COMBINING SIZER, TIMER, AND ADDER MECHANISMS IN PDE MODELS OF CELL POPULATIONS

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Abstract. Cell division is a process that involves many biochemical steps and complex biophysical mechanisms. To simplify the understanding of what triggers cell division, three basic models that subsume more microscopic cellular processes associated with cell division have been proposed. Cells can divide based on the time elapsed since their birth, their size, and/or the volume added since their birth—the timer, sizer, and adder models, respectively. While the populations of cells dividing under sizer and timer rules have been treated individually, we develop a unified PDE model that incorporates all mechanisms, especially that of the adder. Limiting cases of our model reduce to single-mechanism models previously proposed. Specifically, we show that the adder mechanism is not independent of the timer mechanism under deterministic cell growth; however, our adder model provides an easier way to incorporate mechanisms in terms of added volume and exhibit qualitatively different dynamical behavior. We further generalize our PDE model to incorporate mother cell-daughter cell correlations in growth rates. Existence and uniqueness of weak solutions to our PDE model are proved, allowing us to numerically compute the dynamics of cell population densities. Finally, we carry out numerical studies to illustrate blow-up of the average cell size and evolution of cellular growth rates.

Key words. PDE, structured populations, cell size control

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1. Introduction. How cells regulate and maintain their size, as well as sizes of appendages is a long-standing topic in biology. Besides growth of an individual cell, the size distributions of a population of cells is also a quantity of interest. When considering proliferating cell populations, individual cell growth is interrupted by cell division events that generate smaller daughter cells. The biological mechanisms that control when and how a cell divides is a basic problem in cell biology. While complex and involving many processes such as metabolism and volume growth, protein production, DNA replication, chromosome separation (for eukaryotic cells), and fission or cell wall formation [21, 12, 5, 3, 7]. These processes are regulated and may involve intricate biochemical signaling.

Despite the complexity of cell growth and the cell cycle, three hypotheses for cell division control have arisen. Cell division is often assumed to be governed by cell age $a$, cell volume $x$, or added volume since birth $y$ [23, 22, 17]. Volume growth of an individual cell can be straightforwardly measured and can be modeled by an effective empirical law such as $\dot{x} = g(a, x, y, t)$. A commonly used approximation that is supported by observations is the exponential growth law $g[x] = \lambda x$ [20].

The division mechanism employed by a type of cell is probably most directly classified by tracking the volumes $x$, added volumes $y$, and ages $a$ of all division events. The distribution of the event coordinates in $(a, x, y)$-space, accumulated over time, may provide data that favors a mechanistic interpretation. For example, if the division events are concentrated within a narrow range of volumes $x$, one might infer a sizer mechanism. However, comparison among the variabilities of the volumes, added volumes, and ages across all division events is difficult. Moreover, in addition to the intrinsic variability in the mechanism of division, the variability in division sizes and times are sensitive to stochasticity arising in the growth an in the sizes of the new daughter cells. Therefore, it can be difficult to precisely classify the mechanism division.

Much like a growth law $g(a, x, y, t)$ that can depend on size, added size, and age, the three distinct mechanisms of cell division need not be mutually exclusive. The birth rate or probability can be an explicit function of any combination of time since birth (age), size, or volume added since birth. For example, cell division may occur through a cell cycle that is stated only after the cell exceeds a certain volume, rendering the division rate a function of both size and age.

To model cell size control, stochastic maps that relate daughter cell sizes to mother cell sizes have been developed [15, 17, 16]. These models describe how cell sizes evolve with generation and can interpolate between timer, sizer, and adder mechanisms. Kessler and Burov [15] assumed stochastic growth which lead to a stochastic map with multiplicative noise. They found that an adder mechanism can admit “blow-up” in which the expected cell sizes can increase without bound with increasing generation. Modi et al. [17]
assume additive noise and do not find blow-up in an adder model. Stochastic maps of generational cell size do not describe population-level distributions in size or age.

To describe population-level distributions, PDE approaches have been developed. For example, the timer model, in which the cell division rate depends only on age of the cell is described by the well-known McKendrick equation for \( n(a, t) \) the expected density of cells with age \( a \) at time \( t \) \([10, 11, 6] \). The “transport” equation for the cell density takes the form \( \partial_t n(a, t) + \partial_a n(a, t) = -\mu(a)n(a, t) \) with the boundary condition \( n(t, 0) = 2 \int_0^\infty \beta(s)n(s, t)ds \) describing birth or zero-age cells with age-dependent division rate \( \beta(s) \). Note that this timer model does not explicitly track cell sizes. PDE models incorporating sizer mechanisms have also been developed \([18, 9, 19] \). In these studies, it was shown that depending on the size dependent birth rate \( \beta(x) \), cells can diverge in size \( x \) \([14] \). Existence and uniqueness of weak solutions have been proved for certain boundary and initial conditions. These types of models can be partially solved using the method of characteristics but the boundary condition is only can be reduced to a Volterra-type integral equation \([18, 6] \).

Apart from the sizer and the timer models, the adder mechanism has been recently shown to be consistent with E. coli division \([21, 22, 23] \). The adder model is motivated by an initiator accumulation mechanism distinct from those used to justify sizers or timers \([22, 5] \). Here, we systematically develop unified PDE models for populations of cells that divide according to different cell size control mechanisms.

In this manuscript, we will develop higher-dimensional PDEs that can describe cell populations that divide according to more complicated mechanisms that depend on age, size, and added size. In the next section, we formally derive PDEs for a sizer-timer model, in which the division rate is a function of both size and age, and a adder-sizer model, in which the division rate depends on both the cell’s size and the added volume since its own birth. We then demonstrate that a deterministic PDE model that includes age, size, and added size is inconsistent because the age uniquely determine the trajectory of the added size. Thus, in the absence of stochasticity, no PDE can be developed for a combined “adder-sizer-timer model.”

After we demonstrate the existence and uniqueness of a weak solution of the sizer-timer and adder-sizer models, we implement a simple numerical solution and show solutions to population densities \( n(a, x, t) \) and \( n(x, y, t) \) in the Results section. Different forms of the birth function are investigated and their effects on the population densities explored. We also derive the division event frequency, the total population, and the biomass growth rate. Stochastic simulations are also generated and compared with our numerical results.

In the Discussion and Conclusions section, we discuss the advantages and limitations of our PDE approach and propose extensions to the theory to allow for a daughter cell growth law that depends on the growth of of the previous generation. We also propose a diffusive transport equation to approximate population densities in the presence of stochastic growth.

2. Unifying PDE models. Here, we develop a more complete picture of the dynamics of cell populations that proliferate possibly through all division mechanisms, sizer, time, and adder. We wish to incorporate a rate of cell division that, most generally, is a function of a cell’s age, size, and added size. We first consider the sizer and timer mechanisms together and derive the PDEs for the density of cells in age and size.

We then formulate a model that assumes a division rate that is a function of both cell volume and added volume. Finally, we show that if individual cell growth is deterministic, the adder and timer mechanisms are not independent. Therefore, the only self-consistent deterministic population models are those that incorporate timer, sizer, sizer-timer, or adder-sizer mechanisms. In our subsequent derivations, we shall neglect cell apoptosis/death for notational simplicity. Terms including cell death can be easily be included afterwards.

2.1. Sizer-Timer Model. A PDE model of cell division that combines both size- and age- control division mechanisms can be formulated by defining \( n(a, x, t) da dx \) as the expected number of cells at time \( t \) with size in \([x, x + dx]\) and age \([a, a + da]\).

Given time \( t > 0 \), \((a, x) \in \mathbb{R}^2_+, 0 < a < t \), we formally derive the transport equation by defining the total population within a state-space volume \( \Omega \in [0, a] \times [0, x] \) shown in Fig. 1(a):

\[
N(a, x, t) = \int_0^a da' \int_0^x dx' n(a', x', t) \equiv \int_\Omega n(a', x', t) da' dx.
\] (2.1)

The total time rate of change \( dN(a, x, t) / dt \) can be found by using the definition of \( N(a, x, t) \) and taking the
\[
\frac{dN(a, x, t)}{dt} = \lim_{\Delta t \to 0} \frac{1}{\Delta t} \left[ \int_0^{x + \Delta t} da' \int_0^x dx' n(a', x', t + \Delta t) \right.
\]
\[
+ \int_0^a da' \int_0^{x + g(a', x, t) \Delta t} dx' n(a', x', t + \Delta t) - N(a, x, t) \bigg]\]
\[
= \int_0^a da' \int_0^x dx' \frac{\partial n(a', x', t)}{\partial t} + \int_0^a da' \int_0^x g(a, x', t) n(a, x', t) + \int_0^x dx' n(a, x', t).
\]

The time rate of change of the population is simply balanced by birth and death processes that increment or decrement \(N(a, x, t)\). For simplicity of the development, we will first neglect cell death which can be simply added afterwards.

To describe sources of cells into \(\Omega\), we define \(\tilde{\beta}(a', x', z', t)dz'\) as the rate of fission of cells of age \(a'\) and volume \(x'\) to divide into two cells, one with size in \([z', z' + dz']\) and the other with size within \([x' - z', x' - (z' + dz')]\). For binary fission, conservation of daughter cell volumes requires \(\tilde{\beta}(a', x', z', t) = \tilde{\beta}(a', x', z' = x', t)\). This differential division function allows mother cells to divide into two daughter cells of differing sizes (asymmetric division), a process that has been observed in numerous contexts [13, 12, 2]. We also assume that daughter cells must have finite size and that \(\tilde{\beta}(a', x', z' = 0, t) = \tilde{\beta}(a', x', z' = x', t) = 0\). The change in

![Fig. 1. The state space for cell populations. The expected total number of cells at time \(t\) with age within \([0, a]\) and volume (or “size”) within \([0, x]\) is defined as \(N(a, x, t)\). Over an increment in time \(\Delta t\), the domain \(\Omega = [0, a] \times [0, x]\) infinitesimally distorts \(\Omega \rightarrow \Omega + \Delta \Omega\). The total population within this distorted domain changes only due to birth and death. Cells within \(\Omega\) that divide always give rise to two daughters within \(\Omega\), leading to a net change of +1 cell. (b) The \(z'\) and \(x'\) domains of the differential birth rate function \(\tilde{\beta}(x', y', z', t)\). Cells outside of \(\Omega\) can contribute a net +1 or +2 cells in \(\Omega\) depending on the the division patterns defined in the depicted regions.](image)

the number of cells in \(\Omega\) due to fission can arise in a number of ways. First, if a cell in \(\Omega\) divides, it can only produce two cells with size less than \(x\). Thus, such fission events lead to a net change of +1 in the number of cells with \(a = 0\) and size in \([0, x]\). This rate of change can be expressed as

\[
+ 1 \int_0^a da' \int_0^x dx' \int_0^{x'} dz' \tilde{\beta}(a', x', z', t) n(a', x', t).
\]

If a cell with size within \([0, x]\) but with age \(a > a\) divides, it creates two cells with age \(a = 0\) and size within \([0, x]\), leading to a net change of +2 cells. The rate of change incurred from such a cell dividing is thus

\[
+ 2 \int_a^\infty da' \int_0^x dx' \int_0^{x'} dz' \tilde{\beta}(a', x', z', t) n(a', x', t).
\]

For cells with any age \(a' > 0\) but with size \(x' > x\), we have two subcases. If the dividing cell has size \(x < x' < 2x\), it will produce one daughter cell in \(\Omega\) if a daughter cell has size \(0 < z' < x' - x\) or \(x < z' < x'\),
as shown in Fig. 1(b). If \( x' - x < z' < x \), both daughter cells have size \( x \). Thus, division of cells with size \( x < x' < 2x \) leads to the contribution

\[
\int_0^\infty da' \int_0^{2x} dx' \int_0^{z'-x} dz' \beta(a', x', z', t)n(a', x', t) + \int_0^\infty da' \int_0^\infty dx' \int_0^{x'} dz' \beta(a', x', z', t)n(a', x', t) + 2 \int_0^\infty da' \int_0^{2x} dx' \int_{x'-x}^x dz' \beta(a', x', z', t)n(a', x', t).
\]

Finally, if the dividing cell has size \( x' > 2x \), at most one daughter will have size \( x' < x \) (see Fig. 1(b)) and the source from these cells is

\[
\int_0^\infty da' \int_0^{2x} dx' \int_0^x dz' \beta(a', x', z', t)n(a', x', t) + \int_0^\infty da' \int_0^\infty dx' \int_0^{x'} dz' \beta(a', x', z', t)n(a', x', t).
\]

Upon simplifying the above birth terms by using \( \int_0^{x'} dz' = \int_0^x dz' + \int_x^{x'} dz' \) for \( x' > x \) and the symmetry \( \beta(a', x', z', t) = \beta(a', x', x' - z', t) \), we balance the result with the transport term (Eq. 2.7) to find

\[
\int_0^\infty da' \int_0^x dx' \frac{\partial n(a', x', t)}{\partial t} = \int_0^\infty da' \int_0^\infty dx' \int_0^{x'} dz' \beta(a', x', z', t)n(a', x', t) + 2 \int_0^\infty da' \int_0^\infty dx' \int_0^x dz' \beta(a', x', z', t)n(a', x', t)
\]

Upon taking the derivatives \( \frac{\partial^2}{\partial a dx} \), we find the PDE obeyed by \( n(a, x, t) \):

\[
\left( \frac{\partial}{\partial t} + \frac{\partial}{\partial a} \right) n(a, x, t) + \frac{\partial [g(a, x, t)n(a, x, t)]}{\partial x} = -\beta(a, x, t)n(a, x, t)
\]

where the total division rate is defined as \( \beta(a, x, t) := \int_0^x \beta(a, x, z, t)dz \). For the boundary condition at \( a = 0 \), we take the derivative \( \partial / \partial x \) and set \( a \to 0^+ \) to find

\[
\int_0^\infty da' \int_0^\infty dx' \beta(a', x', x, t)n(a', x', t).
\]

Finally, since cells have finite volume, \( n(a, 0, t) = 0 \). Thus, given an initial condition \( n(a, x, t = 0) \equiv n_0(a, x) \), Eqs. 2.8 and 2.9 define the full sizer-timer PDE model for cell populations. This model allows for asymmetric cell division through the differential division rate \( \beta(a, x, z, t)dz \).

**2.2. Adder-Sizer Model.** Recently, there has been experimental evidence of cell division that is driven by an adder mechanism [4, 22]. Thus, we develop an alternative type of PDE model that incorporates growth rates \( g(x, y, t) \) and differential birth rates \( \beta(x, y, z, t)dz \) that, instead of depending on a cell’s age \( a \), are functions of cell size \( x \) and a cell’s volume \( add \ since \ birth \ y \). Such a “sizer-adder” PDE mode can be developed by defining \( n(x, y, t)dx dy \) as the mean number of cells with size in \( [x, x + dx] \) and added volume in \( [y, y + dy] \). Again, as cells have finite size and added volume must be less than total size, \( n(x, y, t) = n(x \leq 0, y, t) = 0 \).

The derivation of the adder-sizer model closely follows that of the sizer-timer model. By defining \( N(x, y, t) = \int_y^y dy' \int_0^x dx' n(x', y', t) \), we define the time rate of change

\[
N(x, y, t) = \int_0^\infty da' \int_0^\infty dx' \beta(a', x', x, t)n(a', x', t).
\]

Finally, since cells have finite volume, \( N(a, 0, t) = 0 \). Thus, given an initial condition \( n(a, x, t = 0) \equiv n_0(a, x) \), Eqs. 2.8 and 2.9 define the full sizer-timer PDE model for cell populations. This model allows for asymmetric cell division through the differential division rate \( \beta(a, x, z, t)dz \).
\[ \frac{\partial N(x, y, t)}{\partial t} + \int_0^x dx' (gn) + \int_0^y dy' (gn) = \int_0^\infty dy' \int_0^x dx' \int_0^{x'} \beta(x', y', z', t)n(x', y', t) + \int_y^\infty dy' \int_0^x dx' \int_0^{x'} \beta(x', y', z', t)n(x', y', t) + 2 \int_0^\infty dy' \int_0^\infty dx' \int_0^x dx' \beta(x', y', z', t)n(x', y', t) \]

(2.10)

The differential birth rates \( \tilde{\beta}(x, y, z, t) \) are now possibly functions of size, added size, and time. The birth processes that contribute to the total population in \([0, x] \times [0, y]\) can be delineated in analogy with those of the sizer-timer model (as shown in Figs. 1(a-b)). By taking the derivative \( \frac{\partial^2}{\partial x \partial y \partial z} \), we find the transport equation for adder-sizer model

\[ \frac{\partial n(x, y, t)}{\partial t} + \frac{\partial [g(x, y, t)n(x, y, t)]}{\partial x} + \frac{\partial [g(x, y, t)n(x, y, t)]}{\partial y} = -\beta(x, y, t)n(x, y, t) \]

(2.11)

where here, the total division rate is defined as \( \beta(x, y, t) := \int_0^x \beta(x, y, z, t) \). For the boundary condition at \( y = 0 \), we take the derivative \( \partial / \partial x \) and set \( y \to 0^+ \) to find

\[ g(x, y = 0, t)n(x, y = 0, t) = 2 \int_x^\infty dx' \int_0^{x'} dy' \tilde{\beta}(x', y', z = x, t)n(x', y', t). \]

(2.12)

The other boundary condition defined by construction is \( n(x = y, y, t) = 0 \).

In the special restricted case of symmetric cell division,

\[ \tilde{\beta}(x, y, z, t) = \beta(x, y, t) \delta(z - x/2). \]

(2.13)

The boundary condition of the adder-sizer model is then slightly simplified to

\[ g(x, y = 0, t)n(x, y = 0, t) = 4 \int_0^{2x} \beta(2x, y', t)n(2x, y', t)dy', \]

(2.14)

Quantities such as the total cell population \( N(t) \) and the mean total biomass \( M(t) \) (the total volume over all cells) can be easily constructed from the density \( n(x, y, t) \):

\[ N(t) = \int_0^\infty dx \int_0^x dy n(x, y, t), \quad M(t) = \int_0^\infty dx \int_0^x dy xn(x, y, t). \]

(2.15)

Higher moments of the total volume can also be readily defined. By applying these operations to Eq. 2.11 and using the boundary condition (Eq. 2.12), we find the dynamics of the total population and biomass

\[ \frac{dN(t)}{dt} = \int_0^\infty dx \int_0^x dy \beta(x, y, t)n(x, y, t) \]

(2.16)

\[ \frac{dM(t)}{dt} = \int_0^\infty dx \int_0^x dy \beta g(x, y, t)n(x, y, t). \]

(2.17)

Similar quantities describing the total population and the mean age of the population can be analogously derived using the sizer-timer model (Eqs. 2.8 and 2.9).

Finally, we also define the distribution of division events over the size and added size variables, accumulated over a time \( T \):
2.2.1. Division probability and splitting rate. We now develop forms for the differential splitting rate function $\dot{\beta}$. In the McKendrick model that is typically applied to demography, a positive age-dependent death rate $\mu(a \to \infty) > 0$ the age-density $n(a, t)$ will remain bounded in age $n(a \to \infty, t) \to 0$, preventing the population from acquiring unbounded age, or “blow-up.” Since we have neglected death in our models, arbitrary birth rates $\beta(x, y, t)$ may lead to finite densities of cells of unbounded size and added size. Thus, without death, the division rate functions are constrained to certain forms in order for the model to be compatible with clear experimental observations.

To determine the allowable forms of $\beta(x, y, z, t)$ in the adder-sizer model, we will invoke a splitting probability that is explicitly a function of only age $a$. For a single cell born at time $t_0 = 0$, the probability that the cell splits within time $[a, a + da]$ is defined by $\gamma(a) da$. The age $a$, however, may depend on cell size, added size, and time. In order to ensure that any single cell will eventually split,

\begin{equation}
\int_0^\infty \gamma(a) da = 1.
\end{equation}

The splitting probability is simply the division rate, conditioned on the cell not having divided up to time $a$. Furthermore, for deterministic growth we can invert the age variable $a(x, y)$ in terms of $x, y$. Thus, the division rate function $\dot{\beta}(x, y)$ can be constructed as

\begin{equation}
\beta(x, y, t) = \frac{\gamma(a(x, y))}{1 - \int_0^{a(x, y)} da' \gamma(a')}.
\end{equation}

For example, for exponential growth, $a(x, y) \ln 2 = \ln(x / (x - y))$. Possible choices for $\gamma(a)$ are Gamma, lognormal, or normal distributions. Without loss of generality, we propose a simple gamma distribution for $\gamma(a)$:

\begin{equation}
\gamma(a) = \frac{1}{\Gamma((a/\sigma_a)^2)} \exp \left[ -\frac{\bar{a} a}{\sigma_a} + \left( \frac{\bar{a}}{\sigma_a} \right)^2 \ln \left( \frac{a \bar{a}}{\sigma_a^2} \right) - \ln a \right]
\end{equation}

where $\bar{a}$ is the mean and $\sigma_a$ is the variance. This type of distribution can be derived from the sum of independent, exponentially distributed ages. In our model, we assume a typical division age $\bar{a}$ that is explicitly a function of a fixed added size parameter $\Delta$

\begin{equation}
\bar{a} \ln 2 = \ln \left( \frac{x - y + \Delta}{x - y} \right).
\end{equation}

In this model, cells born at small initial size $x(0) = x_0 = x - y$ takes longer to divide, while cells born with large size, splits sooner. Using the gamma distribution, we find division rate of the form

\begin{equation}
\beta(x, y) = \frac{\Gamma \left( \frac{\bar{a}^2(x, y)}{\sigma_a^2} \right) \gamma(a(x, y))}{\Gamma \left( \frac{\bar{a}^2(x, y)}{\sigma_a^2}, \frac{a(x, y)}{\sigma_a^2} \right)},
\end{equation}

where $\Gamma(\cdot, \cdot)$ is the upper incomplete gamma function. We plot two examples of the time-independent rate $\beta(x, y)$ in Fig. 2.

Other forms for $\beta(x, y, t)$ can be derived from division probabilities $\gamma(y)$ that are explicit functions of, for example, added size $y$. In this case, the division constraint is $\int_0^\infty \gamma(y') dy' = 1$ and $\beta(x, y)$ will take the form shown in Eq. 2.20 but with an extra factor $g(x, y, t)$ to convert $\beta$ into a rate.
Fig. 2. The size and added-size dependent rate $\beta(x, y)$ constructed using a gamma distribution for the splitting probability $\gamma$ (Eq. 2.21) and Eq. 2.20. In (a) the parameters are $\sigma_a = 0.2$, while in (b) $\sigma_a = 0.5$. Note that $\gamma(a)$ with a higher variance leads to a lower overall cell division rate $\beta$.

With $\beta(x, y, t)$ defined, we still need to construct the full differential division rate $\tilde{\beta}$, which we will assume is a product of the division rate $\beta(x, y, t)$ and a differential division probability. The simplest model is to assume that the differential division probability is a function of only the ratio $r$ between the size of the daughter cell and that of the mother cell, and independent of the cell size just before division. Thus, we assume

$$\tilde{\beta}(x, y, z, t) = \beta(x, y, t) h(z/x)$$

where $r = z/x \in [0, 1]$. Since by definition $\int_0^1 \tilde{\beta}(x, y, z, t) dz = \beta(x, y, t)$ and $h(r)$ is independent of $x$, $\int_0^1 h(r) dr = 1$ and the differential division rate is described by $\tilde{\beta}(x, y, z, t) = \beta(x, y, t) h(z/x)/x$. The boundary condition (Eq. 2.12) can thus be written in the form

$$g(x, 0, t)n(x, 0, t) = 2 \int_x^{\infty} dx' \int_0^1 ds \beta(x', sx', t) h(x/x') n(x', sx', t).$$

A reasonable model for $h(r = x/x')$ is a lognormal form that is symmetric about $r = 1/2$:

$$h(r) = \frac{h_0(r) + h_0(1 - r)}{Z(\sigma_r, \delta)}$$

$$h_0(r) = e^{-\frac{(-\delta + \ln r)^2}{2\sigma_r^2}} e^{-\frac{\ln^2(1 - r)}{2\sigma_r^2}},$$

where the parameters $\delta$ and $\sigma_r$ determine the spread of the function $h(r)$ and the normalization constant

$$Z(\sigma_r, \delta) = \int_0^1 (h_0(r) + h_0(1 - r)) dr.$$
and shows the numerical results for the density $\bar{n}(x, y, t)$, $g(x, y, t)$, or $\beta(x, y, t)$. Similarly,

$$\beta_{i+\frac{1}{2}, j+\frac{1}{2}}((s + \frac{1}{2})h, t) = h^{-3} \int_{ih}^{(i+1)h} dx \int_{jh}^{(j+1)h} dy \int_{kh}^{(k+1)h} dz \beta(x, y, z, t)$$

in the domain $i, j \geq 0$ and $j, k < i$. The discretization of the transport equation can be expressed as

$$\frac{n_{i+\frac{1}{2}, j+\frac{1}{2}}(t+(\Delta t))-n_{i+\frac{1}{2}, j+\frac{1}{2}}(t)}{\Delta t} + \frac{g_{i+\frac{1}{2}, j+\frac{1}{2}}}{h} \hat{n}_{i+\frac{1}{2}, j+\frac{1}{2}} - \frac{g_{i, j+\frac{1}{2}}}{h} \hat{n}_{i, j+\frac{1}{2}} + \frac{g_{i+1, j+\frac{1}{2}}}{h} \hat{n}_{i+1, j+\frac{1}{2}} - \frac{g_{i+1, j}}{h} \hat{n}_{i+1, j} = -\beta_{i+\frac{1}{2}, j+\frac{1}{2}} n_{i+\frac{1}{2}, j+\frac{1}{2}}(t),$$

for $1 \leq i, j \leq L$, where $Lh$ is the maximum size which we take sufficiently large such that $n_{i, j}>K = 0, n_{i, j} = 0$. In Eq. 2.30, $g_{i+1, j+\frac{1}{2}}(t)$ can be taken as $g((i+1)h, (j+\frac{1}{2})h, t)$ while $\hat{n}_{i+1, j+\frac{1}{2}}(t) = f_{jh} dy n((i+\frac{1}{2})h, y, t)$ is the finite-volume numerical approximation for $n(x, y, t)$. The discretized version of the boundary condition (Eq. 2.12) can be expressed as

$$g_{i+\frac{1}{2}, 0} n_{i+\frac{1}{2}, 0}(t) = 2h^2 \sum_{k=i+1}^{K} \sum_{j=0}^{k-1} \beta_{k+\frac{1}{2}, j+\frac{1}{2}} ((i + \frac{1}{2})h, t) n_{k+\frac{1}{2}, j+\frac{1}{2}}(t).$$

The full explicit discretization scheme for the numerical calculation is provided in Appendix B.

Direct Monte-Carlo simulations of the birth process will also be performed and compared with our numerically computed deterministic distributions. By using the probability of division $\gamma dt$, we construct a list of cells that stores their initial size and their current size. This list is updated at every time step $\Delta t$.

The cell sizes grow according to $g(x, y, t)$. If a cell divides, the initial sizes of the daughter cells are randomly chosen according to the distribution $h(z/x)$. The daughter cells then replace the mother cell in the list. Simulations of the underlying stochastic process results in, at any given time, a collection of cells, each with a specific size and added size. This collection of cells represent a realization of the population that should be approximated by the distributions that are solutions to Eqs. 2.11 and 2.12.

3. Results and Discussion. Here, we numerically investigate the adder-sizer model and plot various cell population densities and birth event distributions under different parameter regimes. Our goal is to demonstrate the feasibility of the adder-sizer PDE model, its consistency with direct Monte-Carlo simulations of the corresponding stochastic process, and provide a general qualitative understanding of how the results depend on key parameters.

3.1. Cell and division event densities. We evaluated our adder-sizer PDE model by using the the division rate given in Eq. 2.20 and first assuming the simple and well-accepted growth function $g(x, y, t) = \lambda x$. Fig. 3 shows the numerical results for the density $\bar{n}(x, y, t) = n(x, y, t)/N(t)$ at successive times $t = 1, 4, 12$, respectively.

Stochastic simulations of the underlying process yield cells populations consistent with the deterministic densities derived from the PDE model.

In Fig. 4, we compare the cell densities $\bar{n}(x, y, t)$ the division event densities $\rho_d(x, y, T)$ for two different differential division functions $h(r)$. As before, the more asymmetric the division the broader the cell and event densities.

3.2. Cell Volume Explosion. Within a stochastic map adder model, Kessler and Burov [15] assumed a multiplicative noise and showed that cell sizes can eventually diverge with increasing generation number. When the the added size is variable about a well-defined mean value, no blow-up arises in stochastic map model [17]. However, stochastic maps of generational cell size do not capture population-level distributions in size or age.
Numerically computed densities \( \bar{n}(x, y, t) = n(x, y, t)/N(t) \) using \( g(x, y) = \lambda x \) and \( \tilde{\beta}(x, y, z, t) \) defined by Eqs. 2.20, 2.21, and 2.26. For all plots, we use \( \sigma_r = 0.1 \) in \( \gamma(a) \) (Eq. 2.21) an rescale size in units of \( \Delta \). In (a-c), we use the sharp, single-peaked differential division function \( h(r) \) shown in the inset (\( \sigma_r = 0.1, \delta = 0 \)) and plot \( \bar{n}(x, y, 1), \bar{n}(x, y, 4) \), and \( \bar{n}(x, y, 12) \), respectively. In (d-f), we plot the densities using a broad (in fact, double-peaked) differential division function \( h(r) \) with parameters \( \sigma_r = 0.2, \delta = 0.7 \). In all calculations, we assumed an initial condition corresponding to a single newly born \( (y = 0) \) cell with size \( x = 1 \). For more asymmetric cell division in (d-f), the density spreads faster. In these cases, the densities closely approach a steady-state distribution by about \( t = 12 \). Also shown in each plot are realizations of Monte-Carlo simulations of the discrete process. Individual cells are represented by blue dots which accurately sample the normalized continuous densities \( \bar{n}(x, y, t) \).

Within PDE models that describe population distributions, timer and sizer mechanisms have been shown to exhibit blow-up depending on properties of the birth rate \( \beta(a, x) \) [1, 8, 14]. These studies analyzed the compatibility of stable shape solutions \( n(a) \) and \( n(x) \) with the corresponding PDEs at long times but considered only symmetric cell division. Analysis of the conditions on full differential division rate \( \tilde{\beta}(x, y, z, t) \) that would result in blow-up in the sizer-adder PDE model is more involved. Here, we provide only a heuristic argument for sufficient conditions for blow-up.

One indication of blow-up is a diverging mean cell size

\[
\langle x(t) \rangle = \frac{\int_0^\infty dx \int_0^x dy x n(x, y, t)}{\int_0^\infty dx \int_0^x dy n(x, y, t)} = \frac{M(t)}{N(t)}
\]

For the special case of deterministic exponential growth \( g(x) = \lambda x \), we can write the time evolution of the mean size as

\[
\frac{d\langle x(t) \rangle}{dt} = \left[ \lambda - \langle \tilde{\beta}(x, y, t) \rangle \right] \langle x(t) \rangle,
\]

where

\[
\langle \tilde{\beta}(x, y, t) \rangle = N^{-1}(t) \int_0^\infty dx \int_0^x dy \beta(x, y)n(x, y, t).
\]
Fig. 4. Comparison of cell densities \( \bar{n}(x, y, t) \) and cell division event densities \( \rho_d(x, y, T) \) (Eq. 2.18). The variance \( \sigma_a = 0.1 \) is used in all calculations. In (a) and (b) we plot \( \bar{n}(x, y, t = 12) \) and \( \rho_d(x, y, T) \) using \( \sigma_r = 0.2, \delta = 0 \) while in (c) an (d) we used a broader differential division function in which \( \sigma_r = 0.3, \delta = 0.7 \). Realizations from Monte-Carlo simulations are overlayed. In (b) and (d), divisions are accumulated up to time \( T = 12 \).

If \( \beta(x, y, t) \) is bounded above by \( \lambda \), then we expect blow-up. For \( \beta \) that is not bounded, as in our example (Eq. 2.20), one cannot determine if blow-up occurs without a more detailed analysis.

Since the precise conditions on \( \beta \) leading to cell volume explosion are difficult to find, we will explore this possible phenomena using numerical experiments. We examine numerically the density \( n(x, y, t \to \infty) \) and the mean cell size \( \langle x(t) \rangle \) to indicate whether a blow-up in cell volume occurs. In Fig. 5(a) and (b) we plot

![Fig. 5](image)

Fig. 5. (a) Size distributions \( \bar{n}(x, t) \) for \( \sigma_a = 0.2 \) at times \( t = 1, 2, 4, 10 \) for \( \sigma_a = 1 \). (c) The corresponding mean cells sizes \( \langle x(t) \rangle \). The curve associated with the \( \sigma_a = 0.2 \) saturates while the one corresponding to \( \sigma_a = 1 \) exhibits blow-up.

the marginal distribution \( \bar{n}(x, t) := \int_0^\infty dy n(x, y, t) / \int_0^\infty dx \int_0^\infty dy n(x, y, t) \) for different values of the division rate variability \( \sigma_a \) at different times. The associated division rates correspond to those plotted in Fig. 2(a) and (b). In Fig. 5(c) we plot the mean cell sizes \( \langle x(t) \rangle \) (Eq. 3.1) corresponding to the distributions in (a) and (b). For sufficiently broad division probabilities \( \gamma(a) \) (large \( \sigma_a \)), the division rates \( \beta \) are small, \( \langle x(t) \rangle \) fails to saturate and diverges.
3.3. Mother-daughter growth rate correlation. Neither the PDE models described thus far nor the corresponding stochastic models include memory effects across generations other than through the differential birth rate \( \beta(x, y, z, t)dz \), which determines the daughter cell sizes \( z \) and \( x - z \) as a function of the mother cell size \( x \). However, there is evidence that the growth rate of the mother cell is remembered by the daughter cells. For growth of the form \( g(a, x, t), g(x, y, t) = \lambda x \), the growth rates \( \lambda \) between successive generations \( i, i + 1 \) have been proposed to evolve according to [16]

\[
\lambda_{i+1} = (\lambda_i - \bar{\lambda})R + \bar{\lambda} + \xi,
\]

where \( \xi \) is a random variable, \( 0 \leq R < 1 \) is the successive-generation growth rate correlation, and \( \bar{\lambda} \) is the mean long-term, or preferred growth rate. Given a growth rate \( \lambda_i \) of a mother cell, Eq. (3.4) describes the predicted growth rate \( \lambda_{i+1} \) of its daughter cells. In this model, successive generations of daughter cells have growth rates that converge to \( \bar{\lambda} \). We assume that the random variable has mean zero and is distributed according to the distribution \( P_\xi(\xi) \), which vanishes for \( \xi \leq (1 - R)\bar{\lambda} \) to ensure that the growth rates remain positive.

To incorporate the memory of growth rates between successive generations in the adder-sizer PDE model, we extend the cell density in the growth rate variable \( \lambda \). Thus, \( n(x, y, t, \lambda) \) is the density of cells with volume \( x \), added volume \( y \), and growth rate \( \lambda \). The growth function \( g(x, y, t, \lambda) \) is now explicitly a function of the growth rate \( \lambda \). We propose the extended PDE model

\[
\begin{align*}
\frac{\partial n(x, y, t, \lambda)}{\partial t} + \frac{\partial (gn)}{\partial x} + \frac{\partial (gn)}{\partial y} = -\beta(x, y, t)n(x, y, t, \lambda), \\
g(x, 0, t, \lambda)n(x, 0, t, \lambda) = 2\int_0^\infty d\lambda' \int_0^\infty dx' \int_0^\infty dy' \tilde{\beta}(\tilde{x}, y, x, t)n(\tilde{x}, y, x, t')P_\xi(\lambda - R\lambda' - (1 - R)\bar{\lambda}) \\
\tilde{n}(x, y, x, t) = \tilde{\beta}(x, y, x - \tilde{x}, t), \\
n(x, 0, t, \lambda) = n_0(x, y, t, \lambda),
\end{align*}
\]

where \( P_\xi(\xi) \) is the probability distribution of the randomness in the growth rate memory. A possible symmetric mean zero distribution that that vanishes at \(- (1 - R)\bar{\lambda} \) takes on a log-normal form:

\[
P_\xi(\xi) \propto \exp \left[-\frac{(\ln(\xi + (1 - R)\bar{\lambda}) + b)^2}{2\sigma^2} - \frac{(\ln((1 - R)\bar{\lambda} - \xi) + b)^2}{2\sigma^2}\right].
\]

If we start with one newly born daughter cell at size \( x_0 \) and growth rate \( \lambda_0 \), the initial condition in our PDE model would be \( n_0(x, y, \lambda) = \delta(x - x_0)\delta(y)\delta(\lambda - \lambda_0) \).

Numerical solutions of Eqs. (3.6) shown in Fig. 6 indicate that although \( \bar{\lambda} \) is the same for two different cases, \( R = 0 \) and \( R = 4 \), their corresponding mean growth rates \( \langle \lambda(t) \rangle \) converge to different values. For larger correlations \( R \), the more highly correlated growth rates lead to a narrower distribution in \( \bar{n}(\lambda, t) \). When \( R \) is small, the distribution is broader and cells with small growth rates arise. These cells have a longer lifespan thereby further decreasing \( \langle \lambda(t) \rangle \) to the point of being always less than \( \bar{\lambda} \).

4. Summary & Conclusions. In this paper, we proposed a PDE model that incorporates an adder mechanism in cell division. In the absence of death, we motivated models for the differential birth rate function \( \tilde{\beta}(x, y, z, t) \) that are consistent with normalized division probabilities when cell death is neglected. In Appendix A we showed existence and uniqueness of a weak solution to the PDE model within a time interval \([0, T]\) during which the solution’s support can be bounded. One can prove similar results when both time and space are unbounded as this problem is related to other first-order PDE models that have been studied in more detail.

With a weak solution justified, we explored the sizer-adder PDE via numerical experiments and Monte-Carlo simulations of the underlying stochastic process. Our results show that event-based Monte-Carlo simulations of discrete cells generate realizations of cell configurations that provide accurate samples of the cell densities computed from our PDE model.
When broader differential division rates are used (when cell division is more asymmetric), we find, under the same initial conditions, a broader cell density $n(x, y, t)$ and a broader event density $R_0(x, y, T)$. We also demonstrate numerically, the divergence of the mean cell size $\langle x(t) \rangle$ (Eq. 3.1). We showed that division probabilities that are broader in the age or added size (and smaller in magnitude) more likely lead to mean cell sizes that explode with time. While we could not analytically find the specific conditions that lead to blow-up, we found, in the simple case of exponential cell growth, a simple sufficient bound for the division rate below which cell size explosion occur.

Finally, we translated a stochastic model of cell growth rate correlation between cells of successive generations [15] into our sizer-adder PDE model. By extending the dimension of the density function to include growth rates and allowing for variability in growth rate as new cells are born, we developed a PDE model that incorporated the stochastic nature of growth rate inheritance and that describes evolution of the growth rate distribution of cells. We found that the steady-state value of the mean growth rate depends on the correlation of growth rates between mother and daughter cells. This dependence arises from a subtle interaction between the shape of the growth rate distribution and the teh distribution of variations in the growth rate from one generation to the next.

PDE-type models can be used to model cell densities that evolve according to timer, sizer, or adder mechanisms, as well as combinations of mechanisms such as the sizer-timer model and the sizer-adder model studied here. Under a deterministic cell growth assumption, one might propose a growth rate function $g(a, x, y)$ and birth rate $\beta(a, x, y)$ that depend on all three variables, age $a$, size $x$, and added size $y$. Thus, one might propose a full sizer-timer-adder model of the form $(\partial_a + \partial_x)n + \partial_x(gn) + \partial_y(gn) = -\beta(a, x, y, t)n(a, x, y, t)$ with purported boundary condition $g(0, x, 0, t)n(0, x, 0, t) = 2\int_0^\infty da' \int_x^\infty dx' \int_y^\infty dy' \beta(a', x', y', x, t)n(a', x', y', t)$. However, the three variables are not all independent. For example, if the deterministic added size $y(t)$ is monotonic in time $t$, the age after birth $a$ and the added size $y$ are functions of each other. More generally, if we can determine the evolution of all three variables $(a, x, y)$ given two of them, we cannot construct a meaningful 3+1-dimensional PDE model. One can understand the loss of independence by noticing that when a cell divides, both its daughter cells’ ages and their added volumes reset to $a = y = 0$. Given $x = x(t), a = a(t), a < t$ and $g = g(a, x, y)$, we define the cell size immediately after birth as $x(s), s = t - a$. The added volume is thus $y(\tau) = x(\tau) - x(s), s \leq \tau \leq t$. The dynamics of $x$ can be written as $\frac{dx}{d\tau} = g(x(\tau), x(s), \tau)$. If $g$ is Lipschitz continuous, then $x(s)$ is uniquely given as $x = h(x, t, a)$, which can be solved backward. And $y(\tau) = x(\tau) - h(x, t, a)$, which means $y$ is not an independent variable and we cannot put it into the above PDE as an independent variable, which implies inconsistency of a model that includes both the added size and age. However, if the growth is itself stochastic, one might propose higher order models that can include all types of cell division mechanisms.

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Appendix A. Existence and uniqueness of a weak solution for the adder-sizer model. Here, we show the existence and uniqueness of the solution to the sizer-adder model PDE. The full problem is defined as

\[
\begin{aligned}
\frac{\partial n}{\partial t} + \frac{\partial (ng)}{\partial x} + \frac{\partial (ng)}{\partial y} &= -\beta(x, y, t)n(x, y, t), \\
g(x, 0, t)n(x, 0, t) &= 2 \int_{x}^{\infty} dx' \int_{0}^{x'} dy' \tilde{\beta}(x', y, x, t)n(x', y, t), \\
\beta(x, y, t) &= \int_{0}^{x} \tilde{\beta}(x, y, z, t)dz,
\end{aligned}
\] (A.1)

where the independent variables \((x, y, t) \in \mathbb{R}^2 \cap \{y < x\} \times \mathbb{R}^+\).

First, we assume that

\[0 < g_{\text{min}} \leq g \in C^1(\mathbb{R}^+ \times \mathbb{R}^2 \cap \{y \leq x\}), n_0(x, y) \in L^1 \cap L^\infty(\mathbb{R}^+ \cap \{y < x\}),\]
\[0 \leq \tilde{\beta} \in L^\infty \cap L^1 \cap C^1(\mathbb{R}^+ \times (\mathbb{R}^+)^3 \cap \{y < x, z < x\})\]
\[\beta(x, y, t) \in L^\infty \cap L^1(\mathbb{R}^+ \times (\mathbb{R}^+)^2)\]

and nondimensionalize the size and added size by \(\Delta\), the added size parameter defined in Eq. 2.22. We also impose an additional assumption on \(g\):

\[|g(x, y, t)| < K(t + x + 1), \quad K < \infty.\] (A.3)

We also assume the initial distribution \(n_0(x, y)\) has compact support bounded in \((0, \Omega) \times [0, \Omega), \Omega < \infty.\) From this assumption and A.3, the closure of \(n(x, y, T)\)’s support is compact for any finite time \(T\) since \(n \neq 0\) only when \(y < x\) and

\[\frac{dx}{dt} \leq K(x + t + 1) \leq K(x + T + 1).\]

From Grönwall’s Inequality \(x(s) \leq Ce^{Ms} - (1 + T), \) where \(C < 1 + T + \Omega\) is given by the initial condition. At any finite time \(T\), the support of \(n(x, y, T)\) is bounded and we assume it is contained in \([0, \Omega(T)) \times [0, \Omega(T))\).

Furthermore, by setting \(g, \beta, \tilde{\beta} = 0\) at the given time \(T\) when \((x, y)\) is out of the support of \(n\), we can assume the closure of \(g, \beta, \tilde{\beta}\)’s support to be compact. One can generalize the definition of the weak solution \(n\) to \([0, \infty) \times (\mathbb{R}^+)^2\) as in [18].

Definition A.1 Given time \(T < \infty\) and assuming A.2, for a function \(n \in L^1(((0, \Omega(T))^2 \cap \{y < x\}) \times [0, T]), \Omega(T) < \infty\) with \(n(x, y, t) \neq 0\) in \([0, \Omega(T)) \times [0, \Omega(T)), y < x, t \in [0, T]\), we say that \(n\) satisfies the adder-sizer PDE in the weak sense in time \([0, T]\), if

\[\int_{0}^{T} dt \int_{0}^{\infty} dx \int_{0}^{x} dy n(x, y, t) \left[ \frac{\partial \Psi}{\partial t} + g(x, y, t) \frac{\partial \Psi}{\partial x} + g(x, y, t) \frac{\partial \Psi}{\partial y} - \beta(x, y, t) \Psi(x, y, t) \right] = \int_{0}^{\infty} dx \int_{0}^{x} dy n_0(x, y) \Psi_0(x, y) + \int_{0}^{T} dt \int_{0}^{\infty} dx \Psi(x, 0, t)n(x, 0, t)g(x, 0, t),\]

(A.4)

holds for all test function \(\Psi \in C^1(((0, \Omega(T))^2 \cap \{y < x\}) \times [0, T])\) satisfying \(\Psi(x, y, T) \equiv 0, \Psi(\Omega(T), y, t) = 0\) and \(\Psi(x, x, t) = 0\), where we set \(g, \beta, \tilde{\beta} = 0\) for \(x \geq \Omega(T), x \leq y\) or \(x \leq z\). Upon using the boundary condition in A.1, the right-hand-side becomes...
\[ \int_0^\infty dx \int_0^x dy \, n_0(x,y) \Psi_0(x,y) + 2 \int_0^T dt \int_0^\infty dx \int_0^x dy \int_0^x dz \, \Psi(z,0,t) \beta(x,y,z,t)n(x,y,t). \]

Note that if \( n \in C^1(\mathbb{R}^+ \times ([0,\infty)^2 \cap \{ y < x \}) \) is a classical solution to the PDE (Eq. A.1), then it must also satisfy Eq. A.4 in any time interval \([0,T]\). We refer to [18] for a proof of the existence and uniqueness of a weak solution of a related, simpler renewal equation. However, our adder-sizer PDE is more complex, requiring additional steps to prove existence and uniqueness of a weak solution.

**A.1. Uniqueness.** First, we prove uniqueness of the solution to A.4. Assume there are two weak solutions \( n^{(0)} \) and \( n^{(1)} \) for the adder-sizer PDE satisfying A.4 with the same initial condition \( n_0^{(0)}(x,y) = n_0^{(1)}(x,y) \). Taking the difference between using these purported solutions, we obtain

\[
- \int_0^T dt \int_0^\infty dx \int_0^x dy \, \Delta n(x,y,t) \left[ \frac{\partial \Psi}{\partial t} + g(x,y,t) \frac{\partial \Psi}{\partial x} + g(x,y,t) \frac{\partial \Psi}{\partial y} - \beta(x,y,t) \Psi(x,y,t) \right] = 2 \int_0^T dt \int_0^\infty dx \int_0^x dy \int_0^x dz \, \tilde{\beta}(x,y,z,t) \Delta n(x,y,t),
\]

where \( \Delta n = n^{(1)} - n^{(0)} \).

**A.1.1. Adjoint Problem.** First, we consider the adjoint problem for \( \Psi \) in the given time interval \([0,T]\) and with a with a source term \( S(x,y,t) \):

\[
\frac{\partial \Psi}{\partial t} + g(x,y,t) \frac{\partial \Psi}{\partial x} + g(x,y,t) \frac{\partial \Psi}{\partial y} - \beta(x,y,t) \Psi(x,y,t) = -2 \int_0^x \Psi(z,0,t) \tilde{\beta}(x,y,z,t)dz - S(x,y,t), \quad 0 \leq y < x
\]

\[
\Psi(x,y,T) = 0, \quad \Psi(\Omega(T),y,t) = 0, \quad \Psi(x,x,t) = 0.
\]

**Theorem A.1** Assume A.2, and \( S \in C^1([0,T] \times [0,\Omega(T)]^2) \), \( S(\Omega(T),y,t) = 0 \), and \( S = 0 \) when \( x \leq y \). Then, there exists a unique \( C^1 \) solution to the adjoint problem.

**Proof:** We can transform the above equation into an ODE using the characteristic line, and then use contraction mapping, which is a standard practice in functional analysis to prove for the existence and uniqueness of the solution to a ODE problem. On the left-hand-side of Eq. A.6, we apply the characteristic line method. Setting \( X(c,t) = (x(c,t),y(c,t)) \) on the characteristic lines leads to

\[
\left\{ \begin{array}{l}
\left. \frac{\partial X(c,s)}{\partial s} \right|_t = (g(x,y,s),g(x,y,s)), \quad t \leq s \leq T, \\
X(c,t) = (x_t,y_t), \quad 0 \leq y_t < x_t, x_t - y_t = c.
\end{array} \right.
\]

Since we have \( x(s) - y(s) = x_t - y_t \), the above equation can be simplified as

\[
\frac{\partial X(c,s)}{\partial s} = \tilde{g}(X(c,s),s), x(c,t) = x_t, y(c,t) = x_t - c
\]

where \( \tilde{g}(X(c,s)) = (g(x(c,s),x(c,s) - c,s),g(x(c,s),x(c,s) - c,s)) \). Once \( c \) is fixed and \( x_t \) is given, the above equation becomes an ordinary differential equation. Given \( x_t \), we define

\[
\begin{align*}
\hat{\Psi}(c,s) & := \Psi(X(c,s),s)e^{-\int_c^s \beta(X(c,v),v)dv}, \\
U(c,z,s) & := 2\tilde{\beta}(X(c,s),z,s)e^{-\int_c^s \beta(X(c,v),v)dv}, \quad \hat{S}(c,s) := S(X(c,s),s)e^{-\int_c^s \beta(X(c,v),v)dv}.
\end{align*}
\]

Thus, along the characteristic line we can write A.6 as

\[
(A.7) \quad \frac{\partial}{\partial s} \hat{\Psi}(c,s) = - \int_0^{x(c,s)} \Psi(z,0,s)U(c,z,s)dz - \hat{S}(c,s).
\]
Since \( \Psi(c, T) = 0 \) and \( \Psi(c, t) = \Psi(x, t, c, t) \),

\[
\Psi(x, t, c, t) = \int_t^T \dot{S}(c, s) ds + \int_t^T ds \int_0^{x(c, s)} dz \Psi(z, 0, s) U(c, z, s), \quad 0 < c \leq x_t.
\]

We can see that if \( x \leq y \) or \( x_t \geq \Omega(T) \), \( \Psi(t, x, t, x) = \Psi(t, x, x) = 0 \) since \( U, \dot{S} = 0 \) for \( c \leq 0 \) or \( x_t > \Omega(T) \). Using \( c = x_t \), Eq. A.8 becomes

\[
\Psi(x, 0, t) = \int_t^T \dot{S}(x_t, s) ds + \int_t^T ds \int_0^{x(x, s)} dz \Psi(z, 0, s) U(x_t, z, s).
\]

From condition A.3 we obtain \( x(s) \leq (x_t + 1 + T)e^{K(s-t)} - (1 + T) \). From condition (A.3), we define \( B = 2\|\dot{\beta}\|_\infty < \infty \). Next, we choose \( s = \max\{T - \frac{1}{K} \ln(1 + \frac{1}{2B(1+T)}), T - \frac{1}{K} \ln 2, T - 1\} \) such that

\[
e^{K(T-t)} \leq 1 + \frac{1}{2B(1+T)}, \quad s \leq t \leq T, \quad \text{and choose} \quad x_s \text{ small enough such that} \quad x_s < \min\{1, \frac{1}{8B(T-s)}\}.
\]

We denote a mapping \( T \) defined on the functional space as

\[
T(\Psi)(x, 0, t) = \int_t^T \dot{S}(x_t, s) ds + \int_t^T ds \int_0^{x(x, s)} dz \Psi(z, 0, s) U(x_t, z, s), \quad t \in [s, T], x_t \in [0, x_s].
\]

It is easy to verify that \( T \) is a contraction mapping for \( \Psi(x, 0, t) \) and thus there exists a unique solution \( \Psi_0 \) satisfying A.6 in \( D_0 \) defined as \( D_0 = \{(x, t)|s \leq t \leq T, 0 \leq x \leq x(x_t, t)\} \), then we let \( x^1_s > x_s \) and define \( D_1 = \{(x, t)|s \leq t \leq T, 0 \leq x \leq x(x^1_s, t)\} \) such that the difference of the area of the region \( D_1 \) and \( D_0 \) is less than \( B^{-1} \). So we can define a second mapping \( T_1 \) as

\[
\begin{cases}
T_1(\Psi)(x, 0, t) = \int_t^T ds \int_0^{x(x, s)} dz \Psi(z, 0, s) U(x_t, z, s) + I(x, t), & t \in [s, T], x_t \in [x(t, x_s), x^1_s], \\
I(x, t) = \int_t^T ds \dot{S}(x_t, s) + \int_t^T ds \int_0^{x(x, s)} dz \Psi_0(z, 0, s) U(x_t, z, s).
\end{cases}
\]

\( T_1 \) is also a contraction mapping and we can obtain a \( \Psi_1 \) on \( D_1 \) such that \( T(\Psi_1) = \Psi_1 \). Denote

\[
\begin{cases}
\Psi(x, 0, t) = \Psi_0(x, 0, t), & (x, t) \in D_0, \\
\Psi(x, 0, t) = \Psi_1(x, 0, t), & (x, t) \in D_1,
\end{cases}
\]

and it is easy to verify that \( \Psi \) is \( C^1 \) continuous on \( D_0 \cup D_1 \) by first proving it is continuous and then take the partial derivatives, and \( \Psi \) satisfy A.6 in the region \( D_0 \cup D_1 \).

Following the same procedure, we can extend \( \Psi \) to satisfy A.6 in the region \( t \in [s, T] \). Then, for \( [0, s] \), we choose a \( \bar{s} \) close enough to \( s \) and use the same strategy by defining \( T_2 \) as

\[
\begin{cases}
T_2(\Psi)(x, 0, t) = \int_t^s dr \dot{S}(x_t, r) + \int_t^s dr \int_0^{x(x, r)} dz \Psi(z, 0, r) U(x_t, z, r) + \tilde{I}(x, t), & t \in [\bar{s}, s], \\
\tilde{I}(x, t) = \int_t^T dr \dot{S}(x_t, r) + \int_t^T dr \int_0^{x(x, r)} dz \Psi(z, 0, r) U(x_t, z, r).
\end{cases}
\]

We finally obtain a unique function \( \Psi \) satisfying A.6 in \([0, T] \times [0, \infty)\).

From A.8, the value of \( \Psi \) is determined by \( \dot{S}, \Psi(x, 0, t), U \) and we conclude that there exists a unique \( C^1 \) solution for A.6.
A.1.2. Uniqueness of weak solution for the adder-sizer model. From Section A.1.1 we obtain the existence and uniqueness of \( \Psi \) of the adjoint problem. Given any time \( T \) and \( S(x, y, t) \in C^1(R^+ \times (R^+)^2) \) satisfying the condition in Theorem A.1, since we can set \( g, \beta, \tilde{\beta} \)’s support to be compact in \([0, T] \), we can find a unique \( C^1 \) continuous \( \Psi \) satisfying A.6. By substituting A.6 into A.5, we obtain

\[
(A.12) \quad \int_0^T dt \int_0^{\Omega(T)} dx \int_0^y dy \Delta n(x, y, t) S(x, y, t) = 0
\]

for any \( S(x, y, t) \in C^1(R^+ \times (R^+)^2) \) satisfying \( S(x, y, t) = 0, x \leq y, S(x \geq \Omega(T), y, t) = 0 \), which implies \( n = 0 \) a.e. in \( y < x \leq \Omega(T) \). So at any given time \( T \) the weak solution, if exists, is unique.

One can also set the condition for \( \beta, g \) weaker even when we define the weak solution in unbounded region \([0, \infty) \times (R^+)^2 \cap \{ y < x \} \). In [18] such work is done for the renewal equation. We do not discuss this generalization in detail here.

A.2. Existence of the weak solution. We construct a series of functions \( \{n_i\} \) with a limit \( n \) for this series satisfying A.6 for all test functions \( \Psi \). We use semi-discrete approximation to discretize the PDE and obtain piecewise solutions. As the mesh size becomes smaller, we expect the piecewise solution to converge to a function \( n \) satisfying A.4.

A.2.1. Semi-discrete approximation for the PDE. We choose a uniform grid with mesh size \( h > 0 \) fixed in both \( x \) and \( y \) axis and let time \( t \) be continuous. We denote

\[
(x_i, y_j) = (ih, jh), (x_{i+\frac{1}{2}}, y_{j+\frac{1}{2}}) = ((i + \frac{1}{2})h, (j + \frac{1}{2})h), \quad j < i \in \mathbb{N},
\]

\[
\beta_{i+\frac{1}{2}, j+\frac{1}{2}}(t) = \frac{1}{h^2} \int_{ih}^{(i+1)h} dy \int_{jh}^{(j+1)h} dx \beta(x, y, t), \quad j < i \in \mathbb{N},
\]

\[
\tilde{\beta}_{i+\frac{1}{2}, j+\frac{1}{2}}(s + \frac{1}{2}h, t) = \frac{1}{h^3} \int_{ih}^{(i+1)h} dz \int_{jh}^{(j+1)h} dy \int_{sh}^{(s+1)h} dx \tilde{\beta}(x, y, z, t), \quad s \leq i,
\]

\[
g_{i,j}(t) = g(ih, jh, t), \quad j < i \in \mathbb{N}.
\]

Here, \( \beta_{i+\frac{1}{2}, j+\frac{1}{2}}(t) = h \sum_{s=0}^{i} \tilde{\beta}_{i+\frac{1}{2}, j+\frac{1}{2}}((s + \frac{1}{2})h, t) \). Given a fixed time \( T \), we wish to find a solution of pointwise function \( n^k(t) \), which takes values on the grid points \( (x_{i+\frac{1}{2}}, y_{j+\frac{1}{2}}) \) as we denote above. Then \( n^k \) can be seen as a vector function. According to our assumption there exists \( \Omega \) such that the initial value \( n^0 \) is nonzero within the region \( \{ (x, y) | y < x, x < \Omega \} \), and from our previous illustration we have there exists \( \Omega(T) < \infty \) such that \( n \) is nonzero within the region \( \{ (x, y) | y < x, x < \Omega(T) \} \). So we can take \( h_k = \frac{\Omega(T)}{k} \) so as \( k \) tends to infinity the width of the mesh grid will tend to zero.

By discretizing A.1, we expect the vector function \( n^k(t) \) to satisfy the below equations for \( t \in [0, T] \) and \( 0 < j < i < L \) (\( L \) is the number of discretization points along one direction):
\[
\frac{d}{dt} \sum_{i=1}^{L-1} \sum_{j=0}^{i} |n_{i+\frac{1}{2},j+\frac{1}{2}}(t)| \leq e^{MB} \sum_{i=1}^{L-1} \sum_{j=0}^{i} |n_{i+\frac{1}{2},j+\frac{1}{2}}(0)|,
\]

where \( B = 2\|\beta\|_{\infty} \), \( M = 2B - b \), \( B = \|\beta\|_{\infty} \), and \( b = \min_{i,j} \beta_{i+\frac{1}{2},j+\frac{1}{2}}(t) \).

And the \( L^\infty \) bound is given as

\[
\|n^h(t)\|_{\infty} \leq e^{(2\tilde{\gamma})t} R
\]

where \( R = \max\{\frac{1}{g^{\min}} \tilde{B} e^{MT} \|a(0)\|_1, \|n^h(0)\|_\infty\} \), \( \tilde{\gamma} \) is the \( L^\infty \) bound of \( g \)'s spatial partial derivatives.

**Proof** For the summation of \( n \) over all grid points, we multiply the first equation in (A.14) by \( \text{sign}(n_{i+\frac{1}{2},j+\frac{1}{2}}) \)

for each \( i,j \leq i \) we have,

\[
\sum_{i=1}^{L-1} \sum_{j=0}^{i-1} |n_{i+\frac{1}{2},j+\frac{1}{2}}(t)| + h \sum_{i=1}^{L-1} g_{i+\frac{1}{2},i-\frac{1}{2}}(t) |n_{i+\frac{1}{2},i-\frac{1}{2}}(t)| + h \sum_{j=0}^{L-1} g_{L,j+\frac{1}{2}}(t) |n_{L-1+\frac{1}{2},j+\frac{1}{2}}(t)| +
\]

And by multiplying the second equation in (A.14) by \( \text{sign}(n_{i+\frac{1}{2},j+\frac{1}{2}}) \) for each \( i,j \leq i \) pair and summing over index \( \sum_{i=1}^{L-1} \sum_{j=0}^{i-1} \),

\[
\sum_{i=1}^{L-1} \sum_{j=0}^{i-1} |n_{i+\frac{1}{2},j+\frac{1}{2}}(t)| + h \sum_{i=1}^{L-1} g_{i+\frac{1}{2},i-\frac{1}{2}}(t) |n_{i+\frac{1}{2},i-\frac{1}{2}}(t)| + h \sum_{j=0}^{L-1} g_{L,j+\frac{1}{2}}(t) |n_{L-1+\frac{1}{2},j+\frac{1}{2}}(t)| +
\]

\[
\sum_{i=1}^{L-1} \sum_{j=0}^{i-1} \beta_{i+\frac{1}{2},j+\frac{1}{2}} |n_{i+\frac{1}{2},j+\frac{1}{2}}(t)| \leq h \sum_{i=0}^{L-1} g_{i+\frac{1}{2},0}(t) |n_{i+\frac{1}{2},-\frac{1}{2}}(t)|
\]

We can simplify the above expression to
\[ h^2 \frac{d}{dt} \sum_{i=1}^{L-1} \sum_{j=0}^{i-1} |n_{i+\frac{1}{2}, j+\frac{1}{2}}(t)| + h^2 \sum_{i=1}^{L-1} \sum_{j=0}^{i-1} |n_{i+\frac{1}{2}, j+\frac{1}{2}}(t)| \]
\[ \leq 2h^3 \sum_{i=0}^{L-1} \left| \sum_{i+j=0}^{L-1} \beta_{i+\frac{1}{2}, j+\frac{1}{2}}(t, (i+1/2)h)n_{i+\frac{1}{2}, j+\frac{1}{2}}(t) \right| \]
\[ \leq 2h^2 \sum_{i=1}^{L-1} \sum_{j=0}^{i-1} |n_{i+\frac{1}{2}, j+\frac{1}{2}}(t)||n_{i+\frac{1}{2}, j+\frac{1}{2}}(t)|. \]

We then have
\[ \frac{d}{dt} \sum_{i=1}^{L-1} \sum_{j=0}^{i-1} |n_{i+\frac{1}{2}, j+\frac{1}{2}}(t)| \leq (2B - b) \sum_{i=1}^{L-1} \sum_{j=0}^{i-1} |n_{i+\frac{1}{2}, j+\frac{1}{2}}(t)|, \]
which yields
\[ (A.17) \]
\[ \sum_{i=1}^{L-1} \sum_{j=0}^{i-1} |n_{i+\frac{1}{2}, j+\frac{1}{2}}(t)| \leq e^{Mt} \sum_{i=1}^{L-1} \sum_{j=0}^{i-1} |n_{i+\frac{1}{2}, j+\frac{1}{2}}(t)(0)|. \]

\[ A.17 \] states that the \( l^1 \) norm of all the values on the grid points are uniformly bounded not relevant to \( h \).

Next, estimate the \( L^\infty \) bound of \( n^h \). First, we consider \( j = 0 \) and assume \( S(t) = \max_{1 \leq i \leq L-1} |n_{i+\frac{1}{2}, \frac{1}{2}}(t)|e^{-\tilde{g}^t} \)
for \( t \in [0, T] \). For the maximum value of \( S \) at some index \( i \), we find
\[ \frac{d}{dt} \frac{d}{dt} \sum_{i=1}^{L-1} \sum_{j=0}^{i-1} |n_{i+\frac{1}{2}, j+\frac{1}{2}}(t)| + h\left(g_{i+\frac{1}{2}, \frac{1}{2}}(t)|n_{i+\frac{1}{2}, \frac{1}{2}}(t)| - g_{i-\frac{1}{2}, \frac{1}{2}}(t)|n_{i-\frac{1}{2}, \frac{1}{2}}(t)|\right) \leq 0, \]
and
\[ \frac{d}{dt} \frac{d}{dt} \sum_{i=1}^{L-1} \sum_{j=0}^{i-1} |n_{i+\frac{1}{2}, j+\frac{1}{2}}(t)| + h\left(g_{i+1, \frac{1}{2}}(t)|n_{i+1, \frac{1}{2}}(t)| - g_{i, \frac{1}{2}}(t)|n_{i, \frac{1}{2}}(t)|\right) \leq 0, \quad i = 1. \]

By the assumption that \( g(x, y, t) \geq g_{\min}(t) \geq g_{\min} > 0 \) and \( g < K(T + 1 + \Omega(T)) \), we have
\[ (A.18) \]
\[ \frac{d}{dt} \frac{d}{dt} \sum_{i=1}^{L-1} \sum_{j=0}^{i-1} |n_{i+\frac{1}{2}, j+\frac{1}{2}}(t)|e^{-\tilde{g}^t} \leq h^{-1}g_{i+\frac{1}{2}, \frac{1}{2}}(t)|n_{i+\frac{1}{2}, \frac{1}{2}}(t)|e^{-\tilde{g}^t}, \]
Finally defining \( G(t) = h^{-1} \int_0^t g_{\min}(s)ds \) yields
\[ \frac{d}{dt} \frac{d}{dt} \sum_{i=1}^{L-1} \sum_{j=0}^{i-1} |n_{i+\frac{1}{2}, j+\frac{1}{2}}(t)|e^{-\tilde{g}^t}e^{G(t)} \leq \frac{g_{\min}(t)}{h} \left( \frac{1}{g_{\min}} \right) \max_{1 \leq i \leq L-1} |g_{i+\frac{1}{2}, \frac{1}{2}}(t)|n_{i+\frac{1}{2}, \frac{1}{2}}(t)|e^{G(t)}. \]

From the \( L^1 \) bound, we can deduce
\[ \max_{1 \leq i \leq L-1} \left| g_{i+\frac{1}{2}, \frac{1}{2}}(t)\right|n_{i+\frac{1}{2}, \frac{1}{2}}(t) \leq h^2 \tilde{B}e^{MT} ||n^h(0)||_1 \leq \tilde{B}e^{MT} ||n(0)||_1, \quad t > 0 \]
and conclude that for the function $S(t)e^{G(t)}$

$$S(t)e^{G(t)} \leq S(0) + \frac{1}{g_{\min}} \mathcal{E} e^{\mathcal{M}T \| n(0) \|_1} (e^{G(t)} - 1),$$

and $S(t) \leq \max_{1 \leq i \leq L-1} \left\{ n_{i+\frac{1}{2}, j+\frac{1}{2}}(0), \frac{1}{g_{\min}} \mathcal{E} e^{\mathcal{M}T \| n(0) \|_1} \right\}$, which then gives the $L^\infty$ bound for the pointwise solution $n^h$ when $j = 0$.

Now, we set $R = \max \left\{ \frac{1}{g_{\min}} \mathcal{E} e^{\mathcal{M}T \| n(0) \|_1}, \| n^h(0) \|_{\infty} \right\}$ and estimate $|n_{i+\frac{1}{2}, j+\frac{1}{2}}(t)|$ for $j \geq 0$ by setting $P(t) = \max_{0 \leq i \leq L-1, 0 \leq j \leq L-1} |n_{i+\frac{1}{2}, j+\frac{1}{2}}(t)| e^{-2\bar{y}'t}$ and $S(t) = S(t)e^{-\bar{y}'t} \leq S(t)$. At a fixed time $t$, $P(t)$ is taken on a certain $(i + \frac{1}{2}, j + \frac{1}{2})$, so either $P(t) = S(t)$ or $P(t)$ is taken somewhere $j > 0$. If $i - 1 > j > 0$, we have

$$\frac{d}{dt}(n_{i+\frac{1}{2}, j+\frac{1}{2}}(t)) e^{-2\bar{y}'t} \leq \frac{1}{h} \left( g_{i+\frac{1}{2}, j}(t) - g_{i+1, j+\frac{1}{2}}(t) \right) |n_{i+\frac{1}{2}, j+\frac{1}{2}}(t)| - 2\bar{y}' |n_{i+\frac{1}{2}, j+\frac{1}{2}}(t)| e^{-2\bar{y}'t} \leq 0;$$

if $j = i - 1 > 0$, we have

$$\frac{d}{dt}(n_{i+\frac{1}{2}, j+\frac{1}{2}}(t)) e^{-2\bar{y}'t} \leq \left[ h^{-1} \left( g_{i+\frac{1}{2}, j}(t) - g_{i+1, j+\frac{1}{2}}(t) \right) |n_{i+\frac{1}{2}, j+\frac{1}{2}}(t)| - 2\bar{y}' |n_{i+\frac{1}{2}, j+\frac{1}{2}}(t)| \right] e^{-2\bar{y}'t} \leq 0.$$

For any $t \in (0, T]$ we can set $\bar{t} < t$ to be the lower bound that $P(v) > \tilde{S}(v), v \in (\bar{t}, t]$, if $\bar{t} = 0$ then we have $P(t) \leq P(0) = \| n^h(0) \|_{\infty}$ from above equation, or if $\bar{t} < t$ then we have $P(t) \leq P(\bar{t}) \leq S(\bar{t}) \leq \max_{0 \leq t \leq T} S(t)$ (since $P(t)$ is nonincreasing in $[\bar{t}, t]$ and is evaluated at some $j > 0$). If $\bar{t} = t$ then $P(t) = S(t) \leq \max_{0 \leq t \leq T} S(t) \leq \max_{0 \leq t \leq T} \| n^h(0) \|_{\infty}$, so $P(t) \leq \max_{0 \leq t \leq T} S(t), \| n^h(0) \|_{\infty} = R$, and

$$\| n^h(t) \|_{\infty} \leq e^{2\bar{y}'t} R.$$

We arrive at the second conclusion in Theorem A.2, which states that the $L^\infty$ bound again not related to $h$.

A.2.2. Existence of the weak solution. Given the time $T < \infty$, if we take the limit $h \to 0$, we will obtain a vector functions family $\{ n^{h(k)} \}$, just take $k$ as integer numbers and let $h(k) = \Omega(T)/k$. Now we can obtain piecewise functions based on the vector functions $n^{h(k)}$. By setting $n^{h(k)}(i + \frac{1}{2}, j + \frac{1}{2})(t) = 0$, we define $n^h(t, x, y)$ and related $\beta^h, \tilde{\beta}^h$ as

$$n^h(x, y, t) = \sum_{i = 0}^{L-1} \sum_{j = 0}^{L-1} n^h_{i+\frac{1}{2}, j+\frac{1}{2}}(t) \chi_{\{ ih \leq x < (i+1)h, jh \leq y < (j+1)h \}},$$

$$\beta^h(x, y, t) = \sum_{i = 0}^{L-1} \sum_{j = 0}^{L-1} \beta^h_{i+\frac{1}{2}, j+\frac{1}{2}}(t) \chi_{\{ ih \leq x < (i+1)h, jh \leq y < (j+1)h \}},$$

$$\tilde{\beta}^h(x, y, z, t) = \sum_{i = 0}^{L-1} \sum_{j = 0}^{L-1} \sum_{l = 0}^{L-1} \tilde{\beta}^h_{i+\frac{1}{2}, j+\frac{1}{2}}((l + \frac{1}{2})h, t) \chi_{\{ ih \leq x < (i+1)h, jh \leq y < (j+1)h, lh \leq z < (l+1)h \}},$$

$$n^h(x, 0, t) = n^h_{i+\frac{1}{2}, j+\frac{1}{2}}(t), \quad ih \leq x < (i+1)h.$$
For a given \( \beta \) which gives the result \( n(x, y, 0) \) a.e.,

\[ (A.22) \lim_{k \to \infty} \beta^h(k)(x, y, t) \to \beta(x, y, t) \text{ a.e.} \quad 0 \leq \beta^{h(k)} \leq \| \beta \|_{\infty} < \infty, \]

\[ (A.23) \lim_{k \to \infty} \hat{\beta}^h(k)(x, y, z, t) \to \beta(x, y, z, t) \text{ a.e.} \quad 0 \leq \hat{\beta}^{h(k)} \leq \| \hat{\beta} \|_{\infty} < \infty, \]

\[ (A.24) \lim_{k \to \infty} n^h(k)(x, y, 0) \to n(x, y, 0) \text{ a.e.}. \]

Then, we can easily extend Theorem A.2 for our piecewise constant functions \( n^h(k) \).

**Corollary A.3** Under the conditions of Theorem A.2, we have for any \( t \in [0, T] \) and any \( h, n^h \) satisfies

\[ (A.25) \int_t^{\Omega(T)} dy \int_0^{\Omega(T)} dx |n^h(x, y, t)| \leq e^{Mt} \int_0^{\Omega(0)} dy \int_0^{\Omega(0)} dx |n^h(x, y, 0)|, \]

and

\[ (A.26) ||n^h(t)||_{\infty} \leq \max\{||n(0)||_{\infty}, Be^{MT}||n(0)||_{1}\}e^{2g't}, \]

where \( B, M, g' \) are defined in Theorem A.2. The proof is the direct consequence of Theorem A.2.

The piecewise constant functions \( \{n^h(k)\} \) are uniformly bounded and \( n^h(k) \in L^1 \cap L^\infty([0, T] \times [0, \Omega(T)]^2) \), so \( n^h \) are all \( L^2 \) functions. We have the fact that their exists a function \( n \in L^2([0, T] \times [0, \Omega(T)]^2) \) and \( b(t, x) \) such that there exists a series \( k_i \to \infty \) and

\[ (A.27) \lim_{k \to \infty} n^h(k) \to n, w^* - L^2([0, T] \times [0, \Omega(T)]^2 \cap \{y < x\}) \]

Since \( L^2[0, T] \times [0, \Omega(T)]^2 \) implies \( L^1 \) bound, we can deduce that \( n, b \) are \( L^1 \) functions as desired. For the piecewise constant in space function \( n^h(k), k \in \mathbb{N}^+ \), there exists a function \( n \in L^2([0, T] \times [0, \Omega(T)]^2) \) that \( n^h(k_i) \to n, w^* - L^2([0, T] \times [0, \Omega(T)]^2) \).

To prove this, we need only to verify that there exists a sequence \( n^h(k_i) \) such that for all test functions \( f \in L^2, \int_0^T dt \int_0^{\Omega(T)} dx \int_0^{\Omega(T)} dy n^h(k_i) f \rightarrow \int_0^T dt \int_0^{\Omega(T)} dx \int_0^{\Omega(T)} dy nf \). Since \( L^2 \) space is separable, we have a countable set of basis function \( \{b_i(x, y, t)\} \) for the space \( L^2([0, T] \times [0, \Omega(T)]^2 \cap \{y < x\}) \). Thus, every \( n^h(k) \) can be decomposed as \( n^h(k) = \sum_{i=1}^{\infty} \alpha_i b_i \). The \( n^h(k) \)'s are uniformly \( L^\infty \) bounded, so \( \sum \alpha_i^2 \) are all uniformly bounded. If the bound is \( S \), we can select a sequence \( \{n^h(k_i)\} \) from \( \{n^h(k)\} \) satisfying \( \lim_{i \to \infty} \alpha_i = \alpha < \infty \) so that \( \sum_{i=1}^{\infty} \alpha_i^2 \leq S < \infty \). If we decompose \( n = \sum_{i=1}^{\infty} \alpha_i b_i \), then by decomposing any test function \( \Psi \in L^2([0, T] \times [0, \Omega(T)]^2 \cap \{y < x\}) \) by \( \Psi = \sum_{i=1}^{\infty} \gamma_i b_i \), we have

\[ (A.28) \lim_{i \to \infty} \left| \int_0^T dt \int_0^{\Omega(T)} dx \int_0^{\Omega(T)} dy \left( n^h(k_i) - n \right) \Psi \right| = \left| \sum_{s=1}^{\infty} (\alpha_s^k - \alpha_s) \gamma_s \right| = 0, \]

which gives the result \( n^h(k) \to n, w^* - L^2([0, T] \times [0, \Omega(T)]^2 \cap \{y < x\}) \) as desired.

We can now show that \( n \) is a weak solution by using the first equation in A.14. For any test function \( \Psi \in C^1([0, T] \times [0, \Omega(T)]^2) \), we have \( \Psi(T, x, y) = 0, \Psi(t, x, y) = 0, y \geq x \). We define

\[ \Psi_{i + \frac{1}{2}, j + \frac{1}{2}}(t) = \frac{1}{h^2} \int_{x_i}^{x_{i+1}} dx \int_{y_j}^{y_{j+1}} dy \Psi(t, x, y), \quad j \leq i. \]

For a given \( L \in \mathbb{N}^+ \) and \( h = \frac{\Omega(T)}{L} \), we have
\[\int_0^T dt \sum_{i=1}^{L-1} \sum_{j=0}^{L-2} \left( h^2 \frac{dn_{i+\frac{1}{2},j+\frac{1}{2}}(t)}{dt} \Psi_{i+\frac{1}{2},j+\frac{1}{2}}(t) + h \left[ g_{i+1,j} \Psi_{i+\frac{1}{2},j+\frac{1}{2}}(t) - g_{i,j+1} \Psi_{i+\frac{1}{2},j+\frac{1}{2}}(t) \right] + h^2 \beta_{i+\frac{1}{2},j+\frac{1}{2}}(t) \Psi_{i+\frac{1}{2},j+\frac{1}{2}}(t) \right)\]

Integrating the above equation by parts with respect to time, we find

\[\int_0^T dt \sum_{i=1}^{L-1} \sum_{j=0}^{L-2} \left( h^2 \frac{dn_{i+\frac{1}{2},j+\frac{1}{2}}(t)}{dt} \Psi_{i+\frac{1}{2},j+\frac{1}{2}}(t) + h \left[ g_{i+1,j} \Psi_{i+\frac{1}{2},j+\frac{1}{2}}(t) - g_{i,j+1} \Psi_{i+\frac{1}{2},j+\frac{1}{2}}(t) \right] + h^2 \beta_{i+\frac{1}{2},j+\frac{1}{2}}(t) \Psi_{i+\frac{1}{2},j+\frac{1}{2}}(t) \right)\]

Since we have that \(\Psi_{i+\frac{1}{2},j+\frac{1}{2}}(t) - \Psi_{i+\frac{1}{2},j+\frac{1}{2}}(t) = f_{ih}^{(i+1)h} dx f_{ih}^{(j+1)h} dy \int_0^{x+h} ds \frac{\partial \Psi}{\partial x}(s, y, t), \) \(|n^h|\) is uniformly bounded while \(g\) is \(C^1\) continuous. From above we can pick a series in \(\{n^{h(k)}\}\), denoted by \(\{n^{h(k)}\}\) satisfying (A.27).

We take \(n^h = n^{h(k)}\) in the above formula, since \(\Psi \in C^1[0,T] \times [0,\Omega(T)]^2\), then given any \(\Psi\) we have a positive upper bound \(R(\Psi) < \infty\) for both \(\Psi\) and its any first order partial derivatives. Thus,

\[\left| \int_0^T \sum_{i=1}^{L-1} \sum_{j=0}^{L-2} \left( h^2 n_{i+\frac{1}{2},j+\frac{1}{2}}(t) \frac{d\Psi_{i+\frac{1}{2},j+\frac{1}{2}}(t)}{dt} \right) + \int_0^T dt \int_0^{\Omega(T)} dx \int_0^x dy \frac{n^{h(k)}(x,y,t) \partial \Psi(x,y,t)}{\partial t} \right| \leq \int_0^T dt \sum_{i=1}^{L-1} \int_{ih}^{(i+1)h} \int_{ih}^{(j+1)h} dx \int_0^x dy \frac{n^{h(k)}(x,y,t) \partial \Psi(x,y,t)}{\partial t} \]

As \(i\) tends to infinity, \(\int_0^T dt \sum_{i=1}^{L-1} \int_{ih}^{(i+1)h} dx \int_0^x dy \frac{n^{h(k)}(x,y,t) \partial \Psi(x,y,t)}{\partial t}\) tends to zero since \(\frac{\partial \Psi}{\partial t}\) and \(n^{h(k)}\) are all bounded, and

\[\int_0^T dt \int_0^{\Omega(T)} dx \int_0^x dy h^2 \frac{n^{h(k)}(x,y,t) \partial \Psi(x,y,t)}{\partial t} \to \int_0^T dt \int_0^{\Omega(T)} dx \int_0^x dy h^2 n(x,y,t) \frac{\partial \Psi(x,y,t)}{\partial t} \]

as \(i\) tends to infinity, so the first term in A.29 tends to the limit in A.30.

By the same procedure and using the condition that \(g\) is uniformly continuous in \([0,T] \times [0,\Omega(T)]^2\) (it is \(C^1\), it is easy to verify that the second term in the LHS of A.29 tends to \(f_0^T dt f_0^{\Omega(T)} dx \int_0^{\Omega(T)} dy \frac{\partial \Psi(x,y,t)}{\partial y}\), and the third term in the LHS of A.29 tends to \(f_0^T dx \int_0^{\Omega(T)} ft_0 f_0^{\Omega(T)} dy \frac{\partial \Psi(x,y,t)}{\partial y}\), we turn to the right hand side of A.29, by the same procedure, it is easy to verify the first term tends to \(f_0^T dx \int_0^{\Omega(T)} dy \int_0^x dy \frac{n(x,y,t) \Psi(x,y,t)}{\partial t}\), and the second term tends to \(f_0^T dx \int_0^{\Omega(T)} dy \int_0^x dy \frac{\Psi(x,y,t) \partial \Psi(x,y,t)}{\partial t}\).

The third term will tend to 0 since \(\Psi\) is \(C^1\) continuous and takes 0 on the boundary \(x = 0\) and \(x = \Omega(T)\) and we have the uniform upper bound of \(g, n^h\). The last term tends to \(f_0^T dx \int_0^{\Omega(T)} dy \int_0^x dy \frac{\partial \Psi(x,y,t) \Psi(x,y,t)}{\partial t}\).

By passing to the limit \(i \to \infty\), we obtain that \(n\) exactly satisfy the condition of a weak solution in A.4.

One can follow the proof in [18] and generalize the conclusions to \(R^+ \times (R^+)^2 \cap \{y < x\}\).

**Appendix B. Numerical Scheme.** We denote \(u(t) = (n_1(t), n_2(t), \ldots, n_{L-1}(t))^T\) where \(n_j(t) =
\( \{ n_{j+1}, n_{j+1}, \ldots, n_{L-j} \} \) and \( n_{i \leq j} = 0 \). Equations 2.30 can then be written in the form

\[
\mathbf{u}(t + \Delta t) = \mathbf{A}(t)\mathbf{u}(t),
\]

where

\[
\mathbf{A}(t) = \begin{bmatrix}
B_1 & C_1 & C_2 & C_3 & \cdots & C_{L-2} & C_{L-1} \\
D_2 & B_2 & 0 & 0 & \cdots & 0 & 0 \\
0 & D_3 & B_3 & 0 & \cdots & 0 & 0 \\
\vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\
0 & 0 & 0 & 0 & \cdots & D_{L-1} & B_{L-1}
\end{bmatrix},
\]

and

\[
\mathbf{B}_i = \begin{bmatrix}
0 & 0 & \cdots & 0 \\
\vdots & \vdots & \ddots & \vdots \\
0 & 0 & \cdots & 0 \\
0 & 0 & \cdots & 0
\end{bmatrix},
\]

with

\[
\mathbf{C}_i = \begin{bmatrix}
0 & 0 & \cdots & 0 \\
0 & 0 & \cdots & 0 \\
\vdots & \vdots & \ddots & \vdots \\
0 & 0 & \cdots & 0
\end{bmatrix},
\]

and

\[
\mathbf{D}_i = \begin{bmatrix}
0 & 0 & 0 & \cdots & 0 & 0 \\
\vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\
0 & 0 & \cdots & 0 & \mu g_{i+1} & 0 \\
\vdots & \vdots & \vdots & \cdots & \vdots & \vdots \\
0 & 0 & \cdots & 0 & \mu g_{L-\frac{1}{2}, i-1}
\end{bmatrix}.
\]

**Appendix C. Monte-Carlo Simulations.** In this section we describe the implementation of our Monte-Carlo simulations of the process underlying the adder-sizer mechanism. Suppose we have a list of cells at time \( t \) given as \( S(t) = \{ c_1(x_i, y_i, t, b_1), \ldots, c_i(x_i, y_i, t, b_i) \} \), where \( x_i \) is cell \( i \)'s volume and \( y_i \) is its added volume. The cell's division factor \( b_i \) is determined at birth, which is drawn from a uniform distribution \( U(0, 1) \).

Suppose we have a division of the form 2.20 and \( \tilde{\beta} \) of the form 2.24. We set a time step \( \Delta t = 0.01 \), the maximum allowable time step, and determine the next state of the system at time \( t' \) by the following steps:

1. **Step 1:** For each cell \( i \), calculate its age \( a_i \) at time \( t \) by the exponential growth law \( \frac{dx}{dt} = \lambda x \). We require that \( G_i = \int_0^{a_i} \gamma(a')da' < b_i \) at the beginning of each step for every \( i \).

2. **Step 2:** For each cell, calculate \( G_i = \int_0^{a_i+\Delta t} \gamma(a')da' \). If \( G_i \geq b_i \), then we numerically calculate a \( \Delta t_i \) such that \( \int_0^{a_i+\Delta t_i} \gamma(a')da' \approx b_i \).

3. **Step 3:** Choose the smallest \( \Delta t_i \) among all possible \( \Delta t_i \)'s as the new time step, set time \( t' = t + \Delta t_i \) and let all cells gain an extra volume \( \lambda x_i \Delta t_i \). If there is no such \( \Delta t_i \), which means \( G_i < b_i \) for every \( i \), go to step 5.

4. **Step 4:** Remove cell \( i \) from \( S(t') \), record its volume \( x \) at \( t' \), and generate one random number \( r \in (0, 1) \) observing a distribution which has a probability density function of \( h(r) \), add two new cells in \( S(t') \) as \( c_m(rx, 0, t) \) and \( c_{m+1}(x - rx, 0, t) \).
• Step 5: If $G_{i} < b_{i}$ for all $i$, then set $t' = t$ and let all cells gain an extra volume $\lambda x_{i} \Delta t$.

• Step 6: Return to step 1 until $t' > t_{\max}$, the maximum time of the simulation.

Here, we set the initial added volume of all cells to zero so the condition in step 1 above is automatically satisfied at $t = 0$. For our runs, we used 10 cells of initial volume 0.5 and $t_{\max} = T$ is the same as the maximum time for the numerical PDE experiments. We also generalize the model to incorporate the mother-daughter growth coefficient correlation by including a new label $\lambda_{i}$ to each cell.

REFERENCES