

AGE-DEPENDENT BRANCHING PROCESSES AND
APPLICATIONS TO THE LURIA-DELBRÜCK EXPERIMENT

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Doctor of Philosophy

by
Hesam Oveys
Dr. Stephen Montgomery-Smith, Dissertation Supervisor

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The undersigned, appointed by the Dean of the Graduate School, have examined the dissertation entitled

AGE-DEPENDENT BRANCHING PROCESSES AND
APPLICATIONS TO THE LURIA-DELBRÜCK EXPERIMENT

presented by Hesam Oveys,
a candidate for the degree of Doctor of Philosophy
and hereby certify that in their opinion it is worthy of acceptance.

Professor Nakhlé Asmar

Professor Carmen Chicone

Professor Loukas Grafakos

Professor Stephen Montgomery-Smith

Professor George Smith

*Dedicated to my mother and father for always
encouraging me to strive for nothing short of the best.*

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Contents

Acknowledgements	ii
Abstract	vi
1 Introduction	1
1.1 The Luria-Delbrück Experiment	1
1.2 The problem	3
1.3 Organization	3
2 Probability generating functions	5
3 Cell growth under symmetric division	8
3.1 Preliminaries and assumptions	8
3.2 Constructing the generating function	10
3.2.1 In discrete-time	10
3.2.2 In continuous-time	11
3.3 Existence and uniqueness	12
3.3.1 The generating function space	12
3.3.2 Integration	23
3.3.3 Construction of the map T	26
3.3.4 Unique fixed-point of T	33

3.4	Series solution to the generating function equation	37
3.5	Examples	38
3.5.1	Synchronous cell division	38
3.5.2	Life-span is a lattice distribution	39
3.5.3	Life-span is multi-phase	39
3.5.4	Alternative derivation when life-span is exponential	42
3.5.5	Incorporating death	43
4	Cell growth under asymmetric division	46
4.1	Preliminaries and assumptions	46
4.2	Constructing the generating function	47
4.2.1	In discrete-time	48
4.2.2	In continuous-time	49
4.3	Existence and uniqueness	50
4.4	Series solutions to the generating function equation	54
4.5	Examples	55
4.5.1	Life-span distribution is multi-phase	55
5	Asymptotics of cell growth	57
5.1	Symmetric cell division	57
5.1.1	The expectation $\mathbb{E}[Z_t]$	58
5.1.2	The Laplace transform of $\mathbb{E}[Z_t]$	60
5.1.3	Convergence of $\mathbb{E}[Z_t]$	62
5.1.4	Convergence of $Z_t/\mathbb{E}[Z_t]$	67
5.1.5	Examples	71
5.2	Asymmetric cell division	71
5.2.1	The expectations $\mathbb{E}[X_t]$ and $\mathbb{E}[Y_t]$	73
5.2.2	Convergence of $\mathbb{E}[X_t]$ and $\mathbb{E}[Y_t]$	74

5.2.3	Convergence of $X_t/\mathbb{E}[X_t]$ and $Y_t/\mathbb{E}[Y_t]$	78
5.2.4	Examples	85
6	Distribution of mutant cells	86
6.1	Symmetric cell division	86
6.1.1	Preliminaries and assumptions	86
6.1.2	Constructing the generating function	87
6.2	Asymmetric cell division	90
6.2.1	Preliminaries and assumptions	90
6.2.2	Constructing the generating function	91
6.3	Examples	96
6.3.1	Symmetric cell division	96
6.3.2	Asymmetric cell division	97
	Bibliography	98
	Vita	100

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Hesam Oveys

Dr. Stephen Montgomery-Smith, Dissertation Supervisor

ABSTRACT

Microbial populations adapt to their environment by acquiring advantageous mutations, but in the early twentieth century, questions about how these organisms acquire mutations arose. The experiment of Salvador Luria and Max Delbrück that won them a Nobel Prize in 1969 confirmed that mutations don't occur out of necessity, but instead can occur many generations before there is a selective advantage, and thus organisms follow Darwinian evolution instead of Lamarckian. Since then, new areas of research involving microbial evolution has spawned as a result of their experiment. Determining the mutation rate of a cell is one such area. Probability distributions that determine the number of mutants in a large population have been derived by D. E. Lea, C. A. Coulson, and J. B. S. Haldane. However, not much work has been done when time of cell division is dependent on the cell age, and even less so when cell division is asymmetric, which is the case in most microbial populations. Using probability generating function methods, we rigorously construct a probability distribution for the cell population size given a life-span distribution for both mother and daughter cells, and then determine its asymptotic growth rate. We use this to construct a probability distribution for the number of mutants in a large cell population, which can be used with likelihood methods to estimate the cell mutation rate.

Chapter 1

Introduction

In this chapter, we present the Luria-Delbrück Experiment and the areas of research that have spawned as a consequence of their results. Then, we present the problem this dissertation answers, and then conclude discussing the organization of this dissertation.

1.1 The Luria-Delbrück Experiment

In the early twentieth century, questions about how microorganisms acquire advantageous mutations arose. In 1943, biologists Salvador Luria and Max Delbrück conducted an experiment in order to determine whether mutations occurred out of necessity or could occur many generations before there was a selective advantage. This experiment, dubbed the “Luria-Delbrück Experiment,” helped them win a Nobel Prize in 1969 (see [5]).

In their experiment, Luria and Delbrück grew bacteria in a non-selective medium in multiple tubes for a period of time until they all reached a certain cell density. Then, they plated the cells from each tube on different plates of a selective-medium containing a bacterial virus. Cells that showed resistance to the virus had acquired a virus-resistant mutation. If cells evolved according to a post-exposure hypotheses such as Lamarckian evolution, where cells acquire mutations in response to their environment, then the number

of mutants in each plate would follow a Poisson process where the mean is equal to the variance, making plates with a large number of mutants highly unlikely. But in the experiment of Luria and Delbrück, there were “jackpots,” meaning there were plates with an unusually large number of surviving cells. The only conclusion they could make was that mutation occurred before the cells were plated on the selective medium containing the virus, and thus Charles Darwin’s theory of natural selection applied to microorganisms as well.

Since then, new areas of research involving microbial evolution has spawned from the Luria-Delbrück Experiment which are still being studied today. Since cells can acquire mutations before there is a selective advantage in their environment, questions about their mutation rate have risen. However, traditional methods involving significance tests can’t be used due to the high variability of the data. Instead, we can use likelihood methods, but in order to do so, we need a probability distribution for the mutant cell population size as a function of the unknown mutation rate.

Though unpublished originally, a probability distribution for the number of mutants was presented by John B. S. Haldane (see [8]). However, Haldane’s model had two major issues: it assumed all cells divide synchronously, and the distribution was computationally inefficient. In 1949, D. E. Lea and C. A. Coulson constructed a generating function for the number of mutants in a large population that had a closed-form solution, so computing the probability coefficients was much more efficient. However, they assumed that all cells grow symmetrically with a life-span distribution that was exponential, which is a very broad assumption for how cells grow (see [4]).

In this dissertation, we look to extend on the ideas of Haldane, Lea, and Coulson and develop a probability distribution for the mutant cell population size where we have control of a cell’s life-span distribution. In addition, we develop a distribution for asymmetric cell division, where a cell divides into a mother and daughter cell with different life-span distributions. To do this, we rigorously construct a probability distribution for the cell population size at a certain time given a cell life-span distribution, and then use this to

construct the probability distribution for the mutant cell population size. We then do the same for asymmetric cell division. These results culminate in Theorems 6.1.1 and 6.2.1.

1.2 The problem

Suppose you start with a single cell, and this cell undergoes binary division and divides into two cells. As time passes, the total cell population will grow, but depending on when each cell divides, the population will vary. If a cell divides into two cells identical to itself (symmetrical cell division), then the two children cells will divide similarly to its parent. On the other hand, how will the cell population grow if a cell divides into two cells, where one is identical to itself, but the other is not (asymmetrical cell division)? In addition, suppose during any cell division, a mutation can occur. If this mutation is passed through all the children spawned from the mutated cell, what can we say about the distribution of the mutant cell population size in a sufficiently large cell population?

We answered these questions by constructing branching processes that represent the cell population size and use probability generating function methods to determine its probability distribution at any time. We modeled the case for both symmetrical cell division and asymmetrical cell division. In both cases, the life-span distribution of the cell is dependent on its age, and the distribution is different for mother cells than for daughter cells in the case of asymmetrical division. Then, we determined the asymptotic growth rate of the cell population size, and used this to construct a probability generating function for the mutant cell population size.

1.3 Organization

This dissertation is organized in two main components: cell growth under symmetric division and cell growth under asymmetric division. The results for asymmetric cell division hinge on the results for symmetric cell division, so it is important that one has a good foundation of

cell growth under symmetric division before studying cell growth under asymmetric division.

In Chapter 2, a brief overview of probability generating functions is given, as generating functions are the foundation to all things studied in this dissertation.

In Chapter 3, we rigorously construct a time-dependent generating function (3.17) for the cell population size under symmetric cell division given any life-span distribution when you start from a single cell. Due to integral equation nature of the generating function, we carefully prove existence and uniqueness of a solution. We conclude the chapter with examples by computing the generating function for the cell population size using specific life-span distributions.

Chapter 4 discusses cell growth under asymmetric division, where each cell divides into a “mother cell” and a “daughter cell.” It is analogous to Chapter 3 in organization: first we construct the generating functions (4.9), then prove existence and uniqueness of solutions, and finally conclude with some examples.

In Chapter 5, we study the asymptotic behavior of both cell growth under symmetric and asymmetric division. Specifically, we show that the expected number of cells grows asymptotically at an exponential rate, and that the cell population converges to its expected value. The purpose of this chapter is mainly to discuss the mutant cell population size in Chapter 6, where we assume we start with an effectively infinite population.

Finally, in Chapter 6, we construct a generating function for the mutant cell population size in a sufficiently large cell population for both symmetric and asymmetric cell division. We do this by starting with a sufficiently large cell population, and then determining the expected number of mutations in each time increment in the past. Depending on when the mutation occurred, and whether this mutant cell was a mother cell or a daughter cell, the number of mutants that spawned from that single mutant could be significantly different. Taking these into consideration, we construct generating functions (6.16) and (6.43) for the mutant cell population size for both symmetric and asymmetric cell division. We conclude the chapter with some examples.

Chapter 2

Probability generating functions

In this chapter, a very brief overview of probability generating functions is given to ensure the reader is familiar with the basic properties. The first thing to note is that a probability generating function can only be constructed for discrete random variables outputting non-negative integers. If not, the properties that make generating functions so nice fail to hold.

Definition 2.0.1. Let X be a discrete random variable outputting non-negative integer values. The *probability generating function* (or simply *generating function*) of X is the function

$$G_X(z) := \mathbb{E}[z^X] \tag{2.1}$$

$$= \sum_{k=0}^{\infty} \Pr(X = k)z^k. \tag{2.2}$$

Probability generating functions are power series with non-negative coefficients such that their sum is 1, so their radius of convergence is always at least 1.

Proposition 2.0.1. *If X is a discrete random variable outputting non-negative integer values with generating function $G_x(z)$, then*

$$\mathbb{E}[X] = G'_X(1), \tag{2.3}$$

when it converges.

Below, we define joint probability generating functions, since we will use them in Chapter 4.

Definition 2.0.2. Let X and Y be discrete random variables outputting non-negative integer values. Then the *joint probability generating function* is

$$G_{X,Y}(x, y) := \mathbb{E} [x^X y^Y] \quad (2.4)$$

$$= \sum_{k=0}^{\infty} \sum_{j=0}^{\infty} \Pr(X = k, Y = j) x^k y^j. \quad (2.5)$$

Proposition 2.0.2. If X and Y are independent random variables, both outputting non-negative integer values, then the generating function of $X + Y$ is

$$G_{X+Y}(z) = G_X(z)G_Y(z). \quad (2.6)$$

The following two propositions will be used extensively in Chapter 6 when constructing the generating function for the mutant cell population.

Proposition 2.0.3. If $X = X_k$ are independent and identically distributed random variables outputting non-negative integer values, and

$$Z = \sum_{k=1}^N X_k, \quad (2.7)$$

where N is an independent random variable outputting non-negative integer values, then the generating function of Z is

$$G_Z(z) = G_N(G_X(z)). \quad (2.8)$$

Proposition 2.0.4. If X is a Poisson random variable with parameter λ , then the gener-

ating function for X is

$$G_X(z) = e^{\lambda(z-1)}. \quad (2.9)$$

For a more in-depth look at generating functions, one can refer to almost any book on probability theory, though we only use the above definitions in properties in this dissertation.

Chapter 3

Cell growth under symmetric division

In this chapter, we will construct a time-dependent generating function (3.17) for the cell population size under symmetric cell division (when there is only one type of cell). This generating function will be in the form of an integral equation, so we will proceed to show existence and uniqueness of a solution in section 3.3. We conclude the chapter with some examples of generating functions using different different life-span distributions.

3.1 Preliminaries and assumptions

We start by stating our assumptions about symmetric cell division.

Assumption 3.1.1 (Symmetric cell division). Cells have the following properties:

1. there is only one type of cell: mother cells;
2. all cells are identical and independent to each other;
3. cell life-span is a strictly positive, real-valued random variable \mathcal{T} with distribution P ;

4. at the end of a cell's life, it will divide into two cells.

Let Z_t be a random variable representing the cell population at time $t \geq 0$. We will always assume we start from a single cell, and so $Z_0 = 1$. Our goal is to determine how Z_t is distributed for $t \geq 0$.

Suppose time is discrete and \mathcal{T} only takes non-negative integer values. For clarity, when we say a cell divides at time t , we mean the cell population has increased by two at time $t + 1$ (one time-unit later). We can define Z_t formally as a branching process. Let X_t and \tilde{X}_t be two processes that will help keep count of the cell population of a certain age. They will be distributed as follows:

$$\Pr(X_t = 0) := \Pr(\mathcal{T} = t \mid \mathcal{T} \geq t); \quad (3.1)$$

$$\Pr(X_t = 1) := \Pr(\mathcal{T} > t \mid \mathcal{T} \geq t); \quad (3.2)$$

$$\Pr(\tilde{X}_t = 0) := \Pr(\mathcal{T} > t \mid \mathcal{T} \geq t); \quad (3.3)$$

$$\Pr(\tilde{X}_t = 2) := \Pr(\mathcal{T} = t \mid \mathcal{T} \geq t). \quad (3.4)$$

Let $(Z_t)_i$ represent the cell population at time t that are i -time-units old. Then for $t \geq 1$, we have

$$Z_t = \sum_{i=0}^t (Z_t)_i, \quad (3.5)$$

where

$$(Z_t)_i = \begin{cases} \sum_{k=1}^{(Z_{t-1})_{i-1}} X_{i-1}^{(k)} & 1 \leq i \leq t \\ \sum_{j=0}^{t-1} \sum_{k=1}^{(Z_{t-1})_j} \tilde{X}_j^{(k)} & i = 0 \end{cases} \quad (3.6)$$

and $X_t^{(k)}$ and $\tilde{X}_t^{(k)}$ are independent copies of X_t and \tilde{X}_t , respectively.

Trying to determine the distribution of Z_t using combinatorial methods will be very time consuming, as keeping track of cell age can be cumbersome and tedious. Instead, we will describe the distribution of Z_t with its generating function.

3.2 Constructing the generating function

In order to derive the generating function for the cell population Z_t at any time $t \geq 0$, we will first construct a model in discrete-time, then divide our time increments infinitesimally small, and finally take limits to derive a continuous-time model.

3.2.1 In discrete-time

Define

$$f(t, x) := \mathbb{E} [x^{Z_t}] \quad (3.7)$$

to be the generating function of Z_t for integers $t \geq 0$. Let $\mathcal{T}^{(1)}$ be a copy of \mathcal{T} that represents the time the first cell divides. Suppose the initial cell divides at time $\mathcal{T}^{(1)} = k$. Then two cells identical and independent to the initial cell are created, each of which will produce a cell population $Z_{t-(k+1)}$ for $t > k$. So,

$$Z_t = \begin{cases} 1 & t \leq k \\ Z_{t-(k+1)}^{(1)} + Z_{t-(k+1)}^{(2)} & t > k \end{cases}, \quad (3.8)$$

where $Z_t^{(1)}$ and $Z_t^{(2)}$ are copies of Z_t . Since the two cells grow independently of each other, the generating function of Z_t when $\mathcal{T}^{(1)} = k$ is

$$f_k(t, x) = \begin{cases} x & t \leq k \\ f(t - (k + 1), x)^2 & t > k \end{cases}. \quad (3.9)$$

Using this, we can derive the generating function of Z_t :

$$f(t, x) = \mathbb{E} [x^{Z_t}] \quad (3.10)$$

$$= \sum_{k=1}^{\infty} \mathbb{E} [x^{Z_t} \mathbb{1}_{\mathcal{T}^{(1)}=k}] \quad (3.11)$$

$$= x \Pr(\mathcal{T}^{(1)} > t) + \sum_{k=1}^t \mathbb{E} [x^{Z_t} \mathbb{1}_{\mathcal{T}^{(1)}=k}] \quad (3.12)$$

$$= x \Pr(\mathcal{T}^{(1)} > t) + \sum_{k=1}^t \mathbb{E} [x^{Z_t} | \mathcal{T}^{(1)} = k] \Pr(\mathcal{T}^{(1)} = k) \quad (3.13)$$

$$= x(1 - P(t)) + \sum_{k=1}^t f(t - (k + 1), x)^2 (P(k) - P(k - 1)). \quad (3.14)$$

3.2.2 In continuous-time

We will divide our discrete-time increments in the previous section into even smaller increments. As these increments get infinitesimally small, our time will be continuous. Let $\delta_t > 0$, and suppose \mathcal{T} take values $k\delta_t$ for positive integers k . Then the generating function $f(t, x)$ will become

$$f(t, x) = x \Pr(\mathcal{T} > t) + \sum_{k=1}^{\lfloor t/\delta_t \rfloor} f(t - (k + 1)\delta_t, x)^2 \Pr(\mathcal{T} = k\delta_t) \quad (3.15)$$

$$= x(1 - P(t)) + \sum_{k=1}^{\lfloor t/\delta_t \rfloor} f(t - (k + 1)\delta_t, x)^2 (P(k\delta_t) - P((k - 1)\delta_t)), \quad (3.16)$$

Letting $\delta_t \rightarrow 0^+$, we get a Riemann-Stieltjes integral equation

$$f(t, x) = x(1 - P(t)) + \int_0^t f(t - \tau, x)^2 dP(\tau), \quad (3.17)$$

which will be the foundation for all of our analysis for cell growth under symmetric division.

3.3 Existence and uniqueness

The goal of this section is to rigorously prove there exists a unique solution to (3.17) given any life-span distribution P of a cell. In order to do this, we will construct a space of time-dependent generating functions and a continuous map from this space to itself derived the right-hand side of (3.17), and then show this map has a unique fixed-point using the Banach Fixed-Point Theorem. Along the way, we will prove important properties about our function spaces and map that may help in other applications or proofs.

3.3.1 The generating function space

We need to construct a complete metric space of generating functions. Unless otherwise specified, we will always assume $0 < r < 1$. Let $H^\infty(B(0, r))$ be the usual space of all holomorphic functions bounded on $\partial B(0, r)$ with the usual norm

$$\|\cdot\|_{H^\infty} := \sup_{z \in B(0, r)} |(\cdot)(z)|. \quad (3.18)$$

Definition 3.3.1. Define H_r to be a subspace of $H^\infty(B(0, r))$ such that for each $g \in H_r$,

1. $c_k(g) \geq 0$ for each integer $k \geq 0$ and
2. $\sum_{k=0}^{\infty} c_k(g) = 1$,

where

$$c_k(g) := \frac{g^{(k)}(0)}{k!} \quad (3.19)$$

is the k^{th} coefficient of g in its power series expansion centered at 0. H_r represents the space of all generating functions.

Remark. Although $H^\infty(B(0, r))$ is a Banach space, H_r is not since it is not a vector space. That is, for $g_1, g_2 \in H_r$, $g_1 + g_2$ is clearly not in H_r .

We will show that the space of generating functions H_r has nice properties in the following propositions and theorems, which we will use in the next few sections.

Proposition 3.3.1. *If $g \in H_r$, then $\|g\|_{H^\infty} < g(0) + r$.*

Proof. Since g is holomorphic, we can write g as a power series

$$g(z) = \sum_{k=0}^{\infty} c_k(g) z^k \quad (3.20)$$

in $B(0, r)$. Then, we have

$$|g(z)| = \left| \sum_{k=0}^{\infty} c_k(g) z^k \right| \quad (3.21)$$

$$\leq \sum_{k=0}^{\infty} c_k(g) |z|^k \quad (3.22)$$

$$< g(0) + r \sum_{k=1}^{\infty} c_k(g) \quad (3.23)$$

$$= g(0) + r. \quad (3.24)$$

Therefore,

$$\|g\|_{H^\infty} < g(0) + r. \quad (3.25)$$

■

Remark. When dealing with cell growth, we will always have $g(0) = 0$ since we always start with a single cell and there is no possibility of death.

Now, we will show that that our space of generating functions H_r is complete, which is key when adding a time component in the next section.

Theorem 3.3.2. *H_r is a complete metric space with respect to the norm $\|\cdot\|_{H^\infty}$.*

Proof. Since H_r is a subspace of the complete metric space $H^\infty(B(0, r))$, it is sufficient to show that H_r is closed.

Let $\{g_n\}$ be a convergent sequence of generating functions in H_r such that $g_n \rightarrow g$ with respect to $\|\cdot\|_{H^\infty}$. So, $g_n \rightarrow g$ uniformly. Also, $g \in H^\infty(B(0, r))$ since each $g_n \in H^\infty(B(0, r))$ and $H^\infty(B(0, r))$ is complete. To show $g \in H_r$, we need to show $c_k(g) \geq 0$ for each k and $\sum_{k=0}^{\infty} c_k(g) = 1$.

First, we will show for each i ,

$$c_k(g_n) \rightarrow c_k(g). \quad (3.26)$$

To do this, we can use Cauchy's Integral Formula, which says

$$c_k(g) = \frac{g^{(k)}(0)}{k!} = \frac{1}{2\pi i} \int_{C(0, r)} \frac{g(z)}{z^{k+1}} dz, \quad (3.27)$$

where $C(0, r)$ represents the path along a circle centered at the origin of radius r traversed once counter-clockwise. Since $g_n \rightarrow g$ uniformly and g is bounded on $C(0, r)$, we have for each k ,

$$c_k(g_n) = \frac{1}{2\pi i} \int_{C(0, r)} \frac{g_n(z)}{z^{k+1}} dz \rightarrow \frac{1}{2\pi i} \int_{C(0, r)} \frac{g(z)}{z^{k+1}} dz = c_k(g), \quad (3.28)$$

which proves (3.26).

Now, since $c_k(g_n) \geq 0$ for each i , we must have $c_k(g) \geq 0$ for each k as well. Similarly, we will use (3.26) to show $\sum_{k=0}^{\infty} c_k(g) = 1$. For each g_n , we know

$$\sum_{k=0}^{\infty} c_k(g_n) = 1. \quad (3.29)$$

Since $c_k(g_n) \geq 0$ for each k , then

$$\sum_{k=0}^M c_k(g_n) \leq 1 \quad (3.30)$$

for all $M \in \mathbb{N}$. Computing the limit as $n \rightarrow \infty$ of this finite sum, we have

$$\sum_{k=0}^M c_k(g) \leq 1 \quad (3.31)$$

using (3.26). Since this is true for all $M \in \mathbb{N}$, letting $M \rightarrow \infty$, we have

$$\sum_{k=0}^{\infty} c_k(g) \leq 1. \quad (3.32)$$

To show we have equality in (3.32), by way of contradiction, suppose

$$\sum_{k=0}^{\infty} c_k(g) = L < 1. \quad (3.33)$$

Let $\varepsilon > 0$. Then there exists an $M \in \mathbb{N}$ large enough such that for all $m > M$,

$$\left| L - \sum_{k=0}^m c_k(g) \right| < \varepsilon. \quad (3.34)$$

Also, there exists an $N \in \mathbb{N}$ large enough such that for all $n > N$ and $m > M$,

$$\left| \sum_{k=0}^m c_k(g_n) - \sum_{k=0}^m c_k(g) \right| < \varepsilon, \quad (3.35)$$

and thus

$$\left| L - \sum_{k=0}^m c_k(g_n) \right| < 2\varepsilon. \quad (3.36)$$

Since this is true for all $m > M$, letting $m \rightarrow \infty$, we can conclude

$$\sum_{k=0}^{\infty} c_k(g_n) = L, \quad (3.37)$$

which is a contradiction. So, we must have

$$\sum_{k=0}^{\infty} c_k(g) = 1. \quad (3.38)$$

Therefore, $g \in H_r$, and H_r is closed. ■

Now, we will show our space of generating functions H_r is totally bounded, and thus compact.

Theorem 3.3.3. *H_r is totally bounded in $H^\infty(B(0, r))$.*

Proof. For any $g \in H_r$, $z \in B(0, r)$, and $N \in \mathbb{N}$, we have

$$\left| g(z) - \sum_{k=0}^N c_k(g) z^k \right| = \left| \sum_{k=N+1}^{\infty} c_k(g) z^k \right| \quad (3.39)$$

$$\leq \sum_{k=N+1}^{\infty} |c_k(g)| |z|^k \quad (3.40)$$

$$\leq \sum_{k=N+1}^{\infty} |z|^k \quad (3.41)$$

$$< \sum_{k=N+1}^{\infty} r^k \quad (3.42)$$

$$= \frac{r^{N+1}}{1-r}, \quad (3.43)$$

where (3.41) follows since each $c_k(g) \leq 1$. Let $\varepsilon > 0$. Then there exists an $N_\varepsilon \in \mathbb{N}$ large enough such that

$$\|g - g_\varepsilon\|_{H^\infty} < \frac{r^{N_\varepsilon+1}}{1-r} < \varepsilon \quad (3.44)$$

for all $g \in H_r$, where

$$g_\varepsilon := \sum_{k=0}^{N_\varepsilon} c_k(g) (\cdot)^k. \quad (3.45)$$

So, define the space

$$X_r^\varepsilon := \{g_\varepsilon : g \in H_r\} \quad (3.46)$$

Now, note that X_r^ε is a bounded, finite-dimensional subspace of $H^\infty(B(0, r))$, and therefore is totally bounded. So, there exists a finite subset $S_r^\varepsilon \subset X_r^\varepsilon$ such that

$$X_r^\varepsilon \subset \bigcup_{f \in S_r^\varepsilon} B(f, \varepsilon), \quad (3.47)$$

where $B(f, \varepsilon) := \{h \in H^\infty(B(0, r)) : \|h - f\|_{H^\infty} < \varepsilon\}$. Since every element in H_r is within ε -distance of $g_\varepsilon \in X_r^\varepsilon$, which is within ε -distance of some $f \in S_r^\varepsilon$, we have

$$H_r \subset \bigcup_{f \in S_r^\varepsilon} B(f, 2\varepsilon). \quad (3.48)$$

Therefore, H_r is totally bounded. ■

Corollary 3.3.4. *H_r is compact in $H^\infty(B(0, r))$.*

Proof. By Theorems 3.3.2 and 3.3.3, our space of generating functions H_r is compact in $H^\infty(B(0, r))$. ■

Now that we've constructed a complete, compact metric space of generating functions H_r , we need to construct a “nice” function space of time-dependent generating functions. Our function space must be a complete metric space so that we can satisfy the hypotheses of the Banach Fixed-Point Theorem in a later section, and we have to make sure that the right-hand side of (3.17) is also contained in this space. Immediately, since our distribution function P may not be continuous, we can't impose our space to consist of continuous functions. However, in order for for integration to be well defined, we need to make sure our space consists of functions of bounded variation.

Definition 3.3.2. Define $\mathcal{P}_\mathbb{R}$ to be the set of all partitions of \mathbb{R} . We say a function $f : \mathbb{R} \rightarrow H^\infty(B(0, r))$ has *bounded variation* on \mathbb{R} if

$$V(f) := \sup_{S \in \mathcal{P}_\mathbb{R}} \sum_{k=1}^M \|f(t_k) - f(t_{k-1})\|_{H^\infty} \quad (3.49)$$

is finite, where S is a partition $-\infty < t_0 \leq t_1 \leq \dots \leq t_M < \infty$.

We will denote the the supremum of a function $f : \mathbb{R} \rightarrow H^\infty(B(0, r))$ using the usual norm

$$\|f\|_{L^\infty(H^\infty)} := \sup_{t \in \mathbb{R}} \|f(t)\|_{H^\infty}. \quad (3.50)$$

Definition 3.3.3. Define $BV(\mathbb{R}, H^\infty(B(0, r)))$ to be the space of all functions mapping from \mathbb{R} to $H^\infty(B(0, r))$ with bounded variation on \mathbb{R} with norm

$$\|\cdot\|_{BV(H^\infty)} := \|\cdot\|_{L^\infty(H^\infty)} + V(\cdot). \quad (3.51)$$

It is clear that (3.51) is a valid norm on this space. In fact, $BV(\mathbb{R}, H^\infty(B(0, r)))$ is a Banach space.

Theorem 3.3.5. $BV(\mathbb{R}, H^\infty(B(0, r)))$ is a Banach space.

Proof. It is clear that $BV(\mathbb{R}, H^\infty(B(0, r)))$ is a vector space, and since it's a normed space, it is also a metric space. So it is sufficient to show that $BV(\mathbb{R}, H^\infty(B(0, r)))$ is complete.

Let $\{f_n\}$ be a Cauchy sequence of functions in $BV(\mathbb{R}, H^\infty(B(0, r)))$. Then for all $\varepsilon > 0$, there exists an $N \in \mathbb{N}$ such that

$$\|f_n - f_m\|_{BV(H^\infty)} < \varepsilon \quad (3.52)$$

for all $n, m > N$. Let $t \in \mathbb{R}$. Then

$$\|f_n(t) - f_m(t)\|_{H^\infty} + V(f_n - f_m) < \varepsilon \quad (3.53)$$

and, specifically,

$$\|f_n(t) - f_m(t)\|_{H^\infty} < \varepsilon \quad (3.54)$$

for all $n, m > N$, which implies $\{f_n(t)\}$ is a Cauchy sequence in $H^\infty(B(0, r))$, which is

complete. So, there exists an $f_t \in H^\infty(B(0, r))$ such that $f_n(t) \rightarrow f_t$. Define the function $f : \mathbb{R} \rightarrow H^\infty(B(0, r))$ by $f(t) := f_t$ for $t \in \mathbb{R}$. Letting $m \rightarrow \infty$ in (3.53), we have

$$\|f_n(t) - f(t)\|_{H^\infty} + V(f_n - f) \leq \varepsilon. \quad (3.55)$$

Since this is true for all $n > N$, and $t \in \mathbb{R}$ was arbitrary, we have

$$\|f_n - f\|_{BV(H^\infty)} \leq \varepsilon \quad (3.56)$$

for all $n > N$. So, $f_n \rightarrow f$.

Now, we must show that the limit f is indeed in $BV(\mathbb{R}, H^\infty(B(0, r)))$ by showing f has bounded variation. Let $\varepsilon > 0$. Then there exists an $N \in \mathbb{N}$ large enough such that

$$\|f_N - f\|_{BV(H^\infty)} < \varepsilon, \quad (3.57)$$

and consequently

$$\|f_N - f\|_{L^\infty(H^\infty)} < \varepsilon. \quad (3.58)$$

So,

$$V(f) = \|f\|_{BV(H^\infty)} - \|f\|_{L^\infty(H^\infty)} \quad (3.59)$$

$$\leq \|f_N\|_{BV(H^\infty)} + \varepsilon - \|f\|_{L^\infty(H^\infty)} \quad (3.60)$$

$$= \|f_N\|_{L^\infty(H^\infty)} + V(f_N) - \|f\|_{L^\infty(H^\infty)} \quad (3.61)$$

$$\leq \varepsilon + V(f_N), \quad (3.62)$$

which is finite. So f has bounded variation. ■

Now, we will show that functions in $BV(\mathbb{R}, H^\infty(B(0, r)))$ have many of the same properties as real-valued functions of bounded variation.

Remark. We will use the standard notation for left- and right-sided limits for functions:

$$f(\tau^+) := \lim_{t \rightarrow \tau^+} f(t), \quad (3.63)$$

and

$$f(\tau^-) := \lim_{t \rightarrow \tau^-} f(t). \quad (3.64)$$

We will use the notation

$$D_f = \{t : f \text{ is discontinuous at } t\} \quad (3.65)$$

to represent the set of discontinuities of a function f , where any domain restrictions are understood in context.

Proposition 3.3.6. *If $f \in BV(\mathbb{R}, H^\infty(B(0, r)))$, then $f(t^-)$ and $f(t^+)$ exist for all $t \in \mathbb{R}$.*

Proof. Let $t \in \mathbb{R}$. By way of contradiction, assume $f(t^-)$ does not exist. Then f is discontinuous at t . Then the Cauchy condition fails to hold. So, there exists an $\varepsilon > 0$ such that for all $\delta > 0$, there exist points $\alpha, \beta \in \mathbb{R}$ such that

$$\alpha, \beta \in (t - \delta, t) \quad (3.66)$$

and

$$\|f(\alpha) - f(\beta)\|_{H^\infty} > \varepsilon. \quad (3.67)$$

Define $\delta_1 := 1$. Then there exist points $\alpha_1, \beta_1 \in (t - \delta_1, t)$ such that $\alpha_1 < \beta_1$ and

$$\|f(\alpha_1) - f(\beta_1)\|_{H^\infty} > \varepsilon. \quad (3.68)$$

Recursively define

$$\delta_n := \frac{t - \beta_{n-1}}{2} \quad (3.69)$$

for integers $n \geq 2$, and find corresponding points $\alpha_n, \beta_n \in (\alpha - \delta_n, \alpha)$ such that $\alpha_n < \beta_n$ and

$$\|f(\alpha_n) - f(\beta_n)\|_{H^\infty} > \varepsilon. \quad (3.70)$$

Let $N := \left\lceil \frac{V(f)}{\varepsilon} \right\rceil$. Then, we have

$$V(f) \geq \sum_{k=1}^N \|f(s_k) - f(t_k)\|_{H^\infty} \quad (3.71)$$

$$> N\varepsilon \quad (3.72)$$

$$> V(f), \quad (3.73)$$

which is a contradiction. So, $f(t^-)$ exists. Similarly, we can show $f(t^+)$ exists. \blacksquare

Now, we will show that functions in $BV(\mathbb{R}, H^\infty(B(0, r)))$ can only have countably many discontinuities, just like real-valued functions.

Proposition 3.3.7. *If $f \in BV(\mathbb{R}, H^\infty(B(0, r)))$, then the set D_f is countable, and*

$$\sum_{t \in D_f} \|f(t^+) - f(t^-)\|_{H^\infty} \quad (3.74)$$

is finite.

Proof. Define

$$D_n := \left\{ t \in D_f : \|f(t^+) - f(t^-)\|_{H^\infty} > \frac{1}{n} \right\}. \quad (3.75)$$

First, we will show that $|D_n|$ is finite for each $n \in \mathbb{N}$. Let $t \in D_n$ and $\varepsilon > 0$. Since $f(t^+)$ exists, we can find a $t^* > t$ close enough such that $\|f(t^*) - f(t^+)\|_{H^\infty} < \varepsilon$. Similarly, we

can find a $t_* < t$ close enough such that $\|f(t^-) - f(t_*)\|_{H^\infty} < \varepsilon$. Then, we have

$$\begin{aligned} \|f(t^*) - f(t_*)\|_{H^\infty} &\geq \|f(t^+) - f(t^-)\|_{H^\infty} \\ &\quad - \|f(t^*) - f(t^+)\|_{H^\infty} - \|f(t^-) - f(t_*)\|_{H^\infty} \end{aligned} \quad (3.76)$$

$$> \frac{1}{n} - 2\varepsilon. \quad (3.77)$$

Then,

$$V(f) \geq \sum_{t \in D_n} \|f(t^*) - f(t_*)\|_{H^\infty} \quad (3.78)$$

$$\geq |D_n| \left(\frac{1}{n} - 2\varepsilon \right). \quad (3.79)$$

So, $|D_n|$ must be finite for each $n \in \mathbb{N}$. Finally,

$$D_f = \bigcup_{n=1}^{\infty} D_n, \quad (3.80)$$

which is the countable union of finite sets. So, D_f is countable.

To show

$$\sum_{t \in D_f} \|f(t^+) - f(t^-)\|_{H^\infty} \quad (3.81)$$

is finite, let $\varepsilon > 0$ and write $D_f = \{t_n : n \in \mathbb{N}\}$, and for each $t_n \in D_f$, we can find $(t_n)^* > t_n$ and $(t_n)_* < t_n$ such that

$$\|f(t_n^+) - f(t_n^-)\|_{H^\infty} \leq \frac{\varepsilon}{n^2} + \|f((t_n)^*) - f((t_n)_*)\|_{H^\infty}. \quad (3.82)$$

So,

$$\sum_{t \in D_f} \|f(t^+) - f(t^-)\|_{H^\infty} \leq \sum_{t_n \in D_f} \frac{\varepsilon}{n^2} + \|f((t_n)^*) - f((t_n)_*)\|_{H^\infty} \quad (3.83)$$

$$\leq V(f) + \varepsilon \sum_{n=1}^{\infty} \frac{1}{n^2}. \quad (3.84)$$

Since ε was arbitrary, we can conclude

$$\sum_{t \in D_f} \|f(t^+) - f(t^-)\|_{H^\infty} \leq V(f), \quad (3.85)$$

which is finite. ■

3.3.2 Integration

We will define our notion of integration for functions $f : \mathbb{R} \rightarrow H^\infty(B(0, r))$. Since $H^\infty(B(0, r))$ is a Banach space, we could use the Bochner integral to define integration, but it is convenient for us to rigorously define integration in a traditional Riemann-Stieltjes fashion.

Definition 3.3.4. A function $G : \mathbb{R} \rightarrow \mathbb{R}$ is a *probability distribution* if it is non-decreasing, right-continuous, $\lim_{t \rightarrow -\infty} G(t) = 0$, and $\lim_{t \rightarrow \infty} G(t) = 1$.

Note that all probability distributions have only jump-type discontinuities and

$$\sum_{t \in D_G} |G(t) - G(t^-)| \quad (3.86)$$

is finite, where D_G is the set of all discontinuities of a probability distribution G ([2] page 101).

Definition 3.3.5. Let $H : \mathbb{R} \rightarrow \{0, 1\}$ be the *Heaviside step function* defined as

$$H(t) := \begin{cases} 0 & t < 0 \\ 1 & t \geq 0 \end{cases}. \quad (3.87)$$

Definition 3.3.6. Let $G : \mathbb{R} \rightarrow \mathbb{R}$ be a probability distribution. Define $G_d : \mathbb{R} \rightarrow \mathbb{R}$ to be

$$G_d(t) := \sum_{\tau \in D_G} (G(\tau) - G(\tau^-))H(t - \tau), \quad (3.88)$$

where D_G is the set of all discontinuities of G , and $G_c : \mathbb{R} \rightarrow \mathbb{R}$ to be

$$G_c := G - G_d. \quad (3.89)$$

Remark. For a probability distribution G , we call G_d its “discontinuous part” and G_c its “continuous part.” It is clear that G_c is continuous.

Definition 3.3.7. Let $f : \mathbb{R} \rightarrow H^\infty(B(0, r))$, $G : \mathbb{R} \rightarrow \mathbb{R}$ be a probability distribution, and $I = [a, b]$ be an interval. Let D_G be the set of all discontinuities of G on I . We say that the integral

$$\int_a^b f(\tau) dG(\tau) \quad (3.90)$$

exists if

$$\int_a^b f(\tau) dG_c(\tau) \quad (3.91)$$

exists and

$$\int_a^b f(\tau) dG_d(\tau) := \sum_{t \in D_G} f(t)(G_d(t) - G_d(t^-)) \quad (3.92)$$

is convergent, where (3.91) exists if there exists an $L \in H^\infty(B(0, r))$ such that for all $\varepsilon > 0$,

there exists a partition $S_\varepsilon \in \mathcal{P}_I$, notated as $a = t_0 \leq t_1 \leq \dots \leq t_M = b$, such that

$$\left\| L - \sum_{k=1}^M f(s_k) (G_c(t_k) - G_c(t_{k-1})) \right\|_{H^\infty} < \varepsilon \quad (3.93)$$

for any $s_k \in [t_{k-1}, t_k]$ and any refinement of S_ε . If the integral exists, we say the value of the integral in (3.90) is equal to the sum of L and (3.92).

Remark. If (3.93) holds for a partition $a = t_0 \leq t_1 \leq \dots \leq t_M = b$ and any refinement, then for any $r_k, s_k \in [t_{k-1}, t_k]$, we have

$$\left\| \sum_{k=1}^M (f(r_k) - f(s_k)) (G_c(t_k) - G_c(t_{k-1})) \right\|_{H^\infty} < \varepsilon. \quad (3.94)$$

Since our notion of integration is analogous to the usual Riemann-Stieltjes integral, many traditional properties of integration hold.

Theorem 3.3.8. *Let G be a probability distribution. If $f \in BV(\mathbb{R}, H^\infty(B(0, r)))$, then f is integrable with respect to G on any interval $I = [a, b]$.*

Proof. Let $\varepsilon > 0$. Since G_c is continuous, there exists a partition $S \in \mathcal{P}_I$, notated as $a = t_0 \leq t_1 \leq \dots \leq t_M = b$, such that $|G_c(t_k) - G_c(t_{k-1})| < \varepsilon$ for each subinterval $[t_{k-1}, t_k]$ of S . Then

$$\left\| \sum_{k=1}^M (f(r_k) - f(s_k)) (G_c(t_k) - G_c(t_{k-1})) \right\|_{H^\infty} \leq \varepsilon \sum_{k=1}^M \|f(r_k) - f(s_k)\|_{H^\infty} \quad (3.95)$$

$$\leq \varepsilon V(f) \quad (3.96)$$

for any $r_k, s_k \in [t_{k-1}, t_k]$. Therefore,

$$\int_a^b f(\tau) dG_c(\tau) \quad (3.97)$$

exists. Now,

$$\left\| \sum_{t \in D_G} f(t)(G_d(t) - G_d(t^-)) \right\|_{H^\infty} \leq \|f\|_{L^\infty(H^\infty)} \sum_{t \in D_G} G_d(t) - G_d(t^-), \quad (3.98)$$

which is finite since G has bounded variation. Therefore,

$$\int_a^b f(\tau) dG_d(\tau) \quad (3.99)$$

exists, and so f is integrable with respect to G on I . ■

Corollary 3.3.9. *Let G be a probability distribution. If $f \in BV(\mathbb{R}, H^\infty(B(0, r)))$, then f is integrable with respect to G on \mathbb{R} .*

Proof. In the proof of Theorem 3.3.8, all the estimates hold for any partition on \mathbb{R} since both f and G have bounded variation on \mathbb{R} . ■

3.3.3 Construction of the map T

We will define a subspace of $BV(\mathbb{R}, H^\infty(B(0, r)))$ where all functions map to a generating function in H_r with constant coefficient 0, since this our generating function that represents cell population must also have constant coefficient 0.

Definition 3.3.8. Define $BV_{r,m}$ to be the subspace of $BV(\mathbb{R}, H^\infty(B(0, r)))$ such that for all $f \in BV_{r,m}$,

1. $f(t) \in H_r$ for all $t \in \mathbb{R}$,
2. $c_0(f(t)) = 0$ for all $t \in \mathbb{R}$, and
3. $V(f) \leq m$.

$BV_{r,m}$ represents our space of time-dependent generating functions.

Remark. We only restrict our time-dependent generating functions to have constant coefficient 0 so that all of our functions are nicely bounded by r , not because it is impossible to have zero cells in our model. In fact, if when we define our map in the next section, if $f(0)$ has constant coefficient 0, $f(t)$ necessarily has constant coefficient 0 for $t > 0$.

Since $BV_{r,m} \subset BV(\mathbb{R}, H^\infty(B(0, r)))$, all functions in $BV_{r,m}$ are integrable with respect to any probability distribution on \mathbb{R} , or any interval on \mathbb{R} . In addition, it's important that $BV_{r,m}$ be complete so that we can use the Banach Fixed-Point Theorem. The proof is very similar to the proof in Theorem 3.3.5.

Theorem 3.3.10. *$BV_{r,m}$ is a complete metric space with respect to the norm $\|\cdot\|_{BV(H^\infty)}$.*

Proof. It is sufficient to show $BV_{r,m}$ is closed since it is contained in the Banach space $BV(\mathbb{R}, H^\infty(B(0, r)))$.

Let $\{f_n\}$ be a convergent sequence in $BV_{r,m}$ such that $f_n \rightarrow f$. We must show $f \in BV_{r,m}$. To do so, we must show $f(t) \in H_r$ for all $t \in \mathbb{R}$, $c_0(f(t)) = 0$ for all $t \in \mathbb{R}$, and $V(f) \leq m$. First, for all $t \in \mathbb{R}$, $\{f_n(t)\}$ is convergent in H_r with limit $f(t) \in H_r$ since H_r is complete. Moreover, from (3.26), we have $c_0(f_n(t)) \rightarrow c_0(f(t))$ for all t , and so $c_0(f(t)) = 0$. To show $V(f) \leq m$, let $\varepsilon > 0$. Then there exists an $N \in \mathbb{N}$ large enough such that

$$\|f_N - f\|_{BV(H^\infty)} < \varepsilon, \quad (3.100)$$

and consequently

$$\|f_N - f\|_{L^\infty(H^\infty)} < \varepsilon. \quad (3.101)$$

So,

$$V(f) = \|f\|_{BV(H^\infty)} - \|f\|_{L^\infty(H^\infty)} \quad (3.102)$$

$$\leq \|f_N\|_{BV(H^\infty)} + \varepsilon - \|f\|_{L^\infty(H^\infty)} \quad (3.103)$$

$$= \|f_N\|_{L^\infty(H^\infty)} + V(f_N) - \|f\|_{L^\infty(H^\infty)} \quad (3.104)$$

$$\leq \varepsilon + V(f_N) \quad (3.105)$$

$$\leq \varepsilon + m. \quad (3.106)$$

Since ε was arbitrary, we conclude that

$$V(f) \leq m. \quad (3.107)$$

■

At this point, we have constructed a complete space of generating functions H_r and a complete space of time-dependent generating functions $BV_{r,m}$. Now we are ready to construct a map from $BV_{r,m}$ to itself that represents the right-hand side of (3.17). Like before, let P be the life-span distribution of a cell. So, $P(0) = 0$.

Definition 3.3.9. Define $T : BV_{r,m} \rightarrow BV(\mathbb{R}, H^\infty(B(0, r)))$ to be a map such that for $f \in BV_{r,m}$,

$$(Tf)(t) := (\cdot)(1 - P(t)) + \int_0^t f(t - \tau)^2 dP(\tau) \quad (3.108)$$

for all $t \in \mathbb{R}$.

T is a well-defined map, since if $f, g \in BV_{r,m}$ such that $f = g$, we immediately have $(Tf)(t) - (Tg)(t) = 0$ for all $t \in \mathbb{R}$. We must show that $T(BV_{r,m})$ is contained in $BV_{r,m}$ and that T is also a contraction map. First, we will prove a necessary lemma.

Lemma 3.3.11. *Let $0 < r < 1$ and $f, g \in BV_{r,m}$. Then $V(fg) \leq 2rm$ and $f(t)g(t) \in H_r$ for all $t \in \mathbb{R}$.*

Proof. Let $S \in \mathcal{P}_{\mathbb{R}}$ be any partition $-\infty < t_0 \leq t_1 \leq \dots \leq t_M < \infty$. Then

$$\sum_{k=1}^M \|f(t_k)g(t_k) - f(t_{k-1})g(t_{k-1})\|_{H^\infty} \quad (3.109)$$

$$= \sum_{k=1}^M \|f(t_k)g(t_k) - f(t_{k-1})g(t_k) + f(t_{k-1})g(t_k) - f(t_{k-1})g(t_{k-1})\|_{H^\infty} \quad (3.110)$$

$$\begin{aligned} &\leq \|g\|_{L^\infty(H^\infty)} \sum_{k=1}^M \|f(t_k) - f(t_{k-1})\|_{H^\infty} \\ &\quad + \|f\|_{L^\infty(H^\infty)} \sum_{k=1}^M \|g(t_k) - g(t_{k-1})\|_{H^\infty} \end{aligned} \quad (3.111)$$

$$< r(V(f) + V(g)) \quad (3.112)$$

$$\leq 2rm. \quad (3.113)$$

Since this is true for any partition $S \in \mathcal{P}_{\mathbb{R}}$, we have

$$V(fg) \leq 2rm. \quad (3.114)$$

Now, let $t \in \mathbb{R}$. For simplicity, we will let $h := fg$ and denote $h_t := h(t)$, $f_t := f(t)$, and $g_t := g_t$. It's immediate that $h_t \in H^\infty(B(0, r))$ since $f_t, g_t \in H^\infty(B(0, r))$, and $H^\infty(B(0, r))$ is closed under multiplication. So it is sufficient to show $c_k(h_t) \geq 0$ for each k and $\sum_{k=0}^{\infty} c_k(h_t) =$

1. Using Cauchy products, we have for any $z \in B(0, r)$,

$$h_t(z) = f_t(z)g_t(z) \quad (3.115)$$

$$= \left(\sum_{k=0}^{\infty} c_k(f_t)z^k \right) \left(\sum_{k=0}^{\infty} c_k(g_t)z^k \right) \quad (3.116)$$

$$= \sum_{k=0}^{\infty} \sum_{j=0}^k c_j(f_t)c_{k-j}(g_t)z^k \quad (3.117)$$

So,

$$c_k(h_t) = \sum_{j=0}^i c_j(f_t)c_{k-j}(g_t) \geq 0 \quad (3.118)$$

for each k , since $c_k(f_t) \geq 0$ and $c_k(g_t) \geq 0$ for each k . Finally, using Cauchy products again,

$$\sum_{k=0}^{\infty} c_k(h_t) = \sum_{k=0}^{\infty} \sum_{j=0}^i c_j(f_t)c_{k-j}(g_t) \quad (3.119)$$

$$= \left(\sum_{k=0}^{\infty} c_k(f_t) \right) \left(\sum_{k=0}^{\infty} c_k(g_t) \right) \quad (3.120)$$

$$= 1. \quad (3.121)$$

Therefore, $h_t = f(t)g(t) \in H_r$ for all $t \in \mathbb{R}$. ■

Corollary 3.3.12. *If $0 < r \leq \frac{1}{2}$ and $g \in BV_{r,m}$, then $g^2 \in BV_{r,m}$, and thus integrable with respect to P on \mathbb{R} or any interval on \mathbb{R} .*

Proof. By Proposition 3.3.11, $V(g^2) \leq 2rm \leq m$, and so $g^2 \in BV_{r,m}$. Therefore, g^2 is integrable with respect to P on \mathbb{R} or any interval on \mathbb{R} by Proposition 3.3.8 and Corollary 3.3.9, respectively. ■

Now, we will show that T maps $BV_{r,m}$ to $BV_{r,m}$.

Theorem 3.3.13. *Let $f \in BV_{r,m}$. If $0 < r \leq \frac{m}{2(1+m)}$, then $Tf \in BV_{r,m}$.*

Proof. We will show that $V(Tf) \leq m$, $(Tf)(t) \in H_r$ for all $t \in \mathbb{R}$, and $c_0((Tf)(t)) = 0$ for all $t \in \mathbb{R}$.

Let $S \in \mathcal{P}_{\mathbb{R}}$ be any partition $-\infty < t_0 \leq t_1 \leq \dots \leq t_M < \infty$. Then,

$$\|(Tf)(t_k) - (Tf)(t_{k-1})\|_{H^\infty} \quad (3.122)$$

$$= \left\| \left(\int_0^{t_k} f(t_k - \tau)^2 dP(\tau) - \int_0^{t_{k-1}} f(t_{k-1} - \tau)^2 dP(\tau) \right) \right\|_{H^\infty} \quad (3.123)$$

$$< r|P(t_{k-1}) - P(t_k)| + \left\| \int_0^{t_{k-1}} f(t_k - \tau)^2 - f(t_{k-1} - \tau)^2 dP(\tau) + \int_{t_{k-1}}^{t_k} f(t_k - \tau)^2 dP(\tau) \right\|_{H^\infty} \quad (3.124)$$

$$< 2r|P(t_k) - P(t_{k-1})| + \left\| \int_0^{t_{k-1}} f(t_k - \tau)^2 - f(t_{k-1} - \tau)^2 dP(\tau) \right\|_{H^\infty} \quad (3.125)$$

$$< 2r|P(t_k) - P(t_{k-1})| + 2r \int_0^\infty \|f(t_k - \tau) - f(t_{k-1} - \tau)\|_{H^\infty} dP(\tau). \quad (3.126)$$

Taking sums, we have

$$\sum_{k=1}^M \|(Tf)(t_k) - (Tf)(t_{k-1})\|_{H^\infty} \quad (3.127)$$

$$< \sum_{k=1}^M 2r|P(t_k) - P(t_{k-1})| + 2r \int_0^\infty \sum_{k=1}^M \|f(t_k - \tau) - f(t_{k-1} - \tau)\|_{H^\infty} dP(\tau) \quad (3.128)$$

$$\leq 2r + 2rV(f) \quad (3.129)$$

$$\leq m. \quad (3.130)$$

Since this is true for any partition, we have

$$V(Tf) \leq m. \quad (3.131)$$

Now, let $t \in \mathbb{R}$ and $I = [0, t]$. We will show $(Tf)(t) \in H_r$ and $c_0((Tf)(t)) = 0$. Note

that f^2 is integrable with respect to P on I by Corollary 3.3.12. So, let $\varepsilon > 0$ and $S_\varepsilon \in \mathcal{P}_I$ be a partition $0 = \tau_0 \leq \tau_1 \leq \dots \leq \tau_M = t$ such that

$$\left\| \int_0^t f(t - \tau)^2 dP(\tau) - F_\varepsilon(t) \right\|_{H^\infty} < \varepsilon, \quad (3.132)$$

where

$$F_\varepsilon(t) := \sum_{k=1}^M f(t - s_k)^2 (P_c(\tau_k) - P_c(\tau_{k-1})) + \sum_{s \in D_P} f(s)^2 (P_d(s) - P_d(s^-)) \quad (3.133)$$

and $s_k \in [\tau_{k-1}, \tau_k]$. Now, define

$$G_\varepsilon(t) := (\cdot)(1 - P(t)) + F_\varepsilon(t). \quad (3.134)$$

It is clear that

$$G_\varepsilon(t) \rightarrow (Tf)(t) \quad (3.135)$$

as $\varepsilon \rightarrow 0^+$. We will show $G_\varepsilon(t) \in H_r$ and $c_0(G_\varepsilon(t)) = 0$ for all $\varepsilon > 0$, and since H_r is complete, its limit $(Tf)(t)$ must also be in H_r with $c_0((Tf)(t)) = 0$. Since it is clear that $G_\varepsilon(t) \in H^\infty(B(0, r))$, it is sufficient to show $c_k(G_\varepsilon(t)) \geq 0$ for each $k \geq 1$, $c_0(G_\varepsilon(t)) = 0$, and $\sum_{k=0}^{\infty} c_k(G_\varepsilon(t)) = 1$.

Since $f \in BV_{r,m}$, by Lemma 3.3.11, we have $f(s)^2 \in H_r$ for all $s \in \mathbb{R}$, and so $F_\varepsilon(t)$ must have non-negative coefficients in its power series representation since it is the sum of functions in H_r multiplied by non-negative numbers. Finally, $G_\varepsilon(t)$ must have non-negative coefficients since $1 - P(t) \geq 0$. Moreover, $c_0(G_\varepsilon(t)) = 0$ for the same reasoning.

Now, we have

$$\begin{aligned} \sum_{k=0}^{\infty} c_k(F_\varepsilon(t)) &= \sum_{k=1}^M \sum_{k=0}^{\infty} c_k(f(t - \tau_k)^2)(P_c(\tau_k) - P_c(\tau_{k-1})) \\ &\quad + \sum_{s \in D_P} \sum_{k=0}^{\infty} c_k(f(s)^2)(P_d(s) - P_d(s^-)) \end{aligned} \quad (3.136)$$

$$= P_c(t) + P_d(t) \quad (3.137)$$

$$= P(t), \quad (3.138)$$

where (3.137) comes from the fact $\sum_{k=0}^{\infty} c_k(f(s)^2) = 1$ for all $s \in \mathbb{R}$ since $f \in BV_{r,m}$. So,

$$\sum_{k=0}^{\infty} c_k(G_\varepsilon(t)) = 1 - P(t) + P(t) \quad (3.139)$$

$$= 1. \quad (3.140)$$

■

3.3.4 Unique fixed-point of T

Theorem 3.3.14 (Banach Fixed-Point Theorem). *Suppose X is a complete metric space with norm $\|\cdot\|$ and*

$$T : X \rightarrow X \quad (3.141)$$

is a non-linear map such that there exists a constant $0 \leq \gamma < 1$ where

$$\|T(x) - T(y)\| \leq c\|x - y\| \quad (3.142)$$

for all $x, y \in X$. Then T has a unique fixed-point.

In order to use the Banach Fixed-Point Theorem, we need to show that our map T is a contraction mapping. To do this, we will prove two lemmas that will help organize our

proof.

Lemma 3.3.15. *Let $f, g \in BV_{r,m}$. If $0 < r < 1$, then*

$$\|Tf - Tg\|_{L^\infty(H^\infty)} \leq 2r\|f - g\|_{L^\infty(H^\infty)}. \quad (3.143)$$

Proof. Let $t \in \mathbb{R}$. Then,

$$\|(Tf)(t) - (Tg)(t)\|_{H^\infty} \quad (3.144)$$

$$= \left\| \int_0^t f(t-\tau)^2 - g(t-\tau)^2 dP(\tau) \right\|_{H^\infty} \quad (3.145)$$

$$\leq \int_0^t \|f(t-\tau) - g(t-\tau)\|_{H^\infty} \|f(t-\tau) + g(t-\tau)\|_{H^\infty} dP(\tau) \quad (3.146)$$

$$\leq \|f + g\|_{L^\infty(H^\infty)} \|f - g\|_{L^\infty(H^\infty)} P(t) \quad (3.147)$$

$$< 2r\|f - g\|_{L^\infty(H^\infty)}. \quad (3.148)$$

Since this is true for any $t \in \mathbb{R}$, we have

$$\|Tf - Tg\|_{L^\infty(H^\infty)} \leq 2r\|f - g\|_{L^\infty(H^\infty)}. \quad (3.149)$$

■

Lemma 3.3.16. *Let $f, g \in BV_{r,m}$. If $0 < r < 1$, then*

$$V(Tf - Tg) \leq 2rV(f - g) + (2m + 2r)\|f - g\|_{L^\infty(H^\infty)}. \quad (3.150)$$

Proof. Let $s, t \in \mathbb{R}$ such that $s \leq t$. Then,

$$\|(Tf - Tg)(t) - (Tf - Tg)(s)\|_{H^\infty} \quad (3.151)$$

$$= \left\| \int_0^t (f^2 - g^2)(t - \tau) dP(\tau) - \int_0^s (f^2 - g^2)(s - \tau) dP(\tau) \right\|_{H^\infty} \quad (3.152)$$

$$= \left\| \int_0^s (f^2 - g^2)(t - \tau) - (f^2 - g^2)(s - \tau) dP(\tau) + \int_s^t (f^2 - g^2)(t - \tau) dP(\tau) \right\|_{H^\infty} \quad (3.153)$$

$$= \left\| \int_0^s (f + g)(t - \tau)((f - g)(t - \tau) - (f - g)(s - \tau)) dP(\tau) + \int_0^s (f - g)(s - \tau)((f + g)(t - \tau) - (f + g)(s - \tau)) dP(\tau) + \int_s^t (f + g)(t - \tau)(f - g)(t - \tau) dP(\tau) \right\|_{H^\infty} \quad (3.154)$$

$$\begin{aligned} &< 2r \int_0^\infty \|(f - g)(t - \tau) - (f - g)(s - \tau)\|_{H^\infty} dP(\tau) \\ &+ \|f - g\|_{L^\infty(H^\infty)} \int_0^\infty \|(f + g)(t - \tau) - (f + g)(s - \tau)\|_{H^\infty} dP(\tau) \\ &+ 2r\|f - g\|_{L^\infty(H^\infty)}(P(t) - P(s)). \end{aligned} \quad (3.155)$$

Now, let $S \in \mathcal{P}_\mathbb{R}$ be a partition $\infty < t_0 \leq t_1 \leq \dots \leq t_M < \infty$. Then using (3.155) and taking sums, we have

$$\sum_{k=1}^M \|(Tf - Tg)(t_k) - (Tf - Tg)(t_{k-1})\|_{H^\infty} \quad (3.156)$$

$$< 2rV(f - g) + \|f - g\|_{L^\infty(H^\infty)}V(f + g) + 2r\|f - g\|_{L^\infty(H^\infty)} \quad (3.157)$$

$$\leq 2rV(f - g) + (2m + 2r)\|f - g\|_{L^\infty(H^\infty)}, \quad (3.158)$$

since $V(f + g) \leq V(f) + V(g) \leq 2m$. Since this is true for any partition, we conclude

$$V(Tf - Tg) \leq 2rV(f - g) + (2m + 2r)\|f - g\|_{L^\infty(H^\infty)}. \quad (3.159)$$

■

Proposition 3.3.17. *If $0 < m < \frac{1}{2}$ and $0 < r < \frac{1-2m}{4}$, then T is a contraction mapping.*

Proof. We need to show there exists a $\gamma \in [0, 1)$ such that

$$\|Tf - Tg\|_{BV(H^\infty)} \leq \gamma \|f - g\|_{BV(H^\infty)} \quad (3.160)$$

for all $f, g \in BV_{r,m}$. So, let $f, g \in BV_{r,m}$. From Lemmas 3.3.15 and 3.3.16, we have

$$\|Tf - Tg\|_{BV(H^\infty)} = \|Tf - Tg\|_{L^\infty(H^\infty)} + V(Tf - Tg) \quad (3.161)$$

$$\leq (2m + 4r) \|f - g\|_{L^\infty(H^\infty)} + 2rV(f - g) \quad (3.162)$$

$$\leq (2m + 4r) \left(\|f - g\|_{L^\infty(H^\infty)} + V(f - g) \right) \quad (3.163)$$

$$= (2m + 4r) \|f - g\|_{BV(H^\infty)}. \quad (3.164)$$

So, for $0 < r < \frac{1-2m}{4}$, let $\gamma = 2m + 4r$, and T is a contraction map. ■

Theorem 3.3.18. *If $0 < m < \frac{1}{2}$ and $0 < r < \min\left(\frac{1-2m}{4}, \frac{m}{2(1+m)}\right)$, then T has a unique fixed point.*

Proof. From Theorem 3.3.13, we know $T(BV_{r,m}) \subset BV_{r,m}$ if $0 < r \leq \frac{m}{2(1+m)}$. From Theorem 3.3.10, we know $BV_{r,m}$ is a complete metric space. From Proposition 3.3.17, we know T is a contraction mapping if $0 < r < \frac{1-2m}{4}$. So, by the Banach Fixed-Point Proposition 3.3.14, there exists a unique function $f \in BV_{r,m}$ such that $Tf = f$. That is, for all $t \in \mathbb{R}$, there exists unique time-dependent generating function such that

$$f(t) = (\cdot)(1 - P(t)) + \int_0^t f(t - \tau)^2 dP(\tau). \quad (3.165)$$

■

So, the integral equation we constructed in (3.17) for our generating function that represents cell population size at time t has a unique solution.

Remark. Since analytic functions are uniquely determined, as long as $r > 0$, we can extend our generating function solution f to converge on $B(0, 1)$.

3.4 Series solution to the generating function equation

We express our generating function $f(t, x)$ as a series

$$f(t, x) = \sum_{k=0}^{\infty} c_k(t)x^k, \quad (3.166)$$

which is necessarily convergent for all $t \geq 0$ when $x \in B(0, 1)$. If $f(t, x)$ satisfies our integral equation (3.17), then we must have

$$\sum_{k=0}^{\infty} c_k(t)x^k = x(1 - P(t)) + \int_0^t \left(\sum_{k=0}^{\infty} c_k(t - \tau)x^k \right)^2 dP(\tau) \quad (3.167)$$

$$= x(1 - P(t)) + \int_0^t \sum_{k=0}^{\infty} \sum_{j=0}^i c_j(t - \tau)c_{k-j}(t - \tau)x^k dP(\tau) \quad (3.168)$$

$$= x(1 - P(t)) + \sum_{k=0}^{\infty} \int_0^t \sum_{j=0}^i c_j(t - \tau)c_{k-j}(t - \tau) dP(\tau)x^k. \quad (3.169)$$

Matching up coefficients and noting $c_0(t) = 0$ for all $t \geq 0$, we get

$$c_k(t) = \begin{cases} 1 - P(t) & k = 1 \\ \int_0^t \sum_{j=1}^{k-1} c_j(t - \tau)c_{k-j}(t - \tau) dP(\tau) & k \geq 2 \end{cases}. \quad (3.170)$$

Given a life-span distribution P , one can compute the coefficients of $f(t, x)$ recursively. In section 6.3.1, we'll do this to determine the distribution of the mutant cell population when P is a multi-phase distribution.

3.5 Examples

In this section, $f(t, x)$ will always refer to the generating function of Z_t with life-span distribution P of random variable \mathcal{T} , and f must satisfy (3.17).

3.5.1 Synchronous cell division

J. B. S. Haldane, when constructing a distribution for the mutant population when the cell population is large, assumed that cell division was symmetric and synchronous, meaning all cells divided at the same time. We can illustrate that (3.17) will produce the typical generating function that represents synchronous cell growth. Without loss of generality, we assume our life-span distribution P is

$$P(t) = \begin{cases} 0 & t < 1 \\ 1 & t \geq 1 \end{cases}. \quad (3.171)$$

Using the definition of our integral (3.3.7), our integral equation (3.17) becomes

$$f(t, x) = \begin{cases} x & [t] < 1 \\ f(t-1, x)^2 & [t] \geq 1 \end{cases}. \quad (3.172)$$

Solving this basic recurrence relation, we get the generating function

$$f(t, x) = x^{2^{[t]}} \quad (3.173)$$

for a cell that divides at every time increment, which matches simple, synchronous binary division. In section 6.3.1, we use this generating function to derive Haldane's generating function for the mutant cell population size.

3.5.2 Life-span is a lattice distribution

In Chapter 5, most of our theorems only hold for life-span distributions which are not lattice distributions (see Definition 5.1.2). In this example, we will construct the generating function where P is a lattice distribution.

Let $\delta > 0$ and define P to be

$$P(t) := \begin{cases} 0 & t \leq 0 \\ 1 - 2^{-n} & n\delta \leq t < (n+1)\delta, \quad n \in \mathbb{Z}_{\geq 0} \end{cases}. \quad (3.174)$$

Using the definition of our integral (3.3.7), our integral equation (3.17) becomes

$$f(t, x) = x(1 - P(t)) + \sum_{k=1}^{\lfloor t/\delta \rfloor} f(t - k\delta, x)^2 2^{-k}, \quad (3.175)$$

which can be rewritten as

$$g(n, x) = x2^{-n} + \sum_{k=1}^n g(n - k, x)^2 2^{-k} \quad (3.176)$$

since the generating function doesn't change except at multiples of δ .

3.5.3 Life-span is multi-phase

Suppose P has a “multi-phase” distribution with parameter n , which is a gamma distribution with parameters $\beta = 1$ and $\alpha = n$. Biologically, this means that a cell is more likely to divide around the n^{th} “stage” of its life. If $n = 1$, then a cell is most likely to divide closer to birth, and P would be an exponential distribution. However, when $n = 3$, for example, it would mean the cell takes time to mature before it can divide, which is more realistic biologically.

If P is a multi-phase distribution with parameter $n \in \mathbb{N}$, then

$$dP(y) = \frac{y^{n-1}e^{-y}}{(n-1)!} dy \quad (3.177)$$

Our integral equation (3.17) becomes

$$f(t, x) = x(1 - P(t)) + \int_0^t f(t-y, x)^2 \frac{y^{n-1}e^{-y}}{(n-1)!} dy \quad (3.178)$$

$$= x \int_t^\infty \frac{y^{n-1}e^{-y}}{(n-1)!} dy + \int_0^t f(y, x)^2 \frac{(t-y)^{n-1}e^{-(t-y)}}{(n-1)!} dy, \quad (3.179)$$

where we did a change of variables in the second integral of (3.179).

Theorem 3.5.1. *If P is a multi-phase distribution with parameter $n \in \mathbb{N}$, then the generating function $f(t, x)$ satisfies*

$$\begin{cases} \left(1 + \frac{\partial}{\partial t}\right)^n f = f^2 \\ f(0, x) = 0 \end{cases} . \quad (3.180)$$

Proof. Differentiating (3.179) with respect to t , we have

$$\begin{aligned} \frac{\partial f}{\partial t}(t, x) &= -x \frac{t^{n-1}e^{-t}}{(n-1)!} + \int_0^t f(y, x)^2 \frac{(t-y)^{n-2}e^{-(t-y)}}{(n-2)!} dy \\ &\quad - \int_0^t f(y, x)^2 \frac{(t-y)^{n-1}e^{-(t-y)}}{(n-1)!} dy. \end{aligned} \quad (3.181)$$

Solving for the last integral in (3.179) and substituting it into (3.181), we get

$$\begin{aligned} \frac{\partial f}{\partial t}(t, x) &= -x \frac{t^{n-1}e^{-t}}{(n-1)!} + \int_0^t f(y, x)^2 \frac{(t-y)^{n-2}e^{-(t-y)}}{(n-2)!} dy \\ &\quad + x \int_t^\infty \frac{y^{n-1}e^{-y}}{(n-1)!} dy - f(t, x). \end{aligned} \quad (3.182)$$

Differentiating again, we get

$$\begin{aligned} \frac{\partial^2 f}{\partial t^2}(t, x) &= -x \frac{t^{n-2} e^{-t}}{(n-2)!} + \int_0^t f(y, x)^2 \frac{(t-y)^{n-3} e^{-(t-y)}}{(n-3)!} dy \\ &\quad - \int_0^t f(y, x)^2 \frac{(t-y)^{n-2} e^{-(t-y)}}{(n-2)!} dy - \frac{\partial f}{\partial t}(t, x). \end{aligned} \quad (3.183)$$

Substituting the first integral in (3.182) into (3.183) in a similar fashion, we get

$$\begin{aligned} \frac{\partial^2 f}{\partial t^2}(t, x) &= -x \frac{t^{n-2} e^{-t}}{(n-2)!} - x \frac{t^{n-1} e^{-t}}{(n-1)!} + \int_0^t f(y, x)^2 \frac{(t-y)^{n-3} e^{-(t-y)}}{(n-3)!} dy \\ &\quad + x \int_t^\infty \frac{y^{n-1} e^{-y}}{(n-1)!} dy - 2 \frac{\partial f}{\partial t}(t, x) - f(t, x). \end{aligned} \quad (3.184)$$

Continuing this process of differentiating and substituting, we get

$$\frac{\partial^n f}{\partial t^n}(t, x) = -x \sum_{k=0}^{n-1} \frac{t^k e^{-t}}{k!} + x \int_t^\infty \frac{y^{n-1} e^{-y}}{(n-1)!} dy + f(t, x)^2 - \sum_{k=0}^{n-1} \binom{n}{k} \frac{\partial^k f}{\partial t^k}(t, x) \quad (3.185)$$

Now, the first term on the right-hand side of (3.185) cancels out with the integral once it is evaluated, and we get

$$\frac{\partial^n f}{\partial t^n}(t, x) = f(t, x)^2 - \sum_{k=0}^{n-1} \binom{n}{k} \frac{\partial^k f}{\partial t^k}(t, x), \quad (3.186)$$

which can be rewritten as

$$\left(1 + \frac{\partial}{\partial t}\right)^n f(t, x) = f(t, x)^2. \quad (3.187)$$

■

When $n = 1$, P is an exponential distribution with parameter 1, and the differential equation becomes

$$\begin{cases} \frac{\partial f}{\partial t} = f^2 - f \\ f(0, x) = x \end{cases}, \quad (3.188)$$

which can be solved to obtain the generating function

$$f(t, x) = \frac{xe^{-t}}{1 - x + xe^{-t}}. \quad (3.189)$$

Moreover, the expected cell population at time t is

$$\frac{\partial f}{\partial x}(t, 1) = e^t. \quad (3.190)$$

3.5.4 Alternative derivation when life-span is exponential

In this section, we derive the generating function when the life-span distribution is exponential without the machinery of functional analysis used in the previous sections. Instead, we only use properties of probability generating functions. Consider a branching process where, at each time, a single cell can divide into two with probability p or remain a single cell with probability $1 - p$. Then the probability generating function of the cell population at discrete time $t \in \mathbb{N}$ is given by

$$G(t, x) = g^t(x) \quad (t\text{-compositions}), \quad (3.191)$$

where

$$g(x) = (1 - p)x + px^2 \quad (3.192)$$

is the generating function of a single cell dividing in one time increment. Now, we will divide up our time increments into smaller intervals and divide the probability of a cell dividing in that interval as well.

Let

$$g_n(x) := \left(1 - \frac{p}{n}\right)x + \frac{p}{n}x^2 \quad (3.193)$$

and

$$f(t, x) := \lim_{n \rightarrow \infty} g_n^{nt}(x). \quad (3.194)$$

Then

$$\frac{\partial f}{\partial t}(t, x) = \lim_{h \rightarrow 0} \frac{f(t+h, x) - f(t, x)}{h} \quad (3.195)$$

$$= \lim_{h \rightarrow 0} \lim_{n \rightarrow \infty} \frac{g_n^{n(t+h)}(x) - g_n^{nt}(x)}{h}. \quad (3.196)$$

Letting $h = \frac{1}{n}$, we have

$$\frac{\partial f}{\partial t}(t, x) = \lim_{n \rightarrow \infty} n(g_n^{nt+1}(x) - g_n^{nt}(x)) \quad (3.197)$$

$$= \lim_{n \rightarrow \infty} n(g_n(g_n^{nt}(x)) - g_n^{nt}(x)) \quad (3.198)$$

$$= \lim_{n \rightarrow \infty} n(g(f(t, x)) - f(t, x)) \quad (3.199)$$

$$= \lim_{n \rightarrow \infty} n \left(\left(1 - \frac{p}{n}\right) f(t, x) + \frac{p}{n} (f(t, x))^2 - f(t, x) \right) \quad (3.200)$$

$$= -pf(t, x) + p(f(t, x))^2. \quad (3.201)$$

Now, solving the the differential equation using initial condition $f(0) = x$, we get

$$f(t, x) = \frac{xe^{-pt}}{xe^{-pt} + 1 - x}. \quad (3.202)$$

3.5.5 Incorporating death

Suppose now that upon cell division, a cell can divide into two cells or die. In one time increment, let $0 \leq \theta < 1$ be the probability of death, and let p be the probability it divides into two cells given it doesn't die. Then the probability generating function for the cell population at discrete time $t \in \mathbb{N}$ is

$$G(t, x) = g^t(x) \quad (t\text{-compositions}), \quad (3.203)$$

where

$$g(x) := \theta + (1-p)(1-\theta)x + p(1-\theta)x^2 \quad (3.204)$$

is the generating function of a single cell dividing.

Using a similar approach to the previous section, let

$$g_n(x) := \frac{\theta}{n} + \left(1 - \frac{p}{n}\right) \left(1 - \frac{\theta}{n}\right) x + \frac{p}{n} \left(1 - \frac{\theta}{n}\right) x^2 \quad (3.205)$$

and consider

$$f(t, x) := \lim_{n \rightarrow \infty} g_n^{nt}(x). \quad (3.206)$$

Then

$$\frac{\partial f}{\partial t}(t, x) = \lim_{h \rightarrow 0} \frac{f(t+h, x) - f(t, x)}{h} \quad (3.207)$$

$$= \lim_{h \rightarrow 0} \lim_{n \rightarrow \infty} \frac{g_n^{n(t+h)}(x) - g_n^{nt}(x)}{h}. \quad (3.208)$$

Letting $h = \frac{1}{n}$, we have

$$\frac{\partial f}{\partial t}(t, x) = \lim_{n \rightarrow \infty} n(g_n^{nt+1}(x) - g_n^{nt}(x)) \quad (3.209)$$

$$= \lim_{n \rightarrow \infty} n(g_n(g_n^{nt}(x)) - g_n^{nt}(x)) \quad (3.210)$$

$$= \lim_{n \rightarrow \infty} n(g(f(t, x)) - f(t, x)) \quad (3.211)$$

$$= \lim_{n \rightarrow \infty} n \left(\frac{\theta}{n} + \left(1 - \frac{p}{n}\right) \left(1 - \frac{\theta}{n}\right) f(t, x) + \frac{p}{n} \left(1 - \frac{\theta}{n}\right) (f(t, x))^2 - f(t, x) \right) \quad (3.212)$$

$$= \theta - \theta f(t, x) - p f(t, x) + p f(t, x)^2. \quad (3.213)$$

Now, solving the the partial differential equation

$$\frac{\partial f}{\partial t} = \theta - \theta f - pf + pf^2, \quad (3.214)$$

we have

$$f(t, x) = \frac{\theta e^{\theta C_x + pt} + e^{\theta t + p C_x}}{p e^{\theta C_x + pt} + e^{\theta t + p C_x}}, \quad (3.215)$$

where C_x is a function of x that can be found using the initial condition $f(0, x) = x$.

Chapter 4

Cell growth under asymmetric division

It is of great interest to biologists to model the growth of a cell under asymmetric division; that is, when it divides into two types: a mother cell and a daughter cell. The mother cell is a copy of the parent cell, while the daughter cell typically takes time to grow into a mother cell. Therefore, the life-span distribution for mother cells is different, and often their life-span is shorter than daughter cells.

In this chapter, we will construct time-dependent generating functions (4.9) for the mother and daughter cell population sizes when we start with exactly one mother cell and when we start with exactly one daughter cell. Just like with cell growth under symmetric division, our generating functions will be in the form of an integral equation, so we will proceed to show existence and uniqueness of solutions in section 4.3. We conclude the chapter with some examples of generating functions using different life-span distributions.

4.1 Preliminaries and assumptions

We will start by stating our assumptions about asymmetric cell division.

Assumption 4.1.1 (Asymmetric cell division). Cells have the following properties:

1. there are exactly two types of cells: mother cells and daughter cells;
2. all cells are independent of each other, mother cells are identical to other mother cells, and daughter cells are identical to other daughter cells;
3. cell life-span for mother cells and daughter cells are strictly positive, real-valued random variables \mathcal{T}_x and \mathcal{T}_y , respectively, with distributions P and Q , respectively;
4. at the end of a cell's life, both mother cells and daughter cells will divide into one mother cell and one daughter cell.

Let X_t and Y_t be random variables representing the mother and daughter cell populations at time $t \geq 0$, respectively. When we start with exactly one mother cell and no daughter cells, which is the main case of interest, we will have $X_0 = 1$ and $Y_0 = 0$. On the other hand, when we start with exactly one daughter cell and no mother cells, we will have $X_0 = 0$ and $Y_0 = 1$. Note that X_t and Y_t are *not* independent processes. We will let $Z_t := X_t + Y_t$ represent the total cell population at time $t \geq 0$, always assuming $X_0 = 1$ and $Y_0 = 0$. When we write Z'_t , we will always assume $X_0 = 0$ and $Y_0 = 1$. Just like in Chapter 3, our goal is to determine a distribution for Z_t at any time $t \geq 0$. We will again employ generating function methods.

4.2 Constructing the generating function

In order to derive the generating function for the cell population Z_t at any time $t \geq 0$, we will first construct a model in discrete-time, then divide our time increments infinitesimally small, and finally take limits to derive a continuous-time model. Instead of constructing a generating function for Z_t directly, we will construct a joint distribution generating function for X_t and Y_t and understand the sum of these two processes is the cell population Z_t .

4.2.1 In discrete-time

Suppose time is discrete and the life-span random variables for mother and daughter cells, \mathcal{T}_x and \mathcal{T}_y , only output positive integer values. For clarity, when we say a cell divides at time t , we mean the cell population has increased by two at time $t + 1$.

Define

$$f(t, x, y) := \mathbb{E} [x^{X_t} y^{Y_t} \mid X_0 = 1, Y_0 = 0] \quad (4.1)$$

and

$$g(t, x, y) := \mathbb{E} [x^{X_t} y^{Y_t} \mid X_0 = 0, Y_0 = 1] \quad (4.2)$$

to be the joint generating functions of X_t and Y_t , with different initial values. Let $\mathcal{T}_x^{(1)}$ and $\mathcal{T}_y^{(1)}$ be copies of \mathcal{T}_x and \mathcal{T}_y , respectively, that represent the time the first mother cell divides when we start with one mother cell, and the time first daughter cell divide when we start with one daughter cell. Suppose $\mathcal{T}_x^{(1)} = k$. When we start with exactly one mother cell and no daughter cells, it will produce one mother cell and one daughter cell, both independent of each other. The new mother cell will produce a cell population of $Z_{t-(k+1)}$ for $t > k$, while the daughter cell will produce a cell population of $Z'_{t-(k+1)}$ for $t > k$. So,

$$Z_t = \begin{cases} 1 & t \leq k \\ Z_{t-(k+1)}^{(1)} + Z'_{t-(k+1)} & t > k \end{cases}, \quad (4.3)$$

where $Z_t^{(1)}$ and Z'_t are copies of Z_t and Z'_t . Since the two new cells grow independently of each other, the joint generating function of X_t and Y_t when $\mathcal{T}_x^{(1)} = k$ is

$$f_k(t, x, y) = \begin{cases} x & t \leq k \\ f(t - (k + 1), x, y)g(t - (k + 1), x, y) & t > k \end{cases}. \quad (4.4)$$

Then, in a similar argument to that in Chapter 3, we can conclude

$$f(t, x, y) = x \Pr(\mathcal{T}_x^{(1)} > t) + \sum_{k=1}^t f(t - (k + 1), x, y) g(t - (k + 1), x, y) \Pr(\mathcal{T}_x^{(1)} = k). \quad (4.5)$$

Likewise, suppose $\mathcal{T}_y^{(1)} = j$. Then we can conclude in a similar fashion that

$$Z'_t = \begin{cases} 1 & t \leq j \\ Z_{t-(j+1)}^{(1)} + Z'_{t-(j+1)} & t > j \end{cases}, \quad (4.6)$$

where $Z_t^{(1)}$ and Z'_t are copies of Z_t and Z'_t . Then the joint generating function of X_t and Y_t when $\mathcal{T}_y^{(1)} = j$ is

$$g_j(t, x, y) = \begin{cases} y & t \leq j \\ g(t - (j + 1), x, y) g(t - (j + 1), x, y) & t > j \end{cases}. \quad (4.7)$$

Finally, we can conclude that

$$g(t, x, y) = y \Pr(\mathcal{T}_y^{(1)} > t) + \sum_{j=1}^t f(t - (j + 1), x, y) g(t - (j + 1), x, y) \Pr(\mathcal{T}_y^{(1)} = j). \quad (4.8)$$

4.2.2 In continuous-time

As noted previously, let P be the distribution function of \mathcal{T}_x and Q be the distribution function of \mathcal{T}_y . Then our discrete generating functions (4.5) and (4.8) will converge to

$$\begin{cases} f(t, x, y) = x(1 - P(t)) + \int_0^t f(t - \tau, x, y) g(t - \tau, x, y) dP(\tau) \\ g(t, x, y) = y(1 - Q(t)) + \int_0^t f(t - \tau, x, y) g(t - \tau, x, y) dQ(\tau) \end{cases} \quad (4.9)$$

as we make our discrete-time increments infinitesimally small, as seen in section 3.2.2.

4.3 Existence and uniqueness

Showing that there exists two unique generating functions f and g that satisfy (4.9) given any life-span distributions P for mother cells and Q for daughter cells will be completely analogous to section 3.3, where construction functions spaces and a map so we could use the Banach Fixed-Point Theorem to make our conclusion.

Since all the proofs are similar to section 3.3, propositions and theorems will be stated below, but the proofs will be omitted except when it is not completely analogous to the symmetric cell division case. With each proposition and theorem, the corresponding proposition and theorem in the symmetric cell division case is cited next to it for reference. In the proceeding sections, we will always assume $0 < r < 1$.

Let $H^\infty(B(0, r)^2)$ represent the space of all holomorphic functions of two complex variables bounded on $\partial B(0, r)^2$ with the usual norm

$$\|\cdot\|_{H^\infty} := \sup_{(z_1, z_2) \in B(0, r)^2} |(\cdot)(z_1, z_2)|. \quad (4.10)$$

Definition 4.3.1. Define the subspace H_r^2 of $H^\infty(B(0, r)^2)$ such that for each $g \in H_r^2$,

1. $c_{k,j}(g) \geq 0$ for integers $k, j \geq 0$ and
2. $\sum_{k=0}^{\infty} \sum_{j=0}^{\infty} c_{k,j}(g) = 1$,

where

$$c_{k,j}(g) = \frac{1}{k!j!} \frac{\partial^{k+j} g}{\partial x^k \partial y^j}(0, 0) \quad (4.11)$$

is the coefficient of $x^k y^j$ of g in its power series expansion centered at 0, where x and y are the function parameters. H_r^2 represents our space of joint (2 variables) generating functions, which is analogous to Definition 3.3.1.

Proposition 4.3.1 (Proposition 3.3.1). *If $g \in H_r^2$, then $\|g\|_{H^\infty} < g(0, 0) + r$.*

Theorem 4.3.2 (Theorem 3.3.2). H_r^2 is a complete metric space with respect to the norm $\|\cdot\|_{H^\infty}$.

Definition 4.3.2. We say a function $f : \mathbb{R} \rightarrow H^\infty(B(0, r)^2)$ has *bounded variation* on \mathbb{R} if

$$V(f) := \sup_{S \in \mathcal{P}_{\mathbb{R}}} \sum_{k=1}^M \|f(t_k) - f(t_{k-1})\|_{H^\infty} \quad (4.12)$$

is finite, where S is a partition $-\infty < t_0 \leq t_1 \leq \dots \leq t_M < \infty$. This is analogous to Definition 3.3.2.

We will denote the the supremum of a function \mathbb{R} to $H^\infty(B(0, r)^2)$ using the norm $\|\cdot\|_{L^\infty(H^\infty)}$.

Definition 4.3.3. Define $BV(\mathbb{R}, H^\infty(B(0, r)^2))$ to be the space of all functions $f : \mathbb{R} \rightarrow H^\infty(B(0, r)^2)$ with bounded variation on \mathbb{R} with norm $\|\cdot\|_{BV(H^\infty)}$. This is analogous to Definition 3.3.3.

Theorem 4.3.3 (Theorem 3.3.5). $BV(\mathbb{R}, H^\infty(B(0, r)^2))$ is a Banach space.

Definition 4.3.4. Let $f : \mathbb{R} \rightarrow H^\infty(B(0, r)^2)$, $G : \mathbb{R} \rightarrow \mathbb{R}$ be a probability distribution, and $I = [a, b]$ be an interval. Let D_G be the set of all discontinuities of G on I . We say that the integral

$$\int_a^b f(\tau) dG(\tau) \quad (4.13)$$

exists if

$$\int_a^b f(\tau) dG_c(\tau) \quad (4.14)$$

exists and

$$\int_a^b f(\tau) dG_d(\tau) \quad (4.15)$$

exists, where each integral above is defined the same way as in Definition 3.3.7

Proposition 4.3.4 (Proposition 3.3.8 and Corollary 3.3.9). *Let G be a probability distribution. If $f \in BV(\mathbb{R}, H^\infty(B(0, r)^2))$, then f is integrable with respect to G on any interval $I = [a, b]$ or on \mathbb{R} .*

Definition 4.3.5. Define $BV_{r,m}^2$ to be the subspace of $BV(\mathbb{R}, H^\infty(B(0, r)^2))$ such that for all $f \in BV_{r,m}^2$,

1. $f(t) \in H_r^2$ for all $t \in \mathbb{R}$,
2. $c_{0,0}(f(t)) = 0$ for all $t \in \mathbb{R}$, and
3. $V(f) \leq m$.

$BV_{r,m}^2$ represents our space of time-dependent, joint generating functions. This is the analog to Definition 3.3.8

Remark. We only restrict our time-dependent, joint generating functions to have constant coefficient 0 so that all of our functions are nicely bounded by r , even though in our model, other coefficients must be 0 as well, since it is not possible to have exactly two mother cells and no daughter cells, for example.

Theorem 4.3.5 (Theorem 3.3.10). *$BV_{r,m}^2$ is a complete metric space with respect to the norm $\|\cdot\|_{BV(H^\infty)}$.*

The proceeding Proposition is necessary our solution to (4.9) is in $(BV_{r,m}^2)^2$.

Proposition 4.3.6. *The product space $(BV_{r,m}^2)^2$ is complete metric space with product norm*

$$\|((\cdot)_1, (\cdot)_2)\|_{BV^2(H^\infty)} := \|(\cdot)_1\|_{BV(H^\infty)} + \|(\cdot)_2\|_{BV(H^\infty)}. \quad (4.16)$$

The proof of the above Proposition can be found in most measure theoretic analysis books.

At this point, we have constructed a complete space of joint generating functions H_r^2 and a complete space of time-dependent, joint generating functions $BV_{r,m}^2$. Furthermore, we have a complete product space $(BV_{r,m}^2)^2$ of paired generating functions. Now we are ready to construct a map from $(BV_{r,m}^2)^2$ to itself that represents the right-hand side of (4.9). As before, let P be the life-span distribution of a mother cell and let Q represent the life-span distribution of a daughter cell. So, $P(0) = Q(0) = 0$.

Definition 4.3.6. Define

$$T : (BV_{r,m}^2)^2 \rightarrow (BV(\mathbb{R}, H^\infty(B(0, r))))^2 \quad (4.17)$$

to be a map such that for $(f, g) \in (BV_{r,m}^2)^2$,

$$(T(f, g))(t, s) := \left(\begin{aligned} &(\cdot)_1(1 - P(t)) + \int_0^t f(t - \tau)g(t - \tau) dP(\tau), \\ &(\cdot)_2(1 - Q(s)) + \int_0^s f(s - \tau)g(s - \tau) dQ(\tau) \end{aligned} \right) \quad (4.18)$$

for all $(t, s) \in \mathbb{R}^2$, where $(\cdot)_1$ and $(\cdot)_2$ represent the first and second parameters of functions in $H^\infty(B(0, r)^2)$, respectively. This is analogous to Definition 3.108.

Proposition 4.3.7 (Proposition 3.3.13 and Lemma 3.3.11). *Let $(f, g) \in (BV_{r,m}^2)^2$. If $0 < r \leq \frac{m}{2(1+m)}$, then $T(f, g) \in (BV_{r,m}^2)^2$.*

Remark. All bounds are the same, since to show $T(f, g) \in (BV_{r,m}^2)^2$, we will show that $T_1(f, g), T_2(f, g) \in BV_{r,m}^2$, where T_1 and T_2 are the corresponding scalar functions of T .

Proposition 4.3.8 (Theorem 3.3.17 and Lemmas 3.3.15 and 3.3.16). *If $0 < m < \frac{1}{2}$ and $0 < r < \frac{1-2m}{4}$, then T is a contraction mapping.*

Theorem 4.3.9 (Theorem 3.3.18). *If $0 < m < \frac{1}{2}$ and $0 < r < \min\left(\frac{1-2m}{4}, \frac{m}{2(1+m)}\right)$, then T has a unique fixed point.*

So, the integral equations we constructed in (4.9) for our generating functions that represent the cell population size at time t has a unique solution.

4.4 Series solutions to the generating function equation

If we are only concerned about the total cell population and not specifically the mother and daughter cell populations, we can write our generating functions $f(t, x, y)$ and $g(t, x, y)$ as simply $f(t, x) = f(t, x, x)$ and $g(t, x) = g(t, x, x)$.

So, we can express our generating functions $f(t, x)$ and $g(t, x)$ as series

$$f(t, x) = \sum_{k=0}^{\infty} c_k(t)x^k, \quad (4.19)$$

and

$$g(t, x) = \sum_{k=0}^{\infty} b_k(t)x^k, \quad (4.20)$$

which are necessarily convergent for all $t \geq 0$ when $x \in B(0, 1)$. If $f(t, x)$ and $g(t, x)$ satisfy our integral equations (4.9), then we must have

$$\sum_{k=0}^{\infty} c_k(t)x^k = x(1 - P(t)) + \int_0^t \left(\sum_{k=0}^{\infty} c_k(t - \tau)x^k \right)^2 dP(\tau) \quad (4.21)$$

$$= x(1 - P(t)) + \int_0^t \sum_{k=0}^{\infty} \sum_{j=0}^i c_j(t - \tau)b_{k-j}(t - \tau)x^k dP(\tau) \quad (4.22)$$

$$= x(1 - P(t)) + \sum_{k=0}^{\infty} \int_0^t \sum_{j=0}^i c_j(t - \tau)b_{k-j}(t - \tau) dP(\tau)x^k \quad (4.23)$$

and

$$\sum_{k=0}^{\infty} b_k(t)x^k = x(1 - Q(t)) + \sum_{k=0}^{\infty} \int_0^t \sum_{j=0}^i c_j(t - \tau)b_{k-j}(t - \tau) dQ(\tau)x^k. \quad (4.24)$$

Matching up coefficients and noting $c_0(t) = b_0(t) = 0$ for all $t \geq 0$, we get

$$c_k(t) = \begin{cases} 1 - P(t) & k = 1 \\ \int_0^t \sum_{j=1}^{k-1} c_j(t-\tau) b_{k-j}(t-\tau) dP(\tau) & k \geq 2 \end{cases} \quad (4.25)$$

and

$$b_k(t) = \begin{cases} 1 - Q(t) & k = 1 \\ \int_0^t \sum_{j=1}^{k-1} c_j(t-\tau) b_{k-j}(t-\tau) dQ(\tau) & k \geq 2 \end{cases}. \quad (4.26)$$

Given life-span distributions P and Q , one can compute the coefficients of $f(t, x)$ and $g(t, x)$ recursively. In section 6.3.2, we'll do this to determine the distribution of the mutant cell population when P is a multi-phase distribution.

4.5 Examples

4.5.1 Life-span distribution is multi-phase

The multi-phase distribution discussed in section 3.5.1 is of great importance in the asymmetric cell division case, and inspired us to develop a generating function when the daughter cells take time to mature before they can divide. A good model for this would be to assume mother cells have multi-phase distribution with parameter $n = 1$ or $n = 2$, while daughter cells have multi-phase distribution $n = 2$ or $n = 3$.

Theorem 4.5.1. *If P and Q are multi-phase distributions with parameters n and m , re-*

spectively, then the generating functions $f = f(t, x, y)$ and $g = g(t, x, y)$ satisfy

$$\left\{ \begin{array}{l} \left(1 + \frac{\partial}{\partial t}\right)^n f = fg. \\ \left(1 + \frac{\partial}{\partial t}\right)^m g = fg. \\ f(0, x, y) = x \\ g(0, x, y) = y \end{array} \right. \quad (4.27)$$

The proof to Theorem 4.5.1 is similar to the proof of Theorem 3.5.1.

Chapter 5

Asymptotics of cell growth

In Chapter 6, we will look at the mutant distribution in a large population. In order to do so, we need to know the asymptotics of our generating functions derived in Chapters 3 and 4. In this chapter, we will first rigorously derive the asymptotics under symmetric cell division, and then we will extend the results under asymmetric cell division.

5.1 Symmetric cell division

We start by stating our assumptions about symmetric cell division again.

Assumption 5.1.1 (Symmetric cell division). Cells have the following properties:

1. there is only one type of cell: mother cells;
2. all cells are identical and independent of each other;
3. cell life-span is a strictly positive, real-valued random variable \mathcal{T} with distribution P ;
4. at the end of a cell's life, it will divide into two cells.

As seen in Chapter 3, the generating function for the cell population Z_t at any time $t \geq 0$ is given by

$$f(t, x) = x(1 - P(t)) + \int_0^t f(t - \tau, x)^2 dP(\tau). \quad (5.1)$$

From section 3.3, we know there exists a unique, time-dependent generating function that satisfies (5.1). Moreover, we will treat the integral as a conventional Riemann-Stieltjes integral, with all the usual properties, as defined in Definition 3.3.7. Although continuity of f with respect to the time t is completely dependent on continuity of P , we can differentiate f with respect to the generating function parameter x when $x \in B(0, 1)$ since $f(t, \cdot) \in H^\infty(B(0, 1))$.

In order to determine the asymptotics of the of the cell population size Z_t , we will first compute $\mathbb{E}[Z_t]$ and let $t \rightarrow \infty$. After doing so, we will show $Z_t/\mathbb{E}[Z_t]$ converges to a random variable with expected value 1 so that we can conclude that Z_t grows at an exponential rate as $t \rightarrow \infty$.

5.1.1 The expectation $\mathbb{E}[Z_t]$

Define

$$m(t) := \mathbb{E}[Z_t] \tag{5.2}$$

to be the expected value of Z_t . Using generating functions, we know

$$m(t) = f_x(t, 1), \tag{5.3}$$

when it exists.

Proposition 5.1.1. *The expectation $m(t)$ satisfies the equation*

$$m(t) = 1 - P(t) + 2 \int_0^t m(t - \tau) dP(\tau). \tag{5.4}$$

Proof. Suppose $x \in B(0, 1)$. Then we can differentiate both sides of (5.1) with respect to x , differentiating inside the integral. To see this, we employ Cauchy's Integral Formula. Let

$\varepsilon < 1 - |x|$. Then,

$$\frac{\partial}{\partial x} f(t, x) = 1 - P(t) + \frac{\partial}{\partial x} \left[\int_0^t f(t - \tau, x)^2 dP(\tau) \right] \quad (5.5)$$

$$= 1 - P(t) + \frac{1}{2\pi i} \int_{C(x, \varepsilon)} \int_0^t \frac{f(t - \tau, w)^2}{(w - x)^2} dP(\tau) dw \quad (5.6)$$

$$= 1 - P(t) + \frac{1}{2\pi i} \int_0^t \int_{C(x, \varepsilon)} \frac{f(t - \tau, w)^2}{(w - x)^2} dw dP(\tau) \quad (5.7)$$

$$= 1 - P(t) + \int_0^t \frac{\partial}{\partial x} f(t - \tau, x) dP(\tau), \quad (5.8)$$

where we used Fubini's Theorem in (5.7), since f is convergent on $C(x, \varepsilon)$. Now, write

$$f(t, x) = \sum_{k=0}^{\infty} c_k(t) x^k \quad (5.9)$$

as a series, and note

$$\frac{\partial}{\partial x} f(t, x) = \sum_{k=1}^{\infty} k c_k(t) x^{k-1} \quad (5.10)$$

is also convergent for $x \in B(0, 1)$ and increasing as $x \rightarrow 1^-$ along the real axis since the coefficients are non-negative. So, we have

$$\lim_{x \rightarrow 1^-} f_x(t, x) = 1 - P(t) + \lim_{x \rightarrow 1^-} \int_0^t f_x(t - \tau, x) dP(\tau) \quad (5.11)$$

$$f_x(t, 1) = 1 - P(t) + \int_0^t f_x(t, 1) dP(\tau), \quad (5.12)$$

where we used the Monotone Convergence Theorem to get (5.12), and the result is proven. ■

Proposition 5.1.2. *The expectation $m(t)$ is non-decreasing and finite for $t \geq 0$.*

Proof. Since no cells can die, m must be non-decreasing. Since P is a life-span distribution with $P(0) = 0$ and P is right continuous, then for $\varepsilon > 0$, there exists a $\delta > 0$ such that

$P(\delta) < \varepsilon$. Now, we can rewrite (5.4) as

$$m(t) = 1 - P(t) + 2 \int_0^\delta m(t - \tau) dP(\tau) + 2 \int_\delta^t m(t - \tau) dP(\tau). \quad (5.13)$$

Bounding the integrals and using the fact that m is a non-decreasing function, we get

$$m(t) \leq 1 - P(t) + 2m(t)P(\delta) + 2m(t - \delta)(P(t) - P(\delta)) \quad (5.14)$$

$$\leq 1 + 2\varepsilon m(t) + 2m(t - \delta). \quad (5.15)$$

Solving for $m(t)$, we have

$$m(t) \leq \frac{1 + 2m(t - \delta)}{1 - 2\varepsilon}. \quad (5.16)$$

Since $m(0) = 1$, we can inductively conclude

$$m(n\delta) \leq \frac{1 + 2m((n - 1)\delta)}{1 - 2\varepsilon} \quad (5.17)$$

for all integers $n \geq 1$. So, $m(t)$ is finite for all $t \geq 0$. ■

5.1.2 The Laplace transform of $\mathbb{E}[Z_t]$

In order to determine the asymptotics of m , we need to first review some properties of the Laplace transform.

Definition 5.1.1. Let $h : \mathbb{R} \rightarrow \mathbb{R}$. The *Laplace transform* of h is

$$(\mathcal{L}h)(s) := \int_0^\infty e^{-st} h(t) dt, \quad s \in \mathbb{C}. \quad (5.18)$$

Remark. We will often write $h^* := \mathcal{L}h$ to represent the Laplace transform of h .

Proposition 5.1.3 (see [9], page 92). *If $f, g \in L^1([0, R])$ for all $R > 0$, then*

$$\mathcal{L}(f * g) := (\mathcal{L}f)(\mathcal{L}g), \quad (5.19)$$

provided all three transforms exist.

Proposition 5.1.4. *Let $\varphi : \mathbb{R} \rightarrow \mathbb{R}$ be a function and G be a probability distribution. Define*

$$(\varphi * dG)(t) := \int_0^t \varphi(t - \tau) dG(\tau) \quad (5.20)$$

and

$$g^*(s) := \int_0^\infty e^{-st} dG(t). \quad (5.21)$$

Then,

$$\mathcal{L}(\varphi * dG) = (\mathcal{L}\varphi)g^* \quad (5.22)$$

when all integrals converge.

Proof. Let $s \in \mathbb{C}$. Then

$$(\mathcal{L}\varphi)(s)g^*(s) = \int_0^\infty e^{-st} \varphi(t) dt \int_0^\infty e^{-sy} dP(y) \quad (5.23)$$

$$= \int_0^\infty \int_0^\infty e^{-s(t+y)} \varphi(t) dt dP(y) \quad (5.24)$$

$$= \int_0^\infty \int_y^\infty e^{-s\tau} \varphi(\tau - y) d\tau dP(y) \quad (5.25)$$

$$= \int_0^\infty \int_0^\tau e^{-s\tau} \varphi(\tau - y) dP(y) d\tau \quad (5.26)$$

$$= \mathcal{L}(\varphi * dG)(s), \quad (5.27)$$

where we used Fubini's Theorem to get (5.26). ■

Remark. Our integral defined in (3.3.7) coincides with the traditional Riemann-Stieltjes integral, so properties such as Fubini's Theorem can be easily applied. One can prove this more generally by referring to page 89 of [9].

Now, applying the above properties of the Laplace transform to m from (5.4), for $s \in \mathbb{C}$

such that $\Re s > 0$, we have

$$m^*(s) := (\mathcal{L}m)(s) \tag{5.28}$$

$$= \frac{1}{s} - \frac{1}{s}p^*(s) + 2m^*(s)p^*(s). \tag{5.29}$$

Solving for $m^*(s)$, we get

$$m^*(s) = \frac{1 - p^*(s)}{s(1 - 2p^*(s))}. \tag{5.30}$$

Note that m^* is a meromorphic function (see [9], page 57).

5.1.3 Convergence of $\mathbb{E}[Z_t]$

In order to show that $m(t)$ converges as $t \rightarrow \infty$, we need need to analyze the poles of m^* .

Consider the term

$$\psi(s) := 1 - 2p^*(s) \tag{5.31}$$

in the denominator of (5.30). ψ is analytic when it converges (see [9], page 57), and

$$\psi'(s) = 2 \int_0^\infty te^{-st} dP(t), \tag{5.32}$$

which is non-negative when s is real.

Remark. For clarity, by *root*, we necessarily mean a real-valued zero.

Proposition 5.1.5. *ψ has a unique root $\alpha \in \mathbb{R}$.*

Proof. Notice

$$\psi(0) = -1 \tag{5.33}$$

and

$$\lim_{s \rightarrow \infty} \psi(s) = 1, \tag{5.34}$$

when s is real. Then by the Intermediate Value Theorem, there exists a root $\alpha \in \mathbb{R}$ such

that

$$\psi(\alpha) = 0. \quad (5.35)$$

Since $\psi'(s) \geq 0$ for $s \in \mathbb{R}$, this root must be unique. ■

Remark. In this section, α will always refer to unique root of ψ , unless otherwise stated.

So now that we know α is a unique root of ψ , we need to determine when else $\psi(s) = 0$ when $\Re s = \alpha$.

Definition 5.1.2. A probability distribution P is a δ -lattice distribution if P is constant except at jumps at multiples of some $\delta > 0$.

Proposition 5.1.6. Suppose P is a δ -lattice distribution, then ψ has zeros at $\alpha + i\frac{2\pi n}{\delta}$ for all $n \in \mathbb{Z}$.

Proof. Let $n \in \mathbb{Z}$. Then,

$$\psi\left(\alpha + i\frac{2\pi n}{\delta}\right) = 1 - 2 \int_0^\infty e^{-\alpha t} e^{-i\frac{2\pi n}{\delta}t} dP(t) \quad (5.36)$$

$$= 1 - 2 \sum_{k=1}^\infty e^{-\alpha k\delta} e^{-i\frac{2\pi n}{\delta}k\delta} (P(k\delta) - P((k-1)\delta)) \quad (5.37)$$

$$= 1 - 2 \sum_{k=1}^\infty e^{-\alpha k\delta} (P(k\delta) - P((k-1)\delta)) \quad (5.38)$$

$$= 1 - 2 \int_0^\infty e^{-\alpha t} dP(t) \quad (5.39)$$

$$= 0. \quad (5.40)$$

■

Corollary 5.1.7. If P is a δ -lattice distribution, then m^* has a singularity at $\alpha + i\frac{2\pi n}{\delta}$ for all $n \in \mathbb{Z}$.

If P is a lattice distribution, then there are infinitely many zeros of ψ when $\Re s = \alpha$, but if P is not a lattice distribution, we can show α is the only zero of ψ when $\Re s = \alpha$.

Proposition 5.1.8. *If P is not a lattice distribution and $\alpha + i\tau$ is a zero of ψ , then $\tau = 0$.*

Proof. Since α and $\alpha + i\tau$ are zeros, we have

$$\psi(\alpha) - \psi(\alpha + i\tau) = \int_0^\infty e^{-\alpha t} (e^{-i\tau t} - 1) dP(t) \quad (5.41)$$

$$= \int_0^\infty e^{-\alpha t} (\cos(\tau t) - 1) dP(t) - i \int_0^\infty e^{-\alpha t} \sin(\tau t) dP(t) \quad (5.42)$$

$$= 0, \quad (5.43)$$

So,

$$\int_0^\infty e^{-\alpha t} (\cos(\tau t) - 1) dP(t) = 0, \quad (5.44)$$

and since

$$e^{-\alpha t} (\cos(\tau t) - 1) \leq 0 \quad (5.45)$$

for all $t \geq 0$, we can conclude that

$$\cos(\tau t) - 1 = 0 \quad P\text{-a.e.}, \quad (5.46)$$

which requires $\tau = 0$ or $t \in \frac{2\pi}{\tau}\mathbb{Z}$. But if it's the latter, then P is necessarily a $\frac{2\pi}{\tau}$ -lattice distribution, which is a contradiction. So $\tau = 0$. ■

Corollary 5.1.9. *If P is not a lattice distribution, then m^* is analytic for all $\alpha + i\tau$ when $\tau \neq 0$.*

Proposition 5.1.10. *m^* has a pole at α from (5.35) of order 1 with residue*

$$\frac{1}{4\alpha \int_0^\infty t e^{-\alpha t} dP(t)}. \quad (5.47)$$

Proof. Since ψ is analytic when it converges and has a zero at $s = \alpha$ from Proposition 5.1.5,

we can write $\psi(s)$ as

$$\psi(s) = (s - \alpha)f'(\alpha) + O((s - \alpha)^2) \quad (5.48)$$

$$= 2(s - \alpha) \int_0^\infty te^{-\alpha t} dP(t) + O((s - \alpha)^2) \quad (5.49)$$

$$= (s - \alpha) \left(2 \int_0^\infty te^{-\alpha t} dP(t) + O(s - \alpha) \right). \quad (5.50)$$

So,

$$\lim_{s \rightarrow \alpha} (s - \alpha)m^*(s) = \lim_{s \rightarrow \alpha^+} \frac{1 - p^*(s)}{s \left(2 \int_0^\infty te^{-\alpha t} dP(t) + O(s - \alpha) \right)} \quad (5.51)$$

$$= \frac{1 - p^*(\alpha)}{2\alpha \int_0^\infty te^{-\alpha t} dP(t)} \quad (5.52)$$

$$= \frac{1}{4\alpha \int_0^\infty te^{-\alpha t} dP(t)}, \quad (5.53)$$

so m^* has a pole at α of order 1 with residue (5.47). ■

Now, we will use the Wiener-Ikehara Tauberian Proposition to show m converges to an exponential function if P is not a lattice distribution.

Proposition 5.1.11 (Wiener-Ikehara Theorem, [9] page 233). *If $\varphi(t)$ is a non-negative, non-decreasing function for $t \geq 0$ such that the integral*

$$f(s) = \int_0^\infty e^{-st} \varphi(t) dt, \quad s = \sigma + i\tau \in \mathbb{C} \quad (5.54)$$

converges for $\sigma > 1$, and if for some constant A and some function $g(\tau)$

$$\lim_{\sigma \rightarrow 1^+} f(s) - \frac{A}{s - 1} = g(\tau) \quad (5.55)$$

uniformly in every finite interval $-a \leq \tau \leq a$, then

$$\lim_{t \rightarrow \infty} \varphi(t)e^{-t} = A. \quad (5.56)$$

Theorem 5.1.12. *Suppose P is not a lattice distribution. Let $\alpha \in \mathbb{R}$ be the unique root of*

$$1 - 2 \int_0^\infty e^{-st} dP(t) = 0. \quad (5.57)$$

Then

$$m(t) \sim Ce^{\alpha t}, \quad (5.58)$$

where

$$C = \frac{1}{4\alpha \int_0^\infty te^{-\alpha t} dP(t)}. \quad (5.59)$$

Proof. We will use Proposition 5.1.11. Since $m(t) = \mathbb{E}[Z_t]$, it is non-negative and non-decreasing. Moreover, m^* is meromorphic since $p^*(s)$ converges for all $\Re s \geq 0$. From Proposition 5.1.10, we know we can write m^* as

$$m^*(s) = \sum_{n=-1}^{\infty} a_n (s - \alpha)^n, \quad (5.60)$$

where

$$a_{-1} = \frac{1}{4\alpha \int_0^\infty te^{-\alpha t} dP(t)}. \quad (5.61)$$

So,

$$m^*(s) - \frac{a_{-1}}{s - \alpha} = a_0 + \sum_{n=1}^{\infty} a_n (s - \alpha)^n. \quad (5.62)$$

Now, writing $s = \sigma + i\tau$ and letting $\sigma \rightarrow \alpha^+$ in (5.62), we get

$$\lim_{\Re s \rightarrow \alpha^+} m^*(s) - \frac{a_{-1}}{s - \alpha} = a_0 + \sum_{n=1}^{\infty} a_n (i\tau)^n, \quad (5.63)$$

which must be convergent for all τ on any compact interval since m^* is analytic for all τ from Corollary 5.1.9. Therefore, by the Wiener-Ikehara Theorem,

$$\lim_{t \rightarrow \infty} e^{-\alpha t} m(t) = C, \quad (5.64)$$

and the result is proven. ■

5.1.4 Convergence of $Z_t/\mathbb{E}[Z_t]$

In order to show convergence of $Z_t/\mathbb{E}[Z_t]$, we will first show $\mathbb{E}[Z_t Z_{t+\tau}]$ converges, and use that to show $Z_t/\mathbb{E}[Z_t]$ is Cauchy in $L^2(P)$.

Consider the the two processes Z_t and $Z_{t+\tau}$ for $t, \tau \geq 0$ representing the cell populations at times t and $t + \tau$. Using similar probabilistic techniques from Chapter 3 to construct the generating function f in (5.1), we can construct the joint generating function F of Z_t and $Z_{t+\tau}$ to get

$$\begin{aligned} F(t, \tau, x_1, x_2) &= x_1 x_2 (1 - P(t + \tau)) \\ &\quad + \int_0^t F(t - y, \tau, x_1, x_2)^2 dP(y) \\ &\quad + x_1 \int_t^\tau f(t + \tau - y, x_2)^2 dP(y), \end{aligned} \tag{5.65}$$

where the parameter x_1 corresponds to Z_t and x_2 corresponds to $Z_{t+\tau}$.

Define

$$m_2(t, \tau) := \mathbb{E}[Z_t Z_{t+\tau}] \tag{5.66}$$

to be the expected value of $Z_t Z_{t+\tau}$. Using generating functions, we know

$$m_2(t, \tau) = F_{x_1 x_2}(t, \tau, 1, 1), \tag{5.67}$$

when it exists.

Proposition 5.1.13. *The expectation $m_2(t, \tau)$ satisfies the equation*

$$\begin{aligned} m_2(t, \tau) &= 1 - P(t + \tau) \\ &\quad + 2 \int_0^t m_2(t - y, \tau) dP(y) + m(t - y)m(t + \tau - y) dP(y) \\ &\quad + 2 \int_t^\tau m(t + \tau - y) dP(y). \end{aligned} \tag{5.68}$$

Proof. The proof is similar to the proof of Proposition 5.1.1. We can take derivatives inside the integrals for values in $B(0, 1)$ since all the generating functions converge for $x_1, x_2 \in B(0, 1)$. Since all coefficients are positive and the generating functions are increasing, we can let $x_1, x_2 \rightarrow 1^-$ using the Monotone Convergence Theorem. ■

Proposition 5.1.14. *The expectation $m_2(t, \tau)$ non-decreasing in both arguments and is finite for $t, \tau \geq 0$.*

Proof. Since no cells can die, m_2 must be non-decreasing in both arguments. Now, by Proposition 5.1.2, we know $m(t)$ is finite for all $t \geq 0$, so we can define

$$B(t) := \int_0^t m(t - y)m(t + \tau - y) dP(y) + 2 \int_t^\tau m(t + \tau - y) dP(y), \tag{5.69}$$

which is also finite for all $t \geq 0$. Rewriting (5.68) as

$$m_2(t, \tau) = 1 - P(t + \tau) + 2 \int_0^t m_2(t - y, \tau) dP(y) + B(t), \tag{5.70}$$

we can follow a similar procedure in the proof of Proposition 5.1.2 to conclude

$$m_2(t, \tau) \leq \frac{1 + 2m_2(t - \delta, \tau) + B(t)}{1 - 2\varepsilon}, \tag{5.71}$$

where ε and δ are defined as in Proposition 5.1.2. Since for any $\tau \geq 0$,

$$m_2(0, \tau) = m(\tau), \quad (5.72)$$

we can inductively conclude $m_2(t, \tau)$ is finite for all $t, \tau \geq 0$. ■

Theorem 5.1.15. *If P is not a lattice distribution, then*

$$m_2(t, \tau) \sim C_2 e^{\alpha\tau + 2\alpha t}, \quad (5.73)$$

uniformly in τ , where

$$C_2 = \frac{2C^2 \int_0^\infty e^{-2\alpha y} dP(y)}{1 - 2 \int_0^\infty e^{-2\alpha y} dP(y)}. \quad (5.74)$$

Proof. Multiply both sides of (5.68) by $e^{-\alpha t} e^{-\alpha(t+\tau)}$ and set

$$K(t, \tau) := e^{-\alpha t} e^{-\alpha(t+\tau)} m_2(t, \tau), \quad (5.75)$$

$$d\bar{P}(y) := \frac{e^{-2\alpha y} dP(y)}{\int_0^\infty e^{-2\alpha y} dP(y)}, \quad (5.76)$$

and

$$\gamma = 2 \int_0^\infty e^{-2\alpha y} dP(y) \quad (5.77)$$

to get

$$K(t, \tau) = \gamma \int_0^t K(t-y, \tau) d\bar{P}(y) + h(t, \tau), \quad (5.78)$$

where

$$h(t, \tau) := e^{-\alpha t} e^{-\alpha(t+\tau)} (1 + P(t+\tau)) \quad (5.79)$$

$$+ \gamma \int_0^t e^{-\alpha(t-y)} m(t-y) e^{-\alpha(t+\tau-y)} m(t+\tau-y) d\bar{P}(y) \quad (5.80)$$

$$+ \gamma \int_t^{t+\tau} e^{-\alpha(t-y)} e^{-\alpha(t+\tau-y)} m(t+\tau-y) d\bar{P}(y). \quad (5.81)$$

First, we will show $h(t, \tau)$ converges uniformly in τ by computing the limits of (5.79), (5.80), and (5.81). It's clear as $t \rightarrow \infty$, (5.79) and (5.81) converge to 0 uniformly for all $\tau > 0$. Now, from (5.58), for all $\varepsilon > 0$, there exists at T_ε such that for all $t > T_\varepsilon$, (5.80) is within ε -distance of

$$\gamma \left(\int_0^{T_\varepsilon} e^{-\alpha(t-y)} m(t-y) e^{-\alpha(t+\tau-y)} m(t+\tau-y) d\bar{P}(y) + C^2 (\bar{P}(t) - \bar{P}(T_\varepsilon)) \right), \quad (5.82)$$

as long as P is not a lattice distribution. Letting $t \rightarrow \infty$, (5.82) converges uniformly in τ to

$$\gamma C^2 = 2C^2 \int_0^\infty e^{-2\alpha y} dP(y). \quad (5.83)$$

Since this is true for all $\varepsilon > 0$, we can conclude that (5.80) converges to (5.83). So,

$$\lim_{t \rightarrow \infty} h(t, \tau) = \gamma C^2 \quad (5.84)$$

uniformly in τ . Also, note that

$$\gamma = 2p^*(2\alpha) \leq 1 \quad (5.85)$$

since $p^*(\alpha) = \frac{1}{2}$ and p^* is a non-increasing function. So, using Lemma 2 from [1], we can conclude that

$$\lim_{t \rightarrow \infty} K(t, \tau) = \frac{2C^2 \int_0^\infty e^{-2\alpha y} dP(y)}{1 - 2 \int_0^\infty e^{-2\alpha y} dP(y)}, \quad (5.86)$$

and the result is proven. ■

Now, define

$$W_t := \frac{Z_t}{C e^{\alpha t}}. \quad (5.87)$$

Proposition 5.1.16. *If P is not a lattice distribution, then*

$$\lim_{t \rightarrow \infty} \mathbb{E} \left[(W_{t+\tau} - W_t)^2 \right] = 0 \quad (5.88)$$

uniformly in τ .

Proof.

$$\mathbb{E} \left[(W_{t+\tau} - W_t)^2 \right] = \mathbb{E} [W_{t+\tau}W_{t+\tau}] + \mathbb{E} [W_tW_t] - 2\mathbb{E} [W_{t+\tau}W_t] \quad (5.89)$$

$$= \frac{m_2(t + \tau, 0)}{C^2 e^{2\alpha t} e^{2\tau}} + \frac{m_2(t, 0)}{C^2 e^{2\alpha t}} - \frac{2m_2(t, \tau)}{C^2 e^{2\alpha t} e^\tau}. \quad (5.90)$$

Letting $t \rightarrow \infty$ and using Proposition 5.1.15, the result is proven. \blacksquare

Since $L^2(P)$ is a complete metric space, we get the immediate corollary:

Corollary 5.1.17. *If P is not a lattice distribution, W_t converges in $L^2(P)$ to a random variable W with expected value 1.*

5.1.5 Examples

Suppose P is a multi-phase distribution with parameter n . Then,

$$dP(t) = \frac{t^{n-1} e^{-t}}{(n-1)!} dt \quad (5.91)$$

and the exponential growth rate α of Z_t is the root to

$$1 - 2 \int_0^\infty \frac{t^{n-1} e^{-t(1+s)}}{(n-1)!} dt = 0, \quad (5.92)$$

which can be easily solved to obtain

$$\alpha = 2^{1/n} - 1. \quad (5.93)$$

5.2 Asymmetric cell division

We start by stating our assumptions about asymmetric cell division again.

Assumption 5.2.1 (Asymmetric cell division). Cells have the following properties:

1. there are exactly two types of cells: mother cells and daughter cells;
2. all cells are independent of each other, mother cells are identical to other mother cells, and daughter cells are identical to other daughter cells;
3. cell life-span for mother cells and daughter cells are strictly positive, real-valued random variables \mathcal{T}_x and \mathcal{T}_y , respectively, with distributions P and Q , respectively;
4. at the end of a cell's life, both mother cells and daughter cells will divide into one mother cell and one daughter cell.

Like before, we will let X_t represent the mother cell population and Y_t represent the daughter cell population at time $t \geq 0$. The joint generating functions for the mother cell population X_t and the daughter cell population Y_t at time $t \geq 0$ when you start with exactly one mother cell and no daughter cells, and when you start with exactly one daughter cells and no mother cells, is given by

$$\begin{cases} f(t, x, y) = x(1 - P(t)) + \int_0^t f(t - \tau, x, y)g(t - \tau, x, y) dP(\tau) \\ g(t, x, y) = y(1 - Q(t)) + \int_0^t f(t - \tau, x, y)g(t - \tau, x, y) dQ(\tau) \end{cases} . \quad (5.94)$$

From section 4.3, we know there exist unique, time-dependent joint generating functions that satisfy (5.94). We will proceed analogously to how we did with symmetric cell division with the end result showing $X_t/\mathbb{E}[X_t]$ and $Y_t/\mathbb{E}[Y_t]$ converge. Many of the propositions and theorems are analogous to those in section 5.1. When proofs are clear, the corresponding proposition or theorem in the the symmetric cell division case is indicated.

5.2.1 The expectations $\mathbb{E}[X_t]$ and $\mathbb{E}[Y_t]$

Define the following expectations:

$$m_f(t) := \mathbb{E}[X_t | X_0 = 1, Y_0 = 0] = f_x(t, 1, 1); \quad (5.95)$$

$$m_g(t) := \mathbb{E}[X_t | X_0 = 0, Y_0 = 1] = g_x(t, 1, 1); \quad (5.96)$$

$$n_f(t) := \mathbb{E}[Y_t | X_0 = 1, Y_0 = 0] = f_y(t, 1, 1); \quad (5.97)$$

$$n_g(t) := \mathbb{E}[Y_t | X_0 = 0, Y_0 = 1] = g_y(t, 1, 1). \quad (5.98)$$

As noted above, these expected values correspond to the partial derivatives of the corresponding generating function, provided they exist. $m_f(t)$ represents the expected mother cell population at time t when you start from a single mother cell, while $m_g(t)$ represents the expected mother cell population when you start from a single daughter cell. $n_f(t)$ and $n_g(t)$ are defined similarly for the expected daughter cell population at time t .

Differentiating system (5.94), which we can do for the same reasons as in section 5.1, we get the following propositions.

Proposition 5.2.1. *The expectations $m_f(t)$, $m_g(t)$, $n_f(t)$, and $n_g(t)$ satisfy the systems*

$$\begin{cases} m_f(t) = 1 - P(t) + \int_0^t m_f(t - \tau) + m_g(t - \tau) dP(\tau) \\ m_g(t) = \int_0^t m_f(t - \tau) + m_g(t - \tau) dQ(\tau) \end{cases} \quad (5.99)$$

and

$$\begin{cases} n_f(t) = \int_0^t n_f(t - \tau) + n_g(t - \tau) dP(\tau) \\ n_g(t) = 1 - Q(t) + \int_0^t n_f(t - \tau) + n_g(t - \tau) dQ(\tau). \end{cases} \quad (5.100)$$

Proof. Suppose $x, y \in B(0, 1)$. Then we can differentiate both sides of both equations in both (5.99) and (5.100) in a similar fashion to Proposition 5.1.1. Since these generating functions and their derivatives have positive coefficients and are increasing in both the x

and y parameters, we can let $x, y \rightarrow 1^-$. ■

Proposition 5.2.2. *The expectations $m_f(t)$, $m_g(t)$, $n_f(t)$, and $n_g(t)$ are non-decreasing and finite for $t \geq 0$.*

Proof. Since no cells can die, m_f , m_g , n_f , and n_g must be non-decreasing. Since P and Q are life-span distributions with $P(0) = Q(0) = 0$ and P and Q are right continuous, then for $\varepsilon > 0$, there exists a $\delta > 0$ such that $P(\delta) < \varepsilon$ and $Q(\delta) < \varepsilon$. Now, rewriting and bounding the system (5.99) similarly to the proof of Proposition 5.1.2, we get

$$\begin{cases} m_f(t) \leq 1 + \varepsilon m_f(t) + m_f(t - \delta) + \varepsilon m_g(t) + m_g(t - \delta) \\ m_g(t) \leq \varepsilon m_f(t) + m_f(t - \delta) + \varepsilon m_g(t) + m_g(t - \delta) \end{cases}. \quad (5.101)$$

So,

$$m_f(t) + m_g(t) \leq 1 + 2\varepsilon(m_f(t) + m_g(t)) + 2(m_f(t - \delta) + m_g(t - \delta)), \quad (5.102)$$

and

$$m_f(t) + m_g(t) \leq \frac{1 + 2(m_f(t - \delta) + m_g(t - \delta))}{1 - 2\varepsilon}. \quad (5.103)$$

Since $m_f(0) + m_g(0) = 1$, similar to Proposition 5.1.2, we can inductively conclude $m_f(t) + m_g(t)$ is finite for all $t \geq 0$, and the result is proven for m_f and m_g . n_f and n_g are similar. ■

5.2.2 Convergence of $\mathbb{E}[X_t]$ and $\mathbb{E}[Y_t]$

In order to show $\mathbb{E}[X_t]$ and $\mathbb{E}[Y_t]$ converge, we will first compute their Laplace transforms as we did in section 5.1.2, and then analyze their poles similarly to how we did in the symmetric cell division case in order to conclude the expected values converge.

Define

$$q^*(s) := \int_0^\infty e^{-st} dQ(t), \quad s \in \mathbb{C}. \quad (5.104)$$

Let $s \in \mathbb{C}$ such that $\Re s > 0$. Then,

$$m_f^*(s) := (\mathcal{L}m_f)(s) \quad (5.105)$$

$$= \frac{1}{s} - \frac{1}{s}p^*(s) + m_f^*(s)p^*(s) + m_g^*(s)p^*(s), \quad (5.106)$$

and

$$m_g^*(s) := (\mathcal{L}m_g)(s) \quad (5.107)$$

$$= m_f^*(s)q^*(s) + m_g^*(s)q^*(s), \quad (5.108)$$

Solving for $m_f^*(s)$ and $m_g^*(s)$, we get

$$m_f^*(s) = \frac{1 - p^*(s) - q^*(s) + p^*(s)q^*(s)}{s(1 - p^*(s) - q^*(s))} \quad (5.109)$$

and

$$m_g^*(s) = \frac{(1 - p^*(s))q^*(s)}{s(1 - p^*(s) - q^*(s))}. \quad (5.110)$$

Similarly,

$$n_f^*(s) := (\mathcal{L}n_f)(s) \quad (5.111)$$

$$= n_f^*(s)p^*(s) + n_g^*(s)p^*(s) \quad (5.112)$$

and

$$n_g^*(s) := (\mathcal{L}n_g)(s) \quad (5.113)$$

$$= \frac{1}{s} - \frac{1}{s}q^*(s) + n_g^*(s)q^*(s) + n_f^*(s)q^*(s). \quad (5.114)$$

Solving for $n_f^*(s)$ and $n_g^*(s)$, we get

$$n_f^*(s) = \frac{(1 - q^*(s))p^*(s)}{s(1 - p^*(s) - q^*(s))} \quad (5.115)$$

and

$$n_g^*(s) = \frac{1 - p^*(s) - q^*(s) + p^*(s)q^*(s)}{s(1 - p^*(s) - q^*(s))}. \quad (5.116)$$

Now, in order to analyze the poles of m_f^* , m_g^* , n_f^* , and n_g^* , consider the term

$$\psi(s) := 1 - p^*(s) - q^*(s) \quad (5.117)$$

that's in the denominator of all the Laplace transforms. Then,

$$\psi'(s) = \int_0^\infty te^{-st} d(P(t) + Q(t)), \quad (5.118)$$

which is non-negative when s is real.

Proposition 5.2.3 (Proposition 5.1.5). *ψ has a unique root, $\alpha \in \mathbb{R}$.*

Proposition 5.2.4 (Proposition 5.1.6). *If P and Q are both δ -lattice distributions, then ψ has complex zeros at $\alpha + i\frac{2\pi n}{\delta}$ for $n \in \mathbb{Z}$.*

Corollary 5.2.5 (Corollary 5.1.7). *If P and Q are both δ -lattice distributions, then m_f^* , m_g^* , n_f^* , and n_g^* have singularities at $\alpha + i\frac{2\pi n}{\delta}$ for $n \in \mathbb{Z}$.*

Proposition 5.2.6 (Proposition 5.1.8). *If P and Q are not both δ -lattice distributions, and $\alpha + i\tau$ is a zero of ψ , then $\tau = 0$.*

Corollary 5.2.7 (Corollary 5.1.9). *If P and Q are not both δ -lattice distributions, then m_f^* , m_g^* , n_f^* , and n_g^* are analytic for all $\alpha + i\tau$ when $\tau \neq 0$.*

Proposition 5.2.8 (Proposition 5.1.10). *m_f^* and m_g^* have poles at α of order 1 with*

residues

$$\frac{\int_0^\infty e^{-\alpha\tau} dP(\tau) \int_0^\infty e^{-\alpha\tau} dQ(\tau)}{\alpha \int_0^\infty \tau e^{-\alpha\tau} d(P(\tau) + Q(\tau))} \quad (5.119)$$

and

$$\frac{(\int_0^\infty e^{-\alpha\tau} dQ(\tau))^2}{\alpha \int_0^\infty \tau e^{-\alpha\tau} d(P(\tau) + Q(\tau))}, \quad (5.120)$$

respectively.

Proposition 5.2.9 (Proposition 5.1.10). n_f^* and n_g^* have a poles at α of order 1 with residues

$$\frac{(\int_0^\infty e^{-\alpha\tau} dP(\tau))^2}{\alpha \int_0^\infty \tau e^{-\alpha\tau} d(P(\tau) + Q(\tau))} \quad (5.121)$$

and

$$\frac{\int_0^\infty e^{-\alpha\tau} dP(\tau) \int_0^\infty e^{-\alpha\tau} dQ(\tau)}{\alpha \int_0^\infty \tau e^{-\alpha\tau} d(P(\tau) + Q(\tau))}, \quad (5.122)$$

respectively.

Theorem 5.2.10 (Theorem 5.1.12). Suppose P and Q are not both δ -lattice distributions. Let α be the unique root of

$$1 - \int_0^\infty e^{-s\tau} d(P(\tau) + Q(\tau)) = 0. \quad (5.123)$$

Then,

$$m_f(t) \sim c_1 e^{\alpha t} \quad (5.124)$$

and

$$m_g(t) \sim c_2 e^{\alpha t}, \quad (5.125)$$

where

$$c_1 = \frac{\int_0^\infty e^{-\alpha\tau} dP(\tau) \int_0^\infty e^{-\alpha\tau} dQ(\tau)}{\alpha \int_0^\infty \tau e^{-\alpha\tau} d(P(\tau) + Q(\tau))} \quad (5.126)$$

and

$$c_2 = \frac{\left(\int_0^\infty e^{-\alpha\tau} dQ(\tau)\right)^2}{\alpha \int_0^\infty \tau e^{-\alpha\tau} d(P(\tau) + Q(\tau))}. \quad (5.127)$$

Similarly,

$$n_f(t) \sim d_1 e^{\alpha t} \quad (5.128)$$

and

$$n_g(t) \sim c_1 e^{\alpha t}, \quad (5.129)$$

where

$$d_1 = \frac{\left(\int_0^\infty e^{-\alpha\tau} dP(\tau)\right)^2}{\alpha \int_0^\infty \tau e^{-\alpha\tau} d(P(\tau) + Q(\tau))}. \quad (5.130)$$

So, if we are only concerned with the cell population $Z_t = X_t + Y_t$ when we start with exactly one mother cell, which is usually the case, then

$$\mathbb{E}[Z_t] = m_f(t) + n_f(t) \quad (5.131)$$

$$\sim (c_1 + d_1) e^{\alpha t} \quad (5.132)$$

$$= \frac{\int_0^\infty e^{-\alpha\tau} dP(\tau)}{\alpha \int_0^\infty \tau e^{-\alpha\tau} d(P(\tau) + Q(\tau))} e^{\alpha t}. \quad (5.133)$$

5.2.3 Convergence of $X_t/\mathbb{E}[X_t]$ and $Y_t/\mathbb{E}[Y_t]$

Like before, X_t will represent the mother cell population at time $t \geq 0$ and Y_t will represent the daughter cell population at time $t \geq 0$. Let F represent the joint generating function of $X_t, Y_t, X_{t+\tau}$, and $Y_{t+\tau}$ when you start with exactly one mother cell and no daughter cells, and let G represent the joint generating function when you start with exactly one daughter

cell and no mother cells. Then

$$\begin{aligned}
F(t, \tau, x_1, x_2, y_1, y_2) &= x_1 x_2 (1 - P(t + \tau)) \\
&+ \int_0^t F(t - y, \tau, x_1, x_2, y_1, y_2) G(t - y, \tau, x_1, x_2, y_1, y_2) dP(y) \\
&+ x_1 \int_t^\tau f(t + \tau - y, x_2, y_2) g(t + \tau - y, x_2, y_2) dP(y)
\end{aligned} \tag{5.134}$$

and

$$\begin{aligned}
G(t, \tau, x_1, x_2, y_1, y_2) &= y_1 y_2 (1 - Q(t + \tau)) \\
&+ \int_0^t F(t - y, \tau, x_1, x_2, y_1, y_2) G(t - y, \tau, x_1, x_2, y_1, y_2) dQ(y) \\
&+ y_1 \int_t^\tau f(t + \tau - y, x_2, y_2) g(t + \tau - y, x_2, y_2) dQ(y),
\end{aligned} \tag{5.135}$$

where the parameter x_1 and y_1 correspond to X_t and Y_t , while x_2 and y_2 correspond to $X_{t+\tau}$ and $Y_{t+\tau}$.

Define the following expectations:

$$m_{2,f}(t, \tau) := \mathbb{E}[X_t X_{t+\tau} \mid X_0 = 1, Y_0 = 0] = F_{x_1 x_2}(t, \tau, 1, 1, 1, 1); \tag{5.136}$$

$$m_{2,g}(t, \tau) := \mathbb{E}[X_t X_{t+\tau} \mid X_0 = 0, Y_0 = 1] = G_{x_1 x_2}(t, \tau, 1, 1, 1, 1); \tag{5.137}$$

$$n_{2,f}(t, \tau) := \mathbb{E}[Y_t Y_{t+\tau} \mid X_0 = 1, Y_0 = 0] = F_{y_1 y_2}(t, \tau, 1, 1, 1, 1); \tag{5.138}$$

$$n_{2,g}(t, \tau) := \mathbb{E}[Y_t Y_{t+\tau} \mid X_0 = 0, Y_0 = 1] = G_{y_1 y_2}(t, \tau, 1, 1, 1, 1). \tag{5.139}$$

Proposition 5.2.11 (Proposition 5.1.13). *The expectations $m_{2,f}$ and $m_{2,g}$ satisfy the sys-*

tem

$$\begin{aligned}
m_{2,f}(t, \tau) &= 1 - P(t + \tau) \\
&+ \int_0^t m_{2,f}(t - y, \tau) + m_{2,g}(t - y, \tau) dP(y) \\
&+ \int_0^t m_f(t - y)m_g(t + \tau - y) + m_f(t + \tau - y)m_g(t - y) dP(y) \\
&+ \int_t^{t+\tau} m_f(t + \tau - y) + m_g(t + \tau - y) dP(y)
\end{aligned} \tag{5.140}$$

and

$$\begin{aligned}
m_{2,g}(t, \tau) &= \int_0^t m_{2,f}(t - y, \tau) + m_{2,g}(t - y, \tau) dQ(y) \\
&+ \int_0^t m_f(t - y)m_g(t + \tau - y) + m_f(t + \tau - y)m_g(t - y) dQ(y).
\end{aligned} \tag{5.141}$$

Similarly, we get the following proposition for $n_{2,f}$ and $n_{2,g}$.

Proposition 5.2.12 (Proposition 5.1.13). *The expectations $n_{2,f}$ and $n_{2,g}$ satisfy the system*

$$\begin{aligned}
n_{2,f}(t, \tau) &= \int_0^t n_{2,f}(t - y, \tau) + n_{2,g}(t - y, \tau) dP(y) \\
&+ \int_0^t n_f(t - y)n_g(t + \tau - y) + n_f(t + \tau - y)n_g(t - y) dP(y)
\end{aligned} \tag{5.142}$$

and

$$\begin{aligned}
n_{2,g}(t, \tau) &= 1 - Q(t + \tau) \\
&+ \int_0^t n_{2,f}(t - y, \tau) + n_{2,g}(t - y, \tau) dQ(y) \\
&+ \int_0^t n_f(t - y)m_g(t + \tau - y) + n_f(t + \tau - y)m_g(t - y) dQ(y) \\
&+ \int_t^{t+\tau} n_f(t + \tau - y) + n_g(t + \tau - y) dQ(y).
\end{aligned} \tag{5.143}$$

Just like in the symmetric cell division case from section 5.1, we can make similar arguments to show the expectations are finite.

Proposition 5.2.13 (Proposition 5.1.14). *The expectations $m_{2,f}(t, \tau)$, $m_{2,g}(t, \tau)$, $n_{2,f}(t, \tau)$, $n_{2,g}(t, \tau)$ are non-decreasing in both arguments and finite for $t, \tau \geq 0$*

Now, we can prove the following convergence theorem about $\mathbb{E}[X_t X_{t+\tau}]$ and $\mathbb{E}[Y_t Y_{t+\tau}]$.

Theorem 5.2.14 (Theorem 5.1.15). *If P and Q is not both δ -lattice distributions, then*

$$m_{2,f}(t, \tau) \sim D_1 e^{\alpha t} e^{\alpha(t+\tau)}, \quad (5.144)$$

and

$$n_{2,f}(t, \tau) \sim D_2 e^{\alpha t} e^{\alpha(t+\tau)}, \quad (5.145)$$

uniformly in τ , where

$$D_1 = \frac{c_1 c_2 \int_0^\infty e^{-2\alpha y} dP(t)}{1 - \int_0^\infty e^{-2\alpha y} d(P(t) + Q(t))} \quad (5.146)$$

and

$$D_2 = \frac{d_1 c_1 \int_0^\infty e^{-2\alpha y} Q(t)}{1 - \int_0^\infty e^{-2\alpha y} d(P(t) + Q(t))} \quad (5.147)$$

Proof. Multiply both sides of (5.140) by $e^{-\alpha t} e^{-\alpha(t+\tau)}$ and set

$$K_1(t, \tau) := e^{-\alpha t} e^{-\alpha(t+\tau)} m_{2,f}(t, \tau), \quad (5.148)$$

$$K_2(t, \tau) := e^{-\alpha t} e^{-\alpha(t+\tau)} m_{2,g}(t, \tau), \quad (5.149)$$

$$d\bar{P}(y) := \frac{e^{-2\alpha y} dP(y)}{\int_0^\infty e^{-2\alpha y} dP(y)}, \quad (5.150)$$

and

$$\gamma_1 = \int_0^\infty e^{-2\alpha y} dP(y) \quad (5.151)$$

to get

$$K_1(t, \tau) = \gamma_1 \int_0^t K_1(t-y, \tau) + K_2(t-y) d\bar{P}(y) + h_1(t, \tau), \quad (5.152)$$

where

$$h_1(t, \tau) := e^{-\alpha t} e^{-\alpha(t+\tau)} (1 + P(t + \tau)) \quad (5.153)$$

$$+ \gamma_1 \int_0^t e^{-\alpha(t-y)} m_f(t-y) e^{-\alpha(t+\tau-y)} m_g(t+\tau-y) d\bar{P}(y) \quad (5.154)$$

$$+ \gamma_1 \int_0^t e^{-\alpha(t-y)} m_g(t-y) e^{-\alpha(t+\tau-y)} m_f(t+\tau-y) d\bar{P}(y) \quad (5.155)$$

$$+ \gamma_1 \int_t^{t+\tau} e^{-\alpha(t-y)} e^{-\alpha(t+\tau-y)} m_f(t+\tau-y) d\bar{P}(y) \quad (5.156)$$

$$+ \gamma_1 \int_t^{t+\tau} e^{-\alpha(t-y)} e^{-\alpha(t+\tau-y)} m_g(t+\tau-y) d\bar{P}(y). \quad (5.157)$$

Similarly, multiply both sides of (5.141) by $e^{-\alpha t} e^{-\alpha(t+\tau)}$ and set

$$d\bar{Q}(y) := \frac{e^{-2\alpha y} dQ(y)}{\int_0^\infty e^{-2\alpha y} dQ(y)} \quad (5.158)$$

and

$$\gamma_2 := \int_0^\infty e^{-2\alpha y} dQ(y) \quad (5.159)$$

to get

$$K_2(t, \tau) = \gamma_2 \int_0^t K_1(t-y, \tau) + K_2(t-y) d\bar{Q}(y) + h_2(t, \tau) \quad (5.160)$$

where

$$h_2(t, \tau) := \gamma_2 \int_0^t e^{-\alpha(t-y)} m_f(t-y) e^{-\alpha(t+\tau-y)} m_g(t+\tau-y) d\bar{Q}(y) \quad (5.161)$$

$$+ \gamma_2 \int_0^t e^{-\alpha(t-y)} m_g(t-y) e^{-\alpha(t+\tau-y)} m_f(t+\tau-y) d\bar{Q}(y). \quad (5.162)$$

Similarly to the proof of Theorem 5.1.15, we can show

$$\lim_{t \rightarrow \infty} h_1(t, \tau) = 2\gamma_1 c_1 c_2 \quad (5.163)$$

and

$$\lim_{t \rightarrow \infty} h_2(t, \tau) = 2\gamma_2 c_1 c_2 \quad (5.164)$$

uniformly in τ , since P and Q are not lattice distributions. Now, adding (5.152) and (5.160) and setting

$$K(t, \tau) := K_1(t, \tau) + K_2(t, \tau), \quad (5.165)$$

$$h(t, \tau) := h_1(t, \tau) + h_2(t, \tau), \quad (5.166)$$

and

$$d\bar{R}(y) := \frac{e^{-2\alpha y} d(P(y) + Q(y))}{\gamma_1 + \gamma_2}, \quad (5.167)$$

we get

$$K(t, \tau) = (\gamma_1 + \gamma_2) \int_0^t K(t - y, \tau) d\bar{R}(y) + h(t, \tau). \quad (5.168)$$

Note that $\gamma_1 = p^*(2\alpha)$ and $\gamma_2 = q^*(2\alpha)$. Since $p^* + q^*$ is a decreasing function and $p^*(\alpha) + q^*(\alpha) = 1$, then we must have

$$\gamma_1 + \gamma_2 \leq 1. \quad (5.169)$$

Moreover, from (5.163) and (5.164)

$$\lim_{t \rightarrow \infty} h(t, \tau) = 2(\gamma_1 + \gamma_2)c_1 c_2 \quad (5.170)$$

uniformly in τ . Using Lemma 2 from [1], we can conclude we can conclude that

$$\lim_{t \rightarrow \infty} K(t, \tau) = \frac{2(\gamma_1 + \gamma_2)c_1 c_2}{1 - \gamma_1 - \gamma_2}. \quad (5.171)$$

Looking back at (5.152), we can let $t \rightarrow \infty$ and use (5.171) and (5.163) to conclude that

$$\lim_{t \rightarrow \infty} K_1(t, \tau) = \gamma_1 \lim_{t \rightarrow \infty} K(t, \tau) + \lim_{t \rightarrow \infty} h_1(t, \tau) \quad (5.172)$$

$$= \frac{2\gamma_1 c_1 c_2}{1 - \gamma_1 - \gamma_2}, \quad (5.173)$$

and

$$m_{2,f}(t, \tau) \sim D_1 e^{\alpha t} e^{\alpha(t+\tau)}, \quad (5.174)$$

where

$$D_1 := \frac{c_1 c_2 \int_0^\infty e^{-2\alpha y} dP(t)}{1 - \int_0^\infty e^{-2\alpha y} d(P(t) + Q(t))}. \quad (5.175)$$

Following a similar procedure for $n_{2,f}(t, \tau)$ and $n_{2,g}(t, \tau)$, we get

$$n_{2,f}(t, \tau) \sim D_2 e^{\alpha t} e^{\alpha(t+\tau)}, \quad (5.176)$$

where

$$D_2 := \frac{d_1 c_1 \int_0^\infty e^{-2\alpha y} Q(t)}{1 - \int_0^\infty e^{-2\alpha y} d(P(t) + Q(t))}. \quad (5.177)$$

■

Now, define

$$W_t := \frac{X_t}{c_1 e^{\alpha t}} \quad (5.178)$$

and

$$V_t := \frac{Y_t}{d_1 e^{\alpha t}}. \quad (5.179)$$

Proposition 5.2.15 (Proposition 5.1.16). *If P and Q are not both δ -lattice distributions, then*

$$\lim_{t \rightarrow \infty} \mathbb{E} \left[(W_{t+\tau} - W_t)^2 \right] = 0 \quad (5.180)$$

and

$$\lim_{t \rightarrow \infty} \mathbb{E} \left[(V_{t+\tau} - V_t)^2 \right] = 0 \quad (5.181)$$

uniformly in τ .

Since $L^2(P)$ is a complete metric space, we get the immediate corollary:

Corollary 5.2.16. W_t and V_t converge in $L^2(P)$ to random variables W and V , respectively, both with expected value 1.

5.2.4 Examples

Suppose P and Q are multi-phase distributions with parameter n and m , respectively. Then,

$$dP(t) = \frac{t^{n-1}e^{-t}}{(n-1)!} dt \quad (5.182)$$

and

$$dQ(t) = \frac{t^{m-1}e^{-t}}{(m-1)!} dt \quad (5.183)$$

and the exponential growth rate α for both X_t and Y_t is the root to

$$1 - \int_0^\infty \frac{t^{n-1}e^{-t(1+s)}}{(n-1)!} + \frac{t^{m-1}e^{-t(1+s)}}{(m-1)!} dt = 0, \quad (5.184)$$

which simplifies to finding the roots of

$$(1+s)^{m+n} - (1+s)^m - (1+s)^n = 0. \quad (5.185)$$

Chapter 6

Distribution of mutant cells

In this chapter, we will determine a probability distribution for the mutant cell population size when the total cell population is effectively infinite. We start by making assumptions about the cell population and the expected number of mutations that occur at any given time. The culmination of this dissertation are Theorems 6.1.1 and 6.2.1, where we give explicit formulas for the generating functions for the mutant cell population for symmetric and asymmetric cell division.

6.1 Symmetric cell division

6.1.1 Preliminaries and assumptions

We start by stating our assumptions about cell growth under symmetric division in which cells can possibly mutate.

Assumption 6.1.1 (Symmetric cell division with mutations). Cells have the following properties:

1. there is only one type of cell: mother cells;
2. all cells are identical and independent of each other;

3. cell life-span is a strictly positive, real-valued random variable \mathcal{T} with distribution P ;
4. at the end of a cell's life, it will divide into two cells;
5. when a cell divides, exactly one child cell can mutate with probability μ ;
6. all children spawned from a mutant cell will be mutants with no chance of losing the mutation.

We will be working backwards in time and let the current (time 0) cell population be n . In order for our model to work, we have to assume the following about our mutation rate and current cell population:

Assumption 6.1.2. We will assume n is very large and μ is sufficiently small so the product of μ and n stays fixed as $\mu \rightarrow 0^+$ and $n \rightarrow \infty$ such that

$$\mu n \sim 1. \tag{6.1}$$

6.1.2 Constructing the generating function

We will start by assuming time is discrete and takes values $k\delta_t$ for integers $k \geq 0$, where $\delta_t > 0$. Because we are working backwards in time, $k\delta_t$ represents time k time-units ago.

Consider 2 random variables:

1. the number of mutation events N_k that occurred k time-units ago and
2. the number of mutants M_k that arise from any one mutation event which occurred k time-units ago.

Then the total number of mutants will be given by the formula

$$R = \sum_{k=0}^{\infty} \sum_{j=1}^{N_k} M_k^{(j)} \tag{6.2}$$

where $M_k^{(j)}$ denotes independent copies of M_k . Essentially, we are assuming that k time-units ago, N_k mutation events occurred, and each one of these new mutants will produce a mutant population of M_k . Adding up all all the new mutants and their offspring for each time-unit, we get the total number of mutants R today.

Remark. In practice, k in (6.2) only needs to increase to a point where the population of non-mutants k time-units is much smaller than the current population. However, since we will assume we start with an effectively infinite cell population, mathematically, letting $k \rightarrow \infty$ is okay.

Let $F(t)$ be a function representing the cell population t time-units ago. So, $F(0) = n$.

Assumption 6.1.3. We will assume N_k is a Poisson random variable such that

$$N_k \sim \text{Pois}(\mu(F(k\delta_t) - F((k+1)\delta_t))), \quad (6.3)$$

which is assuming on average, a μ -proportion of new cells created during that time-unit, which corresponds to the number of cell divisions during that time-unit, will become mutants.

The above assumption is safe because of Assumption 6.1.2. Since n is effectively infinite and μ is infinitesimal, we can neglect the cells that were created between time-units $k+1$ and k that were already mutants.

Using Assumption 6.1.3, we obtain the generating function for R :

$$G_R(x) = \prod_{k=0}^{\infty} G_{N_k}(G_{M_k}(x)) \quad (6.4)$$

$$= \prod_{k=0}^{\infty} \exp(\mu(F(k\delta_t) - F((k+1)\delta_t))(G_{M_k}(x) - 1)) \quad (6.5)$$

$$= \exp\left(-\mu n + \mu \sum_{k=0}^{\infty} (F(k\delta_t) - F((k+1)\delta_t)) G_{M_k}(x)\right). \quad (6.6)$$

Letting $\delta_t \rightarrow 0^+$ and replacing $G_{M_k}(x)$ with $f(t, x)$, we get a continuous-time model for (6.6),

$$g_R(x) = \exp\left(-\mu n - \mu \int_0^\infty f(t, x) dF(t)\right). \quad (6.7)$$

Since we are working backwards in time, we can interpret our current time as infinite relative to when we started from a single cell. So, we know that a cell with life-span distribution P grows asymptotically exponential at growth rate α , where α is the root to

$$1 - 2 \int_0^\infty e^{-st} dP(t) = 0, \quad (6.8)$$

as long as P is not a lattice distribution, as seen in section 5.1. This leads us to make the following assumption about the cell population at backwards time t :

Assumption 6.1.4. The cell population at backwards time t is

$$F(t) = ne^{-\alpha t} \quad (6.9)$$

with high probability.

Remark. The above assumption may need to be rigorously verified. Although we know from section 5.1 that cells grow asymptotically exponential, we need to rigorously check that for large enough time T ,

$$\frac{Z_T}{Z_{T-t}} \sim e^{\alpha t}. \quad (6.10)$$

Now, since F has a derivative, we can replace $dF(t)$ in (6.7) with

$$dF(t) = F'(t) dt = n\alpha e^{-\alpha t} dt, \quad (6.11)$$

and arrive at

$$g_R(x) = \exp\left(-m + m\alpha \int_0^\infty f(t, x) e^{-\alpha t} dt\right), \quad (6.12)$$

where we let

$$m := \mu n. \quad (6.13)$$

The above construction culminates to the following theorem:

Theorem 6.1.1. *Let R be a random variable representing the mutant cell population in an effectively infinite cell population n with mutation rate μ , and let $m := \mu n \sim 1$. Let $f(t, x)$ be the generating function for the cell population under symmetric division at time t when you start from a single cell with life-span distribution P , which must satisfy*

$$f(t, x) = x(1 - P(t)) + \int_0^t f(t - \tau, x)^2 dP(\tau). \quad (6.14)$$

Let α be the root of

$$1 - 2 \int_0^\infty e^{-st} dP(t) = 0. \quad (6.15)$$

Then the generating function for R is

$$g_R(x) = \exp\left(-m + m\alpha \int_0^\infty f(t, x)e^{-\alpha t} dt\right). \quad (6.16)$$

6.2 Asymmetric cell division

6.2.1 Preliminaries and assumptions

We start by stating our assumptions about cell growth under asymmetric cell division in which cells can mutate.

Assumption 6.2.1 (Asymmetric cell division with mutations). Cells have the following properties:

1. there are exactly two types of cells: mother cells and daughter cells;
2. all cells are independent of each other, mother cells are identical to other mother cells, and daughter cells are identical to other daughter cells;

3. cell life-span for mother cells and daughter cells are strictly positive, real-valued random variables \mathcal{T}_x and \mathcal{T}_y , respectively, with distributions P and Q , respectively;
4. at the end of a cell's life, both mother cells and daughter cells will divide into one mother cell and one daughter cell;
5. when a cell divides, exactly one child cell can mutate with probability μ ;
6. all children spawned from a mutant cell will be mutants with no chance of losing the mutation.

Similarly to the previous section, we will be working backwards in time and let the current (time 0) cell population be n and continue to assume Assumption 6.1.2.

6.2.2 Constructing the generating function

Construction of the generating function for the mutant cell population will be done similarly to the symmetric cell division case. However, since there are now two cell types, mutants will grow differently depending on whether it was a mother cell that was mutated versus a daughter cell, and we must take that into consideration. Again, let $\delta_t > 0$ and suppose time is discrete and takes outputs $k\delta_t$ for integers $k \geq 0$.

Consider 4 random variables:

1. the number of mutant mother cells N_k^M created k time-units ago;
2. the number of mutant daughter cells N_k^D created k time-units ago;
3. the number of mutants M_k that arise from any one mutant mother cell which was created at k time-units ago;
4. the number of mutants D_k that arise from any one mutant daughter cell which was created at k time-units ago.

Then the total number of mutants will be given by the formula

$$R = R_M + R_D, \quad (6.17)$$

where

$$R_M = \sum_{k=0}^{\infty} \sum_{j=1}^{N_k^M} M_k^{(j)} \quad (6.18)$$

and

$$R_D = \sum_{k=0}^{\infty} \sum_{j=1}^{N_k^D} D_k^{(j)}, \quad (6.19)$$

and where $M_k^{(j)}$ and $D_k^{(j)}$ denote independent copies of M_k and D_k , respectively. This is analogous to the symmetric cell division model in section 6.1.2.

Let $F_m(t)$ and $F_D(t)$ be functions representing the mother and daughter cell population t time-units ago, respectively. So, $F_M(0) + F_D(0) = n$.

Assumption 6.2.2. We will assume N_k^M is a Poisson random variable such that

$$N_k^M \sim \text{Pois}(\mu(F_M(k\delta_t) - F_M((k+1)\delta_t))), \quad (6.20)$$

which is assuming on average, a μ -proportion of new mother cells created during that time-unit will become mutants. Similarly, we will assume N_k^D is a Poisson random variable such that

$$N_k^D \sim \text{Pois}(\mu(F_D(k\delta_t) - F_D((k+1)\delta_t))), \quad (6.21)$$

which is assuming on average, a μ -proportion of new daughter cells created during that time-unit will become mutants.

Assumption 6.2.3. In our model, we are counting the cell population that grows from a single mutant cell, and because cell growth is independent, we can assume R_M and R_D are independent. The above assumption about the number of new mutants is safe for the same

reasons in the previous section involving symmetric cell division.

Using Assumption 6.2.2, we obtain the generating function for R_M

$$G_{R_M}(x) = \prod_{k=0}^{\infty} G_{N_k^M}(G_{M_k}(x)) \quad (6.22)$$

$$= \prod_{k=0}^{\infty} \exp(\mu(F_M(k\delta_t) - F_M((k+1)\delta_t))(G_{M_k}(x) - 1)) \quad (6.23)$$

$$= \exp\left(-\mu F_M(0) + \mu \sum_{k=0}^{\infty} (F_M(k\delta_t) - F_M((k+1)\delta_t)) G_{M_k}(x)\right). \quad (6.24)$$

Letting $\delta_t \rightarrow 0$ and replacing $G_{M_k}(x)$ with $f(t, x)$, we get a continuous-time model for (6.24),

$$g_{R_M}(x) = \exp\left(-\mu F_M(0) - \mu \int_0^{\infty} f(t, x) dF_M(t)\right). \quad (6.25)$$

Similarly, we obtain a continuous-time generating function for R_D ,

$$g_{R_D}(x) = \exp\left(-\mu F_D(0) - \mu \int_0^{\infty} g(t, x) dF_D(t)\right), \quad (6.26)$$

where $g(t, x)$ corresponds to the continuous time generating function of $G_{D_k}(x)$.

Remark. $f(t, x)$ and $g(t, x)$ represent the generating function for the *total* cell population when you start from one mother cell or one daughter cell, respectively. This means $f(t, x) = f(t, x, x)$ and $g(t, x) = g(t, x, x)$ where the right-side of the equalities are the generating functions in (5.94).

Using Assumption 6.2.3, we get

$$g_R(x) = g_{R_M}(x)g_{R_D}(x) \quad (6.27)$$

$$= \exp\left(-\mu n - \mu \int_0^{\infty} f(t, x) dF_M(t) - \mu \int_0^{\infty} g(t, x) dF_D(t)\right). \quad (6.28)$$

Since we are working backwards in time, we can interpret our current time as infinite

relative to when we started from a single cell. So, we know that when mother and daughter cells have life-span distributions P and Q , respectively, and we start from a single mother cell, the total cell population is asymptotically exponential at growth rate α , where α is the root to

$$1 - \int_0^\infty e^{-st} dP(t) - \int_0^\infty e^{-st} dQ(t) = 0, \quad (6.29)$$

as long as P and Q are not both δ -lattice distribution, as seen in section 5.2. In addition, we know that asymptotically, the proportion of mother cells to the total cell population will be

$$\gamma := \frac{c_1}{c_1 + d_1} \quad (6.30)$$

$$= \int_0^\infty e^{-\alpha t} dP(t), \quad (6.31)$$

while the proportion of daughter cells to the total cell population will be

$$1 - \gamma = \frac{d_1}{c_1 + d_1} \quad (6.32)$$

$$= \int_0^\infty e^{-\alpha t} dQ(t), \quad (6.33)$$

where c_1 and d_1 are from (5.126) and (5.127). This leads us to require the following assumption about the cell population at backwards time t :

Assumption 6.2.4. The mother cell population at backwards time t is

$$F_M(t) = n\gamma e^{-\alpha t}, \quad (6.34)$$

and the daughter cell population at backwards time t is

$$F_d(t) = n(1 - \gamma)e^{-\alpha t} \quad (6.35)$$

with high probability.

Remark. Like in the symmetric cell division case, this still needs to be rigorously verified. In addition to verifying that the population at backwards time t is $ne^{(-\alpha t)}$, we also need to rigorously verify the proportion of mother and daughter cells is also maintained.

Now, since both F_M and F_D have derivatives, we can replace $dF_M(t)$ and $dF_D(t)$ in (6.28) with

$$dF_M(t) = F'_M(t) dt = n\gamma\alpha e^{-\alpha t} dt \quad (6.36)$$

and

$$dF_D(t) = F'_D(t) dt = n(1 - \gamma)\alpha e^{-\alpha t} dt \quad (6.37)$$

and arrive at

$$g_R(x) = \exp\left(-m + m\alpha \int_0^\infty (\gamma f(t, x) + (1 - \gamma)g(t, x))e^{-\alpha t} dt\right), \quad (6.38)$$

where we let

$$m := \mu n. \quad (6.39)$$

The above construction culminates to the following theorem:

Theorem 6.2.1. *Let R be a random variable representing the mutant cell population in an effectively infinite cell population n with mutation rate μ , and let $m := \mu n \sim 1$. Let $f(t, x)$ and $g(t, x)$ be the generating functions for the total cell population at time t when you start from a single mother cell and daughter cell, respectively, with life-span distributions P and Q for mother cells and daughter cells, respectively, which must satisfy*

$$\begin{cases} f(t, x) = x(1 - P(t)) + \int_0^t f(t - \tau, x)g(t - \tau, x) dP(\tau) \\ g(t, x) = x(1 - Q(t)) + \int_0^t f(t - \tau, x)g(t - \tau, x) dQ(\tau) \end{cases} . \quad (6.40)$$

Let α be the root of

$$1 - \int_0^\infty e^{-st} dP(t) - \int_0^\infty e^{-st} dQ(t) = 0 \quad (6.41)$$

and

$$\gamma := \int_0^\infty e^{-\alpha t} dP(t). \quad (6.42)$$

Then the generating function for R is

$$g_R(x) = \exp \left(-m + m\alpha \int_0^\infty (\gamma f(t, x) + (1 - \gamma)g(t, x))e^{-\alpha t} dt \right). \quad (6.43)$$

6.3 Examples

6.3.1 Symmetric cell division

Suppose P is an exponential distribution with parameter 1. Then from Theorem 3.5.1, we have

$$f(t, x) = \frac{xe^{-t}}{1 - x + xe^{-t}}, \quad (6.44)$$

and from section 5.1.5, we get

$$\alpha = 1. \quad (6.45)$$

So, our generating function (6.16) becomes

$$g_R(x) = (1 - x)^{\frac{m(1-x)}{x}}, \quad (6.46)$$

which is the Lea-Coulson distribution (see [4]). Expanding (6.46) into its series form, we get

$$g_R(x) = e^{-m} + \frac{1}{2}e^{-m}mx + \frac{1}{24}e^{-m}m(3m+4)x^2 + \frac{1}{48}e^{-m}m(m+2)^2x^3 + \dots \quad (6.47)$$

6.3.2 Asymmetric cell division

Suppose P and Q are multi-phase distributions with parameters 1 and 2, respectively. Then from section 5.2.4, we have

$$\alpha = \frac{\sqrt{5} - 1}{2}, \quad (6.48)$$

and so

$$\gamma = \frac{\sqrt{5} - 1}{2}. \quad (6.49)$$

This essentially models a situation where mother cells have shorter life-spans than daughter cells.

Using the series solution to $f(t, x)$ and $g(t, x)$ discussed in section 4.4 and the Ma-Sandri-Sarkar algorithm (see [6]), we can compute the coefficients one-by-one to compute $g_R(x)$ relatively quickly and get the following probabilities for the first few coefficients:

$$\Pr(R = 0) = e^{-m}, \quad (6.50)$$

$$\Pr(R = 1) = e^{-m} \left(\frac{1}{4} m (\sqrt{5} - 1)^2 \right), \quad (6.51)$$

$$\Pr(R = 2) = e^{-m} \left(\frac{(13\sqrt{5}m + 29m + 22\sqrt{5} + 50)m(\sqrt{5} - 1)}{4(55\sqrt{5} + 123)} \right), \quad (6.52)$$

⋮

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VITA

Hesam Oveys was born on October 19, 1986 in Columbia, Missouri. He graduated from David H. Hickman High School in 2004 and attended the University of Missouri in Columbia, where he graduated with a Bachelor's of Science in Mathematics in 2007. He continued his studies in mathematics by staying at the University of Missouri and pursuing a doctorate degree. Starting August 2015, he will be an instructor at his alma mater.