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Research article

The impact of maturation time distributions on the structure and growth of cellular populations

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Abstract: Here we study how the structure and growth of a cellular population vary with the distribution of maturation times from each stage. We consider two cell cycle stages. The first represents early G1. The second includes late G1, S, G2, and mitosis. Passage between the two reflects passage of an important cell cycle checkpoint known as the restriction point. We model the population as a system of partial differential equations. After establishing the existence of solutions, we characterize the maturation rates and derive the steady-state age and stage distributions as well as the asymptotic growth rates for models with exponential and inverse Gaussian maturation time distributions. We find that the stable age and stage distributions, transient dynamics, and asymptotic growth rates are substantially different for these two maturation models. We conclude that researchers modeling cellular populations should take care when choosing a maturation time distribution, as the population growth rate and stage structure can be heavily impacted by this choice. Furthermore, differences in the models' transient dynamics constitute testable predictions that can help further our understanding of the fundamental process of cellular proliferation. We hope that our numerical methods and programs will provide a scaffold for future research on cellular proliferation.

Keywords: stage and age-structured populations; cell cycle; stable age and stage distributions; method of characteristics; maturation rate; system of first order linear partial differential equations

1. Introduction

In this paper we investigate how the distribution of time spent in the various cell cycle stages impacts the growth and stage structure of a cellular population. For brevity, we will refer to the distribution

of time spent in a stage as the maturation time distribution of the stage. In addition to providing fundamental insights into the process of cellular proliferation, this research can inform diverse models of cellular population growth. Indeed, in the context of medical research, a cellular population's stage structure can impact the efficacy of drug therapy [1–3].

Within the mammalian cell cycle there exists a checkpoint, known as the restriction point or G1/S checkpoint, which controls entry into S phase [4–7]. 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 [4–7]. 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) [6]. As mentioned above, we are especially interested in how the maturation time distributions impact 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). While similar in many respects, an important difference between the model system considered by [8] and our own model system is that while generation number increases indefinitely, cell cycle stages occur in a cycle. As a result, the two models have different boundary conditions, which may considerably impact their dynamics. Another important difference between this work and [8] is that we consider general maturation time distributions and more general initial age distributions, which yield models that are not analytically solvable. 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 [1] by modeling, in addition to age, cell cycle stage. As a result of this extension, our model could 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 are used to study the impact of drug therapy on pancreatic cancer cells. These models assume that, in the absence of treatment or crowding, maturation between cell cycle phases is governed by an exponential distribution, i.e., that cells experience a constant per capita maturation rate. In contrast, we investigate the impact of non-constant maturation 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.

In addition to providing theoretical results relating stable age and stage structures to maturation time distributions, we perform extensive numerical analyses. Our analyses compare and contrast the dynamics and stable stage- and age-distributions of two distinct maturation time distributions: the exponential and the inverse Gaussian distribution. Over several decades, numerous model maturation time distributions have been proposed [9–20]. Still, the most appropriate maturation time distribution remains unknown and is likely context dependent. We focus on the exponential maturation time distribution because it is almost certainly the most frequently used to model progression between cell cycle stages. This is a practical choice. Because the exponential distribution assumes that a cell has a constant probability per unit time of maturing into the next cell cycle stage, the maturation rate for this model is constant. As a result, cell age is an extraneous variable, in that the population stage structure

can be modeled as a system of ordinary differential equations in time alone. For this reason, the exponential model may be considered an ageless model. A drawback of the exponential model is that the assumption of a constant transition rate is generally considered to be biologically unreasonable. Moreover, the exponential distribution provides a poor fit to data (the distribution mode is zero, whereas few, if any, cells are observed to mature from a cell cycle stage at age zero). As a reasonable alternative to the exponential distribution, we consider the inverse Gaussian distribution. This distribution describes the maturation time as a first exit time [21], so that the time to exit a cell cycle stage corresponds to the time it takes a random variable to achieve a threshold value. The corresponding maturation rate is thus age-dependent, and the distribution mode can be shifted away from zero. Moreover, this model has been demonstrated to provide an accurate approximation of the intermitotic time distributions of several cell lines [20]. In considering these two very different distributions, we hope to clarify how the qualitative behavior of the population varies with the choice of maturation time distribution.

Section 2 of this paper introduces the system of partial differential equations (PDEs) used to model the stage-structured cellular population and presents results on the existence of solutions via the method of characteristics. Section 3 derives the steady-state growth rate of the population and presents the stable stage and age structure of the population. Section 4 presents the numerical algorithm for simulating the model's solution and addresses the challenges of simulating the model with age-dependent maturation rates. Section 5 presents the results of numerical simulations and compares and contrasts the growth and structure of populations governed by exponential and inverse Gaussian maturation rates.

2. The PDE model

The PDE population model is presented below.

$$\frac{\partial g}{\partial t}(a,t) + \frac{\partial g}{\partial a}(a,t) = -\beta_g(a)g(a,t); \quad \text{for } a \geq 0,\ t \geq 0 \tag{2.1}$$

$$\frac{\partial f}{\partial t}(a,t) + \frac{\partial f}{\partial a}(a,t) = -\beta_f(a)f(a,t); \quad \text{for } a \geq 0,\ t \geq 0 \tag{2.2}$$

with boundary conditions:

$$g(a,0) = g_0(a) \quad \text{for} \quad a \geq 0, \tag{2.3}$$

$$g(0,t) = 2\int_0^\infty \beta_f(a)f(a,t)da \quad \text{for} \quad t \geq 0, \tag{2.4}$$

$$f(a,0) = f_0(a) \quad \text{for} \quad a \geq 0, \tag{2.5}$$

$$f(0,t) = \int_0^\infty \beta_g(a)g(a,t)da. \quad \text{for} \quad t \geq 0, \tag{2.6}$$

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, and t denotes time. According to (2.1) the rate of change of the density of cells in the first stage ($\frac{\partial g}{\partial t}$) is determined by continuous aging ($\frac{\partial g}{\partial a}$) and the age-dependent, per capita rate at which cells enter the second stage ($\beta_g(a)$). Similarly, (2.2) describes how the age density of cells in the second stage evolves through time. Boundary conditions (2.3) and (2.5) give the initial age density at the beginning of the experiment (it is assumed that this density is known). Finally, (2.3) and (2.5) describe how new cells (with $a = 0$) enter the first and

second stages. Cells in the first stage are "born" when cells in the second stage divide, thereby giving rise to two cells in the first stage, with the age-dependent, per capita rate of $\beta_f(a)$. Cells in the second stage are created when cells in the first stage mature with an age-dependent, per capita rate of $\beta_g(a)$.

2.1. Existence of solutions

In this section we outline the method of proof of the existence of solutions to model equations (2.1)–(2.6) and present the related theorems. Detailed proofs are presented in the appendix.

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 [25], where global existence was shown for a size-structured model with a single stage and bounded size. We 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:

$$\frac{\partial g_{n+1}}{\partial t}(a,t) + \frac{\partial g_{n+1}}{\partial a}(a,t) = -\beta_g(a) g_{n+1}(a,t); \quad \text{for } a \geq 0,\ t \geq 0 \tag{2.7}$$

$$\frac{\partial f_{n+1}}{\partial t}(a,t) + \frac{\partial f_{n+1}}{\partial a}(a,t) = -\beta_f(a) f_{n+1}(a,t),; \quad \text{for } a \geq 0,\ t \geq 0 \tag{2.8}$$

subject to the boundary conditions:

$$g_{n+1}(a,0) = g_0(a) \quad \text{for} \quad a \geq 0, \tag{2.9}$$

$$g_{n+1}(0,t) = 2\int_0^\infty \beta_f(a) f_n(a,t) da \quad \text{for} \quad t \geq 0, \tag{2.10}$$

$$f_{n+1}(a,0) = f_0(a) \quad \text{for} \quad a \geq 0, \tag{2.11}$$

$$f_{n+1}(0,t) = \int_0^\infty \beta_g(a) g_n(a,t) da \quad \text{for} \quad t \geq 0, \tag{2.12}$$

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. Solutions of (2.7)–(2.12) can be found via the method of characteristic equations. Using this method, we arrive at the following solution formulas. Here $B_g(s_1, s_2) := \int_{s_1}^{s_2} \beta_g(\alpha) d\alpha$ and $B_f(s_1, s_2) := \int_{s_1}^{s_2} \beta_f(\alpha) d\alpha$.

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

$$g_{n+1}(a_0,t_0) = e^{-B_g(0,a_0)}\left(2\int_0^\infty \beta_f(\alpha) f_n(\alpha, t_0 - a_0) d\alpha\right), \tag{2.13}$$

$$f_{n+1}(a_0,t_0) = e^{-B_f(0,a_0)}\left(\int_0^\infty \beta_g(\alpha) g_n(\alpha, t_0 - a_0) d\alpha\right). \tag{2.14}$$

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

$$g_{n+1}(a_0,t_0) = g_0(a_0 - t_0) e^{-B_g(a_0 - t_0, a_0)}, \tag{2.15}$$

$$f_{n+1}(a_0, t_0) \quad = \quad f_0(a_0 - t_0)e^{-B_f(a_0-t_0,a_0)}. \tag{2.16}$$

Note that in the region $t < a$, g_n and f_n are independent of n and satisfy (2.7)–(2.8) together with the boundary conditions (2.9) and (2.11) provided β_f and β_g are continuous and g_0 and f_0 are differentiable. Under additional assumptions, it can be shown that g_n and f_n satisfy (2.7)–(2.8) together with the boundary conditions (2.10) and (2.12) also for $a < t$. Indeed we have the following theorem, the assumptions of which may be strengthened to achieve global solutions (please see the appendix).

Theorem 2.1. *Suppose*

(*i*) f_0 *and* g_0 *are nonnegative and continuously differentiable for* $a > 0$,
(*ii*) $\|f_0\|_{L^1[0,\infty)}$, $\|g_0\|_{L^1[0,\infty)}$, $\left\|f_0'\right\|_{L^1[0,\infty)}$, *and* $\left\|g_0'\right\|_{L^1[0,\infty)}$ *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* $\alpha > A^*$, $f_0'(\alpha)$ *and* $g_0'(\alpha)$ *are negative and increasing,*

then for T *sufficiently small there exists solutions of (2.1)–(2.6) on* $\Omega = [0, \infty) \times [0, T)$, *continuously differentiable, except possibly on the line* $a = t$.

Since we have already found a solution formula for $a > t$, our proof is focused on the set $\Omega_1 = \{(a, t)|0 \le a \le t < T\}$, 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,

$$\int_0^\infty \beta_f(\alpha) f_{n-1}(\alpha, t_0 - a_0)d\alpha, \tag{2.17}$$

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 $|f_{n-1}(\alpha, t)| \le |M(\alpha)|$. For this reason, we have adopted condition (*v*) of Theorem 2.1, and adapted previous proofs [26, 27] to work under this alternate condition. Details are presented in the appendix.

3. Stable growth, age- and stage-distributions

In this section we derive the stable age and stage distributions of the model. The stage distribution of the population at time t gives the fraction of the total cells in each stage. For example, the fraction of cells in the first stage is

$$\frac{\int_0^\infty g(a, t)da}{\int_0^\infty f(a, t) + g(a, t)da}.$$

Similarly, the fraction of cells in the second stage at time t is

$$\frac{\int_0^\infty g(a, t)da}{\int_0^\infty f(a, t) + g(a, t)da}.$$

Meanwhile, the age distribution of cells in the first stage at time t is

$$\frac{g(a,t)}{\int_0^\infty g(a,t)da},$$

and that of cells in the second stage is

$$\frac{f(a,t)}{\int_0^\infty f(a,t)da}.$$

If there exists a solution of (2.1)–(2.6) such that the age distributions are constant through time, those distributions are said to be stable age distributions for the model. Hence, the stable age distribution of cells in the first stage is characterized as the solution of the partial differential equation:

$$0 = \frac{\partial}{\partial t}\frac{g(a,t)}{\int_0^\infty g(a,t)da}. \tag{3.1}$$

Similarly, for cells in the second stage. It can be seen that solutions of (3.1) are necessarily separable. Indeed,

$$\frac{\partial}{\partial t}\frac{g(a,t)}{\int_0^\infty g(a,t)da} = \frac{\int_0^\infty g(a,t)da\frac{\partial g}{\partial t} - g(a,t)\int_0^\infty \frac{\partial g}{\partial t}da}{\left(\int_0^\infty g(a,t)da\right)^2} \tag{3.2}$$

$$= \frac{\frac{\partial g}{\partial t}(a,t)}{\int_0^\infty g(a,t)da} + \frac{g(a,t)\int_0^\infty \frac{\partial g}{\partial a}(a,t) + \beta_g(a)g(a,t)da}{\left(\int_0^\infty g(a,t)da\right)^2}, \tag{3.3}$$

where we have assumed the solution is regular enough to allow differentiation through the integral. In regard to this assumption, note we have shown that such regular solutions exist. Indeed by Theorem 2.1, there exist solutions which are continuously differentiable for $a \le t$, thus we may differentiate through the integrals $\int_0^t g(a,t)da$ and $\int_0^t f(a,t)da$. Moreover, in the proof of Theorem 2.1 (see Appendix 1), we show that one can differentiate through the integrals $\int_t^\infty g(a,t)da$ and $\int_t^\infty f(a,t)da$. However, the solution may not be continuous along the line $a = t$. In case, $\int_0^\infty \frac{\partial g}{\partial t}da$ should be replaced $\int_0^\infty \frac{\partial g}{\partial t}da + \lim_{a\to t^-} g(a,t) - \lim_{a\to t^+} g(a,t)$. Similarly, $\int_0^\infty \frac{\partial f}{\partial t}da$ should be replaced by $\int_0^\infty \frac{\partial f}{\partial t}da + \lim_{a\to t^-} f(a,t) - \lim_{a\to t^+} f(a,t)$. Because the later expressions, like the former expressions, are independent of a, this substitutions does not alter the proof that follows.

Now, setting the right-hand-side of (3.3) to zero and supposing, in addition, that $\lim_{a\to\infty} g(a,t) = 0$ (which follows from conditions *ii* and *v* of Theorem 2.1) we find

$$\frac{\frac{\partial g}{\partial t}(a,t)}{g(a,t)} = \frac{g(0,t) - \int_0^\infty \beta_g(a)g(a,t)da}{\int_0^\infty g(a,t)da} \tag{3.4}$$

Integrating through the equality (with respect to t) and noting that the right-hand-side is independent of a, we find

$$\ln\frac{g(a,t)}{g(a,0)} + c(a) = \int_0^t \frac{g(0,t) - \int_0^\infty \beta_g(a)g(a,t)da}{\int_0^\infty g(a,t)da}dt := H(t), \tag{3.5}$$

where $c(a)$ is the 'constant' of integration with respect to t (note it may depend on a). This yields

$$g(a,t) = g(a,0)e^{-c(a)}e^{H(t)}. \tag{3.6}$$

Thus, a solution g for which the age distribution is stable is necessarily separable. Similarly, if f exhibits a stable age distribution, then f must be separable. Hence, in characterizing the stable age distribution we express g and f as $g(a,t) = g_1(t)g_2(a)$ and $f(a,t) = f_1(t)f_2(a)$. Under this assumption, the partial differential equation for g simplifies as

$$g_1'(t)g_2(a) + g_1(t)g_2'(a) = -\beta_g(a)g_1(t)g_2(a), \tag{3.7}$$

which separates as

$$\frac{g_1'(t)}{g_1(t)} = \frac{-g_2'(a)}{g_2(a)} - \beta_g(a). \tag{3.8}$$

The previous equation yields

$$g_1(t) = g_1(0)e^{c_g t}, \tag{3.9}$$
$$g_2(a) = g_2(0)e^{-\int_0^a c_g + \beta_g(s)ds}, \tag{3.10}$$

where c_g is a constant representing the stable growth rate of the population in stage g. Similarly, we find

$$f_1(t) = f_1(0)e^{c_f t}, \tag{3.11}$$
$$f_2(a) = f_2(0)e^{-\int_0^a c_f + \beta_f(s)ds}, \tag{3.12}$$

where c_f is a constant representing the stable growth rate of the population in stage f.

Note that the value of the product $g_1(0)g_2(0)$ uniquely determines the solution ($g(a,t) = g_1(t)g_2(a)$) given by (3.9) and (3.10). This being the case, we set $g_1(0) = 1$. Similarly, we take $f_1(0) = 1$. Then, by (2.4)

$$g(0,t) = e^{c_g t}g_2(0) = 2\int_0^\infty \beta_f(a)e^{c_f t}f_2(a)da. \tag{3.13}$$

From which it follows that $c_g = c_f := c$. Dividing (3.13) by e^{ct} we have

$$g_2(0) = 2\int_0^\infty \beta_f(a)f_2(a)da = 2\int_0^\infty \beta_f(a)f_2(0)e^{(-\int_0^a c+\beta_f(s)ds)}da. \tag{3.14}$$

Similarly,

$$f_2(0) = \int_0^\infty \beta_g(a)g_2(0)e^{(-\int_0^a c+\beta_g(s)ds)}da. \tag{3.15}$$

Substituting the later into the former yields the consistency condition

$$\frac{1}{2} = \left(\int_0^\infty e^{-\int_0^a c+\beta_g(s)ds}\beta_g(a)da\right)\left(\int_0^\infty e^{-\int_0^a c+\beta_f(s)ds}\beta_f(a)da\right). \tag{3.16}$$

This equation can be written more simply in terms of the probability densities of maturation times, $I_g(a)$ and $I_f(a)$. Indeed, using

$$\beta_g(a) = \frac{I_g(a)}{\int_a^\infty I_g(s)ds} = -\frac{d}{da}\left(\ln \int_a^\infty I_g(s)ds\right) \tag{3.17}$$

(see Methods), it follows that

$$I_g(a) = \beta_g(a)\int_a^\infty I_g(s)ds = \beta_g(a)e^{-\int_0^a \beta_g(s)ds}. \tag{3.18}$$

Similarly, we find

$$I_f(a) = \beta_f(a)e^{-\int_0^a \beta_f(s)ds}. \tag{3.19}$$

Substituting the previous two expressions into 3.16 we find

$$\frac{1}{2} = \left(\int_0^\infty e^{-ac} I_g(a)da\right)\left(\int_0^\infty e^{-ac} I_f(a)da\right) = \mathcal{L}\left\{I_g\right\}(c)\mathcal{L}\left\{I_f\right\}(c), \tag{3.20}$$

which we wish to solve for c. Here we consider two cases, in which I_g and I_f are exponential or inverse Gaussian probability density functions. In the case that I_g and I_f are exponential probability density functions, it is easy to solve (3.20) for c. Doing so, we obtain

$$c = \frac{-(\beta_g + \beta_f) + \sqrt{(\beta_g + \beta_f)^2 + 4\beta_g\beta_f}}{2}, \tag{3.21}$$

where β_g and β_f are the constant per capita maturation rates for stages g and f. In the case that I_g and I_f are inverse Gaussian probability density functions, we prefer to obtain the solution of (3.20) numerically.

In summary, to compute the stable age distribution one first solves (3.20) to obtain the asymptotic growth rate, c. Substituting c for c_g and 1 for $g_2(0)$ in (3.10) we find $g_2(a)$. Next, $f_2(0)$ is computed using (3.15), and this value is used to compute $f_2(a)$ according to (3.12) with c in place of c_f. Note that in this procedure, one can vary the population size by altering the value of $g_2(0)$. Figures 8 and 9 below display the models' stable age distributions and verify their stability.

In the following section, we will examine how stable age distributions, stable stage distributions, and growth rates vary between these two models. In so doing it is helpful to note that the stable solution has a single degree of freedom $g_2(0)$, which determines the initial population size.

4. Methods

4.1. 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 matures (transitions) 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 $\lim_{\delta a \to 0} \frac{o(\delta a)}{\delta a} = 0$) be the probability that a cell matures over the interval $[a, a + \delta a]$, given that it has not maturation at age a. That is, $\beta(a)$ is the maturation rate. 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 matures after age, $a + \delta a$, is the probability that the cell does not mature over $[a, a + \delta a]$, given it did not mature up until age a, times the probability that the cell did not mature 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 maturation probability in terms of $R(a)$. Note that, $R(a) = \int_a^\infty I(s)ds$. Therefore

$$\beta(a) = \frac{I(a)}{\int_a^\infty I(s)ds}. \tag{4.1}$$

In general, there may not be a closed form for the maturation rate, $\beta(a)$, so that it must be approximated numerically. In this case, as a grows, the numerator and denominator in the expression for $\beta(a)$ approach zero, and the computation is challenging due to limits on floating-point precision. As a result, it is useful to have a better qualitative characterization of $\beta(a)$ for the purpose of validating numerical simulations. In the following paragraphs, we characterize several important features of the $\beta(a)$ which corresponds to the inverse Gaussian probability density.

First note we may use L'Hôpital's rule to compute the asymptotic value of $\beta(a)$. For the inverse Gaussian distribution

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

so that

$$\lim_{a\to\infty} \beta(a) = \lim_{a\to\infty} \frac{I(a)}{\int_a^\infty I(s)ds} = \lim_{a\to\infty} -\frac{I'(a)}{I(a)} = \lim_{a\to\infty} \frac{3}{2}\frac{1}{a} - \frac{1}{2\sigma^2}\frac{1}{a^2} + \frac{\mu^2}{2\sigma^2} = \frac{\mu^2}{2\sigma^2}. \tag{4.2}$$

Our 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 4.1. *The per capita maturation rate, $\beta(a)$, has exactly one critical point, at which it takes a maximum value. Moreover, if a^* is the age at which $\beta(a)$ takes its maximum value, $\beta(a) < -q(a)$ for $a > a^*$.*

Proof. With $\beta(a) = \dfrac{I(a)}{\int_a^\infty I(s)ds}$ and $I'(a) = I(a)q(a)$, where $-q(a) = \frac{3}{2}\frac{1}{a} - \frac{1}{2\sigma^2}\frac{1}{a^2} + \frac{\mu^2}{2\sigma^2}$, as above we find that

$$\beta'(a) = \frac{\int_a^\infty I(s)ds I(a)q(a) + I^2(a)}{\left(\int_a^\infty I(s)ds\right)^2} < 0 \tag{4.3}$$

$$\iff \beta(a) < -q(a). \tag{4.4}$$

Similarly,

$$\beta'(a) > 0 \iff \beta(a) > -q(a). \tag{4.5}$$

and

$$\beta'(a) = 0 \iff \beta(a) = -q(a). \tag{4.6}$$

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

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 see that $-q'(a) > 0$ 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 (4.5). Fixing $a_0 > \hat{a} > 0$, we have $\beta(a) > -q(a)$ and $\beta'(a) > 0 > -q'(a)$ for $a > a_0 > \hat{a}$. Thus,

$$0 = \lim_{s\to\infty} \beta(s) + q(s) = \lim_{s\to\infty} \int_{a_0}^{s} \beta'(a) + q'(a)da + \beta(a_0) + q(a_0) > \beta(a_0) + q(a_0) > 0, \tag{4.7}$$

which is a contradiction. Therefore, we may define a^* as follows,

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

Note by continuity $\beta'(a^*) = 0$ and $\beta(a^*) = -q(a^*)$. Note also that $a^* > 0$, 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 $0 = \beta'(a^*) > -q'(a^*)$. Then by continuity there exists an interval over which the inequality holds. Moreover, since $\beta(a^*) = -q(a^*)$, there exists $\delta > 0$ such that $\beta(a) > -q(a)$ for $a^* < a < a^* + \delta$. Suppose toward a contradiction that there exists $a > a^*$ such that $\beta(a) \leq -q(a)$. Let $s^* = \inf\{a > a^* \mid \beta(a) \leq -q(a)\}$, and note $s^* \neq a^*$. Thus for $a^* < a < s^*$, $\beta(a) > -q(a)$, and for

$a^* < a < s^*, \beta'(a) > 0$. However, since $-q$ has a single critical point at which is takes a maximum, we know $-q'(a) < 0$ for $a > a^*$. Therefore $\beta'(a) > -q'(a)$ for $a^* < a < s^*$, and

$$\beta(s^*) - \beta(a^*) = \int_{a^*}^{s^*} \beta'(a)da > \int_{a^*}^{s^*} -q'(a)da = -q(s^*) - \beta(a^*). \tag{4.8}$$

That is, $\beta(s^*) > -q(s^*)$. However, 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 $\{a \mid a > a^*, \beta(a) \leq -q(a)\}$ is empty. That is, $\beta(a) > -q(a)$ for $a > a^*$, i.e., $\beta'(a) > 0$ for $a > a^*$. Since we have already noted $-q'(a) < 0$ for $a > a^*$, we find that

$$0 = \lim_{s\to\infty} \beta(s) + q(s) = \lim_{s\to\infty} \int_{a^*}^{s} \beta'(a) + q'(a)da > 0. \tag{4.9}$$

Hence, this case does not occur.

Case 2:

Suppose 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 $\beta(a) \geq -q(a)$. 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 $a^* < a < s^*, \beta'(a) < 0$. 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 age 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 value, $-q'(a) < 0$ 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 and because $\beta(a) \neq -q(a)$ for $a > a^*$, 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 $a > a^*$, as desired

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

□

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

$$\max_{\{a>0\}} \beta(a) \leq \max_{\{a>0\}}(-q(a)) = -q(\hat{a}) \tag{4.10}$$

$$= \frac{9}{8}\sigma^2 + \frac{\mu^2}{2\sigma^2} \tag{4.11}$$

Lemma 4.2. *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, $\frac{1}{3}\frac{1}{\sigma^2} < a^*$.*

Proof. 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

$$-q(a_\infty) = \frac{\mu^2}{2\sigma^2} \iff \tag{4.12}$$

$$0 = \frac{3}{2}\frac{1}{a_\infty} - \frac{1}{2\sigma^2}\frac{1}{a_\infty^2} \iff \tag{4.13}$$

$$0 = \frac{3}{2}a_\infty - \frac{1}{2\sigma^2} \iff \tag{4.14}$$

$$a_\infty = \frac{1}{3}\frac{1}{\sigma^2} \tag{4.15}$$

It follows that $\frac{1}{3}\frac{1}{\sigma^2} = a_\infty < a^*$. Indeed, since $a_\infty < \hat{a} = \frac{2}{3\sigma^2}$, $-q$ 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 $\beta(a)$ is increasing (i.e., $\beta(a) > -q(a)$ for $a < a^*$.) □

4.2. Numerical approximation of β

The practical computation of the maturation rate curve presents difficulties using fixed precision floating point techniques. This is due to the behavior of both the numerator and denominator of $\beta(a)$ as a increases causing the result to become unstable and ultimately undefined.

$$\beta(a) = \frac{I(a)}{\int_a^\infty I(s)ds}. \tag{4.16}$$

$$\lim_{a\to\infty} I(a) = 0 \tag{4.17}$$

$$\lim_{a\to\infty} \int_a^\infty I(s)ds = 0 \tag{4.18}$$

While variable precision arithmetic, as provided by MATLAB, allows for the stable computation of the maturation rate, as the numerator and denominator become small, the required precision increases, which in turn increases the computational expense. Runtimes with an acceptably small mesh sizes were found to be excessive for our choice of parameters. This was resolved by using interpolation to reduce the number of points that need to be evaluated with variable precision arithmetic. This is justified as the maturation rate curve is smooth (both the numerator and denominator are smooth and nonzero). In the absence of a predetermined method for choosing knots, we use an adaptive method: At each iteration, we double the number of knots by evaluating points midway between the existing knots, remembering previously computed knots using a memoization technique. Having the knots, we then interpolate for each point on our desired mesh. The vector of approximate maturation rate values is compared with the previous vector of approximate maturation rate values using the ℓ^2-norm of the

difference. When this error is reduced below a specified threshold, here chosen to be 0.1, the solution is accepted and returned. In this way, an accurate approximation of the maturation rate curve is obtained with acceptable performance (See Figures 1 and 2).

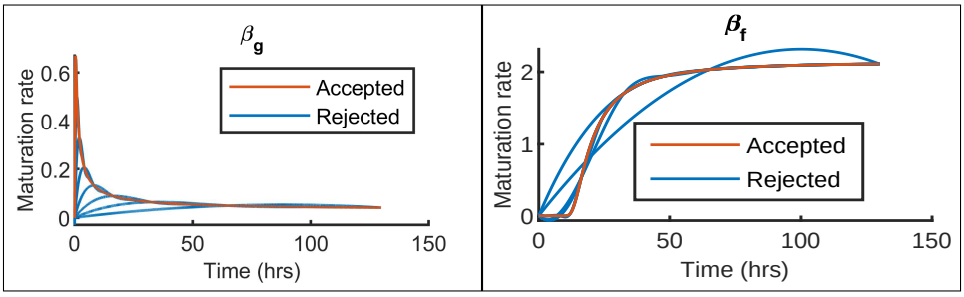

Figure 1. Convergence of maturation rates (β) as the number of knots increases.

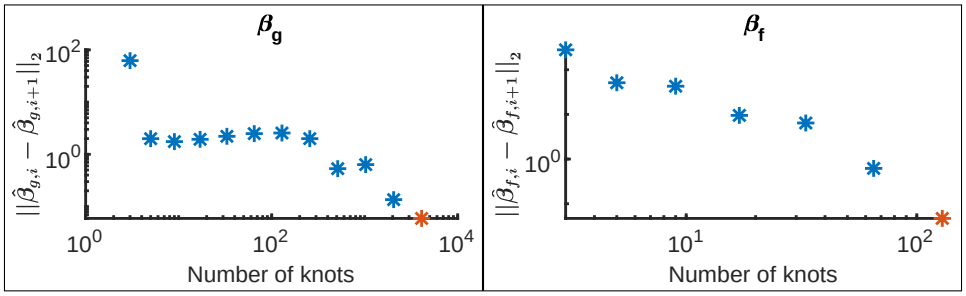

Figure 2. Adaptive error reduction with increasing numbers of knots. Blue denotes rejected solutions and red denotes accepted solution.

4.3. 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 follows:

Let $a = (0, h, 2h, \ldots Ih)$, and $t = (0, h, 2h, \ldots Jh)$, where $Jh = T$, and $Ih = T + a_{max}$. Now define $\hat{\mathbf{g}} = (\hat{g}_{ij}) \in \mathbb{R}^{(I+1)\times(J+1)}$ and $\hat{\mathbf{f}} = (\hat{f}_{ij}) \in \mathbb{R}^{(I+1)\times(J+1)}$ as matrices such that

$$\hat{f}_{i0} = f_0(a_i), \quad i = 1, \ldots I, \tag{4.19}$$

$$\hat{g}_{i0} = g_0(a_i) \quad i = 1, \ldots I, \tag{4.20}$$

$$\hat{f}_{0j} = integral(0, a_I, \beta_g \hat{g}_{:,j}) \quad j = 1, \ldots J, \tag{4.21}$$

$$\hat{g}_{0j} = 2\ integral(0, a_I, \beta_f \hat{f}_{:,j}) \quad j = 1, \ldots J, \tag{4.22}$$

$$\hat{f}_{i+1,j+1} = \hat{f}_{ij} \exp\left\{integral(a_i, a_{i+1}, -\beta_f)\right\} \tag{4.23}$$

$$\hat{g}_{i+1,j+1} = \hat{g}_{ij} \exp\left\{integral(a_i, a_{i+1}, -\beta_g)\right\} \tag{4.24}$$

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}. This algorithm is an extension of that presented in [22] to a PDE system. The consistency and stability of the algorithm can be shown similarly to [22], so we omit the details here. All simulations were performed in MATLAB. These codes can be found in the following repository: `https://github.com/rnleander/Asma`.

5. Results

Here we simulate the model using both inverse Gaussian and exponential maturation time distributions. Parameters for the inverse Gaussian distribution were chosen to fit data on the division times of MCF10A cells, as described in [20]. 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, late G1-M, and the full cell cycle are the same for both models.

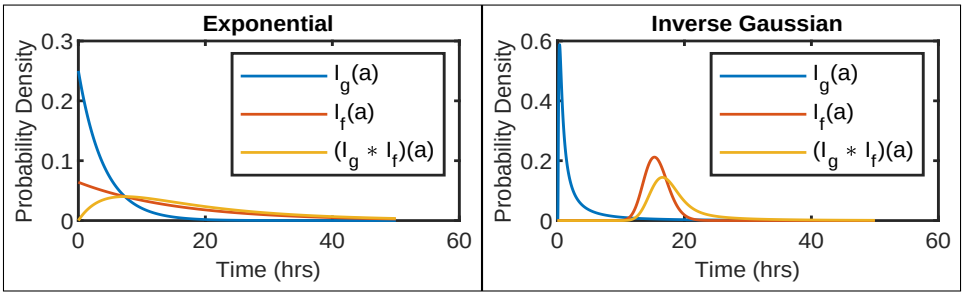

Figure 3. Stage maturation times, I_g and I_f, and total intermitotic time, $(I_g * I_f)(a)$, distributions for both exponential and inverse Gaussian models.

Table 1. Means and variances of model stages.

Model	$Mean_g$	$Variance_g$	$Mean_f$	$Variance_f$
Exponential	4.00	16.0	15.6	244
Inverse Gaussian	4.00	64.9	15.6	367

To explore the models' transient dynamics, we initialize them with their stable stage structures and two unstable age densities (see Section 3); the uniform initial age density (Figures 4 and 6) and the Gaussian initial age density (Figure 5). For the inverse Gaussian model, the stage and age structures oscillate over multiple days when initialized with either unstable age density. However, the amplitude of the oscillations decreases through time, so that the population stage structure approaches the stable stage structure (Figures 4 and 5). In contrast, for the exponential model, the stage structure is insensitive to the initial age density: No matter the initial age density, the stage structure does not evolve

through time provided it is initialized as the stable stage structure. The age distributions behave similarly. Figures 4–7 demonstrate that the inverse Gaussian age distribution stabilizes much more slowly than that of the exponential distribution. We also initialized the models with stable age densities and perturbed stage structures. For these simulations, we perturbed the ratio of cells in early G1 to late G1-M by a factor of two. Again, the exponential model stabilizes much more quickly that the inverse Gaussian model (Figures 11 and 12).

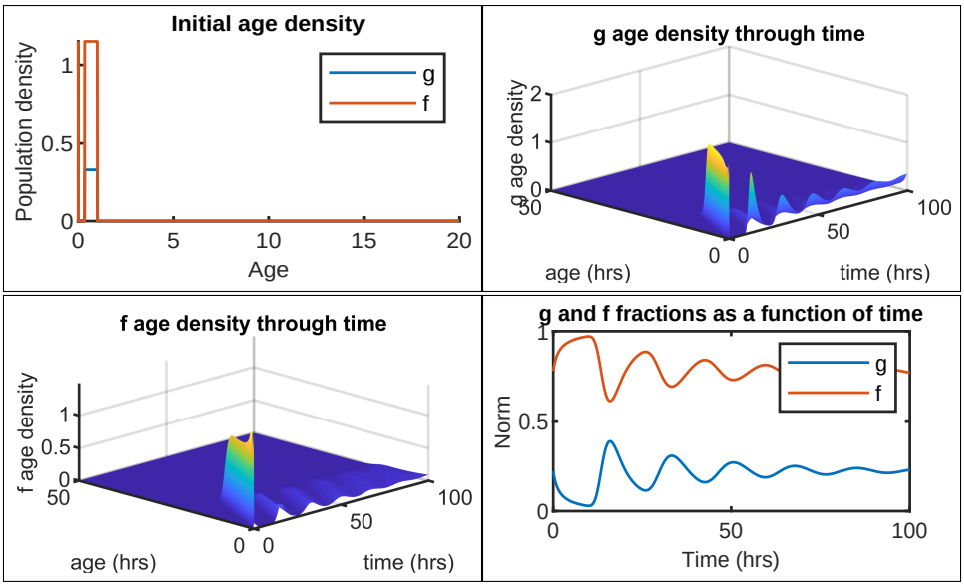

Figure 4. Inverse Gaussian model with uniform initial age density and stable initial age structure. Note that the stage structure oscillates as the age structure evolves.

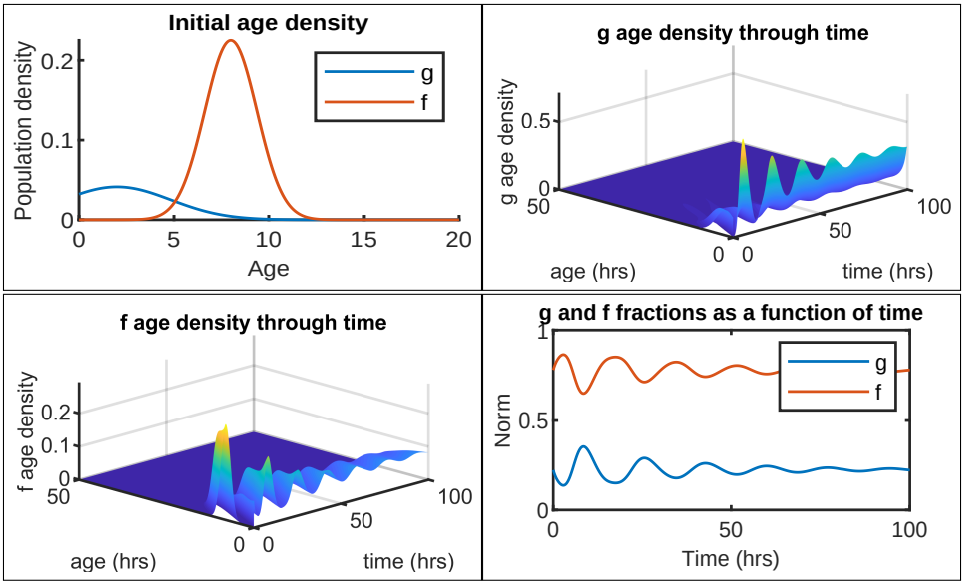

Figure 5. Inverse Gaussian model with Gaussian initial age density and stable initial age structure. Note that the stage structure oscillates as the age structure evolves.

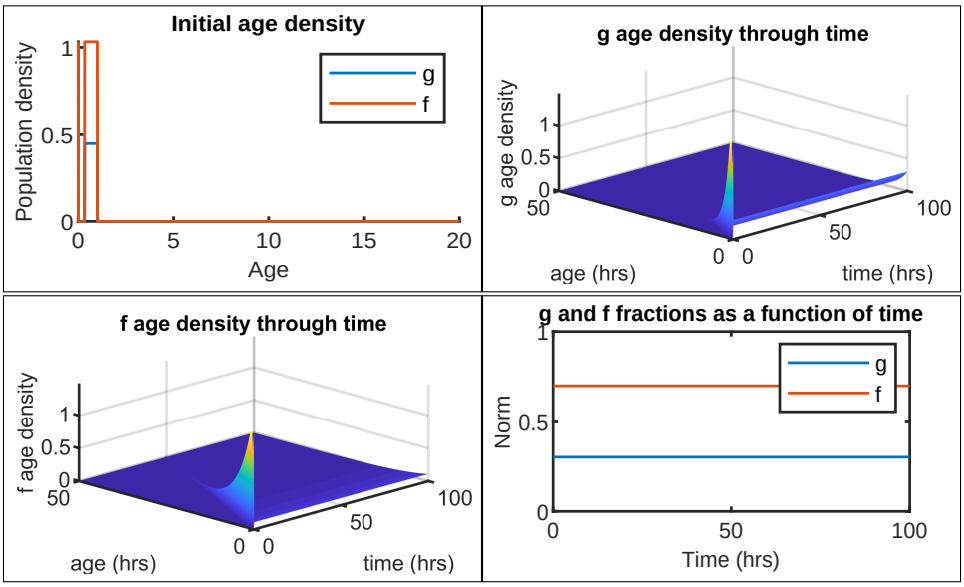

Figure 6. Exponential model with uniform initial age density and stable initial age structure. Note that the stage structure does not evolve, and the age density stabilizes quickly.

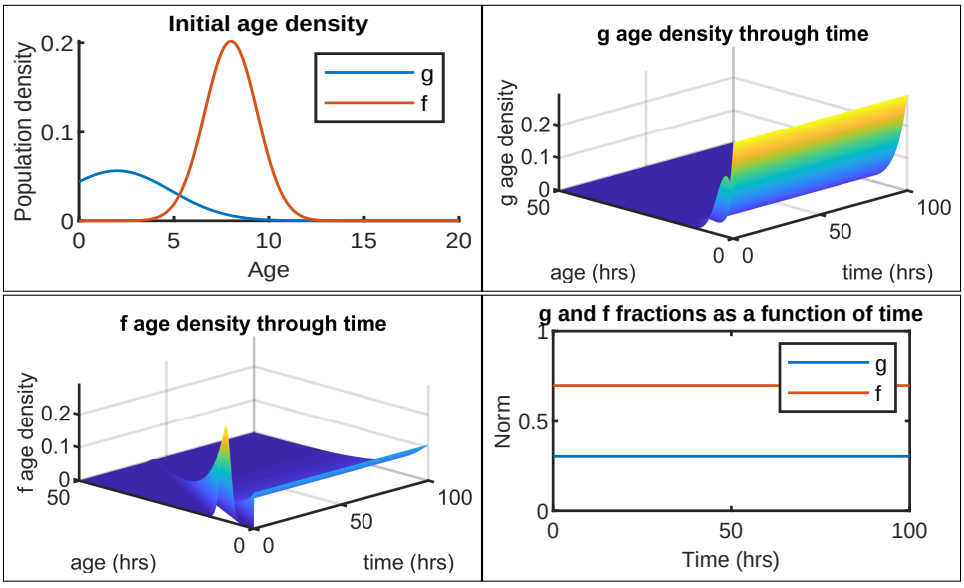

Figure 7. Exponential model with Gaussian initial age density and stable initial age structure. Note that the stage structure does not evolve ,and the age density stabilizes quickly.

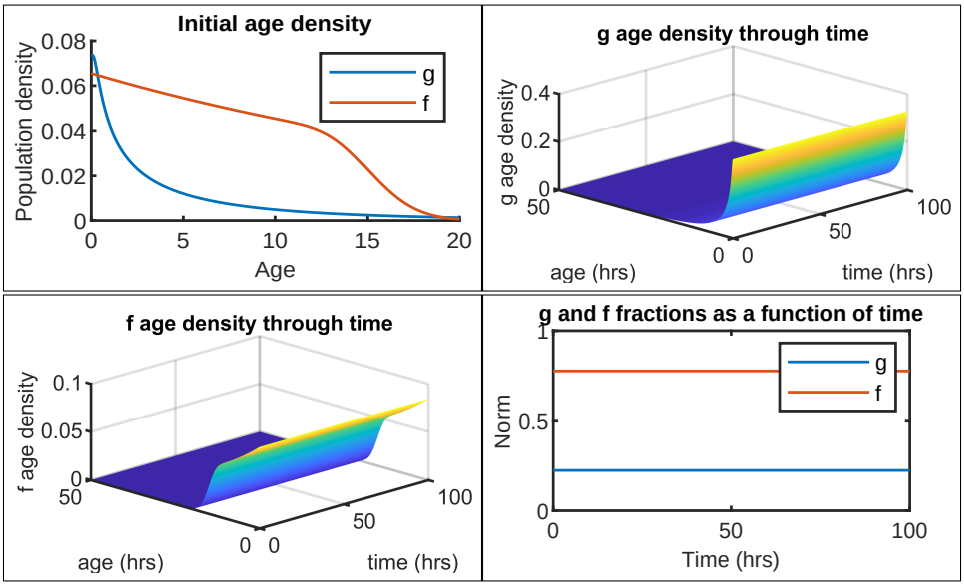

Figure 8. Inverse Gaussian model with stable initial age density and stage structure. Note that when initialized with the stable age density and stable stage structure, neither the stage structure nor the age density evolve through time.

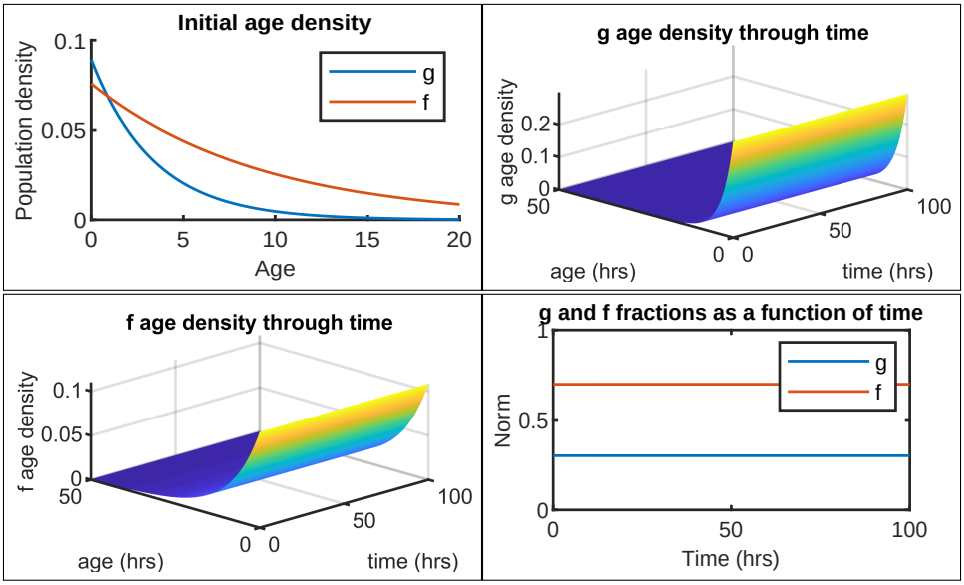

Figure 9. Exponential model with stable initial age density and stage structure. Note that the stage structure and age density do not evolve through time.

The two models also differ in their predicted stable stage distributions (Figures 8 and 9). Despite the fact that, as parameterized, the average time spent in early G1 and late G1-M is identical for both models, the stable exponential stage structure has about 30% of cells in early G1, while the stable inverse Gaussian stage structure has about 22% of cells in early G1.

Finally Figure 10 and Table 2 present the predicted and observed asymptotic growth rates of the population for the two maturation time models. It is interesting to note that, despite exhibiting the same average intermitotic time, the models differ substantially in terms of their asymptotic growth rates. As a result, after 100 hours, a population with exponential maturation times is expected to be almost twice as large as that with inverse Gaussian maturation times.

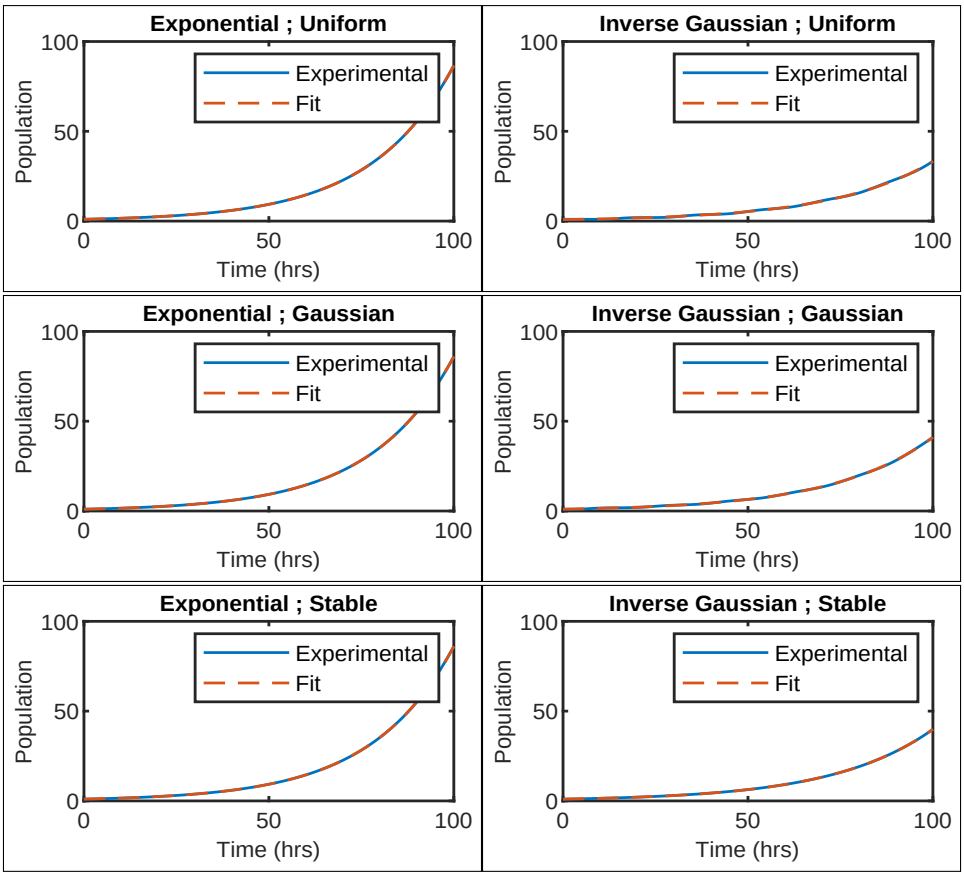

Figure 10. Growth rate curves and exponential growth fits. Note that while oscillation in the inverse Gaussian model does affect the total population, exponential growth remains a good fit.

Table 2. Predicted and fitted exponential growth rates in hr^{-1}. Note that there is some variability in the fitted growth rates for the Inverse Gaussian model with uniform and Gaussian initial conditions due to oscillations that are not present with the stable initial conditions.

Model	Predicted	Uniform	Gaussian	Stable
Exponential	0.04462	0.04455	0.04455	0.04455
Inverse Gaussian	0.03689	0.03673	0.03694	0.03685

6. Conclusion

Our results demonstrate that maturation time distributions can significantly impact the transient dynamics, growth, and structure of a cellular population. Indeed, when employing the ageless exponential maturation time distribution, the population stage structure is insensitive to the initial age density, in that perturbations in the age density do not perturb the stage structure. Moreover, the stage structure and age density stabilize quickly on perturbation. In contrast, the inverse Gaussian model's stage structure exhibits sustained oscillations over several days when the age desnity is perturbed away from the stable age density. This difference represents a major qualitative distinction between the two models. Importantly, the models also differ in their mean-predicted growth rates. That is, when parameterized so that the average time spent in each stage, and thus the average time spent in the full cell cycle, is the same for both models, the asymptotic growth rate of the exponential model is considerably greater. This difference is likely due to the fact that few cells exhibit short maturation times under the inverse Gaussian model. In contrast, short maturation times are common in the exponential model. Thus, the difference in growth rates is likely the result of variability in the time to mature. As a result of these differences, we recommend that modelers take care when choosing a maturation time distribution. Indeed, we hope that our methods and programs can help researchers develop and simulate more accurate, predictive models of cellular population growth. We note that the cell cycle model presented here is well-suited to study the impact of CDK inhibitors, which impact restriction point passage (in our model, maturation into late G1) [23]. The model could also be adapted to study the impact of drugs which target S phase (e.g., gemcitabine) [3]. A second benefit of this work is that it provides testable predictions that can be used to determine if the exponential distribution provides a reasonable approximation to a population's maturation time distribution. In particular, the rapidity with which the exponential model achieves a stable stage distribution is predicted to be a robust feature of the model that would be readily observable via experimentation. In summary, we find evidence that a population's maturation time distribution can inform model development and refinement while deepening our understanding of the fundamental process of cellular proliferation.

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Conflict of Interest

All authors declare no conflicts of interest in this paper.

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Appendix 1: Proof of Existence

In proving Theorem 2.1 we consider $C(\Omega_1)$, the Banach space of continuous, bounded functions on Ω_1 with the norm

$$\|h\|_\infty := \sup_{x\in\Omega_1} h(x). \tag{6.1}$$

We begin by establishing the following lemma.

Lemma 6.1. *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:

$$\begin{aligned} \Big| \int_0^\infty \beta_f(\alpha) f_{n-1}(\alpha, t_k - a_k) d\alpha \;-\; & \int_0^\infty \beta_f(\alpha) f_{n-1}(\alpha, t_0 - a_0) d\alpha \Big| \\ \leq\; & \int_0^\infty \beta_f(\alpha) |f_{n-1}(\alpha, t_k - a_k) - f_{n-1}(\alpha, t_0 - a_0)|\, d\alpha \end{aligned} \tag{6.2}$$

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

where A is chosen so that

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

Note by our assumptions, $t_k - a_k < T$ and $t_0 - a_0 < T$. Hence, there exists $\tau < T$ so that $t_k - a_k \leq \tau$ for $k = 0, 1, \ldots$. Also, since $f_{n-1}(a,t)$ is continuous on the closed and bounded sets $D_1 = \{(a,t)|0 \leq a \leq t \leq \tau\}$ and $D_2 = \{(a,t)|0 \leq t \leq a \leq A+T, 0 \leq t \leq \tau\}$, 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 [24],

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

Now note that the final term to the right of the equality in (6.2) is bounded by our choice of A. Indeed,

$$
\begin{aligned}
\left\|\beta_f\right\|_{\infty} \int_{A+T}^{\infty} |f_0(\alpha - (t_k - a_k))e^{-B_f(\alpha-(t_k-a_k),\alpha)} - f_0(\alpha - (t_0 - a_0))e^{-B_f(\alpha-(t_0-a_0),\alpha)}|\, d\alpha & \\
\leq \left\|\beta_f\right\|_{\infty} \int_{A+T}^{\infty} |f_0(\alpha - (t_k - a_k))|\, d\alpha & \\
+ \left\|\beta_f\right\|_{\infty} \int_{A+T}^{\infty} |f_0(\alpha - (t_0 - a_0))|\, d\alpha & \\
\leq \epsilon & \qquad (6.3)
\end{aligned}
$$

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

$$
\begin{aligned}
|g_1 - g_0|(a,t) &= N e^{-B_g(0,a)} \int_0^{\infty} f_0(\alpha) d\alpha - g_0(a) && (6.4)\\
&\leq N \|f_0\|_{L^1} + \|g_0\|_{\infty} \leq \infty, && (6.5)\\
|f_1 - f_0|(a,t) &\leq N \|g_0\|_{L^1} + \|f_0\|_{\infty} \leq \infty. && (6.6)
\end{aligned}
$$

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 $M := \max\{\|f_1 - f_0\|_{\infty}, \|g_1 - g_0\|_{\infty}\} < \infty$.

In general,

$$
g_{n+1}(a,t) - g_n(a,t) = e^{-B_g(0,a)}\left(\int_0^{\infty} 2\beta_f(\alpha)(f_n(\alpha, t-a)d\alpha - f_{n-1}(\alpha, t-a))d\alpha\right). \qquad (6.7)
$$

Thus, for $a < t < T$

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

$$\begin{aligned} &\leq e^{-B_g(0,a)} \int_0^{t-a} 2\beta_f(\alpha)|f_n - f_{n-1}|d\alpha \\ &= Ne^{-B_g(0,a)}(t-a)\,\|f_n - f_{n-1}\|_\infty \\ &\leq NT\,\|f_n - f_{n-1}\|_\infty \end{aligned} \tag{6.8}$$

That is,

$$\|g_{n+1} - g_n\|_\infty \leq NT\,\|f_n - f_{n-1}\|_\infty\,. \tag{6.9}$$

Similarly,

$$\|f_{n+1} - f_n\|_\infty \leq NT\,\|g_n - g_{n-1}\|_\infty\,. \tag{6.10}$$

(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

$$\|g_{n+1} - g_n\|_\infty \leq NT\,\|f_n - f_{n-1}\|_\infty \tag{6.11}$$

$$\leq (NT)^{n-1}M, \tag{6.12}$$

and

$$\|f_{n+1} - f_n\|_\infty \leq NT\,\|g_n - g_{n-1}\|_\infty \tag{6.13}$$

$$\leq (NT)^{n-1}M. \tag{6.14}$$

Since

$$g_n = g_0 + \sum_{i=1}^{n}(g_i - g_{i-1}), \tag{6.15}$$

we see that

$$g := \lim_{n\to\infty} g_n = g_0 + \sum_{i=1}^{\infty}(g_i - g_{i-1}) \tag{6.16}$$

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

$$T < \frac{1}{N}. \tag{6.17}$$

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

$$f := \lim_{n\to\infty} f_n = f_0 + \sum_{i=1}^{\infty}(f_i - f_{i-1}) \tag{6.18}$$

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 (2.13) - (2.14), and accounting for the possible discontinuity at $a = t$ we find:

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

$$\frac{\partial g_{n+1}}{\partial a}(a,t) = -2e^{-B_g(0,a)} \int_0^{\infty} \beta_f(\alpha)\left(\beta_g(a)(f_n(\alpha, t-a) + \frac{\partial f_n}{\partial t}(\alpha, t-a)\right)d\alpha$$

$$- \quad 2\beta_f(t-a)e^{-B_g(0,a)}\left(\lim_{\alpha\to(t-a)^-} f_n(\alpha,t-a) - \lim_{\alpha\to(t-a)^+} f_n(\alpha,t-a)\right) \tag{6.19}$$

$$\frac{\partial g_{n+1}}{\partial t}(a,t) = 2e^{-B_g(0,a)}\int_0^\infty \beta_f(\alpha)\frac{\partial f_n}{\partial t}(\alpha,t-a)d\alpha$$

$$+ \quad 2\beta_f(t-a)e^{-B_g(0,a)}\left(\lim_{\alpha\to(t-a)^-} f_n(\alpha,t-a) - \lim_{\alpha\to(t-a)^+} f_n(\alpha,t-a)\right) \tag{6.20}$$

$$\frac{\partial f_{n+1}}{\partial a}(a,t) = -e^{-B_f(0,a)}\int_0^\infty \beta_g(\alpha)\left(\beta_f(a)g_n(\alpha,t-a) + \frac{\partial g_n}{\partial t}(\alpha,t-a)\right)d\alpha$$

$$- \quad \beta_g(t-a)e^{-B_f(0,a)}\left(\lim_{\alpha\to(t-a)^-} g_n(\alpha,t-a) - \lim_{\alpha\to(t-a)^+} g_n(\alpha,t-a)\right) \tag{6.21}$$

$$\frac{\partial f_{n+1}}{\partial t}(a,t) = e^{-B_f(0,a)}\int_0^\infty \beta_g(\alpha)\frac{\partial g_n}{\partial t}(\alpha,t-a)d\alpha$$

$$+ \quad \beta_g(t-a)e^{-B_f(0,a)}\left(\lim_{\alpha\to(t-a)^-} g_n(\alpha,t-a) - \lim_{\alpha\to(t-a)^+} g_n(\alpha,t-a)\right) \tag{6.22}$$

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

$$\frac{\partial g_{n+1}}{\partial a}(a,t) = e^{-B_g(a-t,a)}\left(g_0'(a-t) + \beta_g(a-t)g_0(a-t) - \beta_g(a)g_0(a-t)\right) \tag{6.23}$$

$$\frac{\partial g_{n+1}}{\partial t}(a,t) = -e^{-B_g(a-t,a)}\left(g_0'(a-t) - \beta_g(a-t)g_0(a-t)\right) \tag{6.24}$$

$$\frac{\partial f_{n+1}}{\partial a}(a,t) = e^{-B_f(a-t,a)}\left(f_0'(a-t) + \beta_f(a-t)f_0(a-t) - \beta_f(a)f_0(a-t)\right) \tag{6.25}$$

$$\frac{\partial f_{n+1}}{\partial t}(a,t) = -e^{-B_f(a-t,a)}\left(f_0'(a-t) - \beta_f(a-t)f_0(a-t)\right). \tag{6.26}$$

From the above cases we see that g_n and f_n given by (2.13)-(2.16) will satisfy (2.7) - (2.8) together with the boundary conditions (2.9) - (2.12), 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 (6.19)-(6.22), but first we will establish the continuity of the expressions to the right of each equality in (6.19)-(6.22). 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 (6.23)-(6.26), respectively.

Lemma 6.2. *Let f_0, g_0, $\beta_f(\alpha)$ and $\beta_g(\alpha)$ as in Theorem 2.1, and define $\frac{\partial g_n}{\partial t}$, $\frac{\partial f_n}{\partial t}$, $\frac{\partial g_n}{\partial a}$, and $\frac{\partial f_n}{\partial a}$ by (6.20),(6.22),(6.19) and (6.21), respectively.*

(i) $\frac{\partial g_n}{\partial t}$, $\frac{\partial f_n}{\partial t}$, $\frac{\partial g_n}{\partial a}$, and $\frac{\partial f_n}{\partial a}$ 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 $\frac{\partial g_n}{\partial t}$, $\frac{\partial f_n}{\partial t}$, $\frac{\partial g_n}{\partial a}$, and $\frac{\partial f_n}{\partial a}$ 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

$$\begin{aligned}
\left|\frac{\partial g_{n+1}}{\partial t} - \frac{\partial g_n}{\partial t}\right| &\leq Ne^{-B_g(0,a)} \int_0^{t-a} \left|\frac{\partial f_n}{\partial t} - \frac{\partial f_{n-1}}{\partial t}\right| d\alpha && (6.27)\\
&+ Ne^{-B_g(0,a)} \left|\lim_{\alpha\to(t-a)^-} f_n(\alpha, t-a) - \lim_{\alpha\to(t-a)^+} f_{n-1}(\alpha, t-a)\right| \\
&\leq N(t-a)\left\|\frac{\partial f_n}{\partial t} - \frac{\partial f_{n-1}}{\partial t}\right\|_\infty + N\|f_n - f_{n-1}\|_\infty && (6.28)\\
&\leq NT\left\|\frac{\partial f_n}{\partial t} - \frac{\partial f_{n-1}}{\partial t}\right\|_\infty + N(NT)^{n-1}M, && (6.29)
\end{aligned}$$

and

$$\begin{aligned}
\left|\frac{\partial f_{n+1}}{\partial t} - \frac{\partial f_n}{\partial t}\right| &\leq Ne^{-B_f(0,a)} \int_0^{t-a} \left|\frac{\partial g_n}{\partial t} - \frac{\partial g_{n-1}}{\partial t} d\alpha\right| && (6.30)\\
&+ Ne^{-B_f(0,a)} \left|\lim_{\alpha\to(t-a)^-} g_n(\alpha, t-a) - \lim_{\alpha\to(t-a)^+} g_{n-1}(\alpha, t-a)\right| \\
&\leq N(t-a)\left\|\frac{\partial g_n}{\partial t} - \frac{\partial g_{n-1}}{\partial t}\right\|_\infty + N\|g_n - g_{n-1}\|_\infty && (6.31)\\
&\leq NT\left\|\frac{\partial g_n}{\partial t} - \frac{\partial g_{n-1}}{\partial t}\right\|_\infty + N(NT)^{n-1}M. && (6.32)
\end{aligned}$$

Combining these two together :

$$\left\|\frac{\partial g_{n+1}}{\partial t} - \frac{\partial g_n}{\partial t}\right\|_\infty \leq NT\left\|\frac{\partial f_n}{\partial t} - \frac{\partial f_{n-1}}{\partial t}\right\|_\infty + N(NT)^{n-1}M \quad (6.33)$$

$$\left\|\frac{\partial f_{n+1}}{\partial t} - \frac{\partial f_n}{\partial t}\right\|_\infty \leq NT\left\|\frac{\partial g_n}{\partial t} - \frac{\partial g_{n-1}}{\partial t}\right\|_\infty + N(NT)^{n-1}M \quad (6.34)$$

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,

$$\begin{aligned}
\left\|\frac{\partial g_{n+1}}{\partial t} - \frac{\partial g_n}{\partial t}\right\|_\infty &\leq NT\left\|\frac{\partial f_n}{\partial t} - \frac{\partial f_{n-1}}{\partial t}\right\|_\infty + N(NT)^{n-1}M && (6.35)\\
&\leq \dots \\
&\leq \hat{M}(NT)^{n-1} + (n-1)NM(NT)^{n-1}. && (6.36)
\end{aligned}$$

Similarly,

$$\left\|\frac{\partial f_{n+1}}{\partial t} - \frac{\partial f_n}{\partial t}\right\|_\infty \leq \dots \leq \hat{M}(NT)^{n-1} + (n-1)NM(NT)^{n-1}. \quad (6.37)$$

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

$$f_0(a,t) = f_0(a). \tag{6.38}$$
$$g_0(a,t) = g_0(a), \tag{6.39}$$

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

$$\begin{aligned}\frac{\partial g_{n+1}}{\partial t}(a,t) &= 2e^{-B_g(0,a)}\int_0^\infty \beta_f(\alpha)\frac{\partial f_n}{\partial t}(\alpha,t-a)d\alpha \\ &+ 2\beta_f(t-a)e^{-B_g(0,a)}\left(\lim_{\alpha\to(t-a)^-} f_n(\alpha,t-a) - \lim_{\alpha\to(t-a)^+} f_n(\alpha,t-a)\right) \qquad (6.40)\\ \frac{\partial f_{n+1}}{\partial t}(a,t) &= e^{-B_f(0,a)}\int_0^\infty \beta_g(\alpha)\frac{\partial g_n}{\partial t}(\alpha,t-a)d\alpha \\ &+ \beta_g(t-a)e^{-B_f(0,a)}\left(\lim_{\alpha\to(t-a)^-} g_n(\alpha,t-a) - \lim_{\alpha\to(t-a)^+} g_n(\alpha,t-a)\right), \qquad (6.41)\end{aligned}$$

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

$$\frac{\partial g_{n+1}}{\partial t}(a,t) = -e^{-B_g(a-t,a)}\left(g_0'(a-t) - \beta_g(a-t)g_0(a-t)\right) \tag{6.42}$$
$$\frac{\partial f_{n+1}}{\partial t}(a,t) = -e^{-B_f(a-t,a)}\left(f_0'(a-t) - \beta_f(a-t)f_0(a-t)\right). \tag{6.43}$$

From (6.38) and (6.39)

$$\frac{\partial g_0}{\partial t}(a,t) = 0 \quad \text{for} \quad (a,t) \in (0,\infty)\times(0,T) \tag{6.44}$$
$$\frac{\partial f_0}{\partial t}(a,t) = 0 \quad \text{for} \quad (a,t) \in (0,\infty)\times(0,T). \tag{6.45}$$

Also, $f_0(a,t) \equiv f_0(a)$ is continuous. Hence by (6.40) and (6.41)

$$\frac{\partial g_1}{\partial t}(a,t) = 0 \quad \text{for} \quad a < t \tag{6.46}$$
$$\frac{\partial f_1}{\partial t}(a,t) = 0 \quad \text{for} \quad a < t. \tag{6.47}$$

On the other hand, for $t < a$, $\dfrac{\partial g_1}{\partial t}$ and $\dfrac{\partial f_1}{\partial t}$ are given by (6.42) and (6.43), 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 $a < t$:

$$\begin{aligned}\frac{\partial g_2}{\partial t}(a,t) &= 2e^{-B_g(0,a)}\left(\int_0^{t-a}\beta_f(\alpha)\frac{\partial f_1}{\partial t}(\alpha,t-a)d\alpha + \int_{t-a}^\infty \beta_f(\alpha)\frac{\partial f_1}{\partial t}(\alpha,t-a)d\alpha\right) \\ &+ 2\beta_f(t-a)e^{-B_g(0,a)}\left(\lim_{\alpha\to(t-a)^-} f_1(\alpha,t-a) - \lim_{\alpha\to(t-a)^+} f_1(\alpha,t-a)\right) \\ &= -2e^{-B_g(0,a)}\int_{t-a}^\infty \beta_f(\alpha)\beta_f(\alpha-(t-a))e^{-B_f(\alpha-(t-a),\alpha)}f_0(\alpha-(t-a))d\alpha \\ &- 2e^{-B_g(0,a)}\int_{t-a}^\infty \beta_f(\alpha)e^{-B_f(\alpha-(t-a),\alpha)}f_0'(\alpha-(t-a))d\alpha \\ &+ 2\beta_f(t-a)e^{-B_g(0,a)}e^{-B_f(0,t-a)}\left(\int_0^\infty \beta_g(\alpha)g_0(\alpha)d\alpha - f_0(0)\right) \qquad (6.48)\end{aligned}$$

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:

$$\begin{aligned}\frac{\partial g_2}{\partial t}(a,t) = &- 2e^{-B_g(0,a)}\int_0^\infty e^{-B_f(u,u+(t-a))}\beta_f(u+(t-a))\beta_f(u)f_0(u)du \\ &- 2e^{-B_g(0,a)}\int_0^\infty e^{-B_f(u,u+(t-a))}\beta_f(u+(t-a))f_0'(u)du. \end{aligned} \tag{6.49}$$

Thus for $a < t$

$$\begin{aligned}\left|\frac{\partial g_2}{\partial t}(a,t)\right| &\leq 2\left\|\beta_f\right\|_\infty^2 \|f_0\|_{L^1} + 2\left\|\beta_f\right\|_\infty \left\| f_0'\right\|_{L^1} \\ &+ 2\left\|\beta_f\right\|_\infty \left\|\beta_g\right\|_\infty \|g_0\|_{L^1} + 2\left\|\beta_f\right\|_\infty \|f_0\|_\infty \\ &\leq N(\| f_0\|_{L^1} + \| g_0\|_{L^1} + \left\| f_0'\right\|_{L^1} + \| f_0\|_\infty). \end{aligned} \tag{6.50}$$

Therefore,

$$\left\|\frac{\partial g_2}{\partial t} - \frac{\partial g_1}{\partial t}\right\|_\infty < \infty. \tag{6.51}$$

Similarly,

$$\left\|\frac{\partial f_2}{\partial t} - \frac{\partial f_1}{\partial t}\right\|_\infty < \infty. \tag{6.52}$$

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 (6.19) and (6.21) we see that

$$\frac{\partial g_{n+1}}{\partial a}(a_0,t_0) = -\frac{\partial g_{n+1}}{\partial t}(a_0,t_0) - \beta_g(a_0)g_{n+1}(a_0,t_0), \tag{6.53}$$

$$\frac{\partial f_{n+1}}{\partial a}(a_0,t_0) = -\frac{\partial f_{n+1}}{\partial t}(a_0,t_0) - \beta_f(a_0)f_{n+1}(a_0,t_0). \tag{6.54}$$

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 (2.13) and (2.14). The proof is by induction.

Proof. 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

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

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

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

$$+\int_{A+T}^{\infty}\frac{\beta_f(\alpha)(f_n(\alpha,t+\Delta t-a)-f_n(\alpha,t-a))}{\Delta t}d\alpha \tag{6.55}$$

We will handle the first and second terms to the right if the inequality in (6.55) separately. The first term can be expressed as

$$\begin{aligned}\int_0^{A+T}\frac{\beta_f(\alpha)(f_n(\alpha,t+\Delta t-a)-f_n(\alpha,t-a))}{\Delta t}d\alpha &= \int_0^{t-a}\frac{\beta_f(\alpha)(f_n(\alpha,t+\Delta t-a)-f_n(\alpha,t-a))}{\Delta t}d\alpha\\ &+\int_{t-a}^{t-a+\Delta t}\frac{\beta_f(\alpha)(f_n(\alpha,t+\Delta t-a)-f_n(\alpha,t-a))}{\Delta t}d\alpha\\ &+\int_{t-a+\Delta t}^{A+T}\frac{\beta_f(\alpha)(f_n(\alpha,t+\Delta t-a)-f_n(\alpha,t-a))}{\Delta t}d\alpha\end{aligned} \tag{6.56}$$

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 (6.56) 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 (6.56) we have

$$\begin{aligned}\int_{t-a}^{t-a+\Delta t}\beta_f(\alpha)\frac{f_n(\alpha,t+\Delta t-a)-f_n(\alpha,t-a)}{\Delta t}d\alpha &= \frac{1}{\Delta t}\int_{t-a}^{t-a+\Delta t}\beta_f(\alpha)f_n(\alpha,t+\Delta t-a)d\alpha\\ &-\frac{1}{\Delta t}\int_{t-a}^{t-a+\Delta t}\beta_f(\alpha)f_n(\alpha,t-a)d\alpha\end{aligned} \tag{6.57}$$

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

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

Now we show the convergence of the second term in (6.55). Applying the mean value theorem to $f_n(\alpha, t^*(\alpha))$ for $\alpha \geq t^*$,

$$\begin{aligned}\left|\int_{A+T}^{\infty} \frac{\beta_f(\alpha)(f_n(\alpha, t+\Delta t-a) - f_n(\alpha, t-a))}{\Delta t} d\alpha\right| &= \left|\int_{A+T}^{\infty} \beta_f(\alpha)\frac{\partial f_n}{\partial t}(\alpha, t^*(\alpha)) d\alpha\right| \\ &\leq \left\|\beta_f\right\|_\infty \int_{A+T}^{\infty} \left|\frac{\partial f_n}{\partial t}(\alpha, t^*(\alpha))\right| d\alpha \end{aligned} \tag{6.58}$$

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

$$\begin{aligned}&\left\|\beta_f\right\|_\infty \int_{A+T}^{\infty} \left|\frac{\partial f_n}{\partial t}(\alpha, t^*(\alpha))\right| d\alpha \\ &= \left\|\beta_f\right\|_\infty \int_{A+T}^{\infty} \left|e^{-B_f(\alpha - t^*(\alpha), \alpha)}\left(f_0'(\alpha - t^*(\alpha)) + \beta_f(\alpha - t^*(\alpha)) f_0(\alpha - t^*(\alpha))\right)\right| d\alpha \\ &\leq \left\|\beta_f\right\|_\infty \int_{A+T}^{\infty} \left|f_0'(\alpha - t^*(\alpha))\right| d\alpha + \left\|\beta_f\right\|_\infty^2 \int_{A+T}^{\infty} \left|f_0(\alpha - t^*(\alpha))\right| d\alpha. \end{aligned} \tag{6.59}$$

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

$$\begin{aligned}&\left\|\beta_f\right\|_\infty \int_{A+T}^{\infty} \left|f_0'(\alpha - t^*(\alpha))\right| d\alpha + \left\|\beta_f\right\|_\infty^2 \int_{A+T}^{\infty} \left|f_0(\alpha - t^*(\alpha))\right| d\alpha \\ &\leq \left\|\beta_f\right\|_\infty \int_{A+T}^{\infty} \left|f_0'(\alpha - (t+\Delta t - a))\right| d\alpha + \left\|\beta_f\right\|_\infty^2 \int_{A+T}^{\infty} \left|f_0(\alpha - (t+\Delta t - a))\right| d\alpha \\ &\leq \left\|\beta_f\right\|_\infty \int_{A}^{\infty} \left|f_0'(\alpha)\right| d\alpha + \left\|\beta_f\right\|_\infty^2 \int_{A}^{\infty} \left|f_0(\alpha)\right| d\alpha \\ &\leq \frac{\epsilon}{2}. \end{aligned} \tag{6.60}$$

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

$$\begin{aligned}
&\left|\int_{A+T}^{\infty}\beta_f(\alpha)\frac{\partial f_n}{\partial t}(\alpha,t-a)d\alpha\right| \\
&\leq \left\|\beta_f\right\|_{\infty}\int_{A+T}^{\infty}\left|e^{-B_f(\alpha-(t-a),\alpha)}\left(f_0'(\alpha-(t-a))+\beta_f(\alpha-(t-a))f_0(\alpha-(t-a))\right)\right|d\alpha \\
&\leq \left\|\beta_f\right\|_{\infty}\int_{A+T}^{\infty}\left|f_0'(\alpha-(t-a))\right|d\alpha+\left\|\beta_f\right\|_{\infty}^2\int_{A+T}^{\infty}\left|f_0(\alpha-(t-a))\right|d\alpha \\
&\leq \left\|\beta_f\right\|_{\infty}\int_{A}^{\infty}\left|f_0'(\alpha)\right|d\alpha+\left\|\beta_f\right\|_{\infty}^2\int_{A}^{\infty}\left|f_0(\alpha)\right|d\alpha \\
&\leq \frac{\epsilon}{2}. \qquad (6.61)
\end{aligned}$$

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 $(a,t)\in\Omega_1$,

$$\begin{aligned}
\frac{\partial g_{n+1}}{\partial t}(a,t) &= 2e^{-B_g(0,a)}\int_0^{\infty}\beta_f(\alpha)\frac{\partial f_n}{\partial t}(\alpha,t-a)d\alpha \\
&+ 2\beta_f(t-a)e^{-B_g(0,a)}\left(\lim_{\alpha\to(t-a)^-}f_n(\alpha,t-a)-\lim_{\alpha\to(t-a)^+}f_n(\alpha,t-a)\right). \qquad (6.62)
\end{aligned}$$

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 (6.19)–(6.22). Moreover, we see that g_n and f_n satisfy (2.7)–(2.8). 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 (2.7)–(2.8), we see that f and g satisfy (2.1)–(2.2). 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 (2.4) and (2.6).

Proof. Note that:

$$\begin{aligned} g_{n+1}(0,t) &= 2\int_0^\infty \beta_f(a) f_n(a,t)da \\ &= 2\int_0^t \beta_f(a) f_n(a,t)da + 2\int_t^\infty \beta_f(a) f_0(a-t)e^{-B_f(a-t,a)}da \end{aligned} \tag{6.63}$$

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,

$$\begin{aligned} g_{n+1}(0,t) &\to 2\int_0^t \beta_f(a) f(a,t)da + 2\int_t^\infty \beta_f(a) f_0(a-t)e^{-B_f(a-t,a)}da \\ &= 2\int_0^\infty \beta_f(a) f(a,t)da \end{aligned} \tag{6.64}$$

as desired. Similarly, we find that f satisfies the boundary condition (2.6). □

Thus, the proof of Theorem 2.1 is complete.

Theorem 6.3. *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 (2.1)–(2.2) together with the boundary conditions (2.3)-(2.6) 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 (2.1)–(2.2) together with the boundary conditions (2.4) and (2.6) 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 (2.15) and (2.16). 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 (2.15) and (2.16) 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 $\left\|\frac{\partial g_n}{\partial a} - \frac{\partial g}{\partial a}\right\|_\infty \to 0$ and $\left\|\frac{\partial f_n}{\partial a} - \frac{\partial f}{\partial a}\right\|_\infty \to 0$ 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 (6.23) and (6.25). 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 (6.23) and (6.25) 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.

$$\hat{f}_0'(a) = f_0'(a-T)e^{-B_f(a-T,a)} - f_0(a-T)[\beta_f(a-T) - \beta_f(a)]e^{-B_f(a-T,a)} \tag{6.65}$$

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 $\hat{a} > a > A$,

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

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:

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

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 (2.1) and (2.2) subject to the boundary conditions (2.4) and (2.6), 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 (2.13) and (2.14). 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,

$$\begin{aligned} \lim_{a\to\tau^-} \hat{g}_n(a,\tau) &= 2e^{-B_g(0,\tau)}\int_0^\infty \beta_f(\alpha)\hat{f}_0(\alpha)d\alpha \\ &= e^{-B_g(0,\tau)}\hat{g}(0) \\ &= \lim_{a\to\tau^+} \hat{g}_n(a,\tau) \end{aligned} \tag{6.66}$$

Similarly,

$$\lim_{a\to\tau^-} \hat{f}_n(a,\tau) \quad = \quad \lim_{a\to\tau^+} \hat{f}_n(a,\tau) \tag{6.67}$$

Thus, $\hat{f}_n$ and $\hat{g}_n$ converge to continuously differentiable solutions of (2.7) and (2.8) subject to (2.3)–(2.6), 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 $t \le 2T$. Continuing in this way, for all time, we can define solutions of (2.7) and (2.8) subject to the boundary conditions (2.3)–(2.6), continuously differentiable for $a \ne t$. □

7. Appendix 2: Perturbed Stage Structures

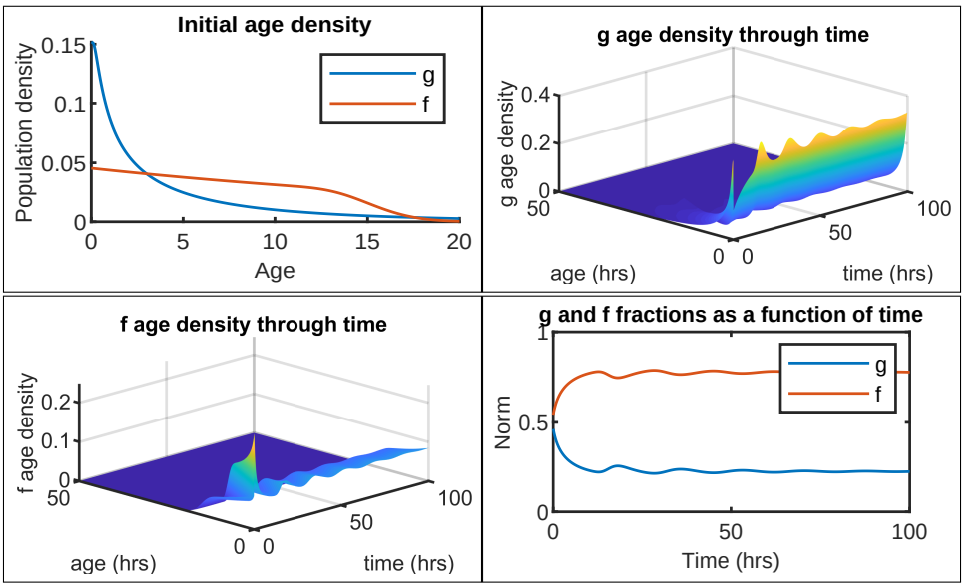

Figure 11. Inverse Gaussian model with stable initial age density and initial stage ratio perturbed by a factor of three. Note that the perturbed initial stage structure alone is sufficient to induce oscillations in both age density and stage structure.

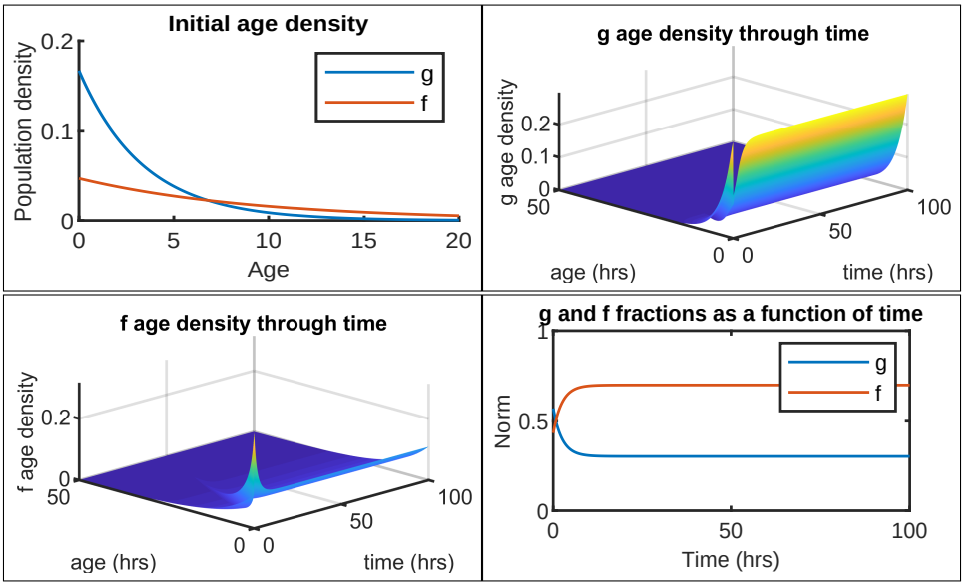

Figure 12. Exponential model with stable initial age density and initial stage ratio perturbed by a factor of three. Note that the stage structure quickly stabilizes and does not overshoot or oscillate.