}{2D}. \tag{9.16}$$

Equating coefficients of $e^{-\alpha^k Ax}$,$e^{-\beta^j Ax}$, $e^{-\alpha^k\beta^j Ax}$ for $k, j \geq 1$ yields

$$c_{k,0} = \frac{(-1)^k(\alpha b)^k c_{0,0}}{\prod\limits_{s=1}^{k}(DA^2\alpha^{2s} + gA\alpha^s - 2b)}, \tag{9.17}$$

$$c_{0,j} = \frac{(-1)^j(\beta b)^j c_{0,0}}{(\prod\limits_{s=1}^{j}(DA^2\beta^{2s} + gA\beta^s - 2b)}, \tag{9.18}$$

$$c_{k,j} = \frac{-b}{(DA^2\alpha^{2k}\beta^{2j} + gA\alpha^k\beta^j - 2b)}(\alpha c_{k-1,j} + \beta c_{k,j-1}), \tag{9.19}$$

for $k, j = 1, 2, \ldots$. It can also be shown directly that the double series $\sum\limits_{k=0}^{\infty}\sum\limits_{j=o}^{\infty}c_{k,j}$ converges absolutely. The absolute convergence of this series is established by the recursive relation (9.19) once it is shown that there are M_j and M_k such that $|c_{k,j}| \leq M_j$ for all k and $|c_{k,j}| \leq M_k$ for all j.

consider $\sum\limits_{k=0}^{\infty} |c_{k,0}|$ and $\sum\limits_{j=0}^{\infty} |c_{0,j}|$. Then,

$$\begin{aligned}
\lim_{k\to\infty} \left|\frac{c_{k+1,0}}{c_{k,0}}\right| &= \lim_{k\to\infty} \frac{(\alpha b)^{k+1} \prod\limits_{s=1}^{k} (DA^2\alpha^{2s} + gA\alpha^s - 2b)}{\prod\limits_{s=1}^{k+1} (DA^2\alpha^{2s} + gA\alpha^s - 2b)(\alpha b)^k} \\
&= 0 < 1,
\end{aligned}$$

and

$$\begin{aligned}
\lim_{k\to\infty} |\frac{c_{j+1,0}}{c_{j,0}}| &= \lim_{j\to\infty} \frac{(\beta b)^{j+1} \prod\limits_{s=1}^{j} (DA^2\beta^{2s} + gA\beta^s - 2b)}{\prod\limits_{s=1}^{j+1} (DA^2\beta^{2s} + gA\beta^s - 2b)(\beta b)^j} \\
&= 0 < 1,
\end{aligned}$$

and so $\sum\limits_{k=0}^{\infty} |c_{k,0}|$ and $\sum\limits_{j=0}^{\infty} |c_{0,j}|$ are convergent by the ratio test; hence there are numbers L and N_0 such that $|c_{k,0}| \leq L$ and $|c_{0,j}| \leq N_0 \ \forall \ k, j$. Let v_1 be the smallest non-negative integer such that

$$\frac{(\alpha+\beta)b}{DA^2\beta^{2v_1} + gA\beta^{v_1} - 2b} < 1,$$

and let $N_1 = max\{|c_{1,0}|, c_{1,1}, ..., |c_1, v_1|, N_0\}$. If $|c_{1,j-1}| \leq N_1$ and $j \geq v_1$,

$$\begin{aligned}
|c_{1,j}| &\leq \frac{(\alpha+\beta)b}{(DA^2\alpha^2\beta^{2j} + gA\alpha\beta^j - 2b)} (\alpha|c_{0,j}| + \beta|c_1, j-1|) \\
&\leq \frac{(\alpha+\beta)bN_1}{(DA^2\alpha^2\beta^{2j} + gA\alpha\beta^j - 2b)} \\
&\leq N_1.
\end{aligned}$$

It follows by induction that $|c_{1,j}| \leq N_1$ for all $j \geq v_1$ and hence for all j. This argument can be applied successively to each row. For the n^{th} row we can define v_n as the smallest non-negative integer such that

$$\frac{(\alpha+\beta)b}{DA^2\alpha^{2n-1}\beta^{2v_n} + gA\alpha^{n-1}\beta^{v_n} - 2b} < 1,$$

and define a new upper bound by let $N_n = max\{|c_{n,0}|, |c_{n,1}|, ..., |c_n, v_n|, N_{n-1}\}$. We can construct a sequence $\{v_n\}$ and $\{N_k\}$ so that $|c_{k,j}| \leq N_n$ for all $k \leq n$ and for all j. Let μ be the smallest positive integer such that

$$\frac{(\alpha+\beta)b}{DA^2\alpha^{2\mu-1} + gA\alpha^{\mu-1} - 2b} < 1.$$

Then $v_n = 0$ for all $n \geq \mu$. Now $N_\mu = max\{|c_{\mu,0}|, N_{\mu-1}\}$ and since $|c_{k,0}| \leq L$ for all k, we can use the bound $N = max\{L, N_{\mu-1}\}$. This bound can be applied to all the rows after the μ^{th} row and hence there is an upper bound for $|c_{k,j}|$.

Remark 2. The problem we had exposed in chapter 7 about λ_1 given by equation (7.24) is also encountered here in the asymmetrical cell division. Here again,

$$\lambda_1 = \mu - Dy_1(0).$$

where y_1 is the first non-SSD eigenfunction. The presence of $y_1(0)$ makes λ_1 unknown since the value of y_1 at $x = 0$ is not known. Exploring the nature of $y_1(0)$ has been left for future work and is not included in this thesis. However, it is possible to show that if such a λ_1 exists, then we can find the first eigenfunction y_1, as well as the higher eigenfunctions on a pattern similar to that used for the symmetric division of cells (see Chapter 7).

We now prove the uniqueness of the SSD solution.

9.1.1 Uniqueness

suppose that y is a solution to equation (9.10). Let

$$\delta_0(x) = \int_x^\infty y(\xi)d\xi, \tag{9.20}$$

Then

$$\lim_{x\to\infty} \delta_0(x) = 0. \tag{9.21}$$

Integrating equation (9.10) w.r.t x from x to ∞ gives

$$D\delta_0''(x) - g\delta_0'(x) + b\delta_0(\alpha x) + b\delta_0(\beta x) - 2b\delta_0(x) = 0. \tag{9.22}$$

Lemma 9.1.1. *Any solution δ_0 to equation* (9.22) *that satisfies equations* (9.21) *cannot have local extrema in* $(0, \infty)$.

Proof. Suppose that δ_0 has a positive local maximum at $M_1 > 0$. Then $\delta_0'(M_1) = 0$, $\delta_0''(M_1) \leq 0$ and consequently

$$D\delta_0''(M_1) - g\delta_0'(M_1) + b\delta_0(M_1) + b\delta_0(M_1) - 2b\delta_0(M_1) = 0.$$

This gives

$$\delta_0(M_1) \leq \frac{1}{2}\{\delta_0(\alpha M_1) + \delta_0(\beta M_1)\}. \tag{9.23}$$

Then we can show that either $\delta_0(\alpha M_1) \geq \delta_0(M_1)$ or $\delta_0(\beta M_1) \geq \delta_0(M_1)$. Since $\delta_0(M_1) > 0$ and $\delta_0(x) \to 0$ as $x \to \infty$, there must be another positive local maximum at $M_2 \geq \beta M_1$ at which $\delta_0(M_2) \geq \delta_0(M_1)$. We can repeat this argument on M_2 to show that there is another local maximum at $M_3 \geq \beta^2 M_1$. It is clear by this means we can construct a sequence $\{M_k\}$ where δ_0 has positive local maxima such that $\{M_k\} \to \infty$ as $k \to \infty$ and that $\delta_0(M_k) \geq \delta_0(M_1) > 0$. The existence of such a sequence however contradicts equation (9.21) and we thus conclude that δ_0 cannot have a local positive maximum in $(0, \infty)$. The above argument can be applied to $-\delta_0$ to show that δ_0 cannot have a negative local minimum in $(0, \infty)$. Evidently δ_0 cannot have a positive local minimum since this requires a positive local maximum. We thus conclude that δ_0 cannot have any local extrema in $(0, \infty)$. $\square$

Theorem 9.1.2. *Let δ_0 be a solution to equation* (9.22) *that satisfies equations* (9.21)*. Then $\delta_0'(x) \neq 0$ for all $x \in (0, \infty)$.*

Proof. Suppose that $\delta_0'(\tau) = 0$ for some $\tau > 0$. The proof of Lemma 9.1.1 shows that either $\delta_0(\alpha\tau) \geq \delta_0(\tau) \geq \delta_0(\beta\tau)$ or $\delta_0(\beta\tau) \geq \delta_0(\tau) \geq \delta_0(\alpha\tau)$. Lemma 9.1.1 precludes the existence of an $x > \tau$ such that $\delta_0(x) > \delta_0(\tau)$ since this would require δ_0 to have a local maximum. Therefore, $\delta_0(\alpha\tau) = \delta_0(\beta\tau) = \delta_0(\tau)$. But δ_0 cannot have a local extrema; consequently $\delta_0(x) = \delta_0(\tau)$ for all $x \in [\tau, \alpha\tau]$. The continuity of δ_0' implies that $\delta_0'(\alpha\tau) = 0$. We can thus repeat the above argument to show that $\delta_0(x) = \delta_0(\tau)$ for all $x \in [\tau, \alpha^2\tau]$. The argument can be repeated any number of times to show that $\delta_0(x) = \delta_0(\tau)$ for all $x \in [\tau, \infty)$. Equation (9.21) therefore implies that $\delta_0(x) = 0$ for all $x \in [\tau, \infty)$. We now show that $\delta_0(x) = 0$ for all $x \in (0, \tau]$. Since $\delta_0(x) = 0$ for all $x \in [\tau, \infty)$, equation (9.22) reduces to

$$\delta_0''(x) - \frac{g}{D}\delta_0'(x) - 2b\delta_0(x) = 0,$$

for $x \in \left[\frac{\tau}{\alpha}, \tau\right]$. We also know that $\delta_0(\tau) = 0$. The unique solution to this initial value problem is $\delta_0(x) = 0$. Therefore $\delta_0(x) = 0$ for all $x \in \left[\frac{\tau}{\alpha}, \tau\right]$. We can repeat this argument any number of times and show that $\delta_0(x) = 0$ for all $x \in (0, \tau]$ and hence $\delta_0(x) = 0$ for all $x > 0$. The function δ_0, however, is continuous at $x = 0$ and this implies that $\delta_0(0) = 0$ i.e., $\int\limits_0^\infty y dx = 0$, which contradicts equation (9.8). □

Corollary 9.1.3 (Positivity of solution)**.** *If y is a solution to equation* (9.10)*, then $y(x) > 0$ for all $x > 0$.*

Proof. The condition (9.8) implies that y must be positive somewhere in $(0, \infty)$. The corollary follows immediately from Theorem 9.1.2 and the relation

$$\delta_0'(x) = -y(x). \tag{9.24}$$

□

Corollary 9.1.4 (Uniqueness)**.** *The solution y to equation* (9.10) *that satisfies equation* (9.21) *is unique.*

Proof. Suppose that y_1 and y_2 are solutions to equation (9.10) subject to (9.21). Let $z = y_1 - y_2$. Redefine δ_0 as $\delta_0(x) = \int\limits_x^\infty z(\xi)d\xi$. Then δ_0 satisfies equation (9.22). Equation $\delta_0(0) = 1$ is replaced by $\delta_0(0) = 0$. The proof of Lemma 9.1.1 is still valid since $\delta_0(0) = 1$ was not used and the proof of Theorem 9.1.2 shows that $\delta_0(x) = 0$ for all $x \in [0, \infty)$. Therefore $\delta_0'(x) = -z(x) = 0$ for all $x \in [0, \infty)$, and consequently $y_1 = y_2$ for all $x \in [0, \infty)$. □

9.1.2 Shape of the SSD solution

The shape of the SSD solution is not obvious from the Dirichlet series (8.11). Numerical experiments, however, suggest strongly that the SSD solution is unimodal (see *Figure* 9.1). Rather than use the Dirichlet series directly, we will use the equation (9.10) to show that the function y must be unimodal. As noted in the last section, it can be shown that $y(x) > 0$ for all $x > 0$.

As discussed earlier, the proof of unimodality for the single nonlocal term, the basic pantograph equation, was established by da Costa *et al.* [13]. The symmetric case $\alpha = \beta = 2$ is covered by this analysis. If $\alpha \neq 2$, then the presence of a second non-local term complicates the analysis and certain arguments valid in the one term case break down for the two term case. To show the unimodality of the pdf solution y analytically, we suppose on the contrary that y is a pdf solution to equation (9.10) that is not unimodal. Without loss of generality we can assume

$$\alpha > 2 > \beta > 1.$$

Then there exists at least one local minimum. Let $\{m_n\}$ be a strictly increasing sequence of points where y has a local minimum and $\{M_n\}$ be a strictly increasing sequence where y has a local maximum. Since equation (9.12) can be written as

$$y'(x) = -Ac_{0,0}e^{-Ax} + \mathrm{O}(e^{-A\beta x}), \tag{9.25}$$

it is clear that $y' = \mathrm{O}(exp(-Ax))$ for large x and y' does not change sign. Accordingly, neither m_n nor M_n tends to infinity as n tends to infinity. Also, $\{m_n\}$ and $\{M_n\}$ have no limit points since y' is holomorphic in the complex half plane and a limit point of extrema implies $y'(z) = 0$ for all $Re(z) > 0$ which is clearly not true. We thus conclude that the sequences are finite. Note that y cannot be piecewise constant in any interval (a, b), $a < b$ of the positive real axis by the same argument and this means y must be strictly decreasing after the last maximum.
Let m_f and M_f be the locations of the last local minimum and maximum respectively i.e. max $\{m_n\} = m_f$ and max $\{M_n\} = M_f$. Then

$$y(m_f) > 0, y'(m_f) = 0, y''(m_f) \geq 0, \tag{9.26}$$

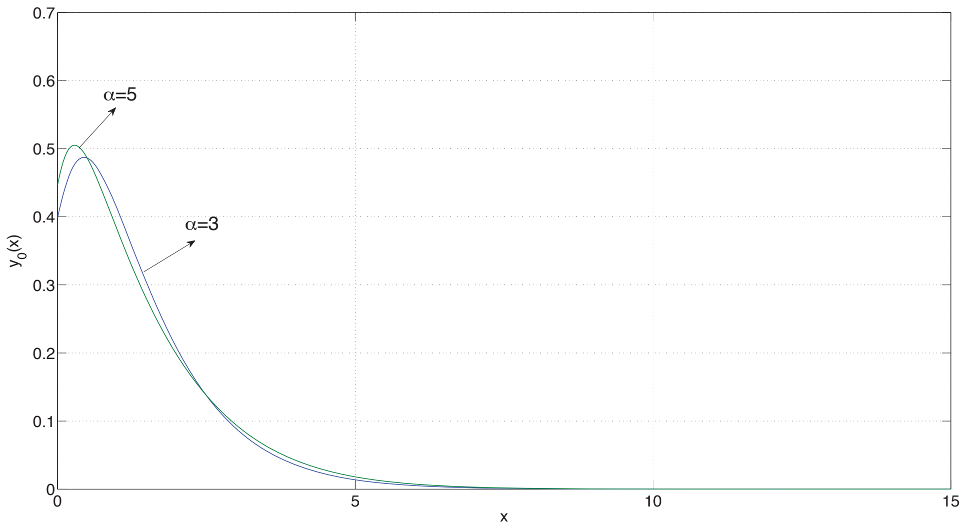

Figure 9.1: The solution $y_0(x)$ given by the Dirichlet series (9.11) for $m = 0, 1$, $D = 1$, $g = 2$, $b = 1$.

and equation (9.10) implies

$$2y(m_f) \geq \alpha y(\alpha m_f) + \beta y(\beta m_f). \tag{9.27}$$

Since $\alpha > 2$ and $y(m_f) > 0$, we have

$$y(m_f) > y(\alpha m_f). \tag{9.28}$$

Since the last maximum at M_f must occur after the last minimum at m_f, equation (9.28) implies that

$$m_f < M_f < \alpha m_f. \tag{9.29}$$

In particular, $y'(\alpha m_f)$ cannot be positive as this could induce another local maximum beyond M_f. Also, at the last maximum M_f, equation (9.10) implies

$$2y(M_f) \leq \alpha y(\alpha M_f) + \beta y(\beta M_f). \tag{9.30}$$

Since

$$2y(m_f) < 2y(M_f), \tag{9.31}$$

Equations (9.27), (9.30) give

$$\alpha y(\alpha m_f) + \beta y(\beta m_f) < \alpha y(\alpha M_f) + \beta y(\beta M_f). \tag{9.32}$$

The function is decreasing after the last maximum and $\alpha m_f < \alpha M_f$, hence,

$$y(\alpha m_f) > y(\alpha M_f). \tag{9.33}$$

Inequalities (9.32) and (9.33) give,

$$\begin{aligned}\alpha y(\alpha M_f) + \beta y(\beta m_f) &< \alpha y(\alpha m_f) + \beta y(\beta m_f)\\ &< \alpha y(\alpha M_f) + \beta y(\beta M_f),\end{aligned}$$

which implies $\beta y(\beta m_f) < \beta y(\beta M_f)$, i.e.,

$$y(\beta m_f) < y(\beta M_f). \tag{9.34}$$

Now $\beta m_f < \beta M_f$ and y is decreasing after the last maximum, consequently

$$m_f < \beta m_f < M_f < \alpha m_f, \tag{9.35}$$

so that

$$y(m_f) < y(\beta m_f). \tag{9.36}$$

Equations (9.30) and (9.33) give

$$\begin{aligned}2y(M_f) &\leq \alpha y(\alpha M_f) + \beta y(\beta M_f)\\ &< \alpha y(\alpha m_f) + \beta y(\beta M_f).\end{aligned} \tag{9.37}$$

Adding and subtracting $\beta y(\beta m_f)$ to equation (9.37) gives

$$2y(M_f) < \alpha y(\alpha m_f) + \beta y(\beta M_f) + \beta y(\beta m_f) - \beta y(\beta m_f),$$

which by using equation (9.27) yields

$$2\left(y(M_f) - y(m_f)\right) < \beta\left(y(\beta M_f) - y(\beta m_f)\right), \tag{9.38}$$

and since $1 < \beta < 2$, equations (9.37) and (9.38) imply

$$\begin{aligned} y(M_f) - y(m_f) &< y(\beta M_f) - y(\beta m_f) \\ &< y(\beta M_f) - y(m_f). \end{aligned} \tag{9.39}$$

Inequality thus (9.39) gives

$$y(M_f) < y(\beta M_f), \tag{9.40}$$

which contradicts the fact that M_f is the last maximum. This proves that y is unimodal for all $\alpha > 2 > \beta > 1$.

9.2 A Bessel-type equation arising in Asymmetrical cell division

In this section, we study the cell growth equation with dispersion (9.6) subject to condition (9.7) for a certain choice of non constant coefficients that correspond to dispersion, growth and splitting rates. This choice of coefficients leads to a Bessel type operator, and it is shown that there is a unique probability distribution function that solves the equation. The solution is constructed using the Mellin transform and is given in terms of an infinite series of modified Bessel functions.

We consider the case in which the dispersion and division rates are quadratic, but the growth rate is linear. Specifically, we study the case in which $D(x) = D^2x^2$, $g(x) = gx$, and $b(x) = c^2x^2$. Here D, g and c are positive constants. For this choice of coefficients, equation (9.6) reduces to

$$(x^2y(x))'' - \hat{g}(xy(x))' + (\hat{\lambda} - \hat{\mu} - \hat{c}^2x^2)y(x) + \hat{c}^2\alpha^3x^2y(\alpha x) + \hat{c}^2\beta^3x^2y(\beta x) = 0,$$

where

$$\hat{g} = \frac{g}{D^2}, \hat{c} = \frac{c}{D}, \hat{\mu} = \frac{\mu}{D^2}, \hat{\lambda} = \frac{\lambda}{D^2}.$$

Dropping circumflexes, it is clear that we can reduce the functional differential equation problem to

$$(x^2y(x))'' - g(xy(x))' + (\lambda - \mu - c^2x^2)y(x) + c^2\alpha^3x^2y(\alpha x) + c^2\beta^3x^2y(\beta x) = 0. \tag{9.41}$$

In addition to the “no-flux” condition (9.7), we impose the decay condition

$$\lim_{x\to\infty}\{(D(x)y(x))' - g(x)y(x)\} = 0. \tag{9.42}$$

The “no-flux” boundary condition (9.7) and the boundary condition (9.42) loom large in all the treatments of the second order cell growth problem. In fact, more fundamental conditions can be imposed. We will drop the boundary conditions and replace them with the requirement that y be a pdf along with certain growth/decay conditions as $x \to \infty$ and as $x \to 0^+$. These growth/decay conditions ensure the existence of a Mellin transform.

In the next section we derive some qualitative results about solutions to equation (9.41) that concern the eigenvalue and uniqueness. In section 9.2.2, we derive and solve an equation for the Mellin transform of y. In section 9.2.3, we develop a solution in the form of an infinite series of modified Bessel functions . The transform is exploited to deduce the asymptotic behaviour of y as $x \to 0^+$. It turns out that the asymptotic behaviour is linked strongly to the parameter g.

9.2.1 Qualitative properties

We are concerned with classical solutions to equation (9.41) that are also pdfs; hence, we require $y \in C^2(0;\infty)$ and $y \in L^1[0;\infty)$. If stronger growth/decay conditions are imposed, then the exact value of λ can be determined. Let $G(\tau_1,\tau_2)$ denote the set of functions f such that $f \in C^2(0;\infty)$, $f(x) = \mathrm{O}(1/x^{\tau_1})$ and $f'(x) = \mathrm{O}(1/x^{\tau_1+1})$ as $x \to 0^+$, and $f(x) = \mathrm{O}(1/x^{\tau_2})$ and $f'(x) = \mathrm{O}(1/x^{\tau_2+1})$ as $x \to \infty$.

Theorem 9.2.1. *Suppose that $y \in G(\tau_1,\tau_2)$ is a pdf solution to equation (9.41), where $\tau_1 < 1$ and $\tau_2 > 4$. Then $\lambda = \mu - g$.*

Proof. The growth/decay conditions placed on the pdf y imply that $x^p y \in L^1[0;\infty)$ for $0 \le p \le 3$. Multiplying equation (9.41) by x and integrating from 0 to ∞ yields

$$
\begin{aligned}
(\lambda - \mu + g)\int_0^\infty xy(x)dx + \big(x^3y'(x) - (g+3)x^2y(x)\big)\Big|_0^\infty \\
&= c^2\int_0^\infty (x^3y(x) - \alpha^3x^3y(\alpha x) - \beta^3x^3y(\beta x))dx \\
&= 0.
\end{aligned}
$$

The growth/decay conditions placed on y ensure that the boundary terms vanish; therefore,

$$
(\lambda - \mu + g)\int_0^\infty xy(x)dx = 0. \tag{9.43}
$$

The function y is a pdf so that $y(x) \geq 0$ for all $x \geq 0$ and y is not identically zero; hence,

$$
\int_0^\infty xy(x)dx > 0.
$$

Equation (9.43) thus implies $\lambda = \mu - g$. $\square$

Under the conditions of Theorem 9.2.1, equation (9.41) can be recast as

$$
(x^2y(x))'' - g(xy(x))' - (c^2x^2 + g)y(x) + c^2\alpha^3x^2y(\alpha x) + c^2\beta^3x^2y(\beta x) = 0. \tag{9.44}
$$

We now focus on solutions to this equation and show that any solution (pdf or otherwise) that is positive at some point in $(0, \infty)$ must be positive for all $x > 0$. The proof of this result is also connected with uniqueness. We begin with a transformation and a Lemma. Suppose that $y \in G(\tau_1, \tau_2)$ is a solution to equation (9.44), where $\tau_1 < 1$ and $\tau_2 > 4$, and let

$$
\Delta(x) = \int_x^\infty \xi^3 y(\xi)d\xi.
$$

The function Δ is well defined for $x \geq 0$, $\Delta \in C^2(0, \infty)$, and

$$\Delta'(x) = -x^3 y(x),$$
$$\Delta''(x) = -x^3 y'(x) - 3x^2 y(x).$$

Now,

$$\begin{aligned}
&\int_x^\infty \left(\xi(\xi^2 y(\xi))'' - g\xi(\xi y(\xi))' - g\xi y(\xi)\right) d\xi \\
=& - x^3 y'(x) - x^2 y(x) + g x^2 y(x) \\
=& \Delta''(x) - \frac{(g+2)\Delta'(x)}{x};
\end{aligned}$$

consequently, (9.44) yields

$$\Delta''(x) - \frac{(g+2)\Delta'(x)}{x} = c^2(\Delta(x) - \frac{1}{\alpha}\Delta(\alpha x) - \frac{1}{\beta}\Delta(\beta x)). \tag{9.45}$$

Lemma 9.2.2. *If $\Delta \in C^2(0, \infty)$ is a non-trivial solution in $(0, \infty)$ to equation* (9.45) *such that*

$$\lim_{x \to \infty} \Delta(x) = 0. \tag{9.46}$$

Then $\Delta'(x) \neq 0$ for all $x > 0$.

Proof. We show first that Δ cannot have local extrema. Suppose first that Δ has a positive local maximum at $x_1 > 0$. Then $\Delta'(x_1) = 0$ and $\Delta''(x_1) \leq 0$; hence

$$\Delta(x_1) \leq \frac{1}{\alpha}\Delta(\alpha x_1) + \frac{1}{\beta}\Delta(\beta x_1). \tag{9.47}$$

Then we can show that either $\Delta(\alpha x_1) \geq \Delta(x_1)$ or $\Delta(\beta x_1) \geq \Delta(x_1)$. Since $\Delta(x_1) > 0$ and $\Delta(x) \to 0$ as $x \to \infty$, there must be another positive local maximum at $x_2 \geq \beta x_1$ at which $\Delta(x_2) \geq \Delta(x_1)$. We can repeat this argument on x_2 to show that there is another local maximum at $x_3 \geq \beta x_2 \geq \beta^2 x_1$ at which $\Delta(x_1) \leq \Delta(x_3)$. It is clear by this means we can construct a sequence $\{x_k\}$ of points at which Δ has positive local maxima such that $\{x_k\} \to \infty$ as $k \to \infty$ and that $\Delta(x_k) \geq \Delta(x_1) > 0$. The existence of such a sequence however contradicts equation (9.46) and we thus conclude that Δ cannot have a local positive maximum in $(0, \infty)$. The above argument can be applied to $-\Delta$ to show that Δ cannot have a negative local minimum in $(0, \infty)$. Evidently Δ cannot have a positive local minimum since this requires a positive local maximum. We thus conclude that Δ cannot have any local extrema in $(0, \infty)$.

Suppose that $\Delta'(x_1) = 0$ for some $x_1 > 0$. Since Δ cannot have local extrema, it follows that $\Delta(x) = \Delta(x_1)$ for all $x \in [x_1, \alpha x_1]$. The continuity of Δ' implies that $\Delta'(\alpha x_1) = 0$. We can thus repeat the above argument to show that $\Delta(x) = \Delta(x_1)$ for all $x \in [x_1, \alpha^2 x_1]$. The argument can be repeated any number of times to show that $\Delta(x) = \Delta(x_1)$ for all $x \in [x_1, \infty)$. Equation (9.46) therefore implies that $\Delta(x) = 0$ for all $x \in [x_1, \infty)$. We now show that $\Delta(x) = 0$ for all $x \in (0, x_1]$. Since $\Delta(x) = 0$ for all $x \in [x_1, \infty)$, equation (9.45) reduces to

$$\Delta''(x) - \frac{(g+2)\Delta'(x)}{x} = c^2(\Delta(x))$$

for $x \in \left[\frac{x_1}{\alpha}, x_1\right]$. We also know that $\Delta(x_1) = 0$ and $\Delta'(x_1) = 0$. The unique solution to this initial value problem is $\Delta(x) = 0$ Therefore $\Delta(x) = 0$ for all $x \in \left[\frac{x_1}{\alpha}, x_1\right]$. We can repeat this argument any number of times and show that $\Delta(x) = 0$ for all $x \in (0, x_1]$ and hence $\Delta(x) = 0$ for all $x > 0$. It is assumed, however, that Δ is nontrivial in $(0, \infty)$; therefore $\Delta'(x) \neq 0$ for all $x > 0$. $\square$

An immediate consequence of Lemma 9.2.2 and the definition of Δ is that y is nonzero for $x > 0$ if it is nonzero at any point in $(0, \infty)$. In particular if y satisfies the condition

$$\int_0^\infty y(x)dx = 1, \tag{9.48}$$

then y must be positive somewhere in $(0, \infty)$ and therefore it must be positive for all $x > 0$. More formally, we have the following result.

Corollary 9.2.3. *Suppose that $y \in G(\tau_1, \tau_2)$ is a nontrivial solution to equation* (9.44) *where $\tau_1 < 1$ and $\tau_2 > 4$. Then $y(x) \neq 0$ for all $x > 0$. In particular if y satisfies condition* (9.48)*, then $y(x) > 0$ for all $x > 0$.*

The above corollary shows that we do not have to impose positivity conditions on solutions to guarantee that they are pdf solutions. The growth/decay conditions and the normalizing condition are sufficient to ensure positivity. Corollary 9.2.3 can also be used to establish a uniqueness result.

Theorem 9.2.4. *If there exists a solution y to equation* (9.44) *that satisfies condition* (9.48) *such that $y \in G(\tau_1, \tau_2)$ for some numbers $\tau_1 < 1$ and $\tau_2 > 4$, then this solution is unique.*

Proof. suppose that y_1 and y_2 are distinct solutions and let $z = y_1 - y_2$. Then there is an $x_1 > 0$ such that $z(x_1) \neq 0$, and without loss of generality z can be defined so that $z(x_1) > 0$. Since y_1 and y_2 also satisfy equation (9.48), we also have

$$\int_0^\infty z(x)dx = 0. \tag{9.49}$$

Now, $z \in G(\tau_1, \tau_2)$ and therefore the function $\hat{\delta}$ defined by

$$\hat{\delta}(x) = \int_x^\infty \xi^3 z(\xi) d\xi.$$

satisfies the conditions of Lemma 9.2.2 and hence $z(x) \neq 0$ for all $x > 0$. Since $z(x_1) > 0$, the function z must be positive on $(0, \infty)$ and therefore

$$\int_0^\infty z(x)dx > 0$$

The last inequality, however, contradicts equation (9.49); therefore $y_1(x) = y_2(x)$ for all $x > 0$. □

9.2.2 A solution for the Mellin transform

Equation (9.44) can be recast in the form

$$x^2 y'' - (g-4)xy' - (c^2x^2 + \lambda)y(x) = -c^2\alpha^3 x^2 y(\alpha x) - c^2\beta^3 x^2 y(\beta x), \tag{9.50}$$

where

$$\lambda = 2(g-1). \tag{9.51}$$

In the above form it is clear that the differential operator is the well known modified Bessel operator. The Mellin transform of y is

$$M[y(x); s] = \int_0^\infty x^{s-1} y(x) dx.$$

Under the growth/decay conditions of Theorem 9.2.1, this transform has a fundamental strip that includes $1 \leq Re(s) \leq 3$. Applying the Mellin transform to equation (9.50), noting that the boundary terms vanish, gives

$$((s-3+g)s + 2(g-1))M(s) = c^2 \left(1 - \frac{1}{\alpha^{s-1}} - \frac{1}{\beta^{s-1}}\right) M(s+2), \tag{9.52}$$

where for succinctness $M(s) = M[y(x); s]$. Condition (9.48) implies

$$M(1) = 1. \tag{9.53}$$

We seek a solution to equation (9.52) of the form

$$M(s) = F(s)Q(s),$$

where

$$((s-3+g)s - \lambda)F(s) = c^2 F(s+2). \tag{9.54}$$

Equation (9.54) is the Mellin transform equation associated with the modified Bessel equation

$$x^2 y''(x) - (g-4)xy'(x) - (c^2x^2 + \lambda)y(x) = 0,$$

which has solutions of the form

$$y(x) = c_1 x^{(g-3)/2} I_\nu(cx) + c_2 x^{(g-3)/2} K_\nu(cx),$$

where I_ν and K_ν denote the modified Bessel functions, the c_k are constants, and

$$\nu = \frac{g+1}{2}.$$

The function I_ν is not bounded as $x \to \infty$, but K_ν decays exponentially as $x \to \infty$ for any ν. We choose a solution F based on the Mellin transform of the homogeneous solution

$$y_h(x) = x^{(g-3)/2} K_\nu(cx);$$

hence,

$$\begin{aligned} M[y_h(x); s] &= \frac{1}{4}\left(\frac{2}{c}\right)^{(2s+g-3)/2} \Gamma\left(\frac{s+g-1}{2}\right)\Gamma\left(\frac{s-2}{2}\right) \\ &= F(s). \end{aligned}$$

Equations (9.54) implies

$$Q(s) = \left(1 - \frac{1}{\alpha^{s-1}} - \frac{1}{\beta^{s-1}}\right) Q(s+2),$$

which has a solution of the form

$$Q(s) = \prod_{k=0}^{\infty}\left(1 - \frac{1}{\alpha^{s+2(k-\frac{1}{2})}} - \frac{1}{\beta^{s+2(k-\frac{1}{2})}}\right),$$

where C is a constant determined by equation (9.53). In particular,

$$C = \frac{4\left(\frac{c}{2}\right)^{(g-1)/2}}{\Gamma\left(\frac{g}{2}\right)\Gamma\left(\frac{-1}{2}\right)\prod_{k=0}^{\infty}\left(1 - \frac{1}{\alpha^{2k}} - \frac{1}{\beta^{2k}}\right)}. \tag{9.55}$$

In summary, a solution to equation (9.52) that satisfies equation (9.53) is

$$M(s) = \frac{C}{4}\left(\frac{2}{c}\right)^{(2s+g-3)/2} \Gamma\left(\frac{s+g-1}{2}\right)\Gamma\left(\frac{s-2}{2}\right)\prod_{k=0}^{\infty}\left(1 - \frac{1}{\alpha^{s+2(k-\frac{1}{2})}} - \frac{1}{\beta^{s+2(k-\frac{1}{2})}}\right). \tag{9.56}$$

Note that the function Q has zeros of order one at $s = 2, 0, -2, -4, \ldots$ and the function $\Gamma\left(\frac{s-2}{2}\right)$ has poles of order one at these points. The function $\Gamma\left(\frac{s-2}{2}\right)Q(s)$ is entire. The singularities of M arise from the term $\Gamma\left(\frac{s+g-1}{2}\right)$ and are poles of order one that lie on the real line. The largest value of s that produces a singularity is $s = 1-g$. The function M is thus meromorphic on $\mathbb{C}$ and holomorphic in the half plane $Re(s) > 1-g$. We show in the next section that the asymptotic behavior of the solution to equation (9.50) as $x \to 0^+$ depends on whether $0 < g < 1$, $g = 1$, or $g > 1$, i.e., on the sign of the eigenvalue λ.

9.2.3 A pdf solution

The infinite product in (9.56) can be written as a double power series in α^s and β^s. This observation prompts us to look for a solution of the form

$$y(x) = \sum_{k=0}^{\infty}\sum_{j=0}^{\infty}(\alpha^k\beta^j x)^{(g-3)/2}a_{k,j}K_\nu(c\alpha^k\beta^j x). \tag{9.57}$$

Substituting (9.57) into equation (9.50) and equating the coefficients of $K_\nu(c\alpha^k\beta^j)$ yields

$$x^2c^2K_\nu''(cx) + xcK_\nu'(cx) - \left(c^2x^2 + \left(\frac{g+1}{2}\right)^2\right)K_\nu(cx) = 0, \tag{9.58}$$

along with the relations,

$$a_{0,j} = \frac{(-1)^j(\beta^3)^j a_{0,0}}{\prod_{s=1}^{j}((\beta^s)^2-1)};\ j = 1, 2, ..., \tag{9.59}$$

$$a_{k,0} = \frac{(-1)^k(\alpha^3)^k a_{0,0}}{\prod_{s=1}^{k}((\alpha^s)^2-1)};\ k = 1, 2, ..., \tag{9.60}$$

and

$$a_{k,j} = \frac{-1}{(\alpha^k\beta^j)^2-1}\{\alpha^3 a_{k-1,j} + \beta^3 a_{k,j-1}\};\ k, j = 1, 2, ... \tag{9.61}$$

Equation (9.58) gives

$$\nu = \frac{g+1}{2}. \tag{9.62}$$

It can be shown directly that the double series $\sum_{k=0}^{\infty}\sum_{j=o}^{\infty}a_{k,j}$ converges absolutely. The absolute convergence of this series is established by the recursive relation (9.61) once it is shown that there exist M_j and M_k such that $|a_{k,j}| \le M_j$ for all k and $|a_{k,j}| \le M_k$ for all j.

The series $\sum_{k=0}^{\infty}|a_{k,0}|$ and $\sum_{j=0}^{\infty}|a_{0,j}|$ are convergent by the ratio test; hence there are numbers L and N_0 such that $|a_{k,0}| \leq L$ and $|a_{0,j}| \leq N_0$ for all k and j. Let v_1 be the smallest non-negative integer such that

$$\frac{\alpha^3 + \beta^3}{\alpha^2 \beta^{2v_1} - 1} < 1,$$

and let $N_1 = max\{|a_{1,0}|, a_{1,1}, ..., |a_1, v_1|, N_0\}$. If $|a_{1,j-1}| \leq N_1$ and $j \geq v_1$, then equation (9.61) implies

$$\begin{aligned} |a_{1,j}| &\leq \frac{1}{(\alpha^2 \beta^{2j} - 1)} (\alpha^3 |a_{0,j}| + \beta^3 |a_1, j-1|), \\ &\leq \frac{(\alpha^3 + \beta^3) N_1}{(\alpha^2 \beta^{2j} - 1)}, \\ &\leq N_1. \end{aligned}$$

It follows by induction that $|a_{1,j}| \leq N_1$ for all $j \geq v_1$ and hence for all j. This argument can be applied successively to each row. For the n^{th} row we can define v_n as the smallest non-negative integer such that

$$\frac{\alpha^3 + \beta^3}{\alpha^{2n} \beta^{2v_n} - 1} < 1,$$

and define a new upper bound by $N_n = max\{|a_{n,0}|, |a_{n,1}|, ..., |a_n, v_n|, N_{n-1}\}$. We can construct a sequence $\{v_n\}$ and $\{N_k\}$ so that $|a_{k,j}| \leq N_n$ for all $k \leq n$ and for all j. Let ϕ be the smallest positive integer such that

$$\frac{\alpha^3 + \beta^3}{\alpha^{2\phi} - 1} < 1,$$

Then $v_n = 0$ for all $n \geq \phi$. Now $N_\phi = max\{|a_{\phi,0}|, N_{\phi-1}\}$ and since $|a_{k,0}| \leq L$ for all k, we can use the bound $N = max\{L, N_{\phi-1}\}$. This bound can be applied to all the rows after the ϕ^{th} row and hence M is an upper bound for $|a_{k,j}|$.

Recall that for any ν,

$$K_\nu(x) \sim \sqrt{\frac{\pi}{2x}} e^{-x},$$

as $x \to \infty$. The series defining y thus converges rapidly and uniformly in compact sets in $(0, \infty)$. Note that the terms in the above series are functions holomorphic in the half plane $Re(z) > 0$ and that the series converges in any compact set of this half plane. The function y defined by equation (9.57) is thus holomorphic in this half plane; *a fortiori*, $y \in C^2(0, \infty)$. It is clear that

$$y(x) \sim \sqrt{\frac{\pi}{2c}} x^{(g-3)/2} e^{-cx},$$

as $x \to \infty$, but the asymptotic behavior of y as $x \to 0^+$ is less obvious particularly since

$$K_\nu(x) \sim \frac{\Gamma(\nu)}{2} \left(\frac{2}{x}\right)^\nu$$

as $x \to 0^+$. The Mellin transform of y can be further exploited to determine this asymptotic behavior. Let f be a function with a Mellin transform $M[f(x); s]$ defined in a fundamental strip $A < \mathrm{Re}(s) < B$. Recall that the inversion formula is

$$f(x) = \frac{1}{2\pi i} \int_{\kappa - i\infty}^{\kappa + i\infty} M[f(x); s] x^{-s} ds,$$

where $A < \kappa < B$. If $f \in C^2(0, \infty)$, then the Riemann-Lebesgue Lemma and integration by parts show that $M[f(x); \sigma + it] = \mathrm{o}(|t^2|)$ as $t \to \pm\infty$, where σ is a fixed real number. If $M[f(x); s]x^{-s}$ can be meromorphically continued to a strip $A_1 < \mathrm{Re}(s) < B$, where $A_1 < A$, and if $A_1 < -N < A$, then the inversion formula and the asymptotic relation can be used to show

$$f(x) = \sum_{\lambda_k \in S} \mathrm{Res}(M[f(x); s]x^{-s}; s = \lambda_k) + \mathrm{O}(x^N), \tag{9.63}$$

where S denotes the set of singularities in the strip $-N < \mathrm{Re}(s) < \kappa$. Here, it is assumed that $M[f(x); s]x^{-s}$ has no singularities on the line $\mathrm{Re}(s) = -N$.

It was shown at the end of Section 9.2.2 that M is holomorphic in the half plane $\mathrm{Re}(s) > 1 - g$. The transform has only simple poles and can be meromorphically continued to $\mathrm{Re}(s) > -(1 + g)$. Since $y \in C^2(0, \infty)$ we can thus use the relation (9.63) in this half plane.

Suppose that $g > 1$ (see *Figure* 9.2). Then M is holomorphic in the right half plane $\mathrm{Re}(s) \geq 0$ and therefore there is an $N > 0$ such that

$$y(x) = \mathrm{O}(x^N),$$

as $x \to 0^+$, so that

$$\lim_{x \to 0^+} y(x) = 0.$$

suppose that $g = 1$. Then M has a pole at $s = 0$, and equation (9.63) yields

$$y(x) = \mathrm{Res}(M(s)x^{-s}; s = 0) + \mathrm{O}(x^N), \tag{9.64}$$

where $0 < N < 1 + g$. Now,

$$\mathrm{Res}\left(\Gamma\left(\frac{s}{2}\right)\Gamma\left(\frac{s-2}{2}\right)\left(1 - \frac{1}{\alpha^{s+1}}\right)\left(1 - \frac{1}{\beta^{s+1}}\right)\right) = -4\left\{\frac{1}{\alpha}log\alpha + \frac{1}{\beta}log\beta\right\},$$

and therefore

$$\mathrm{Res}(M(s)x^{-s}; s = 0) = \frac{C}{2}R(\alpha)(\alpha + \beta - 1)c\left\{\frac{log\alpha}{\alpha} + \frac{log\beta}{\beta}\right\},$$

where

$$R(\alpha) = \prod_{k=2}^{\infty}\left(1 - \frac{1}{\alpha^{2k-1}} - \frac{1}{\beta^{2k-1}}\right).$$

Let $\theta_0(\alpha) = \mathrm{Res}(M(s)x^{-s}; s = 0)$. Equation (9.64) yields

$$\lim_{x \to 0^+} y(x) = \theta_0(\alpha) > 0. \tag{9.65}$$

Finally, suppose that $0 < g < 1$. Then M has a simple pole of order one at $1 - g > 0$. Equation (9.63) implies

$$y(x) = \theta_1(\alpha)x^{g-1} + \mathrm{O}(x^N),$$

where $0 < N < 1 + g$ and

$$\theta_1(\alpha) = \mathrm{Res}(M(s); s = 1 - g) > 0.$$

In this case

$$\lim_{x \to 0^+} y(x) = \infty.$$

Note, however, that $-1 < g - 1 < 0$ so that $y \in L^1(0, \infty)$. The three cases are illustrated in *Figure 9.2.*

Theorem 9.2.5. *Let y be defined by equation* (9.57)*. Then for any positive numbers g and c there are numbers $\tau_1 < 1$ and $\tau_2 > 4$ such that $y \in G(\tau_1, \tau_2)$. The function y is a pdf solution to equation* (9.44) *and it is unique among functions in $G(\tau_1, \tau_2)$.*

Proof. By construction y is a solution to equation (9.44) and it has been shown that $y \in C^2(0, \infty)$. Once it is established that there are numbers $\tau_1 < 1$ and $\tau_2 > 4$ such that $y \in G(\tau_1, \tau_2)$, the other properties of y follow immediately from Corollary 9.2.3 and Theorem 9.2.4.

The above asymptotic analysis shows that

$$y(x) = \mathrm{O}(x^{g-1}) \tag{9.66}$$

as $x \to 0^+$. Since

$$M[y'(x); s] = -(s-1)M(s-1),$$

the asymptotic behavior of y' can be readily deduced from that of y. Briefly, the first pole of $M[y'(x); s]$ is at $s = 2 - g$, and it follows that

$$y'(x) = \mathrm{O}(x^{g-2}) \tag{9.67}$$

as $x \to 0^+$. It is clear that y' also decays exponentially as $x \to \infty$ so that y and y' meet the decay conditions as $x \to \infty$ for any choice of $\tau_2 > 0$. Equations (9.66) and (9.67) imply that there is a number $\tau_1 < 1$ such that y and y' satisfy the requisite growth conditions at the origin. □

9.3 Conclusions

We discussed the cell growth equation with dispersion, first for the constant coefficients case (Section 9.1) and then for a certain choice of non constant coefficients (Section 9.2) that corresponded to dispersion, growth and splitting rates.

For the constant coefficient case, we found the SSD solution to the cell growth equation (9.2) and showed that the solution is unique and positive. We also discussed the shape of the SSD solution and established that the SSD solution is unimodal.

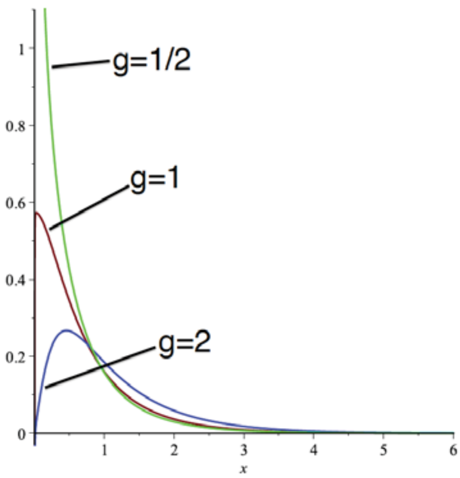

Figure 9.2: Pdf Solutions for $\alpha = 3$, $\beta = \frac{3}{2}$, $c = 1$, $g = \frac{1}{2}, 1, 2$

In Section 9.2, we established that the cell growth equation (9.41) has, under certain growth/decay conditions, a unique solution that is also a pdf. It was shown that the eigenvalue λ is determined uniquely by these conditions along with the requirement that y be positive for some $x > 0$. For this λ, we showed that the solution must be positive for all $x > 0$. The Mellin transform was used to study the asymptotic behavior of the solution as $x \to 0^+$. Although the solution technique is limited, the specific case studied here is useful as a guide for more general cases where explicit solutions are not available. The general theory of eigenvalue problems for functional equations such as (9.2) remains largely unexplored. In all studies it was shown that the eigenvalue problem mimics a singular Sturm-Liouville problem. Future work certainly includes a closer study of equation (9.41) as an eigenvalue problem, and an extension of results to more general coefficients.

Chapter 10

Conclusions

In this thesis we modeled and analyzed the cell growth and division process to gain insight into the cell population dynamics. Living cells which simultaneously grow and divide are usually structured on size and accordingly we constructed a size structured cell population model. The biological relevance of symmetric and asymmetric cell divisions was studied in Chapter 1. Examples of such symmetric and asymmetric cell divisions were also discussed. It was explained that stem cells switch between the two modes of division according to the needs of the body. The rationale for using single-compartment cell growth models was also provided.

A mathematical model encompassing the relevant aspects of cell biology was presented. This model is an extension of that studied by Hall and Wake [24] and incorporates the asymmetric division of cells in addition to the symmetric cell division. A novel aspect of the model is its focus on the biological interpretation of the splitting kernel. Initially, deterministic growth and splitting rates were considered and this led to a first order partial-integro differential equation (equation (4.4)). The cell growth model was then extended to include stochasticity in the growth rate of cells. This extension resulted in a "dispersion-like" model and yielded a second order partial-integro differential equation (equation (4.11)).

In chapters 5 and 8, we studied functional partial differential equations (5.2) and (8.2), subject to appropriate initial and boundary conditions, arising in the cases of symmetric and binary asymmetric cell divisions, respectively. The case of symmetric cell division yielded a functional partial differential equation with only one non-local term whereas the binary asymmetric division resulted in a functional partial differential equation with two non-local terms. However, the focus in both these chapters remained on separable solutions to their corresponding functional partial differential equations. The motivation for the study of such solutions came from experimental results for certain plant cells that suggested solutions of this type, at least as a long term approximation [27]. We found the steady size distribution (SSD) solution y_0 in both these cases and showed that it was unique. A comparison of the SSD solutions arising in the symmetrical and asymmetrical cases is given in Figure 10.1. The blue curve indicates the SSD solution y_0 for the binary symmetrical case, i.e., the case in which a cell of size x divides into $\alpha = 2$ cells each of size $\frac{x}{2}$. The green curve shows the behavior of the SSD solution for binary asymmetrical case, i.e., the case in which a cell of size x divides into two cells of different sizes $\frac{x}{\alpha}$ and $\frac{x}{\beta}$. The graph clearly shows that when the division becomes asymmetric, the peak shifts not only downwards but also to the left. The higher eigenfunctions for the symmetrical as well as for

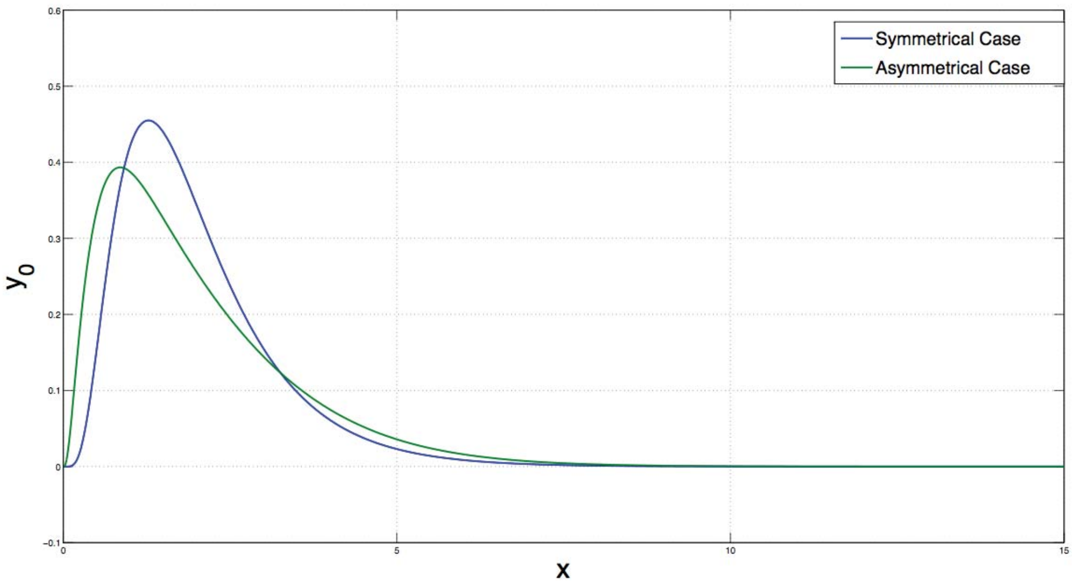

Figure 10.1: SSD Solutions for binary symmetric and asymmetric divisions. For symmetric binary division, we have taken $\alpha = 2$, $g = 2$ units, $b = 1$ unit and for asymmetric binary division we have taken $\alpha = 5, \beta = \frac{5}{4}$, $g = 2$ units, $b = 1$ unit.

the asymmetrical case were obtained. For symmetrical cell division, it was shown that the zeros of the eigenfunctions are nested and the result is given by Theorem 5.2.6. The question of whether the set of eigenfunctions y_m are complete is still open. Suppose that n is a function of the form

$$n(x,t) = \sum_{m=0}^{\infty} c_m y_m(x) e^{-\lambda_m t},$$

where the above series is uniformly convergent for $x \geq 0$. Then it is straightforward to show that such a function is a solution to equation (5.2) (equation (8.2) for the asymmetric case). The problem, however, is that in order to satisfy condition (4.7), the coefficients c_m must satisfy

$$n_0(x) = \sum_{m=0}^{\infty} c_m y_m(x),$$

and this brings to the fore the crucial question about what function space is spanned by the eigenfunctions. This question and other properties of these eigenfunctions remain to be explored, and this will be the subject of future work.

We also developed a novel solution technique to solve the functional partial differential equation (5.2) arising in the symmetrical case for general initial distributions. We obtained a solution valid for the quadrant $x \geq 0, t \geq 0$ (see Theorem 6.4.1). This solution was then used to determine the asymptotic behavior of the solution explicitly. The general solution allowed us to easily get the higher order terms in the asymptotic expressions for the number density. The method is not restricted to the functional equation studied in Chapter 6: the same strategy can be employed to deal with more general functional partial differential equations with advanced arguments. For example, if the division rate b is not constant with respect to x, the same approach in principle can be used. The crux, however, is finding the limiting function. Certainly, future work would include such generalizations. In terms of the cell division model, the general solution developed in Chapter 6 provided more detailed information about how the cell size distribution depends on the initial distribution. It is well known that solutions are asymptotic to the SSD solution as $t \to \infty$, but the analysis underlying this relation does not fully explain or illustrate why the initial data has such a weak influence on the long term solution and how the SSD solution arises. We showed that the weak dependence is a result of the hyperbolic character of the differential operator and the advanced argument. We also showed that the SSD solution arises as the leading order term in an expansion for the limiting function, which represents the solution as $t \to \infty$. In contrast, this limiting solution depends strongly on the boundary data. The expansion also provided the higher order terms in the asymptotic expansion, and these terms correspond to eigenfunctions for the pantograph equation.

In Chapters 7 and 9 we studied our cell growth problem (see equations (7.2) and (9.2)) involving stochastic growth rates, together with appropriate boundary and initial conditions, for the symmetrical and the asymmetrical division of cells respectively. In both the cases, we encountered a second order functional partial differential equation. However, the functional partial differential equation encountered in the symmetrical case (Chapter 7) contained one non-local term whereas the functional partial differential equation that arose in the asymmetrical division of cells (Chapter 9) had two non-local terms. We focused on the SSD solutions to the non-local equations. A comparison of the SSD solutions arising in the symmetrical and asymmetrical cases is given in Figure 10.2. The blue curve indicates the SSD solution y_0 for the binary symmetrical case, i.e., when a cell of size x divides into $\alpha = 2$ cells each of size $\frac{x}{2}$. The green curve shows the behavior of the SSD solution for binary asymmetrical case, i.e., when a cell of size x divides into two cells of different sizes $\frac{x}{\alpha}$ and $\frac{x}{\beta}$. The graph clearly shows that when the division becomes asymmetric, the peak shifts not only upwards but also to the left. Here the dispersion coefficient D is taken to be 1. For the case of symmetric cell division, we obtained a constructive existence theorem for the linear, non-local dispersion-growth equation (7.2) with an arbitrary initial size distribution and with a no-flux boundary condition. We showed that this solution is unique (see Theorem 7.2.3).

Finally, we studied a linear cell growth ordinary differential equation (9.41) with two non-local terms for a certain choice of non-constant coefficients. This choice of coefficients lead to a Bessel type operator and it was shown that the cell growth equation (9.41) has, under certain growth/decay conditions, a unique solution that is also a pdf (see Theorem 9.2.5). It was established that the eigenvalue λ is determined uniquely by these conditions along with the requirement that y be positive for some $x > 0$. For this λ, we showed that the solution must be positive for all $x > 0$. The Mellin transform was used to study the asymptotic behavior of the solution as $x \to 0^+$. Although the solution technique is limited, the specific case studied here is useful as a guide for more general cases where explicit solutions are not available. The general theory of eigenvalue problems for functional equations

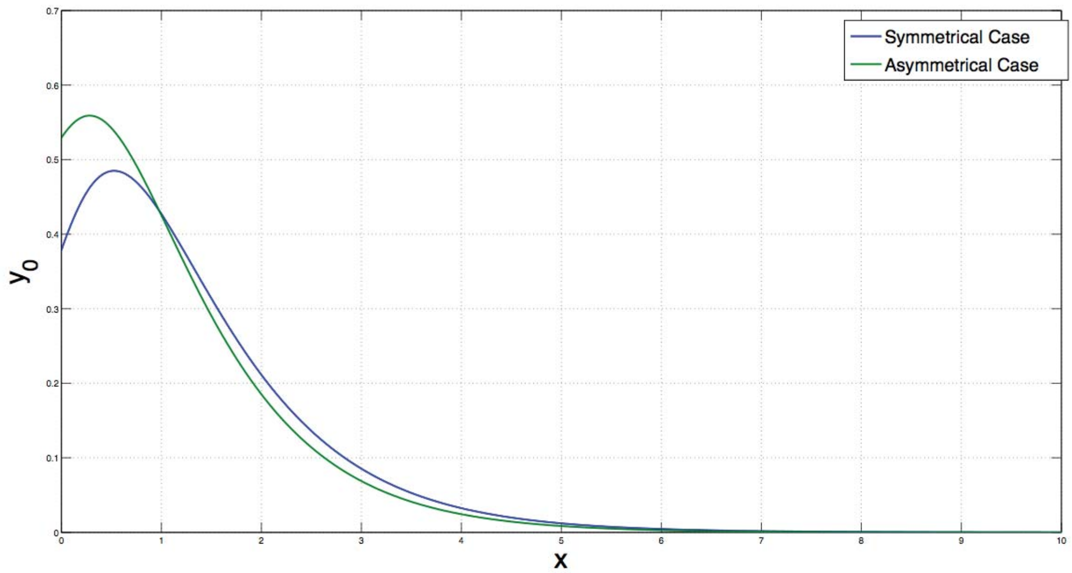

Figure 10.2: SSD Solutions for binary symmetric and asymmetric divisions with stochastic growth rates. For symmetric binary division, we have taken $\alpha = 2$, $D = 1$, $g = 2$ units, $b = 1$ unit and for asymmetric binary division we have taken $\alpha = 2.2$, $D = 1$, $g = 2$ units, $b = 1$ unit.

such as (9.2) remains largely unexplored. In all studies it was shown that the eigenvalue problem mimics a singular Sturm-Liouville problem. Future work certainly includes a closer study of equation (9.41) as an eigenvalue problem, and an extension of results to more general coefficients.

Appendix A

Since a Dirichlet series is uniformly convergent, it can be differentiated term by term. Substituting $m = m - 1$ in equation (5.29) and differentiating the resulting equation with respect to x yields

$$\begin{aligned} y'_{m-1}(x) = K_{m-1} \Bigg(& \frac{-b}{g} \alpha^{-(m-2)} e^{-\frac{b}{g}\alpha^{-(m-2)}x} + \\ & \sum_{r=1}^{\infty} \frac{(-1)^r \alpha^{r(m-1)}}{\alpha^{\frac{r(r-1)}{2}} \prod_{j=1}^{r}(1-\alpha^{-j})} \left(\frac{-b}{g} \alpha^{-(m-2)+r} \right) e^{-\frac{b}{g}\alpha^{-(m-1)+r}x} \Bigg) \\ = {} & A y_m(\alpha x), \end{aligned}$$

where $A = \frac{K_{m-1}}{K_m} \left(\frac{-b}{g} \right) \alpha^{-(m-2)}$.

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