THE IMPACT OF MATURATION TIME DISTRIBUTIONS ON THE STAGE STRUCTURE OF A CELLULAR POPULATION

by

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ABSTRACT

Here we study how the stage structure of a population of cells varies with the distributions of times spent in each stage (which we will refer to as maturation time distributions). We consider a model with two life stages. The first stage represents the beginning of the first gap phase (early G1 phase). The second stage includes the end of the G1 phase, the synthesis phase (S phase), the second gap phase (G2 phase), and the mitosis phase (M phase). The evolution of the age density of cells in each stage is governed by a system of partial differential equations (PDEs) which is presented in Chapter 1. We use the method of characteristics to prove existence of solutions to the model PDE system in Chapter 2. In Chapter 3 we discuss the computation of the maturation rate and the numerical simulation of the system of PDEs. In Chapter 4 we simulate the model using two alternative maturation time distributions in order to illustrate the importance of the maturation time distribution for the population's stage and age structure. Because drug therapies may target specific cell cycle stages, this work can inform future studies aimed at developing more efficient drug therapies.

DEDICATION

I dedicate this work to my parents who are the reason of what I become today. To my great husband who taught me how to believe in myself. This work is also dedicated to all of my family members and my friends who are always with me since I have started this thesis. Each of you have occupied a special place in my heart. You have proved my belief that everyone can be inspired.

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CHAPTER I

INTRODUCTION

In this thesis, we study the stage structure of a population of cells. Specifically, we investigate how the distribution of exit times from each stage of the cell cycle impacts the stage structure of the population. For brevity, we will refer to the distribution of exit times from a cell cycle stage as the maturation time distribution of the stage. This research is motivated by a desire to understand the stage structure of mammalian cell populations, as this structure can impact the efficacy of drug therapies [1, 2, 3].

Within the mammalian cell cycle there exists a checkpoint, known as the restriction point or G1/S checkpoint, which controls entry into S phase [4, 5, 6, 7]. This checkpoint is regulated by growth factor signaling. As such, mammalian cells can coarsely be divided into those that have and those that have not received sufficient growth signals (mitogenic signals) to begin the process of cellular division [4, 5, 6, 7]. Hence, we consider a model with two cell cycle stages, representing the stage prior to restriction point passage (early G1) and the stage delineated by restriction point passage and mitosis (late G1 through M). As mentioned above, we are especially interested in how the maturation time distribution for each stage impacts the stage structure of the population, i.e. the fractions of cells that have and have not passed the restriction point.

This work builds on previous research [1, 8] which considered how division time distributions impact the age or generation structure of a cellular population. For example, [8] investigates the sensitivity of the generation structure to the distribution of division times (i.e. the intermitotic time distribution). The model in [8] is substantially different from our own model in that generation number increases indefinitely while stages occur in a cycle. As a result, the models differ in their boundary conditions. This difference may have a considerable impact on dynamics. The research presented here also differs from that in [8] in that we consider more general distributions of maturation times and more general initial age distributions, which yield models for which an analytical solution formula does not exist. A second paper of interest is [1] which develops methods for incorporating age dependency into models of cellular populations and demonstrates the utility of this approach for the study of drug therapy. Our work extends this research by modeling, in addition to age, cell cycle stage. Thus the model can be used to investigate both age and stage-dependent effects in relation to drug therapy. Indeed, cell cycle dynamics and the stage structure of a cellular population are thought to be important for drug therapy [2]. Finally, this work also relates to [2, 3] where stage-structured models were used to study the impact of drug therapy on pancreatic cancer cells. These models assume that in the absence of treatment or crowding the transition between cell cycle phases is governed by an exponential distribution, i.e. that cells experience a constant per capita maturation rate. In contrast, here we investigate the impact of non-constant transition rates on the stage-structure of a cellular population. In summary, to the best of our knowledge this is the first paper to consider the impact of maturation time distributions on the stage structure of a cellular population.

Our model consists the following system of partial differential equations (PDEs),

$$\frac{\partial g}{\partial t}(a,t) + \frac{\partial g}{\partial a}(a,t) = -\beta_g(a)g(a,t); \quad \text{for } a \geq 0,\ t \geq 0 \tag{1}$$

$$\frac{\partial f}{\partial t}(a,t) + \frac{\partial f}{\partial a}(a,t) = -\beta_f(a)f(a,t); \quad \text{for } a \geq 0,\ t \geq 0 \tag{2}$$

with boundary conditions:

$$g(a,0) = g_0(a) \quad \text{for} \quad a \geq 0, \tag{3}$$

$$g(0,t) = 2\int_0^\infty \beta_f(a) f(a,t)\,da \quad \text{for} \quad t \geq 0, \tag{4}$$

$$f(a,0) = f_0(a) \quad \text{for} \quad a \geq 0, \tag{5}$$

$$f(0,t) = \int_0^\infty \beta_g(a) g(a,t)\,da. \quad \text{for} \quad t \geq 0, \tag{6}$$

Here g gives the density of cells in the first stage, f gives the density of cells in the second stage, a denotes the "age" of a cell relative to the time it entered its current stage (that is, the time since it entered its current stage), and t denotes time. The model assumes that cells enter the second stage from the first with an age-dependent, per capita rate of $\beta_g(a)$. In addition, cells in the second stage divide, giving rise to two cells in the first stage with an age-dependent, per capita rate of $\beta_f(a)$.

CHAPTER II

EXISTENCE OF SOLUTIONS

We establish the existence of solutions using the method of characteristics, which is a technique for solving first-order partial differential equations [9, 10]. This method involves solving an auxiliary system of ordinary differential equations, termed characteristic equations. Below we give the characteristic equations associated with a, t, f, and g in our model (1)-(2), along with their solutions. Here z^g and z^f correspond to the value of the solutions g and f, respectively, along the characteristic curves parameterized by s. That is $z_g(s) = g(a(s), t(s))$ and $z_f(s) = f(a(s), t(s))$. Note that in fact we are working with a family of characteristic equations, parameterized by points on the boundary, $a \equiv 0 \cup t \equiv 0$, where the solution value is prescribed. In the solutions below, $B_g(s_1, s_2) = \int_{s_1}^{s_2} \beta_g(\alpha)d\alpha$ and $B_f(s_1, s_2) = \int_{s_1}^{s_2} \beta_f(\alpha)d\alpha$. In addition, the initial data $a(0), t(0), z_g(0)$, and $z_f(0)$ is determined by the intersection of the characteristic curve with the boundary.

$$\frac{da}{ds} = 1; \quad a(s) = s + a(0) \tag{7}$$

$$\frac{dt}{ds} = 1; \quad t(s) = s + t(0) \tag{8}$$

$$\frac{dz_g}{ds} = -\beta_g(a(s))z_g; \quad z_g(s) = z_g(0)e^{-B_g(s)} \tag{9}$$

$$\frac{dz_f}{ds} = -\beta_f(a(s))z_f; \quad z_f(s) = z_f(0)e^{-B_f(s)} \tag{10}$$

From (7) and (8) we see that the characteristic curves parameterized as $(a(s), t(s))$ are parallel lines with slope one. To find the solution of (1)-(6) at (a_0, t_0), we first find the characteristic curve through this point. There are two cases to consider:

Case 1: $0 \leq a_0 < t_0$

In this case, the characteristic curve through (a_0, t_0) intersects the boundary at $(0, t_0-$

a_0). It follows that $a(s) = s$, $t(s) = s + t_0 - a_0$ and $z_g(0) = g(0, t_0 - a_0)$, so that

$$g(a_0, t_0) = e^{-B_g(0,a_0)} \left(2 \int_0^\infty \beta_f(\alpha) f(\alpha, t_0 - a_0) d\alpha \right). \tag{11}$$

Similarly, for $a_0 < t_0$ we have

$$f(a_0, t_0) = e^{-B_f(0,a_0)} \left(\int_0^\infty \beta_g(\alpha) g(\alpha, t_0 - a_0) d\alpha \right). \tag{12}$$

Case 2: $0 \leq t_0 < a_0$

In this case, the characteristic curve through (a_0, t_0) intersects the boundary at $(a_0 - t_0, 0)$. It follows that $a(s) = s + a_0 - t_0$, $t(s) = s$ and $z_g(0) = g(a_0 - t_0, 0)$, so that

$$g(a_0, t_0) = g_0(a_0 - t_0) e^{-B_g(a_0 - t_0, a_0)}. \tag{13}$$

Similarly, for $a_0 > t_0$ we have

$$f(a_0, t_0) = f_0(a_0 - t_0) e^{-B_f(a_0 - t_0, a_0)}. \tag{14}$$

It is immediate that (13) and (14) solve (1)-(2) together with boundary conditions (3) and (5) for $a > t$, provided f_0 and g_0 are differentiable and $\beta_g(\alpha)$ and $\beta_f(\alpha)$ are continuous. Under additional assumptions, which allow one to differentiate through the integral, (11) and (12) satisfy (1)-(2) together with the boundary conditions (4) and (6) for $a < t$. In the next section we will employ formulas (11) and (12) to establish the existence of solutions to (1)-(2) together with the boundary conditions (4) and (6) for $a < t$.

II.1 Proof of existence of solutions

Here we show solutions of (1)-(6) exist. For this we employ an iterative method in which an approximating sequence is shown to converge to a solution. This method of proof is similar to that from [11], where global existence was shown for a size-structured model with a single stage and bounded size. We will denote the terms of the approximating sequence by g_n and f_n. These functions are defined as solutions of the following system of partial differential equations:

$$\frac{\partial g_{n+1}}{\partial t}(a,t) + \frac{g_{n+1}}{\partial a}(a,t) = -\beta_g(a) g_{n+1}(a,t); \quad \text{for } a \geq 0,\ t \geq 0 \tag{15}$$

$$\frac{\partial f_{n+1}}{\partial t}(a,t) + \frac{f_{n+1}}{\partial a}(a,t) = -\beta_f(a) f_{n+1}(a,t),; \quad \text{for } a \geq 0,\ t \geq 0 \tag{16}$$

subject to the boundary conditions:

$$\begin{aligned}
g_{n+1}(a,0) &= g_0(a) \quad \text{for} \quad a \geq 0, & (17)\\
g_{n+1}(0,t) &= 2\int_0^\infty \beta_f(a) f_n(a,t)da \quad \text{for} \quad t \geq 0, & (18)\\
f_{n+1}(a,0) &= f_0(a) \quad \text{for} \quad a \geq 0, & (19)\\
f_{n+1}(0,t) &= \int_0^\infty \beta_g(a) g_n(a,t)da \quad \text{for} \quad t \geq 0, & (20)
\end{aligned}$$

Notice that g_n is approximating g, which is the distribution of the cells in the first stage of the cell cycle, while f_n is approximating f, which is the distribution of the cells in the second stage of the cell cycle. Note that the solution value on the boundary where $a \equiv 0$ is determined by the previous iterate. Since the characteristic equations are identical to those for (1)-(2), we arrive at the following solution formulas.

Case 1: For $0 \leq a_0 < t_0$

$$\begin{aligned}
g_{n+1}(a_0,t_0) &= e^{-B_g(0,a_0)}\left(2\int_0^\infty \beta_f(\alpha) f_n(\alpha, t_0 - a_0)d\alpha\right), & (21)\\
f_{n+1}(a_0,t_0) &= e^{-B_f(0,a_0)}\left(\int_0^\infty \beta_g(\alpha) g_n(\alpha, t_0 - a_0)d\alpha\right). & (22)
\end{aligned}$$

Case 2: For $0 \leq t_0 < a_0$

$$g_{n+1}(a_0, t_0) = g_0(a_0 - t_0)e^{-B_g(a_0 - t_0, a_0)}, \tag{23}$$

$$f_{n+1}(a_0, t_0) = f_0(a_0 - t_0)e^{-B_f(a_0 - t_0, a_0)}. \tag{24}$$

Note that in the region $t < a$, g_n and f_n are independent of n and satisfy (15)-(16) together with the boundary conditions (17) and (19). Under additional assumptions, it can be shown that for $a < t$, g_n and f_n satisfy (15)-(16) together with the boundary conditions (18) and (20). Indeed we have the following theorem.

Theorem II.1 *Suppose*

(i) f_0 and g_0 are nonnegative and continuously differentiable for $a > 0$,

(ii) $\|f_0\|_{L^1[0,\infty)}$, $\|g_0\|_{L^1[0,\infty)}$, $\|f_0'\|_{L^1[0,\infty)}$, and $\|g_0'\|_{L^1[0,\infty)}$ are finite,

(iii) $\|f_0\|_\infty$ and $\|g_0\|_\infty$ are finite,

(iv) $\beta_f(\alpha)$ and $\beta_g(\alpha)$ are nonnegative, bounded and continuous, and

(v) there exists $A^* > 0$, such that for every $\alpha > A^*$, $f_0'(\alpha)$ is negative and increasing,

then for T sufficiently small there exists solutions of (1)-(6) on $\Omega = [0, \infty) \times [0, T)$, continuously differentiable, except possibly on the line $a = t$.

Since we have already found a solution for $a > t$, we focus our attention on the set $\Omega_1 = \{(a,t)|0 \leq a \leq t < T\}$, where the solution formula is given by

$$g_n(a_0, t_0) = 2e^{-B_g(0,a_0)} \int_0^\infty \beta_f(\alpha) f_{n-1}(\alpha, t_0 - a_0)d\alpha.$$

Establishing the continuity and differentiability of the integral

$$\int_0^\infty \beta_f(\alpha) f_{n-1}(\alpha, t_0 - a_0)d\alpha \tag{25}$$

is our primary task. Standard textbook theorems on this topic do not directly apply due to the requirement that there exist an L^1 function, M, such that, for every t $|f_{n-1}(\alpha, t)| \leq |M(\alpha)|$. For this reason, we have adopted condition (v) of Theorem 2.1, and adapted standard proofs [12, 13] to work under this alternate condition. In proving existence we consider $C(\Omega_1)$, the Banach space of continuous, bounded functions on Ω_1 with the norm

$$||h||_\infty := \sup_{x \in \Omega_1} h(x). \tag{26}$$

We begin by establishing the following lemma.

Lemma II.2 *For f_0, g_0, $\beta_f(\alpha)$, and $\beta_g(\alpha)$ as in Theorem 2.1*
(i) g_n and $f_n \in C(\Omega_1)$ and
(ii) $g := \lim_{n\to\infty} g_n$ and $f := \lim_{n\to\infty} f_n$ belong to $C(\Omega_1)$.

Proof: The proof is by induction. First note that for $(a_0, t_0) \in \Omega_1$,

$$g_n(a_0, t_0) = 2e^{-B_g(0,a_0)} \int_0^\infty \beta_f(\alpha) f_{n-1}(\alpha, t_0 - a_0) d\alpha.$$

Since $e^{-B_g(0,a_0)}$ is continuous, it suffices to show that $\int_0^\infty \beta_f(\alpha) f_{n-1}(\alpha, t_0 - a_0) d\alpha$ is continuous in Ω_1.

Suppose $f_{n-1}(a, t)$ is continuous in Ω_1. Choose $(a_0, t_0) \in \Omega_1$, let $\epsilon > 0$, and let (a_k, t_k) be a sequence of points converging to (a_0, t_0) in Ω_1.

The integral of interest may be written as:

$$
\begin{aligned}
|\int_0^\infty \beta_f(\alpha) f_{n-1}(\alpha, t_k - a_k) d\alpha \;&-\; \int_0^\infty \beta_f(\alpha) f_{n-1}(\alpha, t_0 - a_0) d\alpha| \\
&\le \int_0^\infty \beta_f(\alpha) |f_{n-1}(\alpha, t_k - a_k) - f_{n-1}(\alpha, t_0 - a_0)|\, d\alpha \\
&= \int_0^{A+T} \beta_f(\alpha) |f_{n-1}(\alpha, t_k - a_k) - f_{n-1}(\alpha, t_0 - a_0)|\, d\alpha \\
&+ \int_{A+T}^\infty \beta_f(\alpha) |f_{n-1}(\alpha, t_k - a_k) - f_{n-1}(\alpha, t_0 - a_0)|\, d\alpha,
\end{aligned} \tag{27}
$$

where A is chosen so that

$$\int_A^\infty |f_0(\alpha)|\, d\alpha \le \frac{\epsilon}{2\,\|\beta_f\|_\infty}.$$

Note by our assumptions, $t_k - a_k < T$ and $t_0 - a_0 < T$. Hence, there exists $\tau < T$ so that $t_k - a_k \le \tau$ for $k = 0, 1, \ldots$. Also, since $f_{n-1}(a, t)$ is continuous on the closed and bounded sets $D_1 = \{(a,t) | 0 \le a \le t \le \tau\}$ and $D_2 = \{(a,t) | 0 \le t \le a \le A + T, 0 \le t \le \tau\}$, there exists a constant C so that $f_{n-1}(a,t) < C$ on $D_1 \cup D_2$, and, for every $\alpha \in [0, t_0 - a_0) \cup (t_0 - a_0, A + T]$, as $(a_k, t_k) \to (a_0, t_0)$, $f_{n-1}(\alpha, t_k - a_k) \to f_{n-1}(\alpha, t_0 - a_0)$. Hence, by Lebesgue's Dominated Convergence Theorem [14],

$$\int_0^{A+T} \beta_f(\alpha) |f_{n-1}(\alpha, t_k - a_k) - f_{n-1}(\alpha, t_0 - a_0)|\, d\alpha \to 0.$$

Now note that the final term to the right of the equality in (27) is bounded by our choice of A. Indeed,

$$
\begin{aligned}
\|\beta_f\|_\infty \int_{A+T}^\infty |f_0(\alpha - (t_k - a_k)) e^{-B_f(\alpha - (t_k - a_k), \alpha)} \;&-\; f_0(\alpha - (t_0 - a_0)) e^{-B_f(\alpha - (t_0 - a_0), \alpha)}|\, d\alpha \\
&\le \|\beta_f\|_\infty \int_{A+T}^\infty |f_0(\alpha - (t_k - a_k))|\, d\alpha \\
&+ \|\beta_f\|_\infty \int_{A+T}^\infty |f_0(\alpha - (t_0 - a_0))|\, d\alpha \\
&\le \epsilon
\end{aligned} \tag{28}
$$

Since ϵ was arbitrary, we see that g_n is continuous in Ω_1. Similarly, it can be shown that f_n is continuous in Ω_1. This ends the proof that f_n and g_n are continuous in Ω_1.

Now we show that f_n and g_n have limits in $C(\Omega_1)$. For $a < t$ and $n = 0$ we have

$$\begin{aligned} |g_1 - g_0|(a,t) &= Ne^{-B_g(0,a)} \int_0^\infty f_0(\alpha)d\alpha - g_0(a) && (29)\\ &\leq N \left\|f_0\right\|_{L^1} + \left\|g_0\right\|_\infty \leq \infty, && (30)\\ |f_1 - f_0|(a,t) &\leq N \left\|g_0\right\|_{L^1} + \left\|f_0\right\|_\infty \leq \infty. && (31) \end{aligned}$$

Where $N := \max\left\{2\left\|\beta_g\right\|_\infty, \left\|\beta_f\right\|_\infty, 2\left\|\beta_f\right\|_\infty^2, 2\left\|\beta_g\right\|_\infty^2, 2\left\|\beta_f\right\|_\infty \left\|\beta_g\right\|_\infty\right\}$. Hence, we can define $M := \max\left\{\left\|f_1 - f_0\right\|_\infty, \left\|g_1 - g_0\right\|_\infty\right\} < \infty$.

In general,

$$g_{n+1}(a,t) - g_n(a,t) = e^{-B_g(0,a)} \left(\int_0^\infty 2\beta_f(\alpha)(f_n(\alpha, t-a)d\alpha - f_{n-1}(\alpha, t-a))d\alpha\right). \tag{32}$$

Thus, for $a < t < T$

$$\begin{aligned} |g_{n+1}(a,t) - g_n(a,t)| &= \left|e^{-B_g(0,a)} \int_0^\infty 2\beta_f(\alpha)(f_n(\alpha,t-a) - f_{n-1}(\alpha,t-a))d\alpha\right| \\ &\leq e^{-B_g(0,a)} \int_0^{t-a} 2\beta_f(\alpha)|f_n - f_{n-1}|d\alpha \\ &= Ne^{-B_g(0,a)}(t-a)\left\|f_n - f_{n-1}\right\|_\infty \\ &\leq NT\left\|f_n - f_{n-1}\right\|_\infty && (33) \end{aligned}$$

That is,

$$\left\|g_{n+1} - g_n\right\|_\infty \leq NT\left\|f_n - f_{n-1}\right\|_\infty. \tag{34}$$

Similarly,

$$\left\|f_{n+1} - f_n\right\|_\infty \leq NT\left\|g_n - g_{n-1}\right\|_\infty. \tag{35}$$

(Note that by the triangle inequality and since $\|f_n\|_\infty$ and $\|g_n\|_\infty$ are finite, $\|f_{n+1}\|_\infty$ and $\|g_{n+1}\|_\infty$ are finite as well.) We now have that

$$\|g_{n+1} - g_n\|_\infty \leq NT \|f_n - f_{n-1}\|_\infty \tag{36}$$
$$\leq (NT)^{n-1} M, \tag{37}$$

and

$$\|f_{n+1} - f_n\|_\infty \leq NT \|g_n - g_{n-1}\|_\infty \tag{38}$$
$$\leq (NT)^{n-1} M. \tag{39}$$

Since

$$g_n \;=\; g_0 + \sum_{i=1}^{n} (g_i - g_{i-1}), \tag{40}$$

we see that

$$g := \lim_{n\to\infty} g_n = g_0 + \sum_{i=1}^{\infty} (g_i - g_{i-1}) \tag{41}$$

exists, and the convergence is uniform on Ω_1 by the Weierstrass M-test, provided

$$T < \frac{1}{N}. \tag{42}$$

Therefore, $g \in C(\Omega_1)$. Similarly,

$$f := \lim_{n\to\infty} f_n = f_0 + \sum_{i=1}^{\infty} (f_i - f_{i-1}) \tag{43}$$

exists in $C(\Omega_1)$. This concludes the proof of convergence, so we have established Lemma 2.2. □

Assuming that we may differentiate through the integral in (21) - (22), and accounting for the possible discontinuity at $a = t$ we find:

Case 1 : For $0 \leq a < t$

$$\begin{aligned}
\frac{\partial g_{n+1}}{\partial a}(a,t) &= -2e^{-B_g(0,a)}\int_0^\infty \beta_f(\alpha)\left(\beta_g(a)(f_n(\alpha,t-a)+\frac{\partial f_n}{\partial t}(\alpha,t-a)\right)d\alpha \\
&- 2\beta_f(t-a)e^{-B_g(0,a)}\left(\lim_{\alpha\to(t-a)^-} f_n(\alpha,t-a) - \lim_{\alpha\to(t-a)^+} f_n(\alpha,t-a)\right) \quad (44)\\
\frac{\partial g_{n+1}}{\partial t}(a,t) &= 2e^{-B_g(0,a)}\int_0^\infty \beta_f(\alpha)\frac{\partial f_n}{\partial t}(\alpha,t-a)d\alpha \\
&+ 2\beta_f(t-a)e^{-B_g(0,a)}\left(\lim_{\alpha\to(t-a)^-} f_n(\alpha,t-a) - \lim_{\alpha\to(t-a)^+} f_n(\alpha,t-a)\right) \quad (45)
\end{aligned}$$

$$\begin{aligned}
\frac{\partial f_{n+1}}{\partial a}(a,t) &= -e^{-B_f(0,a)}\int_0^\infty \beta_g(\alpha)\left(\beta_f(a)g_n(\alpha,t-a)+\frac{\partial g_n}{\partial t}(\alpha,t-a)\right)d\alpha \\
&- \beta_g(t-a)e^{-B_f(0,a)}\left(\lim_{\alpha\to(t-a)^-} g_n(\alpha,t-a) - \lim_{\alpha\to(t-a)^+} g_n(\alpha,t-a)\right) \quad (46)\\
\frac{\partial f_{n+1}}{\partial t}(a,t) &= e^{-B_f(0,a)}\int_0^\infty \beta_g(\alpha)\frac{\partial g_n}{\partial t}(\alpha,t-a)d\alpha \\
&+ \beta_g(t-a)e^{-B_f(0,a)}\left(\lim_{\alpha\to(t-a)^-} g_n(\alpha,t-a) - \lim_{\alpha\to(t-a)^+} g_n(\alpha,t-a)\right) \quad (47)
\end{aligned}$$

Case 2 : For $0 \leq t < a$

$$\begin{aligned}
\frac{\partial g_{n+1}}{\partial a}(a,t) &= e^{-B_g(a-t,a)}\left(g_0'(a-t)+\beta_g(a-t)g_0(a-t)-\beta_g(a)g_0(a-t)\right) \quad (48)\\
\frac{\partial g_{n+1}}{\partial t}(a,t) &= -e^{-B_g(a-t,a)}\left(g_0'(a-t)-\beta_g(a-t)g_0(a-t)\right) \quad (49)
\end{aligned}$$

$$\begin{aligned}
\frac{\partial f_{n+1}}{\partial a}(a,t) &= e^{-B_f(a-t,a)}\left(f_0'(a-t)+\beta_f(a-t)f_0(a-t)-\beta_f(a)f_0(a-t)\right) \quad (50)\\
\frac{\partial f_{n+1}}{\partial t}(a,t) &= -e^{-B_f(a-t,a)}\left(f_0'(a-t)-\beta_f(a-t)f_0(a-t)\right). \quad (51)
\end{aligned}$$

From the above cases we see that g_n and f_n given by (21)-(24) will satisfy (15) - (16) together with the boundary conditions (17) - (20), provided we may differentiate through the integral.

Shortly we will show that the first partial derivatives of g_n and f_n are given by (44)-(47), but first we will establish the continuity of the expressions to the right of each equality in (44)-(47). Moreover, we will show these expressions converge uniformly in Ω_1. For convenience, we refer to the integral expressions above as the partial derivatives of f_n and g_n, however, in the following lemma and proof we do not assume this to be the case. That is, in the following lemma $\frac{\partial g_n}{\partial a}$, $\frac{\partial g_n}{\partial t}$, $\frac{\partial f_n}{\partial a}$, and $\frac{\partial f_n}{\partial t}$ stand for the expressions on the right-hand-side of (48)-(51), respectively.

Lemma II.3 *Let f_0, g_0, $\beta_f(\alpha)$ and $\beta_g(\alpha)$ as in Theorem 2.1, and define* $\dfrac{\partial g_n}{\partial t}$, $\dfrac{\partial f_n}{\partial t}$, $\dfrac{\partial g_n}{\partial a}$, *and* $\dfrac{\partial f_n}{\partial a}$ *by (45),(47),(44) and (46), respectively.*

(i) $\dfrac{\partial g_n}{\partial t}$, $\dfrac{\partial f_n}{\partial t}$, $\dfrac{\partial g_n}{\partial a}$, *and* $\dfrac{\partial f_n}{\partial a}$ *belong to* $C(\Omega_1)$

(ii) $\frac{\partial f_n}{\partial t}$, $\frac{\partial f_n}{\partial a}$, $\frac{\partial g_n}{\partial t}$ *and* $\frac{\partial g_n}{\partial a}$ *converge uniformly on* Ω_1.

Proof: The continuity of $\dfrac{\partial g_n}{\partial t}$, $\dfrac{\partial f_n}{\partial t}$, $\dfrac{\partial g_n}{\partial a}$, and $\dfrac{\partial f_n}{\partial a}$ on Ω_1 follows by induction as in the proof of Lemma 2.2.

Now we show the sequences $\frac{\partial f_n}{\partial t}$, $\frac{\partial f_n}{\partial a}$, $\frac{\partial g_n}{\partial t}$ and $\frac{\partial g_n}{\partial a}$ converge uniformly on Ω_1. (Note that these sequences are constant for $a > t$, and hence convergence is uniform in this region as well.)

We see that

$$\begin{aligned} \left|\frac{\partial g_{n+1}}{\partial t} - \frac{\partial g_n}{\partial t}\right| &\leq Ne^{-B_g(0,a)} \int_0^{t-a} \left|\frac{\partial f_n}{\partial t} - \frac{\partial f_{n-1}}{\partial t}\right| d\alpha \qquad (52) \\ &+ Ne^{-B_g(0,a)} \left|\lim_{\alpha\to(t-a)^-} f_n(\alpha, t-a) - \lim_{\alpha\to(t-a)^+} f_{n-1}(\alpha, t-a)\right| \\ &\leq N(t-a)\left\|\frac{\partial f_n}{\partial t} - \frac{\partial f_{n-1}}{\partial t}\right\|_\infty + N\left\|f_n - f_{n-1}\right\|_\infty \qquad (53) \\ &\leq NT\left\|\frac{\partial f_n}{\partial t} - \frac{\partial f_{n-1}}{\partial t}\right\|_\infty + N(NT)^{n-1}M, \qquad (54) \end{aligned}$$

and

$$
\begin{aligned}
\left|\frac{\partial f_{n+1}}{\partial t} - \frac{\partial f_n}{\partial t}\right| &\leq Ne^{-B_f(0,a)} \int_0^{t-a} |\frac{\partial g_n}{\partial t} - \frac{\partial g_{n-1}}{\partial t} d\alpha| \qquad (55)\\
&+ Ne^{-B_f(0,a)} \left| \lim_{\alpha\to(t-a)^-} g_n(\alpha, t-a) - \lim_{\alpha\to(t-a)^+} g_{n-1}(\alpha, t-a)\right| \\
&\leq N(t-a) \left\|\frac{\partial g_n}{\partial t} - \frac{\partial g_{n-1}}{\partial t}\right\|_\infty + N\left\|g_n - g_{n-1}\right\|_\infty \qquad (56)\\
&\leq NT \left\|\frac{\partial g_n}{\partial t} - \frac{\partial g_{n-1}}{\partial t}\right\|_\infty + N(NT)^{n-1}M. \qquad (57)
\end{aligned}
$$

Combining these two together :

$$
\left\|\frac{\partial g_{n+1}}{\partial t} - \frac{\partial g_n}{\partial t}\right\|_\infty \leq NT \left\|\frac{\partial f_n}{\partial t} - \frac{\partial f_{n-1}}{\partial t}\right\|_\infty + N(NT)^{n-1}M \qquad (58)
$$

$$
\left\|\frac{\partial f_{n+1}}{\partial t} - \frac{\partial f_n}{\partial t}\right\|_\infty \leq NT \left\|\frac{\partial g_n}{\partial t} - \frac{\partial g_{n-1}}{\partial t}\right\|_\infty + N(NT)^{n-1}M \qquad (59)
$$

Let $\hat{M} := \max\left\{\left\|\frac{\partial f_2}{\partial t} - \frac{\partial f_1}{\partial t}\right\|_\infty, \left\|\frac{\partial g_2}{\partial t} - \frac{\partial g_1}{\partial t}\right\|_\infty\right\}$. Then,

$$
\begin{aligned}
\left\|\frac{\partial g_{n+1}}{\partial t} - \frac{\partial g_n}{\partial t}\right\|_\infty &\leq NT \left\|\frac{\partial f_n}{\partial t} - \frac{\partial f_{n-1}}{\partial t}\right\|_\infty + N(NT)^{n-1}M \qquad (60)\\
&\leq \dots \\
&\leq \hat{M}(NT)^{n-1} + (n-1)NM(NT)^{n-1}. \qquad (61)
\end{aligned}
$$

Similarly,

$$
\left\|\frac{\partial f_{n+1}}{\partial t} - \frac{\partial f_n}{\partial t}\right\|_\infty \leq \dots \leq \hat{M}(NT)^{n-1} + (n-1)NM(NT)^{n-1}. \qquad (62)
$$

Thus, provided $\hat{M}$ is finite, the sequences of partial derivatives converge uniformly for $t \leq T < \frac{1}{N}$.

To show that $\hat{M}$ is finite, we first consider the base case. For this, it is useful to recall

$$
\begin{aligned}
f_0(a,t) &= f_0(a). \qquad (63)\\
g_0(a,t) &= g_0(a), \qquad (64)
\end{aligned}
$$

Also, for $n > 0$ and $a < t$,

$$\begin{aligned}
\frac{\partial g_{n+1}}{\partial t}(a,t) &= 2e^{-B_g(0,a)} \int_0^\infty \beta_f(\alpha) \frac{\partial f_n}{\partial t}(\alpha, t-a) d\alpha \\
&+ 2\beta_f(t-a)e^{-B_g(0,a)} \left(\lim_{\alpha \to (t-a)^-} f_n(\alpha, t-a) - \lim_{\alpha \to (t-a)^+} f_n(\alpha, t-a) \right) \quad (65) \\
\frac{\partial f_{n+1}}{\partial t}(a,t) &= e^{-B_f(0,a)} \int_0^\infty \beta_g(\alpha) \frac{\partial g_n}{\partial t}(\alpha, t-a) d\alpha \\
&+ \beta_g(t-a)e^{-B_f(0,a)} \left(\lim_{\alpha \to (t-a)^-} g_n(\alpha, t-a) - \lim_{\alpha \to (t-a)^+} g_n(\alpha, t-a) \right), \quad (66)
\end{aligned}$$

while for $n > 0$ and $t < a$

$$\frac{\partial g_{n+1}}{\partial t}(a,t) = -e^{-B_g(a-t,a)} \left(g_0'(a-t) - \beta_g(a-t) g_0(a-t) \right) \quad (67)$$

$$\frac{\partial f_{n+1}}{\partial t}(a,t) = -e^{-B_f(a-t,a)} \left(f_0'(a-t) - \beta_f(a-t) f_0(a-t) \right). \quad (68)$$

From (63) and (64)

$$\frac{\partial g_0}{\partial t}(a,t) = 0 \quad \text{for} \quad (a,t) \in (0,\infty) \times (0,T) \quad (69)$$

$$\frac{\partial f_0}{\partial t}(a,t) = 0 \quad \text{for} \quad (a,t) \in (0,\infty) \times (0,T). \quad (70)$$

Also, $f_0(a,t) \equiv f_0(a)$ is continuous. Hence by (65) and (66)

$$\frac{\partial g_1}{\partial t}(a,t) = 0 \quad \text{for} \quad a < t \quad (71)$$

$$\frac{\partial f_1}{\partial t}(a,t) = 0 \quad \text{for} \quad a < t. \quad (72)$$

On the other hand, for $t < a$, $\dfrac{\partial g_1}{\partial t}$ and $\dfrac{\partial f_1}{\partial t}$ are given by (67) and (68), respectively.

Having computed $\dfrac{\partial g_1}{\partial t}$ and $\dfrac{\partial f_1}{\partial t}$ we are ready to compute $\dfrac{\partial g_2}{\partial t}$ and $\dfrac{\partial f_2}{\partial t}$. For $a < t$:

$$\begin{aligned}
\frac{\partial g_2}{\partial t}(a,t) &= 2e^{-B_g(0,a)}\left(\int_0^{t-a}\beta_f(\alpha)\frac{\partial f_1}{\partial t}(\alpha,t-a)d\alpha + \int_{t-a}^{\infty}\beta_f(\alpha)\frac{\partial f_1}{\partial t}(\alpha,t-a)d\alpha\right)\\
&+ 2\beta_f(t-a)e^{-B_g(0,a)}\left(\lim_{\alpha\to(t-a)^-} f_1(\alpha,t-a) - \lim_{\alpha\to(t-a)^+} f_1(\alpha,t-a)\right)\\
&= -2e^{-B_g(0,a)}\int_{t-a}^{\infty}\beta_f(\alpha)\beta_f(\alpha-(t-a))e^{-B_f(\alpha-(t-a),\alpha)}f_0(\alpha-(t-a))d\alpha\\
&- 2e^{-B_g(0,a)}\int_{t-a}^{\infty}\beta_f(\alpha)e^{-B_f(\alpha-(t-a),\alpha)}f_0'(\alpha-(t-a))d\alpha\\
&+ 2\beta_f(t-a)e^{-B_g(0,a)}e^{-B_f(0,t-a)}\left(\int_0^{\infty}\beta_g(\alpha)g_0(\alpha)d\alpha - f_0(0)\right) \qquad (73)
\end{aligned}$$

For the first two terms to the right of the final equality above, let $u = \alpha - (t-a)$ and $du = d\alpha$, so that we obtain:

$$\begin{aligned}
\frac{\partial g_2}{\partial t}(a,t) = &- 2e^{-B_g(0,a)}\int_0^{\infty} e^{-B_f(u,u+(t-a))}\beta_f(u+(t-a))\beta_f(u)f_0(u)du\\
&- 2e^{-B_g(0,a)}\int_0^{\infty} e^{-B_f(u,u+(t-a))}\beta_f(u+(t-a))f_0'(u)du. \qquad (74)
\end{aligned}$$

Thus for $a < t$

$$\begin{aligned}
\left|\frac{\partial g_2}{\partial t}(a,t)\right| &\le 2\|\beta_f\|_\infty^2\|f_0\|_{L^1} + 2\|\beta_f\|_\infty\|f_0'\|_{L^1} + 2\|\beta_f\|_\infty\|\beta_g\|_\infty\|g_0\|_{L^1} + 2\|\beta_f\|_\infty\|f_0\|_\infty\\
&\le N(\|f_0\|_{L^1} + \|g_0\|_{L^1} + \|f_0'\|_{L^1} + \|f_0\|_\infty). \qquad (75)
\end{aligned}$$

Therefore,

$$\left\|\frac{\partial g_2}{\partial t} - \frac{\partial g_1}{\partial t}\right\|_\infty < \infty. \qquad (76)$$

Similarly,

$$\left\|\frac{\partial f_2}{\partial t} - \frac{\partial f_1}{\partial t}\right\|_\infty < \infty. \qquad (77)$$

This shows that $\hat{M}$ is finite, and the partial derivatives with respect to t converge uniformly to their limits in Ω_1 for $T < \frac{1}{N}$. Furthermore, from (44) and (46) we see that

$$\frac{\partial g_{n+1}}{\partial a}(a_0,t_0) = -\frac{\partial g_{n+1}}{\partial t}(a_0,t_0) - \beta_g(a_0)g_{n+1}(a_0,t_0), \tag{78}$$

$$\frac{\partial f_{n+1}}{\partial a}(a_0,t_0) = -\frac{\partial f_{n+1}}{\partial t}(a_0,t_0) - \beta_f(a_0)f_{n+1}(a_0,t_0). \tag{79}$$

Therefore, the uniform convergence of $\frac{\partial g_n}{\partial a}$ and $\frac{\partial f_n}{\partial a}$ follows from that of $\frac{\partial g_n}{\partial t}$, $\frac{\partial f_n}{\partial t}$, f_n and g_n. □

Now we will show that for every $n \in \mathbb{N}$, f_n and g_n are continuously differentiable with respect to t. Moreover, we can compute $\frac{\partial f_n}{\partial t}$ and $\frac{\partial g_n}{\partial t}$ by differentiating through the integral in (21) and (22). The proof is by induction.

Suppose that f_n is continuously differentiable with respect to t in Ω_1. Let $(a,t) \in \Omega_1$ and choose $\delta > 0$ so that $(a, t \pm \delta) \in \Omega_1$ (or, in case $a = t$, $(a, t+\delta) \in \Omega_1$). Also, suppose $\delta > \Delta t > 0$. Since Ω_1 is convex, we see that $(a, t \pm \Delta t) \in \Omega_1$ for any such Δt. Given $\epsilon > 0$, suppose that $A > A^*$ is chosen such that

$$\|\beta_f\|_\infty \int_A^\infty |f_0'(\alpha)|\, d\alpha + \|\beta_f\|_\infty^2 \int_A^\infty |f_0(\alpha)|\, d\alpha < \frac{\epsilon}{2}.$$

This is possible since f_0' and f_0 are L^1. Now we establish convergence of the difference quotient:

$$\begin{aligned}\int_0^\infty \frac{\beta_f(\alpha)(f_n(\alpha,t+\Delta t-a) - f_n(\alpha,t-a))}{\Delta t}\,d\alpha &= \int_0^{A+T} \frac{\beta_f(\alpha)(f_n(\alpha,t+\Delta t-a) - f_n(\alpha,t-a))}{\Delta t}\,d\alpha \\ &+ \int_{A+T}^\infty \frac{\beta_f(\alpha)(f_n(\alpha,t+\Delta t-a) - f_n(\alpha,t-a))}{\Delta t}\,d\alpha\end{aligned} \tag{80}$$

We will handle the first and second terms to the right if the inequality in (80) separately. The first term can be expressed as

$$\begin{aligned}\int_0^{A+T} \frac{\beta_f(\alpha)(f_n(\alpha,t+\Delta t-a) - f_n(\alpha,t-a))}{\Delta t}\,d\alpha &= \int_0^{t-a} \frac{\beta_f(\alpha)(f_n(\alpha,t+\Delta t-a) - f_n(\alpha,t-a))}{\Delta t}\,d\alpha \\ &+ \int_{t-a}^{t-a+\Delta t} \frac{\beta_f(\alpha)(f_n(\alpha,t+\Delta t-a) - f_n(\alpha,t-a))}{\Delta t}\,d\alpha \\ &+ \int_{t-a+\Delta t}^{A+T} \frac{\beta_f(\alpha)(f_n(\alpha,t+\Delta t-a) - f_n(\alpha,t-a))}{\Delta t}\,d\alpha\end{aligned} \tag{81}$$

Since $f_n(\alpha,t^*)$ and $\frac{\partial f_n}{\partial t}(\alpha,t^*)$ are continuous on the sets $D_1 = \{(\alpha,t^*)|0 \le \alpha \le t^* \le t-a+\delta\}$ and $D_2 = \{(\alpha,t^*)|0 \le t^* \le a \le A+T, 0 \le t^* \le t-a+\delta\}$, by the mean value theorem, the first and third terms to the right of the equality in (81) can be expressed as:

$$\int_0^{t-a} \beta_f(\alpha)\frac{f_n(\alpha,t+\Delta t-a)-f_n(\alpha,t-a)}{\Delta t}d\alpha = \int_0^{t-a} \beta_f(\alpha)\frac{\partial f_n}{\partial t}(\alpha,t^*(\alpha))d\alpha,$$

$$\int_{t-a+\Delta t}^{A+T} \beta_f(\alpha)\frac{f_n(\alpha,t+\Delta t-a)-f_n(\alpha,t-a)}{\Delta t}d\alpha = \int_{t-a+\Delta t}^{A+T} \beta_f(\alpha)\frac{\partial f_n}{\partial t}(\alpha,t^*(\alpha))d\alpha.$$

Where $t^*(a)$ is between $t-a$ and $t-a+\Delta t$. Since $\frac{\partial f_n}{\partial t}(\alpha,t^*)$ is continuous on D_1 and D_2, we have that $\frac{\partial f_n}{\partial t}(\alpha,t^*(\alpha)) \to \frac{\partial f_n}{\partial t}(\alpha,t)$ point-wise as $\Delta t \to 0$. Moreover, since D_1 and D_2 are closed and bounded, there exists a constant C so that $\frac{\partial f_n}{\partial t}(\alpha,t^*) < C$ on $D_1 \cup D_2$. Therefore, by Lebesgue's dominated convergence theorem, as $\Delta t \to 0$,

$$\int_0^{t-a} \beta_f(\alpha)\frac{\partial f_n}{\partial t}(\alpha,t^*(\alpha))d\alpha \to \int_0^{t-a} \beta_f(\alpha)\frac{\partial f_n}{\partial t}(\alpha,t-a)d\alpha$$

and

$$\int_{t-a+\Delta t}^{A+T} \beta_f(\alpha)\frac{\partial f_n}{\partial t}(\alpha,t^*(\alpha))d\alpha \to \int_{t-a+\Delta t}^{A+T} \beta_f(\alpha)\frac{\partial f_n}{\partial t}(\alpha,t-a)d\alpha.$$

For the second term in (81) we have

$$\begin{aligned}\int_{t-a}^{t-a+\Delta t} \beta_f(\alpha)\frac{f_n(\alpha,t+\Delta t-a)-f_n(\alpha,t-a)}{\Delta t}d\alpha &= \frac{1}{\Delta t}\int_{t-a}^{t-a+\Delta t} \beta_f(\alpha)f_n(\alpha,t+\Delta t-a)d\alpha \\ &- \frac{1}{\Delta t}\int_{t-a}^{t-a+\Delta t} \beta_f(\alpha)f_n(\alpha,t-a)d\alpha \qquad (82)\end{aligned}$$

Since $f_n(\alpha,t^*)$ is uniformly continuous on D_1, which contains the domain of integration for the first integral above, as $\Delta t \to 0$,

$$\frac{1}{\Delta t}\int_{t-a}^{t-a+\Delta t} \beta_f(\alpha)f_n(\alpha,t+\Delta t-a)d\alpha \to \lim_{\alpha\to(t-a)^-} \beta_f(\alpha)f_n(\alpha,t-a).$$

Since $f_n(\alpha,t^*)$ is uniformly continuous on the closed and bounded region D_2, which contains the domain of integration for the second integral above, as $\Delta t \to 0$,

$$\frac{1}{\Delta t}\int_{t-a}^{t-a+\Delta t} \beta_f(\alpha)f_n(\alpha,t-a)d\alpha \to \lim_{\alpha\to(t-a)^+} \beta_f(\alpha)f_n(\alpha,t-a).$$

Hence

$$\int_0^{A+T} \frac{\beta_f(\alpha)(f_n(\alpha,t+\Delta t-a)-f_n(\alpha,t-a))}{\Delta t}d\alpha \to \int_0^{A+T} \beta_f(\alpha)\frac{\partial f_n}{\partial t}(\alpha,t-a)d\alpha$$
$$+\lim_{\alpha\to(t-a)^-}\beta_f(\alpha)f_n(\alpha,t-a)$$
$$-\lim_{\alpha\to(t-a)^+}\beta_f(\alpha)f_n(\alpha,t-a).$$

Now we show the convergence of the second term in (80). Applying the mean value theorem to $f_n(\alpha,t^*(\alpha))$ for $\alpha \geq t^*$,

$$\begin{aligned}\left|\int_{A+T}^{\infty} \frac{\beta_f(\alpha)(f_n(\alpha,t+\Delta t-a)-f_n(\alpha,t-a))}{\Delta t}d\alpha\right| &= \left|\int_{A+T}^{\infty}\beta_f(\alpha)\frac{\partial f_n}{\partial t}(\alpha,t^*(\alpha))d\alpha\right| \\ &\leq \|\beta_f\|_\infty \int_{A+T}^{\infty}\left|\frac{\partial f_n}{\partial t}(\alpha,t^*(\alpha))\right|d\alpha\end{aligned} \tag{83}$$

where $t^*(a)$ is between $t-a$ and $t-a+\Delta t$. The integral in the final term can be expanded as:

$$\begin{aligned}&\|\beta_f\|_\infty \int_{A+T}^{\infty}\left|\frac{\partial f_n}{\partial t}(\alpha,t^*(\alpha))\right|d\alpha \\ &= \|\beta_f\|_\infty \int_{A+T}^{\infty}\left|e^{-B_f(\alpha-t^*(\alpha),\alpha)}\left(f_0'(\alpha-t^*(\alpha))+\beta_f(\alpha-t^*(\alpha))f_0(\alpha-t^*(\alpha))\right)\right|d\alpha \\ &\leq \|\beta_f\|_\infty \int_{A+T}^{\infty}|f_0'(\alpha-t^*(\alpha))|\,d\alpha + \|\beta_f\|_\infty^2 \int_{A+T}^{\infty}|f_0(\alpha-t^*(\alpha))|\,d\alpha.\end{aligned} \tag{84}$$

Since $(\alpha-t^*(\alpha)) \geq (\alpha-(t+\Delta t-a)) \geq A$, by (v) of Theorem 2.1, we have that $|f_0'(\alpha-t^*(\alpha))| \leq |f_0'(\alpha-(t+\Delta t-a))|$ and $|f_0(\alpha-t^*(\alpha))| \leq |f_0(\alpha-(t+\Delta t-a))|$.

Thus,

$$
\begin{aligned}
&\|\beta_f\|_\infty \int_{A+T}^{\infty} |f_0'(\alpha - t^*(\alpha))|\, d\alpha + \|\beta_f\|_\infty^2 \int_{A+T}^{\infty} |f_0(\alpha - t^*(\alpha))|\, d\alpha \\
&\leq \|\beta_f\|_\infty \int_{A+T}^{\infty} |f_0'(\alpha - (t+\Delta t - a))|\, d\alpha + \|\beta_f\|_\infty^2 \int_{A+T}^{\infty} |f_0(\alpha - (t+\Delta t - a))|\, d\alpha \\
&\leq \|\beta_f\|_\infty \int_{A}^{\infty} |f_0'(\alpha)|\, d\alpha + \|\beta_f\|_\infty^2 \int_{A}^{\infty} |f_0(\alpha)|\, d\alpha \\
&\leq \frac{\epsilon}{2}. \qquad (85)
\end{aligned}
$$

In summary,

$$\left| \int_{A+T}^{\infty} \frac{\beta_f(\alpha)(f_n(\alpha, t+\Delta t - a) - f_n(\alpha, t-a))}{\Delta t} d\alpha \right| < \frac{\epsilon}{2}.$$

Similarly

$$
\begin{aligned}
&\left| \int_{A+T}^{\infty} \beta_f(\alpha) \frac{\partial f_n}{\partial t}(\alpha, t-a) d\alpha \right| \\
&\leq \|\beta_f\|_\infty \int_{A+T}^{\infty} \left| e^{-B_f(\alpha-(t-a),\alpha)} \left(f_0'(\alpha - (t-a)) + \beta_f(\alpha - (t-a)) f_0(\alpha - (t-a))\right) \right| d\alpha \\
&\leq \|\beta_f\|_\infty \int_{A+T}^{\infty} |f_0'(\alpha - (t-a))|\, d\alpha + \|\beta_f\|_\infty^2 \int_{A+T}^{\infty} |f_0(\alpha - (t-a))|\, d\alpha \\
&\leq \|\beta_f\|_\infty \int_{A}^{\infty} |f_0'(\alpha)|\, d\alpha + \|\beta_f\|_\infty^2 \int_{A}^{\infty} |f_0(\alpha)|\, d\alpha \\
&\leq \frac{\epsilon}{2}. \qquad (86)
\end{aligned}
$$

Thus,

$$\lim_{\Delta t \to 0} \left| \int_{A+T}^{\infty} \frac{\beta_f(\alpha)(f_n(\alpha, t+\Delta t - a) - f_n(\alpha, t-a))}{\Delta t} d\alpha - \int_{A+T}^{\infty} \beta_f(\alpha) \frac{\partial f_n}{\partial t}(\alpha, t-a) d\alpha \right| \leq \epsilon.$$

Therefore the absolute value of

$$
\begin{aligned}
&\int_{0}^{\infty} \frac{\beta_f(\alpha)(f_n(\alpha, t+\Delta t - a) - f_n(\alpha, t-a))}{\Delta t} d\alpha \\
&- \left(\int_{0}^{\infty} \beta_f(\alpha) \frac{\partial f_n}{\partial t}(\alpha, t-a) d\alpha + \lim_{\alpha \to (t-a)^-} \beta_f(\alpha) f_n(\alpha, t-a) - \lim_{\alpha \to (t-a)^+} \beta_f(\alpha) f_n(\alpha, t-a) \right)
\end{aligned}
$$

is less than ϵ. Since $\epsilon > 0$ was arbitrary, for any $(a,t) \in \Omega_1$,

$$\begin{aligned} \frac{\partial g_{n+1}}{\partial t}(a,t) &= 2e^{-B_g(0,a)} \int_0^\infty \beta_f(\alpha) \frac{\partial f_n}{\partial t}(\alpha, t-a) d\alpha \\ &+ 2\beta_f(t-a) e^{-B_g(0,a)} \left(\lim_{\alpha \to (t-a)^-} f_n(\alpha, t-a) - \lim_{\alpha \to (t-a)^+} f_n(\alpha, t-a) \right) \end{aligned} \tag{87}$$

From Lemma 2.3, the expression to the right of the equality above is continuous, hence we have shown that g_n is continuously differentiable with respect to t in Ω_1. Similarly, we find that f_n and g_n are continuously differentiable with respect to both t and a in Ω_1, and their derivatives are given by (44)-(47). Moreover, we see that g_n and f_n satisfy (15)-(16). It then follows from the uniform convergence of the partial derivatives of f_n and g_n together with the convergence of the sequences f_n and g_n, that

$$\lim_{n \to \infty} \frac{\partial f_n}{\partial t} = \frac{\partial f}{\partial t},$$

and

$$\lim_{n \to \infty} \frac{\partial g_n}{\partial a} = \frac{\partial g}{\partial t}.$$

Hence, taking the limit through (15)-(16), we see that f and g satisfy (1)-(2). Moreover, since the convergence is uniform, we have that f and g are continuously differentiable on Ω_1.

To complete the proof of Theorem 2.1, it remains to show that g and f satisfy the boundary conditions (4) and (6). Note that:

$$\begin{aligned} g_{n+1}(0,t) &= 2\int_0^\infty \beta_f(a) f_n(a,t) da \\ &= 2\int_0^t \beta_f(a) f_n(a,t) da + 2\int_t^\infty \beta_f(a) f_0(a-t) e^{-B_f(a-t,a)} da \end{aligned} \tag{88}$$

Since the domain of integration for the first integral is contained in Ω_1 where f_n

converges uniformly to f we have that:

$$2\int_0^t \beta_f(a) f_n(a,t)da \to 2\int_0^t \beta_f(a) f(a,t)da.$$

Thus,

$$\begin{aligned} g_{n+1}(0,t) &\to 2\int_0^t \beta_f(a) f(a,t)da + 2\int_t^\infty \beta_f(a) f_0(a-t)e^{-B_f(a-t,a)}da \\ &= 2\int_0^\infty \beta_f(a) f(a,t)da \end{aligned} \tag{89}$$

as desired. Similarly, we find that f satisfies the boundary condition (6). Thus, the proof of Theorem 2.1 is complete. □

Theorem II.4 *Assume that in addition to conditions $(i)-(v)$ of Theorem 2.1, β_g and β_f are differentiable and*

(vi) For $a > \hat{A}^*$, β_g' and β_f' are non-postive and increasing,

then there exist continuously differentiable solutions of (1)-(2) together with the boundary conditions (3)-(6) on $\Omega = \{(a,t) | 0 \le a, 0 \le t < T\}$, for all $T > 0$.

Proof: By Theorem 2.1 there exist solutions g and f of (1)-(2) together with the boundary conditions (4) and (6) on $\bar{\Omega}_1 = \{(a,t) | 0 \le a \le t \le T\}$, for $T = \frac{1}{2N}$. We may set $\hat{f}_0(a) = f(a,T)$ and $\hat{g}_0(a) = g(a,T)$. Note that $\hat{f}_0$ and $\hat{g}_0$ are continuous and continuously differentiable for $a \neq T$ at which point they are continuous from the left and right, with a jump discontinuity. Also we have that $\hat{f}_0$ and $\hat{g}_0$ are L^∞. This is because $\|g_n - g\|_\infty \to 0$ and $\|f_n - f\|_\infty \to 0$ in $\bar{\Omega}_1$, and, in addition, f and g are L^∞ for $0 \le t \le a$ by (13) and (14). Also, $\hat{f}_0$ and $\hat{g}_0$ are L^1. This follows from the fact that $\hat{f}_0$ and $\hat{g}_0$ are L^∞ and given by (13) and (14) for a large, where f_0 and g_0 are L^1.

Also we have that $\hat{f}_0' = \frac{\partial f}{\partial a}(a,T)$ and $\hat{g}_0' = \frac{\partial g}{\partial a}(a,T)$ are L^∞. This is because $\|\frac{\partial g_n}{\partial a} - \frac{\partial g}{\partial a}\|_\infty \to 0$ and $\|\frac{\partial f_n}{\partial a} - \frac{\partial f}{\partial a}\|_\infty \to 0$ in $\bar{\Omega_1}$, and, in addition, $\frac{\partial f}{\partial a}(a,T)$ and $\frac{\partial f}{\partial a}(a,T)$

are L^∞ for $0 \le t \le a$ by (48) and (50). Also, $\hat{f}_0'$ and $\hat{g}_0'$ are L^1. This follows from the fact that $\hat{f}_0'$ and $\hat{g}_0'$ are L^∞ and given by (48) and (50) for a large, where β_f, β_g are L^∞ and f_0, f_0', g_0 and g_0' are L^1.

Now we will verify that $\hat{f}_0'$ and $\hat{g}_0'$ satisfy condition v.

$$\hat{f}_0'(a) = f_0'(a-T)e^{-B_f(a-T,a)} - f_0(a-T)[\beta_f(a-T) - \beta_f(a)]e^{-B_f(a-T,a)} \tag{90}$$

Since $f_0'(a)$ satisfies v and β_f is decreasing for $a > \hat{A}^*$ we see that $\hat{f}_0'(a)$ is non-positive for $a > A := \max\left\{A^* + T, \hat{A}^* + T\right\}$. Note also that the first term above,

$$f_0'(a-T)e^{-B_f(a-T,a)},$$

is increasing for $a > A$. Indeed, $e^{-B_f(a-T,a)}$ is decreasing for $a > A$, and $f_0'(a-T)$ is negative and increasing for $a > A^*$. Therefore for $\hat{a} > a > A$,

$$f_0'(a-T)e^{-B_f(a-T,a)} \le f_0'(\hat{a}-T)e^{-B_f(a-T,a)} \le f_0'(\hat{a}-T)e^{-B_f(\hat{a}-T,\hat{a})}$$

Now, taking the derivative of the second term,

$$-f_0(a-T)[\beta_f(a-T) - \beta_f(a)]e^{-B_f(a-T,a)},$$

we get:

$$\begin{aligned} -f_0'(a-T)(\beta_g(a-T) - \beta_g(a))e^{-B_g(a-T,a)} &- f_0(a-T)(\beta_g'(a-T) - \beta_g'(a)e^{-B_g(a-T,a)} \\ &+ f_0(a-T)(\beta_g'(a-T) - \beta_g'(a))^2 e^{-B_g(a-T,a)}, \end{aligned}$$

which is positive for $a > A$ by conditions v and vi. Therefore $\hat{f}_0'(a)$ is increasing for a large. Similarly $\hat{g}_0'(a)$ is negative and increasing for a large. Therefore, $\hat{f}_0$ and $\hat{g}_0$ satisfy condition (v) of Theorem 2.1.

Having verified these conditions we can begin to solve (1) and (2) subject to the boundry conditions (4) and (6), with $\hat{f}_0$ and $\hat{g}_0$ in place of f_0 and g_0, and $\hat{f}_n$ and $\hat{g}_n$ in place of f_n and g_n. For simplicity, we may change to time variable to $\tau = t - T$, so that the initial data corresponds to $\tau = 0$. The characteristic equations are unchanged. The only change is the jump discontinuity in $\hat{f}_0$ and $\hat{g}_0$. Note that jump discontinuities do not impact the continuity of the expressions in (21) and (22). Indeed, the proof that these expressions are continuous assumed a jump discontinuity, at $a = t$. In our new variables, that discontinuity is at $a = \tau + T$; $\hat{g}_n$ and $\hat{f}_n$ are in fact continuous at $a = \tau$. Indeed, since

$$f(0,T) = \int_0^\infty \beta_g(\alpha) g(\alpha, T) d\alpha$$

and

$$g(0,T) = 2\int_0^\infty \beta_f(a) f(\alpha, T) d\alpha$$

$\hat{f}_0$ and $\hat{g}_0$ satisfy the boundary conditions

$$\hat{g}_0(0) = 2\int_0^\infty \beta_f(\alpha) \hat{f}_0(\alpha) d\alpha$$

and

$$\hat{f}_0(0) = \int_0^\infty \beta_g(\alpha) \hat{g}_0(\alpha) d\alpha.$$

Therefore, when $a = \tau$ we have,

$$\begin{aligned} \lim_{a \to \tau^-} \hat{g}_n(a,\tau) &= 2e^{-B_g(0,\tau)} \int_0^\infty \beta_f(\alpha) \hat{f}_0(\alpha) d\alpha \\ &= e^{-B_g(0,\tau)} \hat{g}(0) \\ &= \lim_{a \to \tau^+} \hat{g}_n(a,\tau) \end{aligned} \tag{91}$$

Similarly,

$$\lim_{a \to \tau^-} \hat{f}_n(a,\tau) = \lim_{a \to \tau^+} \hat{f}_n(a,\tau) \tag{92}$$

Thus, $\hat{f}_n$ and $\hat{g}_n$ converge to continuously differentiable solutions of (15) and (16) subject to (3)-(6), on $\{(a,\tau) | 0 \le \tau \le T, 0 \le a \le T + \tau\}$. Returning to our original variables, we extend our original solution to $t \leq 2T$. Continuing in this way, for all time, we can define solutions of (15) and (16) subject to the boundary conditions (3)-(6), continuously differentiable for $a \neq t$.

CHAPTER III

COMPUTATION

III.1 Characterization of β

In simulating the model, we need to compute the per capita maturation rates, β_f and β_g, which can be calculated in terms of the maturation time probability densities I_f and I_g. For this, let $R(a, y_0)$ denote the probability that a cell transitions (matures) to the next stage after age a, given that the cell's internal state had value y_0 at $a = 0$. We may sometimes fix y_0 and just write $R(a)$. Now let $\beta(a)\delta a + o(\delta a)$ (where $\lim_{\delta a \to 0} \dfrac{o(\delta a)}{\delta a} = 0$) be the probability that a cell transitions over the interval $[a, a + \delta a]$, given that it has not transitioned at age a. That is, $\beta(a)$ is the transition probability. Then on the one hand

$$R(a + \delta a) = R(a)(1 - \beta(a)\delta a - o(\delta a)).$$

That is, the probability that a cell transitions after age $a + \delta a$ is the probability that the cell does not transition over $[a, a + \delta a]$, given it did not transition up until age a, ages the probability that the cell did not transition up until age a. On the other hand,

$$R(a + \delta a) = R(a) + R'(a)\delta a + o(\delta a).$$

Equating these two expressions for $R(a + \delta a)$ and canceling like terms, we have

$$-\beta(a)R(a)\delta a = R'(a)\delta a + o(\delta a).$$

Dividing by δa and taking the limit as δa goes to zero, we find

$$\beta(a) = \frac{-R'(a)}{R(a)}.$$

Thus, we can determine the transition probability in terms of $R(a)$. Note that, $R(a) = \int_a^\infty I(s)ds$. Therefore

$$\beta(a) = \frac{I(a)}{\displaystyle\int_a^\infty I(s)ds}. \tag{93}$$

If transition ages are exponentially distributed, $\beta(a) \equiv \beta$. In general, there may not be a closed form for β, so that it must be approximated numerically. In this case, a grows, the numerator and denominator in the expression for β approach zero. As a result, the computation of β is challenging due to limits on floating point precision.

In the following paragraphs, we characterize several important features of β for the inverse Gaussian probability density. First note we may use L'Hôpital's rule, to compute the asymptotic value of $\beta(a)$. For

$$I(a) = \frac{1}{\sqrt{2\sigma^2\pi a^3}} e^{-\frac{(\mu a-1)^2}{2a\sigma^2}}$$

$$\lim_{a\to\infty} \beta(a) = \lim_{a\to\infty} \frac{I(a)}{\displaystyle\int_a^\infty I(s)ds} = \lim_{a\to\infty} -\frac{I'(a)}{I(a)} = \lim_{a\to\infty} \frac{3}{2}\frac{1}{a} - \frac{1}{2\sigma^2}\frac{1}{a^2} + \frac{\mu^2}{2\sigma^2} = \frac{\mu^2}{2\sigma^2}.$$

The following characterization of β also involves the ratio

$$-q(a) = -\frac{I'(a)}{I(a)} = \frac{3}{2}\frac{1}{a} - \frac{1}{2\sigma^2}\frac{1}{a^2} + \frac{\mu^2}{2\sigma^2}.$$

Theorem III.5 *The per capita maturation rate $\beta(a)$ has exactly one critical point, at which takes a maximum value. Moreover, if a^* is the age at which $\beta(a)$ takes its maximum value, $\beta(a) < -q(a)$ for $a > a^*$.*

Let $\beta(a) = \frac{I(a)}{\displaystyle\int_a^\infty I(s)ds}$ and $I'(a) = I(a)q(a)$, where $-q(a) = \frac{3}{2}\frac{1}{a} - \frac{1}{2\sigma^2}\frac{1}{a^2} + \frac{\mu^2}{2\sigma^2}$, then:

$$\beta'(a) \quad = \quad \frac{\displaystyle\int_a^\infty I(s)dsI(a)q(a) + I^2(a)}{\left(\displaystyle\int_a^\infty I(s)ds\right)^2} < 0 \tag{94}$$

$$\iff \quad \beta(a) < -q(a). \tag{95}$$

Similarly,

$$\beta'(a) > 0 \iff \beta(a) > -q(a). \tag{96}$$

and

$$\beta'(a) = 0 \iff \beta(a) = -q(a). \tag{97}$$

Also note that as $a \to 0$, $\beta(a) \to 0$, and $-q(a) \to -\infty$. Therefore, for a small $\beta(a) > -q(a)$, and $\beta'(a) > 0$ for a small.

To show that β has a single critical point, we must also consider the behavior of $-q(a)$. Note that

$$-q'(a) = -\frac{3}{2}\frac{1}{a^2} + \frac{1}{\sigma^2}\frac{1}{a^3} = 0 \iff -\frac{3}{2}a + \frac{1}{\sigma^2} = 0 \iff a = \frac{2}{3}\frac{1}{\sigma^2}$$

Set $\hat{a} = \frac{2}{3}\frac{1}{\sigma^2}$. Considering the limits of $-q'(a)$ as $a \to 0$ and $a \to \infty$ we have $-q'(a) > 0$ for $a < \hat{a}$ and $-q'(a) < 0$ for $a > \hat{a}$. Therefore $-q(a)$ takes its maximum value at $\hat{a} = \frac{2}{3\sigma^2}$.

Suppose toward a contradiction that $\beta'(a) \neq 0$ for all $a > 0$, then by continuity, $\beta'(a) > 0$ for $a > 0$. Thus, $\beta(a) > -q(a)$ for $a > 0$ by (96). Fixing $a_0 > \hat{a} > 0$ we have $\beta(a) > -q(a)$ and $\beta'(a) > 0 > -q'(a)$ for $a > a_0 > \hat{a}$, so:

$$0 = \lim_{s\to\infty} \beta(s)+q(s) = \lim_{s\to\infty} \int_{a_0}^s \beta'(a)+q'(a)da+\beta(a_0)+q(a_0) > \beta(a_0)+q(a_0) > 0, \tag{98}$$

which is a contradiction.

Hence, we define

$$a^* = \inf \{a > 0 \mid \beta'(a) = 0\}$$

Note by continuity $\beta'(a^*) = 0$ and $\beta(a^*) = -q(a^*)$. Note also, $a^* > 0$, since $\beta'(a) > 0$ for a small. Therefore, by continuity, $\beta'(a) > 0$ for $a < a^*$, i.e. β is increasing for $a < a^*$.

Case 1:

Suppose that $\beta'(a^*) = 0 > -q'(a^*)$. Since $\beta(a^*) = -q(a^*)$, by continuity there exists an interval over which the above inequality holds. Thus, there exists $\delta > 0$ such that $\beta(a) > -q(a)$ for $a^* < a < a^* + \delta$. Suppose there exists $a > a^*$ such that $\beta(a) < -q(a)$. Let $s^* = \inf \{a > a^* \mid \beta(a) \leq -q(a)\}$. Note $s^* \neq a^*$. So for $a^* < a < s^*$ $\beta(a) > -q(a)$ so $\beta'(a) > 0$ for $a^* < a < s^*$, however, since $-q$ has a single critical point at which is takes a maximum, we know $-q'(a) < 0$ for $a > a^*$. So, $\beta'(a) > -q'(a)$ for $a^* < a < s^*$ Thus;

$$\beta(s^*) - \beta(a^*) = \int_{a^*}^{s^*} \beta'(a)da > \int_{a^*}^{s^*} -q'(a)da = q(s^*) - \beta(a^*) \tag{99}$$

Thus, $\beta(s^*) > -q(s^*)$. By continuity and the definition of s^*, it must be that $\beta(s^*) \leq -q(s^*)$. Thus we have reached a contradiction.

It follows that $\{a > a^* \mid \beta(a) \leq -q(s)\}$ is empty. That is, $\beta(a) > -q(a)$ for $a > a^*$.

Hence

$$0 = \lim_{s\to\infty} \beta(s) + q(s) = \lim_{s\to\infty} \int_{a^*}^{s} \beta'(a) + q'(a)da > \int_{a^*}^{a^*+1} \beta'(a) + q'(a)da > 0 \tag{100}$$

Hence, this case does not occur.

Case 2:

Assume that $0 = \beta'(a^*) < -q'(a^*)$. Then, as in Case 1, there exists δ such that $\beta(a) < -q(a)$ for $a^* < a < a^* + \delta$. Suppose toward a contradiction that there exists

$a > a^*$, so that $\beta(a) > -q(a)$. Let $s^* = \inf \{a > a^* \mid \beta(a) \geq -q(a)\}$. Note we have $s^* > a^*$, and by continuity $\beta(s^*) = -q(s^*)$. However for $a^* < a < s^*$, $\beta(a) < -q(a)$, and hence for $a^* < a < s^*$, $\beta'(a) < 0$ by (94). Since we have already shown Case I cannot happen we also know that $0 = \beta'(s^*) \leq -q'(s^*)$. Since $-q$ has a single maximum, we see that in fact $\beta'(a) < 0 < -q'(a)$, for $a^* < a < s^*$. Thus $\beta(s^*) < -q(s^*)$, and we have reached a contradiction. Thus, there exists no $a > a^*$ such that $\beta(a) \geq q(a)$. Therefore there exists a unique time a^* at which $\beta'(a^*) = 0$, and $\beta(a) < -q(a)$ for $a > a^*$.

Case 3:

Assume that $0 = \beta'(a^*) = -q'(a^*)$. Then since $-q(a)$ has a single critical point at which it takes a maximum values, $-q'(a) < 0$ for $a > a^*$. Therefore, it cannot happen that $\beta(a) = -q(a)$, for $a > a^*$, since we previously showed Case I cannot happen. Thus, in this case too, we see that there is a unique time a^* at which $\beta'(a^*) = 0$. Moreover, if there exists $s^* > a^*$ so that $\beta(s^*) > -q(s^*)$, then by continuity it must be that $\beta(a) > -q(a)$ for every $a > a^*$. Therefore, $\beta'(a) > 0 > -q'(a)$ for $a > a^*$. Contradicting that $lim_{a \to \infty} \beta(a) = -q(a)$. Thus it must be that $\beta(a) < -q(a)$ for $a > a^*$.

Therefore, in any case there is a unique age a^* at which $\beta'(a^*) = 0$. Moreover, $\beta(a) < -q(a)$ for $a > a^*$, so that β is decreasing for $a > a^*$. Since we have already noted that β is increasing for $a > a^*$ we see that β takes its maximum value at a^* as desired. $\square$

Next we derive an estimate of the maximum value of β and a lower bound on the age at which β assumes its maximum value. For this note that since $-q'(a^*) \geq 0$ and

$\beta'(a) < 0$ for $a^* < a$

$$\max_{\{a>0\}} \beta(a) \leq \max_{\{a>0\}}(-q(a)) = -q(\hat{a}) \tag{101}$$

$$= \frac{9}{8}\sigma^2 + \frac{\mu^2}{2\sigma^2} \tag{102}$$

Lemma III.6 *For a^* as above, $\frac{\mu^2}{2\sigma^2} < \beta(a^*) \leq \frac{9}{8}\sigma^2 + \frac{\mu^2}{2\sigma^2}$. Moreover, $\frac{1}{3}\frac{1}{\sigma^2} < a^*$.*

To obtain the estimate on $\beta(a^*) = \max_{\{a>0\}} \beta(a)$ and the lower bound on a^*, we first consider the unique time, a_∞, such that $-q(a_\infty) = \frac{\mu^2}{2\sigma^2}$. That is, we consider the unique finite time at which $-q(a)$ achieves the asymptotic value of $\beta(a)$.

We have

$$-q(a_\infty) = \frac{\mu^2}{2\sigma^2} \iff \tag{103}$$

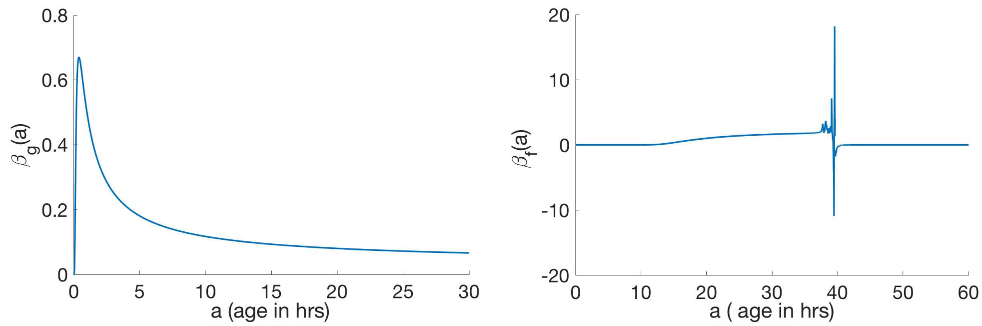
$$0 = \frac{3}{2}\frac{1}{a_\infty} - \frac{1}{2\sigma^2}\frac{1}{a_\infty^2} \iff \tag{104}$$

$$0 = \frac{3}{2}a_\infty - \frac{1}{2\sigma^2} \iff \tag{105}$$

$$a_\infty = \frac{1}{3}\frac{1}{\sigma^2} \tag{106}$$

It follows that $\frac{1}{3}\frac{1}{\sigma^2} = a_\infty < a^*$. Indeed we see that $a_\infty < \hat{a} = \frac{2}{3\sigma^2}$, so $-q$ is increasing for $a < a_\infty$. Were $a^* < a_\infty$, we would have $\beta(a^*) = -q(a^*) < -q(a_\infty) = \frac{\mu^2}{2\sigma^2}$. However, this leads to a contradiction because $\beta(a)$ is strictly decreasing for $a > a^*$ and approaches $\frac{\mu^2}{2\sigma^2}$ as $a \to \infty$. Therefore $a_\infty < a^*$ as desired. Hence, $\beta(a^*) > \beta(a_\infty) > -q(a_\infty) = \frac{\mu^2}{2\sigma^2}$. Where the final inequality follows from the fact that β is increasing (i.e. $\beta(a) > -q(a)$ for $a < a^*$.) $\square$

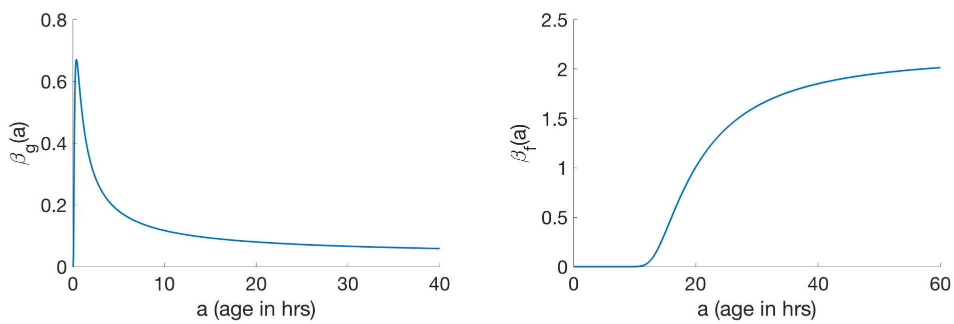
The previous characterization of β is useful for validating the numerical approximation of β. Figure (1(b)) and (2(b)) demonstrate the challenge of computing β numerically. In figure (1(a)) and (1(b)) β was computed directly in MATLAB according to (93). In figure (2(a)) and (2(b)) β was computed according to (93) with the aid of MATLAB's variable precision arithmetic function (vpa.m) [15].



(a) Maturation rate for stage g

(b) Maturation rate for stage f

Figure 1: Direct numerical computation of maturation rates



(a) Maturation rate for stage g

(b) Maturation rate for stage f

Figure 2: Numerical computation of maturation rates using MATLAB's vpa.m

III.2 Numerical Method

In order to solve the system of PDEs numerically we discretize age and time in order to numerically integrate along the model's characteristic curves. The numerical scheme is summarized below.

Given initial data $g_0(a)$, $f_0(a)$, with $g_0(a) = f_0(a) = 0$ for $a > a_{max}$, we approximate the solution of our system for $t < T$ as follow:

Let $a = (0, h, 2h, \ldots Ih)$, and $t = (0, h, 2h, \ldots Jh)$, where $Jh = T$, and $Ih =$

$T + a_{max}$. $\hat{\mathbf{g}} = (\hat{g}_{ij}) \in \mathbb{R}^{(I+1)\times(J+1)}$ and $\hat{\mathbf{f}} = (\hat{f}_{ij}) \in \mathbb{R}^{(I+1)\times(J+1)}$ are matrices with

$$\hat{f}_{i0} = f_0(a_i), \quad i = 1, \dots I, \tag{107}$$

$$\hat{g}_{i0} = g_0(a_i) \quad i = 1, \dots I, \tag{108}$$

$$\hat{f}_{0j} = integral(0, a_I, \beta_g \hat{g}_{:,j}) \quad j = 1, \dots J, \tag{109}$$

$$\hat{g}_{0j} = 2\ integral(0, a_I, \beta_f \hat{f}_{:,j}) \quad j = 1, \dots J, \tag{110}$$

$$\hat{f}_{i+1,j+1} = \hat{f}_{ij} \exp\{integral(a_i, a_{i+1}, -\beta_f)\} \tag{111}$$

$$\hat{g}_{i+1,j+1} = \hat{g}_{ij} \exp\{integral(a_i, a_{i+1}, -\beta_g)\} \tag{112}$$

where $integral(a_i, a_{i+1}, -\beta_f)$ is the approximation of $\int_{a_i}^{a_{i+1}} -\beta_f(\alpha)d\alpha$, using MATLAB's implementation of the trapezoid rule with a uniform grid over $[a_i, a_{i+1}]$ with four points, and $integral(0, a_I, \beta_f \hat{f}_{:,j})$ is the approximation of $\int_0^{a_I} \beta_f(\alpha)\hat{f}(\alpha, t_j)d\alpha$ using the MATLAB's implementation of the trapezoid rule with the grid values in a and the corresponding entries of $\hat{f}_{:,j}$. The grid size h was initially set to .02 and was reduced by half until the relative point-wise error was less than 10^{-2}. The algorithm is discussed in [16]. All simulations were performed in MATLAB.

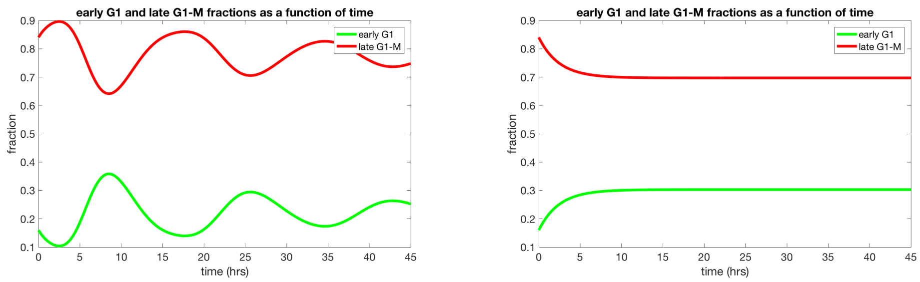
CHAPTER IV

RESULTS

Here we consider two different models for the per capita maturation rate β. These rates correspond to two maturation time distributions, namely the Inverse Gaussian and the exponential distributions. Hence we will refer to one as the inverse Gaussian maturation rate and the other as the exponential maturation rate. Parameters for the inverse Gaussian distribution were chosen to fit data on the division times of MCF10A cells, as described in [17]. The parameters for the exponential distributions were chosen to match the mean of the inverse Gaussian distribution as parameterized by the MCF10A cell data. Thus the average time spent in early G1 and late G1-M are the same in both models.

When the data is parameterized by the inverse Gaussian distribution, the fraction of cells in early G1 and late G1-M is predicted to exhibit oscillations over multiple days. However, the amplitude of the oscillations decreases through time so that the population stage structure appears to approach a steady state wherein approximately 80% of cells are in late G1-M while approximately 20% of cells are in early G1 (see [3(a)]).

When the data is parameterized by the exponential distribution the fraction of cells in early G1 and late G1-M quickly stabilizes to yeild a stable stage structure wherein approximately 30% of cells are in early G1 and approximately 70% of cells are in late G1-M. It is interesting to note that the two models differ, not only in their dynamics but in their predicted steady state stage distribution, despite the fact that the time spent in early G1 and late G1-M is identical for the models as parameterized (see [3(b)].



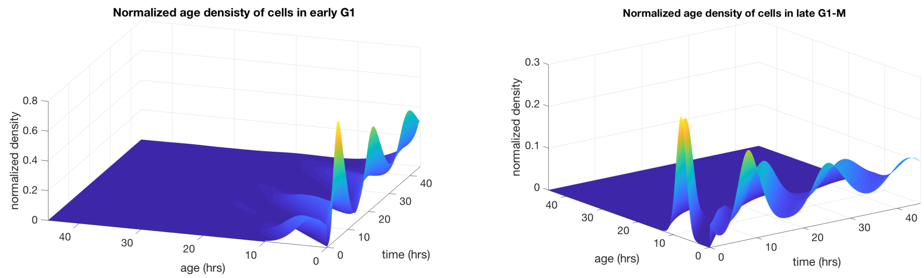
(a) Inverse Gaussian model.

(b) Exponential model.

Figure 3: Fractions of cells in early G1 and late G1-M through time, as predicted by parameterizing MCF10A cell division time data with inverse Gaussian and exponential models as described in the text. Note that the initial stage structure is not available from the data, hence it was chosen arbitrarily, but in consideration of the average time spent in each cell cycle part. Model parameters for the inverse Gaussian model: $\mu_1 = .25$, $\sigma_1 = 1$, $\mu_2 = .064$ $\sigma_2 = .031$. Model parameters for the exponential model: $\lambda_1 = .25$, $\lambda_2 = .064$.

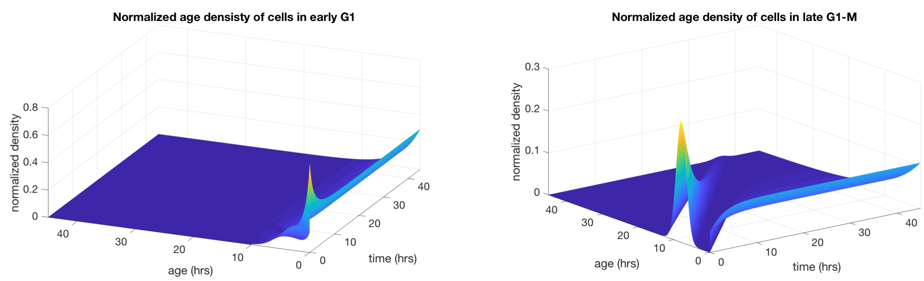
We can also compare the predicted age distributions for the models. Figures [4(a)] and [4(b)] show how the predicted age distributions in early G1 and late G1-M vary through time in the inverse Gaussian model. Figure [5(a)] and [5(b)] show how the predicted age distributions in early G1 and late G1-M vary through time in the exponential model. This figures demonstrate that similar to the stage distribution, the age distribution is much slower to stabilize for the inverse Gaussian model.

These simulations suggest that the distribution of maturation times can have a significant impact on the stage structure of the population, impacting both its dynamics and steady state. Hence maturation time distributions could significantly



(a) Early G1 age distribution (b) Late G1 through M age distribution

Figure 4: Normalized density of cells in early G1 and late G1-M as a function of time and age for the inverse Gaussian model



(a) Early G1 age distribution (b) Late G1 through M age distribution

Figure 5: Normalized density of cells in early G1 and late G1-M as a function of time and age for the exponential model

impact the outcome of drug therapy. We hope that the results and computer code provided here can help in the development of more accurate, predictive models for the evaluation of drug therapy. For this purpose, future work will incorporate drug therapy into the model, for example. As parameterized, the model would be well-suited to study the impact of CDK inhibitors, which impact restriction point passage [18]. The model could also be reparameterized to study the impact of drugs which target S phase (e.g. gemcitabine) [3]. A secondary benefit of this work is that it provides an additional means of validating models of stochastic cell cycle progression. In particular after fitting a distribution model to intermitotic time data, we can then examine the ability of the distribution to simultaneously describe the stage structure of the population. In this way, the research presented here can contribute to the process of model refinement and deepen our understanding of the fundamental process of cell cycle progression.

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