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Steady Size Distributions in Cell Populations

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Abstract

In any population of cells, individual cells grow for some period of time and then divide into two or more parts, called daughters. To describe this process mathematically, we need to specify functions describing the growth rate, size at division, and proportions into which each cell divides. In this thesis, it is assumed that the growth rate of a cell can be determined precisely from its size, but that both its size at division and the proportions into which it divides may be described stochastically, by probability density functions whose parameters are dependent on cell size and age (or birth-size). Special cases are also considered where all cells with the same birth-size divide at the same size, or where all cells divide exactly in half.

We consider a population of cells growing and dividing steadily, such that the total cell population is increasing, but the proportion of cells in any size class remains constant. In Chapter 1, equations are derived which need to be solved in order to deduce the shape of the steady size distribution (or steady size/age or size/birth-size distributions) from any given growth rate and probability distributions describing the division rate and division proportions. In the general case, a Fredholm-type integral equation is obtained, but if the probability of cell division depends on cell size only (i.e. not age or birth-size), and all cells divide into equal-sized daughters, then we obtain a functional differential equation.

In two special cases, the resulting equations simplify considerably, and it is these cases which are explored further in this thesis. The first is where the probability of a cell dividing in any instant of time is a constant, independent of cell age or size. In Chapter 2, the functional differential equation resulting when cells divide into equal-sized daughters is solved for the special case where the growth rate is constant, and in an appendix the case where the growth rate is described by a power law is dealt with. The second case which simplifies is where the time-independent part of the growth rate of a cell is proportional to cell size. This case is particularly important, as it is a good first-order approximation to the real cell growth rate in some structured tissues, and in some bacteria. The special case in which this leads to a functional differential equation is discussed in Chapter 3, and the integral equation arising in the general case is dealt with in Chapter 4. Finally, the conditions under which the integral operator in Chapter 4 will be both square-integrable and non-factorable are discussed in Chapter 5. It is shown that if these conditions are satisfied then a unique, stable, steady size distribution will exist.

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 - Try something even if the chances of success look poor, or
 - Solve a simpler problem then look for ways to generalise!

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Contents

1	Introduction and Model Formulation	1
1.1	Unstructured Population Models	1
1.2	Age-Structured Populations	3
1.3	Populations Structured on Many Properties	4
1.3.1	Models with Age	6
1.3.2	Models without Age	7
1.4	Population Models with Non-Deterministic Growth Rates	8
1.5	Cell Population Models with Size Structure Only	11
1.6	Steady Size Distributions	13
1.7	Cell Populations with age and size structure	17
1.8	Steady Size/Age Distributions	18
1.9	The Simplest Case: A Constant Probability of Division	21
1.10	A Special Case: Cells in One-Dimensional Structured Tissues	22
2	The Equation $y'(x) = -ay(x) + a\alpha y(\alpha x)$	27

2.1	Introduction	27
2.2	Preliminaries	29
2.2.1	$y(0)$ and $y(\infty)$	29
2.2.2	Restrictions on y , α , and a	30
2.2.3	Uniqueness of the Solution	31
2.2.4	Moments of the SSD	32
2.3	Solution of the SSD Equation	33
2.4	Discussion	35
2.4.1	The Constant K	35
2.4.2	Properties of the Solution	36
2.4.3	An Example	37
2.4.4	The Solution for Extreme Values of α	38
2.4.5	The Form of the Time-dependent Number Density $n(x, t)$	42
3	Size-Structured Models for Cells Growing Exponentially	43
3.1	Introduction	43
3.2	Preliminaries	45
3.3	The case $b(x) = bx^k$	47
3.3.1	The Case $k \neq m^{-1}$	48
3.3.2	The Case $k = m^{-1}$	51
3.3.3	Discussion and Examples	52

3.4	A Minimum Size for Division: The Case $b(x) = bx^kH(x - x_1)$	56
3.4.1	Region 1, $x \geq x_1$	56
3.4.2	Region 2, $\frac{x_1}{\alpha} \leq x \leq x_1$	57
3.4.3	Region 3, $x \leq \frac{x_1}{\alpha}$	58
3.4.4	Discussion and Examples	58
3.5	A Minimum and Maximum Size for Cell Division	59
3.5.1	The Solution Method	60
3.5.2	An example	61
4	Cell Populations with Age and Size Structure	64
4.1	Part I: An Integral Equation for the Birth-size Distribution	65
4.1.1	Introduction: Size/Age and Size/Birth-size Distributions	65
4.1.2	Steady Size/birth-size Distributions	67
4.1.3	Growth Rate Proportional to Cell Size	69
4.1.4	Size, size/age, and birth-size distributions	71
4.1.5	A Fredholm Integral Equation for $\phi(s)$ and its Unique Solution	73
4.1.6	Discussion	74
4.2	Part II: Solving the Integral Equation	77
4.2.1	Constant cell division size	77
4.2.2	Hazard Rate Independent of Initial Cell Size	79
4.2.3	Cell Division Size Precisely Determined by Birth-size	83

4.2.4	Numerical Solution	89
4.2.5	Discussion	91
5	Existence, Uniqueness, and Stability of SSDs	94
5.1	Existence and Uniqueness	94
5.1.1	Square-integrability of the Kernel	96
5.1.2	Non-factorability of the Kernel	97
5.2	The Time-dependent Problem	99
5.2.1	Formulation and Simplification	99
5.2.2	Solution using Characteristics	101
5.2.3	The Region Influenced Directly by the Initial Condition	101
5.2.4	The Region Influenced by the Boundary Condition	102
5.3	Stability of the Size/Birth-size Distributions	104
5.3.1	The Laplace Transform of the Operator	104
5.3.2	Eigenvalues of the Operator $\hat{K}(\lambda)$	106
5.3.3	The Inverse Laplace Transform	108
5.4	Examples and Counter-examples	112
5.4.1	Some Stable Cases	112
5.4.2	Some Unstable Cases	113
A	Moments of a Limiting Distribution	120

A.1	Formulation as a Combinatoric Limit	120
A.2	Formulation Involving Polynomial Coefficients	122
A.3	An expression for $[p']f(p)$	123
A.4	Proof of the Main Result	125
A.5	Proof By Induction of the Expression for S_q	127
B	The case $b(x) = b$ with $g(x) = gx^k$	130
C	The General Equation $y'(x) = -p(x)y(x) + q(x)y(ax)$	132
D	Generalised Solutions of the Functional Differential Equation	136
	Bibliography	139

Chapter 1

Introduction and Model Formulation

1.1 Unstructured Population Models

Historically, the earliest population models developed were unstructured - they ignored the properties of individuals and considered only the total number of individuals in the population. In the eighteenth century, Malthus [35] analysed what we now term the human “population explosion”, using the unstructured model of populations which we now write as

$$\frac{dN}{dt}(t) = \gamma N(t), \quad (1.1)$$

where $N(t)$ is the total population at time t . The population’s intrinsic growth rate or *Malthusian parameter*, γ , is given by

$$\gamma = \beta - \mu, \quad (1.2)$$

where β is the population’s birth rate per unit time (per head of population), and μ is the corresponding death rate. If γ is independent of time, and $\gamma > 0$, then the population will grow exponentially for all time. Note that in this model, and throughout this thesis, it is assumed that there is no immigration or emigration of individuals.

An extension of this idea is to allow the Malthusian parameter, $\gamma = \beta - \mu$, to vary with time. For example, γ may be assumed to depend on the environment in some way, with

the population growing at a given instant if $\gamma > 0$ and contracting if $\gamma < 0$. It is possible to look back at historical records and deduce the Malthusian parameter for any given periods in the history of a population — not surprisingly, this turns out to be positive during the “good times”, and negative during wars and famines!

For a more predictive model, it is often assumed that γ is directly dependent on the total population $N(t)$, and therefore only indirectly dependent on t . For example, we may decide that γ should decrease as $N(t)$ increases (possibly because of crowding effects or competition for resources), in which case a differential equation of the form

$$\frac{dN}{dt} = \gamma \left(1 - \left(\frac{N(t)}{N_{\max}}\right)^\lambda\right) N(t) \quad (1.3)$$

may be appropriate, with $\lambda > 0$ so the intrinsic growth rate is negative if $N(t) > N_{\max}$. The intrinsic growth rate for small $N(t)$ is just γ . If $\lambda = 1$, then we have the usual form of the *logistic* equation first discussed by Verhulst [65] in 1838. The solution of (1.3) with $\lambda = 1$, in conjunction with the initial condition $N(0) = N_0$, is

$$N(t) = \frac{N_{\max}}{1 - A e^{\gamma t}}, \quad (1.4)$$

where

$$A = 1 - \frac{N_{\max}}{N_0}. \quad (1.5)$$

The various other extensions of the logistic and alternative unstructured continuous-time population models that have appeared during the last two centuries can generally also be regarded as variations on (1.1) in which γ is dependent either on time t explicitly or on the total population $N(t)$. One alternative which should be mentioned here because of the application it has found in biology generally, and in the study of tumor growth particularly, (Laird [32]; Simpson-Herren and Lloyd [51]), is the *Gompertz growth law*, proposed by Gompertz [12] in 1825. We can regard this model as one where the Malthusian parameter is proportional to the log of the ratio of the current population $N(t)$ to some maximum population size N_{\max} , so

$$\frac{dN}{dt} = \left(-\alpha \log\left(\frac{N(t)}{N_{\max}}\right)\right) N(t). \quad (1.6)$$

If we once again let N_0 be the population at time $t = 0$, then the solution is

$$N(t) = N_0 \left(\frac{N_{\max}}{N_0}\right)^{[1 - e^{-\alpha t}]}. \quad (1.7)$$

Unstructured population models, based on total population alone, are useful where the individuals in a population are indistinguishable or where the observed differences do not

appear to influence the processes of birth and death. However, this is not the case for the cell populations discussed later in this thesis, nor is it the case for human populations. Because of the interest in human population growth, where the death rates and birth rates are most obviously dependent on the age of individuals, the first *structured* population models to appear were those structured on *age*.

1.2 Age-Structured Populations

The obvious deficiency of unstructured population models is that they ignore the differences between individuals. For example, in animal and human populations it is clearly a better approximation to make the birth rate β dependent on the number of females of child-bearing age rather than on the total population. In order to do this, we need a model structured on age at least (the sex structure is often allowed for by ignoring the males altogether, and just modelling the female population!). Early work on age-structured populations was carried out by Euler in the 18th century (for an English translation see Smith and Keyfitz [54]), and in the early twentieth century by Lotka [34] and Sharpe and Lotka [50], with some mathematical rigour added in 1941 by Feller [11]. The problem was first formulated as a partial differential equation by McKendrick [36] in 1926, but it was not until the work of Scherbaum and Rasch [49] in 1957 and von Foerster [66] in 1959 that this approach was taken up again by mathematical demographers.

In this approach, we consider a continuous number density $n(a, t)$, such that at any time t , $\int_{a_1}^{a_2} n(a, t) da$ is the number of individuals with age a lying between a_1 and a_2 . Note that this approach requires that the numbers involved are in some sense "large", so that the approximation of the population by a continuous number density is reasonable. We assume that the proportions of individuals in any age range dying or giving birth are independent of time. It is then possible to define a death rate $\mu(a)$ and a birth rate (or "procreation rate") $\beta(a)$ such that $\mu(a)dt$ and $\beta(a)dt$ give the proportions of individuals of age a which die or give birth respectively in a short time period dt . Then for $t, a > 0$ we have a partial differential equation,

$$\frac{\partial n}{\partial t} + \frac{\partial n}{\partial a} = -\mu(a)n(a, t), \quad (1.8)$$

which can be regarded as a statement of number conservation. Equation (1.8) is known, somewhat unjustly, as "von Foerster's equation". The initial condition at time $t = 0$ is given by

$$n(a, 0) = n_0(a), \quad (1.9)$$

and the boundary condition or “renewal equation” at age $a = 0$ is given by

$$n(0, t) = \int_0^{\infty} \beta(a)n(a, t)da. \quad (1.10)$$

The book by Metz and Diekmann [37] discusses a wide range of structured population models, and has one chapter devoted exclusively to age-structured models. Age-structured models and the von Foerster equation are also discussed in Oster [39], and applications to cell populations are discussed by Trucco ([57], [58]) and Rubinow [46]. A more general approach would be to allow μ and β to depend on t as well (which caters for possible environmental changes), or on the total population $N(t)$ (Gurtin and Macamy [15]).

1.3 Populations Structured on Many Properties

Instead of considering a population structured on just one variable (such as age in the previous section), consider a population where the individuals are distinguished by say m properties, $\underline{x} = \{x_1 \dots x_m\}$. One of these properties may be age, as in the previous section, and others may include such things as mass, height or chemical content. Each individual is born with a set of values for these properties, which may depend in some way on the properties of the parent, then these properties change as time goes on.

In this thesis, attention is restricted to *continuous* properties of individuals only, by which we mean that between birth and death the properties of an individual change continuously. Following the ideas of the previous section, we define a continuous number density $n(\underline{x}, t)$ such that $\int_{\omega_{ab}} n(\underline{x}, t)d\underline{x}$, $\omega_{ab} = \{\underline{x}: x_a \leq x \leq x_b\}$, gives the number of individuals with properties in the range x_a to x_b . We will call the region in which it is possible for n to be non-zero Ω . Then given that there is no immigration or emigration, we can write a simple number balance at $\underline{x} \in \Omega$ symbolically as

$$\frac{\partial}{\partial t}n(\underline{x}, t) + \nabla \cdot \underline{F} = (\text{birth rate}) - (\text{death rate}), \quad (1.11)$$

where \underline{F} is the vector flux of individuals at \underline{x} in the m -dimensional property space. The birth and death rates are defined more clearly below.

One way of characterising continuous structured population models is according to whether the processes are *deterministic*, in the sense that they are completely determined by the properties of the individual \underline{x} and the time t , or whether they are in some sense *stochastic*. Processes we may wish to consider in this light are:

- **Growth rates**, or rates of change of each property x_i . Section 1.4 of this chapter looks briefly at the case where the growth of individuals is described as a stochastic process, but in the rest of this thesis it is assumed that the growth rate of the i th property of an individual is determined entirely by the individual's properties \underline{x} and the time t , so we may write the growth rate of the i th property as

$$\frac{dx_i}{dt} = g_i(\underline{x}, t). \quad (1.12)$$

- **Birth Rates**. Whether or not an adult will give birth will in general be dependent on its properties \underline{x} and time t . We will allow birth to be a stochastic process, by defining a birth rate $\beta(\underline{x}, t)$ such that $\beta(\underline{x}, t)dt$ gives the probability that an adult with properties \underline{x} at time t will give birth in the next short time interval dt . We show later that the case of deterministic birth of individuals can be regarded as a special case of this general case.
- **Death Rates**. We also treat death as a stochastic process, defining a death rate $\mu(\underline{x}, t)$ such that $\mu(\underline{x}, t)dt$ gives the probability that an adult with properties \underline{x} at time t will die in the next short time interval dt . Once again, deterministic death can be regarded as a special case of this general case.
- **Heredity**. Each new-born individual must be given a set of properties to begin with. If heredity were to be modelled deterministically, then the properties of the newborn individual would be precisely given by some function of the properties of the parent. Instead, we describe heredity in a stochastic manner, defining a heredity function $\eta(\underline{x}, \underline{s}, t)$ such that $\eta(\underline{x}, \underline{s}, t)d\underline{x}$ gives the expected number of offspring with properties in the range \underline{x} to $\underline{x} + d\underline{x}$ produced by an individual with properties \underline{s} giving birth at time t . This heredity function η is non-local in that it describes the properties of an individual at one point \underline{x} in the property space in terms of the properties of another point \underline{s} . Note that this formulation also means that the number of newborn individuals produced when an adult gives birth need not be deterministic.

We need to consider two possibilities with respect to newborn individuals:

- Newborn individuals may appear on a boundary of the region Ω . Usually this means that one of the variables is age, a , as in the previous section, and newborn individuals appear as a flux over the boundary at $a = 0$. In Chapter 4 we use a slightly different formulation in terms of birth-size instead of age, where newborn individuals appear on a boundary of a different type.

- Newborn individuals may appear throughout the region Ω . Usually this occurs when there is no age-like variable in the structured population model.

To simplify the following discussion we assume that all properties x_i are restricted to the region $[0, \infty)$, so $\Omega = [0, \infty) \times \dots \times [0, \infty)$.

1.3.1 Models with Age

Consider the case where all our functions are dependent on age a , time t , and m other variables $\underline{x} = (x_1, \dots, x_m)$. Hence we write $n(\underline{x}, a, t)$, $g_i(\underline{x}, a, t)$, $\beta(\underline{x}, a, t)$, $\mu(\underline{x}, a, t)$, and $\eta(\underline{x}, \underline{s}, a, t)$. In this case, in the region Ω the vector flux \underline{F} is given by $\underline{F} = \underline{g}(\underline{x}, a, t)n(\underline{x}, a, t)$, so the number conservation law (1.11) is written as the partial differential equation

$$\frac{\partial n}{\partial t} + \frac{\partial n}{\partial a} + \sum_{i=1}^m \frac{\partial}{\partial x_i} (g_i(\underline{x}, a, t)n) = -\mu(\underline{x}, a, t)n. \quad (1.13)$$

This equation is discussed in Oster and Takahashi [40], and a detailed derivation for the special case of populations structured on age a and one other variable x is given in Sinko and Streifer [52]. For a brief derivation of the general case, see Chapter 3 of Randolph and Larson [43]. Note that because birth occurs on the boundary of Ω , there is no source term on the right hand side of (1.13), and that the term containing the partial derivative with respect to a is particularly simple because $\frac{da}{dt} = 1$. The initial condition corresponding to this PDE should be given in the form

$$n(\underline{x}, a, 0) = n_0(\underline{x}, a). \quad (1.14)$$

The boundary condition (or “renewal equation”) at $a = 0$ may be written as

$$n(\underline{x}, 0, t) = \int_{\Omega} \beta(\underline{s}, a, t) \eta(\underline{x}, \underline{s}, a, t) n(\underline{s}, a, t) d\underline{s} da. \quad (1.15)$$

Fig. 1.1 shows why this is so diagrammatically for $m = 2$ — the number of individuals born in time dt with property 1 in the range x_1 to $x_1 + dx_1$ and property 2 in the range x_2 to $x_2 + dx_2$ is simply the number in the lower box (which has height dt because $\frac{da}{dt} = 1$), and this must equal the sum of the numbers of offspring from the individuals in all possible boxes like the upper one.

If a boundary condition is needed at any of the other boundaries of Ω , we simply use the zero flux conditions

$$g_i(\underline{x}, a, t)n(\underline{x}, a, t)|_{x_i=0} = g_i(\underline{x}, a, t)n(\underline{x}, a, t)|_{x_i=\infty} = 0, \quad i = 1, \dots, m. \quad (1.16)$$

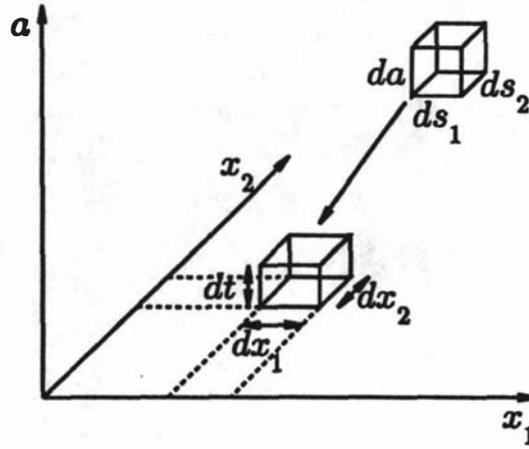


Figure 1.1: The number of new-born individuals appearing over the boundary $a = 0$ in time dt with properties in the range (x_1, x_2) to $(x_1 + dx_1, x_2 + dx_2)$ must equal the sum of all contributions from cells dividing in the appropriate proportions in the same time dt .

For large age, we use

$$n(x, \infty, t) = 0. \quad (1.17)$$

Note that in some population models, a *physiological* or *developmental* age is used instead of *chronological* age. Under this formulation, individuals are still all born with age zero, but some small changes need to be made to (1.13) and (1.15) because $\frac{da}{dt} \neq 1$ for physiological or developmental age. Van Sickle [64], Rubinow [47] and Sundareshan and Fundakowski [56] discuss models of this type, while Weiss [68] allows stochastic variation in the rate of change of physiological age.

1.3.2 Models without Age

If none of the relevant properties of individuals are age-like variables, then a source term is required on the right-hand side of the PDE corresponding to (1.13), but no boundary condition is necessary. The PDE becomes

$$\frac{\partial n}{\partial t} + \sum_{i=1}^m \frac{\partial}{\partial x_i} (g_i(x, t)n) = -\mu(x, t)n + \int_{\Omega} \beta(s, t)\eta(x, s, t)n(s, t)ds. \quad (1.18)$$

The last term in (1.18) comes from equating the number of newborn cells formed in time t in some small m -cube in m -dimensional property space to the sum of contributions from cells

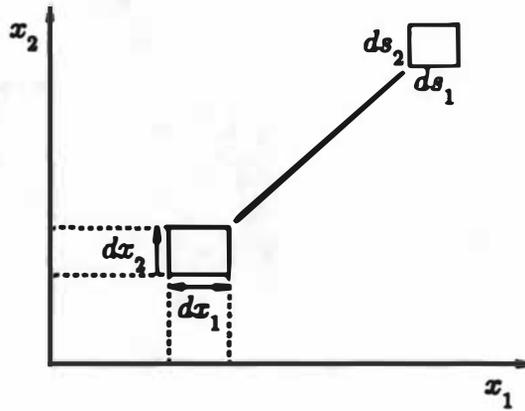


Figure 1.2: The number of new-born individuals appearing in some short time interval dt , with properties in the the range (x_1, x_2) to $(x_1 + dx_1, x_2 + dx_2)$, must equal the sum of all contributions from cells with properties (s_1, s_2) dividing in appropriate proportions in the same time dt .

anywhere in the space dividing in appropriate proportions. Fig. 1.2 shows the situation for $m = 2$, where the number of newborn cells formed in a short time dt with property 1 in the range x_1 to $x_1 + dx_1$ and property 2 in the range $x_2 + dx_2$ is equal to the sum of contributions from cells with any properties (s_1, s_2) dividing in time dt . Alternatively, (1.18) may be obtained by considering a model with age incorporated, but where the functions μ , β , f , and $g_i, i = 1, \dots, m$, are in fact independent of a . We can then integrate (1.13) over all age a , so that

$$\frac{\partial}{\partial t} \left(\int_0^\infty n da \right) + n(\underline{x}, \infty, t) - n(\underline{x}, 0, t) + \sum_{i=1}^m \frac{\partial}{\partial x_i} (g_i(\underline{x}, t) \int_0^\infty n da) = -\mu(\underline{x}, t) \int_0^\infty n da. \quad (1.19)$$

Now we use (1.15) and (1.17) to replace $n(\underline{x}, 0, t)$ and $n(\underline{x}, \infty, t)$ respectively, then replace $\int_0^\infty n(\underline{x}, a, t) da$ by $n(\underline{x}, t)$ to obtain (1.18).

Once again, if boundary conditions are required they are given by the zero-flux conditions

$$g_i(\underline{x}, t)n(\underline{x}, t)|_{x_i=0} = g_i(\underline{x}, t)n(\underline{x}, t)|_{x_i=\infty} = 0, \quad i = 1, \dots, m. \quad (1.20)$$

1.4 Population Models with Non-Deterministic Growth Rates

This thesis is concerned with steady size distributions arising in models of cell populations where birth, death, and heredity processes are stochastic, but growth rates are deterministic. However, it may be that there is experimental evidence showing significant variation

in the growth rates of individuals all with the same measured properties, and in this case the deterministic growth models discussed here would be inappropriate. In this section we take a brief look at the situation where the growth rate of individuals may be regarded as a stochastic process. The changes in a property are assumed to be *local* in the sense that the change in some time interval Δt must tend to zero as $\Delta t \rightarrow 0$.

Consider the growth rate of just one property of individuals, x say, which we will call size. To simplify notation we will write just $n(x, t)$. Then instead of writing the growth rate of x as $g(x)$, we choose some short time period Δt and for each x and t define a probability distribution $\gamma(x, t, \epsilon)$ such that $\gamma(x, t, \epsilon)d\epsilon$ gives the probability that an individual with size x at time t will increase size x by between ϵ and $\epsilon + d\epsilon$ in the next Δt . Then for any x and t , ignoring birth and death terms for the moment, we have

$$n(x, t + \Delta t) = \int_{-\infty}^{\infty} n(x - \epsilon, t) \gamma(x - \epsilon, t, \epsilon) d\epsilon. \quad (1.21)$$

Expanding the expression inside the integral as a partial Taylor series about $n(x, t)\gamma(x, t, \epsilon)$ gives

$$n(x, t + \Delta t) = \int_{-\infty}^{\infty} \left[n(x, t) \gamma(x, t, \epsilon) - \epsilon \frac{\partial}{\partial x} (n(x, t) \gamma(x, t, \epsilon)) + \frac{\epsilon^2}{2!} \frac{\partial^2}{\partial x^2} (n(x, t) \gamma(x, t, \epsilon)) - \dots \right] d\epsilon \quad (1.22)$$

We now assume that the probability density function γ is sharply peaked about its mean for each x and t , so that we may ignore terms of order higher than two. Changing the order of differentiation and integration then gives

$$n(x, t + \Delta t) = n(x, t) \int_{-\infty}^{\infty} \gamma(x, t, \epsilon) d\epsilon - \frac{\partial}{\partial x} \left[n(x, t) \int_{-\infty}^{\infty} \epsilon \gamma(x, t, \epsilon) d\epsilon \right] + \frac{1}{2} \frac{\partial^2}{\partial x^2} \left[n(x, t) \int_{-\infty}^{\infty} \epsilon^2 \gamma(x, t, \epsilon) d\epsilon \right] \quad (1.23)$$

Now to simplify notation we make the following substitutions, using $E[\]$ to indicate expected values for fixed x and t :

$$\int_{-\infty}^{\infty} \gamma(\epsilon) d\epsilon = 1 \quad (1.24)$$

$$\int_{-\infty}^{\infty} \epsilon \gamma(\epsilon) d\epsilon = E[\epsilon] \quad (1.25)$$

$$\int_{-\infty}^{\infty} \epsilon^2 \gamma(\epsilon) d\epsilon = E[\epsilon^2] \quad (1.26)$$

If we now include mortality and birth as in the deterministic case, writing $\mu(x, t)$, $\beta(x, t)$, and $\eta(x, s, t)$, (1.23) becomes

$$n(x, t + \Delta t) = n(x, t) - \frac{\partial}{\partial x} [(n(x, t)E[\epsilon])] + \frac{1}{2} \frac{\partial^2}{\partial x^2} [n(x, t)E[\epsilon^2]]$$

$$- \mu(x, t)n(x, t)\Delta t + \int_{\Omega} \beta(s, t)\eta(x, s, t)n(s, t)ds\Delta t, \quad (1.27)$$

so that

$$\begin{aligned} \frac{n(x, t + \Delta t) - n(x, t)}{\Delta t} = & - \frac{\partial}{\partial x} \left[(n(x, t) \frac{E[\epsilon]}{\Delta t}) \right] + \frac{1}{2} \frac{\partial^2}{\partial x^2} \left[n(x, t) \frac{E[\epsilon^2]}{\Delta t} \right] \\ & - \mu(x, t)n(x, t) + \int_{\Omega} \beta(s, t)\eta(x, s, t)n(s, t)ds. \end{aligned} \quad (1.28)$$

Now we let $\Delta t \rightarrow 0$ and define

$$g(x, t) = \lim_{\Delta t \rightarrow 0} \frac{E[\epsilon]}{\Delta t} \quad (1.29)$$

$$D(x, t) = \lim_{\Delta t \rightarrow 0} \frac{E[\epsilon^2]}{\Delta t} \quad (1.30)$$

so

$$\begin{aligned} \frac{\partial n}{\partial t} = & - \frac{\partial}{\partial x} [g(x, t)n(x, t)] + \frac{1}{2} \frac{\partial^2}{\partial x^2} [D(x, t)n(x, t)] \\ & - \mu(x, t)n(x, t) + \int_{\Omega} \beta(s, t)\eta(x, s, t)n(s, t)ds. \end{aligned} \quad (1.31)$$

This is in the form of a Fokker-Planck equation (Cox and Miller [8]), where $D(x, t)$ is called the *dispersion coefficient*, and $g(x, t)$ approximates the mean growth rate. This second order partial differential equation (1.31) incorporates stochastic birth and death, as in (1.18), as well as stochastic growth rates of individuals. The only difference between this model and the deterministic models we consider elsewhere in this thesis is the term involving the dispersion coefficient $D(x, t)$.

For an alternative but similar approach to deriving (1.31) in the context of structured populations, using the limit as $\Delta t \rightarrow 0$ of short finite transitions, see Ricciardi [44] or Weiss [68]. The book by Cox and Miller [8] discusses both this approach and an approach utilising Wiener processes in a more general context, and also contains a wider discussion of stochastic processes with the property that both the mean and variance are proportional to Δt , so the definitions (1.29) and (1.30) above make sense. For a more general model involving non-deterministic growth and transition probabilities, and another approach to deriving the Fokker-Planck equation, see Rotenberg [45].

In a “dispersion-like” model as described above, the growth rate of an individual is stochastic in nature and the trajectories of individuals with the same initial x value would be expected to cross and re-cross in $x - t$ space (Fig. 1.3(a)). Such a model would be inappropriate if the trajectories of individuals were more like those shown in Fig. 1.3(b). A more appropriate model in this case might be to hypothesise some extra property of

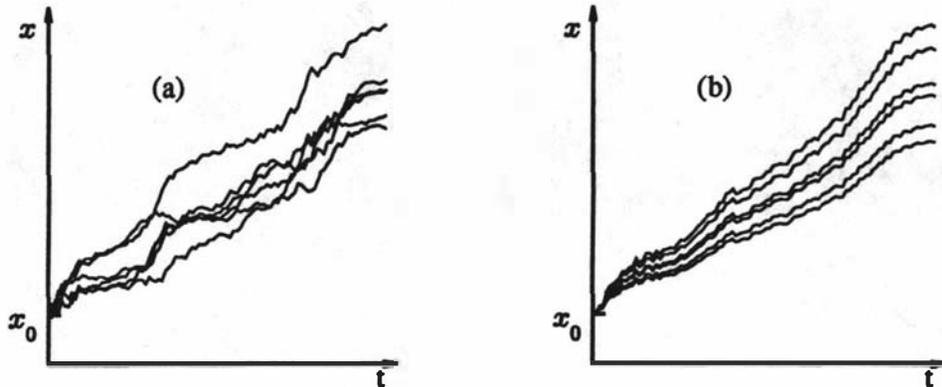


Figure 1.3: Sample trajectories of individuals with size x_0 at time $t = 0$. In case (a) the “dispersion-like” model given by (1.31) may be appropriate, whereas in (b) it would not.

individuals, previously unused, which affects the growth rate of x , and include this as an extra dimension in a deterministic model. However, additional information or hypotheses would then be required to describe how this new variable changes with time, and how it is passed onto newborn individuals, so this approach may not be feasible in many situations. Kirkpatrick [29] makes the same distinction, calling the case shown in Fig. 1.3(b) the *assignment at birth* growth model, and that shown in Fig. 1.3(a) the *variable growth* model.

1.5 Cell Population Models with Size Structure Only

In this thesis we will be concerned with populations of cells which reproduce by fission into two or more parts. During fission the original or parent cell disappears and is replaced by two or more newborn cells, called daughters.

We will call a property of a cell a *size* if it is conserved during cell division, in the sense that the sum of the sizes of the new-born daughter cells must equal the size of the original parent cell. Properties which could be called the size of a cell include mass, volume, quantity of DNA, or in some cases length. A size may only take on positive values. We will restrict our attention to cell populations structured on a single size variable l only, with a strictly positive growth rate which we write as $g_l(l, t) > 0, \forall l$. Our choice of the symbol l for the size variable here is motivated by the work in Chapter 4, where cell *length* is the size

variable chosen. We now write (1.18) as

$$\frac{\partial}{\partial t}n(l,t) + \frac{\partial}{\partial l}gl(l,t)n(l,t) = -\mu(l,t)n(l,t) + \int_0^\infty \beta(s,t)\eta(l,s,t)n(s,t)ds. \quad (1.32)$$

Size-structured models of cell populations were given prominence by a number of researchers in the 1960's, including Collins and Richmond [7], Koch and Schaechter [30], Powell [42] and Painter and Marr [41]. More recently, there has been the mini-review by Tyson [67], the papers by Koppes et al. [31] and Grover et al. [13], papers by Tyson and Diekmann [61] and Tyson and Hannsgen [62], and the book by Metz and Diekmann [37] which contains a good discussion of the special case of (1.32) where all cells divide exactly in half.

When a cell divides, it generally does not split into daughters all of the same size, although this is clearly one limiting case which should be considered (Metz and Diekmann [37]). Experimentally, the most important quantity in predicting the size of a daughter cell from the size of the parent is the *ratio* of the daughter size to the parent size. This suggests that instead of using the heredity function $\eta(l,s,t)$ for cells reproducing by fission, we should define a probability density function $f(p,l,t)$ such that $f(p,l,t)dp$ gives the probability that a particular daughter lies between fraction p and $p + dp$ of the parent cell size, given that the cell was derived from a parent which divided at time t and size l .

Now because p is the ratio of the size of a daughter cell to its parent, and we do not wish to allow negative cell sizes or daughters larger than the parent, we demand that the support of f as a function of p be some subset of $[0,1]$ for all l and t . Further, f is a probability distribution so for all l and t we must have $f(p,l,t) \geq 0, \forall p$ and also

$$\int_0^1 f(p,l,t)dp = 1. \quad (1.33)$$

Finally, conservation of size properties requires that if the mean number of cells formed when an adult cell of size l divides at time t is $\alpha(l,t)$, then we must have

$$\int_0^1 pf(p,l,t)dp = [\alpha(l,t)]^{-1}, \quad (1.34)$$

which requires $\alpha(l,t) > 1$. Note that it is often assumed that cells divide into exactly two parts, in which case α is given the value 2 for all l and t .

We note that $\eta(l,s,t)dl$ should give the average number of daughter cells with size l to $l + dl$ produced by a parent cell of size s at time t , which is terms of f is

$$\eta(l,s,t)dl = \alpha(s,t)f\left(\frac{l}{s},s,t\right)\frac{dl}{s}. \quad (1.35)$$

For simplicity, and because we are interested primarily in populations of cells which do not disappear or die by any mechanism other than fission, we assume that fission is the only way in which cells “die”. Hence the two separate functions β and μ as in Section 1.3 are unnecessary, and we simply define a function $b(l, t)$ such that $b(l, t)dt$ gives the probability that a cell of size l at time t will divide in the next short time interval dt . Using (1.35) and replacing $\beta(l, t)$ and $\mu(l, t)$ by $b(l, t)$, we write (1.32) as

$$\frac{\partial}{\partial t}n(l, t) + \frac{\partial}{\partial l}g_l(l, t)n(l, t) = -b(l, t)n(l, t) + \int_0^\infty b(s, t)\alpha(s, t)f\left(\frac{l}{s}, s, t\right)n(s, t)\frac{ds}{s}. \quad (1.36)$$

The equation given by Sinko and Streifer [53] for the special case where cells always divide into two pieces whose sizes are in some fixed ratio, can be obtained by substitution of the appropriate combination of Dirac delta functions into (1.36). Equation (1.36) is the most general form of the equation for the number density $n(l, t)$ in size-structured populations with deterministic growth and no cell death. However, noting as earlier that heredity is primarily dependent on the ratio of daughter to parent cell size, we assume throughout the remainder of this thesis that:

- The fractional-size pdf, f , is dependent only on the proportion p , so we may write $f(p)$ instead of $f(p, l, t)$. It then follows from (1.34) that α is a constant.

The PDE for a size-structured cell population with deterministic growth and stochastic division is thus

$$\frac{\partial}{\partial t}n(l, t) + \frac{\partial}{\partial l}g_l(l, t)n(l, t) = -b(l, t)n(l, t) + \alpha \int_0^\infty b(s, t)f\left(\frac{l}{s}\right)n(s, t)\frac{ds}{s}, \quad (1.37)$$

which must be solved subject to an initial condition

$$n(l, 0) = n_0(l) \quad (1.38)$$

and the zero-flux boundary condition

$$g_l(0, t)n(0, t) = g_l(\infty, t)n(\infty, t) = 0. \quad (1.39)$$

1.6 Steady Size Distributions

If we now define a hazard rate h_l such that $h_l(l, t)dl$ gives the probability that a cell which reaches size l at time t will divide before reaching size $l + dl$. Then

$$h_l(l, t)dl = b(l, t)dt, \quad (1.40)$$

$$h_l(l, t) = \frac{b(l, t)}{g(l, t)}, \quad (1.41)$$

where we know $g(l, t) > 0$.

Now we are interested in *steady size distributions* (SSDs) which can arise where the total number of cells in the population is increasing, but the proportion of the population in any given size range remains constant. This idea is familiar from the demographic literature, where distributions of such quantities as age and height in a population are regularly tabulated and graphed, and the shape of “steady” age distributions, which develop in the presence of time-independent birth and death rates, are studied (Keyfitz [28]). Steady size distributions have been studied extensively in the bacteriological literature (e.g. Collins and Richmond [7], Lasota and Mackey [33], Koch and Schaechter [30], Tyson and Hannsgen [63]). Fig. (1.4) is an example of a experimentally measured SSD, taken from Harvey et al [22].

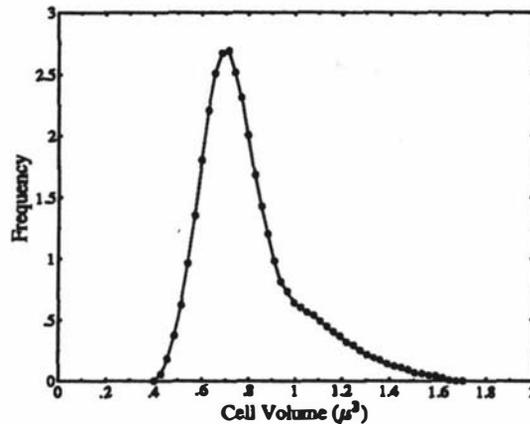


Figure 1.4: An experimentally measured steady size distribution (SSD) for *Escherichia coli* bacteria, taken from Harvey et al [22].

To find the equations governing the form of SSDs, we look for separable solutions of (1.37) such that

$$n(l, t) = N(t)y(l), \quad (1.42)$$

where $N(t)$ is the total cell population at time t , and $y(l)$ is a probability density function with

$$\int_0^{\infty} y(l)dl = 1, \quad (1.43)$$

and $y(l) \geq 0, \forall l$.

In order to find such separable solutions, we assume:

- The hazard rate is time-independent, so we may write $h_l(l)$ instead of $h_l(l, t)$
- The growth rate is separable with respect to time, so we may replace $g_l(l, t)$ by $g(l)r(t)$ say

These assumptions mean we restrict our attention to situations where environmental changes may increase or decrease the growth rate of all cells by the same proportion $r(t)$, but these changes have no effect on the size at which cells divide.

Given these assumptions, and making the substitutions $b(l, t) = h_l(l)g(l)r(t)$ from (1.41) and $n(l, t) = N(t)y(l)$ from (1.42), (1.37) becomes

$$\frac{dN}{dt}y(l) + r(t)N(t)\frac{d}{dl}g(l)y(l) = -r(t)N(t)h_l(l)g(l)y(l) + r(t)N(t)\alpha \int_0^\infty h_l(s)g(s)f\left(\frac{l}{s}\right)y(s)\frac{ds}{s}. \quad (1.44)$$

Separation of variables in this equation leads to

$$\frac{\frac{dN}{dt}}{r(t)N(t)} = \frac{-\frac{d}{dl}g(l)y(l) - h_l(l)g(l)y(l) + \alpha \int_0^\infty h_l(s)g(s)f\left(\frac{l}{s}\right)y(s)\frac{ds}{s}}{y(l)} \equiv Q. \quad (1.45)$$

An expression for the unknown Q may be obtained from the right hand equality here,

$$Qy(l) = -\frac{d}{dl}(g(l)y(l)) - h_l(l)g(l)y(l) + \alpha \int_0^\infty h_l(s)g(s)f\left(\frac{l}{s}\right)y(s)\frac{ds}{s}. \quad (1.46)$$

We now integrate over all l and apply the zero flux boundary condition which from (1.39) is

$$g(0)y(0) = g(\infty)y(\infty) = 0 \quad (1.47)$$

and the normalising condition (1.43) to obtain

$$Q = (\alpha - 1) \int_0^\infty h_l(l)g(l)y(l)dl. \quad (1.48)$$

Also from (1.45), we see that the growth rate of the population as a whole is dependent on this functional Q , with

$$\frac{dN}{dt} = Qr(t)N(t). \quad (1.49)$$

In the simplest case, where the growth rate of individuals is independent of time, we may set $r(t) = 1$ so Q becomes the exponential rate of growth of the population.

An alternative expression for Q may be obtained by considering the rate of increase of the total size of all the individuals in the population. This can be found either by integrating first over all sizes then differentiating with respect to t , or simply by integrating the growth rate over all individuals in the population. Equating these gives

$$\frac{d}{dt} \left[\int_0^{\infty} lN(t)y(l)dl \right] = \int_0^{\infty} N(t)y(l)g(l)dl, \quad (1.50)$$

or

$$\frac{dN}{dt} \left[\int_0^{\infty} ly(l)dl \right] = r(t)N(t) \int_0^{\infty} y(l)g(l)dl, \quad (1.51)$$

then using (1.49) we obtain

$$Q = \frac{\int_0^{\infty} g(l)y(l)dl}{\int_0^{\infty} ly(l)dl}, \quad (1.52)$$

so Q may also be regarded as ratio of the average growth rate of the individuals in the population to their average size.

Rearranging (1.46), the PDE for the SSD $y(l)$ becomes

$$\frac{d}{dl}g(l)y(l) = -(h_l(l)g(l) + Q)y(l) + \alpha \int_0^{\infty} h_l(s)g(s)f\left(\frac{l}{s}\right)y(s)\frac{ds}{s}, \quad (1.53)$$

which must be solved subject to the normalising condition (1.43) and the boundary condition (1.47). Note that (1.48) was deduced by integrating (1.46) and applying the normalisation (1.43) and the boundary condition (1.47), so (1.48) should be regarded as an alternative normalising condition rather than an independent equation. A non-zero normalisation condition of some sort is clearly necessary in order to obtain a non-trivial solution, because (1.53) is homogeneous and therefore admits the solution $y(l) \equiv 0$.

One special case is worth mentioning here, as it is used in both Chapter 2 and Chapter 3 and has been considered extensively in the literature (e.g. Sinko and Streifer [53], Koch and Schaechter [30]). If all cells divide into exactly α pieces each of the same size, we can write

$$f(p) = \delta(p - \alpha^{-1}), \quad (1.54)$$

where $\delta(p - \alpha^{-1})$ is a translated Dirac delta function. We thus obtain the functional differential equation

$$\frac{d}{dl}g(l)y(l) = -(h_l(l)g(l) + Q)y(l) + \alpha^2 h_l(\alpha l)g(\alpha l)y(\alpha l). \quad (1.55)$$

A more direct derivation of (1.55) is discussed in the book by Metz and Diekmann [37].

In Chapter 2, we solve this equation for the simplest possible case, where both g and h_l are constants, and in Chapter 3 the case where $g(l) = gl$ is considered along with various forms of $h_l(l)$. In Appendix D, a general method of solution is presented for equations of the form $y'(x) = -p(x)y(x) + q(x)y(ax)$, which could be used to solve (1.55) in any situation where Q is known.

1.7 Cell Populations with age and size structure

The case where an age variable is included along with a single size variable requires a similar set of definitions to the size-only case:

- $n(l, a, t)$ is the population number density, with $n(l, a, t)dlda$ giving the number of cells in the size range l to $l + dl$ and age range a to $a + da$ at time t .
- $g(l, a, t)$ is the growth rate of a cell of size l and age a at time t .
- $f(p)$ is a pdf such that $f(p)dp$ gives the probability that a particular daughter cell lies between fraction p and fraction $p + dp$ of the parent cell size.
- α , the average number of newborn cells formed when an adult divides, is then given by $\alpha = [\int_0^1 pf(p)dp]^{-1}$.
- $b(l, a, t)$ is the probability per unit time that an adult divides, so that $b(l, a, t)dt$ gives the probability that an adult cell of size l and age a at time t will divide in the next short time interval dt .

Using this notation, the pde for the number density $n(l, a, t)$ becomes (from (1.13))

$$\frac{\partial}{\partial t}n(l, a, t) + \frac{\partial}{\partial a}n(l, a, t) + \frac{\partial}{\partial l}g_l(l, a, t)n(l, a, t) = -b(l, a, t)n(l, a, t). \quad (1.56)$$

This equation is discussed by Heijmans [24], as well as in a review by Oster [38], and a detailed derivation is found in Webb [67]. The initial condition corresponding to (1.56) is given by

$$n(l, a, 0) = n_0(l, a), \quad (1.57)$$

and the zero flux boundary condition is

$$g_l(0, a, t)n(0, a, t) = g_l(\infty, a, t)n(\infty, a, t) = 0. \quad (1.58)$$

To obtain a renewal condition at age $a = 0$ corresponding to (1.35) we substitute $\eta(l, s, a, t) = \frac{a}{s}f(\frac{l}{s})$ into (1.15), giving

$$n(l, 0, t) = \alpha \int_0^\infty \int_0^\infty b(s, a, t) f\left(\frac{l}{s}\right) n(s, a, t) \frac{ds}{s} da. \quad (1.59)$$

Streifer [55] and Sinko and Streifer [52] contain good general discussions of size/age models, including forms of equations (1.56) and (1.59). Gyllenberg and Webb [17] discuss an elaboration of this model in which the cells are divided into populations of “quiescent” and “normal” cells.

1.8 Steady Size/Age Distributions

Corresponding to SSDs in the case of size-structured populations, *steady size/age distributions* can arise in a population of cells with size and age structure, where the proportion of cells in any given size and age range remains steady while the total population grows. This idea was first given prominence in a series of papers by Anderson, Bell and others in the late 1960's (Bell and Anderson [6], Anderson and Peterson [4], Bell [5], and Anderson et al [3]). Following the approach in section (1.6), we look for separable solutions of (1.56) such that

$$n(l, a, t) = N(t)y(l, a), \quad (1.60)$$

and we define the following:

- $N(t)$ is the total population at time t .
- $y(l, a)$ is the steady size/age distribution such that $y(l, a)dlda$ gives the proportion of cells in the size range l to $l + dl$ and the age range a to $a + da$, so

$$\int_0^\infty \int_0^\infty y(l, a)dlda = 1. \quad (1.61)$$

- $r(t)$ and $g(l, a)$ are, respectively, the time-varying and time-independent components of the separable growth rate $g_l(l, a, t)$, such that

$$g_l(l, a, t) = g(l, a)r(t). \quad (1.62)$$

- $h_l(l, a)$ is the time-independent hazard rate such that $h_l(l, a)dl$ gives the probability that a parent cell of size l and age a will divide before reaching size $l + dl$, so

$$h_l(l, a) = \frac{b(l, a, t)}{g(l, a)r(t)}. \quad (1.63)$$

Our assumption that h_l is independent of time is equivalent to assuming that b is proportional to $r(t)$.

Note that these definitions assume the same separability and time-independence properties used in Section 1.6.

Substituting (1.60), (1.62), and (1.63) into (1.56), we obtain

$$\frac{dN}{dt}y(l, a) + N(t)\frac{\partial y}{\partial a}(l, a) + r(t)N(t)\frac{\partial}{\partial l}g(l, a)y(l, a) = -r(t)N(t)h_l(l, a)g(l, a)y(l, a). \quad (1.64)$$

The zero-flux boundary condition (1.58) becomes

$$g(0, a)y(0, a) = g(\infty, a)y(\infty, a) = 0, \quad (1.65)$$

and the renewal condition (1.59) gives

$$y(l, 0) = r(t)\alpha \int_0^\infty \int_0^\infty h_l(s, a)g(s, a)y\left(\frac{l}{s}, a\right)\frac{ds}{s}da. \quad (1.66)$$

Separation of variables in (1.64) is not immediately possible as it was in the case where the population was structured on size only (equation (1.45)). This is reasonable, in the sense that we cannot expect separable solutions for $n(l, a, t)$ of the form given by (1.60) if the growth rate varies with time, because $\frac{dn}{dt} = 1$ implies that any variation of growth in size with time must also affect age structure. We proceed here assuming that $r(t) = 1$ so the growth rate of individuals is independent of time, but in later chapters we explore two more general ways of proceeding:

- In Chapter 4, we reformulate the problem so that instead of looking for steady size/age distributions, we look for steady size/birth-size distributions, which can exist in the presence of a separable time-dependent growth rate, then calculate the corresponding time-dependent size/age distribution from this.
- In Chapter 5, we use a transformed time variable with respect to which steady size/age distributions are possible.

Now setting

$$r(t) \equiv 1, \quad (1.67)$$

separation of variables in (1.64) leads to

$$\frac{\frac{dN}{dt}}{N(t)} = \frac{-\frac{\partial}{\partial a}y(l,a) - \frac{\partial}{\partial l}(g(l,a)y(l,a)) - h_l(l,a)g(l,a)y(l,a)}{y(l,a)} = Q. \quad (1.68)$$

An expression for the unknown constant Q may be obtained by rewriting the right hand equality as

$$Qy(l,a) = -\frac{\partial}{\partial a}y(l,a) - \frac{\partial}{\partial l}(g(l,a)y(l,a)) - h_l(l,a)g(l,a)y(l,a). \quad (1.69)$$

Proceeding as in Section 1.6, we integrate (1.69) over all l and a and apply the normalisation condition (1.61), the zero-flux condition (1.65), and the renewal condition (1.66) to obtain

$$Q = (\alpha - 1) \int_0^\infty \int_0^\infty h_l(l,a)g(l,a)y(l,a)dlda. \quad (1.70)$$

The exponential growth rate of the total population is simply Q , because

$$\frac{dN}{dt} = QN(t). \quad (1.71)$$

Once again, an alternative expression for Q may be obtained by considering the rate of increase of the total size of all the individuals in the population. Following the approach in Section 1.6, we have

$$\frac{d}{dt} \left[\int_0^\infty \int_0^\infty lN(t)y(l,a)dlda \right] = \int_0^\infty \int_0^\infty N(t)y(l,a)g(l,a)dlda, \quad (1.72)$$

or

$$\frac{dN}{dt} \left[\int_0^\infty \int_0^\infty ly(l,a)dlda \right] = N(t) \int_0^\infty \int_0^\infty y(l,a)g(l,a)dlda, \quad (1.73)$$

then using (1.71) we obtain

$$Q = \frac{\int_0^\infty \int_0^\infty g(l,a)y(l,a)dlda}{\int_0^\infty \int_0^\infty ly(l,a)dlda}, \quad (1.74)$$

so once again Q may be regarded as ratio of the average growth rate of the individuals in the population to their average size.

Rearranging (1.69), the PDE for the SSD $y(l)$ becomes

$$\frac{\partial}{\partial a}y(l,a) + \frac{\partial}{\partial l}g(l,a)y(l,a) = -(h_l(l,a)g(l,a) + Q)y(l,a), \quad (1.75)$$

and substituting $r(t) = 1$ into (1.66) the renewal condition at age $a = 0$ is

$$y(l,0) = \alpha \int_0^\infty \int_0^\infty h_l(s,a)f\left(\frac{l}{s}\right)g(s,a)y(s,a)\frac{ds}{s}da. \quad (1.76)$$

This system must be solved subject to the normalising condition (1.61), and the zero flux boundary condition (1.65).

In the special case where all cells divide exactly into α pieces each of the same size, we have

$$f(p) = \delta(p - \alpha^{-1}), \quad (1.77)$$

so the renewal condition may be written simply as

$$y(l, 0) = \alpha^2 \int_0^\infty h_l(\alpha l, a) g(\alpha l, a) y(\alpha l, a) da. \quad (1.78)$$

1.9 The Simplest Case: A Constant Probability of Division

A major difficulty in dealing with (1.53) or (1.75) is the presence of the functional Q . In general, finding Q is difficult, because it involves solving a transcendental equation, or some other iterative technique. For example, (1.53), or (1.75) in conjunction with (1.76), may be solved assuming a zero-flux boundary condition at $l = \infty$ to obtain a solution in terms of the unknown Q . To find Q we then apply the zero-flux boundary condition at $l = 0$, which gives in general a transcendental equation known as a characteristic equation (Gyllenberg [17]). This terminology is similar to that used in demography, where a "characteristic equation" is used to determine the intrinsic rate of growth of age-structured populations (Keyfitz [28]).

There appear to be just two situations in which Q can be known in advance. The first, simpler but less interesting case, arises when

$$h_l(l, a) g(l, a) = b, \quad (1.79)$$

or, in the case of populations structured on size alone,

$$h_l(l) g(l) = b, \quad (1.80)$$

where b is a constant. Note that this b is not the same as $b(l, a, t)$ and $b(l, t)$ defined in sections (1.7) and (1.5) respectively, as in this special case we have $b(l, a, t) = r(t)b$ and $b(l, t) = r(t)b$.

Using (1.79) or (1.80) and (1.48) or (1.70), along with the appropriate normalisation condition for y , we then have simply

$$Q = (\alpha - 1)b. \quad (1.81)$$

Chapter 2 and Appendix B deal with size-structured populations satisfying (1.80), in which each cell divides into α daughters all of the same size. In this case we substitute (1.81) into (1.55), giving the simple functional differential equation

$$\frac{d}{dl}g(l)y(l) = -bay(l) + b\alpha^2y(\alpha l). \quad (1.82)$$

In Chapter 2, a series solution is obtained for this equation in the special case where the growth rate g is a constant, and some interesting properties of the solution are outlined. In Appendix B, a series solution is obtained for the case where $g(l)$ is given by a power law.

1.10 A Special Case: Cells in One-Dimensional Structured Tissues

The second case in which Q may be evaluated immediately is the case where the time-independent component of the growth rate of cells is proportional to cell size, so that

$$g(l, a) = gl. \quad (1.83)$$

or, in the case of a population structured on size only,

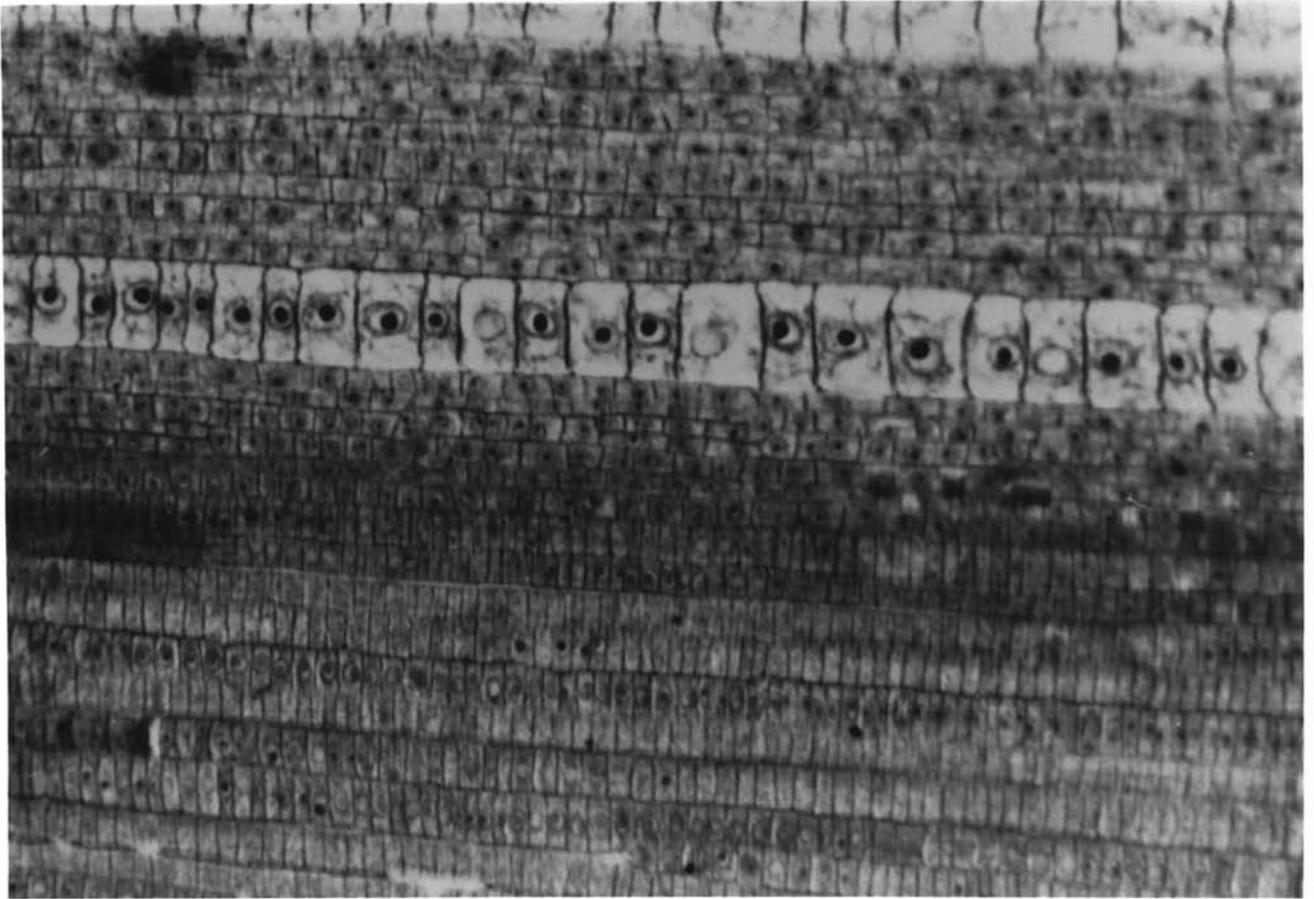
$$g(l) = gl, \quad (1.84)$$

where the g on the right hand side is a constant. The case where cells grow exponentially in size is a sub-case of this, with $r(t)$ a constant. The constant g is arbitrary, as a given cell growth rate g_l specifies what the product $r(t)g$ must be, but neither g nor $r(t)$ is specified uniquely. Indeed, we describe below a situation in which it is natural to choose $g = 1$.

To find Q with (1.83) or (1.84), we substitute into (1.74) or (1.52), respectively, to obtain

$$Q = g. \quad (1.85)$$

One situation in which (1.83) or (1.84) holds is of particular interest to plant scientists and others studying structured tissues. Fig. 1.5 shows a longitudinal section of part of the



←—————→
direction of growth

Figure 1.5: A longitudinal section of part of the meristem of a *Zea mays* root. This reproduction is taken from the data collected by Erickson for the classical paper by Erickson and Sax [9]. Growth of the tissue involves expansion in the direction shown, with cell division occurring by insertion of new cross-walls at right angles to the direction of growth.

meristem of a *Zea mays* root, which is typical of longitudinal sections from roots or leaves in a large number of plant species. Growth of the tissue occurs mainly by expansion in one direction, with cell division occurring by insertion of new cross-walls at right angles to this direction. For this reason we refer to tissues like that shown in Fig. (1.5) as *one-dimensional structured tissues*.

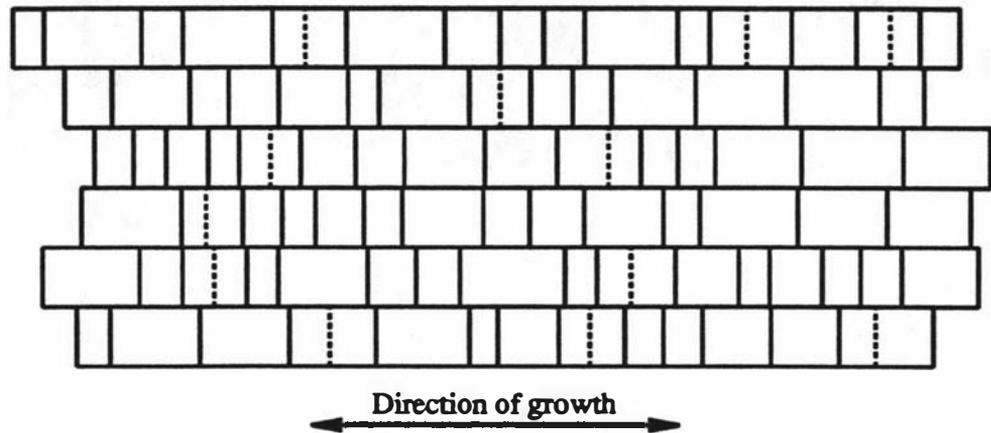


Figure 1.6: An idealised section of plant tissue growing by elongation in one dimension. Cells are arranged in files and are locked together by common longitudinal walls. When cells divide, new cross-walls (dashed lines) form within the parent cell, and two new cells are formed (i.e. $\alpha = 2$). We assume there are sufficient files at right angles to the direction of growth to allow use of continuous number density and probability density functions.

Fig. 1.6 shows an idealised section of a root or leaf, elongating in a spatially homogeneous manner such that any two points a unit distance apart separate at a time-varying rate $r(t)$. The assumption of spatial homogeneity will usually be applicable only to small regions of the growth zone; in large regions the rate of expansion $r(t)$ will vary spatially in the direction of growth shown. As can be seen from Fig. 1.5, different files of cells in a one-dimensional structured tissue may contain different types of cells. We restrict our attention here to files of cells of a single type, where the idealisation exemplified by Fig. 1.6 is a good approximation. We take the size of a cell to be its length, l , in the direction of growth. The important characteristic of a structured tissue in this context is that it grows symplastically, i.e. with longitudinal files of cells locked together so that cells in adjacent files do not slip past each other. This means that all cells in a small region can be assumed to grow at the same relative growth rate $r(t)$, so the growth rate for a cell of size l is

$$g_l(l, a, t) = lr(t), \quad (1.86)$$

or, for size-only models,

$$g_l(l, t) = lr(t). \quad (1.87)$$

The time-independent part of the growth rate is then given by (1.83) or (1.84) with constant $g = 1$.

There are other situations where the time-independent component of the cell growth rate is proportional to cell size. In populations of bacterial cells, an exponential growth rate of the form (1.83) or (1.84) has been assumed by Tyson and Diekmann [61], while experimental evidence shows that exponential growth in cell size is a good approximation for some types of bacteria (Schaechter et al [48], Grover et al [13], Painter and Marr [41]), but not for others (Harvey et al [22], Anderson et al [3], Collins and Richmond [7], Grover et al [13], Painter and Marr [41]).

In the case of a size-structured cell population, substitution of (1.84) and (1.85) into (1.53) leads to

$$l \frac{dy}{dl} = -(lh_l(l) + 2)y(l) + \alpha \int_0^\infty h_l(s) f\left(\frac{l}{s}\right) y(s) ds, \quad (1.88)$$

or in the case where all cells divide into exactly α pieces each of the same size, we obtain from (1.55) the functional differential equation

$$\frac{dy}{dl} = -(h_l(l) + \frac{2}{l})y(l) + \alpha^2 h_l(\alpha l)y(\alpha l). \quad (1.89)$$

In Chapter 3, (1.89) is solved subject to the normalisation condition (1.43), for a range of forms of the hazard rate $h_l(l)$.

For a population structured on size and age, we substitute (1.83) and (1.85) into (1.75) to obtain the partial differential equation

$$\frac{\partial y}{\partial a} + gl \frac{\partial y}{\partial l} = -(glh_l(l, a) + 2g)y(l, a), \quad (1.90)$$

and from (1.76) the renewal condition at $a = 0$ is

$$y(l, 0) = g\alpha \int_0^\infty \int_0^\infty h_l(s, a) f\left(\frac{l}{s}\right) y(s, a) ds da. \quad (1.91)$$

However, as pointed out in section (1.8), the solution of these equations for the steady size/age distribution $y(l, a)$ is valid only in the case where the growth rate of individuals is independent of time, so $r(t) = 1$ and the growth is strictly exponential. In Chapter 4 we reformulate the problem in terms of cell size and cell birth-size, instead of cell size and age, in order to obtain more widely applicable solutions.

In Chapter 5, we look at the question of whether the steady size, size/age, or size/birth-size distributions arising in this case are *stable*. In other words, given any initial distribution of cell size and age or birth-size, we look for conditions under which the size (or size/age or size/birth-size) distribution will approach the calculated steady distributions.

Chapter 2

The Equation $y'(x) = -ay(x) + a\alpha y(\alpha x)$

This chapter is a slight modification of a paper published in the *Journal of the Australian Mathematics Society, series B* (Hall and Wake [18]). The introduction has been abbreviated as most of this material is covered in Chapter 1 (particularly Sections 1.5, 1.6, and 1.9), but some extra mathematical detail, which was omitted in the paper for the sake of brevity, has been inserted into other sections. The notation used is the same as that used in Chapter 1 except that we use x instead of l to represent cell size.

2.1 Introduction

We consider here a cell population structured on one size variable x only, where each parent cell divides evenly to produce exactly α daughters all of the same size. Substituting $f(p) = \delta(p - \alpha^{-1})$ into (1.37) in Section 1.5, the partial differential equation for the number density $n(x, t)$ is

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

We now look for a *steady size distribution*, $y(x)$, which can develop under the conditions outlined in Section 1.6. After following the development in that section, we replace $h_t(l)g(l)$ in (1.55) by the single function $b(x)$ to obtain a functional differential equation for $y(x)$,

$$\frac{d}{dx}(g(x)y(x)) = -[b(x) + Q]y(x) + \alpha^2 b(\alpha x)y(\alpha x), \quad (2.2)$$

where Q is a functional on $y(x)$ given from (1.48) by

$$Q = (\alpha - 1) \int_0^{\infty} b(x)y(x)dx, \quad (2.3)$$

and y is a probability density function so must satisfy the normalisation condition

$$\int_0^{\infty} y(x)dx = 1. \quad (2.4)$$

The case we consider here is the simplest non-trivial case, with $b(x)$ and $g(x)$ both constants, say b and g respectively. As pointed out in Section 1.9, in the case where $b(x)$ is a constant the value of the functional Q can be calculated in advance from (2.3) to be

$$Q = (\alpha - 1)b. \quad (2.5)$$

While this case where g and b are both constants is not particularly realistic, its solution does offer some ideas which can be further explored in more realistic examples, as in Chapter 3. The equation to solve then becomes, after simplification using (2.4),

$$g \frac{dy}{dx} = -bay(x) + b\alpha^2y(ax), \quad (2.6)$$

which is just (1.82) with $g(l)$ replaced by the constant g .

Finally, assuming $g \neq 0$ we can substitute $a = \frac{gb}{g}$, forming the functional differential equation

$$\frac{dy}{dx} = -ay(x) + a\alpha y(ax), \quad (2.7)$$

which we wish to solve subject to the normalising condition (2.4) and a zero-flux boundary condition, which from (1.47) is written

$$y(0) = y(\infty) = 0. \quad (2.8)$$

Kato and Mcleod [27] have studied the equation $y'(x) = ay(\lambda x) + by(x)$ subject to the initial condition $y(0) = y_0$. Here we show how with the aid of the integral condition the solution can be obtained directly by application of the Laplace Transform technique, and that the application of the integral condition (2.4) (instead of the more usual *initial condition* $y(0) = y_0$) leads to a solution which can be regarded as a *probability density function* (pdf), which has a number of interesting properties not previously investigated. We do not

restrict our interest to the case $\alpha = 2$ which is usually used for cell growth, but rather treat (2.7) as an equation in which α can take on any real value $\alpha > 1$. Fractional values, $\alpha = \frac{p}{q}$ say, could be regarded as representing a combination of *fusion* processes, in which a number (q) of individuals fuse together to form one large entity, then this large entity divides into a number (p) of equal parts. We show that pure fusion processes, which would require $\alpha < 1$, cannot have a steady size distribution $y(x)$ satisfying (2.7).

2.2 Preliminaries

We now proceed to study the solution of (2.7) and (2.4) in the region $x \geq 0$, ignoring the manner in which these equations were derived. As a first step in this process, we note that we may restrict our attention to $\alpha > 0$, as $y(\alpha x)$ is undefined for $\alpha < 0$, and $\alpha = 0$ leads trivially to the simple solution $y = ae^{-ax}$. We may also assume $\alpha \neq 1$, as if $\alpha = 1$ then (2.7) reduces immediately to $y'(x) = 0$ which has no solutions satisfying (2.4).

We shall first derive necessary properties of the solution, assuming at this stage that it exists.

2.2.1 $y(0)$ and $y(\infty)$

Condition (2.4) does not directly provide us with the initial condition $y(0)$, but we can show that the realistic assumption $y(0) = y(\infty) = 0$ can be derived from (2.7) and (2.4) alone. If we integrate (2.7) then take limits as $x \rightarrow \infty$ we get

$$\begin{aligned}\lim_{x \rightarrow \infty} (y(x) - y(0)) &= \lim_{x \rightarrow \infty} (-a \int_0^x y(s) ds + a\alpha \int_0^x y(\alpha s) ds), \\ \lim_{x \rightarrow \infty} (y(x)) &= -a + a + y(0),\end{aligned}$$

and so

$$\lim_{x \rightarrow \infty} (y(x)) = y(0). \quad (2.9)$$

Now if $y(0) \neq 0$ then $y(\infty) \neq 0$ so $\int_0^\infty y(x) dx$ does not converge, contradicting (2.4). Hence we must have

$$y(0) = 0 \quad (2.10)$$

and

$$\lim_{x \rightarrow \infty} (y(x)) = 0. \quad (2.11)$$

The first of these results gives us the appropriate initial condition, and the second ensures that $y(x)$ is of exponential order so Laplace transforms can be applied.

It is interesting to note that if $y(0) = 0$, all derivatives of y are also zero at $x = 0$. This can be shown iteratively by first substituting $x = 0$ into (2.7) to show $y' = 0$, then differentiating (2.7) and substituting $x = 0$ to show $y'' = 0$, and so on. Hence the solution is “infinitely flat” and therefore not analytic at $x = 0$.

2.2.2 Restrictions on y , α , and a

Given $y(0) = y(\infty) = 0$, and $\int_0^\infty y(x) dx = 1 > 0$, it follows that $y(x)$ is positive for some range of x values. It therefore has a *maximum* at some point \bar{x} say, so from (2.7) we have

$$0 = -ay(\bar{x}) + a\alpha y(\alpha\bar{x}),$$

and so

$$y(\alpha\bar{x}) = \frac{y(\bar{x})}{\alpha}. \quad (2.12)$$

Hence for $\alpha < 1$ we would conclude $y(\alpha\bar{x}) > y(\bar{x})$ contradicting the assumption that y has its maximum at \bar{x} . Hence we must have

$$\alpha > 1, \quad (2.13)$$

and no SSD can exist in the *fusion* case, where $\alpha < 1$.

We can show $y(x) > 0$ ($\forall x > 0$) by considering the variable $Z(x) = \int_x^\infty y(s) ds$. Integrating equation (2.7) leads to

$$\int_x^\infty y'(s) ds = -aZ(x) + a\alpha \int_x^\infty y(\alpha s) ds,$$

so

$$Z'(x) = -aZ(x) + aZ(\alpha x). \quad (2.14)$$

This is subject of course to the conditions $Z(0) = 1$ (from (2.4)) and $Z(\infty) = 0$.

Assume for the moment that there exists a point $x_1 \in (0, \infty)$ at which $Z'(x_1) = -y(x_1) = 0$, and $Z(x_1) \neq 0$. Then $Z(\alpha x_1) = Z(x_1)$ and there must be a point $x_2 \geq \alpha x_1$ such that $Z'(x_2) = 0$ and $|Z(x_2)| \geq |Z(x_1)|$.

Without loss of generality, assume $Z(x_1) > 0$. Then one of the following must hold:

- (a) $Z'(\alpha x_1) > 0$ in which case such a x_2 must exist, or
- (b) $Z'(\alpha x_1) = 0$ so we can choose $x_2 = \alpha x_1$, or
- (c) $Z'(\alpha x_1) < 0$ so $\exists x^* \in (x_1, \alpha x_1)$ such that $Z'(x^*) = 0$ and $Z(x^*) > Z(x_1)$, so $Z(\alpha x^*) > Z(\alpha x_1)$ also. Then we have $\alpha x_1 < \alpha x^* < \infty$ but $Z(\alpha x^*) > Z(\alpha x_1)$ and $Z(\alpha x^*) > Z(\infty)$, so there must be some point $x_2 > \alpha x_1$ where $Z'(x_2) = 0$ and $Z(x_2) > Z(x_1)$ as required.

The argument for $Z(x_1) < 0$ is almost identical. Hence we can find a sequence of points $(x_n) \rightarrow \infty$ as $n \rightarrow \infty$, at which $Z'(x_n) = 0$, whose images under the function Z , $(Z(x_n)) \not\rightarrow 0$. This contradicts $Z(\infty) = 0$, so it follows that Z has no non-zero stationary points on $(0, \infty)$, so Z is monotonically decreasing with $Z'(x) \leq 0$ ($\forall x > 0$). As $y(x) = -Z'(x)$ we have for $x > 0$

$$y(x) \geq 0, \tag{2.15}$$

so $y(x)$ is a *probability density function* as desired.

Now equation (2.7) can be written as the integral equation

$$y(x) = a \int_x^{\alpha x} y(s) ds, \tag{2.16}$$

so as $y(x) > 0$, a necessary condition for the existence of an SSD must be

$$a > 0. \tag{2.17}$$

2.2.3 Uniqueness of the Solution

Let there be two solutions to (2.7) and (2.4), $y_1(x)$ and $y_2(x)$. Then the variable $Z(x) = \int_x^{\infty} (y_1(s) - y_2(s)) ds$ must satisfy equation (2.14) but this time with the conditions $Z(0) = 0$ and $Z(\infty) = 0$. Now if $Z(x) \neq 0$ for any x , then there must be a stationary point x_1 of Z such

that $Z(x_1) \neq 0$, which by a similar argument to that given above leads to a contradiction. Hence we have $Z(x) \equiv 0$ so $Z'(x) \equiv 0$ and

$$y_1(x) \equiv y_2(x), \quad (2.18)$$

so there can be at most one solution to (2.7) and (2.4).

2.2.4 Moments of the SSD

Because of the integral condition (2.4), it is in fact easier to find the *moments* of the SSD than the function $y(x)$ itself. The n th moment of $y(x)$ about the origin is

$$\mu_n = \int_0^{\infty} x^n y(x) dx \quad (2.19)$$

so we multiply (2.7) by x^n and integrate, giving

$$\int_0^{\infty} x^n y'(x) dx = -a\mu_n + a\alpha \int_0^{\infty} x^n y(\alpha x) dx \quad (2.20)$$

and

$$-n\mu_{n-1} = -a\mu_n + \frac{a}{\alpha^n} \mu_n, \quad (2.21)$$

where we have used integration by parts on the left and the substitution $z = \alpha x$ on the right. This procedure is equivalent to taking the *Mellin Transform* of each side if the equation. We now rearrange (2.21) to obtain an iterative equation for μ_n ,

$$\mu_n = \frac{n}{a(1 - \alpha^{-n})} \mu_{n-1}, \quad (2.22)$$

with from (2.4),

$$\mu_0 = 1. \quad (2.23)$$

Now iterating n times, the n th moment of y about the origin is given by

$$\mu_n = \frac{n!}{a^n \prod_{k=1}^n (1 - \alpha^{-k})}. \quad (2.24)$$

Hence the mean cell size, μ , is given by

$$\mu = \frac{1}{a(1 - \alpha^{-1})}, \quad (2.25)$$

and the variance of the cell size, σ^2 , is

$$\sigma^2 = \frac{1}{a^2(1 - \alpha^{-2})}. \quad (2.26)$$

The third moment about the mean, m_3 , can be shown from (2.24) to be

$$m_3 = \frac{2}{a^3(1 - \alpha^{-3})}. \quad (2.27)$$

so the coefficient of skewness $\sqrt{\beta_1}$ is given by

$$\sqrt{\beta_1} = \frac{m_3}{\sigma^3} = \frac{2(\alpha + 1)\sqrt{\alpha^2 - 1}}{\alpha^2 + \alpha + 1}. \quad (2.28)$$

Thus the coefficient of skewness is dependent on α only.

2.3 Solution of the SSD Equation

We now establish that equations (2.7) and (2.4) have a solution, which by section (2.2.3) is unique. We first take Laplace transforms of each side of (2.7), remembering $y(0) = 0$, giving

$$p\bar{y}(p) = a\alpha \int_0^\infty e^{-px}y(\alpha x)dx - a\bar{y}(p), \quad (2.29)$$

so

$$p\bar{y}(p) = a\bar{y}\left(\frac{p}{\alpha}\right) - a\bar{y}(p). \quad (2.30)$$

Thus we have an iterative equation with an initial value given by the integral condition (2.4),

$$\bar{y}(p) = \frac{1}{1 + \frac{p}{a}}\bar{y}\left(\frac{p}{\alpha}\right), \quad (2.31)$$

with

$$\bar{y}(0) = 1. \quad (2.32)$$

Iterating $n + 1$ times, we get

$$\bar{y}(p) = \frac{1}{\left(1 + \frac{p}{a}\right)\left(1 + \frac{p}{a\alpha}\right)\dots\left(1 + \frac{p}{a\alpha^n}\right)}\bar{y}\left(\frac{p}{\alpha^{n+1}}\right). \quad (2.33)$$

Now as $\alpha > 1$ we know that

$$\lim_{n \rightarrow \infty} \bar{y}\left(\frac{p}{\alpha^{n+1}}\right) = \bar{y}(0) = 1, \quad (2.34)$$

so we get

$$\bar{y}(p) = \lim_{N \rightarrow \infty} \prod_{n=0}^N \frac{1}{(1 + \alpha^{-n} \frac{p}{\alpha})}. \quad (2.35)$$

Expressing this product as a sum of partial fractions we can write

$$\prod_{n=0}^N \frac{1}{(1 + \alpha^{-n} \frac{p}{\alpha})} = \sum_{n=0}^N \frac{Q_n(-a\alpha^n)}{(1 + \alpha^{-n} \frac{p}{\alpha})}, \quad (2.36)$$

where $Q_n(p)$ is the product on the left hand side of this equation *excluding* the factor involving α^{-n} . Thus,

$$Q_n(p) = \frac{1}{(1 + \frac{p}{\alpha})(1 + \alpha^{-1} \frac{p}{\alpha}) \dots (1 + \alpha^{-(n-1)} \frac{p}{\alpha})(1 + \alpha^{-(n+1)} \frac{p}{\alpha}) \dots (1 + \alpha^{-N} \frac{p}{\alpha})} \quad (2.37)$$

and

$$Q_n(-a\alpha^n) = \frac{1}{(1 - \alpha^n)(1 - \alpha^{n-1}) \dots (1 - \alpha)(1 - \alpha^{-1})(1 - \alpha^{-2}) \dots (1 - \alpha^{-(N-n)})}. \quad (2.38)$$

Simplifying and taking limits, we get

$$\bar{y}(p) = \frac{1}{K} \sum_{n=0}^{\infty} \frac{1}{(1 - \alpha)(1 - \alpha^2) \dots (1 - \alpha^n)} \frac{1}{(1 + \alpha^{-n} \frac{p}{\alpha})}, \quad (2.39)$$

where the product in the denominator is given the value 1 when $n = 0$, and

$$K = \prod_{n=1}^{\infty} (1 - \alpha^{-n}). \quad (2.40)$$

Now taking the inverse Laplace transform term by term we get

$$y(x) = \frac{1}{K} \sum_{n=0}^{\infty} \frac{1}{(1 - \alpha)(1 - \alpha^2) \dots (1 - \alpha^n)} a\alpha^n e^{-a\alpha^n x}, \quad (2.41)$$

so noting that $\alpha > 1$, we write

$$y(x) = \frac{a}{K} \sum_{n=0}^{\infty} \frac{(-1)^n \alpha^n e^{-a\alpha^n x}}{(\alpha - 1)(\alpha^2 - 1) \dots (\alpha^n - 1)}. \quad (2.42)$$

This solution is in the same general form as that given by Kato and McLeod [27], but we have simplified the notation slightly by using the convention that when $n = 0$, the empty product in the denominator is given the value 1.

2.4 Discussion

2.4.1 The Constant K

The infinite product in (2.40), which gives the value of K , has been studied in some depth by number theorists and others. Perhaps the best known result involving this product, and one which offers a rapidly convergent way of calculating K , is *Euler's Pentagonal Number Theorem* (Andrews [2]). This is

$$\begin{aligned} \prod_{n=1}^{\infty} (1 - q^n) &= \sum_{n=-\infty}^{\infty} (-1)^n q^{\frac{n(3n-1)}{2}} \\ &= 1 - (q + q^2) + (q^5 + q^7) - (q^{12} + q^{15}) + \dots \end{aligned} \quad (2.43)$$

where $|q| < 1$, so we have

$$K = 1 - (\alpha^{-1} + \alpha^{-2}) + (\alpha^{-5} + \alpha^{-7}) - (\alpha^{-12} + \alpha^{-15}) + \dots \quad (2.44)$$

Another interesting (and rapidly convergent) series for K can be deduced by substituting $p = 0$ in (2.39) and using (2.32), giving

$$K = \sum_{n=0}^{\infty} \frac{(-1)^n}{(\alpha - 1)(\alpha^2 - 1)\dots(\alpha^n - 1)}, \quad (2.45)$$

which could also have been deduced by substitution of $q = \alpha^{-1}$ and $z = -q$ in

$$\sum_{n=0}^{\infty} \frac{q^{\frac{1}{2}n(n-1)} z^n}{(1 - q)(1 - q^2)\dots(1 - q^n)} = \prod_{n=0}^{\infty} (1 + zq^n), \quad (2.46)$$

which is also given by Andrews [2]. Once again, we are using the convention that the product in the denominator is given the value 1 when $n = 0$.

Another expression for K , but one we do not actually use here, can be derived from a formula involving Jacobian elliptic functions. Formula 16.37.1 in Abramowitz and Stegun [1] leads to

$$\prod_{n=1}^{\infty} (1 - q^{2n}) = \pi \left[\frac{m(m-1)}{16q} \right]^{\frac{1}{12}}, \quad (2.47)$$

which could be used to calculate K if we make the substitution $q = \alpha^{-\frac{1}{2}}$. This transfers the problem to relating the elliptic function parameter m to the nome q , which is possible via Landen's transformation.

2.4.2 Properties of the Solution

From a cursory inspection of (2.42) alone, it is not at all obvious that $y(x)$ satisfies all the properties that we deduced earlier it must have.

Firstly, we calculate $y(0)$ by substituting $x = 0$ in equation (2.42), which leads to

$$y(0) = \frac{a}{K} \sum_{n=0}^{\infty} \frac{(-1)^n \alpha^n}{(\alpha - 1)(\alpha^2 - 1) \dots (\alpha^n - 1)}. \quad (2.48)$$

Consider the finite form of the sum on the right hand side. Expanding the α^n in the numerator as $(\alpha^n - 1) + 1$, we get

$$\begin{aligned} & \sum_{n=0}^N \frac{(-1)^n \alpha^n}{(\alpha - 1)(\alpha^2 - 1) \dots (\alpha^n - 1)} \\ &= \sum_{n=0}^N \frac{(-1)^n (\alpha^n - 1)}{(\alpha - 1)(\alpha^2 - 1) \dots (\alpha^n - 1)} + \sum_{n=0}^N \frac{(-1)^n}{(\alpha - 1)(\alpha^2 - 1) \dots (\alpha^n - 1)}. \end{aligned} \quad (2.49)$$

We then drop the first term in the first sum on the right (which is zero), which means that we can cancel $(\alpha^n - 1)$ from numerator and denominator then change the summation variable to $m = n - 1$ so

$$\begin{aligned} & \sum_{n=0}^N \frac{(-1)^n \alpha^n}{(\alpha - 1)(\alpha^2 - 1) \dots (\alpha^n - 1)} \\ &= - \sum_{m=0}^{N-1} \frac{(-1)^m}{(\alpha - 1)(\alpha^2 - 1) \dots (\alpha^m - 1)} + \sum_{n=0}^N \frac{(-1)^n}{(\alpha - 1)(\alpha^2 - 1) \dots (\alpha^n - 1)} \\ &= \frac{(-1)^N}{(\alpha - 1)(\alpha^2 - 1) \dots (\alpha^N - 1)}. \end{aligned} \quad (2.50)$$

Taking limits as $N \rightarrow \infty$, by substituting (2.50) into (2.48) we have

$$y(0) = \frac{a}{K} \lim_{N \rightarrow \infty} \frac{(-1)^N}{(\alpha - 1)(\alpha^2 - 1) \dots (\alpha^N - 1)} = 0, \quad (2.51)$$

because $\alpha > 1$, so the denominator grows without limit as $N \rightarrow \infty$.

To verify by substitution that (2.42) satisfies the integral condition (2.4), we interchange the integral and summation signs (which is valid in view of the uniform convergence of the series), so

$$\begin{aligned} \int_0^{\infty} y(x) dx &= \frac{a}{K} \int_0^{\infty} \sum_{n=0}^{\infty} \frac{(-1)^n \alpha^n e^{-a\alpha^n x}}{(\alpha - 1)(\alpha^2 - 1) \dots (\alpha^n - 1)} \\ &= \frac{1}{K} \sum_{n=0}^{\infty} \frac{(-1)^n}{(\alpha - 1)(\alpha^2 - 1) \dots (\alpha^n - 1)}, \end{aligned}$$

then apply (2.45), giving

$$\int_0^{\infty} y(x) dx = 1 \quad (2.52)$$

as required.

Verifying the expression for the n th moment (2.24) by direct substitution of (2.42) in $\mu_n = \int_0^{\infty} x^n y(x) dx$ requires a similar interchange of order,

$$\begin{aligned} \mu_n &= \int_0^{\infty} x^n y(x) dx \\ &= \frac{a}{K} \sum_{m=0}^{\infty} \frac{(-1)^m \alpha^m}{(\alpha-1)(\alpha^2-1)\dots(\alpha^m-1)} \int_0^{\infty} x^n e^{-a\alpha^m x} dx \\ &= \frac{n!}{K\alpha^n} \sum_{m=0}^{\infty} \frac{(-1)^m}{(\alpha-1)(\alpha^2-1)\dots(\alpha^m-1)\alpha^{mn}}. \end{aligned}$$

We now apply (2.46) with $z = -\alpha^{-(n+1)}$ and $q = \alpha^{-1}$ then simplify further using (2.40), which gives

$$\begin{aligned} \mu_n &= \frac{n!}{K\alpha^n} \prod_{m=0}^{\infty} (1 - \alpha^{-(m+n+1)}) \\ &= \frac{n!}{\alpha^n (1 - \alpha^{-1})(1 - \alpha^{-2})\dots(1 - \alpha^{-n})}, \end{aligned} \quad (2.53)$$

as required.

2.4.3 An Example

Consider a population of cells undergoing binary fission ($\alpha = 2$) with a constant growth rate g of 0.2 size units per second, and a division rate b of 0.1 per cell per second. Then

$$a = \frac{b\alpha}{g} = 1$$

and

$$\begin{aligned} K &= \prod_{n=1}^{\infty} \left(1 - \frac{1}{2^n}\right) \\ &= 1 - \left(\frac{1}{2} + \frac{1}{4}\right) + \left(\frac{1}{32} + \frac{1}{128}\right) - \left(\frac{1}{4096} + \frac{1}{32768}\right) + \dots \\ &\approx .288788. \end{aligned}$$

The mean, variance, and coefficient of skewness of the SSD are obtained by substitution in (2.25), (2.26), and (2.28) respectively, giving

$$\mu = 2, \tag{2.54}$$

$$\sigma^2 = \frac{4}{3} \approx 1.3333, \tag{2.55}$$

$$\text{and } \sqrt{\beta_1} = \frac{6\sqrt{3}}{7} \approx 1.4846. \tag{2.56}$$

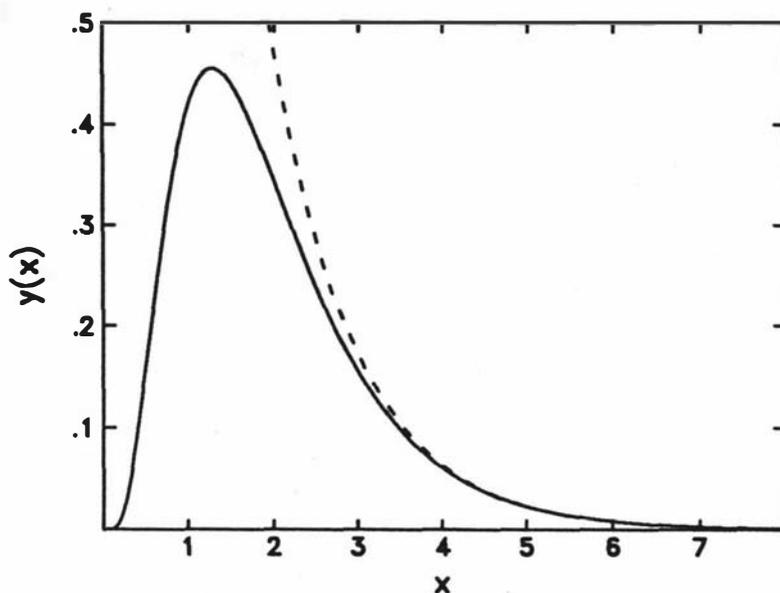


Figure 2.1: The solution for $a = 1$ and $\alpha = 2$. The dashed line is the graph of $y(x) = \frac{a}{x} e^{-\alpha x}$.

Figure 2.1 shows the shape of the SSD function $y(x)$ in this case as given by (2.42).

The qualitative features of Figure 2.1 remain for all a and α . The parameter a acts as a simple scaling factor for x (the substitutions $t = \alpha x$ and $z(t) = y(x)$ make equation (2.7) independent of a). Equation (2.28) shows that the coefficient of skewness is always positive, increasing from 0 to 2 as α increases from 1 to ∞ .

2.4.4 The Solution for Extreme Values of α

In the light of the comments at the end of the example, it is worth considering the form of the solution when $\alpha \rightarrow \infty$ and $\alpha \rightarrow 1^+$. The first is easy — if we write (2.42) in a form

similar to that given in Kato and McLeod [27], namely

$$y(x) = \frac{a}{K} e^{-ax} \left(1 + \sum_{n=1}^{\infty} \frac{(-1)^n \alpha^n e^{-a(\alpha^n - 1)x}}{(\alpha - 1)(\alpha^2 - 1) \dots (\alpha^n - 1)} \right), \quad (2.57)$$

then it is clear that for all α , $y(x) \approx \frac{a}{K} e^{-ax}$ for large x , and that in particular for all $x > 0$ we have

$$\lim_{\alpha \rightarrow \infty} y(x) = \frac{a}{K} e^{-ax}. \quad (2.58)$$

Hence in the limit as $\alpha \rightarrow \infty$, $y(x)$ approaches an *exponential* pdf with parameter a .

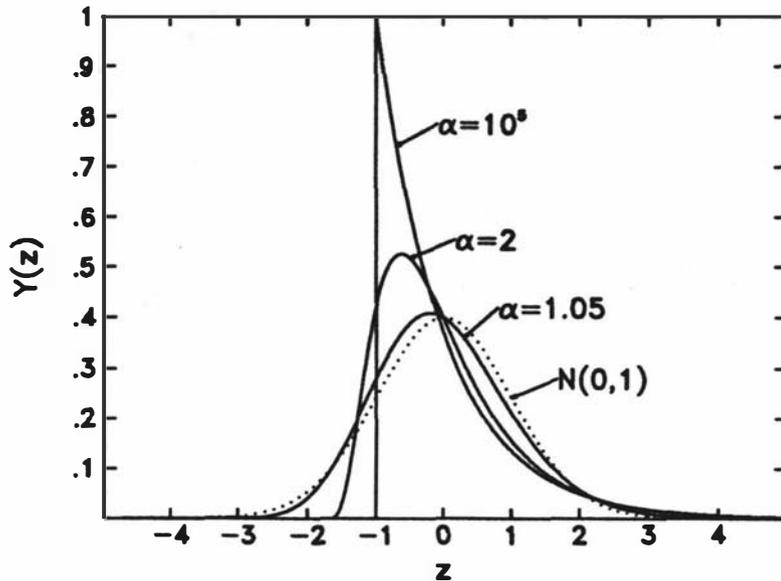


Figure 2.2: The normalised pdf $Y(z) = \sigma y(\sigma z + \mu)$ for various values of α . The dashed line is the pdf of the standard normal distribution.

The limit as $\alpha \rightarrow 1^+$ is much more difficult. Inspection of (2.42) shows that each term in the series becomes infinite as $\alpha \rightarrow 1^+$, and (2.24) shows that all the moments become infinite as well. This suggests that we “normalise” the equation using the transformation

$$z = \frac{x - \mu}{\sigma} \quad (2.59)$$

and

$$Y(z) = \sigma y(x), \quad (2.60)$$

where μ and σ are given by (2.25) and (2.26).

Figure 2.2, which shows $Y(z)$ plotted for various values of α , suggests that in the limit as $\alpha \rightarrow 1^+$, $Y(z)$ approaches the pdf of the standard normal distribution $N(0,1)$.

Substituting (2.60) and (2.59) into (2.4), Y must satisfy the normalisation condition

$$\int_{-\frac{\mu}{\sigma}}^{\infty} Y(z) dz = 1. \quad (2.61)$$

Now differentiating (2.60) and (2.59), we get

$$y'(x) = \frac{Y'(z)}{\sigma^2}, \quad (2.62)$$

and making the appropriate substitutions in $y(\alpha x) = Y(z(\alpha x))$ we have

$$y(\alpha x) = \frac{Y(\alpha z + (\alpha - 1)\frac{\mu}{\sigma})}{\sigma}. \quad (2.63)$$

Now substituting (2.62) and (2.63) into (2.7) we obtain

$$\frac{Y'(z)}{\sigma^2} = -a \frac{Y(z)}{\sigma} + \alpha a \frac{Y(\alpha z + (\alpha - 1)\frac{\mu}{\sigma})}{\sigma}, \quad (2.64)$$

which after substitution for μ and σ using (2.25) and (2.26) gives "normalised" functional differential equation

$$Y'(z) = \frac{\alpha}{\sqrt{\alpha^2 - 1}} [\alpha Y(\alpha z + \sqrt{\alpha^2 - 1}) - Y(z)]. \quad (2.65)$$

Now to find out what happens as $\alpha \rightarrow 1^+$, we expand the $Y(\alpha z + \sqrt{\alpha^2 - 1})$ as a Taylor series about $Y(z)$ up to all terms of order $(\alpha - 1)$, giving

$$Y(\alpha z + \sqrt{\alpha^2 - 1}) = Y(z + [(\alpha - 1)z + \sqrt{\alpha^2 - 1}]), \quad (2.66)$$

so

$$Y(\alpha z + \sqrt{\alpha^2 - 1}) \approx Y(z) + [(\alpha - 1)z + \sqrt{\alpha^2 - 1}]Y'(z) + \frac{\alpha^2 - 1}{2}Y''(z). \quad (2.67)$$

Substituting this expression into (2.65) and simplifying, we get

$$\alpha Y(z) + \alpha^2 z Y'(z) + [(\alpha + 1)\sqrt{\alpha^2 - 1}] Y'(z) + \frac{\alpha^2(\alpha + 1)}{2} Y''(z) = 0. \quad (2.68)$$

Substitution of $\alpha = 1$ now leads to the second order differential equation

$$Y''(z) + zY'(z) + Y(z) = 0, \quad (2.69)$$

with an integral condition given from (2.61) by

$$\int_{-\infty}^{+\infty} Y(z) dz = 1, \quad (2.70)$$

because from (2.25) and (2.26) we have $\lim_{\alpha \rightarrow 1} (\mu/\sigma) = \infty$.

It is trivial to show that

$$Y(z) = Y_1(z) = e^{-\frac{z^2}{2}} \quad (2.71)$$

is a solution of (2.69). A second (independent) solution can then be found by substituting say $Y(z) = Y_2(z) = U(z)Y_1(z)$, leading (after cancellation of $Y_1(x)$) to

$$U''(z) - zU'(z) = 0. \quad (2.72)$$

One solution of this equation is

$$U'(z) = e^{\frac{z^2}{2}}, \quad (2.73)$$

so we may choose

$$Y_2(z) = e^{-\frac{z^2}{2}} \int_0^z e^{\frac{s^2}{2}} ds. \quad (2.74)$$

The general solution of (2.69) is then

$$Y(z) = C_1 Y_1(z) + C_2 Y_2(z), \quad (2.75)$$

where C_1 and C_2 are arbitrary constants, and $Y_1(z)$ and $Y_2(z)$ are given by (2.71) and (2.74) respectively. Now applying (2.70), we note that $\int_c^\infty Y_2(z) dz$ is infinite for all c , so we must have $C_2 = 0$. Hence $C_1 = \frac{1}{\sqrt{2\pi}}$, and the only solution to (2.69) and (2.70) is

$$Y(z) = \frac{1}{\sqrt{2\pi}} e^{-\frac{z^2}{2}}, \quad (2.76)$$

which is the pdf of the standard normal distribution as expected.

Consideration of the neglected terms in $(\alpha - 1)$ shows that we can write, for all α close to 1,

$$Y(z) = \frac{1}{\sqrt{2\pi}} e^{-\frac{z^2}{2}} (1 + o(\sqrt{\alpha - 1})). \quad (2.77)$$

Reverting to the original coordinates, we can then say that for α close to 1,

$$y(x) = \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{(x-\mu)^2}{2\sigma^2}} \left(1 + o(\sqrt{\alpha-1})\right), \quad (2.78)$$

where μ and σ^2 are given by (2.25) and (2.26) respectively. Thus as $\alpha \rightarrow 1^+$, $y(x)$ approaches the pdf of a *normal* distribution.

Clearly, if the limit as $\alpha \rightarrow 1^+$ of the SSD is a normal distribution, the expression given in (2.24) for the n th moment of the distribution should tend to the expression for the corresponding n th moment of the normal distribution. In Appendix A, we show that this is true provided that

$$\lim_{q \rightarrow 1^-} \left[\left(\frac{1+q}{1-q} \right)^{\frac{n}{2}} \sum_{k=0}^n (-1)^k \frac{n!}{(n-k)!k!q^k} \right] = \begin{cases} 0 & , n \text{ odd} \\ (n-1)!! & , n \text{ even} \end{cases} \quad (2.79)$$

This result is then proved, as this has apparently not been done elsewhere in the combinatorial literature.

2.4.5 The Form of the Time-dependent Number Density $n(x, t)$

Assuming that $r(t) = 1$ so the growth rate is independent of time, then substituting $b(x) = b$ and $Q = (\alpha - 1)b$ into (1.49), gives

$$\frac{dN}{dt} = N(t)(\alpha - 1)b, \quad (2.80)$$

so

$$N(t) = N_0 e^{(\alpha-1)bt}, \quad (2.81)$$

where $N_0 = N(0)$. We can now substitute (2.42) and (2.81) into $n(x, t) = N(t)y(x)$ to obtain the separable form of $n(x, t)$ which applies when the size distribution is given by the SSD,

$$\begin{aligned} n(x, t) &= N(t)y(x) \\ &= \frac{aN_0}{K} e^{(\alpha-1)bt} \sum_{n=0}^{\infty} \frac{(-1)^n \alpha^n e^{-a\alpha^n x}}{(\alpha-1)(\alpha^2-1)\dots(\alpha^n-1)}. \end{aligned} \quad (2.82)$$

Chapter 3

Size-Structured Models for Cells Growing Exponentially

This chapter is a slight modification of a second paper published in the Journal of the Australian Mathematics Society, series B (Hall and Wake [19]). The introduction has once again been abbreviated, the first part being in fact identical to that of Chapter 2. The remainder of the paper has been slightly expanded, with some extra mathematical detail being inserted. The notation used is the same as that used in Chapter 1 except that we use x instead of l to represent cell size.

3.1 Introduction

We consider here, as in Chapter 2, a cell population structured on one size variable x only, where each parent cell divides evenly to produce exactly α daughters all of the same size. Substituting $f(p) = \delta(p - \alpha^{-1})$ into (1.37) in Section 1.5, the partial differential equation for the number density $n(x, t)$ is

$$\frac{\partial}{\partial t}(n(x, t)) + \frac{\partial}{\partial x}(g(x, t)n(x, t)) = -b(x, t)n(x, t) + \alpha^2 b(\alpha x, t)n(\alpha x, t). \quad (3.1)$$

We once again look for a *steady size distribution*, $y(x)$, which can develop under the conditions outlined in Section 1.6. After following the development in that section, we replace $h_l(l)g(l)$ in (1.55) by the single function $b(x)$ to obtain a functional differential

equation for $y(x)$,

$$\frac{d}{dx}(g(x)y(x)) = -[b(x) + Q]y(x) + \alpha^2 b(\alpha x)y(\alpha x), \quad (3.2)$$

where Q is a functional on $y(x)$ given from (1.48) by

$$Q = (\alpha - 1) \int_0^\infty b(x)y(x)dx. \quad (3.3)$$

We note here that all cells must be of positive size, so we may set $y(x) \equiv 0$ for $x < 0$, and as $y(x)$ is a *probability density function* it must satisfy the conditions

$$\int_0^\infty y(x)dx = 1, \quad (3.4)$$

and

$$y(x) \geq 0. \quad (3.5)$$

It is difficult to see how to obtain closed-form solutions to (3.2) subject to (3.4) and (3.5) in the most general case, most obviously because of the presence of the unknown functional Q . However, as pointed out in Sections 1.9 and 1.10, in two simple cases we can find Q readily. The first of these is if $b(x) = b$, a constant, so that from (3.3) $Q = (\alpha - 1)b$. A solution for this case with $g(x)$ also constant was given in Chapter 2. In Appendix B, a solution with $b(x)$ constant and $g(x) = gx^{1-k}$ ($k > 0$) is obtained by using the transformation $Z(x) = g(x)y(x)$ to obtain an equation of the same form as equation (3.20) below.

As discussed in Section 1.10, the case where

$$g(x) = gx, \quad (3.6)$$

where the g on the right hand side is a constant, is of particular importance, both for cells in one-dimensional tissues and also for some types of bacterial cells. In this case, as pointed out in Section 1.10, (3.3) may be replaced by

$$Q = g. \quad (3.7)$$

If $r(t) = 1$, then $g(x) = gx$ corresponds to the case where the cells grow in size exponentially during their life cycle.

Substituting (3.6) and (3.7) into (3.2), we obtain a functional differential equation similar to (1.89),

$$gxy'(x) = -[b(x) + 2g]y(x) + \alpha^2 b(\alpha x)y(\alpha x). \quad (3.8)$$

In this chapter we seek solutions to this equation, subject to the normalising and non-negativity conditions (3.4) and (3.5).

3.2 Preliminaries

In Appendix D, it is shown that

$$y = \delta(x), \quad (3.9)$$

where $\delta(x)$ is the Dirac delta function, is a generalised solution of (3.8) for all forms of $b(x)$, and is in fact a solution of (3.2) for any $g(x)$ such that $g(0) = 0$. Further, it is shown that $y(x) = \delta(x)$ is the only non-negative¹ generalised solution satisfying (3.4), and therefore the only generalised solution which may be regarded as a *probability distribution*. The existence of this solution is reasonable in that it says that if we have a population all of size zero at any time, this situation will not change provided $g(0) = 0$.

We now look for classical solutions to (3.8) subject to conditions (3.4) and (3.5). Multiplying (3.8) by x and rearranging gives

$$g[x^2y'(x) + 2xy(x)] = -xb(x)y(x) + \alpha^2xb(\alpha x)y(\alpha x). \quad (3.10)$$

This suggests the change of variable

$$Z(x) = x^2y(x) \quad (3.11)$$

to give

$$gZ'(x) = -\frac{b(x)}{x}Z(x) + \frac{b(\alpha x)}{x}Z(\alpha x). \quad (3.12)$$

Setting

$$a(x) = \frac{b(x)}{gx} \quad (3.13)$$

simplifies (3.12) to

$$Z'(x) = -a(x)Z(x) + \alpha a(\alpha x)Z(\alpha x). \quad (3.14)$$

¹A generalised function $f(x)$ is defined as *non-negative* if for all appropriately "smooth" non-negative test functions $\phi(x)$ we have $\int_{-\infty}^{\infty} f(x)\phi(x)dx \geq 0$.

This equation needs to be solved subject to $Z(x) \geq 0$ and either of the conditions

$$\int_0^{\infty} \frac{Z(x)}{x^2} dx = 1, \quad (3.15)$$

or

$$\int_0^{\infty} a(x) \frac{Z(x)}{x} dx = \frac{1}{\alpha - 1}. \quad (3.16)$$

Here the second condition follows either from $Q = g$, or from integration by parts and substituting from (3.14). Equations (3.14) and (3.15) together are equivalent to (3.14) and (3.16) together.

Note that equation (3.14) can be written in the integral form

$$Z(x) = \int_x^{\infty} a(s)Z(s)ds, \quad (3.17)$$

which despite superficial similarities is very different from the classical Volterra integral equation. It follows that

$$Z(0) = 0, \quad (3.18)$$

then substitution into (3.14) and its derivatives shows that

$$Z^{(n)}(0) = 0, \quad \forall n \geq 0. \quad (3.19)$$

Hence any solution to (3.14) must be non-analytic (“infinitely flat”) at the origin.

In the next three sections we examine solutions of (3.14) subject to (3.15) or (3.16) for different forms of $b(x)$. We find solutions involving series of exponentials for the two cases $b(x) = bx^k$ and $b(x) = bx^k H(x - x_1)$, and then describe a general method of solution in cases where $b(x)$ is zero below some minimum size for division x_1 , and becomes infinite at some maximum cell size x_2 . A general method for solving functional differential equations of the form (3.14), involving series of multiple integrals, is outlined in Appendix C.

3.3 The case $b(x) = bx^k$

In this case, we have $a(x) = \frac{bx^k}{x} = ax^{k-1}$ say (where $a = \frac{b}{x}$), so that (3.14) becomes

$$Z'(x) = x^{k-1}(-aZ(x) + a\alpha^k Z(\alpha x)). \quad (3.20)$$

We now make the substitutions $z = \frac{x^k}{k}$ and $Y(z) = Z(x)$, so

$$Z'(x) = Y'(z) \frac{dz}{dx} = x^{k-1} Y'(z) \quad (3.21)$$

and

$$Z(\alpha x) = Y\left(\frac{(\alpha x)^k}{k}\right) = Y(\alpha^k z), \quad (3.22)$$

then (3.20) becomes (after cancellation of x^{k-1})

$$Y'(z) = -aY(z) + a\alpha^k Y(\alpha^k z). \quad (3.23)$$

This equation is in the same form as that dealt with in Chapter 2, except that the normalisation required will be different. Using (2.42), we can therefore write the solution immediately, which in terms of the variables used here is

$$Y(z) = C \sum_{n=0}^{\infty} \frac{(-1)^n \alpha^{kn}}{(\alpha^k - 1) \dots (\alpha^{kn} - 1)} e^{-a\alpha^{kn} z}, \quad (3.24)$$

where by convention the expression in the denominator is given the value 1 when $n = 0$. This solution is unique apart from the multiplicative constant C . Now reverting to our Z and x notation we obtain

$$Z(x) = C \sum_{n=0}^{\infty} \frac{(-1)^n \alpha^{kn}}{(\alpha^k - 1) \dots (\alpha^{kn} - 1)} e^{-a \frac{x^k}{k} \alpha^{kn}}. \quad (3.25)$$

The probability density function for the SSD is then given (from (3.11)) by

$$y(x) = \frac{Z(x)}{x^2}, \quad (3.26)$$

with the constant C to be evaluated from condition (3.16), which can be written in this case as

$$\int_0^{\infty} x^{k-2} Z(x) dx = \frac{1}{a(\alpha - 1)}. \quad (3.27)$$

Note that if $k = 0$ the transformation, and therefore the solution, is ill-defined, and for $k < 0$ the series does not converge. The solution is therefore valid only for

$$k > 0. \quad (3.28)$$

Obtaining the solution (3.25) was straightforward because we managed to transform the original problem into one for which the solution was known. However, using the integral condition (3.27) to find the constant C is not so easy, as it involves carrying out the the integration in

$$\int_0^\infty x^{k-2} Z(x) dx = C \int_0^\infty \left[\sum_{n=0}^\infty \frac{(-1)^n \alpha^{kn}}{(\alpha^k - 1) \dots (\alpha^{kn} - 1)} x^{k-2} e^{-a \frac{\alpha^{kn} x}{k}} \right] dx \quad (3.29)$$

for all $k > 0$.

For $0 < k \leq 1$, care must be taken over interchanging the integral and summation signs in this expression, as $\int_0^\infty x^p e^{-x} dx$ does not exist for $p \leq -1$. It is necessary to treat two cases separately: $k = m^{-1}$ for some integer m , and $k \neq m^{-1}$ for any such m .

3.3.1 The Case $k \neq m^{-1}$

Firstly, consider the integral $\int_0^\infty x^p Z(x) dx$, where $p \neq -1$. Integrating by parts, we get

$$\int_0^\infty x^p Z(x) dx = \left[\frac{x^{p+1}}{p+1} Z(x) \right]_0^\infty - \frac{1}{p+1} \int_0^\infty x^{p+1} Z'(x) dx. \quad (3.30)$$

Now the square-bracket term is zero because Z is infinitely flat at the origin, and l'Hopital's rule together with the zero-flux boundary condition can be used to show that $\lim_{x \rightarrow \infty} x^p Z(x) = 0$ for all real p . We can then substitute from (3.20) for $Z'(x)$ to give

$$\int_0^\infty x^p Z(x) dx = -\frac{1}{p+1} \left[-a \int_0^\infty x^{p+k} Z(x) dx + a \alpha^k \int_0^\infty x^{p+k} Z(\alpha x) dx \right], \quad (3.31)$$

then change variable from x to αx , giving

$$\int_0^\infty x^p Z(x) dx = \frac{a(1 - \alpha^{-(p+1)})}{p+1} \int_0^\infty x^{p+k} Z(x) dx. \quad (3.32)$$

If we apply this iteration m times, starting with $p = k - 2$, (and remembering that $km \neq 1, \forall m \in I^+$) we get

$$\int_0^\infty x^{k-2} Z(x) dx = \frac{\alpha^m (1 - \alpha^{1-k})(1 - \alpha^{1-2k}) \dots (1 - \alpha^{1-mk})}{(k-1)(2k-1) \dots (mk-1)} \int_0^\infty x^{(m+1)k-2} Z(x) dx. \quad (3.33)$$

Now for all $k > 0$, it is possible to choose $m \in I^+$ such that $k > \frac{1}{m+1}$ — for $k > 1$ we would choose $m = 0$. With such a choice of m , we can now substitute for $Z(x)$ and interchange the summation and integral signs to give

$$\int_0^\infty x^{k-2} Z(x) dx = C \frac{\alpha^m (1 - \alpha^{1-k})(1 - \alpha^{1-2k}) \dots (1 - \alpha^{1-mk})}{(k-1)(2k-1) \dots (mk-1)} \cdot \sum_{n=0}^\infty \frac{(-1)^n \alpha^{kn}}{(\alpha^k - 1) \dots (\alpha^{kn} - 1)} \int_0^\infty x^{(m+1)k-2} e^{-a \frac{x^k}{1}} dx. \quad (3.34)$$

Note that for $k < \frac{1}{m+1}$ the interchange would not be permitted as the resulting integral would not be finite.

Making the natural substitution $z = \frac{a}{k} \alpha^{nk} x^k$ we get

$$x^{mk-1} = \left(\frac{k}{a}\right)^{m-\frac{1}{k}} \alpha^{n(1-mk)} z^{m-\frac{1}{k}} \quad (3.35)$$

and

$$x^{k-1} dx = \frac{\alpha^{-nk}}{a} dz, \quad (3.36)$$

so

$$\int_0^\infty x^{k-2} Z(x) dx = C \left(\frac{k}{a}\right)^{m-\frac{1}{k}} \frac{\alpha^{m-1} (1 - \alpha^{1-k})(1 - \alpha^{1-2k}) \dots (1 - \alpha^{1-mk})}{(k-1)(2k-1) \dots (mk-1)} \cdot \sum_{n=0}^\infty \frac{(-1)^n \alpha^{n(1-mk)}}{(\alpha^k - 1) \dots (\alpha^{kn} - 1)} \int_0^\infty z^{m-\frac{1}{k}} e^{-z} dz. \quad (3.37)$$

In order to simplify this complicated-looking expression, we define

$$K(\alpha, \beta) = \sum_{n=0}^\infty \frac{(-1)^n \beta^n}{(\alpha - 1) \dots (\alpha^n - 1)}, \quad (3.38)$$

which may be regarded as a generalisation of the definition of the constant K in 2.40. The function $K(\alpha, \beta)$ defined in (3.38) has a number of useful properties. Firstly, if we take the well-known identity (e.g. Andrews [2], Goulden and Jackson [14])

$$\sum_{n=0}^\infty \frac{q^{\frac{1}{2}n(n-1)} z^n}{(1-q)(1-q^2) \dots (1-q^n)} = \prod_{n=0}^\infty (1 + zq^n), \quad (3.39)$$

and substitute $q = \alpha^{-k}$ then we get

$$\sum_{n=0}^\infty \frac{\alpha^{kn} z^n}{(\alpha^k - 1)(\alpha^{2k} - 1) \dots (\alpha^{kn} - 1)} = \prod_{n=0}^\infty (1 + z\alpha^{-kn}). \quad (3.40)$$

Substituting $\beta = -\alpha^k z$ gives

$$\sum_{n=0}^{\infty} \frac{(-1)^n \beta^n}{(\alpha^k - 1) \dots (\alpha^{nk} - 1)} = \prod_{n=1}^{\infty} (1 - \beta \alpha^{-kn}) \quad (3.41)$$

so that using the definition of K given in (3.38) we obtain

$$K(\alpha^k, \beta) = \prod_{n=1}^{\infty} (1 - \beta \alpha^{-kn}). \quad (3.42)$$

Secondly, substituting $\beta = \alpha^m$ into (3.42) gives

$$K(\alpha^k, \alpha^m) = \prod_{n=1}^{\infty} (1 - \alpha^{-k(n-1)+m-k}), \quad (3.43)$$

so

$$K(\alpha^k, \alpha^m) = (1 - \alpha^{m-k}) K(\alpha^k, \alpha^{m-k}). \quad (3.44)$$

Now by definition,

$$\Gamma(p) = \int_0^{\infty} x^{p-1} e^{-x} dx, \quad (3.45)$$

so using (3.38) we can write (3.37) as

$$\begin{aligned} & \int_0^{\infty} x^{k-2} Z(x) dx \\ &= C \left(\frac{k}{a}\right)^{m-\frac{1}{k}} \frac{\alpha^{m-1} (1 - \alpha^{1-k})(1 - \alpha^{1-2k}) \dots (1 - \alpha^{1-mk})}{(k-1)(2k-1) \dots (mk-1)} K(\alpha^k, \alpha^{1-mk}) \Gamma(m+1 - \frac{1}{k}) \\ &= C \left(\frac{k}{a}\right)^{-\frac{1}{k}} \frac{(1 - \alpha^{1-k})(1 - \alpha^{1-2k}) \dots (1 - \alpha^{1-mk})}{a(1 - \frac{1}{k})(2 - \frac{1}{k}) \dots (m - \frac{1}{k})} K(\alpha^k, \alpha^{1-mk}) \Gamma(m+1 - \frac{1}{k}). \end{aligned} \quad (3.46)$$

Now we have

$$\Gamma(m+1 - \frac{1}{k}) = (m - \frac{1}{k}) \dots (2 - \frac{1}{k}) (1 - \frac{1}{k}) \Gamma(1 - \frac{1}{k}) \quad (3.47)$$

and, using (3.44) repeatedly,

$$K(\alpha^k, \alpha) = (1 - \alpha^{1-k})(1 - \alpha^{1-2k}) \dots (1 - \alpha^{1-mk}) K(\alpha^k, \alpha^{1-mk}), \quad (3.48)$$

so (3.46) can be simplified to

$$\int_0^{\infty} x^{k-2} Z(x) dx = C \left(\frac{k}{a}\right)^{-\frac{1}{k}} \frac{1}{a} K(\alpha^k, \alpha) \Gamma(1 - \frac{1}{k}). \quad (3.49)$$

So from the integral condition (3.16) we get

$$C = \left(\frac{k}{a}\right)^{\frac{1}{k}} \frac{1}{(\alpha - 1)K(\alpha^k, \alpha)\Gamma(1 - \frac{1}{k})}. \quad (3.50)$$

Note that using (3.42), we could write $K(\alpha^k, \alpha)$ in a somewhat neater form as the infinite product

$$K(\alpha^k, \alpha) = \prod_{n=1}^{\infty} (1 - \alpha^{1-kn}). \quad (3.51)$$

3.3.2 The Case $k = m^{-1}$

For $k = \frac{1}{m}$, $m \in I^+$, if we start with $p = k - 2$ we can only apply the iterative relationship (3.32) used in the previous section $m - 1$ times, giving

$$\int_0^{\infty} x^{k-2} Z(x) dx = \frac{\alpha^{m-1}(1 - \alpha^{1-k})(1 - \alpha^{1-2k}) \dots (1 - \alpha^{1-(m-1)k})}{(k-1)(2k-1) \dots ((m-1)k-1)} \int_0^{\infty} x^{-1} Z(x) dx. \quad (3.52)$$

The integral on the right can be integrated by parts once more, giving

$$\begin{aligned} \int_0^{\infty} x^{-1} Z(x) dx &= - \int_0^{\infty} \log x Z'(x) dx \\ &= a \left[\int_0^{\infty} (\log x) x^{k-1} Z(x) dx - \alpha^k \int_0^{\infty} (\log x) x^{k-1} Z(\alpha x) dx \right] \\ &= a \left[\int_0^{\infty} (\log x) x^{k-1} Z(x) dx - \int_0^{\infty} (\log s - \log \alpha) s^{k-1} Z(s) ds \right], \end{aligned} \quad (3.53)$$

where once again we have used (3.14) to replace $Z'(x)$, so

$$\int_0^{\infty} x^{-1} Z(x) dx = a \log \alpha \int_0^{\infty} x^{k-1} Z(x) dx. \quad (3.54)$$

Now substitute for $Z(x)$ from (3.25) and interchange the integral and summation signs (which is now permitted) to give

$$\begin{aligned} \int_0^{\infty} x^{-1} Z(x) dx &= C a \log \alpha \sum_{n=0}^{\infty} \frac{(-1)^n \alpha^{kn}}{(\alpha^k - 1) \dots (\alpha^{kn} - 1)} \int_0^{\infty} x^{k-1} e^{-\frac{1}{k} \alpha^{kn} x^k} dx \\ &= C \log \alpha \sum_{n=0}^{\infty} \frac{(-1)^n}{(\alpha^k - 1) \dots (\alpha^{kn} - 1)} \int_0^{\infty} s e^{-s} ds. \end{aligned} \quad (3.55)$$

Now $\int_0^\infty se^{-s} ds = 1$, so using (3.38) this simplifies to

$$\int_0^\infty x^{-1} Z(x) dx = CK(\alpha^k, 1) \log \alpha. \quad (3.56)$$

Thus (3.52) becomes

$$\int_0^\infty x^{k-2} Z(x) dx = CK(\alpha^k, 1) \log \alpha \frac{\alpha^{m-1}(1 - \alpha^{1-k})(1 - \alpha^{1-2k}) \dots (1 - \alpha^{1-(m-1)k})}{(k-1)(2k-1) \dots ((m-1)k-1)}. \quad (3.57)$$

Applying the integral condition (3.27) leads to

$$C = \frac{(k-1)(2k-1) \dots ((m-1)k-1)}{(1 - \alpha^{1-k})(1 - \alpha^{1-2k}) \dots (1 - \alpha^{1-(m-1)k})} \frac{1}{\alpha^m (\alpha - 1) K(\alpha^k, 1) \log \alpha}. \quad (3.58)$$

The numerator in the first fraction can be simplified by taking out m factors of k , so

$$(k-1)(2k-1) \dots ((m-1)k-1) = (-1)^{m-1} k^m \frac{1}{k} \left(\frac{1}{k} - 1\right) \left(\frac{1}{k} - 2\right) \dots \left(\frac{1}{k} - (m-1)\right), \quad (3.59)$$

then replacing $\frac{1}{k}$ by m we have

$$(k-1)(2k-1) \dots ((m-1)k-1) = (-1)^{m-1} k^m m(m-1)(m-2) \dots (1) = (-1)^{m-1} k^m m! \quad (3.60)$$

The denominator of the first fraction can also be simplified a little, replacing the numeral 1 in the exponents by mk , then simplifying so

$$\begin{aligned} (1 - \alpha^{1-k})(1 - \alpha^{1-2k}) \dots (1 - \alpha^{1-(m-1)k}) = \\ (-1)^{m-1} (\alpha^{(m-1)k} - 1)(\alpha^{(m-2)k} - 1) \dots (\alpha^k - 1), \end{aligned} \quad (3.61)$$

then from (3.58) we have

$$C = \left(\frac{k}{a}\right)^{\frac{1}{k}} \frac{m!}{(\alpha^k - 1)(\alpha^{2k} - 1) \dots (\alpha^{mk} - 1)} \frac{1}{K(\alpha^k, 1) \log \alpha}, \quad (3.62)$$

where of course $mk = 1$.

3.3.3 Discussion and Examples

We have shown that the SSD in the case $g(x) = gx$ and $b(x) = bx^k$,

$$y(x) = \frac{C}{x^2} \sum_{n=0}^{\infty} \frac{(-1)^n \alpha^{kn} e^{-a \frac{x^k}{1-x^k}}}{(\alpha^k - 1) \dots (\alpha^{kn} - 1)}, \quad (3.63)$$

where $a = \frac{b}{g}$ and

$$C = \begin{cases} \left(\frac{k}{a}\right)^{\frac{1}{k}} \frac{m!}{(\alpha^k - 1)(\alpha^{2k} - 1) \dots (\alpha^{mk} - 1)} \frac{1}{K(\alpha^k, 1) \log \alpha} & , k = \frac{1}{m}, m \in I^+ \\ \left(\frac{k}{a}\right)^{\frac{1}{k}} \frac{1}{(\alpha - 1) K(\alpha^k, a) \Gamma(1 - \frac{1}{k})} & , k \neq \frac{1}{m}, m \in I^+. \end{cases} \quad (3.64)$$

Continuity of C

In order to show that C is a continuous function of k , we need to prove that

$$\lim_{k \rightarrow m^{-1}} K(\alpha^k, \alpha) \Gamma\left(1 - \frac{1}{k}\right) = \frac{(\alpha^k - 1)(\alpha^{2k} - 1) \dots (\alpha^{(m-1)k} - 1)}{m!} K(\alpha^k, 1) \log \alpha. \quad (3.65)$$

Now using (3.42) and separating out the one factor which becomes zero as $k \rightarrow m^{-1}$, we write

$$K(\alpha^k, \alpha) = (1 - \alpha^{1-km}) \prod_{n=1, n \neq m}^{\infty} (1 - \alpha^{1-kn}). \quad (3.66)$$

Similarly, we separate out the factor in $\Gamma\left(1 - \frac{1}{k}\right)$ which causes difficulties as $k \rightarrow m^{-1}$, by applying the iterative relationship $\Gamma(x-1) = \frac{\Gamma(x)}{x-1}$ m times, giving

$$\Gamma\left(1 - \frac{1}{k}\right) = \left[\frac{1}{m - \frac{1}{k}} \right] \frac{\Gamma\left(1 - \frac{1}{k} + m\right)}{\left(1 - \frac{1}{k}\right)\left(2 - \frac{1}{k}\right) \dots \left((m-1) - \frac{1}{k}\right)}. \quad (3.67)$$

Substituting these expansions into the left hand side of (3.65) we have

$$\lim_{k \rightarrow m^{-1}} K(\alpha^k, \alpha) \Gamma\left(1 - \frac{1}{k}\right) = \lim_{k \rightarrow m^{-1}} \left\{ \frac{\Gamma\left(1 - \frac{1}{k} + m\right) \prod_{n=1, n \neq m}^{\infty} (1 - \alpha^{1-kn})}{\left(1 - \frac{1}{k}\right)\left(2 - \frac{1}{k}\right) \dots \left((m-1) - \frac{1}{k}\right)} \left[\frac{1 - \alpha^{1-km}}{m - \frac{1}{k}} \right] \right\} \quad (3.68)$$

Now the limit of the expression in square brackets can be found by a single application of l'Hopital's rule,

$$\begin{aligned} \lim_{k \rightarrow m^{-1}} \left[\frac{1 - \alpha^{1-km}}{m - \frac{1}{k}} \right] &= \lim_{k \rightarrow m^{-1}} \frac{\alpha^{1-km} m \log \alpha}{\left(\frac{1}{k^2}\right)} \\ &= \frac{\log \alpha}{m} \end{aligned} \quad (3.69)$$

Substituting $k = m^{-1}$ into the rest of (3.68) then gives

$$\lim_{k \rightarrow m^{-1}} K(\alpha^k, \alpha) \Gamma\left(1 - \frac{1}{k}\right) = \frac{\Gamma(1) \prod_{n=1, n \neq m}^{\infty} (1 - \alpha^{1-\frac{1}{m}}) \log \alpha}{(-1)^{m-1} (m-1)(m-2) \dots 1 \cdot m}. \quad (3.70)$$

Now

$$\prod_{n=1, n \neq m}^{\infty} (1 - \alpha^{1-\frac{1}{m}}) = \left[\prod_{n=1}^{m-1} (1 - \alpha^{1-\frac{1}{m}}) \right] \left[\prod_{n=m+1}^{\infty} (1 - \alpha^{1-\frac{1}{m}}) \right], \quad (3.71)$$

so after expanding the left-hand product then changing the summation variable in the right-hand product to get it into the form required by (3.42) we get

$$\prod_{n=1, n \neq m}^{\infty} (1 - \alpha^{1-\frac{1}{m}}) = (-1)^{m-1} (\alpha^k - 1)(\alpha^{2k} - 1) \dots (\alpha^{(m-1)k} - 1) K(\alpha^k, 1). \quad (3.72)$$

Substitution of this expression into (3.70) now gives (3.65), so C is a continuous function of k as expected.

Moments of the SSD

When k is an integer, we can obtain the k th moment of the SSD about the origin, $\mu_k = \int_0^\infty x^k y(x) dx$, directly from the integral condition (3.27) as

$$\mu_k = \frac{1}{a(\alpha - 1)}. \quad (3.73)$$

An iterative expression for moments beyond the k th is obtainable by applying a *Mellin Transform* to (3.20): multiplying through by x^{m-1} , where m is an integer, and integrating over all x , remembering that $y(x) = x^{-2}Z(x)$ gives

$$\int_0^\infty x^{m-1} Z'(x) dx = -a\mu_{m+k} + a \int_0^\infty \alpha^k x^{m+k} [x^{-2}Z(\alpha x)] dx. \quad (3.74)$$

Integration by parts on the left and the substitution $z = \alpha x$ on the right then leads to

$$-(m-1)\mu_m = -a\mu_{m+k} + a\alpha^{-(m-1)}\mu_{m+k}, \quad (3.75)$$

so we have the iterative equation

$$\mu_{m+k} = \frac{(m-1)}{a(1 - \alpha^{-(m-1)})} \mu_m \quad (3.76)$$

provided $m > 1$. This enables us to deduce all the moments of the SSD once we have found the k th moment by using (3.73) and all other moments up to the $(k+1)$ th by integration of (3.63) directly.

For example, in the particular case $k = 1$, the mean is

$$\mu = \frac{1}{a(\alpha - 1)} \quad (3.77)$$

and the second moment about the origin ($\mu_2 = \int_0^\infty x^2 y(x) dx = \int_0^\infty Z(x) dx$) can be obtained by integrating (3.25) term by term to give

$$\mu_2 = \frac{1}{a^2(\alpha - 1) \log \alpha}. \quad (3.78)$$

We can then apply (3.76) repeatedly to obtain

$$\mu_n = \frac{(n-2)!}{a^n(\alpha - 1) \log \alpha \prod_{k=1}^{n-2} (1 - \alpha^{-k})}, \quad n > 2. \quad (3.79)$$

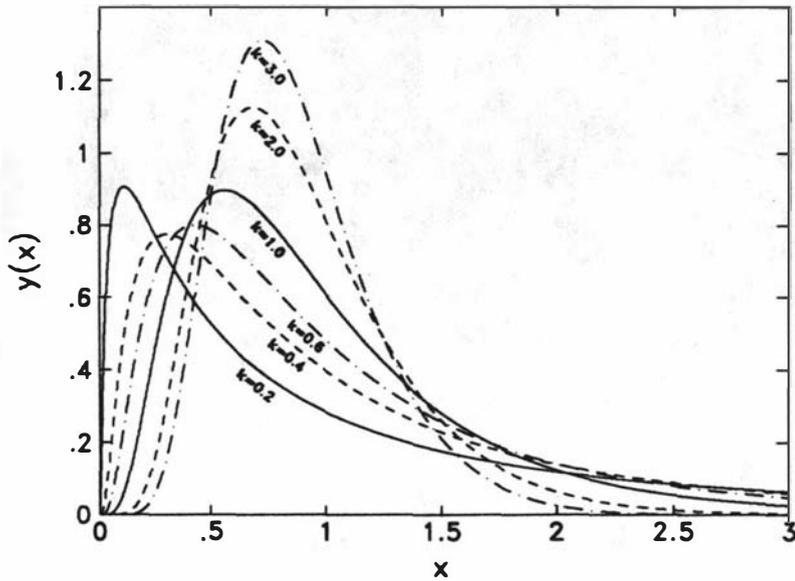


Figure 3.1: SSD probability density functions $y(x)$ for $g(x) = gx$ and $b(x) = bx^k$ for a range of values of k . The variables a and α have been fixed at 1 and 2 respectively.

An Example

Figure 3.1 shows the shape of the SSD function $y(x)$ with $a = 1$ and $\alpha = 2$ for a range of values of k . Consideration of the differential equation formed in the extreme cases shows that as $k \rightarrow 0$, the SSD $y(x)$ approaches the Dirac delta function $\delta(x)$, and as $k \rightarrow \infty$ it approaches (Koch and Schaechter [30]) the function

$$y(x) = \begin{cases} \frac{a}{(\alpha-1)x^2} & , \frac{a}{\alpha} < x < a \\ 0 & , \text{otherwise.} \end{cases} \quad (3.80)$$

3.4 A Minimum Size for Division: The Case $b(x) = bx^kH(x - x_1)$

This case is the same as that discussed in the previous section, except that there is a minimum size $x_1 > 0$ below which cells do not divide. Substituting $b(x) = bx^kH(x - x_1)$, $k > 0$, (where H is the Heavyside or unit step function and b and x_1 are constants) into equation (3.14) we get

$$Z'(x) = x^{k-1}(-aH(x - x_1)Z(x) + a\alpha^kH(\alpha x - x_1)Z(\alpha x)), \quad (3.81)$$

where as in Section 3.3 we have made the substitution $a = \frac{b}{g}$. In this case we choose to couple (3.81) with the integral condition (3.16) as this simplifies to a condition dependent only on $Z(x)$ for $x \geq x_1$, namely

$$\int_{x_1}^{\infty} x^{k-2}Z(x)dx = \frac{1}{a(\alpha - 1)}. \quad (3.82)$$

It is convenient to solve the equation in three regions starting with the region $x > x_1$. We let

$$Z(x) = \begin{cases} Z_1(x), x \geq x_1 & \text{(region 1)} \\ Z_2(x), \frac{x_1}{\alpha} \leq x \leq x_1 & \text{(region 2)} \\ Z_3(x), x \leq \frac{x_1}{\alpha} & \text{(region 3)} \end{cases} \quad (3.83)$$

where continuity considerations require $Z_1(x_1) = Z_2(x_1)$ and $Z_3(\frac{x_1}{\alpha}) = Z_2(\frac{x_1}{\alpha})$.

3.4.1 Region 1, $x \geq x_1$

In this region, (3.81) becomes (3.20), so the solution is

$$Z_1(x) = C \sum_{n=0}^{\infty} \frac{(-1)^n \alpha^{kn}}{(\alpha^k - 1) \dots (\alpha^{kn} - 1)} e^{-a \frac{\alpha^n x^k}{k}}. \quad (3.84)$$

To find the constant C , we substitute $Z(x) = Z_1(x)$ into (3.82) above, giving

$$C \int_{x_1}^{\infty} \left[\sum_{n=0}^{\infty} \frac{(-1)^n \alpha^{kn}}{(\alpha^k - 1) \dots (\alpha^{kn} - 1)} x^{k-2} e^{-a \frac{\alpha^n x^k}{k}} \right] dx = \frac{1}{a(\alpha - 1)}. \quad (3.85)$$

This time there is no difficulty in immediately interchanging the integral and summation operations as the integration starts at $x_1 > 0$ and therefore avoids the singularity at $x = 0$

when $k \leq 1$. Making the change of variable $z = a \frac{\alpha^{nk} x^k}{k}$ in each integral leads to

$$\frac{C}{a} \sum_{n=0}^{\infty} \frac{(-1)^n \alpha^n}{(\alpha^k - 1) \dots (\alpha^{kn} - 1)} \left(\frac{a}{k}\right)^{\frac{1}{k}} \int_{\frac{a}{k} \alpha^{nk} x_1^k}^{\infty} z^{-\frac{1}{k}} e^{-z} dz = \frac{1}{a(\alpha - 1)}. \quad (3.86)$$

Hence we can write

$$C = \left(\frac{k}{a}\right)^{\frac{1}{k}} \frac{1}{(\alpha - 1)S}, \quad (3.87)$$

where

$$S = \sum_{n=0}^{\infty} \frac{(-1)^n \alpha^n}{(\alpha^k - 1) \dots (\alpha^{kn} - 1)} \Gamma\left(1 - \frac{1}{k}, \frac{a}{k} \alpha^{kn} x_1^k\right), \quad (3.88)$$

and $\Gamma(c, x) = \int_x^{\infty} s^{c-1} e^{-s} ds$ is an *incomplete gamma function*.

In the particular case $k = 1$, (3.87) reduces to

$$C = \frac{k}{a(\alpha - 1)S} \quad (3.89)$$

where

$$S = \sum_{n=0}^{\infty} \frac{(-1)^n \alpha^n}{(\alpha^k - 1) \dots (\alpha^{kn} - 1)} E_1\left(\frac{a}{k} \alpha^{kn} x_1^k\right) \quad (3.90)$$

and E_1 is the exponential integral.

3.4.2 Region 2, $\frac{x_1}{\alpha} \leq x \leq x_1$

In this region we have $H(x - x_1) = 0$ and $H(\alpha x - x_1) = 1$ so we may immediately integrate (3.81) to obtain

$$Z_2(x) = a \int_{x_1}^{\alpha x} s^{k-1} Z_1(s) ds. \quad (3.91)$$

This integration can be carried out term by term, using the substitution $z = a \frac{\alpha^{nk} s^k}{k}$, to give

$$Z_2(x) = C \sum_{n=0}^{\infty} \frac{(-1)^n}{(\alpha^k - 1) \dots (\alpha^{kn} - 1)} \left[e^{-a \frac{\alpha^{nk} x^k}{k}} - e^{-a \frac{(\alpha+1)^k x^k}{k}} \right], \quad (3.92)$$

where the constant C is the same as that in the expression for $Z_1(x)$ in (3.84).

3.4.3 Region 3, $x \leq \frac{x_1}{\alpha}$

In this region the (3.81) becomes

$$Z_3'(x) = 0 \quad (3.93)$$

so as we have $Z_3(\frac{x_1}{\alpha}) = Z_2(\frac{x_1}{\alpha}) = 0$ from (3.92) the solution is simply

$$Z_3(x) = 0 \quad (3.94)$$

as expected.

3.4.4 Discussion and Examples

Combining the results above and noting $Z(x) = x^2 y(x)$, the SSD in the case $g(x) = gx$ and $b(x) = bx^k H(x - x_1)$ is given by

$$y(x) = \begin{cases} \frac{C}{x^2} \sum_{n=0}^{\infty} \frac{(-1)^n \alpha^{kn}}{(\alpha^k - 1) \dots (\alpha^{kn} - 1)} e^{-a \frac{(\alpha^n x)^k}{k}}, & x \geq x_1 \\ \frac{C}{x^2} \sum_{n=0}^{\infty} \frac{(-1)^n}{(\alpha^k - 1) \dots (\alpha^{kn} - 1)} \left[e^{-a \frac{\alpha^{kn} x^k}{k}} - e^{-a \frac{\alpha^{(n+1)k} x^k}{k}} \right], & \frac{x_1}{\alpha} \leq x \leq x_1 \\ 0, & x \leq \frac{x_1}{\alpha} \end{cases} \quad (3.95)$$

where

$$C = \left(\frac{k}{a}\right)^{\frac{1}{k}} \frac{1}{(\alpha - 1)S} \quad (3.96)$$

and

$$S = \sum_{n=0}^{\infty} \frac{(-1)^n \alpha^n}{(\alpha^k - 1) \dots (\alpha^{kn} - 1)} \Gamma\left(1 - \frac{1}{k}, \frac{a}{k} \alpha^{kn} x_1^k\right). \quad (3.97)$$

Figure 3.2 shows this piecewise function for $y(x)$ for a range of minimum sizes for cell division x_1 , with $k = 2$, $a = \frac{b}{g} = 1$, and $\alpha = 2$. The discontinuity in the slope of $y(x)$ at $x = x_1$ is a natural consequence of the step change in the probability of cell division $b(x)$ (from 0 to bx_1^k) at this size. The form of $y(x)$ for small values of x_1 approaches the form given in Fig. 2.1 for $k = 2$.

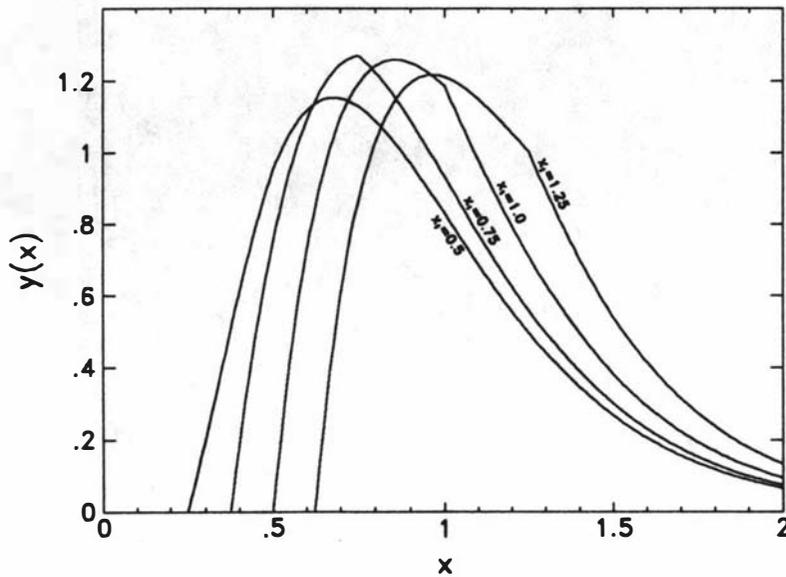


Figure 3.2: SSD probability density functions $y(x)$ for $g(x) = gx$ and $b(x) = bx^\alpha H(x - x_1)$, with $k = 2$, $a = 1$, $\alpha = 2$, and a range of values of x_1

3.5 A Minimum and Maximum Size for Cell Division

Consider the case where $g(x) = gx$ and there exists a minimum size for cell division x_1 as in the previous section, and there is also a maximum cell size x_2 ($0 < x_1 < x_2$) such that all cells divide before they reach size x_2 . This means we are considering non-negative forms of $a(x) = \frac{b(x)}{gx}$ such that

$$a(x) = 0, x \leq x_1, \quad (3.98)$$

$$a(x) \rightarrow \infty, x \rightarrow x_2^-, \quad (3.99)$$

and we will assume $y(x) \equiv 0$ for $x > x_2$. For reasons that will become apparent later we will in fact restrict our attention to forms of $a(x)$ which are integrable over all closed regions $[c,d]$ such that $0 < c < d < x_2$, but with a non-integrable singularity at x_2 , so

$$\int_c^{x_2} a(x) dx = \infty \quad (3.100)$$

for any $c < x_2$.

3.5.1 The Solution Method

The solution, $Z(x)$, to (3.14) can be constructed as follows. Firstly, let m be the largest integer such that $x_1 < x_2 \alpha^{-m}$. In typical cell populations, m is usually quite small — less than 3. Tyson and Diekman [61] give the solution for the special case $m = 0$ and $\alpha = 2$, and show how in this case solutions may be obtained for forms of $g(x)$ other than $g(x) = gx$ by treating Q (see introduction) as an unknown constant to be found numerically. The method outlined here could be similarly extended to more general forms of $g(x)$.

We split $Z(x)$ into regions so that

$$Z(x) = \begin{cases} Z_0(x), & x \geq x_2 \\ Z_k(x), & x_2 \alpha^{-k} \leq x < x_2 \alpha^{-k-1}, 1 < k \leq m+1. \end{cases} \quad (3.101)$$

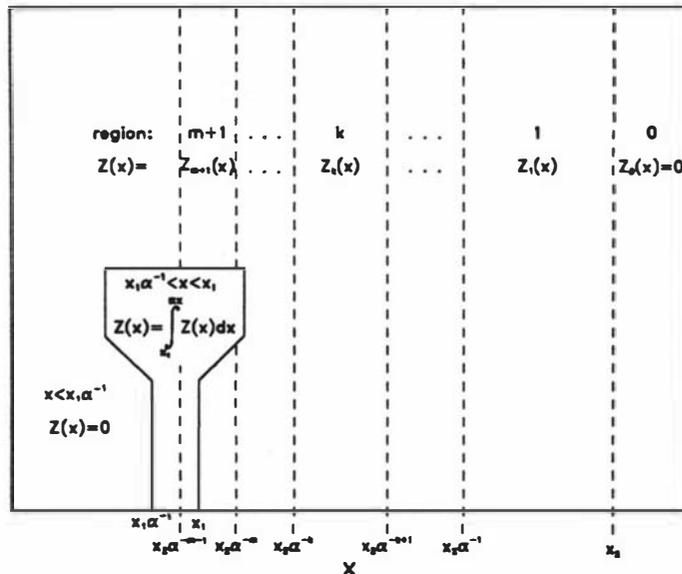


Figure 3.3: Regions used in solving for the SSD. $Z_1(x)$ is found first using (3.103), $Z_2(x)$ to $Z_{m+1}(x)$ are found iteratively using (3.104), then finally $Z(x)$ for $x < x_1$ is found using (3.105).

This scheme is shown in Fig. 3.3. Note that as no cell division occurs below size x_1 , no new cells can appear of size less than $x_1 \alpha^{-1}$, so we must have $Z(x) = 0$ for $x < x_1 \alpha^{-1}$. We now write (3.14) in the form

$$Z'_{k+1}(x) = -a(x)Z_{k+1}(x) + \alpha a(\alpha x)Z_k(\alpha x), k \geq 0. \quad (3.102)$$

This equation can then be used iteratively to find $Z(x)$ over the whole range of sizes of interest. We know $Z_0 \equiv 0$ (because $y(x) = 0$ for $x > x_2$), so it follows from (3.102) that

$$Z_1(x) = Ce^{-A(x)} \quad (3.103)$$

where C is a constant to be evaluated, and $A'(x) = a(x)$. If we now assume that the solution in region k is known, then (3.102) becomes a simple first-order ODE in $Z_{k+1}(x)$, and the solution is

$$Z_{k+1}(x) = e^{\int_x^{x_2} a^{-k}(s) ds} Z_k(x_2 \alpha^{-k}) - \int_{\alpha x}^{x_2 \alpha^{1-k}} e^{\int_x^{m-1} a(s') ds'} a(s) Z_k(s) ds, \quad (3.104)$$

where the limits of the integration have been fixed by the continuity requirement $Z_{k+1}(x_2 \alpha^{-k}) = Z_k(x_2 \alpha^{-k})$. Hence we can deduce the solution $Z_k(x)$ for all $k \geq 1$, then calculate the constant C from either of the integral conditions (3.15) or (3.16). The desired SSD can then be simply calculated from $y(x) = x^{-2}Z(x)$.

Two points are worth noting in this solution process. Firstly, from (3.103), continuity of Z_1 with Z_0 at $x = x_2$ for non-zero C requires that $A(x_2) = \infty$, so x_2 must be a non-integrable singularity of $a(x)$ as pointed out earlier. The alternative would be to allow a discontinuity in $Z(x)$ at x_2 , in which case $y(x)$ would be discontinuous at $x = x\alpha^{-k}$ for $0 \leq k \leq m+1$, so the argument involving continuity used above would be invalid. Equation (3.103) must clearly be used in place of (3.104) for $k = 0$ because the first term in (3.104) becomes a product of infinity and zero. Secondly, once the solution has been found in the size region between x_1 and x_2 using the above process, the solution in the region $x < x_1$ is most simply found by noting that $a(x) \equiv 0$, so the integral form of the equation (3.17) can be used in the form

$$Z(x) = \int_{x_1}^{\alpha x} a(s)Z(s)ds, \quad x < x_1. \quad (3.105)$$

It is clear from this formulation that we will have $Z(x) = 0$ for $x < x_1$ as expected, with continuity of $Z(x)$ at $x = x_1$.

3.5.2 An example

As an analytical example of this process, consider the simplest form of $a(x)$ which satisfies the conditions (3.99), namely

$$a(x) = \begin{cases} \frac{1}{x_2 - x} & , x_1 < x < x_2 \\ 0 & , x < x_1, \end{cases} \quad (3.106)$$

which corresponds to a birth rate $b(x)$ of

$$b(x) = \begin{cases} \frac{gx}{x_2 - x} & , x_1 < x < x_2 \\ 0 & , x < x_1 \end{cases} \quad (3.107)$$

where g is the constant in $g(x) = gx$. We will choose $x_1 = \alpha^{-2}x_2$ exactly, as this is the simplest choice which involves use of all of the equations (3.103), (3.104), and (3.105). In region 1 we then find, using (3.103),

$$\begin{aligned} Z_1(x) &= Ce^{-\int \frac{1}{x_2 - x}} \\ &= Cx_2(1 - \frac{x}{x_2}). \end{aligned} \quad (3.108)$$

In region 2, using (3.104) we obtain

$$Z_2(x) = Cx_2(1 - \frac{x}{x_2})[1 - \alpha \log(1 - \frac{x}{x_2}) + \alpha \log(1 - \alpha^{-1})]. \quad (3.109)$$

Applying integral condition (3.16) we get

$$\int_{x_2\alpha^{-2}}^{x_2\alpha^{-1}} \frac{Z_2(x)}{x(x_2 - x)} dx + \int_{x_2\alpha^{-1}}^{x_2} \frac{Z_1(x)}{x(x_2 - x)} dx = \frac{1}{\alpha - 1} \quad (3.110)$$

which leads to

$$C = \left[(\alpha - 1) \left[(2 + \alpha \log(1 - \alpha^{-1})) \log \alpha + \alpha (S(\alpha^{-1}) - S(\alpha^{-2})) \right] \right]^{-1}, \quad (3.111)$$

where $S(u) = \sum_{n=1}^{\infty} \frac{u^n}{n^2}$.

We now use (3.105) to find the solution in the region $x < x_1$ as

$$\begin{aligned} Z_3(x) &= Cx_2\alpha \left[(1 + \alpha \log(1 - \alpha^{-1})) \left[\frac{x}{x_2} - \alpha^{-3} \right] \right. \\ &\quad \left. + (1 - \alpha \frac{x}{x_2}) [\log(1 - \alpha \frac{x}{x_2}) - 1] - (1 - \alpha^{-2}) [\log(1 - \alpha^{-2}) - 1] \right]. \end{aligned} \quad (3.112)$$

Now using $y(x) = x^{-2}Z(x)$ we can write the SSD $y(x)$ as

$$y(x) = \begin{cases} 0 & , x \leq x_2\alpha^{-3} \\ \frac{Cx_2}{x^2} \left[\alpha \left[(1 + \alpha \log(1 - \alpha^{-1})) \left[\frac{x}{x_2} - \alpha^{-3} \right] \right. \right. \\ \quad \left. \left. + (1 - \alpha \frac{x}{x_2}) [\log(1 - \alpha \frac{x}{x_2}) - 1] \right. \right. \\ \quad \left. \left. - (1 - \alpha^{-2}) [\log(1 - \alpha^{-2}) - 1] \right] \right] & , x_2\alpha^{-3} < x \leq x_2\alpha^{-2} \\ \frac{Cx_2}{x^2} (1 - \frac{x}{x_2}) [1 - \alpha \log(1 - \frac{x}{x_2}) + \alpha \log(1 - \alpha^{-1})] & , x_2\alpha^{-2} < x \leq x_2\alpha^{-1} \\ \frac{Cx_2}{x^2} (1 - \frac{x}{x_2}) & , x_2\alpha^{-1} < x \leq x_2 \\ 0 & , x > x_2. \end{cases} \quad (3.113)$$

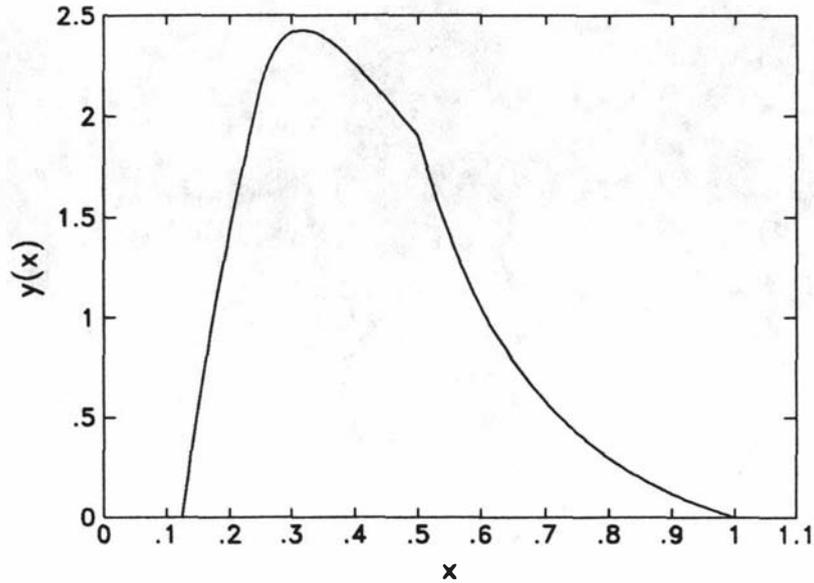


Figure 3.4: The SSD probability density function $y(x)$ for $a(x) = \frac{b(x)}{gx} = (1-x)^{-1}H(x-0.25)$ and $\alpha = 2$.

where C is given by (3.111).

Fig. 3.4 shows this function with binary fission ($\alpha = 2$) and with x_2 equal to one size unit. Substitution is straightforward apart from the calculation of $S(0.5)$ and $S(0.25)$ required to find C . Jolley [26] gives

$$S(0.5) = \frac{\pi^2}{12} - \frac{(\log 2)^2}{2}, \quad (3.114)$$

but the only way to find $S(0.25)$ seems to be to substitute into the series, which actually converges very rapidly in this case. From the form of (3.113) it is clear that x_2 is just a scaling factor, so the solution for other values of x_2 is simply obtained by relabelling the horizontal and vertical axes in Fig. (3.4) as $\frac{x}{x_2}$ and $x_2 y(x)$ respectively.

Chapter 4

Cell Populations with Age and Size Structure

This chapter is a slight modification of a paper published in the Journal of Mathematical Biology (Hall, Wake, and Gandar [20]), with a few general comments having been moved to Chapter 1 and some extra mathematical detail added in places. The development provided in the first three sections of Part I of this chapter, based on the use of cell birth-size rather than cell age, parallels the development based on age in Sections 1.7 and 1.8 of Chapter 1 but is more general in that it allows for non-steady size/age distributions.

In Part I, we first discuss the case where cells grow without structural constraints, then show how the theory of this general case can be simplified and developed when the cells are constrained to grow in one dimension within structured tissues, as in Section 1.10 of Chapter 1. Steady size/age and size/birth-size distributions of cells are expressed in terms of the steady cell birth-size distribution, which is shown to be the principal eigenfunction of a Fredholm integral operator. In Part II, we solve some special cases analytically and present a simple numerical method which can be used in analytically intractable cases.

4.1 Part I: An Integral Equation for the Birth-size Distribution

4.1.1 Introduction: Size/Age and Size/Birth-size Distributions

Consider a population of cells, growing and dividing without mortality so that the total cell population is always increasing. We consider the important attributes of cells to be age, a , and size, l , and assume that the cell population is sufficiently large to be adequately described by a continuous number density $n_a(l, a, t)$ at any time t . Then $n_a(l, a, t)da dl$ gives the number of cells in the age range a to $a + da$ and size range l to $l + dl$, and the total cell population at t is $N(t) = \int_0^\infty \int_0^\infty n_a(l, a, t) da dl$. This size/age approach is the one taken in Sinko and Streifer [52] and Oster [38] amongst others, and contrasts with the simpler size-based approach of Koch and Schaechter [30] and Collins and Richmond [7].

In this chapter, cell size may be taken as being synonymous with cell length. We assume that the growth of each individual cell is *deterministic* in the sense that given its age a (time since it was formed by fission of a parent cell) and size l , then it is possible to determine its growth rate $g_a(l, a, t)$ precisely at any time t . *Dispersive* growth as discussed in Section 1.4 is not considered.

If cell growth rates are deterministic and positive, models in which all functions and number densities are defined in terms of initial cell size s and current size l are equivalent to size/age models. Using this size/birth-size approach, we let $n(l, s, t)$ be the continuous cell number density such that $n(l, s, t)dl ds$ gives the number of cells that were born in the size range s to $s + ds$ and lie in the size range l to $l + dl$ at time t , and we write the cell growth rate as $g_l(l, s, t)$. Fig. 4.1 shows typical paths followed by a cell in l - a and l - s spaces. In this chapter we choose to work in l - s space because, as we shall show later, steady size/birth-size distributions may arise in some situations where the size/age distribution is non-steady. Some simplification is also achieved because individual cells follow straight paths parallel to the l axis in l - s space, whereas paths are generally curved in l - a space (Fig. 4.1).

In the cell division process, we allow for possible variation both in the size at which a cell may divide, and in the proportions into which it divides. Firstly, we specify a "hazard rate" $h_l(l, s, t)$ such that $h_l(l, s, t)dl$ gives the probability that a cell which was born at size s and which reaches size l at time t will divide before reaching size $l + dl$. Secondly, we introduce a "fractional-size" probability density function (pdf) $f(p, l, s, t)$ such that $f(p, l, s, t)dp$ gives

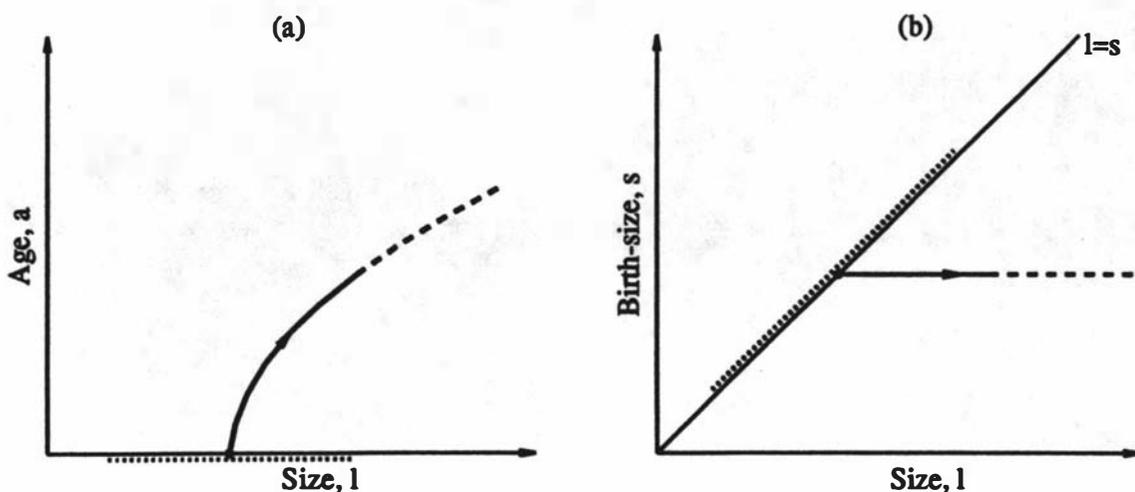


Figure 4.1: Possible paths followed by a single cell in (a) size/age space, and (b) size/birth-size space. The solid lines show cell trajectories, the dashed lines show where cell division may take place, and the dotted lines show where new cells may appear.

the probability that the birth-size of a daughter cell lies between fraction p and $p + dp$ of the parent cell size, given that the parent cell was born at size s and divides at time t and size l . For all l , s , and t , we require $f(p, l, s, t) = 0$ for $p > 1$ and $p < 0$, and

$$\int_0^1 f(p, l, s, t) dp = 1. \quad (4.1)$$

If the mean number of cells formed when an adult cell born at size s and dividing at time t and size l is $\alpha(l, s, t)$, then conservation of total cell size during division means that

$$\int_0^1 pf(p, l, s, t) dp = [\alpha(l, s, t)]^{-1} \quad (4.2)$$

for all l , s , and t .

The special case where all cells divide exactly in half and h_l is independent of initial cell size s (which means we write $h_l(l)$ only and set f equal to a Dirac delta function) has been discussed in Chapter 2 of this thesis and in Tyson and Diekmann [61], amongst others. In this chapter, we deal with uneven cell division, discussing the theory of the more general case in Part I, then, in Part II, solving extreme cases where either the division size of a cell is precisely determined by its birth size s , or where h_l is completely independent of s .

Using the notation established above, number conservation arguments based on the equation (1.11) in Chapter 1 show that the number density, $n(l, s, t)$, must satisfy

$$\frac{\partial}{\partial t} n(l, s, t) + \frac{\partial}{\partial l} g_l(l, s, t) n(l, s, t) = -h_l(l, s, t) g_l(l, s, t) n(l, s, t). \quad (4.3)$$

for $s > 0$ and $l > s$, along with an appropriate boundary condition on the line $l = s$.

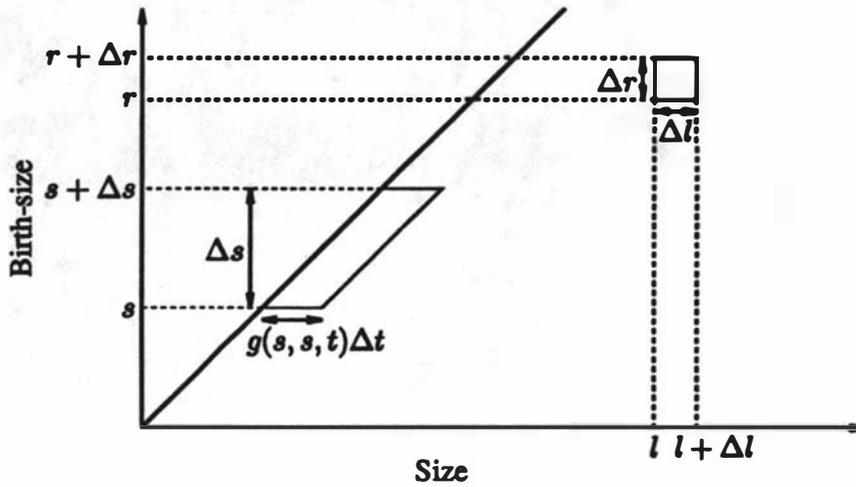


Figure 4.2: Formation of new cells along the line $l = s$ by division of cells in the region $l > s$. The parallelogram indicates the region containing all cells born in the size range s to $s + \Delta s$ in time Δt .

New cells come into existence along $l = s$ as a result of cell division in the region $l > s$. Consider the number of new cells born in the small size range s to $s + \Delta s$ in the short time interval Δt (Fig. 4.2). Summing the contributions from cells dividing all over the feasible region $l > s$, we obtain

$$n(s, s, t)g(s, s, t)\Delta t\Delta s = \sum_{l=s}^{\infty} \sum_{r=0}^l (h_l(l, r, t)g_l(l, r, t)\Delta t) \left(\alpha(l, r, t)f\left(\frac{s}{l}, l, r, t\right)\frac{\Delta s}{l} \right) (n(l, r, t)\Delta l\Delta r). \quad (4.4)$$

The first of the bracketed group of terms on the right hand side is the probability that a cell of size l and birth-size r will divide in time Δt , the second is the mean number of daughter cells in the size range s to $s + \Delta s$ produced by such a division, and the third is the number of cells in the size range l to $l + \Delta l$ with birth-size r to $r + \Delta r$. Dividing through by $\Delta t\Delta s$ and taking limits we obtain the boundary condition in the form of a renewal equation,

$$g_l(s, s, t)n(s, s, t) = \int_s^{\infty} \int_0^l h_l(l, r, t)g_l(l, r, t)\alpha(l, r, t)f\left(\frac{s}{l}, l, r, t\right)n(l, r, t)dr\frac{dl}{l}. \quad (4.5)$$

4.1.2 Steady Size/birth-size Distributions

We now make the following assumptions:

- The hazard rate, h_l , is time-independent, i.e. $h_l = h_l(l, s)$.
- The fractional-size pdf, f , is dependent only on the proportion p , i.e. $f = f(p)$. It then follows from (4.2) that α is a constant. Then (4.1) and (4.2) become

$$\int_0^1 f(p) dp = 1 \quad (4.6)$$

and

$$\int_0^1 pf(p, l, s, t) dp = [\alpha(l, s, t)]^{-1} \quad (4.7)$$

respectively.

- The growth rate is separable with respect to time, i.e. $g_l(l, s, t) = g(l, s)r(t)$ say.

We are interested in the situation where the total number of cells in the population is increasing, but the proportion of the population currently in any given size range and born in a given size range remains constant. Under these conditions, the cell number density function $n(l, s, t)$ is separable, and we may write

$$n(l, s, t) = N(t)y(l, s), \quad (4.8)$$

where $y(l, s)$ is a probability density function so

$$\int_0^\infty \int_s^\infty y(l, s) dl ds = 1, \quad (4.9)$$

and of course we need $y(l, s) \geq 0, \forall l, s$. The proportion of cells in the size l_1 to l_2 which were born in the size range s_1 to s_2 is given by $\int_{l_1}^{l_2} \int_{s_1}^{s_2} y(l, s) ds dl$. We will refer to $y(l, s)$ as the steady size/birth-size distribution.

Substituting (4.8) into (4.3), we now obtain

$$\frac{dN}{dt} y(l, s) + N(t)r(t) \frac{\partial}{\partial l} (g(l, s)y(l, s)) = -N(t)r(t)h_l(l, s)g(l, s)y(l, s), \quad (4.10)$$

and the renewal equation, (4.5), becomes

$$g(s, s)y(s, s) = \alpha \int_s^\infty \int_0^l y(l, r)h_l(l, r)g(l, r)f\left(\frac{s}{l}\right)dr \frac{dl}{l}. \quad (4.11)$$

Integrating (4.10) over all s and l , substituting $g(s, s)y(s, s)$ from (4.11) leads to

$$\frac{dN}{dt} = QN(t)r(t), \quad (4.12)$$

where Q is the functional on y defined by

$$Q = (\alpha - 1) \int_0^\infty \int_s^\infty y(l,s) h_l(l,s) g(l,s) dl ds. \quad (4.13)$$

Substituting the expression for dN/dt given in (4.12) into (4.10), we obtain a partial differential equation for $y(l,s)$,

$$\frac{\partial g(l,s)y(l,s)}{\partial l} = -(h_l(l,s)g(l,s) + Q)y(l,s). \quad (4.14)$$

Thus the problem of finding the steady size/birth-size distribution $y(l,s)$ becomes one of solving (4.14) with its boundary condition, (4.11), subject to the normalising condition (4.9). Note that (4.13) can be obtained by integrating (4.14) over all l and s then using (4.9) and (4.11), so (4.13) is an alternative normalising condition rather than an independent equation.

4.1.3 Growth Rate Proportional to Cell Size

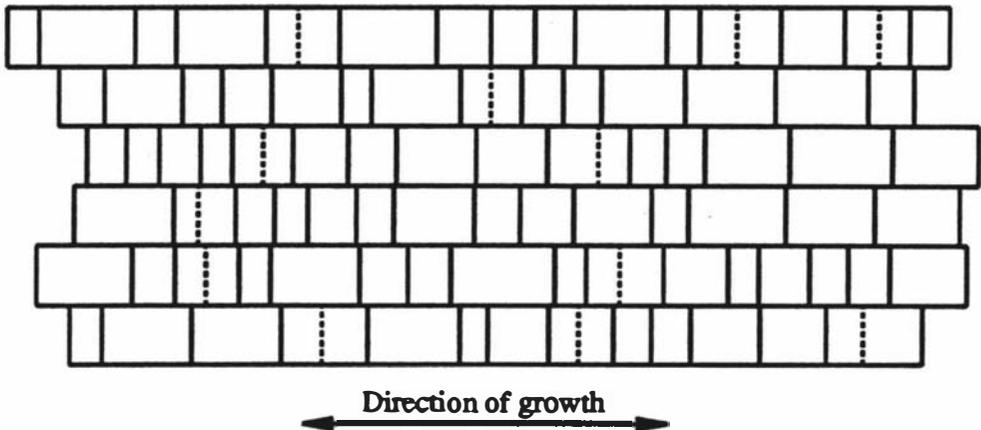


Figure 4.3: An idealised section of plant tissue growing by elongation in one dimension. Cells are arranged in files and are locked together by common longitudinal walls. When cells divide, new cross-walls (dashed lines) form within the parent cell, and two new cells are formed (i.e. $\alpha = 2$). We assume there are sufficient files at right angles to the direction of growth to allow use of continuous number density and probability density functions.

In this chapter we are interested in steady cell size distributions in plant tissues growing in one dimension only. Fig. 4.3 reproduces Fig 1.6 from Chapter 1, showing an idealised

section of a root or leaf, elongating in a spatially homogeneous manner such that any two points a unit distance apart separate at a time-varying rate $r(t)$. We take the size of a cell to be its length, l , in the direction of growth. Plants grow symplastically, i.e. with longitudinal files of cells locked together so that cells in adjacent files do not slip past each other. This means that all cells in a small region may be assumed to grow at the same relative growth rate $r(t)$, so that

$$g_l(l, s, t) = lr(t). \quad (4.15)$$

This assumption is central to all that follows, as it leads to considerable simplification of the more general theory.

Now the total length of all cells in a section of tissue as in Fig. 4.3 is $\int_0^\infty l \int_0^l n(l, s, t) ds dl$, and the rate of change caused by cell growth is $\int_0^\infty \int_0^l g_l(l, s, t) n(l, s, t) ds dl$. Using (4.8) and (4.15) we then have

$$\frac{d}{dt} \left(\int_0^\infty l \int_0^l y(l, s) N(t) ds dl \right) = \int_0^\infty \int_0^l lr(t) y(l, s) N(t) ds dl. \quad (4.16)$$

Interchanging the order of differentiation and integration and substituting for dN/dt using (4.12) yields simply

$$Q = 1, \quad (4.17)$$

which is the same as (1.85) with the constant $g \equiv 1$. Substituting this value of Q and $g(l, s) = l$ into (4.14), we obtain

$$l \frac{\partial y(l, s)}{\partial l} = -(h_l(l, s)l + 2)y(l, s), \quad (4.18)$$

and the renewal equation (4.11) may be rewritten as

$$sy(s, s) = \alpha \int_s^\infty \int_0^l y(l, r) h_l(l, r) f\left(\frac{s}{l}\right) dr dl. \quad (4.19)$$

Since both (4.18) and (4.19) are homogeneous, any solution of this system will contain an arbitrary multiplicative constant. This constant can be evaluated either using the unit integral condition (4.9), or using (4.13) with $Q = 1$, i.e.,

$$(\alpha - 1) \int_0^\infty \int_s^\infty ly(l, s) h_l(l, s) dl ds = 1. \quad (4.20)$$

Following standard reliability or demographic theory, we now introduce a *survivor function*, $B_l(l, s)$, which is the probability that a cell initially of size s will survive without division to at least size l . In terms of the hazard rate h_l , $B_l(l, s)$ is given by

$$B_l(l, s) = e^{-\int_s^l h_l(\sigma, s) d\sigma}. \quad (4.21)$$

If for a given birth size s , there is a *maximum cell size* $L(s)$ such that $\int_s^l h_l(\sigma, s) d\sigma$ is finite for $l < L(s)$ but $\int_s^{L(s)} h_l(\sigma, s) d\sigma$ is infinite, then $B(L(s), s) = 0$, and we set $y(l, s) = 0$ outside the region $s \leq l \leq L(s)$. The derivative of B_l ,

$$b_l(l, s) = -\frac{\partial B_l(l, s)}{\partial l}, \quad (4.22)$$

is a pdf such that $b_l(l, s) dl$ gives the probability that a cell initially of size s will divide in the size range l to $l + dl$. From (4.21) and (4.22) it follows that

$$b_l(l, s) = h_l(l, s) B_l(l, s). \quad (4.23)$$

The characteristics of (4.18) are parallel to the l axis, so (4.18) can be integrated directly (cf. Sinko and Streifer [52] where the problem is formulated in terms of cell size and age) to give

$$y(l, s) = \frac{s\phi(s)}{l^2} B_l(l, s), \quad (4.24)$$

where ϕ is a function yet to be found, and $B_l(l, s)$ is the survivor function given by (4.21).

4.1.4 Size, size/age, and birth-size distributions

We leave to one side for the moment the question of how $\phi(s)$ in (4.24) is to be evaluated, and look at ways in which various other distributions may be expressed in terms of $\phi(s)$.

Integrating (4.24), we obtain the one-dimensional cell size pdf $Y(l) = \int_0^l y(l, s) ds$,

$$Y(l) = \frac{1}{l^2} \int_0^l s\phi(s) B_l(l, s) ds. \quad (4.25)$$

To describe a size/age distribution, we define a pdf $y_a(l, a, t)$ such that $y_a(l, a, t) da dl$ gives the proportion of cells whose ages lie in the range a to $a + da$ and whose sizes lie between l and $l + dl$. In general, the size/age distribution may be non-steady when the size/birth-size distribution is steady. The growth rate of an individual cell of size l (and any initial size s) is given by (4.15), so we solve $dl/dt = r(t)l$ to obtain

$$s = le^{-\int_{t-a}^t r(t') dt'}. \quad (4.26)$$

Given this relationship between s and a , we must have $y_a(l, a, t) da = -y(l, s) ds$ where $ds = -r(t - a)le^{-\int_{t-a}^t r(t') dt'} da$, so

$$y_a(l, a, t) = r(t - a)le^{-\int_{t-a}^t r(t') dt'} y(l, le^{-\int_{t-a}^t r(t') dt'}). \quad (4.27)$$

Using (4.24), we can then obtain $y_a(l, a, t)$ in terms of $\phi(l)$ as

$$y_a(l, a, t) = r(t - a)e^{-2\int_{t-a}^t r(t') dt'} \phi(le^{-\int_{t-a}^t r(t') dt'}) B_l(l, le^{-\int_{t-a}^t r(t') dt'}). \quad (4.28)$$

Steady size/age distributions $y_a(l, a)$ are only possible if the growth rate is steady, i.e. when $r(t)$ is a constant, say g . In this case, we obtain

$$y_a(l, a) = ge^{-2ga} \phi(le^{-ga}) B_l(l, le^{-ga}). \quad (4.29)$$

From (4.28), the size distribution of newborn cells is just

$$y_a(l, 0, t) = r(t)\phi(l), \quad (4.30)$$

so we may interpret $\phi(l)$ as a multiple of the pdf describing the newborn cell size distribution. Substituting (4.24) into (4.9) and integrating by parts, we have

$$\int_0^\infty \phi(s) ds - \int_0^\infty s\phi(s) \left[\int_s^\infty \frac{b_l(l, s)}{l} dl \right] ds = 1. \quad (4.31)$$

Similarly, substituting (4.24) into (4.20) gives

$$\int_0^\infty s\phi(s) \left[\int_s^\infty \frac{b_l(l, s)}{l} dl \right] ds = (\alpha - 1)^{-1} \quad (4.32)$$

Adding (4.31) to (4.32), we then obtain the condition

$$\int_0^\infty \phi(s) ds = (1 - \alpha^{-1})^{-1}, \quad (4.33)$$

which will be used to normalise $\phi(s)$ where required in Part II of this chapter. If we now define a birth-size distribution $y_0(s)$ such that $y_0(s) ds$ gives the probability that a given newborn cell lies in the size range s to $s + ds$, then as y_0 is proportional to ϕ and $\int_0^\infty y_0(s) ds = 1$, we must have

$$y_0(s) = (1 - \alpha^{-1})\phi(s). \quad (4.34)$$

4.1.5 A Fredholm Integral Equation for $\phi(s)$ and its Unique Solution

An integral equation for $\phi(s)$ is obtained by substituting the solution (4.24) into the boundary condition (4.19), giving

$$\phi(s) = \alpha \int_s^\infty \int_0^l r \phi(r) b_l(l, r) f\left(\frac{s}{l}\right) \frac{1}{r^2} dr dl, \quad (4.35)$$

where b_l is given by (4.22). We then change the order of integration, writing (4.35) in the form of a homogeneous Fredholm integral equation,

$$\phi(l) = \alpha \int_0^\infty K(l, s) \phi(s) ds, \quad (4.36)$$

where the kernel $K(l, s)$ is given by

$$K(l, s) = s \int_s^\infty f\left(\frac{l}{r}\right) b_l(r, s) \frac{dr}{r^2}, \quad (4.37)$$

and we note that $f(\frac{l}{r}) = 0$ if $r < l$. Changing the variable of integration to $p = \frac{l}{r}$ gives as an alternative form for the kernel,

$$K(l, s) = \frac{s}{l} \int_0^1 f(p) b_l\left(\frac{l}{p}, s\right) dp. \quad (4.38)$$

We assume that f and b_l are such that this kernel $K(l, s)$ exists and is square-integrable on the appropriate subset of the $l - s$ plane. We wish to show that (4.36), with a kernel given by (4.37) or (4.38), has just one independent, non-negative solution. Hochstadt [25] shows that every continuous, strictly positive kernel $K(l, s)$ on a finite rectangle has a largest positive eigenvalue, and that associated with this principal eigenvalue there is only one independent eigenfunction. This eigenfunction is also strictly positive (or strictly negative). Zabreyko et al. [69] show that this result can be extended to non-negative kernels like $K(l, s)$ given by (4.37) or (4.38), provided that the kernels are *non-factorable* in the appropriate subset of the $l - s$ plane. That is, for any $\phi \geq 0, \neq 0$ and $l > 0$, we must have

$$\int_0^\infty K^{(N)}(l, s) \phi(s) ds > 0, \quad (4.39)$$

for some $N \geq 0$, where $K^{(N)}$ is the N th iterated kernel as defined in either Hochstadt [25] or Kabreyko et al. [69]. A non-negative kernel satisfying (4.39) must then have a largest positive eigenvalue, and corresponding to this eigenvalue there is just one independent eigenfunction, which is non-negative (or non-positive) but not identically zero. Biologically, (4.39) is equivalent to restricting f and b_l to functions such that an ancestral cell of some

birth-size can produce, after a finite number of generations, a descendent cell with any other birth-size in the domain considered. A set of precise conditions on f and b_l , which are sufficient to ensure that the kernel $K(l, s)$ given by (4.38) is both square-integrable and non-factorable, is presented in Section 5.1.

Let the largest positive eigenvalue be λ , and let $\phi(l)$ be a multiple of the corresponding eigenfunction chosen such that ϕ is non-negative. Then

$$\int_0^{\infty} K(l, s)\phi(s)ds = \lambda\phi(l), \quad (4.40)$$

and, using (4.37), it follows that

$$\begin{aligned} \lambda \int_0^{\infty} l\phi(l)dl &= \int_0^{\infty} l \left(\int_0^{\infty} K(l, s)\phi(s)ds \right) dl \\ &= \int_0^{\infty} l \int_0^{\infty} s \int_s^{\infty} f\left(\frac{l}{r}\right)b_l(r, s)\frac{1}{r^2}dr\phi(s)dsdl. \end{aligned} \quad (4.41)$$

Changing the order of integration gives

$$\lambda \int_0^{\infty} l\phi(l)dl = \int_0^{\infty} s\phi(s) \int_s^{\infty} b_l(r, s) \int_0^{\infty} f\left(\frac{l}{r}\right)\frac{l}{r}dl dr ds. \quad (4.42)$$

Noting that $f(p) = 0$ for $p > 1$ and using (4.7) and the fact that $\int_s^{\infty} b_l(r, s)dr = 1, \forall s$, we obtain

$$\lambda \int_0^{\infty} l\phi(l)dl = \alpha^{-1} \int_0^{\infty} s\phi(s)ds. \quad (4.43)$$

As $\phi(s)$ is non-negative and not identically zero, we therefore have

$$\lambda = \alpha^{-1}. \quad (4.44)$$

Thus α^{-1} is the principal eigenvalue of the kernel $K(l, s)$ in (4.37) or (4.38), and it follows that the Fredholm integral equation (4.36) has just one independent solution, which is also non-negative (or non-positive) but not identically zero. Hence there will be just one function $\phi(l)$ satisfying both (4.36) and (4.33), and as the integral is positive this $\phi(l)$ will in fact be non-negative and not identically zero.

4.1.6 Discussion

We have shown in (4.24) that the steady size/birth-size pdf, $y(l, s)$, for cells in small regions within one-dimensional plant tissues, can be expressed in terms of $\phi(s)$, a multiple

of the cell birth-size pdf. The corresponding size/age distribution $y_a(l, a, t)$ is given by (4.28) and the one-dimensional steady size distribution $Y(l)$ given by (4.25). All of these solutions depend on $\phi(s)$, which is the eigenfunction of the Fredholm kernel (4.37) or (4.38), normalised by (4.33). In the Part II of this chapter we show that this eigenfunction can be found in some special cases using analytical techniques, and more generally by a simple numerical iteration.

However, even without finding the birth-size distribution $\phi(s)$, it is possible to make some comments on the general shapes of the functions $y(l, s)$, $Y(l)$, and $y_a(l, a, t)$, given realistic forms of the pdfs $f(p)$ and $b_l(l, s)$. Biological considerations dictate that there will be limits on the proportions into which a cell can divide, so the support of f must be $[p_1, p_2]$ with $0 < p_1 < p_2 < 1$. Similarly, for any initial cell size s , there will be some minimum size $L^*(s)$, below which a cell cannot divide, and some maximum size, $L(s)$, by which it will definitely have divided, with $s < L^*(s) < L(s)$ (Fig. 4.4). Both $L^*(s)$ and $L(s)$ should be *monotonic non-decreasing* functions of s , because cells which are born at a larger size should in general also divide at a larger size, but the functions $L^*(s)/s$ and $L(s)/s$ should be *monotonic decreasing* in the sense that cells which are born at a smaller size in general need to grow to a greater multiple of their initial size before dividing.

If we let the support of $\phi(s)$ be $[s_{\min}, s_{\max}]$, a cell of birth-size s_{\min} must divide as an adult so that the smallest possible size for any of its offspring is also s_{\min} . Thus s_{\min} is the solution of

$$s_{\min} = p_1 L^*(s_{\min}), \quad (4.45)$$

and this will be unique because of the monotonicity of $L^*(s)/s$. Similarly, s_{\max} is the unique solution of

$$s_{\max} = p_2 L(s_{\max}). \quad (4.46)$$

In Fig. 4.4 the regions in which $y(l, s)$ can be non-zero are shaded. In region A there is no cell division, so $B_l(l, s) = 1$, and from (4.24) $y(l, s)$ varies as $1/l^2$ along any line parallel to the l axis. Cell division occurs in region B, so $y(l, s)$ drops faster than $1/l^2$ there, reaching zero on the line $l = L(s)$. In some situations, it is possible for $L^*(s_{\min})$ to be greater than s_{\max} , in which case for $L^*(s_{\min}) > l > s_{\max}$, the integral in (4.25) is a constant, so $Y(l)$ obeys an inverse-square law. This occurs irrespective of the precise forms of $f(p)$ or $b_l(l, s)$, provided that the condition $L^*(s_{\min}) > s_{\max}$ is satisfied. This "inverse square" behaviour in a central region is apparent in published examples of steady cell size pdfs $Y(l)$ where the relative growth rate of cells is roughly constant in this region. (e.g. Collins and Richmond [7]).

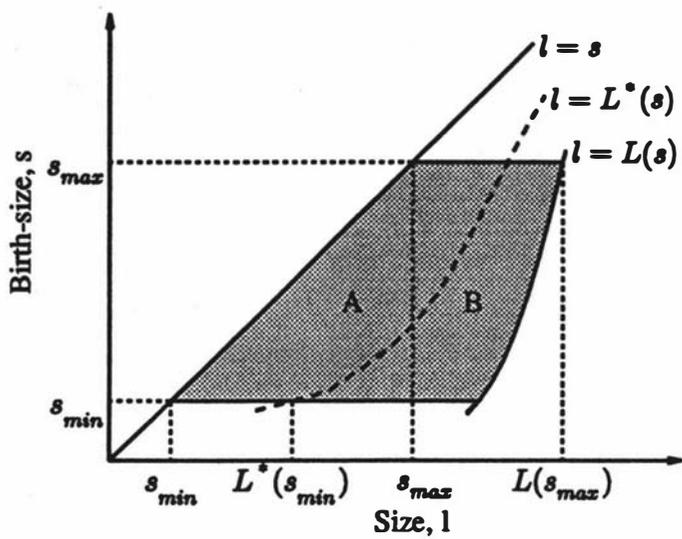


Figure 4.4: Regions in which $y(l,s)$ is non-zero. Cell division takes place in region B only, where $l > L^*(s)$.

4.2 Part II: Solving the Integral Equation

In Part II, we solve (4.36) for various choices of $f(p)$ and $b_l(l, s)$, using (4.33) to normalise the solution, $\phi(s)$. In each case, the size/birth-size distribution, $y(l, s)$ and the overall size distribution, $Y(l)$ are then calculated from (4.24) and (4.25) respectively and an example is displayed in graphical form.

4.2.1 Constant cell division size

Consider the simplest possible case with uneven division, where all cells divide at the same size, L . We do not impose restrictions on the form of $f(p)$, so we consider the feasible region for cells to be the triangle shaded in Fig. 4.5. Since all cells divide on the line $l = L$,

$$b_l(l, s) = \delta(l - L), \quad (4.47)$$

where δ represents the Dirac delta function. Hence the kernel, (4.37), of the homogeneous Fredholm equation becomes

$$K(l, s) = \frac{s}{L^2} f\left(\frac{l}{L}\right), \quad (4.48)$$

and (4.36) becomes

$$\phi(l) = \frac{\alpha}{L^2} f\left(\frac{l}{L}\right) \int_0^L s \phi(s) ds. \quad (4.49)$$

The integral in (4.49) does not depend on l , so we may write simply

$$\phi(l) = A f\left(\frac{l}{L}\right). \quad (4.50)$$

We now substitute this $\phi(l)$ into the integral condition, (4.33), to obtain

$$A = \frac{1}{(1 - \alpha^{-1})L}, \quad (4.51)$$

so that

$$\phi(l) = \frac{1}{(1 - \alpha^{-1})L} f\left(\frac{l}{L}\right). \quad (4.52)$$

From (4.24) we then have

$$y(l, s) = \frac{1}{(1 - \alpha^{-1})L} \frac{s}{L^2} f\left(\frac{s}{L}\right), \quad (4.53)$$

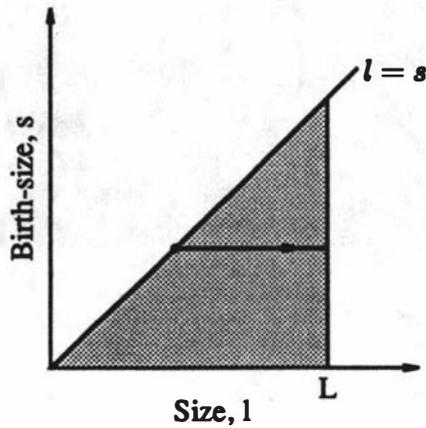


Figure 4.5: The feasible region when all cells divide at the same size, L . A cell born on the line $l = s$ divides on reaching the vertical line $l = L$.

and the one-dimensional steady size distribution is found using (4.25) to be

$$Y(l) = \frac{L}{(1 - \alpha^{-1})l^2} \int_0^l sf(s)ds. \quad (4.54)$$

Fig. 4.6(a) shows $y(l,s)$ in the case where $f(p)$ is a normal distribution with mean 0.5 (so $\alpha = 2$) and standard deviation 0.1. Note that if the standard deviation of the normal distribution were chosen to be much larger, care would need to be taken in truncating it so that the support of f is limited to $[0,1]$. The corresponding one-dimensional size distribution $Y(l)$ is shown in Fig. 4.6(b), with the line $Y = L/l^2$ shown as a dashed line for comparison.

The size/age distribution corresponding to (4.53) may be obtained from (4.28). In the particular case where the growth rate is steady with $r(t) = g$, (4.29) gives the steady size/age distribution as

$$y_a(l, a) = \frac{g}{(1 - \alpha^{-1})L} f\left(\frac{l}{L}e^{-ga}\right)e^{-2ga}. \quad (4.55)$$

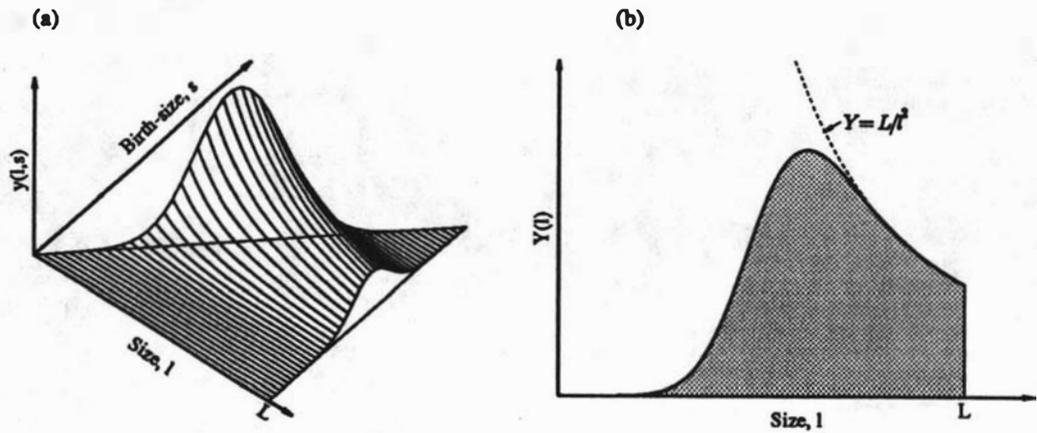


Figure 4.6: (a) The steady size/birth-size pdf $y(l,s)$ and (b), the steady size pdf $Y(l)$ in the case where $f(p)$ is a normal distribution with mean 0.5 and standard deviation 0.1.

4.2.2 Hazard Rate Independent of Initial Cell Size

A general solution process

Consider the case where the hazard rate $h_i(l,s)$ is independent of the initial cell size s , i.e. $h_i = h_i(l)$. The stability of the steady size distribution in this model has been discussed in Heijmans [23], and a solution procedure for the special case $f(p) = \delta(p - 1/\alpha)$ has been described in Chapter 2 of this thesis.

From (4.21) we have

$$B_l(l,s) = e^{-\int_s^l h_i(l') dl'}, \quad l > s, \quad (4.56)$$

which is clearly not independent of s in general. It is useful, therefore, to define

$$B_l^*(l) = e^{-\int_0^l h_i(l') dl'}, \quad (4.57)$$

with the corresponding pdf

$$b_l^*(l) = -\frac{dB_l^*(l)}{dl}. \quad (4.58)$$

Thus we can write

$$B_l(l,s) = \frac{B_l^*(l)}{B_l^*(s)}, \quad l > s, \quad (4.59)$$

so for any l and s ,

$$b_l(l, s) = \frac{b_l^*(l)}{B_l^*(s)} H(l - s), \quad (4.60)$$

where H is the unit step function. Because the hazard rate is independent of cell birth-size, the minimum and maximum sizes for cell division, $L^*(s)$ and $L(s)$, (Fig. 4.4) become constants, L^* and L respectively. All cells must then divide in the region (L^*, L) (Fig. 4.7(a)). If the support of f is $[p_1, p_2]$, with $0 < p_1 < p_2 < 1$, the feasible region for cells is that shaded in Fig. 4.7(a). With this notation, $b_l^*(l)$ may be specified as any pdf on (L^*, L) , then $b_l(l, s)$ can be found using (4.60). For $s < L^*$, $b_l(l, s)$ is identical to $b_l^*(l)$, so $b_l^*(l)dl$ may be interpreted the probability that a cell with birth size less than L^* will divide between size l and size $l + dl$.

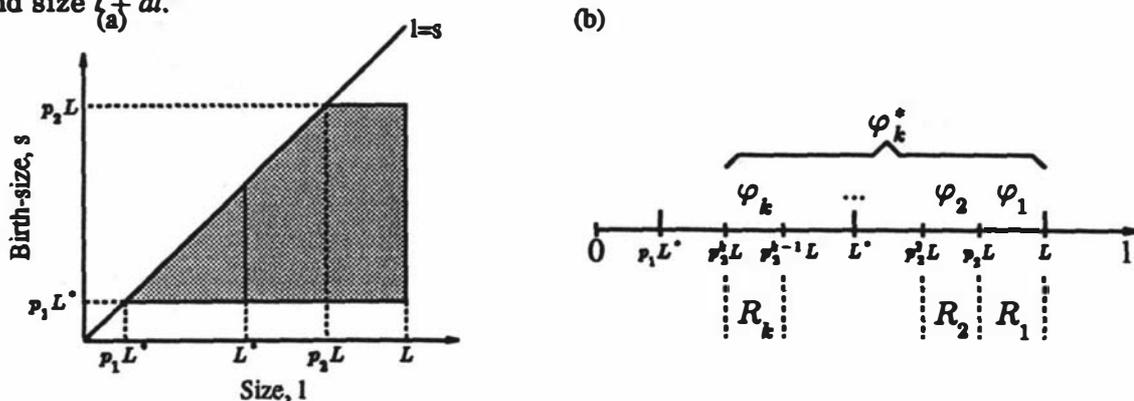


Figure 4.7: (a) The feasible region for cells when the hazard rate is independent of initial cell size. Cell division takes place only where $l > L^*$. (b) The regions used in solving for the eigenfunction $\phi(l)$. See text for details.

Given this form of $b_l(l, s)$, we may write the kernel (4.38) of the Fredholm integral equation as

$$K(l, s) = \frac{s}{lB_l^*(s)} \int_{p_1}^{p_2} f(p)b_l^*\left(\frac{l}{p}\right)H\left(\frac{l}{p} - s\right)dp, \quad (4.61)$$

so we obtain from (4.36), after a change of integration order,

$$\phi(l) = \frac{\alpha}{l} \int_{p_1}^{p_2} f(p)b_l^*\left(\frac{l}{p}\right) \left[\int_0^{\frac{l}{p}} \frac{s\phi(s)}{B_l^*(s)} ds \right] dp, \quad (4.62)$$

where the upper limit of the integral with respect to s has come from Heaviside function in (4.61). We now define

$$\varphi(l) = \frac{\phi(l)}{\int_0^\infty \frac{s\phi(s)}{B_l^*(s)} ds}, \quad (4.63)$$

so (4.62) may be rewritten as

$$\varphi(l) = \frac{\alpha}{l} \int_{p_1}^{p_2} f(p) b_l^* \left(\frac{l}{p} \right) \left[1 - \int_{\frac{l}{p}}^{\infty} \frac{s \varphi(s)}{B_l^*(s)} ds \right] dp. \quad (4.64)$$

Now $p < p_2 < 1$, so in the inner integral $s > l/p_2 > l$. Hence (4.64) expresses $\varphi(l)$ in terms of $\varphi(s) | s > l/p_2$, which suggests that we may solve iteratively for $\varphi(l)$ in a finite number of steps provided that p_2 is strictly less than 1. To provide a starting point for this iteration, we observe from Fig. 4.7(a) that $\varphi(l) = 0$ for $l > p_2 L$ and for $l < p_1 L^*$. We divide the region $p_1 L^* < l \leq L$ (Fig. 4.7(b)) into m sub-regions, where m is the smallest integer such that $p_2^m L \leq p_1 L^*$, with the k th region R_k as

$$R_k = \{l \mid p_2^k L < l \leq p_2^{k-1} L\}, \quad 1 \leq k \leq m. \quad (4.65)$$

The m th region may be "truncated", having a lower bound of $p_1 L^*$ instead of $p_2^m L$. Then we denote the solution in region R_k by $\varphi_k(l)$, and the solution in the union of regions R_1 to R_k by $\varphi_k^*(l)$, as shown in Fig. 4.7(b).

Starting with region R_1 we have

$$\varphi_1(l) = 0, \quad (4.66)$$

$$\varphi_2(l) = \frac{\alpha}{l} \int_{p_1}^{p_2} f(p) b_l^* \left(\frac{l}{p} \right) dp, \quad (4.67)$$

\vdots

$$\varphi_k(l) = \frac{\alpha}{l} \int_{p_1}^{p_2} f(p) b_l^* \left(\frac{l}{p} \right) \left[1 - \int_{\frac{l}{p}}^{\infty} \frac{s \varphi_{k-1}^*(s)}{B_l^*(s)} ds \right] dp, \quad (4.68)$$

\vdots

The iteration stops at $\varphi_m(l)$, at which stage we know $\varphi(l)$ in the entire region $(p_1 L^*, p_2 L)$. Hence, from (4.63), $\phi(l)$ is

$$\phi(l) = A \varphi(l), \quad (4.69)$$

where from the integral condition (4.33),

$$A = \left[(1 - \alpha^{-1}) \int_0^{\infty} \varphi(s) ds \right]^{-1}. \quad (4.70)$$

We can then use (4.24), (4.25), and (4.28) to find $y(l, s)$, $Y(l)$, and $y_a(l, a, t)$ respectively.

The "no overlap" case

In the particular case where there is no overlap in size between the size distributions of newborn cells and of parent cells ($L^* \geq p_2 L$ in Fig. 4.7), a much simpler solution can be presented. In this case the inner integral in (4.62) is a constant, A_1 say, so that (4.62) may be written as

$$\phi(l) = A_1 \frac{\alpha}{l} \int_{p_1}^{p_2} f(p) b_l^* \left(\frac{l}{p} \right) dp. \quad (4.71)$$

The constant A_1 is evaluated using the integral condition (4.33). After simplification using (4.6) and (4.2) we obtain

$$A_1 = \left[(\alpha - 1) \int_{L^*}^L \frac{b_l^*(l)}{l} dl \right]^{-1}. \quad (4.72)$$

Substituting (4.71) into (4.24), we have

$$y(l, s) = A_1 \alpha \frac{B_l^*(l)}{l^2} \int_{p_1}^{p_2} f(p) b_l^* \left(\frac{s}{p} \right) dp, \quad (4.73)$$

and then from (4.25) the steady size pdf is

$$Y(l) = A_1 \alpha \frac{B_l^*(l)}{l^2} \int_{p_1}^{p_2} p f(p) \left(1 - B_l^* \left(\frac{l}{p} \right) \right) dp. \quad (4.74)$$

This expression for $Y(l)$ is a particular case of a more general result given in Tyson and Diekmann [61].

The general form of the size-age distribution at time t may be found by substituting (4.71) into (4.28), or if the growth rate is steady with $r(t) = g$ we use (4.29) to obtain

$$y(l, a) = A_1 \alpha \frac{B_l^*(le^{-ga})}{l} \int_{p_1}^{p_2} f(p) b_l^* \left(\frac{le^{-ga}}{p} \right) dp. \quad (4.75)$$

As an illustrative example which can be solved analytically, we choose $f(p)$ to be the quartic with minima at $(p_1, 0)$ and $(p_2, 0)$, scaled so that (4.6) is satisfied and truncated so that $f(p) = 0$ for $p > p_2$ and for $p < p_1$,

$$f(p) = 30 \frac{(p_2 - p)^2 (p - p_1)^2}{(p_2 - p_1)^5} H(p_2 - p) H(p - p_1). \quad (4.76)$$

For $b_l^*(l)$ we choose a quartic similarly truncated at minima at $(L^*, 0)$ and $(L, 0)$,

$$b_l^*(l) = 30 \frac{(L - l)^2 (l - L^*)^2}{(L - L^*)^5} H(L - l) H(l - L^*). \quad (4.77)$$

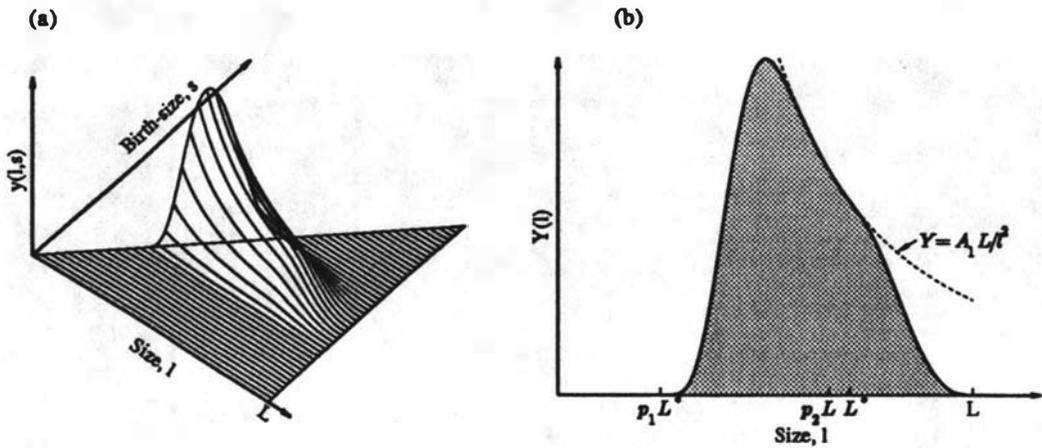


Figure 4.8: (a) The steady size/birth-size pdf $y(l,s)$ and (b) the steady size pdf $Y(l)$ where $f(p)$ is a quartic truncated at minima at $p_1 = 0.35$ and $p_2 = 0.65$, and b_l^* is also a quartic, truncated at minima at $L^* = 0.7L$ and L .

The factor 30 comes from the requirement that f and b_l^* are both probability density functions, so each must have unit integral. In the example shown in Fig. 4.8, we have chosen $p_1 = 0.35$, $p_2 = 0.65$, and $L^* = 0.7L$, so the condition $L^* < p_2 L$ is satisfied. We have then used equations (4.73) and (4.74) to obtain $y(l,s)$ and $Y(l)$ as shown in Fig. 4.8 (a) and (b) respectively. If we chose different forms of $f(p)$ and $b_l^*(l)$, the two-dimensional size/birth-size distribution $y(l,s)$ as in Fig. 4.8(a) would still consist of a set of “inverse square” lines along the characteristics up to $l = L^*$, then a more rapid decrease down to $y(l,s) = 0$. The dashed line in Fig. 4.8(b) is the line $Y = A_1 L / l^2$, which closely matches the solution $Y(L)$ on a region larger than just $(p_2 L, L^*)$.

4.2.3 Cell Division Size Precisely Determined by Birth-size

The Simplified Kernel

In the previous section, we considered the case in which the hazard rate is completely independent of initial cell size. Here we consider the opposite extreme, where cell division size is precisely determined by initial size, i.e. where all cells born at one size will divide at the same larger size. This means that the minimum and maximum sizes for cell division, $L^*(s)$ and $L(s)$ (Fig. 4.4), are made to coincide, so we set

$$B_l(l,s) = 1 - H(l - L(s)), \quad (4.78)$$

where H is the unit step function, and

$$b_l(l, s) = \delta(l - L(s)), \quad (4.79)$$

where δ is the Dirac delta function. Thus, cells born at size s grow without division until they reach $l = L(s)$ and then divide.

Under these conditions, we can substitute (4.79) into the kernel of the Fredholm integral (4.37) to obtain

$$K(l, s) = \frac{s}{(L(s))^2} f\left(\frac{l}{L(s)}\right), \quad (4.80)$$

so the equation for $\phi(l)$ is

$$\phi(l) = \alpha \int_0^\infty \frac{s}{(L(s))^2} f\left(\frac{l}{L(s)}\right) \phi(s) ds. \quad (4.81)$$

Once again, ϕ must satisfy the integral condition (4.33), and we note that $f(l/L(s)) = 0$ for $L(s) < l$.

Despite its apparent simplicity (4.81) is not easy to deal with in general. In the following, we choose a realistic form for $L(s)$ together with the simplest possible form of $f(p)$ in order to obtain a series solution.

A Special Case: A Power Law $L(s)$, and a Uniform Distribution for $f(p)$

We consider here the special case

$$L(s) = L^{1-\gamma} s^\gamma, \quad 0 < \gamma < 1, \quad (4.82)$$

where L is now a parameter with units of length. We make $0 < \gamma < 1$ so that $L(s)$ satisfies the requirements set out in section 4.1.6, that $L(s)$ is monotonic non-decreasing on $(0, L)$ and $L(s)/s$ is monotonic decreasing.

The kernel, (4.80), of the Fredholm integral equation then becomes

$$K(l, s) = \frac{s^{1-2\gamma}}{L^{2(1-\gamma)}} f\left(\frac{l}{L^{1-\gamma} s^\gamma}\right). \quad (4.83)$$

For $f(p)$, we choose the uniform distribution on $(0, 2\alpha^{-1})$,

$$f(p) = \frac{\alpha}{2} H(2\alpha^{-1} - p), \quad (4.84)$$

so that the mean of the distribution is α^{-1} as required by (4.7). This choice of f is unrealistic, but it allows us to illustrate the use of analytical solution techniques. Note that for this form of $f(p)$ it is necessary that $\alpha \geq 2$, to prevent formation of daughter cells larger than parent cells.

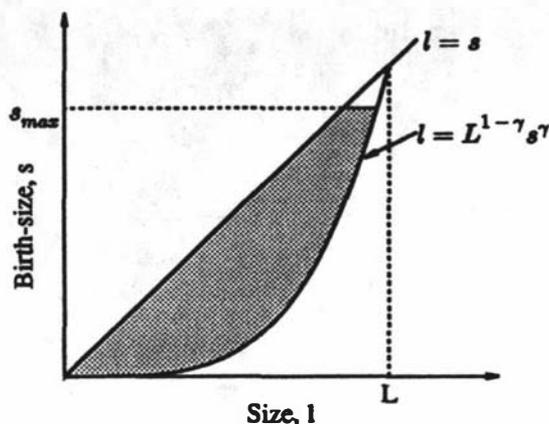


Figure 4.9: The feasible region for cells when $L(s) = L^{1-\gamma} s^\gamma$, and $f(p) = H(2\alpha^{-1} - p)\alpha/2$. For $\alpha = 2$, $s_{\max} = L$, but in this figure $\alpha > 2$, so from (4.85) $s_{\max} < L$.

For this form of $f(p)$, $p_1 = 0$, so from (4.45) we have $s_{\min} = 0$. Substituting (4.82) and $p_2 = 2\alpha^{-1}$ into (4.46), we obtain

$$s_{\max} = \left(\frac{2}{\alpha}\right)^{\frac{1}{1-\gamma}} L, \quad (4.85)$$

which gives the feasible region for cells shaded in Fig. 4.9. Note that if $\alpha = 2$, we would have $s_{\max} = L$ so the shading would continue up to the point where the line $l = s$ meets the line $l = L^{1-\gamma} s^\gamma$. In the shaded region, substitution of (4.83) into (4.36) gives

$$\phi(l) = \frac{\alpha^2}{2} \int_0^{s_{\max}} H\left(\frac{2}{\alpha} - \frac{l}{L^{1-\gamma} s^\gamma}\right) \frac{s^{1-2\gamma}}{L^{2(1-\gamma)}} \phi(s) ds \quad (4.86)$$

which can be written as

$$\phi(l) = \frac{2}{s_{\max}^{2(1-\gamma)}} \int_{\left(\frac{l}{s_{\max}}\right)^{\frac{1}{\gamma}} s_{\max}}^{s_{\max}} s^{1-2\gamma} \phi(s) ds. \quad (4.87)$$

Differentiating both sides of (4.87) we obtain

$$\phi'(l) = -\left(\frac{l}{s_{\max}}\right)^{\frac{2}{\gamma}} \frac{2s_{\max}^2}{\gamma l^3} \phi\left(\left(\frac{l}{s_{\max}}\right)^{\frac{1}{\gamma}} s_{\max}\right). \quad (4.88)$$

To turn this into a simpler dimensionless form, we make the substitution $l = s_{\max} e^{-m}$, with $M(m) = \phi(l)$, so

$$M'(m) = \phi'(l) \frac{dl}{dm} = -s_{\max} e^{-m} \phi'(l) \quad (4.89)$$

and

$$M(\gamma^{-1}m) = \phi(s_{\max}e^{-\gamma^{-1}m}) = \phi\left(s_{\max}\left(\frac{l}{s_{\max}}\right)^{\frac{1}{\gamma}}\right). \quad (4.90)$$

Substitution into (4.87) then gives after some simplification the functional differential equation

$$M'(m) = 2\gamma^{-1}e^{-2m(\gamma^{-1}-1)}M(\gamma^{-1}m). \quad (4.91)$$

Earlier success applying Laplace transform techniques to functional differential equations involving terms like $M(\gamma^{-1}m)$ (see Chapter 2) encouraged us to try this approach here. Taking Laplace transforms of both sides of (4.91), we obtain

$$p\bar{M}(p) = 2\bar{M}((p-2)\gamma+2), \quad (4.92)$$

which we write in the iterative form

$$\bar{M}(p) = \frac{2}{p}\bar{M}((p-2)\gamma+2). \quad (4.93)$$

Iterating $N+1$ times, we get

$$\bar{M}(p) = \frac{1}{\frac{\ell}{2}[(\frac{\ell}{2}-1)\gamma+1][(\frac{\ell}{2}-1)\gamma^2+1]\dots[(\frac{\ell}{2}-1)\gamma^N+1]}\bar{M}((p-2)\gamma^{N+1}+2), \quad (4.94)$$

which taking limits $N \rightarrow \infty$ gives

$$\bar{M}(p) = \left[\lim_{N \rightarrow \infty} \prod_{n=0}^N \frac{1}{[(\frac{\ell}{2}-1)\gamma^n+1]} \right] \bar{M}(2). \quad (4.95)$$

This limit exists, because $\gamma < 1$. Expressing this product as a sum of partial fractions,

$$\prod_{n=0}^N \frac{1}{[(\frac{\ell}{2}-1)\gamma^n+1]} = \sum_{n=0}^N \frac{Q_n(2(1-\gamma^{-n}))}{[(\frac{\ell}{2}-1)\gamma^n+1]}, \quad (4.96)$$

where

$$Q_n(p) = \frac{1}{\frac{\ell}{2}[(\frac{\ell}{2}-1)\gamma+1]\dots[(\frac{\ell}{2}-1)\gamma^{n-1}+1][(\frac{\ell}{2}-1)\gamma^{n+1}+1]\dots[(\frac{\ell}{2}-1)\gamma^N+1]}, \quad (4.97)$$

so that

$$Q_n(2(1-\gamma^{-n})) = \frac{1}{(1-\gamma^{-n})\dots(1-\gamma^{-1})(1-\gamma)\dots(1-\gamma^{N-n})}. \quad (4.98)$$

Hence in the limit as $N \rightarrow \infty$, we have

$$Q_n(2(1-\gamma^{-n})) = \frac{(-1)^n}{(\gamma^{-n}-1)\dots(\gamma^{-1}-1)K(\gamma)}, \quad (4.99)$$

where

$$K(\gamma) = \prod_{n=1}^{\infty} (1 - \gamma^n). \quad (4.100)$$

The constant K referred to in Chapter 2 is in fact $K(\alpha)$, where the function K is given by (4.100), so for a discussion of this function, including alternative expressions and series, the reader is referred to Section (2.4.1).

We now write (4.95) as

$$\bar{M}(p) = \frac{\bar{M}(2)}{K(\gamma)} \sum_{n=0}^{\infty} \frac{(-1)^n}{(\gamma^{-1} - 1) \dots (\gamma^{-n} - 1)} \left[\frac{1}{(\frac{p}{2} - 1)\gamma^n + 1} \right] \quad (4.101)$$

so

$$\bar{M}(p) = \frac{2\bar{M}(2)}{K(\gamma)} \sum_{n=0}^{\infty} \frac{(-1)^n \gamma^{-n}}{(\gamma^{-1} - 1) \dots (\gamma^{-n} - 1)} \left[\frac{1}{p + 2(\gamma^{-n} - 1)} \right], \quad (4.102)$$

where we are using the convention that the empty product in the denominator is given the value 1 when $n = 0$.

Taking inverse Laplace transforms term by term we obtain

$$M(m) = A \sum_{n=0}^{\infty} \frac{(-1)^n \gamma^{-n}}{(\gamma^{-1} - 1) \dots (\gamma^{-n} - 1)} e^{-2m(\gamma^{-n} - 1)} \quad (4.103)$$

where A is a constant to be evaluated from (4.33). Reverting to the original coordinates, we substitute $e^{-m} = l/s_{\max}$ and $M(m) = \phi(l)$, giving

$$\phi(l) = A \sum_{n=0}^{\infty} \frac{(-1)^n \gamma^{-n}}{(\gamma^{-1} - 1) \dots (\gamma^{-n} - 1)} \left(\frac{l}{s_{\max}} \right)^{2(\gamma^{-n} - 1)}. \quad (4.104)$$

To find the unknown constant A , we apply the integral condition, (4.33), using s_{\max} as the upper limit of integration. This gives

$$A = \left[(1 - \alpha^{-1}) s_{\max} \sum_{n=0}^{\infty} \left(\frac{(-1)^n \gamma^{-n}}{(\gamma^{-1} - 1) \dots (\gamma^{-n} - 1)} \frac{1}{2\gamma^{-n} - 1} \right) \right]^{-1} \quad (4.105)$$

The size/birth-size distribution in the region shaded in Fig. 4.9 is found by substituting of (4.104) into (4.24), setting $B_i(l, s) = 1$ so

$$y(l, s) = A \frac{s}{l^2} \sum_{n=0}^{\infty} \frac{(-1)^n \gamma^{-n}}{(\gamma^{-1} - 1) \dots (\gamma^{-n} - 1)} \left(\frac{s}{s_{\max}} \right)^{2(\gamma^{-n} - 1)}. \quad (4.106)$$

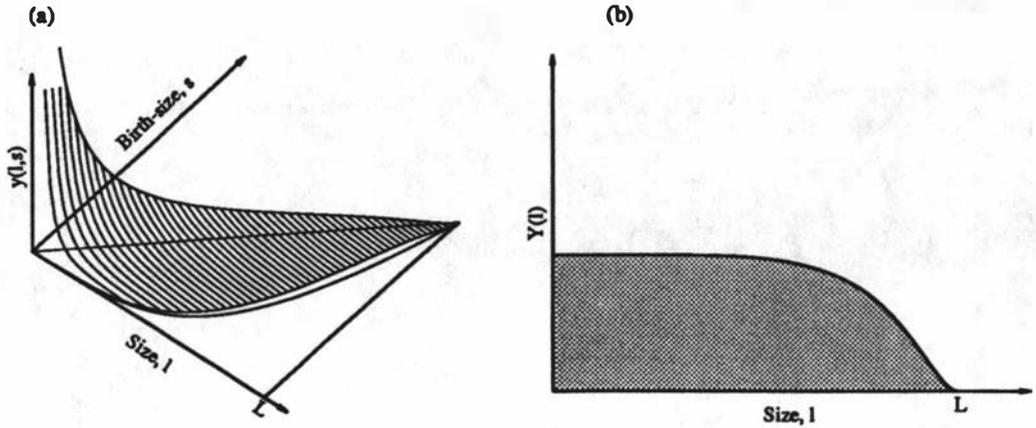


Figure 4.10: (a) The steady size/birth-size pdf $y(l,s)$ and (b) the steady size pdf $Y(l)$ when $f(p)$ is the uniform distribution on $(0,1)$ and $L(s) = L^{1-\gamma}s^\gamma$ with $\gamma = 0.25$.

Fig. 4.10(a) shows the steady size/birth-size distribution $y(l,s)$ obtained with $\alpha = 2$ and the arbitrary $\gamma = 0.25$. For this value of γ , the series in (4.106) converges very rapidly, even for $s = s_{\max}$. The singularity at $(0,0)$ appears as a consequence of choosing $f(p)$ as a uniform distribution extending to $p = 0$. As $l,s \rightarrow 0$ along the line $l = s$, $y(l,s) \rightarrow \infty$, but as $l,s \rightarrow 0$ along the line $l = L^{1-\gamma}s^\gamma$, $y(l,s) \rightarrow 0$.

To find the steady size distribution $Y(l)$, we substitute (4.104) into (4.25) and integrate term by term between a lower limit of $s = l^{1/\gamma}L^{1-1/\gamma}$ and an upper limit of l (for $l < s_{\max}$) or s_{\max} (for $l \geq s_{\max}$). This gives

$$Y(l) = \frac{As_{\max}^2}{2f^2} \sum_{n=0}^{\infty} \frac{(-1)^n}{(\gamma^{-1} - 1) \dots (\gamma^{-n} - 1)} F_n(l) \tag{4.107}$$

where

$$F_n(l) = \begin{cases} \left(\frac{l}{s_{\max}}\right)^{2\gamma^{-n}} - \left(\frac{l}{L^{1-\gamma}s_{\max}^\gamma}\right)^{2\gamma^{-(n+1)}}, & 0 \leq l < s_{\max}, \\ 1 - \left(\frac{l}{L^{1-\gamma}s_{\max}^\gamma}\right)^{2\gamma^{-(n+1)}}, & s_{\max} \leq l \leq L^{1-\gamma}s_{\max}^\gamma. \end{cases} \tag{4.108}$$

Fig. 4.10(b) shows the form of $Y(l)$ in the case where $\alpha = 2$ (so $s_{\max} = L$) and $\gamma = 0.25$. This one dimensional size distribution has a finite non-zero value at $l = 0$, and the series in (4.107) converges rapidly for all values of l .

The general form of the corresponding size/age distribution can be found by substituting (4.104) into (4.28). In the particular case where the growth rate is constant, with $r(t) = g$,

we obtain

$$y(l, a) = A e^{-2\beta a} \sum_{n=0}^{\infty} \frac{(-1)^n \gamma^{-n}}{(\gamma^{-1} - 1) \dots (\gamma^{-n} - 1)} \left(\frac{l}{s_{\max}} e^{-\beta a} \right)^{2(\gamma^{-n} - 1)} \quad (4.109)$$

4.2.4 Numerical Solution

In earlier sections, we demonstrated methods for finding solutions to the homogeneous Fredholm integral equation (4.36) with a kernel given by (4.37) or (4.38), in some special cases, and with the solution, $\phi(l)$, normalised so that it satisfied the integral condition (4.33). In the general case, the eigenfunction $\phi(l)$ corresponding to the principal eigenvalue α^{-1} must be found numerically. Here we scale all cell sizes so that $s_{\max} \leq 1$, then use the straightforward iteration

$$\phi^{(0)}(l) = 1, \quad 0 < l \leq 1, \quad (4.110)$$

$$\phi^{(n+1)}(l) = \alpha \int_0^1 K(l, s) \phi^{(n)}(s) ds, \quad (4.111)$$

to estimate $\phi(l) = \lim_{n \rightarrow \infty} \phi^{(n)}(l)$. Once such an eigenfunction is found, we can normalise using (4.33) to obtain $\phi(l)$ and, as before, apply (4.24), (4.25), and (4.29) to find $y(l, s)$, $Y(l)$, and $y_a(l, a)$. Figs. 4.11 and 4.12 illustrate two examples of solutions using this technique. In each case we obtained convergence to within four decimal places in $\phi(l)$ within eight integral iterations. Varying $\phi^{(0)}(l)$ to other forms such as triangular or normal distributions did not affect the final solution $\phi(l)$, and actually improved the rate of convergence.

Figs. 4.11(a) and (b) show the steady size/birth-size and steady size distributions in the case where cell division size is precisely determined by cell birth-size, as in Section 4.2.3, with the cell division size given by (4.82) and the kernel given by (4.83), but with $f(p)$ as a normal distribution,

$$f(p) = \frac{1}{\sqrt{2\pi}\sigma_f} e^{-\frac{(p-\mu_f)^2}{2\sigma_f^2}}, \quad (4.112)$$

with mean $\mu_f = 0.5$ (so that from (4.2), $\alpha = 2$) and standard deviation $\sigma_f = 0.1$. This is more realistic than the uniform distribution for f used in Section 4.2.3. We choose $\gamma = 0.25$, so the feasible region for cells is the same as it was for the solution given Fig. 4.10(a). As there is almost no overlap between the size distribution of dividing cells and the size distribution of newborn cells, the dashed line $Y = [\int_0^L s \phi(s) ds] / l^2$ in Fig. 4.11(b) touches the line $Y = Y(l)$.

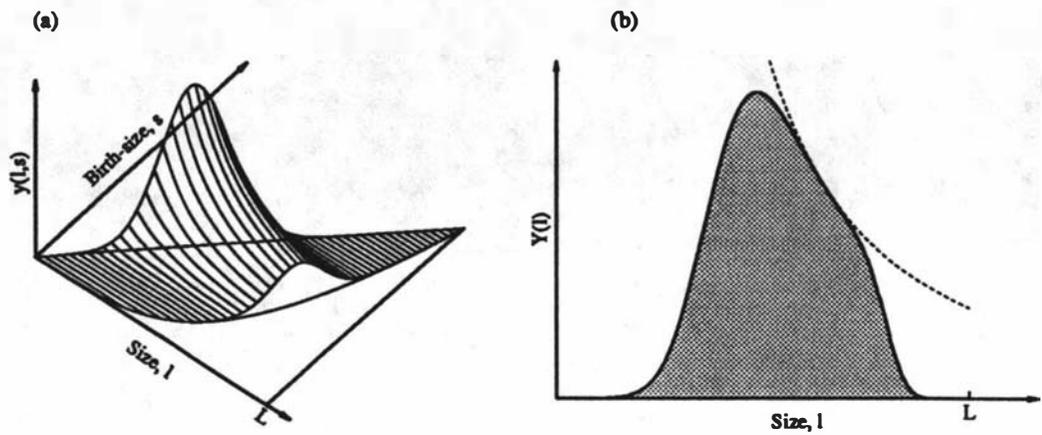


Figure 4.11: (a) The steady size/birth-size pdf, $y(l, s)$, and (b) the steady size pdf, $Y(l)$, where $f(p)$ is given by (4.112), and all cells divide on the line $l = L(s)$ with $L(s)$ given by (4.82). The dashed line in (b) is the line $Y = [\int_0^L s\phi(s)ds]/l^2$.

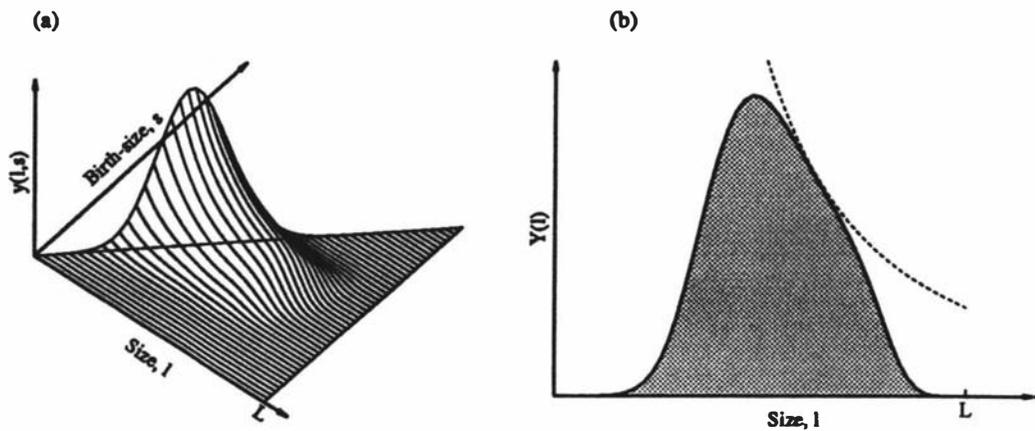


Figure 4.12: (a) The steady size/birth-size pdf $y(l, s)$ and (b), the steady size pdf $Y(l)$ where $f(p)$ is given by (4.112), and the cell division size is variable, with $b_l(l, s)$ given by (4.113). The dashed line in (b) is once again the line $Y = [\int_0^L s\phi(s)ds]/l^2$.

As a second example, we again choose $f(p)$ to be the normal distribution (4.112) with $\mu_f = 0.5$ and $\sigma_f = 0.1$, but rather than force a cell of initial size s to divide exactly at size $L(s)$ given by (4.82) we allow some variation about this. We do this by setting $b_l(l, s)$, for any s , to be a normal distribution with mean $L(s)$ and standard deviation dependent on s , so that

$$b_l(l, s) = \frac{1}{\sqrt{2\pi}\sigma_b(s)} e^{-\frac{(l-L(s))^2}{2(\sigma_b(s))^2}}. \quad (4.113)$$

We choose $\sigma_b(s)$, the standard deviation of this distribution, to be

$$\sigma_b(s) = f_b \frac{(L(s) - s)(L - L(s))}{(L - s)} \quad (4.114)$$

where f_b is a constant. Fig. 4.12(a) and (b) show the steady size/birth-size and steady size distributions respectively when $L(s)$ is given by (4.82) with $\gamma = 0.25$ as before, and with $f_b = 0.3$ in (4.114).

4.2.5 Discussion

In all the models described in this chapter, we have assumed the following:

- (I_S) — The cell population is spatially homogeneous, so we may ignore the location of cells in space.
- (I_g) — Cell growth rate is proportional to current cell size, but may vary with time, so $g(l, s, t) = r(t)l$.
- (I_B) — The probability that a cell initially of size s will survive without division to size l is independent of time, i.e. $B_l = B_l(l, s)$.
- (I_f) — The pdf describing the proportions into which a parent cell may divide is independent of both time and current or initial size of the parent cell, i.e. $f = f(p)$.

If we follow a cohort of cells as in Fig. 4.3 as it moves along a leaf or root, it passes first through the meristem where both cell division and cell growth are occurring, then through a growth-only region, then finally passes into mature tissue. If we choose a cohort which covers just a short length of root or leaf, it is possible to satisfy assumption (I_S) fairly closely, so as discussed in Section 4.1.3, symplastic growth assures us that assumption (I_g)

also holds. The time-invariance implied by assumptions (I_B) and (I_f) will hold only in parts of the meristem in which B_l and f do not change significantly with spatial position, but provided that the rate of change of B_l and f with position is slow compared with the mean distance covered by a cell during its lifetime, steady size and size/birth-size distributions calculated using the models described here should be close to the size and size/birth-size distributions observed. Assumption (I_f) has been made for the sake of simplicity, but there is little data available to support or contradict this.

Of course, the models here may be applied to cell growth in situations other than one-dimensional plant tissues, but we have not addressed this question specifically. We have taken cell size to be synonymous with cell length, but it could equally well be any other property which is conserved when cells divide, such as cell mass, volume, or DNA content. Some types of bacterial cells have been observed to grow approximately exponentially in size (for example, see Schaechter et al. [48] or Bell and Anderson [6]), so assumption (I_g) may be made in these situations. Plant tissue growth is symplastic whether the cells are growing in one, two, or three dimensions, so in all these cases, provided that we consider a region of tissue in which (I_S) holds, we could expect (I_g) to hold too.

Our specific choices of forms for B_l and f have been guided in earlier sections by a desire for simplification, but it is interesting to note that the birth-size independence postulated in Section 4.2.2 has been assumed in a number of papers on bacterial cell size distributions (Koch and Schaechter [30], Collins and Richmond [7], Tyson and Diekmann [61]). This assumption is made because it is very difficult to measure cell birth-size (or alternatively cell age), so simple one-dimensional models for $Y(l)$ are the only ones which can be compared easily with existing data. However, a comparison of Figs. 4.8(b), 4.11(b), and 4.12(b) shows that very similar shapes for $Y(l)$ may be obtained from what are fundamentally quite different models, so one should be wary asserting that a particular model is correct on the grounds of the predicted one-dimensional size distributions. The two-dimensional size/birth-size distributions shown in Figs. 4.8(a), 4.11(a), and 4.12(a) show greater variation, so these (or size/age distributions) might be a better basis for comparison of models if measurement difficulties could be overcome. It is unclear whether the most general type of model with distributions like those in Fig. 4.12 provides a significant improvement in accuracy over more deterministic models with distributions like those in Fig. 4.11.

The "power law" used for $L(s)$ in Sections 4.2.3 and 4.2.4 is the simplest form which satisfies the requirements for "realism" outlined in Section 4.1.6, but of course other forms

are also possible. If we look at Figs. 4.11 or 4.12, we see that only the central section of the line $l = L(s)$ actually affects the solution, so the precise form of $L(s)$ over all s is unimportant. A normal distribution for $f(p)$, which we used in the examples shown in Figs. 4.6, 4.11, and 4.12, seems a reasonable assumption, but its standard deviation must be chosen to be sufficiently small so that $\int_0^1 f(p) dp = 1$ is a reasonable approximation. While there is little experimental evidence for any particular choice of f , the assumption of a normal distribution is certainly more realistic than the assumption that all cells divide exactly in half, as in the models of Hall and Wake [19] and Bell and Anderson [6]. Tyson and Diekmann [61] point out that in the case of exponential growth of cell size and division of cells exactly in half, the steady size distribution is not asymptotically stable, whereas Heijmans [23] shows that if cells are allowed to divide unevenly, the steady size distribution in the birth-size-independent case is approached asymptotically.

Chapter 5

Existence, Uniqueness, and Stability of SSDs

The objective of this chapter is to examine the existence, uniqueness, and stability of the steady size/birth-size distributions discussed in Chapter 4, where the growth rate of cells is given by $g_l(l) = r(t)l$.

5.1 Existence and Uniqueness

Consider the Fredholm integral equation (4.36) for the birth-size distribution $\phi(l)$ in Chapter 4, with the kernel given by (4.37) or (4.38). In Section 4.1.5 we noted that there is just one non-negative solution $\phi(l)$ which satisfies both the integral equation (4.36) and the normalising condition (4.33), provided that the kernel is both *square-integrable* and *non-factorable*.

Let the support of f be $\tau(f) = [p_1, p_2]$, where $0 \leq p_1 < p_2 \leq 1$, as in Section (4.1.6). We show here that the kernel will be square-integrable and non-factorable provided that:

- (A_l) There exist continuous functions $L^*(s) \geq s$ and $L(s) \geq L^*(s)$ such that $b_l(l, s) > 0$ for $L^*(s) < l < L(s)$ and $b_l(l, s) = 0$ elsewhere, and of course $\int_{L^*(s)}^{L(s)} b_l(l, s) dl = 1$. This situation is shown in Fig. 4.4. We permit $b_l(l, s)$ to be a Dirac delta function of

the form $b_l(l, s) = \delta(l - L(s))$ if desired, in which case we have $L^*(s) = L(s)$.

- (A_f) f is bounded, so there exists a constant $M_f > 0$ such that

$$f(p) \leq M_f. \quad (5.1)$$

- (A_m) There exists a minimum cell birth-size s_{\min} , and a maximum cell birth-size s_{\max} , such that

$$p_1 L^*(s_{\min}) = s_{\min}, \quad (5.2)$$

and

$$p_2 L(s_{\max}) = s_{\max}, \quad (5.3)$$

with $0 \leq s_{\min} < s_{\max}$. Further, we require that for all $s \in (s_{\min}, s_{\max})$, we must have $p_2 L(s) \leq s_{\max}$ and $p_1 L^*(s) \geq s_{\min}$. This enables us to restrict the domain of the integral operator to functions $\phi(s)$ such that the support of ϕ is contained in $[s_{\min}, s_{\max}]$, that is

$$\tau(\phi) \subseteq [s_{\min}, s_{\max}]. \quad (5.4)$$

- (A_s) For $s \in (s_{\min}, s_{\max})$, we require that $p_1 L^*(s) < s$ and $p_2 L(s) > s$. In fact, in order to prove that the kernel is non-factorable, we need to strengthen these inequalities, and require that for all $s \in (s_{\min}, s_{\max})$,

$$\forall \varepsilon > 0, \exists \delta > 0 : \forall s \geq s_{\min} + \varepsilon, p_1 L^*(s) \leq (1 - \delta)s, \quad (5.5)$$

and

$$\forall \varepsilon > 0, \exists \delta > 0 : \forall s \leq s_{\max} - \varepsilon, p_2 L(s) \geq (1 + \delta)s. \quad (5.6)$$

In the particular case where $s_{\min} = 0$, which from (5.2) can occur either because $p_1 = 0$ or $L^*(s) = s$, one extra condition is required in order to ensure that the kernel is square-integrable:

- (A_0) If $s_{\min} = 0$ then there must exist constants $M_b > 0$ and $\sigma < 1$ such that $\forall s \in (0, s_{\max}]$,

$$\int_l^{L(s)} \frac{b_l(r, s)}{r^2} dr \leq \frac{M_b}{(ls)^\sigma}, \quad s \leq l \leq L(s). \quad (5.7)$$

One consequence of (5.7) is that the expected value of the inverse square of cell division size, $\int_s^{L(s)} \frac{b_l(r, s)}{r^2} dr$, must grow more slowly than M_b/s^2 as $s \rightarrow 0$.

5.1.1 Square-integrability of the Kernel

Consider the kernel (4.37), which as $f(p) = 0$ for $p > 1$ may be written in the form

$$K(l,s) = s \int_{\max(l,s)}^{\infty} f\left(\frac{l}{r}\right) \frac{b_l(r,s)}{r^2} dr. \quad (5.8)$$

From (5.1) we have

$$K(l,s) \leq sM_f \int_{\max(l,s)}^{\infty} \frac{b_l(r,s)}{r^2} dr, \quad (5.9)$$

so as

$$\frac{1}{r^2} \leq \frac{1}{\max(l,s)^2}, \quad r \geq \max(l,s), \quad (5.10)$$

and $b_l(r,s)$ is a probability density function in r for all s , we have

$$K(l,s) \leq \frac{sM_f}{\max(l,s)^2}. \quad (5.11)$$

Hence provided that $s_{\min} > 0$ we have

$$K(l,s) \leq \frac{s_{\max}M_f}{s_{\min}^2}, \quad (5.12)$$

so

$$\int_{s_{\min}}^{s_{\max}} \int_{s_{\min}}^{s_{\max}} |K(l,s)|^2 dlds \leq \frac{(s_{\max} - s_{\min})^2 s_{\max}^2 M_f^2}{s_{\min}^4}, \quad (5.13)$$

and the kernel is square-integrable as required.

If $s_{\min} = 0$, then using (5.7) and (5.9), we find that the kernel must satisfy

$$K(l,s) \leq \frac{sM_fM_b}{s^\sigma [\max(l,s)]^\sigma}, \quad (5.14)$$

so

$$\int_0^{s_{\max}} \int_0^{s_{\max}} |K(l,s)|^2 dlds \leq M_f^2 M_b^2 \int_0^{s_{\max}} \int_0^{s_{\max}} \frac{s^{2-2\sigma}}{[\max(l,s)]^{2\sigma}} dlds. \quad (5.15)$$

We now split the inner integral into two parts, $l > s$ and $l < s$, so

$$\int_0^{s_{\max}} \int_0^{s_{\max}} |K(l,s)|^2 dlds \leq M_f^2 M_b^2 \left[\int_0^{s_{\max}} \int_0^s s^{2-4\sigma} dlds + \int_0^{s_{\max}} \int_s^{s_{\max}} s^{2-2\sigma} l^{-2\sigma} dlds \right], \quad (5.16)$$

then changing the order of integration in the second term we obtain

$$\int_0^{s_{\max}} \int_0^{s_{\max}} |K(l,s)|^2 dlds \leq M_f^2 M_b^2 \left[\int_0^{s_{\max}} s^{2-4\sigma} \int_0^s dlds + \int_0^{s_{\max}} l^{-2\sigma} \int_0^l s^{2-2\sigma} ds dl \right]. \quad (5.17)$$

As $\sigma < 1$ we can carry out the integrations to obtain

$$\int_0^{s_0} \int_0^{s_{\max}} |K(l,s)|^2 dlds \leq \frac{M_f^2 M_b^2 s_{\max}^{4(1-\sigma)} (2-\sigma)}{2(1-\sigma)(3-2\sigma)}, \quad (5.18)$$

so the kernel (5.8) is square-integrable as required.

5.1.2 Non-factorability of the Kernel

Zabreyko et al [69] define a square-integrable kernel $K(l, s)$ on a bounded domain Ω to be non-factorable if and only if for any square-integrable function $\phi(l) \geq 0$, $\phi(l) \not\equiv 0$, which is not identically zero, and any $l \in \Omega$, there exists an iteration $K^{(N)}(l, s)$ of the kernel,

$$K^{(N)}(l, s) = \int_{\Omega} \int_{\Omega} \dots \int_{\Omega} K(l, s_1) K(s_1, s_2) \dots K(s_{N-1}, s) ds_{N-1} \dots ds_2 ds_1, \quad (5.19)$$

such that

$$\int_{\Omega} K^{(N)}(l, s) \phi(s) ds > 0. \quad (5.20)$$

Heijmans [24] uses the term *non-supporting* instead of non-factorable.

Given a non-negative $\phi(s)$ such that $\phi(s) > 0$ for $s \in (s_l, s_u) \subset (s_{\min}, s_{\max})$, and $l \in (s_{\min}, s_{\max})$, then if $l \in (s_l, s_u)$, (5.20) is satisfied for all $N \geq 0$. Otherwise, we must have either $l \in (s_{\min}, s_l]$ or $l \in [s_u, s_{\max})$. Here we consider only the first of these cases, as the proof in the second case is almost identical.

Given $l \in (s_{\min}, s_l]$, choose $\varepsilon = l - s_{\min}$ and a corresponding δ from (5.5). Because $f(p) > 0$ for $p \in (p_1, p_2)$, $p_1 < p_2$, and $b_l(r, s) > 0$ for $L(s) < r < L^*(s)$, the kernel (5.8) must satisfy

$$K(l', s) > 0, \quad p_1 L^*(s) < l' < p_2 L(s). \quad (5.21)$$

Hence given $\phi(s) > 0$, $s_l < s < s_u$, we must have

$$\int_{s_{\min}}^{s_{\max}} K(l', s) \phi(s) ds > 0, \quad p_1 L^*(s_l) < l' < p_2 L(s_u), \quad (5.22)$$

so applying (5.5) and (5.6), we have

$$\int_{s_{\min}}^{s_{\max}} K(l', s) \phi(s) ds > 0, \quad (1 - \delta) s_l < l' < s_u. \quad (5.23)$$

Now we choose the smallest integer N such that

$$l > (1 - \delta)^N s_l, \quad (5.24)$$

that is the smallest positive integer such that

$$N > \frac{\log(\frac{l}{s_l})}{\log(1 - \delta)}. \quad (5.25)$$

Iterating the argument leading to (5.23) N times then gives

$$\int_{s_{\min}}^{s_{\max}} K^{(N)}(l', s) \phi(s) ds > 0, \quad (1 - \delta)^N s_l < l' < s_u, \quad (5.26)$$

so from (5.24) we have

$$\int_{s_{\min}}^{s_{\max}} K^{(N)}(l, s)\phi(s)ds > 0. \quad (5.27)$$

A very similar argument can be applied if $l \in [s_u, s_{\max})$, so we conclude that the kernel (5.8) is non-factorable.

5.2 The Time-dependent Problem

5.2.1 Formulation and Simplification

We consider here the time-dependent problem giving rise to the steady size/birth-size distributions discussed in Chapter 4. The time-dependent number density is the solution of (4.3),

$$\frac{\partial}{\partial t}n(l, s, t) + \frac{\partial}{\partial l}g_l(l, s, t)n(l, s, t) = -h_l(l, s, t)g_l(l, s, t)n(l, s, t), \quad (5.28)$$

subject to an initial condition

$$n(l, s, 0) = n_0(l, s), \quad (5.29)$$

and the boundary or renewal condition given by (4.5),

$$g_l(s, s, t)n(s, s, t) = \int_s^\infty \int_0^t h_l(l, r, t)g_l(l, r, t)\alpha(l, r, t)f\left(\frac{s}{l}, l, r, t\right)n(l, r, t)dr\frac{dl}{l}. \quad (5.30)$$

The notation used here is exactly that used in Chapter 4. As in that chapter, we consider the special case arising when

$$g_l(l, s, t) = r(t)l, \quad (5.31)$$

$$h_l(l, s, t) = h_l(l, s), \quad (5.32)$$

and

$$f(p, l, r, t) = f(p). \quad (5.33)$$

The probability distribution $f(p)$ must have support $\tau(f) \subseteq [0, 1]$ and satisfy

$$\therefore \int_0^1 f(p)dp = 1, \quad (5.34)$$

and

$$\int_0^1 pf(p)dp = \alpha^{-1}, \quad (5.35)$$

and α must be a constant. As in Chapter 4, we define

$$B_l(l, s) = e^{-\int_s^l h(r)dr}, \quad (5.36)$$

and the probability density function

$$b_l(l, s) = -\frac{\partial B_l}{\partial l} = h_l(l, s)B_l(l, s). \quad (5.37)$$

Making the appropriate substitutions into (5.28) gives the time-dependent PDE

$$\frac{\partial}{\partial t}n(l, s, t) + \frac{\partial}{\partial l}[r(t)ln(l, s, t)] = -h_l(l, s)r(t)ln(l, s, t). \quad (5.38)$$

with a boundary condition given from (5.30) by

$$sn(s, s, t) = \int_s^\infty \int_0^l h_l(l, r)\alpha f\left(\frac{s}{l}\right)n(l, r, t)drdl, \quad (5.39)$$

and an initial condition given by (5.29).

In order to avoid the explicit dependence of the PDE (5.38) on time t , we replace t by the dimensionless time-like variable

$$t' = R(t), \quad (5.40)$$

where

$$R(t) = \int_0^t r(\tau)d\tau. \quad (5.41)$$

Note that if $r(t) = 1$ then $t' = t$. Also, for any $r(t)$, t' is the log of the factor by which the total biomass has grown since $t = 0$. We can ensure that t' is positive for $t > 0$ and that (5.40) is invertible, if we require that

$$r(t) \geq r_{\min} > 0, \quad (5.42)$$

where r_{\min} is a constant. From (5.40) we have

$$\frac{\partial n}{\partial t} = r(t)\frac{\partial n}{\partial t'}, \quad (5.43)$$

so substituting (5.40) into (5.38) we have

$$\frac{\partial n}{\partial t} + l\frac{\partial n}{\partial l} = -(lh_l(l, s) + 1)n(l, s, t), \quad (5.44)$$

where we have replaced t' by t in order to avoid excessive notational complexity in what follows. Note that the boundary condition (5.39) and the initial condition (5.29) remain unchanged despite the change in the nature of the time variable t . Equation (5.40) has transformed (5.38) into (5.44), which represents the case where $r(t) = 1$, so from (5.31) the growth rate of cells may be regarded as just

$$g_l(l, s, t) = l. \quad (5.45)$$

In the following, we consider just this special case, on the understanding that we can transform to the more general case using the inverse of (5.40).

5.2.2 Solution using Characteristics

To integrate along characteristics, we choose as new variables in (5.44) $\eta = le^{-t}$ and $\tau = t$, so $l = \eta e^\tau$, to obtain

$$\frac{\partial n}{\partial \tau} = -(\eta e^\tau h_l(\eta e^\tau, s) + 1)n. \quad (5.46)$$

This first order PDE has the solution

$$n = e^{-\tau} B_l(\eta e^\tau, s) \psi(\eta, s), \quad (5.47)$$

where ψ is an "arbitrary" function to be determined by either the boundary condition (5.39) or the initial condition (5.29), whichever is appropriate. Reverting to the original variables, we obtain

$$n(l, s, t) = e^{-t} B_l(l, s) \psi(le^{-t}, s). \quad (5.48)$$

We now define a "birth rate" function $\Phi(t, s)$ such that $\Phi(t, s) ds dt$ gives the number of cells born in a short time dt in the size range s to $s + ds$. Then

$$\begin{aligned} \Phi(t, s) &= n(s, s, t) \frac{dl}{dt} \Big|_{l=s} \\ &= n(s, s, t) g_l(s, s, t) \\ &= sn(s, s, t) \\ &= se^{-t} \psi(se^{-t}, s), \end{aligned} \quad (5.49)$$

because from (5.45) we have $g_l(s, s, t) = s$, and from (5.36), $B_l(s, s) = 1$. Hence

$$\psi(l, s) = \frac{\Phi(-\log(\frac{l}{s}), s)}{l} \quad (5.50)$$

so (5.48) may be written as

$$n(l, s, t) = \frac{B_l(l, s)}{l} \Phi(t - \log(\frac{l}{s}), s). \quad (5.51)$$

5.2.3 The Region Influenced Directly by the Initial Condition

For the region

$$t < \log\left(\frac{l}{s}\right), \quad (5.52)$$

we substitute (5.51) into the initial condition (5.29) which gives

$$\Phi\left(-\log\left(\frac{l}{s}\right), s\right) = \frac{l}{B_l(l, s)} n_0(l, s) \quad (5.53)$$

so

$$\Phi(t, s) = \frac{se^{-t}}{B_l(se^{-t}, s)} n_0(se^{-t}, s), \quad (5.54)$$

and

$$\Phi\left(t - \log\left(\frac{l}{s}\right), s\right) = \frac{le^{-t}}{B_l(le^{-t}, s)} n_0(le^{-t}, s). \quad (5.55)$$

Substituting this into (5.51) then gives

$$n(l, s, t) = \frac{B_l(l, s)}{B_l(le^{-t}, s)} e^{-t} n_0(le^{-t}, s). \quad (5.56)$$

Note that the fraction at the start of this expression cannot exceed 1, so provided that n_0 is bounded, $n(l, s, t)$ must decay exponentially in the supremum norm in this region.

5.2.4 The Region Influenced by the Boundary Condition

For the region

$$t > \log\left(\frac{l}{s}\right) \quad (5.57)$$

we substitute (5.51) into the boundary condition (5.39) which leads to

$$\Phi(t, s) = \int_0^\infty \int_0^t \alpha f\left(\frac{s}{l}\right) b_l(l, r) \Phi\left(t - \log\left(\frac{l}{r}\right), r\right) dr \frac{dl}{l}. \quad (5.58)$$

Changing the order of integration, then making the change of variable $a = \log\left(\frac{l}{r}\right)$ in the inner integral, gives

$$\Phi(t, s) = \int_0^\infty \int_0^\infty \alpha f\left(\frac{s}{r} e^{-a}\right) b_l(re^a, r) \Phi(t - a, r) da dr. \quad (5.59)$$

We need to split the inner integral in (5.59) into two parts, with separate integrals for the regions $a > t$ and $a < t$. In the region $a > t$, $\Phi(t - a, r)$ is given by (5.54) as

$$\Phi(t - a, r) = \frac{re^{a-t}}{B_l(re^{a-t}, r)} n_0(re^{a-t}, r), \quad a > t. \quad (5.60)$$

Hence (5.59) becomes

$$\Phi(t,s) = \int_0^\infty \int_0^t \alpha f\left(\frac{s}{r}e^{-a}\right) b_l(re^a, r) \Phi(t-a, r) da dr + \Phi_0(t,s), \quad (5.61)$$

where

$$\Phi_0(t,s) = \int_0^\infty \int_t^\infty \alpha f\left(\frac{s}{r}e^{-a}\right) b_l(re^a, r) \frac{re^{a-t}}{B_l(re^{a-t}, r)} n_0(re^{a-t}, r) da dr. \quad (5.62)$$

The form of $\Phi(t,s)$ as $t \rightarrow \infty$ is discussed in the following section.

5.3 Stability of the Size/Birth-size Distributions

We are interested in the properties of $n(l, s, t)$, and therefore of $\Phi(t, s)$, as $t \rightarrow \infty$. In order to show that the steady size/birth-size distributions calculated in Chapter 4 are stable, we need to show that for large t , we may write for some $\phi(s)$,

$$\Phi(t, s) = e^t(\phi(s) + o(1)). \quad (5.63)$$

Because we have transformed to a dimensionless time variable, we anticipate that the coefficient of t in the exponent is simply one. If we can show that $\Phi(t, s)$ takes the form (5.63), then as in Chapter 4 we may interpret $\phi(s)$ as the steady size distribution of newborn cells.

In order to establish (5.63), we follow the approach of Heijmans [24], and look at the properties of a family of operators on the Laplace transform of Φ rather than study the properties of the integral operator in (5.61) directly. All of the conditions (\mathcal{A}_l) , (\mathcal{A}_f) , (\mathcal{A}_m) , (\mathcal{A}_r) , and if necessary (\mathcal{A}_0) , specified in Section (5.1), are assumed to hold throughout this section. We also assume that the initial cell size/birth-size distribution, $n_0(l, s)$, is zero outside the region $s_{\min} < s < s_{\max}$, $s < l < L(s)$.

5.3.1 The Laplace Transform of the Operator

We now proceed to take Laplace transforms of both sides of equation (5.61), denoting the Laplace transform of Φ by $\hat{\Phi}$ and the Laplace transform of Φ_0 by $\hat{\Phi}_0$. Then we have

$$\hat{\Phi}(\lambda, s) = \int_0^\infty \int_0^\infty \int_0^t \alpha f\left(\frac{s}{r} e^{-a}\right) b_l(re^a, r) \Phi(t-a, r) e^{-\lambda t} da dt dr + \hat{\Phi}_0(\lambda, s). \quad (5.64)$$

The Laplace transform of $\Phi_0(t, s)$, $\hat{\Phi}_0(\lambda, s)$, exists and is analytic for $\lambda > 0$ provided that n_0 is bounded and has as its support the "feasible region" shaded in Fig. 4.4. Now we make the change of variable $a' = t - a$, giving

$$\hat{\Phi}(\lambda, s) = \int_0^\infty \int_0^\infty \int_0^t \alpha f\left(\frac{s}{r} e^{-(t-a')}\right) b_l(re^{(t-a')}, r) \Phi(a', r) e^{-\lambda t} da' dt dr + \hat{\Phi}_0(\lambda, s), \quad (5.65)$$

then swap the order of the two inner integrals and change variables again using $t' = t - a'$, so that

$$\hat{\Phi}(\lambda, s) = \int_0^\infty \int_0^\infty \int_0^\infty \alpha f\left(\frac{s}{r} e^{-t'}\right) b_l(re^{t'}, r) \Phi(a', r) e^{-\lambda t'} e^{-\lambda a'} dt' da' dr + \hat{\Phi}_0(\lambda, s). \quad (5.66)$$

Now replace the dummy variables a' and r' by t and a respectively, then change the order of the inner integrals again to obtain

$$\hat{\Phi}(\lambda, s) = \int_0^\infty \left[\int_0^\infty \alpha f\left(\frac{s}{r}e^{-a}\right) b_l(re^a, r) e^{-\lambda a} da \right] \hat{\Phi}(\lambda, r) dr + \hat{\Phi}_0(\lambda, s). \quad (5.67)$$

This is in the usual form of an inhomogenous Fredholm integral equation,

$$\hat{\Phi}(\lambda, l) = \int_0^\infty \hat{k}_\lambda(l, s) \hat{\Phi}(\lambda, s) ds + \hat{\Phi}_0(\lambda, l), \quad (5.68)$$

where

$$\hat{k}_\lambda(l, s) = \int_0^\infty \alpha f\left(\frac{l}{s}e^{-a}\right) b_l(se^a, s) e^{-\lambda a} da. \quad (5.69)$$

Alternatively, we can substitute $r = se^a$ to obtain

$$\hat{k}_\lambda(l, s) = \alpha s^\lambda \int_s^\infty f\left(\frac{l}{r}\right) b_l(r, s) r^{-(\lambda+1)} dr. \quad (5.70)$$

More formally, using operator terminology we may write

$$\hat{\Phi}(\lambda) = \hat{K}(\lambda) \hat{\Phi}(\lambda) + \hat{\Phi}_0(\lambda), \quad (5.71)$$

where $\hat{K}(\lambda)$ is the operator defined by

$$(\hat{K}(\lambda)\psi)(l) = \int_0^\infty \hat{k}_\lambda(l, s) \psi(s) ds. \quad (5.72)$$

Inverting (5.71), we have

$$\hat{\Phi}(\lambda) = (I - \hat{K}(\lambda))^{-1} \hat{\Phi}_0(\lambda), \quad (5.73)$$

where I is the identity operator. We define an operator

$$R(\lambda) = (I - \hat{K}(\lambda))^{-1}. \quad (5.74)$$

Now in order to evaluate the inverse Laplace transform of $\hat{\Phi}(\lambda)$ precisely, we would want to be able to find all the singularities of $R(\lambda)$ and their orders. However, as we are interested only in that part of $\Phi(t, s)$ which grows most rapidly at large time, it is sufficient to find just the λ with the largest real part for which $R(\lambda)$ is singular. It is clear that $R(\lambda)$ can be singular only if $\hat{K}(\lambda)$ has an eigenvalue of one, so we now proceed to find the maximum value of λ for which this is possible.

5.3.2 Eigenvalues of the Operator $\hat{K}(\lambda)$

Consider first the case where λ is real.

The kernel of the operator \hat{K} given by (5.70) and the kernel K given by (5.8) both have the same support, so the argument used in Section (5.1.2) to show that the kernel $K(l,s)$ is non-factorable is equally applicable to the kernel \hat{k}_λ . Hence the kernel \hat{k}_λ is non-factorable for all $\lambda > 0$.

The kernel \hat{k}_λ is clearly square-integrable for $\lambda \geq 1$, as in this case we have $\hat{k}_\lambda(l,s) \leq \alpha K(l,s)$, $\forall s, l \in [s_{\min}, s_{\max}]$, and $K(l,s)$ has been shown to be square-integrable in section (5.1.1). For $\lambda < 1$, the situation is somewhat more complex. Provided that $s_{\min} > 0$, we can use arguments as in Section 5.1.1 to obtain

$$\int_{s_{\min}}^{s_{\max}} \int_{s_{\min}}^{s_{\max}} |\hat{k}_\lambda(l,s)|^2 dl ds \leq \frac{\alpha^2 (s_{\max} - s_{\min})^2 s_{\max}^2 \lambda M_f^2}{s_{\min}^{2+2\lambda}}, \quad (5.75)$$

so $\hat{k}_\lambda(l,s)$ is square-integrable (cf. 5.13). If $\lambda < 1$ and $s_{\min} = 0$, then we need to assume (5.7), and consider only $\lambda > 2\sigma - 1$. Then from (5.70), noting the restrictions to $f(p)$ and $b_l(l,s)$ applied in Section 5.1,

$$\hat{k}_\lambda(l,s) \leq \alpha s^\lambda M_f \int_{\max(l,s)}^{L(s)} b_l(r,s) r^{-(\lambda+1)} dr, \quad (5.76)$$

so as $L(s)$ is finite we may write

$$\hat{k}_\lambda(l,s) \leq \alpha s^\lambda M_f \int_{\max(l,s)}^{L(s)} b_l(r,s) \frac{L(s)^{1-\lambda}}{r^2} dr. \quad (5.77)$$

Then applying (5.7) and an argument identical to that used in deriving (5.18), we obtain

$$\int_{s_{\min}}^{s_{\max}} \int_{s_{\min}}^{s_{\max}} |\hat{k}_\lambda(l,s)|^2 dl ds \leq \frac{\alpha^2 M_f^2 M_b^2 L_{\sup}^{2(1-\lambda)} s_{\max}^{2(1+\lambda-2\sigma)} (1+\lambda-\sigma)}{(1+\lambda-\sigma)(1+2\lambda-2\sigma)}, \quad (5.78)$$

where $L_{\sup} = \sup(L(s))$, $0 \leq s \leq s_{\max}$. Hence the kernel (5.70) is square-integrable if $s_{\min} = 0$ provided $\lambda > 2\sigma - 1$, which is not too restrictive because $2\sigma - 1 < \sigma < 1$.

Hence if $f(p)$ and $b_l(l,s)$ satisfy the conditions outlined in Section 5.1, there exists a constant $\lambda_0 < 1$ such that for all $\lambda > \lambda_0$, the kernel $\hat{k}_\lambda(l,s)$ given by (5.70) is both square-integrable and non-factorable. From the above, we may choose $\lambda_0 = 0$ if $s_{\min} > 0$, or $\lambda_0 = 2\sigma - 1$ if $s_{\min} = 0$. As pointed out in Section (4.1.5), this means that the operator $\hat{K}(\lambda)$ must have a largest positive eigenvalue which is simple, and all other eigenvalues of $\hat{K}(\lambda)$ have real part strictly less than this.

The kernel $\hat{k}_\lambda(l, s)$ is also square-integrable and non-factorable for all complex $\lambda : \Re(\lambda) > \lambda_0$ (where $\Re(\lambda)$ is the real part of λ), because from (5.70) we have $|\hat{k}_\lambda(l, s)| \leq |\hat{k}_{\Re(\lambda)}(l, s)|$.

Let γ_{\max} be the largest positive eigenvalue corresponding to the kernel \hat{k}_λ , for some $\lambda > \lambda_0$, and let $\phi(l)$ be a multiple of the corresponding eigenfunction chosen such that ϕ is non-negative, and not identically zero. Then

$$\gamma_{\max} \phi(l) = \int_0^\infty \hat{k}_\lambda(l, s) \phi(s) ds, \quad (5.79)$$

so substituting from (5.70), multiplying by l^λ and integrating gives

$$\begin{aligned} \gamma_{\max} \int_0^\infty l^\lambda \phi(l) dl &= \int_0^\infty l^\lambda \left(\int_0^\infty \hat{k}_\lambda(l, s) \phi(s) ds \right) dl \\ &= \int_0^\infty \alpha l^\lambda \int_0^\infty s^\lambda \int_s^\infty f\left(\frac{l}{r}\right) b_l(r, s) \frac{1}{r^{1+\lambda}} dr \phi(s) ds dl. \end{aligned} \quad (5.80)$$

Changing the order of integration, we have

$$\begin{aligned} \gamma_{\max} \int_0^\infty l^\lambda \phi(l) dl &= \int_0^\infty s^\lambda \phi(s) \int_s^\infty b_l(r, s) \int_0^\infty \alpha f\left(\frac{l}{r}\right) \left(\frac{l}{r}\right)^\lambda \frac{dl}{r} dr ds \\ &= \int_0^\infty s^\lambda \phi(s) \int_s^\infty b_l(r, s) dr ds \int_0^1 \alpha f(p) p^\lambda dp, \end{aligned} \quad (5.81)$$

because $f(p) = 0$ for $p > 1$. Hence as $\int_s^\infty b_l(r, s) dr = 1, \forall s$, and $\phi(l)$ is non-negative and not identically zero we have

$$\gamma_{\max} = \alpha \int_0^1 f(p) p^\lambda dp. \quad (5.82)$$

For this to hold, λ must clearly be real.

We consider three possible cases:

- If $\lambda = 1$, then $\gamma_{\max} = 1$ is an eigenvalue of the operator $\hat{K}(\lambda)$, and all other eigenvalues of $\hat{K}(\lambda)$ have real part strictly less than one.
- If $\lambda > 1$, then as p^λ is monotonic decreasing with λ for $p \in [0, 1]$, we must have $\gamma_{\max} < 1$. This means that $\gamma = 1$ cannot be an eigenvalue of $\hat{K}(\lambda)$.
- If $\lambda < 1$, then the monotonicity of p^λ implies $\gamma_{\max} > 1$, and all other eigenvalues of $\hat{K}(\lambda)$ must have real part strictly less than γ_{\max} . There must be some λ_k say such that if $\lambda_k < \lambda < 1$, then all eigenvalues apart from γ_{\max} (which is greater than one) must have real part less than one. Hence for $\lambda_k < \lambda < 1$, it is impossible $\hat{K}(\lambda)$ to have an eigenvalue of one.

If we now let $\lambda_1 = \max(\lambda_0, \lambda_k) < 1$, we can say that the only value of λ with real part greater than λ_1 for which $\hat{K}(\lambda)$ has an eigenvalue of one is $\lambda = 1$.

5.3.3 The Inverse Laplace Transform

It follows immediately from the previous section that the operator $R(\lambda)$ given by (5.74) has a singularity at $\lambda = 1$, and no other singularities in the region $\lambda > \lambda_1$. Now the operator $\hat{K}(\lambda)$ is analytic in a neighbourhood of $\lambda = 1$, so in this neighbourhood we may use the Taylor series expansion

$$\hat{K}(\lambda) = \sum_{n=0}^{\infty} (\lambda - 1)^n K_n, \quad (5.83)$$

where the K_n operators are not functions of λ . If the order of the pole of $R(\lambda)$ at $\lambda = 1$ is $p \geq 1$, then we may write a Laurent series expansion for $R(\lambda)$,

$$R(\lambda) = \sum_{n=-p}^{\infty} (\lambda - 1)^n R_n, \quad (5.84)$$

where $R_{-p} \neq 0$. Now from the definition of $R(\lambda)$, (5.74),

$$R(\lambda)(I - \hat{K}(\lambda)) = (I - \hat{K}(\lambda))R(\lambda) = I, \quad (5.85)$$

so substituting the series (5.83) and (5.84), then multiplying through by $(\lambda - 1)^p$ gives

$$\begin{aligned} \left(\sum_{n=0}^{\infty} (\lambda - 1)^n R_{n-p} \right) \left(I - \sum_{n=0}^{\infty} (\lambda - 1)^n K_n \right) &= \left(I - \sum_{n=0}^{\infty} (\lambda - 1)^n K_n \right) \left(\sum_{n=0}^{\infty} (\lambda - 1)^n R_{n-p} \right) \\ &= (\lambda - 1)^p I. \end{aligned} \quad (5.86)$$

Equating coefficients of $(\lambda - 1)^0$ then gives

$$R_{-p}(I - K_0) = (I - K_0)R_{-p} = 0, \quad (5.87)$$

and equating coefficients of $(\lambda - 1)^1$ we have

$$-R_{-p}K_1 + R_{1-p}(I - K_0) = \begin{cases} 0, & p > 1 \\ I, & p = 1. \end{cases} \quad (5.88)$$

Let us assume that $p > 1$ and look for a contradiction. Then from (5.87) and (5.88) it follows that

$$R_{-p}K_1R_{-p} = 0. \quad (5.89)$$

Now in (5.87), we have $K_0 = \hat{K}(1)$ and $R_{-p} \neq 0$, so the right hand equality can hold only if for all ψ , $R_{-p}\psi$ is an eigenfunction corresponding to the eigenvalue $\gamma = 1$ of $\hat{K}(1)$. Also $K_1 = \frac{d}{d\lambda} \hat{K}(\lambda)|_{\lambda=1}$, which is a strictly negative operator, so $R_{-p}K_1R_{-p}$ cannot be the zero operator. Hence $p = 1$ and $R(\lambda)$ has a simple pole at $\lambda = 1$.

We now proceed to find the inverse Laplace transform of $\hat{\Phi}(\lambda)$, which is given by

$$\begin{aligned}\Phi(t) &= \frac{1}{2\pi i} \int_{c-i\infty}^{c+i\infty} e^{\lambda t} \hat{\Phi}(\lambda) d\lambda \\ &= \frac{1}{2\pi i} \int_{c-i\infty}^{c+i\infty} e^{\lambda t} R(\lambda) \hat{\Phi}_0(\lambda) d\lambda\end{aligned}\quad (5.90)$$

where $c > 1$ as shown in Fig. 5.1. Consider the integral around the closed path shown in Fig. 5.1, in the limit as $\epsilon \rightarrow \infty$, with $\lambda_1 < d < 1$. It follows from the previous section that this path encloses just the one simple pole at $\lambda = 1$, so the total integral around the path is equal to $2\pi i$ times the residue of the pole at $\lambda = 1$. That is,

$$\frac{1}{2\pi i} \oint_{\Gamma} e^{\lambda t} R(\lambda) \hat{\Phi}_0(\lambda) d\lambda = \text{residue} \left(e^{\lambda t} R(\lambda) \hat{\Phi}_0(\lambda) \right) |_{\lambda=1}. \quad (5.91)$$

As both $e^{\lambda t}$ and $\hat{\Phi}_0(\lambda)$ are analytic in a neighbourhood of $\lambda = 1$, and $R(\lambda)$ has a simple pole at $\lambda = 1$, we have

$$\text{residue} \left(e^{\lambda t} R(\lambda) \hat{\Phi}_0(\lambda) \right) |_{\lambda=1} = e^t R_{-1} \hat{\Phi}_0(1). \quad (5.92)$$

Now as noted above, R_{-1} is the operator which maps any non-zero function directly to an eigenfunction of the operator $\hat{K}(1)$. Provided that $\Phi_0(t, s)$ is not identically zero, $\hat{\Phi}_0(1)$ is not identically zero either. Hence we have

$$R_{-1} \hat{\Phi}_0(1)(s) = C\phi(s), \quad (5.93)$$

where $\phi(s)$ is a normalised eigenfunction of $\hat{K}(1)$, and C is a non-zero constant dependent on the $\hat{\Phi}_0(1)$ and therefore on Φ_0 . We note that $\hat{K}(1)$ is the integral operator with a kernel given by (5.8) or (4.37), so $\phi(s)$ is a multiple of the steady birth-size distribution as discussed earlier. If we choose to normalise $\phi(s)$ using (4.33), then the function ϕ referred to in (5.93) is exactly the same function ϕ as in Chapter 4.

We note that in the limit as $\epsilon \rightarrow \infty$, the integrals along the upper and lower edges of the path in Fig. 5.1 approach zero, so from (5.90) we have

$$\Phi(t, s) = \frac{1}{2\pi i} \left[(2\pi i) \left(\text{residue} \left(e^{\lambda t} R(\lambda) \hat{\Phi}_0(\lambda, s) \right) |_{\lambda=1} \right) + \int_{d-i\infty}^{d+i\infty} e^{\lambda t} R(\lambda) \hat{\Phi}_0(\lambda, s) d\lambda \right]. \quad (5.94)$$

Now the residue at $\lambda = 1$ can be found from (5.92) and (5.93) to be

$$\text{residue} \left(e^{\lambda t} R(\lambda) \hat{\Phi}_0(\lambda) \right) |_{\lambda=1} = e^t C\phi(s), \quad (5.95)$$

and

$$\left| \frac{1}{2\pi i} \int_{d-i\infty}^{d+i\infty} e^{\lambda t} R(\lambda) \hat{\Phi}_0(\lambda) d\lambda \right| \leq M(s) e^{dt}, \quad (5.96)$$

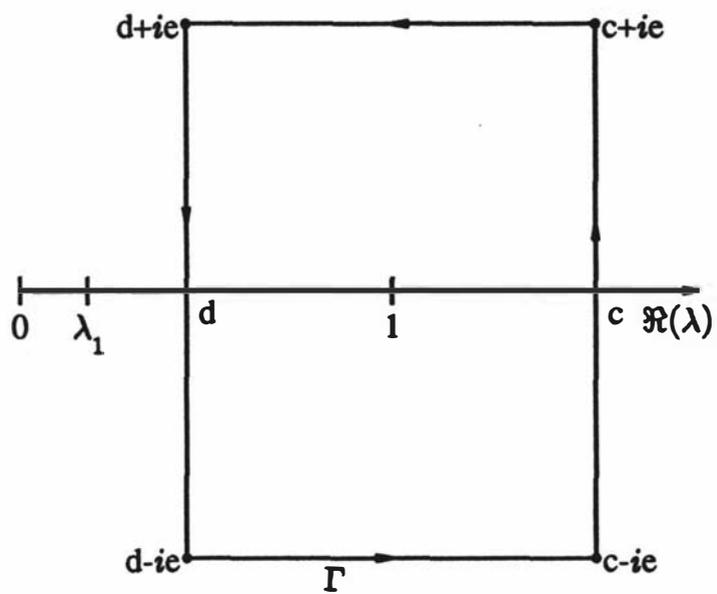


Figure 5.1: The integration path in the complex plane, Γ , used to estimate $\Phi(t,s)$. We choose $c > 1$, $\lambda_1 < d < 1$, and let $e \rightarrow \infty$.

where

$$M(s) = \frac{1}{2\pi} \left| \int_{-\infty}^{\infty} R(d - i\eta) \hat{\Phi}_0(d - i\eta, s) d\eta \right|. \quad (5.97)$$

Substituting (5.95) and (5.96) into (5.94), we get

$$\Phi(t, s) - C\phi(s)e^t \leq M(s)e^{dt}, \quad \forall \lambda_1 < d < 1, \quad (5.98)$$

so for large t it is possible to write

$$\Phi(t, s) = e^t (C\phi(s) + o(1)) \quad (5.99)$$

as required, because $e^{(1-d)t}$ must decay with t for $d < 1$. Hence, given the conditions outlined in Section 5.1, the steady birth-size distribution can be regarded as stable, so the steady size and steady size/birth-size distributions will also be stable. We note that (5.99) is expressed in terms of dimensionless time. If we transform back to real time using (5.40), and let the birth rate function in terms of real time be $\Phi'(t, s) = \Phi(t', s)$, then we have simply

$$\Phi'(t, s) = e^{R(t)} (C\phi(s) + o(1)), \quad (5.100)$$

so the stability in terms of dimensionless time implies stability in real time.

5.4 Examples and Counter-examples

Section 5.3 shows that the sufficient conditions for unique steady size distributions (SSDs) and steady size/birth-size distributions to exist, discussed in Section 5.1, are also sufficient to ensure that they will be stable. By this we mean that given an initial cell size distribution $n_0(l, s)$ such that n_0 is not identically zero, n_0 is bounded, and $n_0 = 0$ outside the feasible region shaded in Fig. 4.4, then after a sufficiently large time we will have

$$n(l, s, t) = e^{R(t)}(Cy(l, s) + o(1)), \quad (5.101)$$

where $y(l, s)$ is the steady size/birth-size distribution given by (4.24).

5.4.1 Some Stable Cases

We consider here the cases solved analytically in Chapter 4, assuming that in each case the initial size distribution $n_0(l, s)$ is zero outside the region defined by $s_{\min} < s < s_{\max}$, $s < l < L(s)$.

The simple case discussed in Section 4.2.1, where all cells divide at the same size, with $b_l(l, s)$ given by (4.47), is stable provided that $f(p)$ is bounded. As $L^*(s) = L(s) = L$, we have $s_{\min} = p_1L$ from (5.2), and $s_{\max} = p_2L$ from (5.3), which satisfies (A_l) and (A_m) . To check that (A_r) is satisfied, let us consider first (5.5). We have for $s \geq s_{\min} + \varepsilon$,

$$p_1L^*(s) = p_1L = s_{\min} \leq s(1 - \frac{\varepsilon}{s}), \quad (5.102)$$

so (5.5) is satisfied with $\delta = \varepsilon/s_{\max}$. We can show that (5.6) holds in a similar manner, so (A_r) is satisfied. In the particular case where $s_{\min} = 0$, we have for $s \leq l < L$,

$$\int_l^L \frac{b_l(r, s)}{r^2} dr = \frac{1}{L^2}, \quad (5.103)$$

so we can satisfy (A_0) by choosing $\sigma = 0$ and $M_b = 1/L^2$. If we also choose a bounded f , so that (A_f) is satisfied, then it follows that the case where all cells divide at the same size is stable.

In the case where the hazard rate is independent of initial cell size, discussed in Section 4.2.2, we have L^* and L as constants with $L^* < L$, and also $s_{\min} = p_1L^*$ and $s_{\max} = p_2L$ (Fig. 4.7). Conditions (A_l) and (A_m) are clearly satisfied, and (A_r) follows in much the same

way as in the case where all cells divide at the same size. As $p_1 > 0$ so $s_{\min} > 0$, we do not need to check (\mathcal{A}_0) , so we conclude that the steady size/birth-size distribution will be stable provided that $f(p)$ is bounded (so (\mathcal{A}_f) is satisfied).

In Section 4.2.3, we discussed the case where $b_l(l, s) = \delta(l - L(s))$, with $L^*(s) = L(s) = L^{1-\gamma}s^\gamma$, and $f(p) = H(1 - p)$ so $p_1 = 0$ and $p_2 = 1$. Conditions (\mathcal{A}_l) and (\mathcal{A}_f) are clearly satisfied, and from Section 4.2.3 we have $s_{\min} = 0$ and s_{\max} given by (4.85), so (\mathcal{A}_m) holds. To show that (\mathcal{A}_r) is satisfied, we note first that $p_1 L^*(s) = 0$ so (5.5) is satisfied, then we consider (5.6). Given $\varepsilon > 0$, we have for $s \leq s_{\max} - \varepsilon$,

$$p_2 L(s) = L^{1-\gamma}s^\gamma = s\left(\frac{L}{s}\right)^{1-\gamma}. \quad (5.104)$$

As in Section 4.2.3, we assume that $\alpha \geq 2$, so from (4.85) we have $s_{\max} \leq L$. Hence $s < L - \varepsilon$ and the factor $(\frac{L}{s})^{1-\gamma}$ is strictly greater than one. Thus there exists a δ such that $p_2 L(s) \geq s(1 + \delta)$, so (\mathcal{A}_r) is satisfied. Finally, as $b_l(l, s) = \delta(l - L(s))$, with $L^*(s) = L(s) = L^{1-\gamma}s^\gamma$, we have for all $s \leq l \leq L(s)$,

$$\int_l^{L(s)} \frac{b_l(r, s)}{r^2} dr = \frac{1}{L(s)^2} = \frac{1}{L(s)^\sigma L(s)^{2-\sigma}}. \quad (5.105)$$

Now if we choose $\sigma = \frac{2\gamma}{\gamma+1} < 1$, and note that $L(s)^\sigma \geq l^\sigma$ and $L(s)^{2-\sigma} = (L^{1-\gamma}s^\gamma)^{2-\sigma}$, we obtain after some simplification

$$\int_l^{L(s)} \frac{b_l(r, s)}{r^2} dr \leq \frac{1}{L^{2(1-\sigma)}(ls)^\sigma}, \quad (5.106)$$

so (\mathcal{A}_0) is satisfied with $M_b = L^{-2(1-\sigma)}$. Hence the case dealt with in Section 4.2.3 is stable.

5.4.2 Some Unstable Cases

We consider here some examples in which one or more of the conditions specified in Section 5.1 are violated in some way, and show using elementary arguments in each case that a unique stable size/birth-size distribution will not in general be approached at large time.

Multiple solutions for s_{\min} and s_{\max}

Let us choose $L^*(s)$, $L(s)$, s_{\min} , and s_{\max} such that conditions (\mathcal{A}_l) and (\mathcal{A}_m) are satisfied, and choose $f(p)$ to be bounded (so (\mathcal{A}_f) holds) with $p_1 > 0$ (so (\mathcal{A}_0) is unnecessary). However,

we violate (A_1) by allowing there to be points $s_{\min,i} \in (s_{\min}, s_{\max})$ such that

$$p_1 L^*(s_{\min,i}) = s_{\min,i}, \quad (5.107)$$

and points $s_{\max,i} \in (s_{\min}, s_{\max})$ such that

$$p_2 L(s_{\max,i}) = s_{\max,i}. \quad (5.108)$$

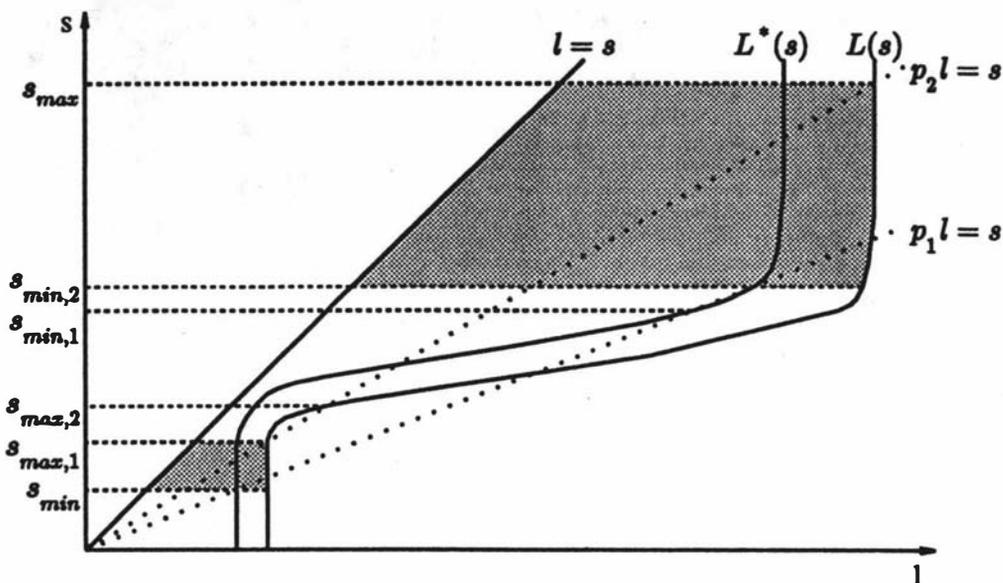


Figure 5.2: A case where the steady size distribution is not unique because (A_1) fails. We have $s_{\min}/L^*(s_{\min}) = s_{\min,1}/L^*(s_{\min,1}) = s_{\min,2}/L^*(s_{\min,2}) = p_1$ and $s_{\max}/L(s_{\max}) = s_{\max,1}/L(s_{\max,1}) = s_{\max,2}/L(s_{\max,2}) = p_2$. All cells divide between the lines $l = L^*(s)$ and $l = L(s)$.

The example we consider is shown in Fig. 5.2, where there are two points, $s_{\min,1}$ and $s_{\min,2}$, satisfying (5.107), and two points, $s_{\max,1}$ and $s_{\max,2}$, satisfying (5.108), with $s_{\max,1} < s_{\max,2} < s_{\min,1} < s_{\min,2}$ as shown. If we restricted the domain of possible cell birth-sizes to $(s_{\min}, s_{\max,1})$, by choosing $n_0(l, s)$ to be zero outside the lower shaded region in Fig. 5.2, then a steady birth-size distribution would develop with support $(s_{\min}, s_{\max,1})$, say $\phi_1(s)$. Similarly, If we restricted the domain of possible cell birth-sizes to $(s_{\min,2}, s_{\max})$, by choosing $n_0(l, s)$ to be zero outside the upper shaded region in Fig. 5.2, then a steady birth-size distribution would develop with support $(s_{\min,2}, s_{\max})$, say $\phi_2(s)$. Hence in this case a steady cell birth-size distribution may develop given any $n_0(l, s)$, but on (s_{\min}, s_{\max}) this distribution will not be unique, as changing $n_0(l, s)$ will change the linear combination of $\phi_1(s)$ and $\phi_2(s)$ which will make up the final steady birth-size distribution.

Mean cell size always decreasing

We first consider the way in which the mean cell size changes with the generation-by-generation iteration

$$\phi_{k+1}(l) = \alpha \int_0^{\infty} K(l,s) \phi_k(s) ds. \quad (5.109)$$

The mean cell size after the iteration is

$$\bar{\phi}_{k+1} = \frac{\int_0^{\infty} l \phi_{k+1} dl}{\int_0^{\infty} \phi_{k+1} dl} = \frac{\alpha \int_0^{\infty} l \int_0^{\infty} K(l,s) \phi_k(s) ds dl}{\int_0^{\infty} \int_0^{\infty} K(l,s) \phi_k(s) ds dl}, \quad (5.110)$$

which, after manipulations similar to those used in deriving (4.43) from (4.40), gives

$$\bar{\phi}_{k+1} = \frac{\int_0^{\infty} s \phi_k(s) ds}{\alpha \int_0^{\infty} s \int_s^{\infty} \frac{b_l(r,s)}{r} dr \phi_k(s) ds}. \quad (5.111)$$

Now we consider the particular case where, within the support of ϕ_k , we have

$$b_l(l,s) = \begin{cases} \frac{1}{ms - m^*s}, & m^*s \leq l \leq ms \\ 0, & \text{otherwise,} \end{cases} \quad (5.112)$$

with $1 \leq m^* < m$. Then

$$s \int_s^{\infty} \frac{b_l(r,s)}{r} dr = \frac{1}{m - m^*} \log\left(\frac{m}{m^*}\right), \quad (5.113)$$

so (5.111) gives

$$\bar{\phi}_{k+1} = \frac{m - m^*}{\alpha \log\left(\frac{m}{m^*}\right)} \bar{\phi}_k. \quad (5.114)$$

As an example, we consider the case shown in Fig. (5.3), where $\alpha = 2$ and

$$b_l(l,s) = \begin{cases} \frac{1}{L(s)-s}, & s \leq l \leq L(s) \\ 0, & \text{otherwise,} \end{cases} \quad (5.115)$$

where $L^*(s) = s$ and

$$L(s) = \begin{cases} (2p_2^{-1} - 1)s, & 0 < s < \frac{L}{2p_2^{-1} - 1} \\ L, & \frac{L}{2p_2^{-1} - 1} \leq s < L. \end{cases} \quad (5.116)$$

Hence we have

$$L(s)p_2 = \begin{cases} (2 - p_2)s, & 0 < s < \frac{L}{2p_2^{-1} - 1} \\ p_2L, & \frac{L}{2p_2^{-1} - 1} \leq s < L, \end{cases} \quad (5.117)$$

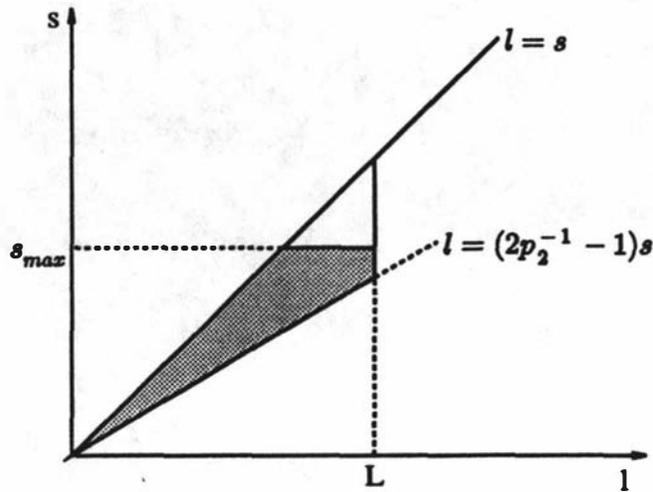


Figure 5.3: A case in which there is no steady size distribution because the mean size gets smaller every generation. Cells may exist in the shaded region only, with $b_l(l, s)$ given by (5.115).

and it can be shown that (\mathcal{A}_l) , (\mathcal{A}_f) , (\mathcal{A}_m) , and (\mathcal{A}_r) are all satisfied if we choose $s_{\min} = 0$ and $s_{\max} = p_2 L$. However, (\mathcal{A}_0) is not satisfied, because for example for $s < \frac{L}{2p_2^{-1} - 1}$ we have from (5.115) and (5.116),

$$\int_s^{L(s)} \frac{b_l(r, s)}{r^2} dr = \frac{1}{(2p_2^{-2} - 1)s^2}. \quad (5.118)$$

Indeed, this example cannot have a steady birth-size distribution, because given any birth-size distribution ϕ_k and $p_2 < 1$, we have from (5.114) with $m^* = 1$ and $m = 2p_2^{-1} - 1$,

$$\begin{aligned} \bar{\phi}_{k+1} &\leq \frac{(p_2^{-1} - 1)}{\log(2p_2^{-1} - 1)} \bar{\phi}_k \\ &< \bar{\phi}_k, \end{aligned} \quad (5.119)$$

where we have used $p_2 \geq 0.5$ and the fact that $L(s) \leq (2p_2^{-1} - 1)s$. Hence after each iteration the mean cell size gets smaller, so there can be no steady cell size distribution.

Mean cell birth-size always increasing

Consider a case in which (\mathcal{A}_m) is violated because there is no maximum birth-size s_{\max} , and for large s , $b_l(l, s)$ is given by 5.112. Then by choosing m^* sufficiently large, we can show in

a similar manner to the example above that the mean cell size must always increase, so no steady size distribution is possible.

It is interesting to note that the stability proof in Heijmans [24], for the case where all cells split exactly in half, fails if the domain of the kernel is not bounded by a requirement that all cells must divide before reaching some maximum cell size. As a simple example, using Heijmans' notation we choose a growth rate given by

$$g(x) = x + 1, \quad (5.120)$$

a fission rate of $b(a, x)$ given by

$$b(a, x) = \begin{cases} 0, & a \leq \log(3) \\ 1, & a > \log(3), \end{cases} \quad (5.121)$$

and a death rate given by

$$\mu(a, x) = 0. \quad (5.122)$$

Here a stands for cell age and x for cell size, and $b(a, x)dt$ gives the probability that a cell of age a and size x divides in a short time interval dt (in the notation of Section 1.8, $b(a, x) = h_f(x, a)g(x, a)$). Then the minimum age at which a cell can divide is $a_0 = \log(3)$, and all of Heijmans' assumptions (A_g) , (A_b) , (A_μ) , and (A_d) are satisfied, as well his Assumption 6.4. However, it is a simple matter to show that a cell which is born at size x will reach size $3x + 2$ at age a_0 , so its division size must be greater than size $3x + 2$, and both daughter cells will have size greater than $1.5x + 1$, which is strictly greater than x . Hence all daughter cells will be born at a strictly larger size than the parent cells, so no stable size distribution is possible.

$f(p)$ a delta function

Here we consider the the stability of the case dealt with in Chapter 3, where cells divide into α daughters all of the same size, so

$$f(p) = \delta(p - \alpha^{-1}), \quad (5.123)$$

where δ is the Dirac delta function. A number of authors have pointed that a population of cells growing exponentially in size and dividing exactly in half will not, in general, approach a stable size distribution (e.g. Trucco [59], Hannsgen et al [21], Tyson and Diekmann [61], and Heijmans [24]). However, as we found in Chapter 3, a steady but unstable size distribution can exist, and we note the justification given a footnote in Tyson and Diekmann [61] for studying the steady size distribution in this unstable case:

“Our rationale is that any small aberration from either true exponential growth or exactly symmetric division yields *stable* distributions which are close to the ones we calculate.”

Clearly, if $f(p)$ is given by (5.123) then assumption (A_f) cannot be satisfied, so we would not necessarily expect this case to be stable even if all the other assumptions were satisfied. A simple “mind experiment” shows that a stable size distribution cannot be approached because there is no “spreading” of cells into wider size-classes. Consider a group of cells whose sizes at time $t = 0$ all lie between l_1 and l_2 (Fig. 5.4(a)), but which may have any distribution of ages or birth-sizes, and for simplicity choose $r(t) = 1$ so the growth rate is simply $g_t(l) = l$. Any offspring produced by these cells in the next instant of time will lie between sizes $\alpha^{-1}l_1$ and $\alpha^{-1}l_2$, as shown. A short time τ later, we have the situation shown in Fig. 5.4(b), where the original cells now lie between sizes $l_1 e^\tau$ and $l_2 e^\tau$ and their daughter cells have all grown to sizes between $\alpha^{-1}l_1 e^\tau$ and $\alpha^{-1}l_2 e^\tau$. But any cells newborn at $t = \tau$ will fall exactly into the latter size range, i.e. $(\alpha^{-1}l_1 e^\tau, \alpha^{-1}l_2 e^\tau)$, and all cells born between time $t = 0$ and $t = \tau$ will also lie in this size range at time $t = \tau$. Fig. 5.4(c) shows the situation after a large time, with cells from a number of generations present. The cells from each generation are confined to a small range of sizes, with the size limits increasing exponentially with time until all cells of that generation have divided. Hence no stable size distribution is approached.

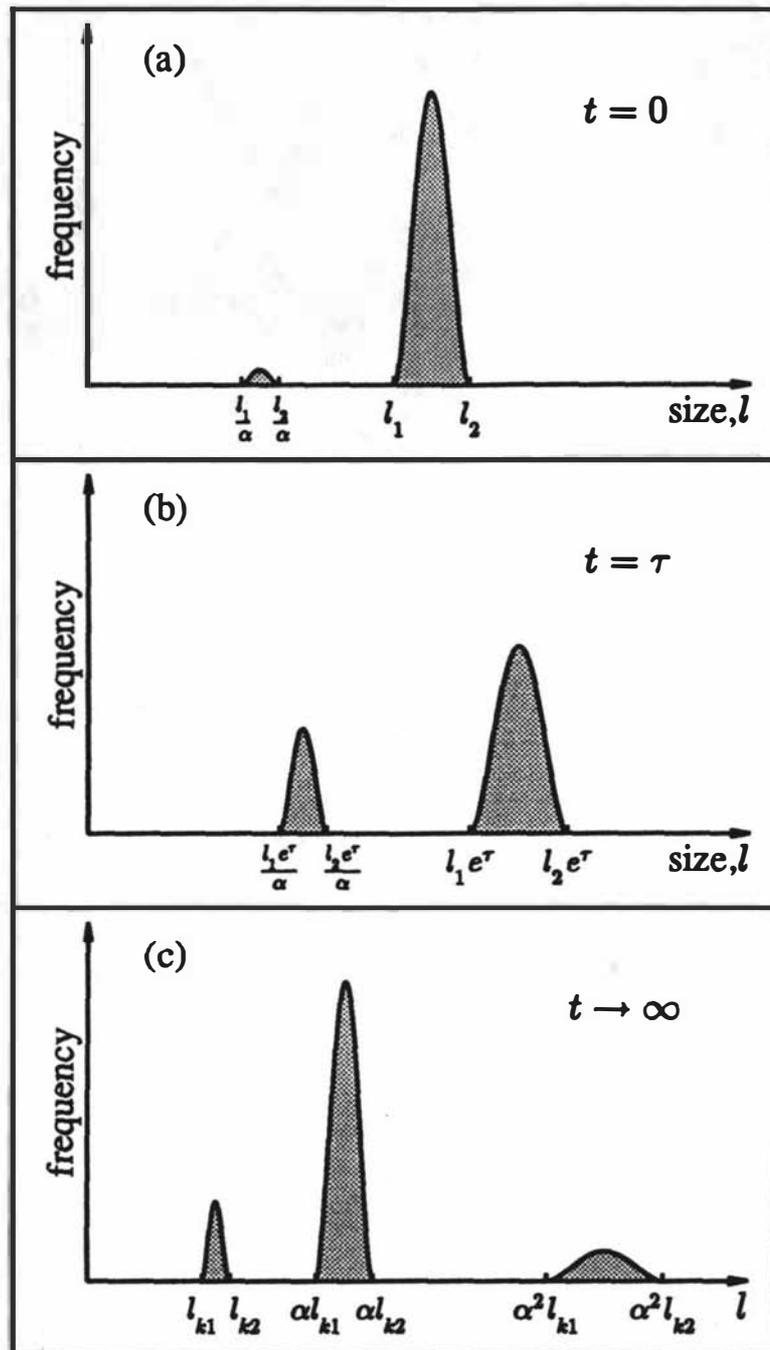


Figure 5.4: Time series of size distributions where cells grow exponentially in size and divide into exactly α equal-sized daughters. (a) At $t = 0$, an initial size distribution has support (l_1, l_2) , with daughter cells being born in the size interval $(\alpha^{-1}l_1, \alpha^{-1}l_2)$. (b) A short time τ later, all cells born between $t = 0$ and $t = \tau$ lie in the size range $(\alpha^{-1}l_1 e^\tau, \alpha^{-1}l_2 e^\tau)$. (c) At large time, as $t \rightarrow \infty$, each generation of cells still present lies within a range of sizes (l_{k1}, l_{k2}) , where $l_{k2}/l_{k1} = l_2/l_1$.

Appendix A

Moments of a Limiting Distribution

In Chapter 2, we showed that in the limit as $\alpha \rightarrow 1^+$, the solution of the functional differential equation $y'(x) = -ay(x) + a\alpha y(\alpha x)$, $x > 0$, subject to the normalising condition $\int_0^\infty y(x)dx = 1$, tends to a normal distribution. If this is the case, it follows that all the moments of the $y(x)$ given by (2.42) should tend to the corresponding moments of the normal distribution as $\alpha \rightarrow 1^+$.

A.1 Formulation as a Combinatoric Limit

Rewriting the expression given by (2.24) for the n th moment about the origin in terms of $q = \alpha^{-1}$, we obtain

$$E[x^n] = \frac{n!}{a^n(1-q)(1-q^2)\dots(1-q^n)}, \quad (\text{A.1})$$

for all positive integers n , where the notation $E[\]$ indicates the expected value. We write the mean and variance (from (2.25) and (2.26)) as

$$\mu = \frac{1}{a(1-q)} \quad (\text{A.2})$$

and

$$\sigma^2 = \frac{1}{a^2(1-q^2)} \quad (\text{A.3})$$

respectively. Then, using the binomial expansion of $(x - \mu)^n$, we obtain

$$E[(x - \mu)^n] = \sum_{k=0}^n \binom{n}{k} \left(\frac{1}{a(1-q)}\right)^{n-k} \frac{k!(-1)^{n-k}}{a^k(1-q)(1-q^2)\dots(1-q^k)}, \quad (\text{A.4})$$

so that

$$E\left[\left(\frac{x - \mu}{\sigma}\right)^n\right] = n!(1 - q^2)^{\frac{n}{2}} \sum_{k=0}^n \frac{(-1)^{n-k}}{(n-k)!(1-q)^{n-k}(1-q)(1-q^2)\dots(1-q^k)}. \quad (\text{A.5})$$

Borrowing some notation from combinatorics, we may write this as

$$E\left[\left(\frac{x - \mu}{\sigma}\right)^n\right] = \left(\frac{1+q}{1-q}\right)^{\frac{n}{2}} \sum_{k=0}^n (-1)^{n-k} \frac{n!}{(n-k)!k!_q}, \quad (\text{A.6})$$

where we define $k!_q$ to be

$$k!_q = \prod_{i=1}^k \frac{1 - q^i}{1 - q} = \prod_{i=0}^{k-1} (1 + q + q^2 + \dots + q^i), \quad (\text{A.7})$$

as in Goulden and Jackson [14]. Note that in the limit as $q \rightarrow 1^-$, $k!_q$ approaches the usual factorial,

$$\lim_{q \rightarrow 1^-} k!_q = k!, \quad (\text{A.8})$$

so $k!_q$ is called a q -analog factorial.

Now if the SSD, $y(x)$, tends to a *normal* distribution as $q \rightarrow 1^-$ (i.e. as $\alpha \rightarrow 1^+$), then the distribution of the variable $(x - \mu)/\sigma$ must tend to the unit normal distribution $N(0, 1)$. The n th moment of the normal distribution is given by

$$\mu_n^{N(0,1)} = \begin{cases} 0 & , n \text{ odd} \\ (n-1)!! & , n \text{ even} \end{cases}, \quad (\text{A.9})$$

where $(n-1)!!$ is the so-called "double factorial", which for n even is given by

$$(n-1)!! = 1.3.5\dots(n-1) = \frac{n!}{2^{\frac{n}{2}} \frac{n}{2}!}. \quad (\text{A.10})$$

Comparing (A.6) with (A.9), for the limit of the distribution of $(x - \mu)/\sigma$ as $q \rightarrow 1^-$ (i.e. as $\alpha \rightarrow 1^+$) to be a unit normal distribution, we must have

$$\lim_{q \rightarrow 1^-} \left[\left(\frac{1+q}{1-q}\right)^{\frac{n}{2}} \sum_{k=0}^n (-1)^k \frac{n!}{(n-k)!k!_q} \right] = \begin{cases} 0 & , n \text{ odd} \\ (n-1)!! & , n \text{ even} \end{cases} \quad (\text{A.11})$$

While there are some results in the literature which are superficially similar to (A.11) (Goulden and Jackson [14]), this result itself does not appear, nor apparently any other results from which (A.11) could easily be deduced. The following proof starts from what could be regarded as "first principles" and is therefore rather long!

A.2 Formulation Involving Polynomial Coefficients

From (A.7), we have for $k, n \in I^+$ and $k < n$,

$$n!_q = k!_q(1 + q + \dots + q^k) \dots (1 + q + \dots + q^{n-1}), \quad (\text{A.12})$$

so the left hand side of (A.11) can be written as

$$\begin{aligned} & \lim_{q \rightarrow 1^-} \left[\left(\frac{1+q}{1-q} \right)^{\frac{n}{2}} \sum_{k=0}^n (-1)^k \frac{n!}{(n-k)!k!_q} \right] \\ &= \lim_{q \rightarrow 1^-} \left[\frac{(1+q)^{\frac{n}{2}}}{n!_q} \frac{\sum_{k=0}^n (-1)^k \frac{n!}{(n-k)!} (1+q+\dots+q^k) \dots (1+q+\dots+q^{n-1})}{(1-q)^{\frac{n}{2}}} \right]. \end{aligned} \quad (\text{A.13})$$

The limit as $q \rightarrow 1$ of the fraction in square brackets in this expression is $\frac{2^{\frac{n}{2}}}{n!}$. Expressing the right-hand fraction in terms of $p = 1 - q$ gives

$$\lim_{q \rightarrow 1^-} \left[\left(\frac{1+q}{1-q} \right)^{\frac{n}{2}} \sum_{k=0}^n (-1)^k \frac{n!}{(n-k)!k!_q} \right] = \frac{2^{\frac{n}{2}}}{n!} \lim_{p \rightarrow 0^+} \frac{f(p)}{p^{\frac{n}{2}}}, \quad (\text{A.14})$$

where

$$f(p) = \sum_{k=0}^n (-1)^k \frac{n!}{(n-k)!} \prod_{l=k}^{n-1} \sum_{i=0}^l (1-p)^i. \quad (\text{A.15})$$

For (A.11) to hold, it follows from (A.14) that

$$\lim_{p \rightarrow 0^+} \left[\frac{f(p)}{p^{\frac{n}{2}}} \right] = \begin{cases} 0 & , n \text{ odd} \\ \frac{n!(n-1)!!}{2^{\frac{n}{2}}} & , n \text{ even.} \end{cases} \quad (\text{A.16})$$

Now $f(p)$ is a polynomial in p , so the limit in (A.16) can exist only if all coefficients of p^r in $f(p)$ are zero for $r < \frac{n}{2}$. The coefficient of p^r with $r = \frac{n}{2}$ (n even only) must be chosen so that (A.11) holds, but coefficients of p^r for $r > \frac{n}{2}$ are irrelevant. Hence (A.11) will hold provided that

$$[p^r]f(p) = \begin{cases} 0 & , r < \frac{n}{2} \\ \frac{n!(n-1)!!}{2^{\frac{n}{2}}} & , r = \frac{n}{2}, n \text{ even} \end{cases} \quad (\text{A.17})$$

where the notation $[p^r]f(p)$ is used to indicate the coefficient of p^r in $f(p)$.

A.3 An expression for $[p^l]f(p)$

Now

$$(1-p)^i = \sum_{j=0}^i (-1)^j \binom{i}{j} p^j \quad (\text{A.18})$$

so after a change of order of summation we have

$$\sum_{i=0}^l (1-p)^i = \sum_{j=0}^l (-1)^j p^j \sum_{i=j}^l \binom{i}{j}. \quad (\text{A.19})$$

We can now apply the combinatorial identity

$$\sum_{i=j}^l \binom{i}{j} = \binom{l+1}{j+1}, \quad (\text{A.20})$$

which can be proved easily by induction on l , to obtain

$$\sum_{i=0}^l (1-p)^i = \sum_{j=0}^l (-1)^j \binom{l+1}{j+1} p^j. \quad (\text{A.21})$$

Substituting this result into (A.15) we obtain

$$f(p) = \sum_{k=0}^n (-1)^k \frac{n!}{(n-k)!} \prod_{l=k}^{n-1} \sum_{i=0}^l \binom{l+1}{i+1} (-p)^i. \quad (\text{A.22})$$

For each k , consider

$$[(-p)^k] \prod_{l=k}^{n-1} \sum_{i=0}^l \binom{l+1}{i+1} (-p)^i \quad (\text{A.23})$$

as a product of $(n-k)$ terms, which we number according to the l value, from k to $(n-1)$. The constant term in the product is then simply the product of the constant terms in each of the factors,

$$[p^0] \prod_{l=k}^{n-1} \sum_{i=0}^l \binom{l+1}{i+1} (-p)^i = \prod_{l=k}^{n-1} \binom{l+1}{1} = \frac{n!}{k!}, \quad (\text{A.24})$$

so that

$$[p^0]f(p) = \sum_{k=0}^n (-1)^k \frac{n!}{(n-k)!} \frac{n!}{k!} = n! \sum_{k=0}^n (-1)^k \binom{n}{k}. \quad (\text{A.25})$$

We can then apply the identity

$$\sum_{k=0}^n (-1)^k \binom{n}{k} = \begin{cases} 0 & , n > 0 \\ 1 & , n = 0 \end{cases},$$

so for all $n > 0$ we have

$$[p^0]f(p) = 0 \quad (\text{A.26})$$

Hence in order to establish (A.17) we may now restrict our attention to $0 < r \leq \frac{n}{2}$. Note, in particular, that the term in (A.22) with $k = n$ is a constant, so we ignore that term from here on and sum over all k up to $(n - 1)$ only. Note also that we may assume

$$n \geq 2r. \quad (\text{A.27})$$

Now for any $r > 0$, we choose some partition $\underline{i} = (i_1, i_2, \dots, i_m)$ of r , such that $r = i_1 + i_2 + \dots + i_m$, and $i_j > 0, \forall j$. Note that therefore the *order* of the partition, m , must satisfy

$$m \leq r, \quad (\text{A.28})$$

and equality can occur only in the case where $\underline{i} = (1, 1, \dots, 1)$.

For the chosen partition \underline{i} , we choose the constant term from all factors in (A.23) except that we choose the term involving p^{i_1} from the j_1 th factor, the term involving p^{i_2} from the j_2 th factor, and in general the term involving p^{i_j} from the j_q th factor, with $j_1 < j_2 < \dots < j_m$. Note that if $m > n - k$, this would not be possible, so such a partition could not give rise to terms in p^r for the chosen k value. We then calculate the coefficient of $(-p)^r$ corresponding to the selection $\underline{j} = (j_1, j_2, \dots, j_m)$ of factors and the partition \underline{i} , by taking the expression (A.24) for $[p^0]$ and adjusting it for each of the factors j_q , so

$$[(-p)^r]_{\underline{i}, \underline{j}} \prod_{l=k}^{n-1} \sum_{i=0}^l \binom{l+1}{i+1} (-p)^i = \frac{n!}{k!} \prod_{q=1}^m \pi(q), \quad (\text{A.29})$$

where

$$\pi(q) = \begin{cases} 0 & , j_q < i_q \\ \frac{j_q!}{(i_q+1)!(j_q-i_q)!} & , j_q \geq i_q \end{cases}.$$

This notation ensures that if there is no term involving p^i in the chosen factor, then $\pi(q) = 0$. Since $[(-p)^\nu]f(p) = (-1)^\nu [p^\nu]f(p)$, summing over all partitions i (which implicitly sums over all m as well), and summing within each over all possible factor sequences j leads to

$$[p^\nu]f(p) = n!(-1)^\nu \sum_{k=0}^{n-1} (-1)^k \binom{n}{k} \sum_i \sum_{j_1=k}^{n-m} \pi(1) \sum_{j_2=j_1+1}^{n-(m-1)} \pi(2) \dots \sum_{j_q=j_{q-1}+1}^{n-q} \pi(q) \dots \sum_{j_{m-1}=j_{m-2}+1}^{n-2} \pi(m-1) \sum_{j_m=j_{m-1}+1}^{n-1} \pi(m). \quad (\text{A.30})$$

If $k > n - m$, then any partitions of order m should not contribute to the sum. This can be achieved by ensuring at all stages that if the lower limit of a sum is greater than the upper limit, a contribution of zero is made to any resulting total.

We now shift the summation with respect to i to the left, and reverse the order of all the other sums to get

$$[p^\nu]f(p) = \sum_i \sum_{j_m=m-1}^{n-1} \pi(m) \sum_{j_{m-1}=m-2}^{j_m-1} \pi(m-1) \dots \sum_{j_q=m-q}^{j_{q+1}-1} \pi(q) \dots \sum_{j_2=1}^{j_3-1} \pi(2) \sum_{j_1=0}^{j_2-1} \pi(1) n! (-1)^\nu \sum_{k=0}^i (-1)^k \binom{n}{k}. \quad (\text{A.31})$$

A.4 Proof of the Main Result

In order to progress step-wise through the multiple sum in (A.31), we introduce the abbreviation S_q to represent the inner sum in this expression back to summation with respect to j_q . That is,

$$S_q \equiv \sum_{j_q=m-q}^{j_{q+1}-1} \pi(q) \dots \sum_{j_2=1}^{j_3-1} \pi(2) \sum_{j_1=0}^{j_2-1} \pi(1) n! (-1)^\nu \sum_{k=0}^i (-1)^k \binom{n}{k}. \quad (\text{A.32})$$

Note that if $q = m$, we replace the upper limit of the outer sum by $n - 1$ so that S_m gives the total coefficient of p^ν for the particular partition i .

Given $n > 0$, it can be proved by induction on m that

$$\sum_{k=0}^m (-1)^k \binom{n}{k} = (-1)^m \binom{n-1}{m}, m < n, \quad (\text{A.33})$$

so the sum with respect to j_1 in (A.31) is

$$S_1 = \sum_{j_1=0}^{j_2-1} \pi(1)n!(-1)^r(-1)^{j_1} \binom{n-1}{j_1} \quad (\text{A.34})$$

We now substitute for $\pi(1)$ using (A.30), and use the fact that $\pi(1) = 0$ for $j_1 < i_1$ to raise the lower limit of this sum from $j_1 = 0$ to $j_1 = i_1$. A change of summation variable from j_1 to $j_1 - i_1$ then yields

$$S_1 = n!(-1)^r \frac{(-1)^{i_1}}{(i_1+1)!} \sum_{j_1=0}^{j_2-i_1-1} (-1)^{j_1} \frac{(n-1)!}{(n-j_1-i_1-1)!}, \quad (\text{A.35})$$

which can be written as

$$S_1 = n!(-1)^r(-1)^{i_1} \frac{(n-1)!}{(i_1+1)!(n-(i_1+1))!} \sum_{j_1=0}^{j_2-i_1-1} (-1)^{j_1} \binom{n-(i_1+1)}{j_1}. \quad (\text{A.36})$$

In the next section we show by induction on q that S_q can be written as

$$S_q = \Psi(q) \sum_{j_q=0}^{j_{q+1}-s(q)} (-1)^{j_q} \binom{n-s(q)}{j_q} + \sum_{c=q}^{s(q)-1} a_c \sum_{j_q=0}^{j_{q+1}-c} (-1)^{j_q} \binom{n-c}{j_q} \quad (\text{A.37})$$

where the a_c can be any constants,

$$s(q) = \sum_{c=1}^q (i_c + 1), \quad (\text{A.38})$$

and

$$\Psi(q) = n!(-1)^r(-1)^{\sum_{d=1}^q i_d} \frac{(n-1)!}{\prod_{d=1}^q (i_d+1)!(n-s(q))!} \frac{1}{\prod_{d=1}^{q-1} (n-s(d))}. \quad (\text{A.39})$$

Now

$$[p^r \mathcal{V}(p)] = \sum_{\underline{i}} S_m \quad (\text{A.40})$$

so substituting $q = m$ and $s(m) = \sum_{c=1}^m (i_c + 1) = r + m$ into (A.37) we have

$$[p^r \mathcal{V}(p)] = \sum_{\underline{i}} \Psi(m) \sum_{j_m=0}^{n-(r+m)} (-1)^{j_m} \binom{n-(r+m)}{j_m} + \sum_{c=m}^{r+m-1} a_c \sum_{j_m=0}^{n-c} (-1)^{j_m} \binom{n-c}{j_m}, \quad (\text{A.41})$$

where the a_c are a set of constants.

In (A.41), $c \leq r + m - 1$, so $c \leq 2r - 1$ from (A.28) and, using (A.27), $c < n$. Hence $n - c > 0$ so from (A.26) the last sum in (A.41) must be zero for all c , so all terms involving the constants a_c are zero. Also, from (A.26), the first sum in (A.41) is zero for $m < r$ because $n \geq 2r$. However, as pointed out after (A.28), the only partition of r for which $m \not< r$ is the partition $i = (1, 1, \dots, 1)$, so this is the only partition we need retain in (A.41). Hence, substituting $i_q = 1, \forall q$ into (A.39) and (A.41) we get, for $n \geq 2r$,

$$[p^r]f(p) = n!(-1)^r(-1)^r \frac{(n-1)!}{(2^r)(n-2r)!(n-2)(n-4)\dots 4 \cdot 2} \sum_{j_m=0}^{n-2r} (-1)^{j_m} \binom{n-2r}{j_m}. \quad (\text{A.42})$$

Since this sum is zero for $n > 2r$, and one for $n = 2r$, we get finally

$$[p^r]f(p) = \begin{cases} 0 & , n > 2r \\ \frac{n!(n-1)!!}{2^{\frac{n}{2}}} & , n = 2r \end{cases}, \quad (\text{A.43})$$

which is equivalent to (A.17), as required.

A.5 Proof By Induction of the Expression for S_q

We know from (A.36) that the expression for S_q , (A.37), is correct when $q = 1$. We now assume (A.37) is true for some q and show it must then be true when q is replaced by $q + 1$ and hence true for all q up to n . Then we have, from the definition (A.32),

$$S_{q+1} = \sum_{j_{q+1}=q}^{j_{q+2}-1} \pi(q+1) \left[\Psi(q) \sum_{j_q=0}^{j_{q+1}-s(q)} (-1)^{j_q} \binom{n-s(q)}{j_q} + \sum_{c=q}^{s(q)-1} a_c \sum_{j_q=0}^{j_{q+1}-c} (-1)^{j_q} \binom{n-c}{j_q} \right]. \quad (\text{A.44})$$

If we apply (A.33) to both the sums with respect to j_q , and raise the lower limit on the outer sum in each case to take account of the fact that the inner sum is zero if its lower limit exceeds the upper, we obtain

$$S_{q+1} = \Psi(q)(-1)^{s(q)} \sum_{j_{q+1}=s(q)}^{j_{q+2}-1} \pi(q+1) \left[(-1)^{j_{q+1}} \binom{n-s(q)-1}{j_{q+1}-s(q)} \right] + \sum_{c=q}^{s(q)-1} a_c (-1)^c \sum_{j_{q+1}=c}^{j_{q+2}-1} \pi(q+1) \left[(-1)^{j_{q+1}} \binom{n-c-1}{j_{q+1}-c} \right]. \quad (\text{A.45})$$

Now we note that for any $c > 0$ and $i \leq j$, it is possible to choose a set of constants b_d such that

$$j_q(j_q - 1)\dots(j_q - i_q + 1) = (j_q - c)(j_q - (c + 1))\dots(j_q - (c + i_q) + 1) + \sum_{d=0}^{i_q-1} b_d(j_q - c)(j_q - (c + 1))\dots(j_q - (c + d) + 1) \quad (\text{A.46})$$

The coefficients, b_d , could be evaluated by equating coefficients of powers of j , but we avoid this step as we are not interested in the actual values. Hence, substituting (A.30) into (A.45) and rearranging, we can write for some new set of constants b_{cd} ,

$$S_{q+1} = \left[\frac{\Psi(q)}{(i_{q+1} + 1)!} (-1)^{s(q)} \right] \sum_{j_{q+1}=s(q)+i_{q+1}}^{j_{q+2}-1} \left[(j_{q+1} - s(q))(j_{q+1} - (s(q) + 1))\dots(j_{q+1} - (s(q) + i_{q+1}) + 1) (-1)^{j_{q+1}} \binom{n - s(q) - 1}{j_{q+1} - s(q)} \right] + \sum_{c=q}^{s(q)} \sum_{d=0}^{i_{q+1}-1} b_{cd} \sum_{j_{q+1}=c+d}^{j_{q+2}-1} \left[\frac{(j_{q+1} - c)(j_{q+1} - (c + 1))\dots(j_{q+1} - (c + d) + 1)}{(i_{q+1} + 1)!} (-1)^{j_{q+1}} \binom{n - c - 1}{j_{q+1} - c} \right]. \quad (\text{A.47})$$

Note that the lower limits of the outer sums have been raised again because the product is zero in the intermediate cases, and that the unknown constants in the expansion of the first sum have been included in the second, which is why the upper limit on the sum with respect to d has been raised to $s(q)$.

We now note that the last sum in (A.47) can be rearranged to give

$$\sum_{j_{q+1}=c+d}^{j_{q+2}-1} \left[\frac{(j_{q+1} - c)(j_{q+1} - (c + 1))\dots(j_{q+1} - (c + d) + 1)}{(i_{q+1} + 1)!} (-1)^{j_{q+1}} \binom{n - c - 1}{j_{q+1} - c} \right] = (n - (c + 1))(n - (c + 2))\dots(n - (c + d)) \sum_{j_{q+1}=c+d}^{j_{q+2}-1} (-1)^{j_{q+1}} \binom{n - (c + d) - 1}{j_{q+1} - (c + d)} \quad (\text{A.48})$$

and that a similar rearrangement of the first sum with respect to j_{q+1} can be made, with c replaced by $s(q)$ and d replaced by i_{q+1} . We now change the summation variable from j_{q+1} to $j_{q+1} - (s(q) + i_{q+1})$ in the first sum, and from j_{q+1} to $j_{q+1} - (c + d)$ in the last, and also replace the summation variable c by $c + 1$. Then, grouping "like binomials", we have for a new set of constants a_c ,

$$S_{q+1} = \left[\frac{\Psi(q)}{(i_{q+1} + 1)!} (-1)^{s(q)} (n - s(q) + 1)\dots(n - (s(q) + i_{q+1})) (-1)^{s(q)} (-1)^{i_q} \right]$$

$$\begin{aligned}
& \sum_{j_{q+1}=0}^{j_{q+2}-(s(q)+i_{q+1})-1} \left[(-1)^{j_{q+1}} \binom{n-(s(q)+i_{q+1})-1}{j_{q+1}} \right] \\
& + \sum_{c=q+1}^{s(q)+i_{q+1}} a_c \sum_{j_{q+1}=0}^{j_{q+2}-c} \left[(-1)^{j_{q+1}} \binom{n-c}{j_{q+1}} \right], \tag{A.49}
\end{aligned}$$

where the upper limit of the sum with respect to c has been increased from $s(q) + 1$ to $s(q) + i_{q+1}$ by setting the appropriate constants a_c to zero.

Now $s(q) + (i_{q+1} + 1) = s(q + 1)$ and the first expression in square brackets of (A.49) simplifies to $\Psi(q + 1)$, so we have finally

$$\begin{aligned}
S_{q+1} = & \Psi(q + 1) \sum_{j_{q+1}=0}^{j_{q+2}-s(q+1)} \left[(-1)^{j_{q+1}} \binom{n-s(q+1)}{j_{q+1}} \right] \\
& + \sum_{c=q+1}^{s(q+1)-1} a_c \sum_{j_{q+1}=0}^{j_{q+2}-c} \left[(-1)^{j_{q+1}} \binom{n-c}{j_{q+1}} \right] \tag{A.50}
\end{aligned}$$

as required.

Appendix B

The case $b(x) = b$ with $g(x) = gx^k$

Here we consider again the special case described in Section 1.9, where the product of the hazard rate, h_l , and the time-independent part of the growth rate, g , is assumed to be constant ((1.79) or (1.80)). As pointed out in Section 1.9, this means that the probability of cell division in a short time interval dt is independent of cell size l and cell age a , but is proportional to the time-dependent part of the growth rate $r(t)$. We assume also that all cells divide into exactly α daughters all of the same size, but instead of assuming that the time-independent part of the growth rate g is a constant as in Chapter 2, we assume

$$g(l) = gl^{1-k}, \quad k > 0, \quad (\text{B.1})$$

where the g on the right hand side is a constant. Substituting (B.1) into (1.82), the functional differential equation for the SSD $y(l)$ becomes

$$\frac{d}{dl} gl^{1-k} y(l) = -b\alpha y(l) + b\alpha^2 y(\alpha l). \quad (\text{B.2})$$

Now if we substitute

$$Z(l) = g(l)y(l) = gl^{1-k}y(l) \quad (\text{B.3})$$

and

$$a = \frac{b\alpha}{g} \quad (\text{B.4})$$

into (B.2) we obtain

$$Z'(l) = k^{-1}(-aZ(l) + \alpha a^k Z(\alpha l)). \quad (\text{B.5})$$

As pointed out in Section 3.1, this is exactly of the form (3.20), the solution of which is given by (3.25),

$$Z(l) = C \sum_{n=0}^{\infty} \frac{(-1)^n \alpha^{kn}}{(\alpha^k - 1) \dots (\alpha^{kn} - 1)} e^{-a \frac{\alpha^{kn}}{l}}. \quad (\text{B.6})$$

To find the constant C in this case, we use the normalisation condition obtained by substituting (B.3) into (1.43), which is

$$\int_0^{\infty} Z(l) l^{k-1} dl = g. \quad (\text{B.7})$$

Substituting the solution (B.6) into (B.7), we obtain

$$C = g \left[\int_0^{\infty} \sum_{n=0}^{\infty} \frac{(-1)^n \alpha^{kn}}{(\alpha^k - 1) \dots (\alpha^{kn} - 1)} l^{k-1} e^{-a \frac{\alpha^{kn}}{l}} dl \right]^{-1}. \quad (\text{B.8})$$

As $k > 0$, we may now simply interchange the order of summation and integration, and perform the integration term by term to obtain

$$\begin{aligned} \int_0^{\infty} \sum_{n=0}^{\infty} \frac{(-1)^n \alpha^{kn}}{(\alpha^k - 1) \dots (\alpha^{kn} - 1)} l^{k-1} e^{-a \frac{\alpha^{kn}}{l}} dl &= \sum_{n=0}^{\infty} \frac{(-1)^n \alpha^{kn}}{(\alpha^k - 1) \dots (\alpha^{kn} - 1)} \int_0^{\infty} l^{k-1} e^{-a \frac{\alpha^{kn}}{l}} dl \\ &= \sum_{n=0}^{\infty} \frac{(-1)^n \alpha^{kn}}{(\alpha^k - 1) \dots (\alpha^{kn} - 1)} \frac{1}{a \alpha^{nk}} \\ &= \frac{1}{a} \sum_{n=0}^{\infty} \frac{(-1)^n}{(\alpha^k - 1) \dots (\alpha^{kn} - 1)}. \end{aligned} \quad (\text{B.9})$$

Now if we use the definition of $K(\alpha, \beta)$ given by (3.38), the sum on the right hand side is simply $K(\alpha^k, 1)$, so from (B.8), C is given by

$$C = \frac{ga}{K(\alpha^k, 1)}. \quad (\text{B.10})$$

Hence the solution of (B.5) subject to (B.7) may be written as

$$Z(l) = \frac{ga}{K(\alpha^k, 1)} \sum_{n=0}^{\infty} \frac{(-1)^n \alpha^{kn}}{(\alpha^k - 1) \dots (\alpha^{kn} - 1)} e^{-a \frac{\alpha^{kn}}{l}}, \quad (\text{B.11})$$

so the SSD $y(x)$ is given from (B.3) as

$$y(l) = \frac{al^{k-1}}{K(\alpha^k, 1)} \sum_{n=0}^{\infty} \frac{(-1)^n \alpha^{kn}}{(\alpha^k - 1) \dots (\alpha^{kn} - 1)} e^{-a \frac{\alpha^{kn}}{l}}. \quad (\text{B.12})$$

Appendix C

The General Equation

$$y'(x) = -p(x)y(x) + q(x)y(\alpha x)$$

Equation (1.55) gives the general form of the functional differential equation arising in the case of a population structured on size only, where all cells divide into exactly α pieces all of the same size. Here we develop a general series solution for equations of this form, assuming that a value for Q is given.

Consider the functional differential equation of the general form

$$y'(x) = -p(x)y(x) + q(x)y(\alpha x), \quad (\text{C.1})$$

where $\alpha > 1$ and we are interested only in the region $x > 0$. We wish to find an expression for the solution to this equation, assuming for the moment that it exists.

Firstly, let us assume that there is a maximum value of x , x^* say, such that

$$y(x) \equiv 0, x > x^*. \quad (\text{C.2})$$

We then write $y(x)$ as

$$y(x) = \begin{cases} 0, & x \geq x^* \\ y_k(x), & x^* \alpha^{-k} \leq x < x^* \alpha^{-(k-1)}. \end{cases} \quad (\text{C.3})$$

We will refer to the range of x values $x^* \alpha^{-k} \leq x < x^* \alpha^{-(k-1)}$ as region k , so the regions are labelled in the same way as in Fig. 3.3. The solution in region k we will call $y_k(x)$.

In region 0, we have simply

$$y_0(x) = 0. \quad (C.4)$$

In region 1, from (C.4) we have $y(\alpha x) = 0$, so (C.1) gives

$$y_1'(x) = -p(x)y_1(x), \quad (C.5)$$

so if we let $P(x)$ be an anti-derivative of $p(x)$ we have

$$y_1(x) = Ce^{-P(x)}, \quad (C.6)$$

where C is an arbitrary constant.

In region $k + 1$, $k > 0$, (C.1) gives

$$y_{k+1}'(x) = -p(x)y_{k+1}(x) + q(x)y_k(\alpha x), \quad (C.7)$$

which if we let

$$W_k(x) = e^{P(x)}y_k(x) \quad (C.8)$$

for all k simplifies to

$$W_{k+1}'(x) = -\alpha f(\alpha x)W_k(\alpha x), \quad (C.9)$$

where

$$f(x) = -\alpha^{-1}q(x\alpha^{-1})e^{(P(x\alpha^{-1})-P(x))}. \quad (C.10)$$

We now assume that $y(x)$, and therefore $W(x)$, is continuous at $x = x^*\alpha^{-k}$ so (C.9) can be written in integral form as

$$W_{k+1}(x) = W_k(x^*\alpha^{-k}) + \int_{\alpha x}^{x^*\alpha^{1-k}} f(s)W_k(s)ds. \quad (C.11)$$

From (C.6) we know $W_1(x) = C$, so it is possible to apply (C.11) repeatedly. By induction, we can then show

$$W_k(x) = C \left[1 + \sum_{n=1}^{k-1} \int_{\alpha x}^{x^*\alpha^{1-n}} f(s_n) \int_{\alpha s_n}^{x^*\alpha^{2-n}} f(s_{n-1}) \dots \int_{\alpha s_2}^{x^*} f(s_1) ds_1 \dots ds_{n-1} ds_n \right], \quad (C.12)$$

so the solution to (C.1) can be written as

$$y(x) = Ce^{-P(x)} \left[1 + \sum_{n=1}^{k-1} \int_{\alpha x}^{x^*\alpha^{1-n}} f(s_n) \int_{\alpha s_n}^{x^*\alpha^{2-n}} f(s_{n-1}) \dots \int_{\alpha s_2}^{x^*} f(s_1) ds_1 \dots ds_{n-1} ds_n \right], \quad (C.13)$$

$$x^*\alpha^{-k} \leq x < x^*\alpha^{-(k-1)}$$

in the case where (C.2) holds. Note that for all $x > 0$, only a finite number of integrals are required, but if x^* is particularly large or x is particularly small, the number of integrals required could be very large. In applications where the x is cell size, there will normally be a minimum size x_0 say below which it is known that $y(x) = 0$, so for all "feasible" cell sizes x in the range $x_0 \leq x \leq x^*$, the number of terms in the sum in (C.13) will not exceed $\log(x^*/x_0)/\log(\alpha)$.

Now if we choose some x and let $x^* \rightarrow \infty$, then it is apparent that $k \rightarrow \infty$ also. Hence we can find the solution to (C.1) without the restriction (C.2) by taking limits of (C.13) as $x^* \rightarrow \infty$ and $k \rightarrow \infty$. The result, independent of the order in which these limits are taken and the value of x , is

$$y(x) = Ce^{-P(x)} \left[1 + \sum_{n=1}^{\infty} \int_{\alpha x}^{\infty} f(s_n) \int_{\alpha s_n}^{\infty} f(s_{n-1}) \dots \int_{\alpha s_2}^{\infty} f(s_1) ds_1 \dots ds_{n-1} ds_n \right], \quad (C.14)$$

provided of course that the integrals exist and the sum converges. A necessary condition for all the integrals to exist is clearly that $\lim_{x \rightarrow \infty} f(x) = 0$, but it appears that the most straightforward way to check whether the series solution (C.14) exists is to calculate the multiple integrals and substitute to check for convergence of the series. All solutions given in this thesis for the case where cells divide into exactly α pieces of equal size can be regarded as special cases of either the infinite series (C.14) or the finite series (C.13).

For example, in the case considered in Section 3.3, in (3.20) we have

$$p(x) = \alpha x^{k-1} \quad (C.15)$$

so

$$P(x) = \frac{\alpha}{k} x^k, \quad (C.16)$$

and

$$q(x) = \alpha \alpha^k x^{k-1}. \quad (C.17)$$

From (C.10) we then have

$$f(x) = -\alpha x^{k-1} e^{-(1-\alpha^{-k})\frac{\alpha}{k}x^k}, \quad (C.18)$$

so

$$\int_{\alpha x}^{\infty} f(s_1) ds_1 = \frac{-\alpha^k}{(\alpha^k - 1)} e^{-(\alpha^k - 1)\frac{\alpha}{k}x^k}. \quad (C.19)$$

Once again using induction, we can show that

$$\int_x^\infty f(s_n) \int_{s_n}^\infty f(s_{n-1}) \dots \int_{s_2}^\infty f(s_1) ds_1 \dots ds_{n-1} ds_n = \frac{(-1)^n \alpha^{nk} e^{-(\alpha^k - 1) \frac{1}{k} x^k}}{(\alpha^k - 1)(\alpha^{2k} - 1) \dots (\alpha^{nk} - 1)}. \quad (\text{C.20})$$

The solution then becomes

$$y(x) = C e^{-\frac{1}{k} x^k} \left[1 + \sum_{n=1}^{\infty} \frac{(-1)^n \alpha^{nk} e^{-(\alpha^k - 1) \frac{1}{k} x^k}}{(\alpha^k - 1)(\alpha^{2k} - 1) \dots (\alpha^{nk} - 1)} \right]. \quad (\text{C.21})$$

This is just a slight rearrangement of the solution for $Z(x)$ given in (3.25).

Appendix D

Generalised Solutions of the Functional Differential Equation

We consider here the possible *generalised* solutions of (3.8), which can arise at size $x = 0$ because the growth rate is zero at size zero.

Firstly, we show that the Dirac delta function $\delta(x)$ is a solution of (3.8) for any given $b(x)$. Intuitively, this corresponds to the idea that if the growth rate is zero at size zero (as it is for $g(x) = gx$), then given an initial population all of size 0, the whole population will remain at size 0 for all time!

The following elementary results hold for any function $b(x)$:

$$\int_0^{\infty} b(x)\delta(x)dx = b(0), \quad (\text{D.1})$$

$$b(x)\delta(x) = b(0)\delta(x), \quad (\text{D.2})$$

$$b(\alpha x)\delta(\alpha x) = b(0)\frac{\delta(x)}{\alpha}, \quad (\text{D.3})$$

and we note also that

$$x\delta'(x) = -\delta(x). \quad (\text{D.4})$$

Substitution of $y(x) = \delta(x)$ into (3.8) then leads to the trivial identity

$$-g\delta(x) = -[b(0) + (\alpha - 1)b(0) + g]\delta(x) + \alpha^2 b(0)\frac{\delta(x)}{\alpha}, \quad (\text{D.5})$$

so $y(x) = \delta(x)$ is always a solution of (3.8). Note that $\delta(x)$ also satisfies the unit integral condition (3.4) and the non-negativity condition (3.5), so $y(x) = \delta(x)$ satisfies all the conditions required to be a SSD.

In general, $\delta(x)$ is NOT the only generalised solution with point support the origin. To see whether other generalised solutions are possible, we substitute the most general possible solution with point support at the origin,

$$y(x) = \sum_{n=0}^{\infty} C_n \delta^{(n)}(x), \quad (\text{D.6})$$

into (3.8), then equate coefficients of each derivative of the delta function. Using the identities above, we obtain a set of equations of the form

$$(gn - S)C_n = (-1)^n (1 - \alpha^{1-n}) \sum_{j=n}^{\infty} \binom{j}{n} b^{(j-n)}(0) (-1)^j C_j \quad (\text{D.7})$$

where

$$S = (\alpha - 1) \sum_{j=0}^{\infty} (-1)^j b^{(j)}(0) \quad (\text{D.8})$$

Substituting $n = 0$ leads to

$$-SC_0 = -S \quad (\text{D.9})$$

so either $S = 0$ or $C_0 = 1$, then substituting $n = 1$ gives

$$C_1(g - S) = 0 \quad (\text{D.10})$$

so either $S = g$ or $C_1 = 0$.

For $n > 1$ the equation contains as many C_j terms as there are non-zero derivatives of $b(x)$ at $x = 0$, so the situation becomes very complex. However, it is clear that if $b^{(m)}(0) \neq 0$ but $b^{(j)}(0) = 0$ for all $j > m$, then it is possible to choose C_2 up to C_{m+1} arbitrarily, then all C_j 's for $j > m + 1$ can be expressed in terms of these. The term $\binom{j}{n}$ on the right hand side seems to ensure that the coefficients will get smaller as n increases. In other words, it is possible to in general choose solutions of the form

$$y(x) = \delta(x) + \sum_{n=2}^{\infty} C_n \delta^{(n)}(x), \quad (\text{D.11})$$

where the C_n 's are non-zero.

For example, if $b'(0) <> 0$ but $b^{(j)} = 0$ for $j > 1$, then $S = (\alpha - 1)b(0)$ and we get as a solution

$$y(x) = \delta(x) + A[\delta^{(2)}(x) + \sum_{n=3}^{\infty} A_n \delta^{(n)}(x)] \quad (D.12)$$

where A is arbitrary and

$$A_n = 2 \frac{((\alpha - \alpha^{-1})b(0) - 2g) \dots ((\alpha - \alpha^{2-n})b(0) - (n-1)g)}{[(1 - \alpha^{-1}) \dots (1 - \alpha^{2-n})]n!(b'(0))^{n-2}} \quad (D.13)$$

Note that because all derivatives of the delta function have zero integral, solutions of the form (D.11) satisfy the unit integral condition (3.4). We now define *non-negativity* of a generalised function $t(x)$ in the natural way, such that

- A generalised function $t(x)$ is *non-negative* iff $\forall \phi \in S$ (where S is the set of "smooth" test functions) such that $\phi(x) \geq 0, \forall x, \int_{-\infty}^{\infty} t(x)\phi(x)dx \geq 0$.

Then we have

$$\int_{-\infty}^{\infty} \delta^{(n)}(x)\phi(x)dx = (-1)^n \phi^{(n)}(0), \quad (D.14)$$

so from (D.12),

$$\int_{-\infty}^{\infty} y(x)\phi(x)dx = \phi(0) + \sum_{n=2}^{\infty} C_n (-1)^n \phi^{(n)}(0). \quad (D.15)$$

Now for any $n > 1$, it is possible to choose a ϕ such that $-C_n (-1)^n \phi^{(n)}(0) > \phi(0)$ for any finite C_n , and $\phi^{(j)} = 0, \forall j \neq n, j \geq 2$. Therefore if $C_n \neq 0$ for any $n \geq 2$, $y(x)$ cannot be said to be non-negative.

Hence $y(x) = \delta(x)$ is the only non-negative generalised solution of (3.8).

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