ESTIMATES FOR APPROXIMATE SOLUTIONS TO A FUNCTIONAL DIFFERENTIAL EQUATION MODEL OF CELL DIVISION

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Abstract

The functional partial differential equation (FPDE) for cell division,

$$\frac{\partial}{\partial t}n(x,t) + \frac{\partial}{\partial x}(g(x,t)n(x,t))$$
$$= -(b(x,t) + \mu(x,t))n(x,t) + b(\alpha x,t)\alpha n(\alpha x,t) + b(\beta x,t)\beta n(\beta x,t),$$

is not amenable to analytical solution techniques, despite being closely related to the first-order partial differential equation (PDE)

$$\frac{\partial}{\partial t}n(x,t) + \frac{\partial}{\partial x}(g(x,t)n(x,t)) = -(b(x,t) + \mu(x,t))n(x,t) + F(x,t),$$

which, with known $F(x,t)$, can be solved by the method of characteristics. The difficulty is due to the advanced functional terms $n(\alpha x,t)$ and $n(\beta x,t)$, where $\beta \geq 2 \geq \alpha \geq 1$, which arise because cells of size x are created when cells of size αx and βx divide. The nonnegative function, $n(x,t)$, denotes the density of cells at time t with respect to cell size x. The functions $g(x,t)$, $b(x,t)$ and $\mu(x,t)$ are, respectively, the growth rate, splitting rate and death rate of cells of size x. The total number of cells, $\int_0^\infty n(x,t)\,dx$, coincides with the L^1 norm of n. The goal of this paper is to find estimates in L^1 (and, with some restrictions, L^p for $p > 1$) for a sequence of approximate solutions to the FPDE that are generated by solving the first-order PDE. Our goal is to provide a framework for the analysis and computation of such FPDEs, and we give examples of such computations at the end of the paper.

1. Introduction and model

1.1. Introduction The goal of this paper is to give precise estimates for a sequence of approximations to the solution of a functional partial differential equation (FPDE)

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that models the growth and splitting of cells. In this model, introduced by Zaidi et al. [21], the cell density $n(x, t)$ is a function of cell size x and time t. Thus, the number of cells having a size between x_1 and x_2 is

$$\int_{x_1}^{x_2} n(x, t)\, dx.$$

Assuming that cells of size x divide into two smaller cells with size x/α and x/β, $(1/\alpha + 1/\beta = 1)$, the authors of [21] derived the model

$$\frac{\partial}{\partial t} n(x, t) + \frac{\partial}{\partial x}(g(x, t)n(x, t)) = -\{b(x, t) + \mu(x, t)\}n(x, t) + b(\alpha x, t)\alpha n(\alpha x, t)$$
$$+ b(\beta x, t)\beta n(\beta x, t), \tag{1.1}$$

$$n(0, t) = 0, \quad n(x, 0) = f(x), \quad \lim_{x \to \infty} n(x, t) = 0. \tag{1.2}$$

The extra functions appearing in this equation are the cell growth rate g, splitting (or birth) rate b and death rate μ. The function $f(x)$ is the density of cells at time 0.

The sequence of approximations to the FPDE is obtained by solving first-order partial differential equations (PDE). This provides a basis on which to construct computational schemes and also provides a simple, constructive proof of the existence of solutions. In some cases, it may be possible to use the approach as a basis for constructing analytical solutions, as was done by Zaidi et al. [20] in the case of a similar model with g, b and μ being constants. We illustrate the use of these estimates for the computation of solutions to the FPDE for the two cases g constant and g linearly depending on cell size x.

We start by reformulating the model as an integral conservation equation. We consider the case for which g is a function of x and t. For simplicity, we also initially assume that b and μ are constants, but then later show how the theory can be modified to allow for nonconstant b and μ.

1.2. Growth curves and an integral conservation law   It is worth reformulating the model as an integral conservation law, both because it clarifies the physical interpretation of the model and because it will be useful in computing our estimates. This *conservation of cells* is illustrated in Figure 1.

In this model, individual cells grow at a rate $g(x, t)$ dependent on cell size x and time t. Thus, the size $X(t)$ of a cell, until it divides, satisfies the ordinary differential equation

$$X'(t) = g(X(t), t). \tag{1.3}$$

We assume that small cells will grow, so there is a function $a(t) > 0$ such that

$$g(x, t) > 0 \quad \text{for } 0 < x < a(t)$$

and that g and $\partial g/\partial x$ are continuous for $x \in [0, \infty)$, $t \in [0, t_1]$ for some $t_1 > 0$. We also assume that solutions of the ordinary differential equation (1.3) starting on the nonnegative x- or t-axes exist for $t \leq t_1$. From now on, we will assume that $0 \leq t \leq t_1$.
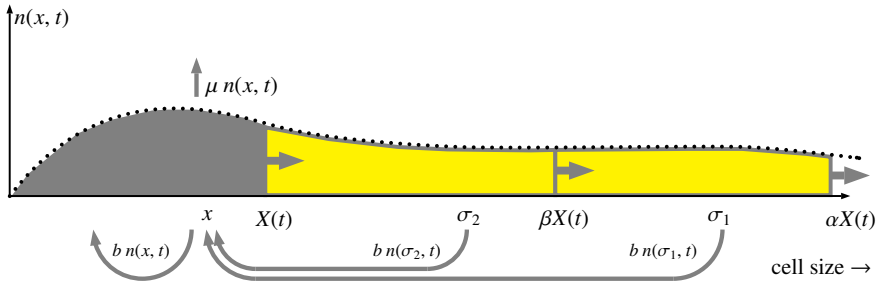
FIGURE 1. The growth, death and division of cells influencing cell density $n(x, t)$.

We do not require that $g(0, t) = 0$, but if $g(0, t) > 0$ we will need to impose a boundary condition $n(0, t) = 0$ corresponding to the fact that cells cannot grow from zero size.

It is useful to consider growing cohorts of cells of size between 0 and $X(t)$. The number $N(t)$ of such cells is

$$N(t) = \int_0^{X(t)} n(x, t)\, dx.$$

In this model, $N'(t)$, the rate of change of $N(t)$, is only due to the following variables.

- The rate of arrival of cells arising from splitting of larger cells. Cells split into sizes of fraction $1/\alpha$ or $1/\beta$ of their original sizes, so there are two contributions arising from the intervals $[X(t), \alpha X(t)]$ and $[X(t), \beta X(t)]$, and the rates are

$$b \int_{X(t)}^{\alpha X(t)} n(\sigma_1, t)\, d\sigma_1, \quad b \int_{X(t)}^{\beta X(t)} n(\sigma_2, t)\, d\sigma_2.$$

  Note that these intervals overlap. In fact, they are the same interval if $\alpha = \beta = 2$.
- The rate of splitting of cells in the interval $[0, X(t)]$. Each splitting results in one extra cell, so the rate of this occurring is

$$b \int_0^{X(t)} n(x, t)\, dx.$$

- The death rate of cells in the interval $[0, X(t)]$,

$$\mu \int_0^{X(t)} n(x, t)\, dx.$$

Balancing these terms yields the conservation law

$$\frac{d}{dt} \int_0^{X(t)} n(x, t)\, dx = b \int_{X(t)}^{\alpha X(t)} n(\sigma_1, t)\, d\sigma_1 + b \int_{X(t)}^{\beta X(t)} n(\sigma_2, t)\, d\sigma_2$$

$$+ (b - \mu) \int_0^{X(t)} n(x, t)\, dx.$$

It is useful to rewrite the integral

$$\int_{X(t)}^{\alpha X(t)} n(\sigma_1, t)\, d\sigma_1 = \int_0^{\alpha X(t)} n(\sigma_1, t)\, d\sigma_1 - \int_0^{X(t)} n(\sigma_1, t)\, d\sigma_1$$

$$= \alpha \int_0^{X(t)} n(\alpha x, t)\, dx - \int_0^{X(t)} n(x, t)\, dx,$$

where we have made a substitution $\sigma_1 = \alpha x$ in one of the integrals. A similar modification of the integral involving β allows us to write

$$\frac{d}{dt} \int_0^{X(t)} n(x, t)\, dx = \int_0^{X(t)} b\alpha n(\alpha x, t) + b\beta n(\beta x, t) - (b + \mu)n(x, t)\, dx. \qquad (1.4)$$

Integration of this gives

$$\int_0^{X(t)} n(x, t)\, dx = \int_0^t \int_0^{X(s)} b\alpha n(\alpha x, s) + b\beta n(\beta x, s) - (b + \mu)n(x, s)\, dx\, ds \qquad (1.5)$$

and thus we require the following condition for our model.

CONDITION M 1. *Equation* (1.5) *holds for all growth curves $X(t)$ starting on either the nonnegative x-axis or the nonnegative t-axis. If $g(0, t) = 0$ for all t, then we need only consider such growth curves starting on the x-axis, because those starting on the t-axis will stay on the t-axis.*

We need to include in the model the feature that cell sizes are finite. However, the mathematics is simplified by allowing the cell-size variable x to take values in $[0, \infty)$. The size of cells in the model is determined by the initial cell density $f(x)$. If $f(x) = 0$ for $x > X_0$, then the model should tell us that $n(x, t) = 0$ for $x > X(t)$, where $X(t)$ is the growth curve satisfying $X(0) = X_0$.

For some functions $g(x, t)$ the cell growth curves are bounded for $t > 0$ even when the initial cell size tends to infinity. For example, if $g(x, t) = kx(a - x)$ where k and a are positive constants then the cell growth curves satisfy the logistic equation and one finds that the curve satisfying $X(0) = x_0$ is given by

$$X(t) = \frac{ax_0}{x_0 + (a - x_0)e^{-kat}}.$$

Graphs of these curves are shown in Figure 2. These curves have the interesting feature that

$$\lim_{x_0 \to \infty} \frac{ax_0}{x_0 + (a - x_0)e^{-kat}} = X^*(t) = \frac{a}{1 - e^{-kat}},$$

which corresponds to the red envelope curve shown in Figure 2.

In such cases, for which the growth curve satisfying $X(0) = x_0$ approaches a curve $X^*(t) < \infty$ as $x_0 \to \infty$, we need to define the cell density $n(x, t) = 0$ for $x \geq X^*(t)$. This ensures that the terms $n(\alpha x, t)$ and $n(\beta x, t)$ in equation (1.5) are defined, even when $(\alpha x, t)$ and $(\beta x, t)$ are points lying to the right of $(X^*(t), t)$. Hence, we include the following condition for our model.
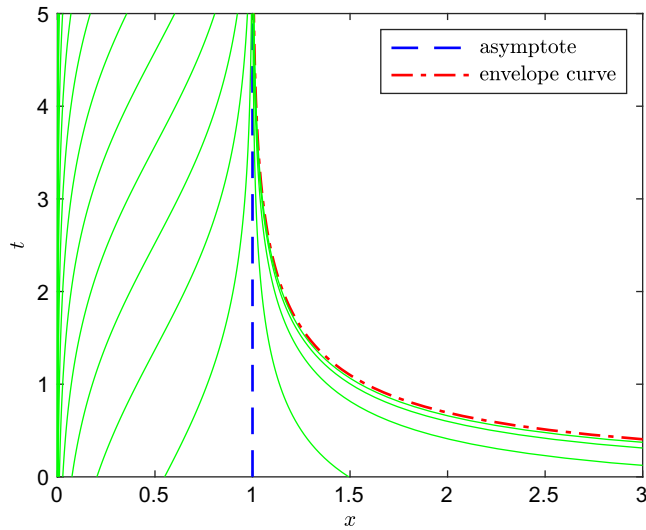
FIGURE 2. Growth curves for the logistic equation, with cell growth rate $g(x, t) = kx(a - x)$, $a = k = 1$.

CONDITION M 2. *If the growth curves admit an envelope curve $X^*(t)$, then $n(x, t) = 0$ for $x \geq X^*(t)$.*

We should check that if our model equation (1.5) is satisfied and if the density n happens to be continuously differentiable, then the functional partial differential equation (1.1) is satisfied. If n is continuously differentiable, then we can write

$$\frac{d}{dt} \int_0^{X(t)} n(x, t)\, dx = n(X(t), t)X'(t) + \int_0^{X(t)} \frac{\partial n}{\partial t}(x, t)\, dx$$

$$= g(X(t), t)n(X(t), t) + \int_0^{X(t)} \frac{\partial n}{\partial t}(x, t)\, dx$$

$$= \int_0^{X(t)} \frac{\partial n}{\partial t}(x, t) + \frac{\partial}{\partial x}(g(x, t)n(x, t))\, dx. \tag{1.6}$$

The assumed smoothness of n allows us to differentiate (1.5) to retrieve (1.4), which, using (1.6), can be written as

$$0 = \int_0^{X(t)} \left[\frac{\partial n}{\partial t}(x, t) + \frac{\partial}{\partial x}\{g(x, t)n(x, t)\} + (b + \mu)n(x, t) - b\alpha n(\alpha x, t) - b\beta n(\beta x, t) \right] dx. \tag{1.7}$$

Equation (1.7) holds for an arbitrary growth curve $X(t)$. In particular, given arbitrary $\tilde{x} > 0$, $\tilde{t} > 0$, we can let $X(t)$ be the growth curve passing through the value $\tilde{x}$ at time $\tilde{t}$. Thus, we can write

$$0 = \int_0^{\tilde{x}} \left[\frac{\partial n}{\partial t}(x, \tilde{t}) + \frac{\partial}{\partial x}\{g(x, \tilde{t})n(x, \tilde{t})\} + (b + \mu)n(x, \tilde{t}) - b\alpha n(\alpha x, \tilde{t}) - b\beta n(\beta x, \tilde{t}) \right] dx.$$

If we now differentiate this equation with respect to $\tilde{x}$, we see that the integrand must vanish. As $\tilde{x}$ and $\tilde{t}$ are arbitrary, it follows that if n is differentiable, then it is a solution of the FPDE (1.1).

Note however that $n(x, t)$ is merely a cell density, so there is no physical expectation that $n(x, t)$ is differentiable with respect to either of its arguments. Indeed, it is easy to devise plausible situations for which the initial density $n(x, 0) = f(x)$ has discontinuities, such as

$$f(x) = \begin{cases} K, & x_1 < x < x_2, \\ 0, & \text{otherwise,} \end{cases}$$

where K is a positive constant. Consequently, in order to capture physically meaningful solutions, we require

CONDITION M 3. $n(x, t) \geq 0, \quad \displaystyle\int_0^\infty n(x, t)\, dx < \infty.$

We also need to impose the following initial condition.

CONDITION M 4. $n(x, 0) = f(x) \geq 0, \quad \displaystyle\int_0^\infty f(x)\, dx < \infty.$

This completes our description of the model. The focus in the rest of this paper will be to generate a sequence of solutions of first-order PDEs and show, by finding precise estimates, that it converges to solutions of the models M1–M4.

1.3. Related literature   This model for asymmetric cell division that we analyse here was recently discussed by Zaidi et al. [21], where the authors studied properties of eigenfunction solutions with the assumption that the birth, growth and death rates (b, g and μ) are constants. That method seems promising in that the authors were able to construct explicit formulae for eigenfunctions. However, it is still not clear what space of functions these eigenfunctions span.

The model discussed by Zaidi et al. [21] is closely related to another model studied by the same authors in [20], where this time they studied the case of symmetric division of cells into two or more daughter cells. In the latter paper, again with the assumption of constant coefficients, the authors developed an explicit series solution of their equations. The terms in their series are found by solving first-order PDEs, so that approach is similar to what we use here. The construction of analytical solutions in [20] was dependent on their FPDE being relatively simple with constant parameters. Even with these assumptions, the construction was a remarkable achievement and indicates that such analytical solutions would be impossible to find for more general FPDEs. Thus, our goal is different in that we wish to use the idea to develop simple computational methods. The model discussed in [21] was studied in a much earlier paper [6], in which the authors considered steady size distributions of solutions. Related studies by this group include [4] and papers in which this type of model is applied to tumour cells [2] and plankton [3].

The model discussed in this paper allows for asymmetric cell division. There has been a great deal of experimental work done in this area that shows that the contents of cells, including proteins and DNA, are often asymmetrically shared between two daughter cells. We refer to the paper [14] for a review of this work on animal and yeast cells.

We consider nonconstant growth rate of cells in this paper. There is evidence that cells do not grow at a constant rate. In particular, there is evidence (see the paper by Taheri-Araghi et al. [17] who discussed this and nonconstant splitting) that certain types of bacterial cells grow exponentially. A recent analysis of a FPDE for this case can be found in the work of van Brunt et al. [19]. Precise measurements of growth rates can now be found experimentally; in a recent *Nature* article, Kafri et al. [9] discussed, using HeLa cells [16], a new technique to measure cell growth rate and showed that it appears to be linked to the cell cycle.

Regarding the mathematical analysis, models of cell division have been studied, starting with the work of Diekmann et al. [5] in 1984. Later works of Laurençot and Perthame [10] and Michel et al. [11, 12] use a technique involving entropy. This kind of approach is detailed in Perthame's book [15] for various models.

Heijmans [7] has studied a model of asymmetrical cell division which involves splitting of cells into a probability distribution of sizes. With the assumption of a positive growth rate depending on cell size x, Heijmans applied semigroup theory to prove the existence and develop properties of solutions.

For further results on the analysis of growth fragmentation models and an extensive bibliography on such work, we cite the recent paper of Mischler and Scher [13].

2. Two related first-order partial differential equations

Consider the problem

$$\begin{cases} \dfrac{\partial}{\partial t}u(x,t) + \dfrac{\partial}{\partial x}(g(x,t)u(x,t)) = -(b+\mu)u(x,t) + h(x,t), & x>0,\ t>0, \\ u(0,t) = 0, & t>0, \\ u(x,0) = u_0(x), & x>0. \end{cases} \tag{2.1}$$

The first-order PDE appearing in this problem is closely related to our model FPDE (1.1), the nonhomogeneous term $h(x,t)$ replacing the nonlocal terms in (1.1).

Equation (2.1) is readily solved by the method of characteristics, detailed in most standard texts on PDEs, such as John's book [8]. The characteristic curves for this PDE are the family of solutions to the ordinary differential equation

$$X'(t) = g(X(t), t)$$

with initial condition, either $X(t_0) = 0$ for $t_0 > 0$ or $X(0) = x_0$ for $x_0 \geq 0$ (see Figure 3). These characteristic curves are identical to the cell growth curves.
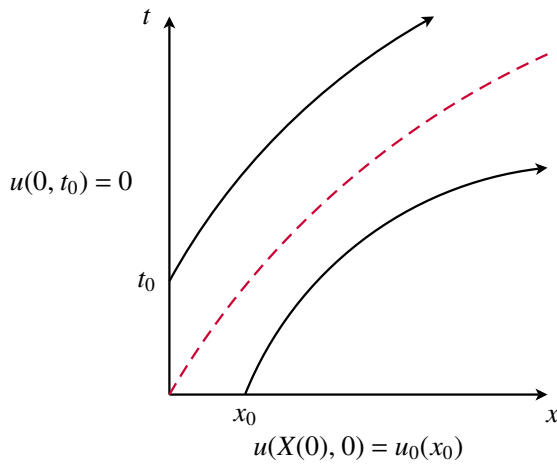
FIGURE 3. Characteristic curves for the partial differential equation (2.1).

Along the characteristics, we find that $u(X(t), t)$ satisfies the ordinary differential equation

$$\frac{d}{dt}u(X(t), t) = \frac{\partial u}{\partial t} + \frac{\partial u}{\partial x}X'(t)$$
$$= \frac{\partial u}{\partial t} + \frac{\partial u}{\partial x}g(X(t), t)$$
$$= -\frac{\partial g}{\partial x}(X(t), t)\,u(X(t), t) - (b + \mu)u(X(t), t) + h(X(t), t) \qquad (2.2)$$

and the initial condition either $u = 0$ for $t = t_0$ or $u = u_0(x_0)$ for $t = 0$, depending on whether the characteristic starts on the t-axis or the x-axis.

We can find the value of u along characteristic curves by integrating the differential equation (2.2):

$$u(X(t), t) =$$
$$\begin{cases} \int_{t_0}^{t} \exp\left(-\int_{s}^{t} \frac{\partial g}{\partial x}(X(\tau), \tau)\,d\tau - (b+\mu)(t-s)\right)h(X(s), s)\,ds, & X(t_0) = 0, \\[2mm] u_0(x_0)\exp\left(-\int_{0}^{t} \frac{\partial g}{\partial x}(X(\tau), \tau)\,d\tau - (b+\mu)t\right) & \\[2mm] \qquad + \int_{0}^{t} \exp\left(-\int_{s}^{t} \frac{\partial g}{\partial x}(X(\tau), \tau)\,d\tau - (b+\mu)(t-s)\right)h(X(s), s)\,ds, & X(0) = x_0. \end{cases} \qquad (2.3)$$

Another useful PDE is found by integrating (2.1), giving

$$\int_{0}^{x} \frac{\partial}{\partial t}u(\sigma, t)\,d\sigma + g(x, t)u(x, t) = -(b + \mu)\int_{0}^{x} u(\sigma, t) + h(\sigma, t)\,d\sigma,$$

which, if we set

$$U(x,t) = \int_0^x u(\sigma, t)\, d\sigma, \quad H(x,t) = \int_0^x h(\sigma, t)\, d\sigma, \quad U(x,0) = U_0(x) = \int_0^x u_0(\sigma)\, d\sigma, \tag{2.4}$$

gives the following PDE problem for U:

$$\begin{cases} \dfrac{\partial U}{\partial t} + g(x,t)\dfrac{\partial U}{\partial x} = -(b+\mu)U(x,t) + H(x,t), & x > 0,\ t > 0, \\ U(0,t) = 0, & t > 0, \\ U(x,0) = U_0(x), & x > 0. \end{cases}$$

Along the characteristics, we find that $U(X(t),t)$ satisfies the ordinary differential equation

$$\begin{aligned} \frac{d}{dt}U(X(t),t) &= \frac{\partial U}{\partial t} + \frac{\partial U}{\partial x}X'(t) \\ &= \frac{\partial U}{\partial t} + \frac{\partial U}{\partial x}g(X(t),t) \\ &= -(b+\mu)U(X(t),t) + H(X(t),t), \end{aligned} \tag{2.5}$$

and the initial condition either $U = 0$ for $t = t_0$ or $U = U_0(x_0)$ for $t = 0$, depending on whether the characteristic starts on the t-axis or the x-axis.

We can find the value of U along characteristic curves by integrating the differential equation (2.5):

$$U(X(t),t) = \begin{cases} \displaystyle\int_{t_0}^t e^{-(b+\mu)(t-s)}H(X(s),s)\, ds, & X(t_0) = 0, \\ U_0(x_0)e^{-(b+\mu)t} + \displaystyle\int_0^t e^{-(b+\mu)(t-s)}H(X(s),s)\, ds, & X(0) = x_0. \end{cases} \tag{2.6}$$

If we rewrite (2.5) and (2.6) using $U(x,t) = \int_0^x u(\sigma,t)\, d\sigma$, then we get some useful identities for u that will help us in our proof of existence of solutions for our model:

$$\frac{d}{dt}\int_0^{X(t)} u(\sigma,t)\, d\sigma = -(b+\mu)\int_0^{X(t)} u(\sigma,t)\, d\sigma + \int_0^{X(t)} h(\sigma,t)\, d\sigma\, ds,$$

$$\int_0^{X(t)} u(\sigma,t)\, d\sigma$$

$$= \begin{cases} \displaystyle\int_{t_0}^t e^{-(b+\mu)(t-s)}\int_0^{X(s)} h(\sigma,s)\, d\sigma\, ds, & X(t_0) = 0, \\ e^{-(b+\mu)t}\displaystyle\int_0^{x_0} u_0(\sigma)\, d\sigma + \int_0^t e^{-(b+\mu)(t-s)}\int_0^{X(s)} h(\sigma,s)\, d\sigma\, ds, & X(0) = x_0. \end{cases} \tag{2.7}$$

Letting $x_0 \to \infty$ in (2.7) gives the useful L^1 identity,

$$\int_0^{X^*(t)} u(\sigma, t)\, d\sigma = e^{-(b+\mu)t} \int_0^\infty u_0(\sigma)\, d\sigma + \int_0^t e^{-(b+\mu)(t-s)} \int_0^{X^*(s)} h(\sigma, s)\, d\sigma\, ds, \quad (2.8)$$

where $X^*(t)$ is the limit of the characteristic $X(t)$ as $x_0 \to \infty$. However, if $X^*(t) < \infty$, we are free to define $h(x, t) = 0$, $u(x, t) = 0$ for $x > X^*(t)$, so we can write

$$\int_0^\infty u(\sigma, t)\, d\sigma = e^{-(b+\mu)t} \int_0^\infty u_0(\sigma)\, d\sigma + \int_0^t e^{-(b+\mu)(t-s)} \int_0^\infty h(\sigma, s)\, d\sigma\, ds. \quad (2.9)$$

3. Approximate solutions

In this section, we approximate solutions of (1.5) with solutions of first-order PDEs and give formulae for the errors in $L^1(0, \infty)$. We focus on the case of constant μ and b, but see Remark 3.5 for a brief discussion on the nonconstant case.

We assume the existence of a unique solution to (1.5) with initial condition $n(\cdot, 0) = f \in L^1(0, \infty)$. References for existence–uniqueness results are given in Section 1.3. We also assume the existence–uniqueness of the relevant first-order PDEs. In fact, in our applications we are interested mainly in the cases for which these solutions can be written in closed form, so existence is not an issue.

We define a sequence of approximations as solutions to the first-order PDEs

$$\frac{\partial}{\partial t} n_k(x, t) + \frac{\partial}{\partial x}(g(x, t)n_k(x, t)) = -(b + \mu)n_k(x, t) + b\alpha n_{k-1}(\alpha x, t) + b\beta n_{k-1}(\beta x, t), \quad (3.1)$$

$$n_k(0, t) = 0, \quad n_k(x, 0) = f(x) \quad (3.2)$$

for $k = 1, 2, \ldots$, where $n_0(x, t) \equiv 0$.

THEOREM 3.1. *The sequence of approximations satisfies*

$$0 \le n_j(x, t) \le n_{j+1}(x, t), \quad j \ge 0.$$

Further, for each $t \ge 0$ and each nonnegative integer j, there exists $t_1 \in [0, t]$ such that

$$\|n(\cdot, t) - n_j(\cdot, t)\|_{L^1} = \int_0^\infty n(x, t) - n_j(x, t)\, dx$$
$$= \frac{(2bt)^j}{j!} \exp(-2bt_1 + (b - \mu)t) \int_0^\infty f(x)\, dx$$
$$= \frac{(2bt)^j}{j!} \exp(-2bt_1)\|n(\cdot, t)\|_{L^1}.$$

PROOF. Let $m_j(x, t) = n_j(x, t) - n_{j-1}(x, t)$ for $j \ge 1$. Then m_j satisfies

$$\frac{\partial}{\partial t} m_j(x, t) + \frac{\partial}{\partial x}(g(x, t)m_j(x, t)) = -(b + \mu)m_j(x, t) + h_j(x, t), \quad (3.3)$$

where

$$h_1(x, t) = 0; \quad h_j(x, t) = b\alpha m_{j-1}(\alpha x, t) + b\beta m_{j-1}(\beta x, t), \quad j > 1.$$

The functions m_j satisfy the boundary conditions $m_j(0, t) = 0$ and initial conditions

$$m_j(x, 0) = \begin{cases} f(x), & j = 1, \\ 0, & j > 1. \end{cases}$$

The function $h_1 = 0$, so inspection of (2.3) tells us that $m_1 \geq 0$ and (2.9) gives

$$\int_0^\infty m_1(x, t)\, dx = e^{-(b+\mu)t} \int_0^\infty f(x)\, dx.$$

We also have

$$\int_0^\infty h_j(x, t)\, dx = \int_0^\infty [b\alpha m_{j-1}(\alpha x, t) + b\beta m_{j-1}(\beta x, t)]\, dx$$

$$= 2b \int_0^\infty m_{j-1}(x, t)\, dx.$$

Equation (2.3) tells us that $m_j \geq 0$ for all $j \geq 1$ and we also have, by (2.9),

$$\int_0^\infty m_{j+1}(x, t)\, dx = 2b \int_0^t \int_0^\infty e^{-(b+\mu)(t-s)} m_j(x, s)\, dx\, ds, \quad j \geq 1.$$

Iterating this gives

$$\int_0^\infty m_{j+1}(x, t)\, dx = \frac{(2bt)^j}{j!} e^{-(b+\mu)t} \int_0^\infty f(x)\, dx, \quad j \geq 1. \tag{3.4}$$

By comparison with the power series for e^{2bt}, the series

$$\sum_{j=1}^\infty m_j(x, t)) = \sum_{j=1}^\infty \{n_j(x, t) - n_{j-1}(x, t)\}$$

is convergent in L^1 for each t. We also see that the limit $n(x, t)$ satisfies

$$\int_0^\infty n(x, t)\, dx = \sum_{j=0}^\infty \frac{(2bt)^j}{j!} e^{-(b+\mu)t} \int_0^\infty f(x)\, dx = e^{(b-\mu)t} \int_0^\infty f(x)\, dx.$$

We need to verify that $n(x, t)$ is indeed the solution to (1.5). But n_j was constructed to satisfy

$$\frac{d}{dt} \int_0^{X(t)} n_j(x, t)\, dx = \int_0^{X(t)} b\alpha n_{j-1}(\alpha x, t) + b\beta n_{j-1}(\beta x, t) - (b + \mu) n_j(x, t)\, dx.$$

Integrating this with respect to t gives

$$\int_0^{X(t)} n_j(x, t) \, dx - \int_0^{X(0)} f(x) \, dx$$

$$= \int_0^t \int_0^{X(s)} b\alpha n_{j-1}(\alpha x, s) + b\beta n_{j-1}(\beta x, s) - (b + \mu)n_j(x, s) \, dx \, ds.$$

The L^1 convergence allows us to pass to the limit to get (1.5).

Finally,

$$\|n(\cdot, t) - n_j(\cdot, t)\|_{L^1} = e^{-(b+\mu)t} \|f\|_{L^1} \sum_{k=j}^{\infty} \frac{(2bt)^k}{k!}.$$

But the series on the right-hand-side of this equation is the remainder for the Taylor series for e^{2bt}. By Taylor's theorem [1], this is precisely $e^{2bt_2}(2bt)^j/j!$ for some $t_2 \in (0, t)$. We get the formulae in the statement of the theorem by setting $t_1 = t - t_2$. □

REMARK 3.2. The result on L^1 convergence concerns nonnegative initial data f. However, any $f \in L^1(0, \infty)$ can be written as $f = f^+ - f^-$, where f^+ and f^- are nonnegative members of $L^1(0, \infty)$. It follows that a solution exists for all $f \in L^1$. If $n = n^+ - n^-$, where n^+ and n^- are the solutions with initial data f^+ and f^-, then

$$\int_0^{\infty} |n(x, t)| \, dx \leq \int_0^{\infty} |n^+(x, t)| \, dx + \int_0^{\infty} |n^-(x, t)| \, dx$$

$$= e^{(b-\mu)t} \int_0^{\infty} f^+(x) \, dx + e^{(b-\mu)t} \int_0^{\infty} f^-(x) \, dx$$

$$= e^{(b-\mu)t} \int_0^{\infty} |f(x)| \, dx.$$

This result also gives a measure of the difference between the two solutions n_1 and n_2 with initial data f_1 and f_2, because $n_1 - n_2$ is the solution with initial data $f_1 - f_2$ and hence

$$\int_0^{\infty} |n_1(x, t) - n_2(x, t)| \, dx \leq e^{(b-\mu)t} \int_0^{\infty} |f_1(x) - f_2(x)| \, dx.$$

REMARK 3.3. (Convergence in weighted L^p norm). The natural space for solutions is L^1, but if we additionally assume that g is a positive function that depends only on x and that there is a constant G such that $g(x)/g(\alpha x) < G$, $g(x)/g(\beta x) < G$, then we also get convergence with respect to the weighted L^p norm $\| \ \|_p$ given by

$$\|u\|_p = \left(\int_0^{\infty} g(x)^{p-1} |u(x)|^p \, dx \right)^{1/p}.$$

The proof is similar to the L^1 case, but instead of U given by equation (2.4), we use U_p given by

$$U_p(x, t) = \int_0^x g(\sigma)^{p-1} u^p(\sigma, t)\, d\sigma,$$

which satisfies the first-order PDE

$$\frac{\partial U_p}{\partial t} + g(x)\frac{\partial U_p}{\partial x} = -p(b+\mu)U_p(x, t) + p\int_0^x g(\sigma)^{p-1} u^{p-1}(\sigma, t) h(\sigma, t)\, d\sigma. \quad (3.5)$$

Aside from this, the main difference in the proof is that Hölder's inequality [18] is used to estimate terms arising from the integral in (3.5) and one finds that

$$\|n(\cdot, t)\|_p \leq e^{bG^{1/q}(\alpha^{1/q}+\beta^{1/q})t}\|f\|_p,$$

where $1/p + 1/q = 1$.

If we denote by $S_j(t)$ and $S(t)$ the mappings $f \to n_j(\cdot, t)$ and $f \to n(\cdot, t)$, respectively, then Theorem 3.1 yields

$$\|S(t) - S_j(t)\| \leq \frac{(2bt)^j}{j!}\exp((b-\mu)t).$$

Clearly, the approximation is more accurate for small t. We can exploit this by iterating the approximation using small time steps of size $\Delta t > 0$. We wish to compute the error in the resulting approximation $(S_j(\Delta t))^k f$ to $n(\cdot, k\Delta t) = S(k\Delta t)f$ for k a positive integer.

THEOREM 3.4. *Let $f \in L^1(0, \infty)$ be nonnegative, let k be a positive integer, let $\Delta t > 0$ and let $t_k = k\Delta t$. Then*

$$\|S(t_k)f - (S_j(\Delta t))^k f\|_{L^1} \leq \frac{(2b\Delta t)^j}{j!} k e^{(b-\mu)t_k}\|f\|_{L^1} = \frac{(2b\Delta t)^j}{j!} k\|S(t_k)f\|_{L^1}.$$

PROOF. Note that $n(\cdot, \Delta t) \geq S_j(\Delta t)f$. Hence,

$$n(\cdot, 2\Delta t) = S(\Delta t)n(\cdot, \Delta t) \geq S(\Delta t)S_j(\Delta t)f \geq (S_j(\Delta t))^2 f.$$

Clearly, we can continue this and find that

$$n(\cdot, i\Delta t) \geq (S_j(\Delta t))^i f$$

for each positive integer i. Thus,

$$\|S(t_k)f - (S_j(\Delta t))^k f\|_{L^1} = \int_0^\infty n(x, t_k) - (S_j(\Delta t))^k f\, dx$$

$$= e^{(b-\mu)k\Delta t}\|f\|_{L^1} - \left(\sum_{i=0}^{j-1} \frac{(2b\Delta t)^i}{i!} e^{-(b+\mu)\Delta t}\right)^k \|f\|_{L^1},$$

where we have used equation (3.4) with $t = \Delta t$.

Letting

$$x = e^{(b-\mu)\Delta t}, \quad y = \sum_{i=0}^{j-1} \frac{(2b\Delta t)^i}{i!} e^{-(b+\mu)\Delta t},$$

we may write

$$e^{(b-\mu)k\Delta t} - \left(\sum_{i=0}^{j-1} \frac{(2b\Delta t)^i}{i!} e^{-(b+\mu)\Delta t} \right)^k = x^k - y^k$$

$$= (x - y) \sum_{l=0}^{k-1} x^{k-1-l} y^l$$

$$\leq (x - y)kx^{k-1}.$$

Taylor's theorem gives

$$x - y = \frac{(2b\Delta t)^j}{j!} \exp(-2b\tau + (b - \mu)\Delta t) \leq \frac{(2b\Delta t)^j}{j!} \exp((b - \mu)\Delta t),$$

where $\tau \in (0, \Delta t)$. Hence,

$$\|S(t_k)f - (S_j(\Delta t))^k f\|_{L^1} \leq (x - y)kx^{k-1} \|f\|_{L^1}$$

$$\leq \frac{(2b\Delta t)^j}{j!} ke^{(b-\mu)t_k} \|f\|_{L^1}. \qquad \square$$

REMARK 3.5. *(The case of variable μ and b)* Recall that μ is the cell death rate and b is the cell splitting rate and these are expected to depend on cell size x; it is of interest to see how to modify the analysis for this case. We assume that μ and b are bounded, nonnegative functions of x and let M and B respectively denote the least upper bounds of $\mu(x)$ and $b(x)$ for $x \in [0, \infty)$. Instead of equation (3.1) for the approximating sequence, we use

$$\frac{\partial}{\partial t} n_k(x, t) + \frac{\partial}{\partial x} (g(x)n_k(x, t)) = -(B + M)n_k(x, t) + (B + M - b(x) - \mu(x))n_{k-1}(x, t)$$

$$+ b(\alpha x)\alpha n_{k-1}(\alpha x, t) + b(\beta x)\beta n_{k-1}(\beta x).$$

The coefficient $B + M - b(x) - \mu(x)$ is nonnegative, ensuring that the approximation sequence is nonnegative. Instead of (3.4), we now have

$$\int_0^\infty m_{j+1}(x, t) \, dx \leq \frac{\{(3B - B_1 + M - M_1)t\}^j}{j!} e^{-(B+M)t} \int_0^\infty f(x) \, dx, \quad j \geq 1,$$

where M_1 and B_1 are, respectively, the greatest lower bounds of $\mu(x)$ and $b(x)$ for $x \in [0, \infty)$. This results in an estimate for the solution,

$$\int_0^\infty n(x, t) \, dx \leq e^{(2B-B_1-M_1)t} \int_0^\infty f(x) \, dx.$$

4. Examples

We illustrate Theorems 3.1 and 3.4 with two examples. For each example, b and μ are constants. Example 4.1 concerns the usual constant-g case, while Example 4.2 concerns $g(x) = \gamma x$, where one can think of γ as a constant relative growth rate.

In each case, we seek solutions to (3.1) and (3.2) in the form

$$n_j(x, t) = \sum_{k=1}^{j} m_k(x, t),$$

where the functions m_k are defined in the proof of Theorem 3.1 as solutions of the first-order PDEs (3.3). The calculations are simplified by the observation that

$$\tilde{m}_k(x, t) \equiv e^{(b+\mu)t} m_k(x, t)$$

satisfy the equations

$$\frac{\partial \tilde{m}_j}{\partial t} + \frac{\partial}{\partial x}(g\tilde{m}_j) = \tilde{h}_j, \quad x > 0, \quad t > 0, \tag{4.1}$$

where

$$\tilde{h}_1(x, t) = 0; \quad \tilde{h}_j(x, t) = b\alpha\tilde{m}_{j-1}(\alpha x, t) + b\beta\tilde{m}_{j-1}(\beta x, t), \quad j > 1. \tag{4.2}$$

The functions $\tilde{m}_j$ satisfy the boundary conditions $\tilde{m}_j(0, t) = 0$ and initial conditions

$$\tilde{m}_j(x, 0) = \begin{cases} f(x), & j = 1, \\ 0, & j > 1. \end{cases} \tag{4.3}$$

4.1. Example (constant g, b, μ)   In this case, $\tilde{m}_1$ satisfies

$$\frac{\partial \tilde{m}_1}{\partial t} + g\frac{\partial \tilde{m}_1}{\partial x} = 0, \quad x > 0, \quad t > 0$$

with initial condition $\tilde{m}_1(x, 0) = f(x)$ and boundary condition $\tilde{m}_1(0, t) = 0$. If we extend the domain of f to $\mathbb{R}$ by defining $f(x) = 0$ for $x < 0$, then we may write

$$\tilde{m}_1(x, t) = f(x - gt).$$

One then finds from (4.1) that

$$\tilde{m}_2(x, t) = \frac{b\beta}{g}\{F_1(\alpha x - gt) - F_1(\alpha(x - gt))\} + \frac{b\alpha}{g}\{F_1(\beta x - gt) - F_1(\beta(x - gt))\},$$

where F_1 is the first integral (antiderivative) of f,
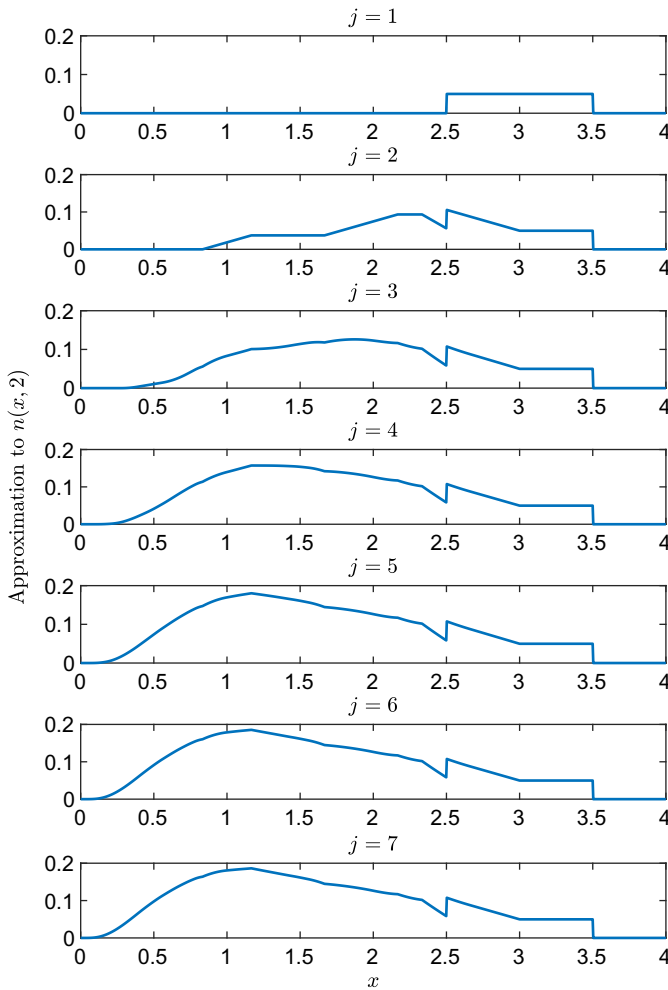
$$F_1(x) = \int_0^x f(s)\, ds.$$

FIGURE 4. The first seven approximations given by Theorem 3.1 for $n(x, 2)$, as discussed in Example 4.1.

It is easy to verify that $\tilde{m}_{j+1}(x, t)$ is simply a linear combination of functions of the form $F_j(kx - ct)$ for various constants k and c, where F_j is the jth integral of f,

$$F_j(x) = \int_0^x F_{j-1}(s)\, ds = \frac{1}{(j-1)!} \int_0^x (x-s)^{j-1} f(s)\, ds.$$

We note that, because the domain of f was extended so that $f(x) = 0$ for $x < 0$, each F_j also vanishes on $(-\infty, 0)$.

Figure 4 shows the first seven approximations to $n(x, 2)$ for the case $b = 0.5$, $\mu = g = 1$, $\alpha = 3$, $\beta = 3/2$ and initial density
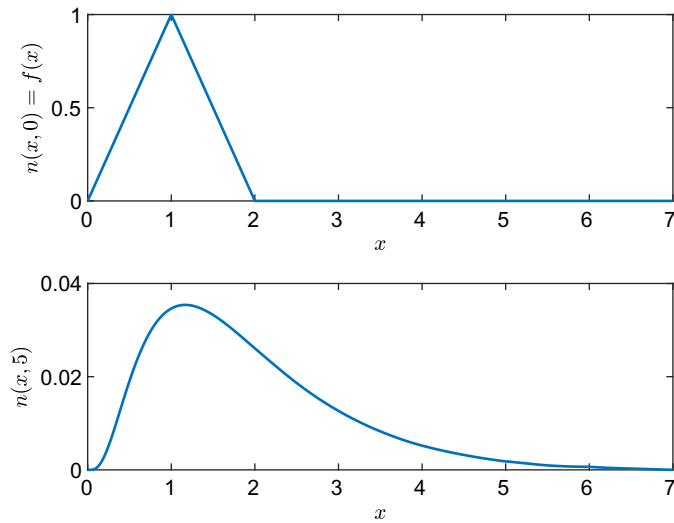
FIGURE 5. The initial value $n(x, 0) = f(x)$ and the computed value of $n(x, 5)$ as discussed in Example 4.1.

$$f(x) = \begin{cases} 1, & 1.5 \le x \le 2.5, \\ 0, & \text{otherwise.} \end{cases}$$

According to Theorem 3.1, the L^1 error for $n_7(\cdot, 2)$ is

$$\frac{2^7}{7!} \exp(-1 - t_1) \approx 0.0093 \exp(-t_1)$$

for $t_1 \in (0, 2)$. The actual L^1 error is approximately 0.0017.

Next, we illustrate Theorem 3.4 with the same model. In this case, the time interval is partitioned into sub-intervals of length dt and we solve equations (4.1) and (4.2) for $\tilde{m}_j(x, t) = \tilde{m}_j^k(x, t)$ for $t \in [k\,dt, (k + 1)\,dt]$, $k = 0, 1, \ldots$, where the initial values of these functions are given by equation (4.3) for $k = 0$ and by the following for $k \ge 1$:

$$\tilde{m}_j^k(x, k\,dt) = \begin{cases} \tilde{m}_j^{k-1}(x, kt), & j = 1, \\ 0, & j > 1. \end{cases}$$

For this computation, we use the initial function for n plotted in Figure 5, which also gives a plot of $n(x, 5)$ calculated using this method.

Theorem 3.4 gives an estimate of the L^1 error of the approximation shown in Figure 5. We applied the method of Theorem 3.4 with $j = 4$ to compute the solution with a range of step sizes. We also calculated the L^1 errors, which, according to Theorem 3.4, we expect to be $O(dt^3)$, because the number of steps, k, is $O(1/dt)$. Figure 6 shows the computed L^1 errors and the upper bound predicted by Theorem 3.4.
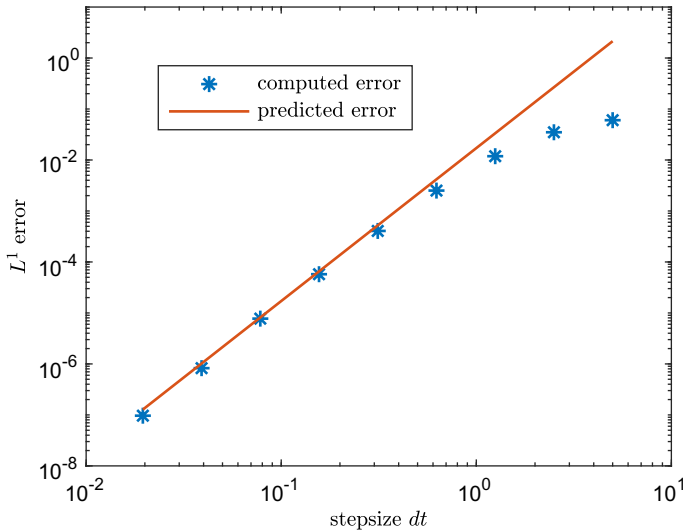
FIGURE 6. The computed L^1 error and the predicted upper bound of the error in $n(x, 5)$ obtained from Theorem 3.4 with $j = 4$. The calculations are for the model of Example 4.1 with $n(x, 0)$ as shown in Figure 5.

At the beginning of each time step, we are essentially solving a new problem with initial data from the previous step. One extra requirement for this method is the need to suitably represent the functions $n(x, k \, dt)$ for $k = 1, 2, \ldots$. We chose cubic splines to represent the functions, because this satisfied the need to be able to, at each time step, integrate these functions a few times and to be able to evaluate $n(\alpha x, k \, dt)$, $n(\beta x, k \, dt)$.

4.2. Example (linear growth rate $g(x) = \gamma x$; γ, b and μ constant) We briefly mention this case, because there is evidence that it occurs in nature [17]. In this case, the functions m_j of Theorem 3.1 are particularly simple to calculate, and the characteristic projections (cell growth curves) are exponentials, $x(t) = x_0 e^{\gamma t}$. Consequently, $\alpha x(t)$ and $\beta x(t)$ are also characteristic projections. One easily finds that

$$m_1(x, t) = f(xe^{-\gamma t})e^{-(b+\mu+\gamma)t},$$
$$m_2(x, t) = (\alpha f(\alpha xe^{-\gamma t}) + \beta f(\beta xe^{-\gamma t}))bte^{-(b+\mu+\gamma)t}.$$

Other values of m_j have a similar form and it is relatively easy to carry out the approximations of Theorems 3.1 and 3.4.

5. Concluding remarks

The goal of this paper is to make use of the analytical properties of first-order partial differential equations in order to compute solutions of related functional partial

differential equations. This is the spirit of the work of Zaidi et al. [20], who constructed explicit solutions of a functional PDE from the general solution of a related PDE.

The challenging calculations required in [20] for a relatively simple functional PDE suggests that such explicit constructions are unlikely for most functional PDEs. However, we show in this paper that similar ideas can still be used to *compute* solutions of functional PDEs. For this, we focused on a model for asymmetrical cell division and constructed a sequence of solutions to PDEs that converge to the solution of the functional PDE. The simplicity of this development was based on a reformulation of the model in terms of an integral conservation law and well-known properties of linear first-order PDEs. We illustrated such computations for the cases of constant growth rate and linear growth rate. The technique used to obtain the precise estimates for the approximations is applicable to other similar models.

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