Partial Differential Equations in Applied Mathematics 11 (2024) 100814

Contents lists available at ScienceDirect

Partial Differential Equations in Applied Mathematics

journal homepage: www.elsevier.com/locate/padiff

Dynamics of cell growth: Exponential growth and division after a minimum cell size

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ARTICLE INFO

Keywords:
Functional partial differential equations
Nonlocal partial differential equations

ABSTRACT

In this paper, we consider a mathematical model for cell division using a Pantograph-type nonlocal partial differential equation, accompanied by relevant initial and boundary conditions. This formulation results in a nonlocal singular eigenvalue problem. We explore the possible eigenvalues that may lead to nontrivial solutions. We then consider cells that divide once they achieve a minimum size. Our model incorporates asymmetric cell division and exponential growth. We show that, unlike the constant growth rate case, a probability density function eigenvalue can be determined explicitly. Additionally, we demonstrate that a stochastic growth rate produces eigenfunctions expressed as an infinite series of modified Bessel functions. We extend our findings to encompass a wider range of dispersion and growth rates. The implications of this work are significant for understanding the dynamics of cell populations in biological systems. The work has potential applications in cancer research and developmental biology, where cell growth and division play critical roles.

1. Introduction

Functional (nonlocal) partial differential equations with advanced arguments of the pantograph-type arise in several applications. For instance, these appear in internet protocols,[1] fragmentation in polymers,[2–4] dynamics of neurons[5] and cell growth models.[6–9] In particular, a second order modified Fokker–Planck functional partial differential equation (PDE)

$$-(D(x,t)n(x,t))_{xx} + n_t(x,t) + (G(x,t)n(x,t))_x + B(x,t)n(x,t) = +\alpha B(\alpha x,t)n(\alpha x,t) + \beta B(\beta x,t)n(\beta x,t), \tag{1}$$

arises in a cell division model with stochastic growth rate of cells.[10] Here, $n(x,t)$ denotes the number density of cells of size x at time t and the positive coefficients $D(x,t)$, $B(x,t)$ and $G(x,t)$ represent the dispersion, growth and division rates of cells. Also, $\alpha > 2 > \beta > 1$ correspond to asymmetric cell division and satisfy

$$\frac{1}{\alpha} + \frac{1}{\beta} = 1.$$

The functional PDE (1) is supplemented with the initial condition

$$n(x,t) = n_0(x), \tag{2}$$

and the boundary conditions

$$\lim_{x\to 0^+} ((-D(x,t)n(x,t))_x + G(x,t)n(x,t)) = 0, \tag{3}$$

$$\lim_{x\to \infty} ((-D(x,t)n(x,t))_x + G(x,t)n(x,t)) = 0, \tag{4}$$

and the condition

$$\lim_{x\to \infty} n(x,t) = 0. \tag{5}$$

Due to functional terms $n(\alpha x,t)$ and $n(\beta x,t)$ in (1), there is a scarcity of techniques for solving the initial–boundary value problem for non-constant coefficients. Consequently, even for a restricted class of coefficients, there are no general methods for solving such problems. For constant coefficients, however, Wake et al.[10] studied the long time asymptotic behaviour of solutions and determined steady size distribution (SSD) solutions of the form

$$n(x,t) = N(t)y(x), \tag{6}$$

where N is the total population at time t and y is a probability density function. Efendiev et al.[11] then determined the general solution to the initial boundary value problem (1), (3)–(4) for constant coefficients. The separable solutions usually correspond to SSD solutions, at least for constant coefficients.

Hall and Wake[7] notes the interest in 'SSD solutions which can develop in a growing population' if $D(x,t) = D(x)$, $G(x,t) = G(x)$ and $B(x,t) = B(x)$. For this choice of coefficients, Eqs. (6) and (1) give

$$N(t) = Ce^{-\Lambda t},$$

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https://doi.org/10.1016/j.padiff.2024.100814
Received 27 May 2024; Received in revised form 26 June 2024; Accepted 8 July 2024
Available online 11 July 2024
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where C and Λ are constants, and,

$$-(D(x)y(x))_{xx} + (G(x)y(x))_x + (B(x) - \Lambda)y(x) = \alpha B(\alpha x)y(\alpha x) + \beta B(\beta x)y(\beta x). \tag{7}$$

Also, conditions (3) and (4) imply

$$\lim_{x\to 0^+} ((-D(x)y(x))' + G(x)y(x)) = 0, \tag{8}$$

$$\lim_{x\to \infty} ((-D(x)y(x))' + G(x)y(x)) = 0, \tag{9}$$

where the function y is required to be a probability density function so that

$$\int_0^\infty y(x)dx = 1. \tag{10}$$

Eq. (7) is an example of a pantograph equation with advanced arguments. There are no methods to solve (7), subject to conditions (8)–(10), for any class of coefficients. Nonetheless, the problem has been studied for certain choices of coefficients. For instance, it has been studied for the simpler case of constant coefficients,[10] for linear dispersion[12] and for quadratic dispersion with linear growth and quadratic division rates.[13]

In this paper, we explicitly determine eigenvalues and the corresponding eigenfunctions to the problem (7)–(10) for certain classes of biologically realistic non-constant coefficients. We first assume that cells divide only after they have reached a certain minimum size. Earlier work[14,15] that entails minimum cell size division, assumes a constant growth rate of cells. Here, we assume exponential growth of cells, i.e. cells grow proportionally to their sizes. Cooper[16] explains that exponential growth is more biologically realistic than constant growth. The exponential growth, mathematically, corresponds to $G(x) = gx$, $g > 0$. The division rate can then be modelled by

$$B(x) = bx^r H(x - \theta),$$

where H is the Heaviside function and $\theta, b, g > 0$ and $r \in \mathbb{Z}^+$. For constant growth rates, a minimum cell size division was considered by Diekmann et al.[14] but they had an upper bound on the maximum cell size. The limiting case where there is no upper bound on the cell size was discussed by van-Brunt et al.[15], but their analysis did not determine an eigenvalue explicitly and the eigenfunction is in terms of the eigenvalue.

In the next section, we determine bounds on the eigenvalue Λ and discuss plausible eigenvalues that may yield nontrivial solutions to the problem (7)–(10). In Section 3, we determine the eigenvalue explicitly for exponential growth of cells and minimum cell size division. We also determine the steady size distribution solution to the problem. In Section 4, we study the effects of quadratic dispersion and determine the eigenvalue explicitly. We show that eigenfunctions involve an infinite series of modified Bessel functions. In Section 5, we generalize the results for $G(x) = gx^r$, $g > 0, r < 1$, for certain dispersion coefficients.

2. Eigenvalues

In this section we discuss bounds on Λ that may yield nontrivial solutions to the nonlocal eigenvalue problem (7)–(10). For constant coefficients ($D(x) = D > 0, G(x) = G > 0$ and $B(x) = B > 0$), Wake et al.[10] determined the unique eigenvalue,

$$\Lambda = b(\alpha - 1),$$

and the corresponding eigenfunction y as a certain Dirichlet series. Efendiev et al.[11] showed that, for large time, the solution of Wake et al. is an attracting solution to the functional PDE (1) subject to conditions (2)–(4). That is, as $t \to \infty$,

$$\|n(x,t) - e^{-\Lambda t}y(x)\| \to 0.$$

The separable solution $n(x,t) = e^{-\Lambda t}y(x)$ is then referred to as the steady size distribution (SSD) solution (see Fig. 1). We note that, at least for

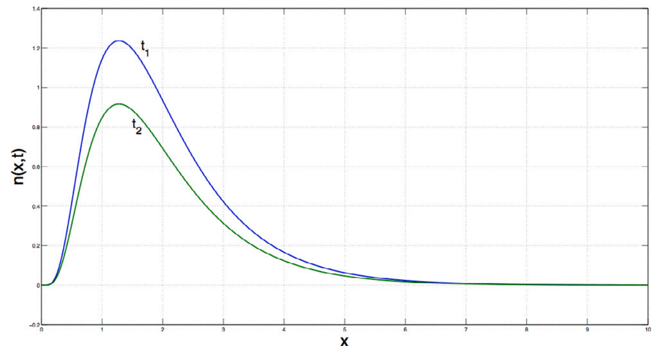

Fig. 1. The number density n for large times t_1 and t_2.

constant coefficients, the SSD solution is positive and unimodal. For non-constant coefficients, however, the existence of the eigenvalues, the corresponding eigenfunctions and the convergence of solutions of (1)–(4) to the steady size distribution solution $n(x,t) = e^{-\Lambda t}y(x)$, for sufficiently large time, are not known. It is, therefore, of interest to determine eigenvalues that do not yield a positive nontrivial solution. If y is a solution to (7)–(10), then Eq. (10) implies that y has to be positive somewhere in the interval $(0,\infty)$. Eq. (6) then implies the existence of a positive global maximum M, such that $y'(M) = 0$, and (7) gives

$$(-D''(M) + G'(M) + B(M) - \Lambda)y(M) - D(M)y''(M) = \alpha B(\alpha M)y(\alpha M) + \beta B(\beta M)y(\beta M). \tag{11}$$

Since M is a maximum of y, so $y''(M) \leq 0$, and $-D(M)y''(M) \geq 0$. Consequently, Eq. (11) gives

$$(-D''(M) + G'(M) + B(M) - \Lambda)y(M) \leq \alpha B(\alpha M)y(\alpha M) + \beta B(\beta M)y(\beta M) \leq (\alpha B(\alpha M) + \beta B(\beta M))y(M).$$

Since $y(M)$ is positive, the above inequality yields

$$-D''(M) + G'(M) + B(M) - \Lambda \leq \alpha B(\alpha M) + \beta B(\beta M). \tag{12}$$

The challenge with the above inequality is that M is not known, since y is not known in general. However, for certain classes of dispersion, growth and division rates, inequality (12) gives bounds on Λs that do not yield nontrivial solutions to the problem (7)–(10). For instance, if for all $x > 0$, D'' is either zero or a decreasing function, G is a constant or an increasing function and B is a decreasing function such that $B(x) > \alpha B(\alpha x) + \beta B(\beta x)$, then (12) gives

$$\Lambda > 0. \tag{13}$$

However, if y is a positive solution to (7)–(10) then the integration of (7) from 0 to ∞ with respect to x, and conditions (8) and (9) yield

$$\Lambda = -\int_0^\infty B(x)y(x)dx,$$

so that,

$$\Lambda < 0. \tag{14}$$

We conclude from inequalities (13) and (14) that that there does not exist any positive nontrivial solution to (7) subject to conditions (8)–(10) if, for all $x > 0$, D'' is either zero or a decreasing function, G is a constant or an increasing function and B is a decreasing function such that $B(x) > \alpha B(\alpha x) + \beta B(\beta x)$. For instance, if $D(x) = 0$, $G = gx$ and $B(x) = bx^r$, where b and g are positive constants and $r < -2$, then (7) does not have a positive nontrivial solution that satisfies (8)–(10). However, for $r \in \mathbb{Z}^+$, we show in the next section that there does exist an eigenvalue which can be determined explicitly, since $B(x)$ is not greater than $\alpha B(\alpha x) + \beta B(\beta x)$.

Also, inequality (14) implies that any equation of the form (7) with $\Lambda \geq 0$, subject to conditions (8)–(10), does not have a positive solution.

We now show that if $\Lambda < 0$ and if for all x, $B(x) > \alpha B(\alpha x) + \beta B(\beta x)$, then there is no nontrivial solution to (7)–(10) if $G'(x) > D''(x)$ for all $x > 0$. To show this, we assume on the contrary that for $\Lambda < 0$ and for all $x > 0$ such that $B(x) > \alpha B(\alpha x) + \beta B(\beta x)$, there exists a nontrivial solution y such that $G'(x) > D''(x)$. Since $\Lambda < 0$, Inequality (12) yields

$$-D''(M) + G'(M) + B(M) \leq \alpha B(\alpha M) + \beta B(\beta M),$$

so that,

$$-D''(M) + G'(M) < 0,$$

or,

$$G'(M) < D''(M),$$

which contradicts the assumption that $G' > D''$ for all $x > 0$. Conversely, if $G' < D''$ for all $x > 0$, then (12) gives

$$B(M) - \Lambda < \alpha B(\alpha M) + \beta B(\beta M),$$

so that,

$$\Lambda > 0,$$

which contradicts the assumption that $\Lambda < 0$.

Lastly, inequality (12) can be used to determine whether (7)–(10) does not have a positive nontrivial solution for certain values of Λ. Specifically, if D'', G', and B are bounded, i,e., if there exists constants M_1, M_2 and M_3 such that $|D''| \leq M_1$, $G' \leq M_2$, and $B \leq M_3$ then (12) gives

$$\Lambda \leq D''(M) - G'(M) - B(M) + \alpha B(\alpha M) + \beta B(\beta M),$$

and since $B > 0$,

$$\Lambda \leq D''(M) - G'(M) + \alpha B(\alpha M) + \beta B(\beta M),$$

so that,

$$|\Lambda| \leq |D''(M)| + |G'(M)| + |\alpha B(\alpha M)| + |\beta B(\beta M)| = M_1 + M_2 + (\alpha+\beta) M_3. \quad (15)$$

In particular, if $D = dx^2$, $G = gx$ and $B = b$, where d, g and b are positive constants, then (15) implies that $\Lambda \leq 2d + g + b(\alpha+\beta)$. Consequently, a functional equation of the form (7) does not have a nontrivial solution if $\Lambda > 2d + g + b(\alpha+\beta)$.

3. $D(x) = 0$, $G(x) = gx$ And $B(x) = bx^r H(x-\theta)$ for $\theta, b, g > 0$ and $r \in \mathbb{Z}^+$

We consider the first order version of the problem (7)–(9). The choice, $G(x) = gx$, models exponential growth of cells, which is both biologically and mathematically different from linear growth of cells ($G(x) = g > 0$). Mathematically, the large time dynamics of solutions are different for the linear and exponential growth of cells, at least for certain classes of division rates. Cooper[16] explains that exponential growth is more biologically realistic than the constant growth. A closely related problem was studied by van-Brunt et al.[15] for symmetric cell division ($\alpha = \beta = 2$) and constant growth rate, but their analysis did not determine an eigenvalue explicitly and the eigenfunction is in terms of the eigenvalue. Also, their analysis breaks down for the asymmetric division ($\alpha > 2 > \beta > 1$) problem (7)–(9). Here, we determine an eigenvalue and the corresponding eigenfunction explicitly for asymmetric cell division problem (7)–(9) with exponential growth.

In the absence of dispersion, the problem (7)–(9) with 'exponential' growth rate reduces to

$$(gxy(x))' + (B(x) - (\lambda - \mu))\, y(x) = \alpha B(\alpha x) y(\alpha x) + \beta B(\beta x)\, y(\beta x), \quad (16)$$

along with the conditions

$$\lim_{x\to 0^+} xy(x) = 0, \qquad \lim_{x\to\infty} xy(x) = 0. \quad (17)$$

The eigenvalue λ can be determined explicitly by multiplying (16) by x and integrating over the interval $(0,\infty)$. This gives

$$\lambda = \mu - g,$$

and consequently (16) reduces to

$$xy'(x) + \left(\tilde{B}(x) + 2\right) y(x) = \alpha \tilde{B}(\alpha x) y(\alpha x) + \beta \tilde{B}(\beta x) y(\beta x), \quad (18)$$

where $\tilde{B}(x) = \frac{B(x)}{g}$. We drop the tildes and consider the division rate $B(x) = bx^r H(x-\theta)$. This yields

$$xy'(x) + (bx^r H(x-\theta) + 2)\, y(x) = b\alpha^{r+1} x^r H(\alpha x - \theta) y(\alpha x) + b\beta^{r+1} x^r H(\beta x - \theta) y(\beta x). \quad (19)$$

Eq. (19) yields a system of four equations of the form

$$xy_1'(x) + 2y_1(x) = 0, \qquad 0 \leq x < \frac{\theta}{\alpha}, \quad (20)$$

$$xy_2'(x) + 2y_2(x) = b\alpha^{r+1} x^r y_4(\alpha x), \qquad \frac{\theta}{\alpha} \leq x < \frac{\theta}{\beta}, \quad (21)$$

$$xy_3'(x) + 2y_3(x) = b\alpha^{r+1} x^r y_4(\alpha x) + b\beta^{r+1} x^r y_4(\beta x), \qquad \frac{\theta}{\beta} \leq x < \theta, \quad (22)$$

$$xy_4'(x) + (bx^r + 2) y_4(x) = b\alpha^{r+1} x^r y_4(\alpha x) + b\beta^{r+1} x^r y_4(\beta x), \qquad x \geq \theta. \quad (23)$$

Eq. (20) and the condition $\lim_{x\to 0^+} xy_1(x) = 0$ yield the trivial solution

$$y_1(x) = 0. \quad (24)$$

Also, the continuity at endpoints yields the conditions

$$y_2(\theta/\alpha) = 0, \quad (25)$$

$$y_2(\theta/\beta) = y_3(\theta/\beta), \quad (26)$$

$$y_3(\theta) = y_4(\theta). \quad (27)$$

Eq. (23) contains functional terms $y_4(\alpha x)$ and $y_4(\beta x)$. Once y_4 is known, Eqs. (21)–(22) are local in character and can be solved using standard methods. Eq. (23) is solved by converting the equation to

$$xw'(x) + bx^r w(x) = \frac{b}{\alpha}\alpha^r x^r y(\alpha x) + \frac{b}{\beta}\beta^r x^r w(\beta x), \quad (28)$$

using the transformation

$$y_4(x) = \frac{w(x)}{x^2}.$$

Eq. (28) has been discussed in the literature.[17] The solution to (28) is of the form

$$w(x) = \sum_{k=0}^{\infty}\sum_{j=0}^{\infty} a_{k,j} \exp\left(\frac{-b}{r}\alpha^{rk}\beta^{rj}x^r\right), \quad (29)$$

where

$$a_{k,0} = \frac{(-1)^k \alpha^{(r-1)k}}{\prod_{s=1}^{k}(\alpha^{rs}-1)} a_{0,0}, \quad (30)$$

$$a_{0,j} = \frac{(-1)^j \beta^{(r-1)j}}{\prod_{s=1}^{j}(\beta^{rs}-1)} a_{0,0}, \quad (31)$$

$$a_{k,j} = \frac{-1}{\left(\alpha^{rk}\beta^{rj}-1\right)}\left(\alpha^{r-1}a_{k-1,j} + \beta^{r-1}a_{k,j-1}\right). \quad (32)$$

Here $a_{0,0}$ is chosen so that the pdf condition is satisfied. Consequently,

$$y_4(x) = C\sum_{k=0}^{\infty}\sum_{j=0}^{\infty} a_{k,j} x^{-2} \exp\left(\frac{-b}{r}\alpha^{rk}\beta^{rj}x^r\right), \quad (33)$$

where $a_{k,j}$'s are defined as in (30)–(32) and the constant C is to be determined. The convergence of the double series and the uniqueness of y_4 can be established using the analysis in Ref. 13. Since y_4 is known, the right side of Eq. (21) is a known function and consequently,

$$y_2(x) = \sum_{k=0}^{\infty}\sum_{j=0}^{\infty} \frac{1}{\alpha^{rk+1}\beta^{rj}} a_{k,j} x^{-2}\left\{\exp\left(-\frac{b}{r}\alpha^{rk}\beta^{rj}\theta^r\right) - \exp\left(-\frac{b}{r}\alpha^{r(k+1)}\beta^{rj}x^r\right)\right\},$$

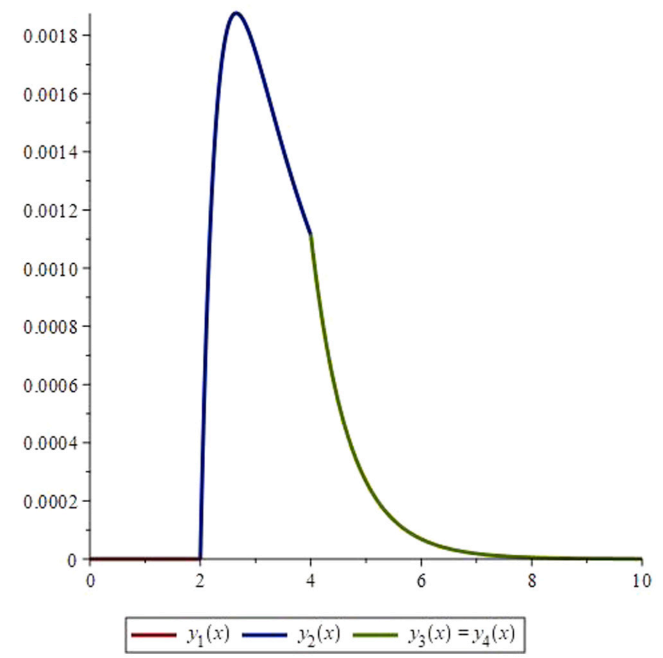

Fig. 2. Solution y_1 given by (24), y_2 given by (34), y_3 given by (35) and y_4 given by (33) for $\alpha = \beta = 2$, and $\theta = 4$. We note that for $\alpha = \beta = 2$, the graph of y_3 equals y_4.

(34)

where y_2 satisfies the continuity condition (25). Similarly, Eqs. (33), (34) and (22) give

$$y_3(x) = K\sum_{k=0}^{\infty}\sum_{j=0}^{\infty} a_{k,j} x^{-2}\{ \frac{-1}{\alpha^{rk+1}\beta^{rj}} \exp\left(-\frac{b}{r}\alpha^{r(k+1)}\beta^{rj}x^r\right) - \frac{1}{\alpha^{rk}\beta^{rj+1}} \exp\left(-\frac{b}{r}\alpha^{rk}\beta^{r(j+1)}x^r\right)\}, \tag{35}$$

where the K constant is determined using the continuity condition (26)–(27). This gives

$$K = \frac{\sum_{k=0}^{\infty}\sum_{j=0}^{\infty} \frac{\beta^2}{\theta^2(\alpha^{rk+1}\beta^{rj})} a_{k,j} \left\{\exp\left(-\frac{b}{r}\alpha^{rk}\beta^{rj}\theta^r\right) - \exp\left(-\frac{b}{r}\alpha^{r(k+1)}\beta^{r(j-1)}\theta^r\right)\right\}}{\sum_{k=0}^{\infty}\sum_{j=0}^{\infty} a_{k,j}\frac{\beta^2}{\theta^2}\left\{\frac{-1}{\alpha^{rk+1}\beta^{rj}}\exp\left(-\frac{b}{r}\alpha^{r(k+1)}\beta^{r(j-1)}\theta^r\right) - \frac{1}{\alpha^{rk}\beta^{rj+1}}\exp\left(-\frac{b}{r}\alpha^{rk}\beta^{rj}\theta^r\right)\right\}}.$$

Consequently, the constant C in (33) is of the form

$$C = \frac{K\sum_{k=0}^{\infty}\sum_{j=0}^{\infty} a_{k,j}\theta^{-2}\left\{\frac{-1}{\alpha^{rk+1}\beta^{rj}}\exp\left(-\frac{b}{r}\alpha^{r(k+1)}\beta^{rj}\theta^r\right) - \frac{1}{\alpha^{rk}\beta^{rj+1}}\exp\left(-\frac{b}{r}\alpha^{rk}\beta^{r(j+1)}\theta^r\right)\right\}}{\sum_{k=0}^{\infty}\sum_{j=0}^{\infty} a_{k,j}\theta^{-2}\exp\left(\frac{-b}{r}\alpha^{rk}\beta^{rj}\theta^r\right)}.$$

The graph of y is plotted in Fig. 2.

4. $D(x) = Dx^2$, $G(x) = gx$ And $B(x) = bx^r H(x-\theta)$, for $\theta, b, g, D > 0$ and $r \in \mathbb{Z}^+$

In this section we discuss the second order case and consider a quadratic dispersion rate, linear growth rate (which corresponds to 'exponential' growth of cells) and division of cells that is attained after a certain minimum size.

We note that a related problem was considered in Ref. 13 for quadratic division rate $B(x) = bx^2$, and $D(x) = Dx^2$, $G(x) = gx$, $b, g, D > 0$, and the unique probability density function (pdf) solution to the problem was determined in terms of a certain series of modified Bessel functions. We first extend the results of Ref. 13 to a broader class of division rates $B(x) = bx^r$, $r \in \mathbb{Z}^+$.

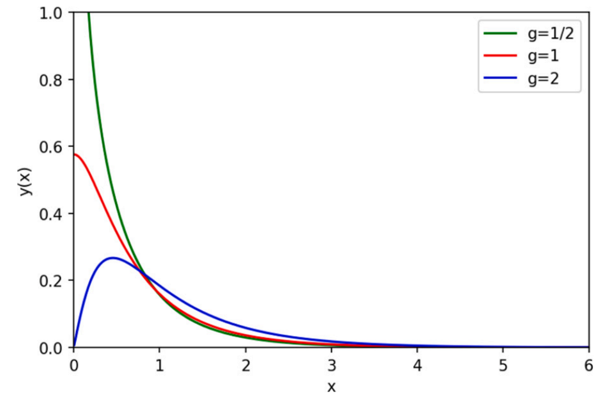

Fig. 3. Solution y given by (37)–(40) for $\alpha = 3$, $\beta = 1.5$, $r = 2$ and g=0.5, 1 and 2.

For these division and growth rates, the functional PDE

$$\left(x^2 y(x)\right)'' - g\,(xy(x))' + (\lambda - \mu - bx^r)\, y(x) = -bx^r\alpha^{r+1}y(\alpha x) - bx^r\beta^{r+1}y(\beta x),$$

subject to the conditions

$$\lim_{x\to 0^+}\left\{\left(x^2y(x)\right)' - gxy(x)\right\} = 0,$$
$$\lim_{x\to\infty}\left\{\left(x^2y(x)\right)' - gxy(x)\right\} = 0,$$

can be reduced to

$$x^2y''(x) - (g-4)\,xy'(x) - (bx^r + \Lambda)\,y(x) = -b\alpha^{r+1}x^r y(\alpha x) - b\beta^{r+1}x^r y(\beta x), \tag{36}$$

where $\Lambda = 2(g-1)$, and entails a solution (see Fig. 3) of the form

$$y(x) = \sum_{k=0}^{\infty}\sum_{j=0}^{\infty}\left(\alpha^k\beta^j x\right)^{\frac{g-3}{2}} a_{k,j} K_\nu\left(\frac{2}{r}c\left(\alpha^k\beta^j x\right)^{\frac{r}{2}}\right), \tag{37}$$

where K_ν is a modified Bessel function, and

$$a_{k,0} = \frac{(-1)^k\left(\alpha^{r+1}\right)^k a_{0,0}}{\prod_{s=1}^{k}\left(\alpha^{rs}-1\right)}, \tag{38}$$

$$a_{0,j} = \frac{(-1)^k\left(\beta^{r+1}\right)^k a_{0,0}}{\prod_{s=1}^{k}\left(\beta^{rs}-1\right)}, \tag{39}$$

and

$$a_{k,j} = \frac{-1}{\left(\alpha^{rk}\beta^{rj}-1\right)}\left\{\alpha^{r+1}a_{k-1,j} + \beta^{r+1}a_{k,j-1}\right\}. \tag{40}$$

The convergence and uniqueness of the solution can be established using the analysis in Ref. 13.

We now turn our attention to the problem (7)–(9), with $D(x) = Dx^2$, $G(x) = gx$ and $B(x) = bx^r H(x-\theta)$, where H is the Heaviside function, r is any positive integer and $\theta, b, g, D > 0$. Here, we can explicitly determine the eigenvalue λ and determine a unique pdf solution to the PDE

$$\begin{aligned}&\left(x^2y(x)\right)'' - g\,(xy(x))' + (\lambda - \mu - bx^r H(x-\theta))\,y(x)\\ &= -bx^r\alpha^{r+1}H(\alpha x - \theta)y(\alpha x) - bx^r H(\beta x - \theta)\beta^{r+1}y(\beta x),\end{aligned} \tag{41}$$

subject to the conditions

$$\begin{aligned}&\lim_{x\to 0^+}\left\{\left(x^2y(x)\right)' - gxy(x)\right\} = 0\\ &\lim_{x\to\infty}\left\{\left(x^2y(x)\right)' - gxy(x)\right\} = 0.\end{aligned} \tag{42}$$

The eigenvalue is determined under stronger conditions on decay and growth. To impose the conditions, we define $F(\gamma_1, \gamma_2)$ to be the class of functions g that satisfy

1. $g \in C^2(0,\infty)$,
2. As $x \to 0^+$, $g \sim O\left(\frac{1}{x^{\gamma_1}}\right)$ and $g' \sim O\left(\frac{1}{x^{\gamma_1+1}}\right)$, and
3. As $x \to +\infty$, $g \sim O\left(\frac{1}{x^{\gamma_2}}\right)$ and $g' \sim O\left(\frac{1}{x^{\gamma_2+1}}\right)$,

and assume that $y(x) \in F(\gamma_1,\gamma_2)$ for $\gamma_1 < 1$ and $\gamma_2 > 3$ and that $xy(x) \in L^1[0,\infty)$.

The multiplication of (41) with x and integration over $(0,\infty)$ with respect to x yields the eigenvalue

$$\lambda = \mu - g.$$

This reduces Eq. (41) to

$$\begin{aligned} &x^2 y''(x) - (g-4)\,xy'(x) - (bx^r H(x-\theta) + \Lambda)\,y(x) \\ &= -b\alpha^{r+1}x^r H(\alpha x - \theta)y(\alpha x) - b\beta^{r+1}x^r H(\beta x - \theta)y(\beta x), \end{aligned} \tag{43}$$

where $\Lambda = 2(g-1)$.

Eq. (43) can be expressed as a system of four equations of the form

$$x^2 y_1''(x) - (g-4)\,xy_1'(x) - \Lambda y_1(x) = 0, \quad 0 \le x < \frac{\theta}{\alpha}, \tag{44}$$

$$x^2 y_2''(x) - (g-4)\,xy_2'(x) - \Lambda y_2(x) = -b\alpha^{r+1}x^r y_4(\alpha x), \quad \frac{\theta}{\alpha} \le x < \frac{\theta}{\beta}, \tag{45}$$

$$\begin{aligned} x^2 y_3''(x) - (g-4)\,xy_3'(x) - \Lambda y_3(x) &= -b\alpha^{r+1}x^r y_4(\alpha x) \\ &\quad - b\beta^{r+1}x^r y_4(\beta x), \quad \frac{\theta}{\beta} \le x < \theta, \end{aligned} \tag{46}$$

$$\begin{aligned} x^2 y_4''(x) - (g-4)\,xy_4'(x) - (bx^r + \Lambda)\,y_4(x) &= -b\alpha^{r+1}x^r y_4(\alpha x) \\ &\quad - b\beta^{r+1}x^r y_4(\beta x), \quad x \ge \theta. \end{aligned} \tag{47}$$

Eqs. (44)–(47) are supplemented with continuity conditions at the end points. This gives

$$\lim_{x\to(\theta/\alpha)^-} y_1(x) = \lim_{x\to(\theta/\alpha)^+} y_2(x), \tag{48}$$

$$\lim_{x\to(\theta/\beta)^-} y_2(x) = \lim_{x\to(\theta/\beta)^+} y_3(x), \tag{49}$$

$$\lim_{x\to\theta^-} y_3(x) = \lim_{x\to\theta^+} y_4(x). \tag{50}$$

We note that (47) is nonlocal in character. If y_4 is known then Eqs. (44)–(46) are ordinary differential equations and can easily be solved using standard techniques. The solution y_4 to Eqs. (47) is, however, given by (37)–(40). Consequently, (44) gives

$$y_1(x) = C_1 x^{g-1} + C_2 x^{-2}.$$

The condition that $y(x) \in O\left(\frac{1}{\tau_1}\right)$ for $\tau_1 < 1$ as $x \to 0^+$ implies that $C_2 = 0$. This reduces the above equation to

$$y_1(x) = C_1 x^{g-1}.$$

Since (45) and (46) are inhomogeneous Cauchy–Euler equations, we have

$$\begin{aligned} y_2(x) = C_3 x^{g-1} + C_4 x^{-2} - x^{g-1} \sum_{k=0}^{\infty}\sum_{j=0}^{\infty} \frac{b\alpha^{r+1}\left(\alpha^{k+1}\beta^j\right)^{\frac{g-3}{2}}}{(g+1)} I_1 \\ + x^{-2} \sum_{k=0}^{\infty}\sum_{j=0}^{\infty} \frac{b\alpha^{r+1}\left(\alpha^{k+1}\beta^j\right)^{\frac{g-3}{2}}}{(g+1)} I_2, \end{aligned}$$

and

$$\begin{aligned} y_3(x) = y_2(x) - x^{g-1} \sum_{k=0}^{\infty}\sum_{j=0}^{\infty} \frac{b\beta^{r+1}\left(\alpha^{k}\beta^{j+1}\right)^{\frac{g-3}{2}}}{(g+1)} I_1 \\ + x^{-2} \sum_{k=0}^{\infty}\sum_{j=0}^{\infty} \frac{b\beta^{r+1}\left(\alpha^{k}\beta^{j+1}\right)^{\frac{g-3}{2}}}{(g+1)} I_2, \end{aligned}$$

where,

$$I_1 = \int x^{\frac{1+2r-g}{2}} K_\nu\left(\frac{2c}{r}\left(\alpha^{k+1}\beta^j x\right)^{\frac{r}{2}}\right) dx,$$

and

$$I_2 = \int x^{\frac{g+3+2r}{2}} K_\nu\left(\frac{2c}{r}\left(\alpha^{k+1}\beta^j x\right)^{\frac{r}{2}}\right) dx.$$

The constants C_1, C_2 and C_3 are determined by the continuity conditions (48)–(50).

5. $D(x) = Dx^{r+1}$, $G(x) = gx^r$ And $B(x) = b$ for $b, g, D > 0$ and $r < 1$

In this section, we show that if the dispersion and the growth rates are related in a certain manner, the problem (7)–(9) entails an eigenvalue and a unique probability density function solution that can be determined explicitly. Specifically, we consider (7)–(9) for $D(x) = Dx^{r+1}$, $G(x) = gx^r$, and $B(x) = b$ for $r < 1$ and $b, g, D > 0$. For this choice of coefficients, (7) reduces to

$$\left(Dx^{r+1}y(x)\right)'' - (gx^r y(x))' + (\lambda - \mu - b)\,y(x) = -b\alpha y(\alpha x) - b\beta y(\beta x),$$

so that,

$$\left(x^{r+1}y(x)\right)'' - (\hat{g}x^r y(x))' + \left(\hat{\lambda} - \hat{\mu} - \hat{b}\right) y(x) = -\hat{b}\alpha y(\alpha x) - \hat{b}\beta y(\beta x), \tag{51}$$

where $\hat{\lambda} = \frac{\lambda}{D}$, $\hat{\mu} = \frac{\mu}{D}$, $\hat{b} = \frac{b}{D}$, and $\hat{g} = \frac{g}{D}$. Also, conditions (8) and (9) give

$$\lim_{x\to0^+}\left\{\left(x^{r+1}y(x)\right)' - \hat{g}x^r y(x)\right\} = 0,$$
$$\lim_{x\to\infty}\left\{\left(x^{r+1}y(x)\right)' - \hat{g}x^r y(x)\right\} = 0.$$

For simplicity, we omit the circumflexes. This reduces the above problem to the PDE

$$\left(x^{r+1}y(x)\right)'' - (gx^r y(x))' + (\lambda - \mu - b)\,y(x) = -b\alpha y(\alpha x) - b\beta y(\beta x), \tag{52}$$

and the conditions

$$\begin{aligned} &\lim_{x\to0^+}\left\{\left(x^{r+1}y(x)\right)' - gx^r y(x)\right\} = 0, \\ &\lim_{x\to\infty}\left\{\left(x^{r+1}y(x)\right)' - gx^r y(x)\right\} = 0. \end{aligned} \tag{53}$$

To determine λ, Eq. (52) can be integrated from 0 to ∞ with respect to x. This, using conditions in (53), gives

$$\lambda = \mu - b.$$

Consequently, Eq. (52) reduces to

$$\left(x^{r+1}y(x)\right)'' - (gx^r y(x))' - 2by(x) = -b\alpha y(\alpha x) - b\beta y(\beta x).$$

The transformation

$$w(x) = x^r y(x),$$

converts the above PDE to

$$x^r (xw(x))'' - gx^r w'(x) - 2bw(x) = -b\alpha^{1-r}w(\alpha x) - b\beta^{1-r}w(\beta x),$$

which can be further converted to the PDE

$$z\Psi''(z) + a\psi'(z) - 2B\Psi(z) = -B\hat{\alpha}\Psi(\hat{\alpha}z) - B\hat{\beta}\Psi(\hat{\beta}z) \tag{54}$$

using the transformation

$$\Psi(z(x)) = w(x),$$

where $z(x) = \frac{x^{1-r}}{1-r}$, $a = 1 + \frac{1-g}{1-r}$, $B = \frac{b}{1-r}$, $\hat{\alpha} = \alpha^{1-r}$ and $\hat{\beta} = \beta^{1-r}$. We note that $\hat{\alpha}$ and $\hat{\beta}$ are greater than 1, so that the PDE (54) has advanced arguments.

Also, the boundary conditions in (53) imply

$$\lim_{z\to0^+}\left\{z\Psi'(z) + (a-1)\Psi(z)\right\} = 0,$$
$$\lim_{z\to\infty}\left\{z\Psi'(z) + (a-1)\Psi(z)\right\} = 0.$$

Due to a linear term in the coefficient of the highest derivative, we are motivated to seek solutions in terms of modified Bessel functions.[12]

That is, we seek solutions of the form

$$\Psi(z) = \sum_{k=0}^{\infty}\sum_{j=0}^{\infty} e_{k,j}\left(\hat{\alpha}^k\hat{\beta}^j z\right)^{\frac{\nu}{2}} K_\nu\left(c\sqrt{\hat{\alpha}^k\hat{\beta}^j z}\right), \tag{55}$$

where $\nu = 1-a = \frac{g-1}{1-r}$ and $c = 2\sqrt{2B} = 2\sqrt{\frac{2b}{1-r}}$.

Eqs. (54) and (55), and the comparison of the coefficients of $K_\nu\left(c\sqrt{\hat{\alpha}^k\hat{\beta}^j z}\right)$ give

$$c^2 z K_\nu''\left(c\sqrt{z}\right) + c\sqrt{z}K_\nu'\left(c\sqrt{z}\right) - \left(c^2z^2-\nu^2\right)K_\nu\left(c\sqrt{z}\right),$$

along with the relations

$$e_{k,0} = \frac{(-1)^k\hat{\alpha}^k e_{0,0}}{2^k\prod_{s=1}^k\left(\hat{\alpha}^s-1\right)},$$

$$e_{0,j} = \frac{(-1)^j\hat{\beta}^j e_{0,0}}{2^j\prod_{s=1}^j\left(\hat{\beta}^s-1\right)},$$

and

$$e_{k,j} = \frac{-1}{2\left(\hat{\alpha}^k\hat{\beta}^j-1\right)}\left(\hat{\alpha}e_{k-1,j}+\hat{\beta}e_{k,j-1}\right).$$

Consequently,

$$y(x) = \sum_{k=0}^{\infty}\sum_{j=0}^{\infty} e_{k,j}\left(\frac{\alpha^k\beta^j}{\theta}\right)^{\frac{g-2}{2}} x^{\frac{g-1-2r}{2}} K_\nu\left[c\left(\frac{\alpha^k\beta^j x}{\theta}\right)^{\frac{1-r}{2}}\right], \tag{56}$$

where $\theta = (1-r)^{\frac{1}{1-r}}$, and

$$e_{k,0} = \frac{(-1)^k\alpha^{k(1-r)}e_{0,0}}{2^k\prod_{s=1}^k\left(\alpha^{s(1-r)}-1\right)},$$

$$e_{0,j} = \frac{(-1)^j\beta^{j(1-r)}e_{0,0}}{2^j\prod_{s=1}^j\left(\beta^{s(1-r)}-1\right)},$$

and

$$e_{k,j} = \frac{-1}{2\left(\alpha^{k(1-r)}\beta^{j(1-r)}-1\right)}\left(\alpha^{(1-r)}e_{k-1,j}+\beta^{(1-r)}e_{k,j-1}\right).$$

The convergence of the double series (57) and the uniqueness can be established mimicking the analysis in Ref. 13.

The asymptotics of y as $x \to 0^+$ can be ascertained from the asymptotics of Ψ as $z \to 0^+$ using Mellin transforms. The Mellin transform of (55) and the decay condition at infinity yield

$$s(s-1)(1-a)M(s-1) = 2b\left(1-\frac{1}{2\alpha^{s-1}}-\frac{1}{2\beta^{s-1}}\right)M(s), \tag{57}$$

where

$$M(s) = \int_0^\infty x^{s-1}y(x)dx.$$

We seek a solution to (57) of the form

$$M(s) = F(s)Q(s), \tag{58}$$

where $F(s)$ is the Mellin transform of the homogeneous equation

$$z_h\Psi''(z_h) + a\psi'(z_h) - 2B\Psi(z_h) = 0,$$

and satisfies

$$s(s-1)(1-a)F(s-1) = 2bF(s). \tag{59}$$

Consequently,

$$\begin{aligned} F(s) &= M\{z_h(x)\} \\ &= c^{-s-\frac{\nu}{2}}\cdot 2^{2s+\nu}\Gamma(s)\Gamma(s+\nu). \end{aligned} \tag{60}$$

Also, $Q(s)$ can be ascertained using (57) and (59). This gives

$$Q(s) = \prod_{k=0}^{\infty}\left(1-\frac{1}{2\alpha^{s+k}}-\frac{1}{2\beta^{s+k}}\right). \tag{61}$$

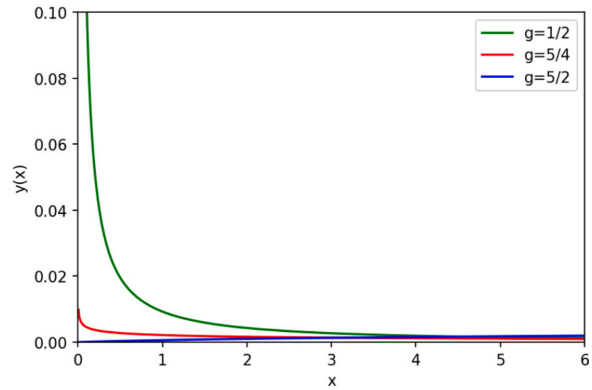

Fig. 4. Solution y given by (56) for $r = \frac{1}{2}$ $\alpha = 3$, $\beta = 1.5$ and g=0.5, 1.25 and 2.5.

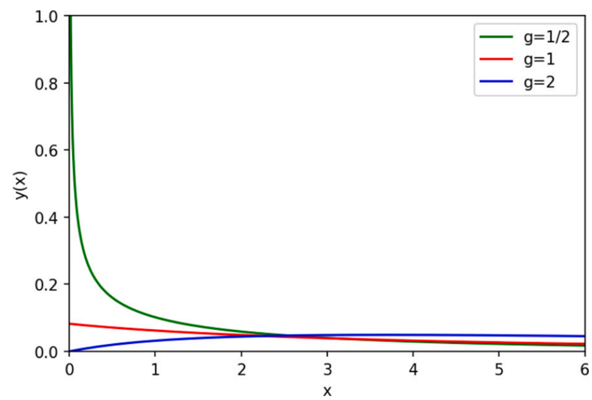

Fig. 5. Solution y given by (56) for $r = 0$, $\alpha = 3$, $\beta = 1.5$ and g= 0.5, 1 and 2.

Eqs. (58), (60) and (61) give

$$M(s) = K\cdot c^{-s-\frac{\nu}{2}}\cdot 2^{2s+\nu}\Gamma(s)\Gamma(s+\nu)\prod_{k=0}^{\infty}\left(1-\frac{1}{2\alpha^{s+k}}-\frac{1}{2\beta^{s+k}}\right). \tag{62}$$

We note that the infinite product in (62) has zeros at $s = 0, -1, -2, \ldots$, and $\Gamma(s)$ has poles at precisely these points. Consequently, the singularities appear only from the term $\Gamma(s+\nu)$, which are poles of order one and lie on the real line. The largest of these singularities is at $s = -\nu = \frac{1-g}{1-r}$. The function is thus meromorphic on $\mathbb{C}$ and holomorphic in the half plane $\mathrm{Re}(s) > \frac{1-g}{1-r}$.

Clearly, as $z \to 0^+$, $\Psi(z) \in O(z^\nu)$, where $\nu = \frac{g-1}{1-r}$. So that, $y(x) \in O\left(x^{\frac{g-(1+r-r^2)}{1-r}}\right)$. Consequently, if $g > 1+r-r^2$, the solution tends to 0 as $x \to 0^+$. Further, if $g = 1+r-r^2$, the solution equals a constant as $x \to 0^+$. Also, if $g < 1+r-r^2$, the solution tends to infinity as $x \to 0^+$ (see Figs. 4 and 5).

6. Conclusions

In this paper, we solved a cell division model (7)–(9) for certain choices of biologically realistic non-constant growth, division and dispersion rates of cells. In particular, we considered the coefficients

1. $D(x) = 0$, $G(x) = gx$ and $B(x) = bx^rH(x-\theta)$ for $\theta, b, g > 0$ and $r \in \mathbb{Z}^+$,
2. $D(x) = Dx^2$, $G(x) = gx$ and $B(x) = bx^rH(x-\theta)$, for $\theta, b, g, D > 0$ and $r \in \mathbb{Z}^+$,
3. $D(x) = Dx^{r+1}$, $G(x) = gx^r$ and $B(x) = b$ for $b, g, D > 0$ and $r < 1$,

and determined the eigenvalues and the corresponding eigenfunctions explicitly.

This first two cases are markedly different from the constant growth rate case ($D(x) = 0$, $G(x) = g$ and $B(x) = bH(x - \theta)$ for $\theta, b, g > 0$)[15] in which the solution entails an eigenvalue that is not determined explicitly. Under appropriate conditions, an expression for the eigenvalue is

$$\lambda = \frac{\int_0^\infty G(x)y(x)}{\int_0^\infty xy(x)}.$$

Since $G(x) = gx$ in Sections 3 and 4, the eigenvalue can be explicitly determined from the expression. The technique presented can be adapted for other choices of non-constant coefficients. The crux, however, is determining the eigenvalue explicitly.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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