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Chapter 1

Introduction

Modelling cell populations is of great importance for instance in bacteriology and cell biology, since it enables us to compare theories in cell kinetics and cell growth with real observations. Modern mathematical population modelling has its roots in the beginning of the century when Sharpe and Lotka (*cf.* (Sharpe & Lotka, 1911)) introduced the first structured model in demography. These first deterministic models were *age*-structured, meaning that every individual in the population is characterised by its age. Other structures, as we will see later, can be size, weight, growth etc. and will be referred to as the *types* of the individuals. Sharpe and Lotka conjectured the existence of a *stable age distribution* introducing a renewal equation treatment. An *age distribution* gives the proportion of individuals in various intervals at a certain time, and *stable* indicates that the composition of the population has stabilised with respect to the age. The existence of such a distribution was, and is, of great importance, since it gives that no matter what the initial age distribution is, the composition of age will tend to the stable one. In cell populations this would mean that it is possible to generate a large population from one single cell. Despite its importance it was first in (Feller, 1941) that a rigorous proof of the conjecture was given, using probabilistic arguments. The first deterministic proof using partial differential equations and functional analysis was given in (Webb, 1983).

One of the most influential papers on structured *cell* populations seems to be (Bell & Anderson, 1967), which gave rise to the so-called Bell-Anderson model. In this model the individuals are characterised by their *size* (*e.g.* mass, volume, DNA-content). The use of branching processes to model cell populations was pioneered by Bellman and Harris in (Bellman & Harris, 1948), where the Galton-Watson branching process was generalised to a process where each individual first lives a random amount of time, independently of the others, and then gives birth to a random number of children. A natural special case is then to consider a population with binary splitting such as in a cell model. But up to this point the branching process approach only considered individuals of the same type. A multi-type Bellman-Harris process was treated for the first time in (Ney, 1964), working with finite number of types. The next step was to consider general type spaces. In (Athreya & Ney, 1972) the problem was stated in terms of functional analysis, but a more rigorous probabilistic approach with general branching processes (Crump-Mode-Jagers) was done in (Nerman, 1984). Since then much work has been done, in stochastic as well as in deterministic modelling. Some stochastic references are (Jagers, 1975), (Jagers, 1992a), (Jagers, 1992b), and (Jagers & Nerman, 1996) and deterministic (Heijmans, 1984), (Lasota & Mackey, 1984) and (Tyson & Diekmann, 1986) to mention a few.

In this paper we present a general branching process version of the Bell-Anderson model based on (Jagers, 1992b) and (Taib, 1996), and leaning on the Markov Renewal theory described in (Shurenkov, 1992a and b), and then we specialise it to the Two-Subcycle cell cycle model described in (Sennerstam & Strömberg, 1995). We break down the problem into smaller, more manageable pieces and work our way up, step by step, towards the full model.

In Chapter 2 we introduce some terminology and notation from general multi-type branching processes due to (Jagers, 1989), which will be used consistently in all our models.

In Chapter 3 we describe the Markov Renewal Theory due to Shurenkov in (Shurenkov, 1992a and b). This theory is needed to show the stability of different composition aspects of the models.

In Chapter 4 our first cell model is presented. Here we develop the *equal* cell division model in (Taib, 1996) to a model with *unequal* cell division, and treat the equal cell division as a special case of this. We both treat the model in its full generallity and under the assumption of a critical size that each cell has to pass before mitosis. We prove the existence of the Malthusian parameter generally for equal cell division and by adding the assumption of a critical size for unequal cell division.

In Chapter 5 we present the theory of doubly infinite populations due to (Jagers & Nerman, 1996), where an individual is sampled at random in an old population, and the population is described from her point of view in time. We introduce an alternative way of getting asymptotic results to the one presented in Chapter 2 using this new way of viewing the population.

In Chapter 6 we use the results from the previous chapter to study the asymptotics of the cell model defined in Chapter 4. We introduce the concepts of α- and β-curves and calculate them for our model. We also manage to give an analytic expression of the stable size distribution for our cell model.
In Chapter 7 we approach the Two-Subcycle model first in biological terms and then by constructing the general branching process model. We study the asymptotics of the model and draw some illustrative plots to be compared with the simulation results in (Sennerstam & Strömberg, 1995).

Chapter 2

General Multi-Type Branching Processes

In this chapter we introduce some terminology and definitions from general branching processes mainly following (Jagers, 1989). More details can be found in (Nerman, 1984).

2.1. Basics

A general branching population starts from one ancestor labelled 0. She gets a number of children which can be labelled according to the elements in $N = \{1, 2, 3, \ldots\}$. Her grandchildren are elements in N^2 and so forth, so that the set of all possible individuals in the population, the *Ulam-Harris space*, is

$$I = \bigcup_{n=0}^{\infty} N^n, \quad N^0 = \{0\}.$$

An individual $x \in N^n$ has the form $(x_1, \ldots, x_n)$, which means that she is the $x_n th$ child of the $x_{n-1} th$ child of $\ldots$ of the $x_1 th$ child of 0. When two sequences $x, y \in I$ are concatenated as xy we mean an individual with first x's and then y's coordinates. We use the convention $x0 = 0x = x$.

The set of all possible life careers is denoted Ω, the *life space*, and it is equipped with a σ-algebra $\mathcal{A}$ assumed to be rich enough to carry information about entities like ages at childbearing, lifespans etc. We write ω_x for the life career of an individual $x \in I$ and we define a sequence of random variables $0 \leq \tau(1) \leq \tau(2) \leq \ldots \leq \infty$, where $\tau(i) : \Omega \to \mathrm{R}_+ \cup \{\infty\}$, $\tau(i)(\omega)$ being the age at childbearing *no.* i for an individual with life career $\omega \in \Omega$. $\tau(i) = \infty$ is

interpreted as child *no.* i is never born, *i.e.* the individual begets less than i children. We use $\tau_x(i)$ to denote the age of $x \in I$ at the i*th* childbearing. The *life span* $\lambda : \Omega \to \mathrm{R}_+ \cup \{\infty\}$ is also a random variable and we use λ_x to denote the life span of $x \in I$.
At birth each individual gets (or inherits) a type from a *type space* $(S, \mathcal{S})$, where S can be any abstract space with a countably generated σ-algebra $\mathcal{S}$. We define measurable functions $\sigma(i) : \Omega \to S$ where $\sigma(i)(\omega)$ gives the type of the ith child of an individual with life career ω.
From the life space we construct the *population space* $(S \times \Omega^I, \mathcal{S} \times \mathcal{A}^I)$ where

$$(\Omega^I, \mathcal{A}^I) = \prod_{x \in I} (\Omega, \mathcal{A}).$$

A typical element in Ω^I will be denoted ω^I and $\omega_x^I = \{\omega_{xy}\}_{y \in I}$ describes the lives of x and her progeny.
We need to introduce shift operators $\mathcal{D}_x : S \times \Omega^I \to S \times \Omega^I$ defined by

$$\mathcal{D}_x(s, \omega^I) = (\sigma_x, \omega_x^I)$$

and interpreted as the operator that renders x an ancestor. The process shifted by $\mathcal{D}_x$ is called the *daughter process* of x.
To be able to count the population with respect to some property (*e.g.* being alive, being a mother etc.) we introduce *random characteristics*. These are real valued processes

$$\chi : S \times \Omega^I \times \mathrm{R} \to \mathrm{R}_+$$

where $\chi(s, \omega^I, t)$ is the contribution of an s-type individual at age t with life and daughter process described by ω^I. Unless otherwise stated χ is assumed to be non-negative and vanishing for negative times t. The characteristic χ_x pertaining to $x \in I$ is defined as $\chi_x = \chi \circ \mathcal{D}_x$ and we write χ for χ_0. When χ_x only depends on x's own life and type it is said to be *individual*. The birth times, τ_x, of individuals are defined inductively by

$$\begin{aligned} \tau_0 &= 0 \\ \tau_i &= \tau(i)(\omega_0) \\ \tau_{xi} &= \tau_x + \tau_x(i)(\omega_x) \end{aligned}$$

and *the branching process counted by* χ is defined to be

$$z_t^\chi = \sum_{x \in I} \chi_x(t - \tau_x).$$

Since τ_x is x's birth time, $t - \tau_x$ stands for x's age at time t and z_t^χ is simply the sum of all scores evaluated at the individual's actual age at this time. When $\chi(a) = \mathbf{1}_{\mathrm{R}_+}(a)$, z_t^χ is just the total number of individuals born up to time t, and will be denoted y_t.

We equip the population space with a set of probability kernels $P(s, A)$, $s \in S$, $A \in \mathcal{A}$. $P(s, \cdot)$ is called the *life law* for an s-type individual, which means that the individual chooses a life from $(\Omega, \mathcal{A})$ according to $P(s, \cdot)$. Assume that given the types of a set of individuals the daughter populations of the set are independent of the history of the set. This is called the *Markov property* for multi-type populations and it implies the *branching property*: given the pre-history of a set of individuals not stemming from each other, their daughter populations are conditionally independent. Under these assumptions it can be shown (*cf.* (Jagers, 1989)) that such a kernel defines a unique probability measure P_s on the population space, for each $s \in S$, where s is the type of the ancestor.

The *reproduction point process* is defined through

$$\xi(\omega, A \times B) = \#\{i : \sigma(i)(\omega) \in A, \tau(i)(\omega) \in B\}$$

where $A \in \mathcal{S}$ and $B \in \mathcal{B}$, the Borel-σ-algebra on R_+. From now on we will omit ω and use the notation $\xi(A \times B)$. The *reproduction kernel* is defined through

$$\mu(r, A \times [0, t]) = \mathrm{E}_r[\xi(A \times [0, t])]$$

and is interpreted as the expected number of children with types in A to an individual with type r and age in [0,t] (*i.e.* from birth up to age t). Kernels are discussed further in Chapter 3.
If we assume the population to be supercritical and Malthusian with Malthusian parameter α (defined in 3.2), we will see in 3.2 that μ determines a measure π on $(S, \mathcal{S})$ and a function h on S such that under certain conditions

$$\lim_{t \to \infty} e^{-\alpha t} E_s[z_t^\chi] = \frac{E_\pi[\hat{\chi}(\alpha)]}{\alpha\beta} h(s)$$

and

$$\lim_{t\to\infty} \frac{z_t^{\chi}}{y_t} = E_\pi[\hat{\chi}(\alpha)] \quad a.s.$$

where $E_\pi[X] = \int_S E_s[X]\pi(ds)$, $\hat{\chi}(\alpha) = \int_{\mathrm{R}_+} e^{-\alpha t}\chi(t)dt$, and β is a real number defined in 3.2 and referred to as the *stable age at childbearing* (with some caution, *cf.* (Jagers & Nerman, 1996)).

Chapter 3

Markov Renewal Theory

In the study of the asymptotic expected behaviour of a multi-type branching population, Markov Renewal Theory provides us with some useful tools. In this section, we give some definitions and results due to (Shurenkov, 1992a and b).

3.1. General theory

First let $(E, \mathcal{E})$ be a measurable space and $\mathcal{B}$ the Borel-σ-algebra on R_+. Let $K(x, dy \times dt)$ be a non-negative kernel on $(E \times \mathrm{R}_+, \mathcal{E} \times \mathcal{B})$, *i.e.* $K(x, A \times B)$ is a non-negative measure on $(E \times \mathrm{R}_+, \mathcal{E} \times \mathcal{B})$ for each $x \in E$ and an $\mathcal{E}$-measurable function for each $A \in \mathcal{E}$ and $B \in \mathcal{B}$. Sums and products of non-negative kernels are again non-negative kernels and *the basis* $\hat{K}$ *of* K is defined by

$$\hat{K}(x, dy) = \int_{\mathrm{R}_+} K(x, dy \times dt).$$

The *potential of* K is the kernel

$$U(x, dy \times dt) = \sum_{n \geq 0} K^n(x, dy \times dt)$$

where

$$K^n(x, dy \times dt) = \int\limits_{E \times \mathrm{R}_+} K^{n-1}(x, dz \times du) K(z, dy \times dt - u)$$

with $K^0(x, dy \times dt) = \mathbf{1}_{(x,0)}(dy \times dt)$ and $K^1 = K$.

Next we give some definitions needed to state some desired results.

Definition 3.1.1. *$\hat{K}$ is called σ-finite if there exists a strictly positive $\mathcal{E}\times\mathcal{E}$-measurable function f such that*

$$\int_E f(x,y)\hat{K}(x,dy) < \infty$$

for each $x \in E$.

The existence of such a function follows directly from the alternative definition of σ-finiteness: there is a sequence $A_n \in \mathcal{E}$ where $\bigcup_n A_n = E$ such that $\hat{K}(\cdot, A_n) < \infty, \forall n$.

Definition 3.1.2. *The Perron root ρ of $\hat{K}$ is defined by*

$$\rho(\hat{K})^{-1} = \sup\{\lambda \in \mathrm{R}_+ : \sum_{n\geq 0} \lambda^n \hat{K}^n \quad \text{is } \sigma\text{−finite}\}$$

Note that $\rho(\hat{K})$ may equal zero or infinity. It is not obvious how to interpret the Perron root, but it gives an idea of how close the kernel is to a probability measure and equals one when this is the case.

Definition 3.1.3. *$\hat{K}$ is called m-positive if there exists a non-negative non-trivial σ-finite measure m on $(E, \mathcal{E})$ such that for $A \in \mathcal{E}$*

$$m(A) > 0 \Rightarrow \hat{K}(x, A) > 0$$

for all $x \in E$.

An m-positive kernel gives mass to each set that is sufficiently large (with respect to m).

Definition 3.1.4. *$\hat{K}$ is called conservative if*

$$\sum_{n\geq 0} \int_{E\times E} g(y)\hat{K}^n(x,dy)m(dx) = \infty$$

for all strictly positive $\mathcal{E}$-measurable functions g and for all non-zero measures m such that the kernel $\sum_{n\geq 0}\hat{K}^n$ is m-positive.

This property could be compared with recurrence in Markov theory. The expected number of returns to a set with positive mass should be infinite. When $\mathcal{E}$ is countably generated the following lemma can be used as an alternative definition of conservativity.

Lemma 3.1.5. *If $\mathcal{E}$ is countably generated then $\hat{K}$ is conservative if and only if there exists a σ-finite non-zero measure m on $(E, \mathcal{E})$ such that*

$$m(A) > 0 \Rightarrow \sum_{n \geq 0} \hat{K}^n(x, A) = \infty, \quad A \in \mathcal{E}$$

for all $x \in E$.

We are finally able to give the results of an abstract version of the Perron-Frobenius Theorem (*cf.* (Shurenkov, 1992a)).

Theorem 3.1.6. *If $\hat{K}$ is m-positive and conservative with positive and finite Perron root ρ, then there exists a σ-finite measure π on $(E, \mathcal{E})$ and a positive and finite (π-a.e.) $\mathcal{E}$-measurable function h such that*

$$\int_E \hat{K}(x, A)\pi(dx) = \rho\, \pi(A), \quad A \in \mathcal{E}$$

and

$$\int_E h(y)\hat{K}(x, dy) = \rho\, h(x)$$

for π-almost every $x \in E$. The measure and the function are unique up to multiplicative constants.

Next we want to approach the classical Key Renewal Theorem that describes the asymptotics of convolutions

$$U * g(x, t) = \int_{E \times \mathrm{R}_+} g(y, t - u) U(x, dy \times du).$$

To do this we need some additional definitions.

Definition 3.1.7. *$K(x, dy \times dt)$ is called d-lattice, $d > 0$, if for some function $c : E \to [0, d)$ the kernel is concentrated on the lattice*

$$\{(t, x) : t \in \mathrm{R}_+, x \in E, t = c(x) - c(y) + nd \text{ for some } n = 0, 1, \ldots\}$$

for l-almost every $y \in E$.

Definition 3.1.8. *A measurable function $g : E \times \mathrm{R}_+ \to \mathrm{R}_+$ is called directly Riemann integrable (π) if*

$$\sum_{n \geq 0} \int_E \sup_{n \leq t \leq n+1} g(x, t)\pi(dx) < \infty$$

and

$$\lim_{\delta \to 0_+} \delta \sum_{n \geq 0} \int_E \left(\sup_{n\delta \leq t \leq (n+1)\delta} g(x,t) - \inf_{n\delta \leq t \leq (n+1)\delta} g(x,t) \right) \pi(dx) = 0.$$

Denote

$$\beta = \int\limits_{E \times E \times \mathrm{R}_+} t\, h(y) K(x, dy \times dt) \pi(dx).$$

Theorem 3.1.9. (Key Markov Renewal Theorem)
Assume that $K(x, dy \times dt)$ is non-lattice and let $\hat{K}(x, dy)$ be conservative with Perron root equal to 1. Let $\mathcal{E}$ be countably generated and assume that $0 < \beta < \infty$. Assume further that the function $g \geq 0$ defined on $E \times \mathrm{R}_+$ is directly Riemann integrable and that

$$\pi\{x \in E : \sup_{t \geq 0} U * g(x,t) < \infty\} > 0. \tag{3.1.1}$$

Then

$$U * g(x,t) \to \frac{h(x)}{\beta} \int_{E \times \mathrm{R}_+} g(y,u) \pi(dy) du$$

as $t \to \infty$.

If the set E is countable or finite the statement in the theorem is true without the condition (3.1.1).

3.2. Expectations of branching processes

In this section we apply the general theory from the previous section to the expectation of branching processes. We want to use the Key Renewal Theorem 3.1.9 to study the asymptotics of $E_r[z_t^\chi]$, the expectation of a branching population counted by χ starting in an r-type ancestor. To do this we need to introduce some new properties. We recall from Section 2.1 that the reproduction kernel μ is defined according to

$$\mu(r, A \times B) = E_r[\xi(A \times B)], \quad r \in S,\ A \in \mathcal{S},\ B \in \mathcal{B}.$$

The *total population measure* is defined as

$$y(A \times B) = \#\{x \in I; \sigma_x \in A, \tau_x \in B\}, \quad A \in \mathcal{S},\ B \in \mathcal{B}$$

and the *expected total population measure* as

$$\nu(r, A \times B) = E_r[y(A \times B)], \quad r \in S, \; A \in \mathcal{S}, \; B \in \mathcal{B}$$

The relation between μ and ν can be seen through *the* nth *daughter generation*

$$\xi^{(n)}(A \times B) = \#\{x \in N^n; \sigma_x \in A, \tau_x \in B\}, \; n \geq 1$$

and $\xi^{(0)}(A \times B) = \mathbf{1}_{(\sigma_0, 0)}(A \times B)$. Because of the branching property defined in Section 2.1 (*cf.* Jagers (1989)) we get

$$\mu^n(r, A \times B) = E_r[\xi^{(n)}(A \times B)]$$

and it can be shown (*cf.* (Nerman, 1984)) that

$$\nu(r, \cdot) = \sum_{n=0}^{\infty} \mu^n(r, \cdot), \quad \forall r \in S.$$

From this we get that (also proved in (Nerman, 1984))

$$E_r[z_t^\chi] = \int_{S \times \mathrm{R}_+} E_s[\chi_0(t-u)]\nu(r, ds \times du) = \nu * E_r[\chi(t)].$$

The population is said to be *Malthusian* if there is a number α, the *Malthusian parameter*, such that the kernel $\hat{\mu}_\alpha$

$$\hat{\mu}_\alpha(r, ds) = \int_{\mathrm{R}_+} e^{-\alpha t} \mu(r, ds \times dt)$$

is conservative and has Perron root one. The population is called *supercritical* if $\alpha > 0$, *critical* if $\alpha = 0$ and *subcritical* if $\alpha < 0$. We will only concern ourselves with the supercritical case. By the abstract Perron-Frobenius Theorem (3.1.6) μ determines a σ-finite measure π on $(S, \mathcal{S})$ and an $\mathcal{S}$-measurable a.e. $[\pi]$ finite function h such that

$$\begin{aligned} h(r) &= \int_S h(s)\hat{\mu}_\alpha(r, ds) \\ \pi(ds) &= \int_S \hat{\mu}_\alpha(r, ds)\pi(dr) \end{aligned}$$

where both π and h are unique up to multiplicative constants.

If $h \in L^1[\pi]$ and $0 < \beta < \infty$ where

$$\beta = \int\limits_{S\times S\times \mathrm{R}_+} te^{-\alpha t}h(s)\mu(r, ds \times dt)\pi(dr)$$

we say that we have *strong α-recurrence.* β might (with some caution, *cf.* (Jagers & Nerman, 1996)) be interpreted as the *stable age at childbearing.* Now we can, and will, norm to $\int_S h(s)\pi(ds) = 1$. With the homogeneity assumption $\inf h > 0$, π becomes finite and can be normed to a probability measure. In Chapter 5 we will refer to π as *the stable birth type distribution.* Finally we assume that the reproduction kernel is non-lattice and satisfies

$$\sup_s \mu(s, S \times [0, a]) \quad < \quad 1 \tag{3.2.1}$$

for some $a > 0$.
All these conditions (on μ alone) can be summarised by referring to the population as *strictly Malthusian.*

Define $\mu_\alpha = e^{-\alpha t}\mu$. If we define μ_α^n from μ_α in the same manner as μ^n from μ we get the Markov renewal kernel

$$\nu_\alpha(r, ds \times dt) = \sum_{n=0}^{\infty} \mu_\alpha^n(r, ds \times dt)$$

and thus by the same arguments as above

$$E_r[e^{-\alpha t} z_t^\chi] = \nu_\alpha * E_r[e^{-\alpha t}\chi(t)].$$

Hence μ_α plays the role of K and $\hat{\mu}_\alpha$ that of $\hat{K}$ in Section 3.1. Now under the conditions in the Key Renewal Theorem (3.1.9) with $g(s,t) = E_s[e^{-\alpha t}\chi(t)]$ we get

$$\lim_{t\to\infty} E_r[e^{-\alpha t} z_t^\chi] = \frac{h(r)}{\beta}\int_{S\times \mathrm{R}_+} E_s[e^{-\alpha u}\chi(u)]\pi(ds)du = \frac{E_\pi[\hat{\chi}(\alpha)]}{\alpha\beta}h(r)$$

where $\hat{\chi}(\alpha) = \displaystyle\int_{\mathrm{R}_+} \alpha e^{-\alpha u}\chi(u)du$ and $E_\pi[X] = \int_S E_s[X]\pi(ds)$.

In Chapter 5 we state a result in Theorem 5.3.2 that gives the asymptotics of $e^{-\alpha t} z_t^\chi$, *i.e.* not only of the expectation but for the *actual* composition.

3.3. Existence of the Malthusian parameter

In the previous section we saw that in order for the stable birth type distribution to exist, it is sufficient to show the existence of a number α such that the kernel $\hat{\mu}_\alpha$ has Perron root one and is conservative. This α is what we call the Malthusian parameter. In this section we give the conditions needed following (Shurenkov, 1992b). We return to the notation used in Section 3.1 with $(E, \mathcal{E})$ as our measurable space and K as a kernel on $(E \times \mathrm{R}_+, \mathcal{E} \times \mathcal{B})$. We assume that the kernel K is *semi-homogeneous*, *i.e.*

$$K(x \times u, A \times I) = K(x \times 0, A \times [I - u])$$

for all $x \in E,\ u \in \mathrm{R}_+,\ A \in \mathcal{E},\ I \in \mathcal{B}$ where

$$I - u = \{v \in \mathrm{R}_+ : u + v \in I\}.$$

Note that we use the convention $K(x, A \times B) = K(x \times 0, A \times B)$.

As before we let $\hat{K}$ denote the basis of K, that is

$$\hat{K}(x, dy) = \int_{\mathrm{R}_+} K(x, dy \times dt).$$

Lemma 3.3.1. *Let $\mathcal{E}$ be countably generated and assume that $\hat{K}$ is σ-finite. Then there exists a probability distribution $F(x, y; dt)$ on $(\mathrm{R}_+, \mathcal{B})$ which is $\mathcal{E} \times \mathcal{E}$-measurably dependent on $x, y \in E$ and such that*

$$K(x, dy \times dt) = \hat{K}(x, dy) F(x, y; dt)$$

or

$$K(x, A \times I) = \int_A F(x, y; I) \hat{K}(x, dy)$$

for $x \in E,\ A \in \mathcal{E},\ I \in \mathcal{B}$.

For proof *cf.* Shurenkov (1992a) p.33.

We let $\alpha \geq 0$ and define

$$\hat{K}_\alpha(x, dy) = \int_{\mathrm{R}_+} e^{-\alpha t} K(x, dy \times dt) = \int_{\mathrm{R}_+} e^{-\alpha t} \hat{K}(x, dy) F(x, y; dt).$$

We want to know the conditions for $\alpha > 0$ to exist such that $\rho(\hat{K}_\alpha) = 1$.

Theorem 3.3.2. *Assume that* $F(x, y; \{0\}) = 0$ *for all* $x, y \in E$ *and that* $1 < \rho(\hat{K}) < \infty$ *(the Perron root of the kernel* $\hat{K}$*). Assume further that there is a non-negative* $\mathcal{E}$*-measurable function* q *and a probability measure* m *on* $(E, \mathcal{E})$ *such that*

(i) $\hat{K}(x, A) \geq q(x)m(A) \quad \forall x \in E,\ A \in \mathcal{E}$

(ii) $\displaystyle\int_E q(x)m(dx) > 0$

(iii) $\displaystyle 0 < \int_E q(y)V(x, dy) < \infty \quad \forall x \in E$

(iv) $\displaystyle\int_{E\times E} q(y)V(x, dy)m(dx) < \infty$

where V *is the potential of the non-negative kernel*

$$L(x, A) = \hat{K}(x, A) - q(x)m(A),$$

i.e. $V(x, A) = \sum_{n\geq 0} L^n(x, A)$. *Then the equation* $\rho(\hat{K}_\alpha) = 1$ *has a unique solution* $\alpha = \alpha^*$ *and the kernel* $\hat{K}_{\alpha^*}$ *is conservative.*

For proof *cf.* Shurenkov (1992b) p.6.

Chapter 4

A Cell Model with Unequal Cell Division

In this chapter we use the ideas of the preceding chapters to formulate and describe a quite general cell population model, based on (Jagers, 1992b) and (Taib, 1996).

4.1. The reproduction kernel

Our population consists of ordinary, unspecified cells, where each cell inherits a type at birth, grows during a stochastic time span, and when its cell cycle is completed it divides into two not necessarily equal daughter cells. In this chapter the type will be the birth size of the cell (*e.g.* mass, volume, DNA-content etc.), but in Chapter 7 we introduce something we call pseudo-cells that are born with the same size but with different growth functions. Hence the growth function will be the type in that model.

The Ulam-Harris space of all possible cells reduces to

$$I = \bigcup_{n=0}^{\infty} \{1, 2\}^n$$

and we will still have the convention that $\{1, 2\}^0 = \{0\}$.

The type space is now an interval $S = [0, M)$ on the real line, where $M < \infty$ is the largest possible size of a cell, and $\mathcal{S}$ is the Borel-σ-algebra on S. A cell with birth size $r \in \mathrm{S}$ chooses a life career ω from $(\Omega, \mathcal{A})$ using $P(r, \cdot)$, the law of cells of type r.

We construct the population space $(\mathrm{S}\times\Omega^I, \mathcal{S}\times\mathcal{A}^I)$ as before and, as mentioned in Chapter 2, under the assumption that the daughter processes of different cells are conditionally independent, there exists a unique probability measure P_r on the entire population process, where $r\in S$ is the type of the ancestor.
The size of a cell with initial size r increases with time according to some growth function g, which is completely deterministic here (but random in Chapter 7). We let $m(r,t)$ denote the size of an r-type cell at age t. The functions m and g are related by the initial value problem $\frac{dm}{dt}=g(m)$ and $m(r,0)=r$.
The cell grows and then splits into two daughter cells *unequally*, which means that the daughter cells will not necessarily have the same size (or type) at birth. Note that we will not allow for cell death in this model so our branching population is *supercritical*. Let λ denote the age of the cell at division (or the cell cycle time) and let the distribution of λ be given by its hazard rate function $b(s)$, $s\in S$. $b(s)$ is roughly speaking the probability that the cell divides at size s.
A cell of type r is assumed to divide into the fractions δ and $1-\delta$, where δ is a random variable in $(0,1)$ with density function $f_\delta(m,p)$, $0<p<1$, and m is the size at cell division (or rather $m(r,\lambda)$). The dependence of the actual size m enters because it seems reasonable to assume that the bigger the cell is when it divides, the bigger the variance of δ. We will assume that f_δ is unimodal and that δ is symmetrically distributed around $\frac{1}{2}$, *i.e.* $\mathrm{E}_r[\delta]=\frac{1}{2}$ $\forall r\in S$ and $f_\delta(m,p)=f_\delta(m,1-p)$.

Let $T(x)=\int_0^x \frac{1}{g(y)}dy$, $x\in S$. To see how to interpret this function, consider

$$T(x)-T(r)=\int_r^x \frac{1}{g(y)}dy \tag{4.1.1}$$

Making a change of variable $y=m(r,t)$ yields $dy=dm(r,t)=g(m(r,t))dt$ and (4.1.1) becomes

$$\int_0^u \frac{g(m(r,t))}{g(m(r,t))}dt=\int_0^u dt=u,$$

where u is the time it takes for a cell to grow from size r to size x, thus $T(x)-T(r)$ is precisely this time. Since $T(m(r,t))-T(r)=t$, $m(r,t)=T^{-1}(T(r)+t)$. Further let $C(x)=\int_0^x \frac{b(y)}{g(y)}dy$ and $Q(x)=b(x)/xg(x)$.
The reproduction kernel $\mu(r, ds\times dt)$, which is the expected number of children with birth sizes in ds to a cell of type r with age in dt, takes the form

$$
\begin{aligned}
\mu(r, ds \times dt) &= \mathrm{E}_r[\xi(ds \times dt)] \\
&= \mathrm{E}_r[\mathbf{1}(\lambda \in dt)(\mathbf{1}(\delta\, m(r,\lambda) \in ds) + \mathbf{1}((1-\delta)m(r,\lambda) \in ds))] \\
&= 2\int_0^\infty \mathbf{1}(u \in dt) \int_0^1 \mathbf{1}(p\, m(r,u) \in ds) f_\delta(m(r,u), p) dp \\
&\quad\; b(m(r,u)) e^{-\int_0^u b(m(r,v))dv} du
\end{aligned}
$$

where the 2 comes from the fact that δ and $(1-\delta)$ are identically distributed. The inner integral is zero everywhere except when $p = s/m(r,u)$ and $dp = ds/m(r,u)$ so we have

$$
\begin{aligned}
\mu(r, ds \times dt) &= 2\int_0^\infty \mathbf{1}(u \in dt) f_\delta(m(r,u), s/m(r,u)) \frac{b(m(r,u))}{m(r,u)} \\
&\quad\; e^{-\int_0^u b(m(r,v))dv} du\, ds.
\end{aligned} \tag{4.1.2}
$$

Making a change of variable in the same manner as above with $x = m(r,u)$, we get that $du = \frac{dx}{g(x)}$ and the kernel becomes

$$
\mu(r, ds \times dt) = 2\int_r^{2M} \mathbf{1}(T(x)-T(r) \in dt) f_\delta(x, s/x) Q(x) e^{-(C(x)-C(r))} dx ds. \tag{4.1.3}
$$

4.2. Existence of the stable birth size distribution

In this section we want to use the results from the renewal theory presented in Chapter 3 on the basis of our reproduction kernel, defined through

$$
\begin{aligned}
\hat{\mu}_\alpha(r, ds) &= \int_0^\infty e^{-\alpha t} \mu(r, ds \times dt) = \\
&= 2\int_0^\infty \int_r^{2M} e^{-\alpha t - (C(x)-C(r))} \mathbf{1}(T(x)-T(r) \in dt) f_\delta(x, s/x) Q(x) dx\, dt\, ds \\
&= 2\int_r^{2M} e^{-\alpha(T(x)-T(r)) - (C(x)-C(r))} f_\delta(x, s/x)\, Q(x) dx\, ds.
\end{aligned} \tag{4.2.1}
$$

We want to choose α so the kernel has Perron root $\rho(\hat{\mu}_\alpha) = 1$. Then $\hat{\mu}_\alpha$ would be as close to a probability kernel as possible and $\hat{\mu}_\alpha(r, A)$ could be thought of as measuring the transition of the type r to some subspace A of S.

In the remaining of this section it will be assumed that the cells divide *equally*, *i.e.* the density function f_δ of the division fractions has all its mass concentrated at the point $\delta = \frac{1}{2}$, thus

$$f_\delta(x, s/x)ds = \mathbf{1}(\frac{x}{2} \in ds).$$

Hence the integral in (4.1.3) is equal to zero except when $x = 2s$ and $dx = 2ds$.
The reproduction kernel becomes

$$\mu(r, ds \times dt) \quad = \quad 4\,\mathbf{1}(T(2s) - T(r) \in dt)e^{-(C(2s)-C(r))}\frac{b(2s)}{g(2s)}ds \quad (4.2.2)$$

and the corresponding basis is

$$\hat{\mu}_\alpha(r, ds) \quad = \quad 4\,e^{-\alpha(T(2s)-T(r))-(C(2s)-C(r))}\frac{b(2s)}{g(2s)}ds. \quad (4.2.3)$$

Here we get problems when $2s < r$ since then the cell has to shrink to make the transition from r to ds possible, and we do not allow that. We need some mechanism that puts the kernel in (4.2.3) to 0 for all un-allowed transitions. We want to do this such that even if a transition is impossible in one step, it might (and shall) be possible in n steps for some $n > 1$. For instance in (Jagers, 1992b) it is shown that iteration of the kernel in (4.2.3) yields

$$\hat{\mu}^n_\alpha(r, ds) \quad = \quad \hat{\mu}_\alpha(r, ds)(\int_S \hat{\mu}_\alpha(x, dx))^{n-1} \quad (4.2.4)$$

Here it is clear that if $\hat{\mu}_\alpha(r, ds) = 0$ then $\hat{\mu}^n_\alpha(r, ds) = 0$ for all $n \in N$. These problems were not pointed out in (Jagers, 1992b). It is only under an extra assumption on the kernel, which is added in Section 4.3, that the iteration in (4.2.4) works. Here we treat the general case.

Let us write the basis with an indicator so that

$$\hat{\mu}_\alpha(r, ds) = 4\,e^{-\alpha(T(2s)-T(r))-(C(2s)-C(r))}\frac{b(2s)}{g(2s)}\mathbf{1}(2s > r)ds. \quad (4.2.5)$$

Iterating this yields

$$\begin{aligned}
\hat{\mu}_\alpha^2(r,ds) &= \int_S \hat{\mu}_\alpha(v,ds)\hat{\mu}_\alpha(r,dv) \\
&= \int_S 4\, e^{-\alpha(T(2s)-T(v))-(C(2s)-C(v))} \frac{b(2s)}{g(2s)} \mathbf{1}(2s>v)ds \\
&\qquad 4\, e^{-\alpha(T(2v)-T(r))-(C(2v)-C(r))} \frac{b(2v)}{g(2v)} \mathbf{1}(2v>r)dv.
\end{aligned}$$

We see that it is not possible to do the rearrangement done in (4.2.4). Instead we use the theory presented in Section 3.3 to prove the existence of the Malthusian parameter. We want to use Theorem 3.3.2 for this and introduce the kernel $\hat{\mu}$ called the basis of μ in Chapter 3

$$\begin{aligned}
\hat{\mu}(r,ds) &= \int_{\mathrm{R}_+} \mu(r, ds\times dt) \\
&= 4\int_{\mathrm{R}_+} \mathbf{1}((T(2s)-T(r))\in dt)e^{-(C(2s)-C(r))}\frac{b(2s)}{g(2s)}ds \\
&= 4\, e^{-(C(2s)-C(r))}\frac{b(2s)}{g(2s)}\mathbf{1}(2s>r)ds. \qquad (4.2.6)
\end{aligned}$$

We recall the definition of the Perron root

$$\rho(\hat{\mu})^{-1} = \sup\{\lambda\in\mathrm{R}_+ : \sum_{n\geq 0}\lambda^n\hat{\mu}^n \quad \text{is } \sigma\text{−finite}\}.$$

In Theorem 3.3.2 the Perron root of $\hat{\mu}$ is supposed to satisfy $1<\rho(\hat{\mu})<\infty$.

Lemma 4.2.1. *The kernel $\hat{\mu}$ for equal cell division defined in (4.2.6) has Perron root $\rho(\hat{\mu})=2$.*

Proof. Since $\hat{\mu}(r,A)\leq\hat{\mu}(r,S)=2$ for all $r\in S$, $A\in\mathcal{S}$, we also have $\hat{\mu}^n(r,A)\leq 2^n$ and for $A\in\mathcal{S}$

$$\sum_{n\geq 0}\lambda^n\hat{\mu}^n(r,A)\leq\sum_{n\geq 0}\lambda^n 2^n<\infty \quad\text{if}\quad \lambda<\frac{1}{2}.$$

By the definition of the Perron root this yields $\dfrac{1}{\rho(\hat{\mu})}\geq\dfrac{1}{2}$ and hence $\rho(\hat{\mu})\leq 2$.

On the other hand since $r < M$ (because $S = [0, M)$)

$$\hat{\mu}(r, A) = 4 \int\limits_{A\cap[\frac{r}{2},M)} e^{-(C(2s)-C(r))} \frac{b(2s)}{g(2s)} ds \geq 4 \int\limits_{A\cap[\frac{M}{2},M)} e^{-C(2s)} \frac{b(2s)}{g(2s)} ds = \varphi(A) \quad (4.2.7)$$

where φ is a non-null finite measure on $(S, \mathcal{S})$. This yields

$$\hat{\mu}^n(r, A) \geq 2^{n-1} \varphi(A) \quad r \in S, \; A \in \mathcal{S}$$

and

$$\sum_{n \geq 0} \lambda^n \hat{\mu}^n(r, A) \geq \sum_{n \geq 0} \lambda^n 2^{n-1} \varphi(A) = \frac{\varphi(A)}{2} \sum_{n \geq 0} \lambda^n 2^n$$

and $\sum\limits_{n \geq 0} \lambda^n 2^n = \infty$ if $\lambda \geq \dfrac{1}{2}$ so we have $\dfrac{1}{\rho(\hat{\mu})} \leq \dfrac{1}{2}$ or $\rho(\hat{\mu}) \geq 2$.

Hence $\rho(\hat{\mu}) = 2$.

∎

Note: If a measure φ exists so that $\hat{\mu}(r, A) = \mu(r, A \times \mathrm{R}_+) \geq \varphi(A)$, the lemma above holds for unequal cell division as well.

In Theorem 4.2.2 below we show the existence of the Malthusian parameter. Its proof relies heavily on Theorem 3.3.2. Unfortunately Theorem 3.3.2 gives only sufficient conditions and is thus is not sharp enough for our purposes. To use it we have added some assumptions on the hazard rate function b of the life length λ. First we assume that the cell has to divide before it reaches size $2M$, *i.e.* b is such that

$$\int_0^{2M} \frac{b(v)}{g(v)} dv = \infty \quad \text{and} \quad \int_0^{2M-\epsilon} \frac{b(v)}{g(v)} dv < \infty \quad \forall \epsilon > 0.$$

Second we assume that the probability of passing size M before division is greater than $\frac{1}{2}$, *i.e.* $e^{-C(M)} > \frac{1}{2}$. These conditions will be subject to further research.

Theorem 4.2.2. *In the case with equal cell division and reproduction kernel*

$$\mu(r, ds \times dt) = 4\,\mathbf{1}((T(2s) - T(r)) \in dt)\mathbf{1}(2s > r) e^{-(C(2s)-C(r))} \frac{b(2s)}{g(2s)} ds$$

the Malthusian parameter exists.

Proof. If we can prove that all the conditions in Theorem 3.3.2 hold, we are done.
Since S is countably generated and since $\hat{\mu}$ is finite (and hence σ-finite) Lemma 3.3.1 implies that there exists a probability distribution $F(r,s;dt)$ on $(\mathrm{R}_+,\mathcal{B})$ such that

$$\mu(r, ds \times dt) = \hat{\mu}(r, ds)F(r, s; dt).$$

The condition $F(r,s;\{0\}) = 0$ for all $r,s \in S$ follows directly if the life length λ is continuously distributed. For discrete life lengths we can define $P(\lambda = 0) = 0$ (it is natural to assume that each individual does not reproduce in $\{0\}$ almost surely).

Moreover, from Lemma 4.2.1 we get that $\rho(\hat{\mu}) = 2$. Next we want to find a non-negative $\mathcal{S}$-measurable function q and a probability measure m on $(S,\mathcal{S})$ such that

$$(i) \quad \hat{\mu}(r,A) \geq q(r)m(A) \quad \forall r \in S,\ A \in \mathcal{S}$$
$$(ii) \quad \int_S q(s)m(ds) > 0$$
$$(iii) \; 0 < \int_S q(s)V(r,ds) < \infty \quad \forall r \in S$$
$$(iv) \quad \int_{S\times S} q(s)V(r,ds)m(dr) < \infty$$

where V is the potential of the non-negative kernel

$$L(r,A) = \hat{\mu}(r,A) - q(r)m(A).$$

We see that since $r < M$

$$\begin{aligned}\hat{\mu}(r,A) &= 4 \int\limits_{A\cap[\frac{r}{2},M)} e^{-(C(2s)-C(r))}\frac{b(2s)}{g(2s)}ds \\ &> e^{-C(M)}\, 4 \int\limits_{A\cap[\frac{M}{2},M)} e^{-(C(2s)-C(M))}\frac{b(2s)}{g(2s)}ds = e^{-C(M)}\hat{\mu}(M,A)\end{aligned}$$

so we let $q(r) = 2e^{-C(M)}$ and $m(A) = \frac{\hat{\mu}(M,A)}{\hat{\mu}(M,S)} = \frac{\hat{\mu}(M,A)}{2}$. For this choice of q and m, it is now possible to verify the conditions $(i) - (iv)$.

(i) : This follows immediately. Actually the inequality is strict, $\hat{\mu}(r,A) > q(r)m(A)$.

(ii) : Follows from

$$\int_S q(s)m(ds) = \int_S e^{-C(M)}\hat{\mu}(M,ds) = 2e^{-C(M)} \geq 1.$$

(iii) :Since $\hat{\mu}(r,A) > q(r)m(A)$ we get $L(r,A) > 0$ $\forall r \in S,\ A \in \mathcal{S}$, and hence

$$\int_S q(s)V(r,ds) > 0 \ \ \forall r \in S.$$

For this integral to be finite we need $V(r,ds)$ has to be bounded for all $r, s \in S$, and since

$$V(r,ds) = \sum_{n\geq 0} L^n(r,ds)$$

it is sufficient if $L(r,ds) < 1$ $\forall r, s \in S$. We have

$$L(r,A) = \hat{\mu}(r,A) - e^{-C(M)}\hat{\mu}(M,A)$$

and $L(r,A) < 1$ means that the process with type space $[0, \frac{M}{2}]$ is subcritical (since L is the reproduction kernel for this process). Since $L(r,A) < 1 \Leftrightarrow e^{-C(M)} > \frac{1}{2}$ we get $V(r,ds) < \infty \quad \forall r, s \in S$. Since $q(s)V(r,ds)$ is bounded in the bounded interval S we also have

$$\int_S q(s)V(r,ds) < \infty \quad \forall r \in S.$$

(iv) : This follows from (iii) since m is a probability measure on $(S, \mathcal{S})$ so $q(s)V(r,ds)m(dr) \leq q(s)V(r,ds)$ $\forall r, s \in S$ and also bounded on $S \times S$.

All the conditions in Theorem 3.3.2 hold so there is an α such that $\rho(\hat{\mu}_\alpha) = 1$. This α is by definition the Malthusian parameter.

■

4.3. The non-overlapping case

In the previous section we said that in order for the iteration in (4.2.4) of $\hat{\mu}_\alpha$ to work we need an extra assumption of the kernel. It is natural to assume that a newborn cell can never have bigger size than a cell that is about to split. In other words we assume that there is a critical size m_0 such that a newborn cell always has size less than m_0, and then it grows and passes m_0 before it divides. The type space becomes $S = [\frac{m_0}{2}, m_0)$, and we can let the hazard rate function $b(s),\ s \in [\frac{m_0}{2}, 2m_0]$ make sure that a cell does not divide until it has size in $[m_0, 2m_0]$.

The kernel becomes

$$\hat{\mu}_\alpha(r, ds) = 2\int_{m_0}^{2m_0} e^{-\alpha(T(x)-T(r))-(C(x)-C(r))} f_\delta(x, s/x)Q(x)dx.$$

and iterating this yields

$$\begin{aligned}
\hat{\mu}_\alpha^2(r, ds) &= \int_S \hat{\mu}_\alpha(v, ds)\hat{\mu}_\alpha(r, dv) \\
&= \int_S 2\int_{m_0}^{2m_0} e^{-\alpha(T(x)-T(v))-(C(x)-C(v))} f_\delta(x, s/x)Q(x)dx \\
&\qquad 2\int_{m_0}^{2m_0} e^{-\alpha(T(y)-T(r))-(C(y)-C(r))} f_\delta(y, v/y)Q(y)dy\, dv \\
&= \int_S 2\int_{m_0}^{2m_0} e^{-\alpha(T(x)-T(r))-(C(x)-C(r))} f_\delta(x, s/x)Q(x)dx \\
&\qquad 2\int_{m_0}^{2m_0} e^{-\alpha(T(y)-T(v))-(C(y)-C(v))} f_\delta(y, v/y)Q(y)dy\, dv \\
&= \hat{\mu}_\alpha(r, ds)\int_S \hat{\mu}_\alpha(v, dv) = \hat{\mu}_\alpha(r, ds)I(\alpha).
\end{aligned}$$

The rearrangement will not cause us any problems here since $r < m_0$ always holds. Generally we get

$$\hat{\mu}_\alpha^n(r, ds) = \hat{\mu}_\alpha(r, ds)(\int_S \hat{\mu}_\alpha(x, dx))^{n-1} = \hat{\mu}_\alpha(r, ds)I^{n-1}(\alpha)$$

and we see that this is the iteration we attempted in (4.2.4).

We want to choose α such that the Perron root becomes one for $\hat{\mu}_\alpha$ (*cf.* Chapter 3). Since I is a non-negative, non-increasing function of α and $I(\alpha) \to 0$ as $\alpha \to \infty$, we can choose α such that $I(\alpha) = 1$.
For $\lambda \geq 0$ we get

$$\sum_{n\geq 0} \lambda^n \hat{\mu}_\alpha^n(r, ds) = \hat{\mu}_\alpha(r, ds) \sum_{n\geq 0} \lambda^n I^{n-1}(\alpha) = \hat{\mu}_\alpha(r, ds) \sum_{n\geq 0} \lambda^n.$$

This sum converges for $\lambda < 1$ and diverges for $\lambda \geq 1$ and hence the Perron root is one and α is the Malthusian parameter.

We want $\hat{\mu}_\alpha$ to be conservative.

Lemma 4.3.1. *$\hat{\mu}_\alpha$ defined as above is conservative if it is m-positive.*

Proof. Lemma (3.1.5) gives that $\hat{\mu}_\alpha$ is conservative if there is a σ-finite, non-zero measure m on $(S, \mathcal{S})$ such that

$$m(A) > 0 \Rightarrow \sum_{n\geq 0} \hat{\mu}_\alpha^n(r, A) = \infty, \;\; A \in \mathcal{S}$$

for all $r \in S$. But

$$\sum_{n\geq 0} \hat{\mu}_\alpha^n(r, A) = \sum_{n\geq 0} \hat{\mu}_\alpha(r, A) I^{n-1}(\alpha) = \sum_{n\geq 0} \hat{\mu}_\alpha(r, A)$$

and this sum is infinite whenever $\hat{\mu}_\alpha(r, A) > 0$. Thus the kernel is conservative if for all $r \in S$

$$m(A) > 0 \Rightarrow \hat{\mu}_\alpha(r, A) > 0, \;\; A \in \mathcal{S}$$

i.e. if it is m-positive.

■

Theorem 4.3.2. *The kernel $\hat{\mu}_\alpha$ is conservative.*

Proof. Notice that

$$\hat{\mu}_\alpha(r, A) = \int_{S\cap A} 2 \int_{m_0}^{2m_0} e^{-\alpha(T(x)-T(r))-(C(x)-C(r))} f_\delta(x, s/x) Q(x) dx \, ds$$

and take

$$m(A) = \int_{S\cap A} 2 \int_{m_0}^{2m_0} e^{-\alpha T(x)-C(x)} f_\delta(x, s/x) Q(x) dx \, ds.$$

Since $m(S)>0$, m is a non-zero measure and since

$$\hat{\mu}_\alpha(r,A) = e^{\alpha T(r)+C(r)}m(A)$$

$\hat{\mu}_\alpha$ must be m-positive and thus by Lemma 4.3.1 conservative. ■

From Theorem (3.1.6) it follows that there exist a σ-finite measure π and a non-negative π-$a.e.$ finite function h such that

$$\begin{aligned} h(r) &= \int_S h(s)\hat{\mu}_\alpha(r,ds),\ r\in S \\ \pi(A) &= \int_S \hat{\mu}_\alpha(r,A)\pi(dr),\ A\in\mathcal{S}. \end{aligned}$$

From that theorem we also know that these equations determines h and π uniquely up to multiplicative constants, but we want h and π to satisfy the conditions

$$\int_S \pi(ds) = 1 \qquad \text{and} \qquad \int_S h(s)\pi(ds) = 1 \tag{4.3.1}$$

as well. In our model we can get h and π explicitly. Starting with h we have

$$\begin{aligned} h(r) &= \int_S h(s)\ 2\int_{m_0}^{2m_0} e^{-\alpha(T(x)-T(r))-(C(x)-C(r))}f_\delta(x,s/x)Q(x)dx\,ds \\ &= e^{\alpha T(r)+C(r)}\int_S h(s)\ 2\int_{m_0}^{2m_0} e^{-\alpha T(x)-C(x)}f_\delta(x,s/x)Q(x)dx\,ds \end{aligned}$$

and we put

$$h(r) = c_1 e^{\alpha T(r)+C(r)},\ r\in S$$

where c_1 is a yet unknown constant. Further we have that

$$\begin{aligned} \pi(A) &= \int_S \hat{\mu}_\alpha(r,A)\pi(dr) \\ &= \int\limits_S \int\limits_{S\cap A} 2\int\limits_{m_0}^{2m_0} e^{-\alpha(T(x)-T(r))-(C(x)-C(r))}f_\delta(x,s/x)Q(x)dx\,ds\,\pi(dr) \\ &= \int\limits_{S\cap A} 2\int\limits_{m_0}^{2m_0} e^{-\alpha T(x)-C(x)}f_\delta(x,s/x)Q(x)dx\,ds \int_S e^{\alpha T(r)+C(r)}\pi(dr) \end{aligned}$$

and we put

$$\pi(A) = c_2 \int_{S\cap A} 2 \int_{m_0}^{2m_0} e^{-\alpha T(x)-C(x)} f_\delta(x, s/x) Q(x) dx\, ds$$

where c_2 is another unknown constant. The constants c_1 and c_2 are to be chosen such that the conditions in (4.3.1) are satisfied. The first condition gives

$$\int_S \pi(ds) = \int_S c_2\, 2 \int_{m_0}^{2m_0} e^{-\alpha T(x)-C(x)} f_\delta(x, s/x) Q(x) dx\, ds = 1$$

and hence

$$c_2 = (\int_S 2 \int_{m_0}^{2m_0} e^{-\alpha T(x)-C(x)} f_\delta(x, s/x) Q(x) dx\, ds)^{-1}.$$

To determine c_1 we see that

$$\begin{aligned}
\int_S h(s)\pi(ds) &= \int_S c_1\, e^{\alpha T(s)+C(s)} c_2\, 2 \int_{m_0}^{2m_0} e^{-\alpha T(x)-C(x)} f_\delta(x, s/x) Q(x) dx\, ds \\
&= c_1\, c_2 \int_S 2 \int_{m_0}^{2m_0} e^{-\alpha(T(x)-T(s))-(C(x)-C(s))} f_\delta(x, s/x) Q(x) dx\, ds \\
&= c_1\, c_2 \int_S \hat{\mu}_\alpha(s, ds) = c_1\, c_2\, I(\alpha) = c_1\, c_2.
\end{aligned}$$

Thus $c_1 = (c_2)^{-1} = \int_S 2 \int_{m_0}^{2m_0} e^{-\alpha T(x)-C(x)} f_\delta(x, s/x) Q(x) dx\, ds.$

With h and π like this we get in our model that

$$\int_S \hat{\mu}_\alpha(r, ds) = \int_S h(r)\pi(ds) = h(r)$$

which means that the population is already stable. The very first individual born into the population (*i.e.* everyone except the ancestor) inherits a type according to π.

Chapter 5

The Doubly Infinite Stable Population Process

Up to this point we have used the Key Renewal Theorem 3.1.9 to study the asymptotics of our branching population. In this chapter we introduce an alternative theory, due to (Jagers & Nerman, 1996), to achieve the same results. The concept *ego* introduced here is used in the study of the asymptotics of the population through the remains of this work.

5.1. The population space

A proper branching population either becomes extinct or its size grows to infinity (*cf.* (Jagers, 1992a)). If the population does not die out its composition will stabilise. This means that the composition of the population has a limit as time passes, the so-called *stable population composition.* In general branching processes we often start the population with one ancestor and count it by random characteristics χ. We can either study the limit of the average score among all born starting from one ancestor, or consider a very old population that has already stabilised. The idea here is to sample a typical individual at random, call her *ego* or 0 for short, and describe the population from her point of view letting the sampling moment be at time 0. Even if it might seem a bit artificial, it is mathematically more convenient to sample ego among all born instead of among all individuals alive at the sampling moment. However, all the theory presented here (as we shall see later) can be extended to the latter case as well. Ego will have progeny in the usual Ulam-Harris manner, but she will also have a mother, a grandmother and so on. For this we need a richer space of individuals

$$J = \bigcup_{j=0}^{\infty} \{-j\} \times I$$

where 0 is ego, -1 is ego's mother, -2 ego's grandmother and so on. $\{0\} \times I$ denotes ego and her possible progeny and $\{-j\} \times I$ is all possible individuals stemming from ego's jth grandmother $-j$ *except* for $-(j-1)$ and her progeny.
We need to relate ego to her ancestors and do this by their *birth ranks* $(i_0, i_1, i_2, \ldots) \in N^\infty$, *i.e.* their ordinal numbers in sibship, where i_j is $-j$'s birth order. For individuals *not* being an ancestor of ego we do the interpretation that if $-(j-1)$ has rank r then $-ji$ has rank i for $i < r$ and rank $i-1$ for $i \geq r$. Any other individual $x \in J$ in $-j$'s daughter population will be treated as before. The birth times for individuals in J are defined through

$$\begin{aligned}
\tilde{\tau}_0 &= -a \\
\tilde{\tau}_{-j} &= \tilde{\tau}_{-(j-1)} - \tilde{\tau}_{-j}(i_{j-1}) \\
\tilde{\tau}_{-jk} &= \begin{cases} \tilde{\tau}_{-j} + \tilde{\tau}_{-j}(k) & \text{if } k < i_{j-1} \\ \tilde{\tau}_{-j} + \tilde{\tau}_{-j}(k+1) & \text{if } k \geq i_{j-1} \end{cases}
\end{aligned}$$

and the types are defined similarly

$$\begin{aligned}
\tilde{\sigma}_0 &= \tilde{\sigma}_{-1}(i_0) \\
\tilde{\sigma}_{-j} &= \tilde{\sigma}_{-j-1}(i_j) \\
\tilde{\sigma}_{-jk} &= \begin{cases} \tilde{\sigma}_{-j}(k) & \text{if } k < i_{j-1} \\ \tilde{\sigma}_{-j}(k+1) & \text{if } k \geq i_{j-1}. \end{cases}
\end{aligned}$$

For all other individuals $xk \in J$, $x \in J, k \in N$, $\tilde{\tau}_{xk} = \tilde{\tau}_x(k)$ and $\tilde{\sigma}_{xk} = \tilde{\sigma}_x(k)$ in the same manner as τ and σ in Chapter 2.
We also need information about ego's age at sampling. The population space will now be *the pedigree space*

$$\mathbf{\Omega} = \Omega^J \times N^\infty \times \mathrm{R}_+$$

and it is equipped with the product-σ-algebra $\mathcal{C} = \mathcal{A}^J \times 2^{N^\infty} \times \mathcal{B}(\mathrm{R}_+)$. A *pedigree* is an element of $\mathbf{\Omega}$ and have the form $((\omega_x)_{x \in J}, (i_k)_{k=1}^{\infty}, a)$ where

$\omega_x \in \Omega$, ego is the i_1th child of the i_2th child of the ..., and a is the age of ego at sampling.

In order to centre the time of the population around an individual $x \in N^n$ we need mappings $\pi_x : I \to J_n$ where $J_n = \bigcup_{j=0}^{n}\{-j\} \times I$ is the set of possible individuals stemming from $-n$. Let $y \in I$ be an individual with the first $n-k$ co-ordinates common with x, $k = 1, \ldots, n$, such that

$$y = (x_1, \ldots, x_{n-k}, j, y'),\ j \in N, y' \in I.$$

Then π_x can be defined through

$$\pi_x(y) = \begin{cases} (-k, j, y') & \text{if } j < x_{n-k+1} \\ (-k, j-1, y') & \text{if } j \geq x_{n-k+1} \end{cases}$$

and $\pi_x(x) = 0$. This will preserve the family relations in J. Such mappings define operators $\Pi_x : S \times \Omega^I \to \Omega^{J_n} \times N^\infty$ where

$$\Pi_x(\sigma_0, \{\omega_y\}_{y \in I}) = (\{\omega_{\pi_x^{-1}(y)}\}_{y \in J}, \{\pi_x^{-1}(-j)\}_{j=1}^{\infty}).$$

Note that since $x \in N^n$ and we take infinitely many steps backwards the individuals in $J \setminus J_n$ do not exist in I. These are assigned arbitrary elements of Ω and N as life careers and birth ranks respectively. The only restriction is that the type of the original ancestor should be preserved:

$$\sigma_0 = \sigma_{\pi_x^{-1}(-n)} = \tilde{\sigma}_{-n}.$$

Now *the stable population measure* $\tilde{P}$ on $(\mathbf{\Omega}, \mathcal{C})$ should be such that for any well-behaved function φ on $\mathbf{\Omega}$, the expectation $\tilde{E}[\varphi]$ with respect to $\tilde{P}$ is asymptotically the average among all born of $\varphi(\Pi_x, t - \tau_x)$ as $t \to \infty$ on the set of non-extinction $(\{y_t \to \infty\})$.

The single type case is described in (Jagers & Nerman, 1984) and it is shown that under certain conditions

$$\tilde{E}[\varphi] = \sum_{x \in N^n} E[e^{-\alpha\tau_x}\hat{\varphi}(\Pi_x, \alpha)]$$

where $\hat{\varphi}(\Pi_x, \alpha) = \alpha \int_0^\infty e^{-\alpha u}\varphi(\Pi_x, u)du$.

In the multitype case this corresponds to

$$\tilde{E}[\varphi] = \sum_{x \in N^n} E_\pi[e^{-\alpha\tau_x}\hat{\varphi}(\Pi_x, \alpha)]$$

where $E_\pi[X] = \int_S E_s[X]\pi(ds)$ and π is the stable birth type distribution presented in Section 3.2.

5.2. The stable population measure

As mentioned in the previous section we can study properties of the population via random characteristics either by starting with an ancestor and consider the limits, or by sampling an individual at random in an already stabilised population. Now it would be convenient if we could construct a probability measure on the pedigree space $(\mathbf{\Omega}, \mathcal{C})$. Then, instead of defining everything in terms of averages, we could make probabilistic statements of the population directly. It turns out to be possible to construct such a measure and in Section 5.3 we will see that this measure arises as the limit of the average score among all born into a population.

In order to give a definition of *the stable population measure* we need to introduce some random elements of $(\mathbf{\Omega}, \mathcal{C})$. Let T_0 denote ego's age at the sampling moment, S_0 her type, and R_0 her rank. T_1 is ego's mother's age at ego's birth, S_1 her type and R_1 her rank and so on backwards. Let $Z^0, Z^1, Z^2, \dots$ denote the daughter population of ego, of ego's mother *except* Z^0, of ego's grandmother *except* Z^1 and so on.

Definition 5.2.1. *The stable population measure $\tilde{P}$ on $(\mathbf{\Omega}, \mathcal{C})$ satisfies*

$$\tilde{P}(Z^0 \in A_0, T_0 \in dt_0, S_0 \in ds_0, R_0 = i_0; Z^1 \in A_1, T_1 \in dt_1, S_1 \in ds_1, R_1 = i_1;$$
$$\dots; Z^n \in A_n, T_n \in dt_n, S_n \in ds_n, R_n = i_n) =$$
$$E_\pi[e^{-\alpha\tau_{i_n}}; \sigma_{i_n} \in ds_n] E_{s_n}[e^{-\alpha t_n}; A_n \cap \{\sigma_{i_{n-1}} \in ds_{n-1}, \tau_{i_{n-1}} \in dt_n\}] \cdots$$
$$\cdots E_{s_1}[e^{-\alpha t_1}; A_1 \cap \{\sigma_{i_0} \in ds_0, \tau_{i_0} \in dt_1\}] \alpha e^{-\alpha t_0} dt_0 P_{s_0}(A_0)$$

for all $n \in N, A_j \in \mathcal{A}^I, t_j \in \mathrm{R}_+, s_j \in S, i_j \in N, j = 0, 1, \dots, n$.

This definition contains all information about properties of the population, viewed as centred around ego. It provides us with a useful tool to make explicit statements about types, ranks, interbirth times and so on (*cf.* (Jagers & Nerman, 1996)).

5.3. Convergence towards the stable population composition

In Section 5.2 we mentioned that the stable population measure appears as the limit of the average score among all born in a population. In this section we will see that this indeed is the case. We recall that

$$J_n = \bigcup_{j=0}^{n} \{-j\} \times I$$

is the set of possible individuals stemming from $-n$, egos nth grandmother. If we consider $-n$ as the ancestor 0, and identify I and J_n such that all family relations are preserved, we can do the same identification with $(\Omega^I, \mathcal{A}^I)$ and $(\Omega^{J_n}, \mathcal{A}^{J_n})$. Now we fix $n \in N$, $\iota = (i_{n-1}, \dots, i_0) \in N^n$, $A \in \mathcal{A}^I$ and $a \in \mathrm{R}_+$ and consider a subset of $\mathcal{C}$,

$$E = [0, a] \times (i_0, \dots, i_{n-1}) \times N^\infty \times A \times \Omega^{J \setminus J_n}.$$

The interpretation of this is that an individual $x \in I$ with property E has age less than a, is the i_0th child of the i_1th child of ... of the $i_{n-1}th$ child of some individual $y \in I$, where y has daughter process in A. Individuals in $J \setminus J_n$ do not exist in I and they are just assigned arbitrary elements of Ω and N as life careers and birth ranks respectively.

Now we want to count all individuals with property E, but since characteristics can not depend backwards in time, we have to use a trick. Instead of counting all such $x \in I$ we count their nth ancestor instead. This means that we count all $y \in I$ where y has daughter process in A, $y\iota$ will be born and $t - \tau_{y\iota} \in [0, a]$. We define a random characteristic on $(S \times \Omega^I, \mathcal{S} \times \mathcal{A}^I)$

$$\chi^E(t) = \mathbf{1}_A \mathbf{1}_{[0,a]}(t - \tau_\iota)$$

so that $z_t^{\chi^E}$ is the number of individuals born up to time t with property E. If the conditions in the Renewal Theorem (3.1.9) are satisfied we get

$$\lim_{t \to \infty} e^{-\alpha t} E_s[z_t^{\chi^E}] = h(s) \frac{E_\pi[\hat{\chi}^E(\alpha)]}{\alpha \beta}.$$

A proof of this is found in (Jagers, 1989).

We recall that $y_t = z_t^{\mathbf{1}_{\mathrm{R}_+}}$ is the total number of born up to time t. If $\sup_s \mu(s, S \times [0, \epsilon]) < 1$ for some $\epsilon > 0$, then $e^{-\alpha t} E_s[y_t]$ is bounded and since $E_\pi[\hat{\chi}(\alpha)] = 1$ for $\chi(t) = \mathbf{1}_{\mathrm{R}_+}(t)$ we get

$$\frac{E_s[z_t^{\chi^E}]}{E_s[y_t]} \to E_\pi[\hat{\chi}^E(\alpha)]$$

where $E_s[z_t^{\chi^E}]/E_s[y_t]$ is called the *composition in expectation* for an individual of type s. Now we can give our first result.

Lemma 5.3.1. *For sets E as above*

$$E_\pi[\hat{\chi}^E(\alpha)] = \tilde{P}(E).$$

For proof *cf.* (Olofsson, 1994) p.62.

This result can be extended to hold for all subsets of $\mathrm{R}_+ \times N^\infty \times \Omega^J$ which depend only n steps backwards for fixed but arbitrary n (*cf.* (Jagers & Nerman, 1996). Now we turn to the *actual composition* $z_t^{\chi^E}/y_t$ of the population.
To get convergence here we need the so called $\boldsymbol{x}\,\mathbf{log}\,\boldsymbol{x}$-condition, which is

$$E_\pi[\bar{\xi}\log^+\bar{\xi}] < \infty$$

where $\bar{\xi} = \int_{S\times\mathrm{R}_+} e^{-\alpha t} h(s)\xi(ds \times dt)$, $h(s)$ the reproductive value of the type s and ξ is the reproduction point process (*cf.* Chapter 2).

Theorem 5.3.2. *Assume that the conditions in the Key Renewal Theorem are satisfied. Assume further $\boldsymbol{x}\,\mathbf{log}\,\boldsymbol{x}$ and that $\xi(S \times \mathrm{R}_+) < \infty$. If y_t is uniformly integrable over its starting type $\sigma_0 = s \in S$, then as $t \to \infty$*

$$e^{-\alpha t} z_t^{\chi^E} \to \frac{E_\pi[\hat{\chi}^E(\alpha)]}{\alpha\beta} w$$

in $L^1[P_s]$ for π-almost all $s \in S$, where w is a non-negative random variable with $E_s[w] = h(s)$.

Since $e^{-\alpha t} y_t \to w/\alpha\beta$ as $t \to \infty$, by adding the condition $\inf_s P_s(w > 0) > 0$ to the ones above, we get

$$\frac{z_t^{\chi E}}{y_t} \to \tilde{P}(E)$$

in P_s-probability on $\{y_t \to \infty\}$ for π-almost all $s \in S$ as $t \to \infty$.

Chapter 6

Asymptotics of the Cell Model

In this chapter we will discuss the asymptotics of our cell model introduced in Chapter 4. When looking at a population one can either consider all cells *alive* at the moment, or all cells *born* into the population up till now. Even if it seems more natural to look at all cells alive, it is mathematically more convenient to consider all born. In this chapter we will concentrate on all born cells, but we will also show that all the results presented can easily be achieved for all cells alive as well.

6.1. The α and β curves

The α-curve is the graph of the function $\alpha(a)$ describing the proportion of cells still undivided at age a as a function of a. An alternative interpretation is that $\alpha(a)$ is the probability that the age at division of a cell sampled at random is larger than a. In other words, the α-curve describes the probability that *ego* (*cf.* Chapter 5) is still undivided at some age a. The stable population measure in definition (5.2.1) describes the entire population from ego's point of view and hence in particular ego's life length. Since ego's type is distributed according to π under $\tilde{P}$, we can write

$$\alpha(a) = \tilde{P}(\lambda_0 > a) = \int_S P_r(\lambda_0 > a)\pi(dr) = P_\pi(\lambda_0 > a)$$

where λ_0 is the cell cycle time for ego. Now, since $b(s)$, $s \in S$ is the hazard rate function of the cell cycle time, we get

$$\alpha(a) = \int_S P_r(\lambda_0 > a)\pi(dr) = \int_S e^{-\int_0^a b(m(r,v))dv}\pi(dr).$$

The β-curves are used to describe the proportions of sister cells, cousin cells etc., with life lengths that differ by more than a time units. The β_1-curve describes this for sister cells, β_2 for cousin cells and so on. The question is whether to study ego and her sister and cousins *or* ego's daughters and grand daughters. For symmetry reasons the latter is mathematically more convenient. In Section 5.3 we saw that the stable population measure is the limit of the average score among all born, when counting the population with some random characteristic.

We begin with the β_1-curve and define a characteristic χ, such that z_t^χ counts the number of sister cells born up to time t with life lengths that differ by more than a time units. If we let x' denote the sister of x we get

$$z_t^\chi = \sum_{x:\tau_x \le t} \mathbf{1}(|\lambda_x - \lambda_{x'}| > a) = 2 \sum_{x:\tau_{x1} \le t} \mathbf{1}(|\lambda_{x1} - \lambda_{x2}| > a).$$

If we instead construct a characteristic that considers the born daughters of each cell this yields

$$z_t^{\chi'} = \sum_{x:\tau_x \le t} \mathbf{1}(|\lambda_{x1} - \lambda_{x2}| > a)\mathbf{1}_{\mathrm{R}_+}(t - \tau_{x1}) = \sum_{x:\tau_{x1} \le t} \mathbf{1}(|\lambda_{x1} - \lambda_{x2}| > a) = \frac{1}{2} z_t^\chi.$$

In Section 5.3 we used that as $t \to \infty$

$$\frac{z_t^\chi}{y_t} \to E_\pi[\hat{\chi}(\alpha)]$$

in probability (on the set of non-extinction), where π describes ego's type. This gives

$$E_\pi[\hat{\chi}(\alpha)] = 2\, E_\pi[\hat{\chi}'(\alpha)]$$

and hence we can study the β-curves in ego's progeny, *i.e.* the difference in life lengths between her daughters, granddaughters and so on. The β_1-curve in the case with unequal division is

$$
\begin{aligned}
\beta_1(a) &= 2\,E_\pi[\hat{\chi}'(\alpha)] = 2 \int\limits_{S\times \mathrm{R}_+} \alpha e^{-\alpha u} E_r[\mathbf{1}(|\lambda_1-\lambda_2|>a)\mathbf{1}_{\mathrm{R}_+}(u-\tau_1)]du\,\pi(dr) \\
&= 2\int_S E_r\left[\ \mathbf{1}(|\lambda_1-\lambda_2|>a)\int_{\tau_1}^{\infty} \alpha e^{-\alpha u} du\ \right]\pi(dr) \\
&= 2\int_S E_r[e^{-\alpha\tau_1}\mathbf{1}(|\lambda_1-\lambda_2|>a)]\pi(dr) \\
&= 2\int_S E_r[e^{-\alpha\lambda_0}\mathbf{1}(|\lambda_1-\lambda_2|>a)]\pi(dr) \\
&= 2\,\tilde{E}[e^{-\alpha\lambda_0}\mathbf{1}(|\lambda_1-\lambda_2|>a)] \\
&= 2\int_S E_r[e^{-\alpha\lambda_0}P_r(|\lambda_1-\lambda_2|>a\,|\mathcal{A}_0)]\pi(dr).
\end{aligned}
$$

where $\mathcal{A}_0 \subset \mathcal{A}^I$ is the sub-σ-algebra generated by ego's life career. Moreover

$$
P_r(|\lambda_1-\lambda_2|>a\,|\mathcal{A}_0) = \iint\limits_{|x-y|>a} P_r(\lambda_1\in dx, \lambda_2 \in dy\,|\mathcal{A}_0).
$$

Assume that ego divides in fractions δ and $1-\delta$ and denote her life length by λ_0. Then ego's daughters get the types $\delta\, m(r,\lambda_0)$ and $(1-\delta)m(r,\lambda_0)$. Since the lives of ego's daughters are conditionally independent given their types, we get

$$
P_r(\lambda_1\in dx, \lambda_2\in dy\,|\,\mathcal{A}_0) \;=\; P_{\delta\, m(r,\lambda_0)}(\lambda_1\in dx)P_{(1-\delta)m(r,\lambda_0)}(\lambda_2\in dy)
$$

and

$$
\begin{aligned}
P_{\delta\, m(r,\lambda_0)}(\lambda_1\in dx) &= h(\delta\, m(r,\lambda_0),x)dx \\
P_{(1-\delta)m(r,\lambda_0)}(\lambda_2\in dy) &= h((1-\delta)m(r,\lambda_0),y)dy
\end{aligned}
$$

where $h(r,x) = b(m(r,x))e^{-\int_0^x b(m(r,v))dv}$.
Finally we get

$$
\begin{aligned}
\beta_1(a) &= 2\int_S \iint\limits_{|x-y|>a} E_r[e^{-\alpha\lambda_0}P_{\delta\, m(r,\lambda_0)}(\lambda_1\in dx)P_{(1-\delta)m(r,\lambda_0)}(\lambda_2\in dy)]\pi(dr) \\
&= 2\int_S \iint\limits_{|x-y|>a} \int_{\mathrm{R}_+}\int_0^1 e^{-\alpha u} h(p\, m(r,u),x) \\
&\quad h((1-p)m(r,u),y)h(r,u)f_\delta(m(r,u),p)dp\,du\,dx\,dy\,\pi(dr).
\end{aligned}
$$

The β_2 concerns, as mentioned before, the difference in life lengths between cousin cells. In the previous section, when dealing with sister cells, we saw that this difference could be studied in ego's progeny instead of between ego and her sister. With the same argument we consider the β_2-curve in ego's progeny as well. The calculations proceed in the same manner as above, and even though the expressions will be somewhat unwieldy, the idea is the same.

Since it is difficult to see directly what the probability looks like in terms of the stable measure, we go via characteristics as in the previous section. The number of cousin cells born up to time t with life lengths that differs with more than a time units is

$$\begin{aligned} z_t^{\chi} = 2\sum_{x\in I}(&\mathbf{1}(|\lambda_{x11}-\lambda_{x21}|>a)+\mathbf{1}(|\lambda_{x11}-\lambda_{x22}|>a)+\mathbf{1}(|\lambda_{x12}-\lambda_{x21}|>a)+\\ &+\mathbf{1}(|\lambda_{x12}-\lambda_{x22}|>a))\mathbf{1}_{\mathrm{R}_+}(t-\tau_{x11})\mathbf{1}_{\mathrm{R}_+}(t-\tau_{21}). \end{aligned}$$

Thus we have four differences among each cell's granddaughters, but since these are equally distributed and we only consider the expectation we put as our characteristic

$$\begin{aligned} \chi(u) &= 2(\mathbf{1}(|\lambda_{11}-\lambda_{21}|>a)+\mathbf{1}(|\lambda_{11}-\lambda_{22}|>a)+\mathbf{1}(|\lambda_{12}-\lambda_{21}|>a)\\ &\quad+\mathbf{1}(|\lambda_{12}-\lambda_{22}|>a))\mathbf{1}_{\mathrm{R}_+}(u-\tau_{11})\mathbf{1}_{\mathrm{R}_+}(u-\tau_{21}) =\\ &= 8\,\mathbf{1}(|\lambda_{11}-\lambda_{21}|>a)\mathbf{1}_{\mathrm{R}_+}(u-\tau_{11})\mathbf{1}_{\mathrm{R}_+}(u-\tau_{21}). \end{aligned}$$

This gives

$$\begin{aligned} \beta_2(a) &= E_\pi[\hat{\chi}(\alpha)]\\ &= \int_{S\times\mathrm{R}_+}\alpha\,e^{-\alpha u}E_r[8\,\mathbf{1}(|\lambda_{11}-\lambda_{21}|>a)\mathbf{1}_{\mathrm{R}_+}(u-\tau_{11})\mathbf{1}_{\mathrm{R}_+}(u-\tau_{21})]du\,\pi(dr)\\ &= 8\int_S E_r[e^{-\alpha(\max(\tau_{11},\tau_{21}))}\mathbf{1}(|\lambda_{11}-\lambda_{21}|>a)]\pi(dr)\\ &= \tilde{E}[8\,e^{-\alpha(\lambda_0+\max(\lambda_1,\lambda_2))}\mathbf{1}(|\lambda_{11}-\lambda_{21}|>a)] \end{aligned}$$

where λ_0, λ_1 and λ_2 denote the life lengths of ego and her daughters respectively. If we let δ_0, δ_1 and δ_2 be the fractions in which they divide, the two grandchildren of ego in the characteristic get types $\delta_1\,m(\delta_0\,m(r,\lambda_0),\lambda_1)$

and $\delta_2\, m((1-\delta_0)m(r,\lambda_0),\lambda_2)$ respectively. The calculations proceed in the same manner as in the previous section and we get

$$\begin{aligned}\beta_2(a) &= \tilde{E}[8\, e^{-\alpha(\lambda_0+\max(\lambda_1,\lambda_2))}\mathbf{1}(|\lambda_{11}-\lambda_{21}|>a)] \\ &= \int_S E_r[8\, e^{-\alpha(\lambda_0+\max(\lambda_1,\lambda_2))}P_r(|\lambda_{11}-\lambda_{21}|>a|\mathcal{A}_0,\mathcal{A}_1,\mathcal{A}_2)]\pi(dr) \quad (6.1.1)\end{aligned}$$

where $\mathcal{A}_0,\ \mathcal{A}_1$ and $\mathcal{A}_2$ are the sub-σ-algebras of $\mathcal{A}^I$ generated by ego's and her daughter's lives respectively. Now since

$$\begin{aligned}&P_r(|\lambda_{11}-\lambda_{21}|>a|\mathcal{A}_0,\mathcal{A}_1,\mathcal{A}_2) = \\ &= \iint\limits_{|x-y|>a} P_{\delta_1\, m(\delta_0\, m(r,\lambda_0),\lambda_1)}(\lambda_{11}\in dx)P_{\delta_2\, m((1-\delta_0)m(r,\lambda_0),\lambda_2)}(\lambda_{21}\in dy)\end{aligned}$$

we get in (6.1.1)

$$\begin{aligned}\beta_2(a) \;=\; &\int_S \iint\limits_{|x-y|>a} \int_{\mathrm{R}_+}\int_{\mathrm{R}_+}\int_{\mathrm{R}_+}\int_0^1\int_0^1\int_0^1 e^{-\alpha(l_0+\max(l_1,l_2))}h(r,l_0) \\ &h(p_0\, m(r,l_0),l_1)h((1-p_0)m(r,l_0),l_2)h(p_1\, m(p_0\, m(r,l_0),l_1),x) \\ &h(p_2\, m((1-p_0)m(r,l_0),l_2),y)f_\delta(m(r,l_0),p_0) \\ &f_\delta(m(p_0\, m(r,l_0),l_1),p_1)f_\delta(m((1-p_0)m(r,l_0),l_2),p_2) \\ &dp_0\, dp_1\, dp_2\, dl_0\, dl_1)\, dl_2)\, dx\, dy\, \pi(dr)\end{aligned}$$

where $h(r,x) = b(m(r,x))\, e^{-\int_0^x b(m(r,v))dv}$.

6.2. Sampling among all cells alive

So far all results in this chapter have been considered for all cells *born* up to a time t. Even if this is mathematically convenient, a less artificial way would be to study all cells *alive* at time t. We denote the number of cells alive at time t with z_t^γ, where γ is the characteristic

$$\gamma(u) = \mathbf{1}(0<u<\lambda).$$

As before we have that

$$e^{-\alpha t}z_t^\gamma \to \frac{E_\pi[\hat{\gamma}(\alpha)]}{\alpha\beta}w$$

where w is a random variable with $E_s[w] = h(s),\ s\in S$. We get

$$\begin{aligned}
E_\pi[\hat{\gamma}(\alpha)] &= \int\limits_{S\times\mathrm{R}_+} \alpha e^{-\alpha u} E_r[\gamma(u)] du\, \pi(dr) \\
&= \int\limits_{S\times\mathrm{R}_+} \alpha e^{-\alpha u} P_r(\lambda > u) du\, \pi(dr) \\
&= \int\limits_{S\times\mathrm{R}_+} \alpha e^{-\alpha u - \int_0^u b(m(r,v))dv} du\, \pi(dr).
\end{aligned}$$

To illustrate this we calculate the α-curve for all cells alive. Recall that $\alpha(a)$ is the probability of surviving age a. The characteristic that counts all cells that are alive and have life lengths longer than a is

$$\chi(u) = \mathbf{1}(\lambda > a)\mathbf{1}(\lambda > u)\mathbf{1}_{\mathrm{R}_+}(u) = \mathbf{1}(\lambda > \max(a,u))\mathbf{1}_{\mathrm{R}_+}(u).$$

Now

$$\begin{aligned}
E_\pi[\hat{\chi}(\alpha)] &= \int\limits_{S\times\mathrm{R}_+} \alpha e^{-\alpha u} E_r[\mathbf{1}(\lambda > \max(a,u))] du\, \pi(dr) \\
&= \int\limits_{S\times\mathrm{R}_+} \alpha e^{-\alpha u - \int_0^{\max(a,u)} b(m(r,v))dv} du\, \pi(dr)
\end{aligned}$$

and the α-curve when ego is sampled among all cells alive becomes

$$\alpha^\gamma(a) = \frac{E_\pi[\hat{\chi}(\alpha)]}{E_\pi[\hat{\gamma}(\alpha)]} = \frac{\int_{S\times\mathrm{R}_+} \alpha e^{-\alpha u - \int_0^{\max(a,u)} b(m(r,v))dv} du\, \pi(dr)}{\int_{S\times\mathrm{R}_+} \alpha e^{-\alpha u - \int_0^{u} b(m(r,v))dv} du\, \pi(dr)}.$$

The β-curves can be calculated in the same manner.

6.3. The stable size distribution

When a cell is sampled at random we do not know when it was born. Therefore it is of interest to know not only the stable birth type distribution, but also the stable *size* distribution. If $\mathcal{M}$ is ego's size at sampling, we want to know the probability $\tilde{P}(\mathcal{M} \leq v)$. It is more natural to calculate this probability among all cells alive rather than among all born. To count the number of living cells with sizes less than v we use the characteristic

$$\chi(u) = \mathbf{1}(m(\sigma_0, u) \le v)\mathbf{1}(\lambda_0 > u)\mathbf{1}_{\mathrm{R}_+}(u).$$

Now

$$\begin{aligned} E_\pi[\hat{\chi}(\alpha)] &= \int\limits_{S\times \mathrm{R}_+} \alpha e^{-\alpha u} E_r[\mathbf{1}(m(r,u) \le v)\mathbf{1}(\lambda > u)]du\,\pi(dr) \\ &= \int\limits_{S\times \mathrm{R}_+} \alpha e^{-\alpha u}\mathbf{1}(m(r,u) \le v)P_r(\lambda > u)du\,\pi(dr) \\ &= \int\limits_{S\times \mathrm{R}_+} \alpha e^{-\alpha u}\mathbf{1}(m(r,u) \le v)e^{-\int_0^u b(m(r,y))dy}du\,\pi(dr). \end{aligned}$$

Making a change of variable with $x = m(r,u)$ (as usual) gives

$$E_\pi[\hat{\chi}(\alpha)] = \int_S \int_r^{2M} \alpha e^{-\alpha(T(x)-T(r))-(C(x)-C(r))}\frac{\mathbf{1}(x \le v)}{g(x)}\pi(dr)\,dx.$$

Using $E_\pi[\hat{\gamma}(\alpha)]$ from the previous section and making a change of variable similar to the one above gives

$$E_\pi[\hat{\gamma}(\alpha)] = \int_S \int_r^{2M} \alpha e^{-\alpha(T(x)-T(r))-(C(x)-C(r))}\frac{dx}{g(x)}\pi(dr)$$

and we get

$$\tilde{P}(\mathcal{M} \le v) = \frac{\int_0^v \int_0^x e^{-\alpha(T(x)-T(r))-(C(x)-C(r))}(1/g(x))\pi(dr)\,dx}{\int_s^{2M}\int_{\mathrm{R}_+} e^{-\alpha(T(y)-T(s))-(C(y)-C(s))}(1/g(y))dy\,\pi(ds)}$$

so that the fraction under the first integral sign constitute the density function of $\mathcal{M}$.

Chapter 7

The Two-Subcycle Model

The two-subcycle cell cycle model discussed in this chapter, is described more in detail in (Sennerstam & Strömberg, 1995).

7.1. The biological model

Usually the cell cycle is defined as the period between two consecutive mitotic events (*i.e.* between two cell divisions). The cycle is divided in four phases, $G_1 + S + G_2 + M$, where S is the period when essentially the DNA division takes place, M is the mitosis and G_1 and G_2 are preparation periods of S and M respectively. The idea here is that the cell cycle constitutes of two simultaneously running subcycles, the DNA-division-cycle (DDC) and the cell-growth-cycle (CGC). The DDC (or the *chromosome cycle*) causes the genome to double, and in the CGC (or the *cytoplasmic cycle*) the cell doubles its size. In the simplest case the DDC and the CGC span over the same time interval and cells divide symmetrically (Fig. 7.1). This is the Bell-Anderson model and it is treated in (Taib, 1996) and further analysed in Chapter 4 of this work. If this time interval is assumed to be constant this means that every cell is born with size m_0, grows to $2m_0$ and divides in two cells, both with birth size m_0.

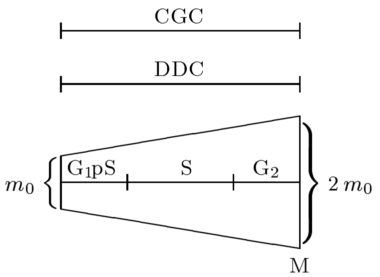


Fig. 7.1. The DDC and the CGC span the same time interval.

In the case that we will concentrate on, the cell grows rather slowly and the CGC extends past cell division (Fig. 7.2(a)). The cell divides unequally and each daughter cell continues to grow to complete its mother's CGC. This is called the post-M phase (G$_1p$M). When the cell reaches the critical size m_0 a "start" event is triggered, and the cell enters its own DDC and CGC and the pre-S phase (G$_1p$S) begins. Because of the unequal division of the mother the daughter cells will reach size m_0 at different time points. During G$_1p$M the daughter cells have the same growth function as the mother. At the "start" each cell chooses a new growth function, or a new growth parameter from some parameter space. Since it is assumed that the cells inherit properties from their mother, we also assume that sister cells choose growth functions somewhat similarly.
A third case is when the cell grows rapidly from "start" and the CGC is completed before the DDC is, and before the mitosis is activated (Fig. 7.2(b)). Then the cell is thought to enter a new S-phase, generating a tetraploid cell (*i.e.* a cell with four sets of chromosomes).

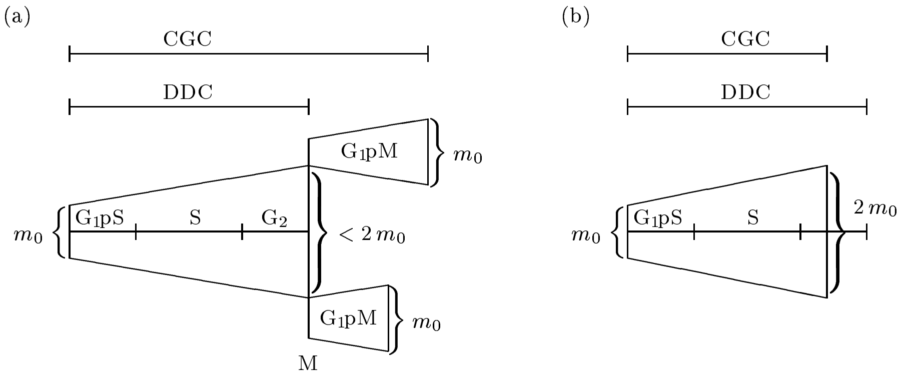


Fig. 7.2. (a) When the growth rate is small, the CGC extends past mitosis.
(b) When the growth rate is high, the cell reaches size $2\,m_0$ before mitosis.

Now we consider the second case shown in Fig. 7.2. (a). As mentioned above the newborn daughter cells have the same growth function g as their mother until they reach the critical size m_0. The daughter cells are thought to still belong to their mother's CGC initiated in the previous cycle.
When each daughter cell reaches the critical size she is considered as "grown-up" enough to start a life of her own. She enters her own DDC and chooses a new growth function. Two sister cells are thought to get similar growth functions due to some inheritance from the mother. Here this inheritance

is represented as a latent growth factor that the mother hands over to her daughters when they reach the critical size. By latent we mean that the mother carries this growth factor along without using it in her own growth. It has no effect until it is received by the daughters. The daughter cells choose new growth functions g_1' and g_2' respectively, influenced by the latent growth factor generating a similarity between sister cells. The procedure is illustrated in Fig 7.3. below.

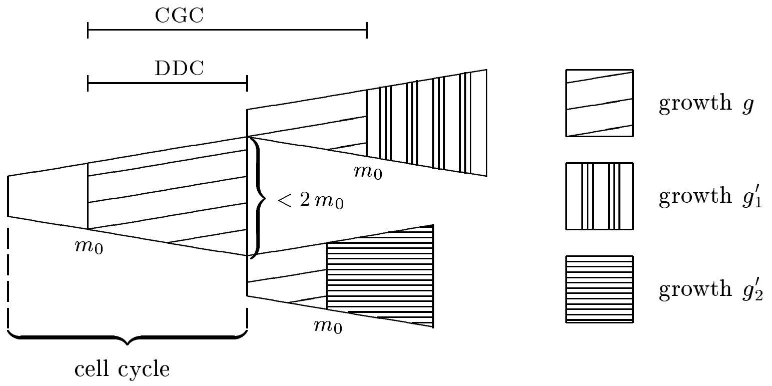


Fig. 7.3. The cell growth in two generations. Different patterns indicate different growth functions. A daughter cell continues her mother's CGC, with the same growth as the mother, until she reaches the critical size m_0. Then she chooses a new growth function.

A more mathematical approach to this model is discussed in Section 7.3.

7.2. The embedded single-type process

In this section we still assume that all cells have the same growth function g. We consider the cell model in Chapter 4, where we assume no cell death and no quiescence. Every cell lives a finite time and then it divides in two daughter cells. In the non-overlapping case in 4.3 we also assume that every newborn cell has size less than m_0 and that it always passes size m_0 before it divides. So if we count the cells when they reach size m_0 instead of when they actually are born, we get a single-type process. Every cell has type m_0 and we consider it alive until both daughter cells reach size m_0. The life span is now divided in two parts, $\lambda = \lambda' + \lambda''$ (Fig. 7.4.).

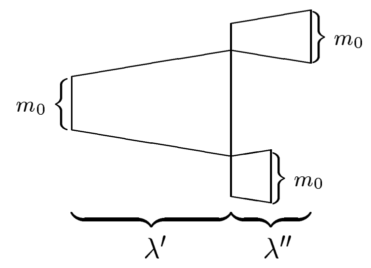


Fig. 7.4. The life starts when the cell reaches size m_0 and ends when both daughters have reached size m_0.

The reproduction point process for a single-type process is just

$$\xi([0,t]) = \#\{i : 0 \leq \tau(i) \leq t\}$$

and the reproduction kernel a measure on R_+ with.

$$\mu(dt) = E[\xi(dt)]$$

where $E = E_{m_0}$. This gives

$$\begin{aligned} \mu(dt) &= E[\xi(dt)] = 2\,E[\mathbf{1}(\lambda' + T(m_0) - T(\delta\, m(m_0, \lambda')) \in dt)] \\ &= 2 \int_{\mathrm{R}_+} \int_0^1 \mathbf{1}(u + T(m_0) - T(p\, m(m_0, u)) \in dt) \\ &\qquad\qquad b(m(m_0, u))\, e^{-\int_0^u b(m(m_0,v))dv} f_\delta(m(m_0, u), p) dp\, du \end{aligned}$$

Making a change of variable with $x = m(m_0, u)$ gives

$$\mu(dt) = 2 \int_{m_0}^{2m_0} \int_0^1 \mathbf{1}(T(x) - T(px) \in dt) e^{-(C(x) - C(m_0))} \frac{b(x)}{g(x)} f_\delta(x, p) dp\, dx.$$

Integrating over time in the usual manner gives

$$\begin{aligned} \hat{\mu}(\alpha) &= \int_{\mathrm{R}_+} e^{-\alpha t} \mu(dt) = \\ &= 2 \int_{m_0}^{2m_0} \int_0^1 e^{-\alpha(T(x) - T(px)) - (C(x) - C(m_0))} \frac{b(x)}{g(x)} f_\delta(x, p) dp\, dx \quad (7.2.1) \end{aligned}$$

and α is the Malthusian parameter if $\hat{\mu}(\alpha) = 1$. Now we can achieve all of the asymptotic results presented in Chapter 6 using single-type theory (*cf.*

(Jagers & Nerman, 1984)). We illustrate this by calculating the β_1-curve discussed in 6.1. Defining a characteristic χ, then under certain conditions it holds that as $t \to \infty$

$$\frac{z_t^\chi}{y_t} \to E[\hat{\chi}(\alpha)].$$

We have shifted the cell cycle and the population now consists of something that we can call *pseudo-cells*. When calculating the β_1-curve we still want the probabilities for *real* cells, *i.e.* we want to translate the characteristic in Section 6.1

$$\chi(u) = \mathbf{1}(|\lambda_1 - \lambda_2| > a)\mathbf{1}_{\mathrm{R}_+}(u - \tau_1).$$

to our shifted model. We assign score one to each pseudo-mother when the *real* daughters are born (*i.e.* the pseudo-mother has already divided) and differ in life lengths with more than a units. The characteristic becomes

$$\begin{aligned}\chi(u) &= \mathbf{1}(\lambda_0' < u)\mathbf{1}(|(\tau_1 - \lambda_0') + \lambda_1' - ((\tau_2 - \lambda_0') + \lambda_2')| > a) \\ &= \mathbf{1}(\lambda_0' < u)\mathbf{1}(|\tau_1 + \lambda_1' - (\tau_2 + \lambda_2')| > a) \qquad (7.2.2)\end{aligned}$$

where τ_1 and τ_2 are the birth times for the pseudo-daughters, *i.e.*

$$\begin{aligned}\tau_1 &= T(m_0) - T(\max(\delta, 1-\delta)m(m_0, \lambda_0')) + \lambda_0' \\ \tau_2 &= T(m_0) - T(\min(\delta, 1-\delta)m(m_0, \lambda_0')) + \lambda_0'\end{aligned}$$

thus

$$\begin{aligned}E[\hat{\chi}(\alpha)] &= \int_{\mathrm{R}_+} \alpha e^{-\alpha u} E[\chi(u)]du \\ &= E[\mathbf{1}(|\tau_1 + \lambda_1' - (\tau_2 + \lambda_2')| > a) \int_{\mathrm{R}_+} \alpha e^{-\alpha u}\mathbf{1}(\lambda_0' < u)du] \\ &= E[e^{-\alpha\lambda_0'}\mathbf{1}(|\lambda_1' - T(\max(\delta, 1-\delta)m(m_0, \lambda_0')) + \\ &\qquad -(\lambda_2' - T(\min(\delta, 1-\delta)m(m_0, \lambda_0')))| > a)] \\ &= \int_{\mathrm{R}_+}\int_{\mathrm{R}_+}\int_{\mathrm{R}_+}\int_0^1 e^{-\alpha u_0}\mathbf{1}\Big(|u_1 - T(\max(p, 1-p)m(m_0, u_0)) + \\ &\qquad -(u_2 - T(\min(p, 1-p)m(m_0, u_0)))| > a\Big)\cdot \\ &\qquad \cdot f_\delta(m(m_0, u_0), p)h(m_0, u_0)h(m_0, u_1)h(m_0, u_2)dp\, du_0\, du_2\, du_2\end{aligned}$$

where $h(m_0, u) = b(m(m_0, u))e^{-\int_0^u b(m(m_0, v))dv}$.
Normally we would have that $\beta_1(a) = E[\hat{\chi}(\alpha)]$, since we calculate β_1 among all *born* (*cf.* Chapter 2). But here we count our cells in a little special

way, so the characteristic "being born" here should assign score one to each pseudo-mother whose *real* daughters are born, *i.e.* we give the pseudo-cell score one if she has already divided. The characteristic for this is

$$\chi'(u) = \mathbf{1}(\lambda_0' < u) \tag{7.2.3}$$

and in the same manner as before

$$E[\hat{\chi}'(\alpha)] = E[e^{-\alpha\lambda_0'}] = \int_{\mathrm{R}_+} e^{-\alpha u} h(m_0, u) du.$$

Finally this gives

$$\beta_1(a) = \frac{E[\hat{\chi}(\alpha)]}{E[\hat{\chi}'(\alpha)]}.$$

We will return to the characteristics (7.2.2) and (7.2.3) in Section 7.4.

7.3. The Two-Subcycle branching process model

In the biological model described in Section 7.1 we assumed that the cell begins with the same growth function as the mother, and then changes it when it reaches the critical size m_0. Due to some inheritance from the mother, two sister cells are thought to choose new growth functions somewhat similarly. In (Sennerstam & Strömberg, 1995) this inheritance is represented as a *latent growth factor* that is handed over from the mother to the daughters at the critical size. The mother's own growth is not affected by this factor but just something she carries with her during her life cycle. How to treat this change of growth function mathematically is discussed in this section.

In the previous section we introduced a shift of the cell cycle that made the non-overlapping cell model described in Section 4.3 a single type model. The new population consists of what we called *pseudo-cells*, that are shifted to begin their life when the *real* cell reaches the critical size. This means that all of the pseudo-cells have the same birth size and hence the same type. By using this shift on the Two-Subcycle model we avoid problems with the cell changing its growth during its life time. All the pseudo-cells have the same birth size, but now we let the *growth function* be the inherited type.

We assume that the two pseudo-cells choose (or inherit) growth functions which depend on the latent growth factor g_L *and* on an individual contribution η. In (Sennerstam & Strömberg, 1995) the cells grow *exponentially*, so we will concentrate on that case here, that is when

$$m_g(r,t) = r\,e^{gt}$$

and hence

$$\frac{dm_g}{dt} = r\,g\,e^{gt} = g\,m_g(r,t)$$

which means that the cell's change in size at time t is proportional to the cell's actual size at time t. In this case g is a growth *parameter* or growth *rate* and two sister cells choose new parameters according to

$$\begin{aligned} g_1' &= g_L + \eta_1 \\ g_2' &= g_L + \eta_2 \end{aligned}$$

where g_L is the latent growth factor now treated as a parameter, and η_1 and η_2 can be thought of as independent, identically distributed random variables representing the cells' individual contributions to their respective growth.
The type is now two-dimensional $\mathbf{g} = (g, g_L)$, where g is the growth parameter of the pseudo-cell and g_L the latent growth factor carried along to be handed over to the daughters, and we let $(\Gamma, \mathcal{G})$ denote the new, two-dimensional type space. We let $d\mathbf{g}' = dg' \times dg_L'$ and the reproduction kernel takes the form

$$\begin{aligned} &\mu(\mathbf{g}, d\mathbf{g}' \times dt) = \\ &= 2\,E_{\mathbf{g}}[\mathbf{1}(\lambda' + T(m_0, g) - T(\delta m_g(m_0, \lambda'), g) \in dt)\mathbf{1}(g_L + \eta \in dg')\mathbf{1}(\mathcal{L} \in dg_L')] \end{aligned}$$

where η is distributed as η_1 and $\mathcal{L}$ is a random variable representing the choice of the latent growth factor to be handed over to the next generation. The index g on $m_g(m_0, \lambda')$ just indicates what growth function is used in the function m.
Now the question is whether η and $\mathcal{L}$ are to be independent. Assume for instance that the cell (the real cell) is fairly big, maybe its birth size is bigger than m_0, and that g_L is also big in some sense. Then the cell could be thought to compensate this by choosing a smaller η. In (Sennerstam & Strömberg, 1995) however, η and $\mathcal{L}$ are assumed to be independent of each other and everything else, so we make that assumption here too. We also assume that the distributions of η and $\mathcal{L}$ have densities f_η and $f_{\mathcal{L}}$ respectively, and the reproduction kernel becomes

$$
\begin{aligned}
&\mu(\mathbf{g}, d\mathbf{g}' \times dt) = \\
&= 2\, E_{\mathbf{g}}[\mathbf{1}\{(\lambda' + T(m_0, g) - T(\delta m_g(m_0, \lambda'), g)) \in dt\}] f_\eta(g' - g_L) f_{\mathcal{L}}(g'_L) dg' dg'_L \\
&= 2 \int_{\mathrm{R}_+} \int_0^1 \mathbf{1}\{(u + T(m_0, g) - T(p\, m_g(m_0, u), g)) \in dt\} \\
&\qquad b(m_g(m_0, u)) e^{-\int_0^u b(m_g(m_0, v)) dv} f_\delta(m_g(m_0, u), p) dp\, du \\
&\qquad f_\eta(g' - g_L) f_{\mathcal{L}}(g'_L) dg\, dg'_L.
\end{aligned}
$$

Except for the contributions of η and $\mathcal{L}$ this expression looks very similar to the reproduction measure $\mu(dt)$ in the previous section. The only difference is that here we have to keep track of what growth rate g the pseudo-cell is using.
With the same change of variable as usual, namely $x = m_g(m_0, u)$, we get

$$
\begin{aligned}
&\mu(\mathbf{g}, d\mathbf{g}' \times dt) = \\
&= 2 \int_{m_0}^{2m_0} \int_0^1 \mathbf{1}\{(T(x, g) - T(px, g)) \in dt\} \frac{b(x)}{g(x)} e^{-\int_{m_0}^x \frac{dy}{g(y)}} f_\delta(x, p) dp\, dx \\
&\qquad f_\eta(g' - g_L) f_{\mathcal{L}}(g'_L) dg'\, dg'_L
\end{aligned}
$$

and the basis of the kernel becomes

$$
\begin{aligned}
\hat{\mu}_\alpha(\mathbf{g}, d\mathbf{g}') &= \int_{\mathrm{R}_+} e^{-\alpha t} \mu(\mathbf{g}, d\mathbf{g}' \times dt) \\
&= 2 \int_{m_0}^{2m_0} \int_0^1 e^{-\alpha(T(x,g) - T(px,g)) - (C(x,g) - C(m_0,g))} \frac{b(x)}{g(x)} f_\delta(x, p) dp\, dx \\
&\qquad f_\eta(g' - g_L) f_{\mathcal{L}}(g'_L) dg'\, dg'_L.
\end{aligned}
$$

Now we want to find the stable type distribution π of our kernel, which is given by the integral equation

$$
\pi(A) = \int_\Gamma \hat{\mu}_\alpha(\mathbf{g}, A) \pi(d\mathbf{g}) \tag{7.3.1}
$$

subject to the condition $\int_\Gamma \pi(d\mathbf{g}) = 1$. If we let $\mathbf{g} = (g, g_L)$ and $d\mathbf{g}' = dg' \times dg'_L$, as before, we get

$$\begin{aligned}
\pi(A) &= \int_\Gamma \int_{\Gamma\cap A} \hat{\mu}_\alpha(\mathbf{g}, d\mathbf{g}')\pi(d\mathbf{g}) \\
&= \int_\Gamma 2 \int_{m_0}^{2m_0}\int_0^1 e^{-\alpha(T(x,g)-T(px,g))-(C(x,g)-C(m_0,g))} \frac{b(x)}{g(x)} f_\delta(x,p)dp\,dx \\
&\qquad \int_{\Gamma\cap A} f_\eta(g'-g_L)f_{\mathcal{L}}(g'_L)d\mathbf{g}'\,\pi(d\mathbf{g}).
\end{aligned}$$

We want to find an expression that solves the integral equation. Then this is π (possibly not normalised), since the solution is unique up to multiplication by constants. Each cell chooses its growth by taking the mother's latent factor and adding an individual contribution. Since η and $\mathcal{L}$ are thought to be independent, this should hold asymptotically as well and then π should be a product measure over the product space $(\Gamma, \mathcal{G}) = (\Gamma_1 \times \Gamma_2, \mathcal{G}_1 \times \mathcal{G}_2)$, such that

$$\psi_1(dg')\psi_2(dg'_L) = \int_\Gamma \hat{\mu}_\alpha(\mathbf{g}, d\mathbf{g}')\psi_1(dg)\psi_2(dg_L). \tag{7.3.2}$$

We rewrite our kernel to get a more manageable expression

$$\hat{\mu}(\mathbf{g}, d\mathbf{g}') = \hat{\mu}(\alpha, g)f_\eta(g'-g_L)f_{\mathcal{L}}(g'_L)dg'dg'_L$$

where

$$\hat{\mu}(\alpha, g) = 2\int_{m_0}^{2m_0}\int_0^1 e^{-\alpha(T(x,g)-T(px,g))-(C(x,g)-C(m_0,g))} \frac{b(x)}{g(x)} f_\delta(x,p)dp\,dx$$

i.e. the same kernel as (7.2.1) in Section 7.2 except that we have to keep track of the growth g here. Now (7.3.2) becomes

$$\begin{aligned}
\psi_1(dg')\psi_2(dg'_L) &= \int_{\Gamma_1}\int_{\Gamma_2} \hat{\mu}(\alpha, g)f_\eta(g'-g_L)f_{\mathcal{L}}(g'_L)\psi_2(dg_L)\psi_1(dg)dg'dg'_L \\
&= \int_{\Gamma_1} \hat{\mu}(\alpha, g)\psi_1(dg)\int_{\Gamma_2} f_\eta(g'-g_L)\psi_2(dg_L)\,dg'\,f_{\mathcal{L}}(g'_L)dg'_L
\end{aligned}$$

and we can put

$$\begin{aligned}
\psi_2(dg'_L) &= f_{\mathcal{L}}(g'_L)dg'_L \\
\psi_1(dg') &= c\int_{\Gamma_2} f_\eta(g'-g_L)\psi_2(dg_L)\,dg' = c\int_{\Gamma_2} f_\eta(g'-g_L)f_{\mathcal{L}}(g_L)dg_L\,dg' \\
&= c\,f_{\eta+\mathcal{L}}(g')dg'.
\end{aligned}$$

where $c = \int_{\Gamma_1} \hat{\mu}(\alpha, g)\psi_1(dg)$. Now we want π to be a probability measure, *i.e.*

$$\int_{\Gamma} \pi(d\mathbf{g}) = \int\limits_{\Gamma_1\times\Gamma_2} \psi_1(dg)\psi_2(dg_L) = 1.$$

We see that ψ_2 is already a probability measure, and in order for ψ_1 to be that we need to have that $c = 1$. If the Malthusian parameter exists we know from Theorem 3.1.6 that the measure π exists. We find π by solving the integral equation (7.3.1). But since the solution is unique we have that if the equation is solvable, the Malthusian parameter exists. This follows from the eigenvalue property in Theorem 3.1.6, *i.e.* we want to find α and a function h such that

$$\begin{aligned} h(\mathbf{g}) &= \int_{\Gamma} h(\mathbf{g}')\hat{\mu}_\alpha(\mathbf{g}, d\mathbf{g}') \\ \text{and} \qquad \int_{\Gamma} & h(\mathbf{g})\pi(d\mathbf{g}) = 1. \end{aligned}$$

Since $\pi = \psi_1 \times \psi_2$ we let $h(g, g_L) = h_1(g)h_2(g_L)$ where h_1 and h_2 are the reproductive values corresponding to ψ_1 and ψ_2 respectively. If $\mathbf{g} = (g, g_L)$ and $d\mathbf{g}' = dg' \times dg'_L$ then

$$\begin{aligned} h_1(g)h_2(g_L) &= \int\limits_{\Gamma_1\times\Gamma_2} h_1(g')h_2(g'_L)\hat{\mu}_\alpha(\mathbf{g}, d\mathbf{g}') \\ &= \hat{\mu}(\alpha, g)\int_{\Gamma_1} h_1(g')f_\eta(g' - g_L)dg' \int_{\Gamma_2} h_2(g'_L)f_{\mathcal{L}}(g'_L)dg'_L \end{aligned}$$

and we put $h_1(g) = \hat{\mu}(\alpha, g)$ and assume that the functions in our kernel are nice so we can choose α such that

$$\int_{\Gamma_1} \hat{\mu}(\alpha, g)\psi_1(dg) = 1.$$

Then α is the Malthusian parameter. Hence, since ψ_1 is a probability measure as well, the stable birth type distribution is for $d\mathbf{g}' = dg' \times dg'_L$

$$\begin{aligned} \pi(d\mathbf{g}') &= \psi_1(dg')\psi_2(dg'_L) \\ &= \int\limits_{\Gamma_2} f_\eta(g' - y)f_{\mathcal{L}}(y)dy \; f_{\mathcal{L}}(g'_L)dg'_L \, dg' \\ &= f_{\eta+\mathcal{L}}(g')f_{\mathcal{L}}(g'_L)dg'dg'_L. \end{aligned}$$

7.4. Asymptotics of the Two-Subcycle model

In the Two-Subcycle model we have shifted the cell cycle and consider something we call *pseudo-cells.* But when calculating the α-curve we still want it for the *real* cells, so we have to translate our model back to the real world.

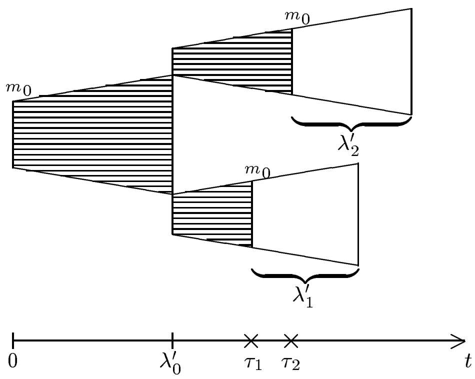


Fig. 7.6. The ego pseudo-cell is the patterned part. Its life starts at time 0 and τ_1 and τ_2 are the times of birth of the two pseudo-children respectively.

We want to construct random characteristics that count each real cell with the desired properties described by the α- and the β-curves.

7.4.1. The α- and β_1-curves and size distributions

We recall from Chapter 6 that the α-curve $\alpha(a)$ is the probability that a cell, sampled at random from a stabilised population, is still undivided at some age a, *i.e.*

$$\alpha(a) = \tilde{P}(\lambda_0 > a) = P_\pi(\lambda_0 > a) = \int_\Gamma P_{\mathbf{g}}(\lambda_0 > a)\pi(d\mathbf{g}).$$

We want to count each real cell with life length $> a$. The easiest way is to view this from each pseudo-mother and consider her real daughter's life lengths. The characteristic that gives score one for each real daughter born and with life length $> a$ at time u is

$$\chi_\alpha(u) = \mathbf{1}(\lambda_0' < u)\left(\mathbf{1}(a + \lambda_0' < \tau_1 + \lambda_1') + \mathbf{1}(a + \lambda_0' < \tau_2 + \lambda_2')\right).$$

The index on χ indicates what function the characteristic is for. In this case the α-curve. In Chapter 6 we used that as $t \to \infty$

$$\frac{z_t^\chi}{y_t} \to E_\pi[\hat{\chi}(\alpha)]$$

in probability (on the set of non-extinction),

where

$$E_\pi[\hat{\chi}(\alpha)] = \int_{\Gamma\times\mathrm{R}_+} \alpha e^{-\alpha u} E_{\mathbf{g}}[\chi(u)]du\,\pi(d\mathbf{g})$$

and y_t is the number of born into the population. Recall, however (*cf.* Section 7.2), that the characteristic counting all born becomes a little different in our embedded model. In the α-curve we give the pseudo-mother a score for each daughter, which means that the characteristic for counting all born is now

$$\chi'_\alpha(u) = 2\,\mathbf{1}(\lambda'_0 < u)$$

i.e. a factor 2 comes in compared with the characteristic in (7.2.3). Thus

$$\alpha(a) = \frac{E_\pi[\hat{\chi}_\alpha(\alpha)]}{E_\pi[\hat{\chi}'_\alpha(\alpha)]}$$

where π now is the stable type distribution on the type space $(\Gamma, \mathcal{G})$. The expectations are

$$\begin{aligned} E_\pi[\hat{\chi}_\alpha(\alpha)] &= \\ &= \int_\Gamma E_{\mathbf{g}}[e^{-\alpha\lambda'_0}(\mathbf{1}(a+\lambda'_0<\tau_1+\lambda'_1)+\mathbf{1}(a+\lambda'_0<\tau_2+\lambda'_2))]\pi(d\mathbf{g}). \end{aligned} \quad (7.4.1)$$

and in the same manner

$$E_\pi[\hat{\chi}'_\alpha(\alpha)] = 2\int_\Gamma E_{\mathbf{g}}[e^{-\alpha\lambda'_0}]\pi(d\mathbf{g}). \quad (7.4.2)$$

If we want to calculate the α-curve for all cells *alive*, we use the characteristic

$$\begin{aligned} \chi^\gamma_\alpha(u) &= \mathbf{1}(\lambda'_0 < u < \tau_1 + \lambda'_1)\mathbf{1}(\lambda'_0 + a < \tau_1 + \lambda'_1) + \\ &\quad + \mathbf{1}(\lambda'_0 < u < \tau_2 + \lambda'_2)\mathbf{1}(\lambda'_0 + a < \tau_2 + \lambda'_2). \end{aligned}$$

where the γ on χ^γ_α indicates that it is among all cells alive. The characteristic that counts all cells alive at time u (*cf.* Section 6.2) is

$$\gamma_\alpha(u) = \mathbf{1}(\lambda'_0<u<\tau_1+\lambda'_1)+\mathbf{1}(\lambda'_0<u<\tau_2+\lambda'_2) \quad (7.4.3)$$

The α-curve among all alive is

$$\alpha^\gamma(a) = \frac{E_\pi[\hat{\chi}^\gamma_\alpha(\alpha)]}{E_\pi[\hat{\gamma}_\alpha(\alpha)]}$$

where

$$\begin{aligned}
E_\pi[\hat{\chi}^\gamma_\alpha(\alpha)] &= \int_\Gamma E_{\mathbf{g}}[\mathbf{1}(\lambda'_0 + a < \tau_1 + \lambda'_1)(e^{-\alpha\lambda'_0} - e^{-\alpha(\tau_1+\lambda'_1)})]\pi(d\mathbf{g}) \\
&\quad + \int_\Gamma E_{\mathbf{g}}[\mathbf{1}(\lambda'_0 + a < \tau_2 + \lambda'_2)(e^{-\alpha\lambda'_0} - e^{-\alpha(\tau_2+\lambda'_2)})]\pi(d\mathbf{g}) \\
E_\pi[\hat{\gamma}_\alpha(\alpha)] &= \int_\Gamma E_{\mathbf{g}}[2e^{-\alpha\lambda'_0} - e^{-\alpha(\tau_1+\lambda'_1)} - e^{-\alpha(\tau_2+\lambda'_2)}]\pi(d\mathbf{g}).
\end{aligned}$$

The β-curves $\beta(a)$ are the probabilities that the life lengths between two sister cells, cousin cells etc. differ with more than a time units. The β_1-curve is this probability for sister cells. We saw in Section 7.2 that the characteristic among all *born*, that gives score one to each pseudo-mother who's *real* daughters differ in life lengths with more than a time units, is

$$\begin{aligned}
\chi_{\beta_1}(u) &= \mathbf{1}(\lambda'_0 < u)\mathbf{1}(|(\tau_0 - \lambda'_0) + \lambda'_1 - ((\tau_2 - \lambda'_0) + \lambda'_2)| > a) \\
&= \mathbf{1}(\lambda'_0 < u)\mathbf{1}(|\tau_1 + \lambda'_1 - (\tau_2 + \lambda'_2)| > a)
\end{aligned}$$

and since we now count sister *pairs* instead of each sister cell

$$\chi'_{\beta_1}(u) = \mathbf{1}(\lambda'_0 < u).$$

This gives

$$\begin{aligned}
E_\pi[\hat{\chi}_{\beta_1}(\alpha)] &= \int_\Gamma E_{\mathbf{g}}[e^{-\alpha\lambda'_0}\mathbf{1}(|\tau_1 + \lambda'_1 - (\tau_2 + \lambda'_2)| > a)]\pi(d\mathbf{g}) \quad (7.4.4) \\
E_\pi[\hat{\chi}'_{\beta_1}(\alpha)] &= E_\pi[e^{-\alpha\lambda'_0}]. \quad (7.4.5)
\end{aligned}$$

When calculating the β_1-curve among all cells *alive* the number of sister pairs alive and with life lengths that differ with more than a units is counted by

$$\chi^\gamma_{\beta_1}(u) = \mathbf{1}(\lambda'_0 < u < \min(\tau_1 + \lambda'_1, \tau_2 + \lambda'_2))\mathbf{1}(|\tau_1 + \lambda'_1 - (\tau_2 + \lambda'_2)| > a).$$

and the characteristic for being alive becomes

$$\gamma_{\beta_1}(u) = \mathbf{1}(\lambda'_0 < u < \min(\tau_1 + \lambda'_1, \tau_2 + \lambda'_2))$$

since both sisters have to be alive for the pair to be counted.

The size distributions of the cell population can be found through characteristics in the same manner. For instance the *stable birth size distribution* among all cells alive is given by

$$\tilde{P}(\mathcal{M}_B^\gamma \leq x) = \frac{E_\pi[\hat{\chi}_B(\alpha)]}{E_\pi[\hat{\gamma}_B(\alpha)]}$$

where

$$\begin{aligned}
\chi_B(u) &= \mathbf{1}(\lambda_0' < u < \tau_1 + \lambda_1')\mathbf{1}(\max(\delta, 1-\delta) m_g(m_0, \lambda_0') \leq x) \\
&\quad + \mathbf{1}(\lambda_0' < u < \tau_2 + \lambda_2')\mathbf{1}(\min(\delta, 1-\delta) m_g(m_0, \lambda_0') \leq x) \\
\gamma_B(u) &= \mathbf{1}(\lambda_0' < u < \tau_1 + \lambda_1') + \mathbf{1}(\lambda_0' < u < \tau_2 + \lambda_2')
\end{aligned}$$

The *stable division size distribution* among all *born* is given by

$$\chi_D(u) = \mathbf{1}(m_g(m_0, u) \leq x)$$

and

$$\tilde{P}(\mathcal{M}_D \leq x) = E_\pi[\hat{\chi}_D(\alpha)] = \int_\Gamma P_{\mathbf{g}}(m_g(m_0, \lambda_0') \leq x)\pi(d\mathbf{g}).$$

Among all alive the formula becomes a bit more complicated since we have to consider the real daughters of a pseudo-cell and thereby take into consideration the fact that the daughter cells change growth rate at the critical mass m_0. We get

$$\begin{aligned}
\chi_D^\gamma(u) &= \mathbf{1}(\lambda_0' < u < \tau_1 + \lambda_1')\mathbf{1}(m_{g_L+\eta_1}(m_0, \lambda_1') \leq x) \\
&\quad + \mathbf{1}(\lambda_0' < u < \tau_2 + \lambda_2')\mathbf{1}(m_{g_L+\eta_2}(m_0, \lambda_2') \leq x).
\end{aligned}$$

The stable size distribution, *i.e.* the distribution of ego's size at sampling moment, can be found in the same manner. The characteristic for this becomes quite complicated, but the calculations proceed as the ones above.

7.4.2. Special case: deterministic life lengths

In (Sennerstam & Strömberg, 1995) it is assumed that the DDC is mainly constant. In this section we follow them and put $\lambda' \equiv d$ in our formulas in the previous section, where $d > 0$ is some constant. We also use their assumption that the cells grow exponentially (*cf.* Section 7.3), *i.e.*

$$m_g(m_0, d) = m_0\, e^{gd}$$

and

$$T(x_1, g) - T(x_2, g) = \int_{x_2}^{x_1} \frac{dy}{gy} = \frac{1}{g}\log\frac{x_1}{x_2}.$$

If we begin with the α-curve among all *born* we get for (7.4.1)

$$E_\pi[\hat{\chi}_\alpha(\alpha)] = e^{-\alpha d} \int_\Gamma E_{\mathbf{g}}[\mathbf{1}(a < \tau_1) + \mathbf{1}(a < \tau_2)]\pi(d\mathbf{g})$$

and for (7.4.2)

$$E_\pi[\hat{\chi}'_\alpha(\alpha)] = 2e^{-\alpha d}.$$

The growth of the two daughter cells, up to size m_0, is given by $\mathbf{g} = (g, g_L)$, so the variation in τ_1 and τ_2 comes from the variation in the division fraction δ. The pseudo-mother's size when she actually divides is $m_g(m_0, d)$. As in Section 7.2 we get

$$\tau_1 = T(m_0, g) - T(\delta\, m_g(m_0, d), g) + d \qquad (7.4.6)$$

$$\tau_2 = T(m_0, g) - T((1-\delta)m_g(m_0, d), g) + d \qquad (7.4.7)$$

and

$$\begin{aligned}
\alpha(a) &= \frac{E_\pi[\hat{\chi}_\alpha(\alpha)]}{E_\pi[\hat{\chi}'_\alpha(\alpha)]} = \int_\Gamma E_{\mathbf{g}}[\mathbf{1}(a < \tau_1)]\pi(d\mathbf{g}) \\
&= \int_\Gamma \int_0^1 \mathbf{1}(a < T(m_0, g) - T(p\, m_g(m_0, d), g) + d) \\
&\qquad f_\delta(m_g(m_0, d), p)dp\, \pi(d\mathbf{g}) \\
&= \int_{\Gamma_1} \int_0^1 \mathbf{1}(a < -\log p^{1/g}) f_\delta(m_0\, e^{gd}, p)dp\, \psi_1(dg).
\end{aligned}$$

When calculating the α-curve among all cells *alive* we get for the characteristic that counts all cells alive at time u in (7.4.3)

$$\begin{aligned}
E_\pi[\hat{\gamma}_\alpha(\alpha)] &= \int_\Gamma E_{\mathbf{g}}[2e^{-\alpha\lambda'_0} - e^{-\alpha(\tau_1+\lambda'_1)} - e^{-\alpha(\tau_2+\lambda'_2)}]\pi(d\mathbf{g}) \\
&= 2e^{-\alpha d} - e^{-\alpha d} \int_\Gamma E_{\mathbf{g}}[e^{-\alpha\tau_1} + e^{-\alpha\tau_2}]\pi(d\mathbf{g}).
\end{aligned}$$

Using the expressions (7.4.6) and (7.4.7) for τ_1 and τ_2 respectively gives

$$\begin{aligned}
E_{\mathbf{g}}[e^{-\alpha\tau_1} + e^{-\alpha\tau_2}] &= 2\int_0^1 e^{-\alpha(T(m_0,g) - T(p\, m_g(m_0,d),g)+d)} f_\delta(m_g(m_0, d), p)dp \\
&= 2\int_0^1 p^{\alpha/g} f_\delta(m_0\, e^{gd}, p)dp = \hat{\mu}(\alpha, g).
\end{aligned}$$

The last equality holds since λ' is deterministic. This gives

$$E_\pi[\hat{\gamma}_\alpha(\alpha)] = 2e^{-\alpha d} - e^{-\alpha d}\int_{\Gamma_1} \hat{\mu}(\alpha, g)\psi_1(dg) = e^{-\alpha d}$$

since $\int_{\Gamma_1} \hat{\mu}(\alpha, g)\psi_1(dg) = 1$ (*cf.* previous section).

For the characteristic corresponding to the α-curve itself we get

$$\begin{aligned}
E_\pi[\hat{\chi}^\gamma_\alpha(\alpha)] &= \int_\Gamma E_{\mathbf{g}}[\mathbf{1}(\lambda'_0+a<\tau_1+\lambda'_1)(e^{-\alpha\lambda'_0} - e^{-\alpha(\tau_1+\lambda'_1)})]\pi(d\mathbf{g}) \\
&\quad +\int_\Gamma E_{\mathbf{g}}[\mathbf{1}(\lambda'_0+a<\tau_2+\lambda'_2)(e^{-\alpha\lambda'_0} - e^{-\alpha(\tau_2+\lambda'_2)})]\pi(d\mathbf{g}) \\
&= e^{-\alpha d}\int_\Gamma E_{\mathbf{g}}[\mathbf{1}(a<\tau_1)(1-e^{-\alpha\tau_1})+\mathbf{1}(a<\tau_2)(1-e^{-\alpha\tau_2})]\pi(d\mathbf{g}) \\
&= 2e^{-\alpha d}\int_{\Gamma_1}\int_0^1 \mathbf{1}(a<T(m_0,g)-T(p\, m_g(m_0,d),g)+d) \\
&\qquad (1-e^{-\alpha(T(m_0,g)-T(p\, m_g(m_0,d),g)+d)})f_\delta(m_0\, e^{gd}, p)dp\,\psi_1(dg) \\
&= 2e^{-\alpha d}\int_{\Gamma_1}\int_0^1 \mathbf{1}(a < -\log p^{1/g})(1-p^{\alpha/g})f_\delta(m_0\, e^{gd}, p)dp\psi_1(dg).
\end{aligned}$$

Finally this gives

$$\alpha^\gamma(a) = 2\iint_{\Gamma_1}{}_0^1 \mathbf{1}(a<-\log p^{\alpha/g})(1-p^{\alpha/g})f_\delta(m_0\, e^{gd}, p)dp\,\psi_1(dg). \quad (7.4.8)$$

For the β_1-curve among all *born* we have for (7.4.4)

$$E_\pi[\hat{\chi}_{\beta_1}(\alpha)] = e^{-\alpha d}\int_\Gamma E_{\mathbf{g}}[\mathbf{1}(|T(\delta\, m_g(m_0,d),g) - T((1-\delta)m_g(m_0,d),g)|>a)]\pi(d\mathbf{g})$$

and for (7.4.5)

$$E_\pi[\hat{\chi}'_{\beta_1}(\alpha)] = e^{-\alpha d}.$$

This gives

$$\begin{aligned}
\beta_1(a) &= \iint_\Gamma{}_0^1 \mathbf{1}(|T(p\, m_g(m_0,d),g) - T((1-p)m_g(m_0,d),g)|>a) \\
&\qquad f_\delta(m_g(m_0,d),p)dp\,\pi(d\mathbf{g}) \\
&= \int_{\Gamma_1}\int_0^1 \mathbf{1}(|\frac{1}{g}\log\frac{p}{1-p}| > a)f_\delta(m_0\, e^{gd}, p)dp\,\psi_1(dg). \qquad (7.4.9)
\end{aligned}$$

The β_1-curve among all *alive* becomes in the same manner

$$\beta_1^\gamma(a) = \frac{E_\pi[\hat{\chi}^\gamma_{\beta_1}(\alpha)]}{E_\pi[\hat{\gamma}_{\beta_1}(\alpha)]} = \frac{\int_\Gamma E_{\mathbf{g}}[(1-e^{-\alpha\tau_1})\mathbf{1}(|\tau_1-\tau_2|>a)]\pi(d\mathbf{g})}{\int_\Gamma E_{\mathbf{g}}[(1-e^{-\alpha\tau_1})]\pi(d\mathbf{g})} \tag{7.4.10}$$

$$= \frac{\int_{\Gamma_1}\int_0^1 (1-\max(p,1-p)^{\alpha/g})\mathbf{1}(|\frac{1}{g}\log\frac{p}{1-p}|>a) f_\delta(m_0\, e^{gd},p)dp\,\psi_1(dg)}{\int_{\Gamma_1}\int_0^1 (1-\max(p,1-p)^{\alpha/g}) f_\delta(m_0\, e^{gd},p)dp\,\psi_1(dg)}.$$

The stable birth size distribution among all cells *alive* is

$$\tilde{P}(\mathcal{M}_B^\gamma \le x) = 2\int_{\Gamma_1}\int_0^1 \mathbf{1}(p\, m_0\, e^{gd} \le x)(1-p^{\alpha/g}) f_\delta(m_0\, e^{gd},p)dp\,\psi_1(dg).$$

The stable division size distribution among all born is

$$\tilde{P}(\mathcal{M}_D \le x) = \int_{\Gamma_1} \mathbf{1}(m_0\, e^{gd} \le x)\psi_1(dg).$$

and among all alive with $\gamma(u)$ as before we get for $\mathbf{g} = (g, g_L)$

$$\begin{aligned}\tilde{P}(\mathcal{M}_D^\gamma \le x) \quad = \quad & 2\int_\Gamma\int_{\Gamma_1}\int_0^1 \mathbf{1}(m_0\, e^{(g_L+g')d} \le x)(1-p^{\alpha/g}) f_\eta(g') f_\delta(m_0\, e^{gd},p) \\ & dp\, dg'\, \pi(d\mathbf{g}).\end{aligned}$$

7.4.3. Plots

In this section we combine the analytical results concerning the Two-Subcycle model with the numerical values used in the simulation study of (Sennerstam & Strömberg, 1995). As a result we obtain a numerical value of the Malthusian parameter and we plot the functions described previously in this section. We use the parameters defined in (Sennerstam & Strömberg, 1995):

Critical cell size (m_0)	7 (rel. size units)
DDC (d)	8 (hr)
Latent growth factor ($\mathcal{L}$)	$\sim N(0.06, 0.005^2)$
Individual growth contribution (η)	$\sim N(0, 0.015^2)$
$\mathcal{L}+\eta$	$\sim N(0.06, 0.005^2+0.015^2)$
$\Gamma_1 = \Gamma_2$	$(0, 0.12)$

The Malthusian parameter is the value α such that

$$\int_{\Gamma_1} \hat{\mu}(\alpha, g)\psi_1(dg) = 1$$

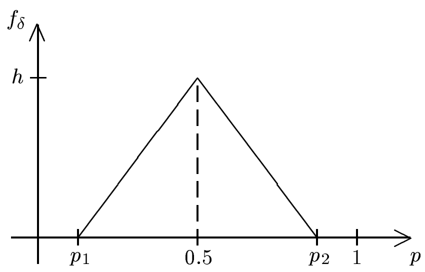
where

$$\begin{aligned}\hat{\mu}(\alpha, g) &= 2\int_{m_0}^{2m_0} e^{-\alpha(T(x,g)-T(px,g))-(C(x,g)-C(m_0,g))}\frac{b(x)}{g(x)}f_\delta(x,p)dp\,dx\\ \psi_1(dg) &= f_{\eta+\mathcal{L}}(g)dg.\end{aligned}$$

The assumptions of deterministic $\lambda' \equiv d$ and exponential growth give that the Malthusian parameter is the α such that

$$2\int_{\Gamma_1}\int_0^1 p^{\alpha/g} f_\delta(m_0\, e^{gd}, p) f_{\eta+\mathcal{L}}(g)dp\,dg = 1.$$

We let f_δ be the density function of a triangular distribution.



Since a newborn cell has size $< m_0$ the mother cell has to divide such that $p_1 \leq \delta \leq p_2$ where $p_2 = 1 - p_1$ and the condition

$$m_0\, e^{gd} - m_0 \leq \delta\, m_0\, e^{gd} \leq m_0$$

gives that $p_2 = e^{-gd}$.
Now

$$f_\delta(m_0\, e^{gd}, p) = \begin{cases} h^2(p - (1 - p_2)) & \text{if } p_1 \leq p \leq \frac{1}{2} \\ h^2(p_2 - p) & \text{if } \frac{1}{2} \leq p \leq p_2 \end{cases}$$

where $h = \frac{1}{p_2 - \frac{1}{2}}$.

All these assumptions give that the Malthusian parameter becomes

$$\alpha \approx 0.0574.$$

The α- and β_1-curves among all born into the population and alive at sampling calculated in Section 7.4.2 look pretty much the same. Figures 7.7 and 7.8 show them for sampling among all cells alive. The density functions for the stable birth size distribution and the stable division size distribution among all born become as in Fig. 7.9 and 7.10. Notice that there is a small probability that a cell has division size larger than $2m_0(=14)$, which would lead to at least one daughter cell with birth mass $> m_0$. This is because we have normally distributed growth rates. In reality a situation like this would lead to a tetraploid cell (*cf.* Section 7.1). The birth size density is cut at size $= 7$. Since each cell has to have birth size less than $m_0 = 7$ the density function of the division fraction δ is constructed to depend on the growth. Hence it becomes 0 for sizes > 7. In reality this would mean that the cell does not divide if its size is larger than $2m_0$, which is also the assumption (again the tetraploid cell argument). If we instead let f_δ be the density of a normal distribution the curve would be as in Fig. 7.11.

Fig. 7.7. The α-curve in (7.4.8).

Fig. 7.8. The β_1-curve in (7.4.10).

Fig. 7.9. The density of the stable birth size.

Fig. 7.10. The density of the stable division size.

Fig. 7.11. The density of the birth size with δ normally distributed.

Notation

I	the Ulam-Harris space of all possible indiviudals
Ω	the life space
$\mathcal{A}$	the σ-algebra of Ω
$(S, \mathcal{S})$	the type space
$(\Gamma, \mathcal{G})$	the type space when growth is the type
$(S \times \Omega^I, \mathcal{S} \times \mathcal{A}^I)$	the population space
$P(s, \cdot)$	the life law of an s-type individual
P_s	the probability measure on the population space
J	the doubly infinite space of individuals
$\boldsymbol{\Omega}$	$= \Omega^J \times N^\infty \times \mathrm{R}_+$, the pedigree space
$\mathcal{C}$	$= \mathcal{A}^J \times 2^{N^\infty} \times \mathcal{B}(\mathrm{R}_+)$, the σ-algebra of $\boldsymbol{\Omega}$
$\tilde{P}$	the stable population measure
ω	a life career in Ω
τ	birth time for individuals in I
$\tau(i)$	age at ith childbearing for individuals in I
σ	type for individuals in I
λ	life span
λ'	the time from size m_0 to division
λ''	the time between birth and reaching size m_0
$\tilde{\tau}$	birth time for individuals in J
$\tilde{\sigma}$	type for individuals in J
$\mathcal{D}$	daughter process operator
$\mathcal{M}$	the size of ego at sampling
α	the Malthusian parameter
$\alpha(a)$	the probability of getting older than age a
$\alpha^\gamma(a)$	$\alpha(a)$ for all individuals alive
β	the stable age at childbearing
$\beta_1(a)$	the probability of difference in sisters' life lengths

$\beta_2(a)$	as β_1 but for cousins
$\beta_1^\gamma(a)$	$\beta_1(a)$ for all individuals alive
δ	division fraction of a cell
$(\eta, \mathcal{L})$	random element of $(\Gamma, \mathcal{G})$
χ	a random characteristic
χ'	the random characteristic for all born in the embedded model
γ	the random characteristic for all individuals alive
ξ	the reproduction point process
ρ	the Perron root
π	the stable birth type distribution
$\psi_1 \times \psi_2$	$= \pi$ in the Two-Subcycle model
μ	the reproduction kernel
$\hat{\mu}_\alpha$	$\int_{\mathrm{R}_+} e^{-\alpha t}\mu(\cdot, \cdot \times dt)$
$\hat{\mu}$	$\int_{\mathrm{R}_+} \mu(\cdot, \cdot \times dt)$, the basis of μ
$\hat{\mu}(\alpha)$	$\int_{\mathrm{R}_+} e^{-\alpha t}\mu(dt)$, the single type case
y_t	the total number of individuals born up to time t
z_t^χ	the branching process counted by χ
b	hazard rate function of λ
d	constant for λ' when deterministic
f_δ	density function for δ
f_η	density function for η
$f_\mathcal{L}$	density function for $\mathcal{L}$
g, g'	growth functions
g_L, g'_L	latent growth factors
$\mathbf{g}$	element of $(\Gamma, \mathcal{G})$
h	reproductive value
$m(r,t)$	the size of an r-type individual at time t
$m_g(r,t)$	as m but keeping track of the growth function g
m_0	critical size
$C(x)$	$\int_0^x \frac{b(v)}{g(v)} dv$
T	growth time
$Q(x)$	$b(x)/xg(x)$
N	the natural numbers, $\{1, 2, \ldots\}$
R_+	the positive real line
DDC	DNA division cycle
CGC	cell growth cycle

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