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ASYMMETRICAL CELL DIVISION WITH EXPONENTIAL GROWTH

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Abstract

An advanced pantograph-type partial differential equation, supplemented with initial and boundary conditions, arises in a model of asymmetric cell division. Methods for solving such problems are limited owing to functional (nonlocal) terms. The separation of variables entails an eigenvalue problem that involves a nonlocal ordinary differential equation. We discuss plausible eigenvalues that may yield nontrivial solutions to the problem for certain choices of growth and division rates of cells. We also consider the asymmetric division of cells with linear growth rate which corresponds to "exponential growth" and exponential rate of cell division, and show that the solution to the problem is a certain Dirichlet series. The distribution of the first moment of the biomass is shown to be unimodal.

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1. Introduction

It is usual to structure cell populations, growing and dividing at the same time, on size (DNA content). The resulting mathematical model is typically a nonlocal partial differential equation (PDE). A simple size-structured model was developed by Sinko and Streifer [17] and later studied by Metz and Diekmann [13], Hall and Wake [6] and Heijmans [9] among others. The type of cell division determines the number of nonlocal terms in the corresponding equation modelling the cell growth and division process. A symmetric division of cells which produces equal-sized daughter cells leads to a PDE with one nonlocal term. Hall and Wake [6] formulated such a model, which was then studied by them [7], Basse et al. [2], Begg et al. [3] and Zaidi et al. [26].

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The model involves the nonlocal PDE

$$\frac{\partial}{\partial t}n(x,t) + \frac{\partial}{\partial x}(G(x,t)n(x,t)) = 4B(2x,t)n(2x,t) - B(x,t)n(x,t), \tag{1.1}$$

where the number density n, the growth rate $G > 0$ and the frequency of division $B > 0$ are functions of size $x > 0$ and time $t > 0$. The number 2 corresponds to the number of daughter cells produced when a cell divides. The nonlocal term arises from the kernel of a fragmentation coagulation equation. Specifically, it is assumed that a cell of size x divides to make two cells of size $x/2$. This leads to a kernel with a term of the form $B(\xi)2\delta(\xi/2 - x)$. The kernel is integrated from x to ∞. An alternative interpretation is given in Sinko and Streifer [17, 18].

Although many cells divide symmetrically, there are certain cell populations which divide asymmetrically. In an asymmetric mode of division, daughter cells of different sizes are produced when a cell divides. For instance, the fruitfly *Drosophila melanogaster* and the worms *Caenorhaabditis elegans (C. elegans)* undergo asymmetric cell division [14]. The asymmetric cell division model [19, 28] involves a first-order nonlocal PDE with two nonlocal terms, namely,

$$\frac{\partial}{\partial t}n(x,t) + \frac{\partial}{\partial x}(G(x,t)n(x,t)) = \alpha B(\alpha x,t)n(\alpha x,t) + \beta B(\beta x,t)n(\beta x,t) - B(x,t)n(x,t), \tag{1.2}$$

where $\alpha > 2 > \beta > 1$. The PDE (1.2) models asymmetric division of a cell of size x into two daughter cells of sizes x/α and x/β. Assuming a conservation of "size" (that is, no mass loss, or no DNA loss during division),

$$\frac{1}{\alpha} + \frac{1}{\beta} = 1. \tag{1.3}$$

Equations (1.1) and (1.2) are supplemented by the conditions

$$\lim_{x\to 0^+}(G(x,t)n(x,t)) = 0 \tag{1.4}$$

and

$$\lim_{x\to\infty}(G(x,t)n(x,t)) = 0 \tag{1.5}$$

for all $t \geq 0$. In addition, an initial condition

$$n(x,0) = n_0(x) \tag{1.6}$$

is prescribed, where n_0 is a probability distribution function satisfying (1.4) and (1.5).

Hall and Wake [6] considered separable solutions to equation (1.1) for the case of constant division and growth rates, and for the growth rate $G(x,t) = gx$, $g > 0$, and division rate $B(x,t) = bx^r$, $b > 0$ and $r > 0$ [7]. They noted that the choice of $G = gx$, $g > 0$, is "plausible biologically, and has been discussed in the biological literature". Van Brunt et al. [21] also noted the biological data that supports this choice of growth rate and its correspondence with "exponential growth". The "exponential" growth rate

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case was also studied by Powell [16] and Koch and Schaechter [12]. With this choice of G, Hall and Wake [7] considered an exponential rate of division which was a more general form of B as compared to that considered by Tyson and Diekmann [20].

The separable solutions are of the form $n(x,t) = e^{-\lambda t}y(x)$, where λ is a constant of separation and y satisfies

$$\frac{d}{dx}(G(x)y(x)) = -(B(x) - \lambda)y(x) + \alpha^2 B(\alpha x)y(\alpha x) \tag{1.7}$$

along with the conditions

$$\lim_{x\to 0^+}(G(x)y(x)) = 0, \tag{1.8}$$

$$\lim_{x\to \infty}(G(x)y(x)) = 0, \tag{1.9}$$

where $G(x,t) = G(x)$ and $B(x,t) = B(x)$. Equation (1.7), for constant division and growth rates, is the well-known pantograph equation. It arises in various physical and biological phenomena, such as absorption of light in the Milky Way [1], current collection of an electric train [15], a ruin problem [5] and a cell-growth model [4]. Kato and McLeod [11] and Iserles [10] gave a detailed analysis of the pantograph equation. Second-order generalizations of the first-order equation (1.7), arising in a cell-growth model, have been studied [23, 25, 27]. Nonconstant coefficients for equation (1.7) have also been discussed [22, 24]. For the asymmetric cell division, the extension of (1.7) yields

$$\frac{d}{dx}(G(x)y(x)) = -(B(x) - \lambda)y(x) + \alpha B(\alpha x)y(\alpha x) + \beta B(\beta x)y(\beta x) \tag{1.10}$$

along with the conditions (1.8) and (1.9). Equation (1.10) is also supplemented with the condition

$$\int_0^\infty y(x)\,dx = 1. \tag{1.11}$$

The assumption that biomass remains finite for all $t \geq 0$ yields

$$\int_0^\infty xy(x)\,dx < \infty.$$

The separable solutions can be written in the form $n(x,t) = N_0 e^{-\lambda t}y(x)$, where N_0 is the initial number of cells and y is a probability density function that is positive and unimodal. These solutions usually correspond to the long-time asymptotic solutions to (1.2)–(1.6), at least for constant coefficients. In the next section, we discuss certain values of λ that do not yield positive (nontrivial and) nonunimodal solutions to (1.10), subject to the conditions (1.8) and (1.9), for certain class of growth and division rates. In Section 3, we solve the boundary value problem (1.10), (1.8) and (1.9) for $G(x) = gx$, $g > 0$, and division rate $B(x) = bx^r$, $b > 0$ and $r > 0$. In Section 3.3, we show that the distribution of the first moment of the biomass, obtained in Section 3, is unimodal.

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2. Bounds on λ

We first discuss certain conditions on λ if (1.10) has a positive nontrivial solution. For certain choices of $G(x)$ and $B(x)$, the separable solutions are the "steady size distributions", and solutions to the nonlocal PDE (1.2), subject to the conditions (1.4)–(1.6), converge to the separable solutions for sufficiently large time. The experimental data also shows the evolution of the number density of cells to a certain "positive", "unimodal", constant shape for large time [8]. It is of interest to find values of λ that do not yield positive separable solutions. If y is a positive nontrivial solution to (1.10) that satisfies (1.8), (1.9) and (1.11), then there exists a positive global maximum M such that $y'(M) = 0$ and

$$G'(M)y(M) + (B(M) - \lambda)y(M) = \alpha B(\alpha M)y(\alpha M) + \beta B(\beta M)y(\beta M).$$

Since the right-hand side of the above equation is positive,

$$G'(M) + B(M) - \lambda > 0,$$

so that

$$\lambda < G'(M) + B(M). \tag{2.1}$$

Although B and G are known explicitly, the above bound on λ is of limited utility in general, since the global maximum 'M' of y may not be known without solving (1.10). However, (2.1) may be helpful in determining whether (1.10) does not have a positive nontrivial solution for a given λ for certain classes of growth and division rates. For instance, if $|G'| \le M_1$ and $|B| \le M_2$, for some positive real numbers M_1 and M_2, then $\lambda \le M_3$, where $M_3 = M_1 + M_2$. In particular, for the biologically relevant case $G(x) = g > 0$ and $B(x) = b > 0$, if y is a positive nontrivial solution to (1.10), then (2.1) yields

$$\lambda < b.$$

Consequently, any differential equation of the form (1.10) with $\lambda \ge b$ does not have a positive nontrivial solution.

Further, if y is a nontrivial solution to (1.10), then

$$\begin{aligned}(G'(M) + B(M) - \lambda)y(M) &= \alpha B(\alpha M)y(\alpha M) + \beta B(\beta M)y(\beta M)\\ &< (\alpha B(\alpha M) + \beta B(\beta M))y(M),\end{aligned}$$

so that

$$\lambda > G'(M) + B(M) - \alpha B(\alpha M) - \beta B(\beta M). \tag{2.2}$$

Also, integrating (1.10) from 0 to ∞ and using (1.8), (1.9) and (1.11) yields

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

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so that if y is a positive solution to (1.10), the above relation suggests that

$$\lambda < 0. \tag{2.3}$$

Consequently, any equation of the form (1.10) with $\lambda \geq 0$ does not have a positive (and a unimodal) solution.

If B is a decreasing function such that $B(x) > \alpha B(\alpha x) + \beta B(\beta x)$ for all $x > 0$, and if G is either a constant or an increasing function on $(0, \infty)$, then (2.2) yields

$$\lambda > 0.$$

Consequently, for this choice of G and B, any equation of the form (1.10) with $\lambda \leq 0$ does not have a nontrivial solution. Equation (2.3) implies that there cannot be a positive nontrivial solution to (1.10) that satisfies (1.11).

The above discussion is summarized in the following result.

THEOREM 2.1. *Let $y(x)$ to be a positive nontrivial solution to the problem* (1.8)–(1.11).

(1) *If $y(x)$ has a global maximum M, then $\lambda < \min(0, G'(M) + B(M))$.*
(2) *No solution exists if B is a decreasing function such that $B(x) > \alpha B(\alpha x) + \beta B(\beta x)$ for all $x > 0$ and if G is either a constant or an increasing function on $(0, \infty)$ ($\lambda > 0$ in this case, so* (1) *is not satisfied).*

3. Exponential growth case

In this section, we consider (1.10) for the growth rate $G(x) = gx$, $g > 0$, and the division rate $B(x, t) = bx^r$, $b > 0$ and $r > 0$. The transformation

$$y = \frac{\tilde{y}}{x^2}$$

converts the equation

$$\frac{d}{dx}(gxy(x)) + (B(x) - \lambda)y(x) = \alpha B(\alpha x)y(\alpha x) + \beta B(\beta x)y(\beta x)$$

to

$$gx\tilde{y}'(x) + (B(x) - \Lambda)\tilde{y}(x) = \frac{1}{\alpha}B(\alpha x)\tilde{y}(\alpha x) + \frac{1}{\beta}B(\beta x)\tilde{y}(\beta x),$$

where $\Lambda = \lambda + g$. Dropping the tildes reduces the above equation to

$$gxy'(x) + (B(x) - \Lambda)y(x) = \frac{1}{\alpha}B(\alpha x)y(\alpha x) + \frac{1}{\beta}B(\beta x)y(\beta x). \tag{3.1}$$

Equation (3.1) can be recast as

$$y'(x) + \tilde{B}(x)y(x) - \tilde{\Lambda}\frac{y(x)}{x} = \frac{1}{\alpha}\tilde{B}(\alpha x)y(\alpha x) + \frac{1}{\beta}\tilde{B}(\beta x)y(\beta x), \tag{3.2}$$

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where $\tilde{B}(x) = B(x)/gx$ and $\tilde{\Lambda} = \Lambda/g$. Also, the assumption that biomass remains finite for all $t \geq 0$ yields

$$\int_0^\infty \frac{y}{x}\,dx < \infty.$$

To determine the eigenvalue Λ, equation (3.2) can be integrated, using conditions (1.8) and (1.9), from 0 to ∞ with respect to x. This yields $\tilde{\Lambda} = 0$, so that

$$\Lambda = 0. \tag{3.3}$$

Consequently, $\lambda = -g$. Since λ is negative, Theorem 2.1 suggests that the possibility of the existence of a positive, nontrivial solution y cannot be precluded.

Equation (3.1) thus reduces to

$$gxy'(x) + bx^r y(x) = \frac{1}{\alpha} b\alpha^r x^r y(\alpha x) + \frac{1}{\beta} b\beta^r x^r y(\beta x). \tag{3.4}$$

3.1. A Mellin transform solution We first convert the differential equation (3.4) to an algebraic equation using Mellin transforms. Van Brunt and Vlieg-Hulstman [22] noted that Mellin transforms highlight the role of solutions to the associated local "homogeneous" equation

$$gxu'(x) + bx^r u(x) = 0. \tag{3.5}$$

Since the Mellin transform $M(s)$ of a function $y(x)$ is given by

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

the Mellin transform of equation (3.4), using (1.8) and (1.9), yields

$$-sgM(s) = \left(\frac{1}{\alpha^{s+1}} + \frac{1}{\beta^{s+1}} - 1\right) M(s + r). \tag{3.6}$$

Also, condition (1.11) implies that

$$M(1) = 1. \tag{3.7}$$

We seek solutions to (3.6) of the form

$$M(s) = K(s)F(s), \tag{3.8}$$

where $K(s)$ is the Mellin transform of the solution u to the homogeneous "local" equation (3.5) and satisfies the equation

$$-sgK(s) + bK(s + r) = 0 \tag{3.9}$$

and F is a function to be determined. Since (3.5) is a "local" equation, the solution u to (3.5) is given by

$$u(x) = ce^{-(b/g)(x^r/r)}$$

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for some constant c, so that the Mellin transform of u yields

$$K(s) = \frac{c}{r}\left(\frac{b}{rg}\right)^{-s/r}\Gamma\left(\frac{s}{r}\right). \tag{3.10}$$

The function F can be determined using equations (3.6) and (3.9). This gives

$$-sgK(s)F(s) = \left(\frac{1}{\alpha^{s+1}} + \frac{1}{\beta^{s+1}} - 1\right)K(s+r)F(s+r),$$

which, using (3.9), yields the recursive relation

$$F(s) = -\left(\frac{1}{\alpha^{s+1}} + \frac{1}{\beta^{s+1}} - 1\right)F(s+r),$$

so that

$$F(s) = \prod_{k=0}^{\infty}\left(1 - \frac{1}{\alpha^{s+1+kr}} + \frac{1}{\beta^{s+1+kr}}\right). \tag{3.11}$$

Consequently, equations (3.8), (3.10) and (3.11) give

$$M(s) = \frac{c}{r}\left(\frac{b}{rg}\right)^{-s/r}\Gamma\left(\frac{s}{r}\right)\prod_{k=0}^{\infty}\left(1 - \frac{1}{\alpha^{s+1+kr}} + \frac{1}{\beta^{s+1+kr}}\right). \tag{3.12}$$

The products in (3.12) have zeros of order one, and the Γ function has poles of order one, at the points $s = -\nu r$, where ν is a nonnegative integer. Consequently, the function $M(s)$ is entire.

3.2. A probability density function solution The product in equation (3.12) can be expressed as a double power series in α^s and β^s. This prompts us to seek a solution to (3.4) of the form

$$y(x) = \sum_{k=0}^{\infty}\sum_{j=0}^{\infty} d_{k,j}\exp\left(-\alpha^{rk}\beta^{rj}\frac{b}{g}\frac{x^r}{r}\right), \tag{3.13}$$

where $d_{k,j}$ are to be determined. Equation (3.13) gives

$$y'(x) = \sum_{k=0}^{\infty}\sum_{j=0}^{\infty} d_{k,j}\left(-\alpha^{rk}\beta^{rj}\frac{b}{g}\right)c_{k,j}\exp\left(-\alpha^{rk}\beta^{rj}\frac{b}{g}\frac{x^r}{r}\right)x^{r-1},$$

$$y(\alpha x) = \sum_{k=0}^{\infty}\sum_{j=0}^{\infty} d_{k,j}\exp\left(-\alpha^{r(k+1)}\beta^{rj}\frac{b}{g}\frac{x^r}{r}\right),$$

$$y(\beta x) = \sum_{k=0}^{\infty}\sum_{j=0}^{\infty} d_{k,j}\exp\left(-\alpha^{rk}\beta^{r(j+1)}\frac{b}{g}\frac{x^r}{r}\right),$$

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so that

$$g\sum_{k=0}^{\infty}\sum_{j=0}^{\infty}\Big(-\alpha^{rk}\beta^{rj}\frac{b}{g}\Big)d_{k,j}\exp\Big(-\alpha^{rk}\beta^{rj}\frac{b}{g}\frac{x^r}{r}x^r\Big)+b\sum_{k=0}^{\infty}\sum_{j=0}^{\infty}d_{k,j}\exp\Big(-\alpha^{rk}\beta^{rj}\frac{b}{g}\frac{x^r}{r}x^r\Big)$$
$$=b\alpha^{r-1}\sum_{k=0}^{\infty}\sum_{j=0}^{\infty}d_{k,j}\exp\Big(-\alpha^{r(k+1)}\beta^{rj}\frac{b}{g}\frac{x^r}{r}\Big)x^r$$
$$+b\beta^{r-1}\sum_{k=0}^{\infty}\sum_{j=0}^{\infty}d_{k,j}\exp\Big(-\alpha^{rk}\beta^{r(j+1)}\frac{b}{g}\frac{x^r}{r}\Big)x^r.$$

Equating coefficients yields

$$d_{k,0}=\frac{(-1)^k\alpha^{rk}}{\alpha^k\prod_{s=1}^{k}(\alpha^{rs}-1)}d_{0,0},$$
$$d_{0,j}=\frac{(-1)^j\beta^{rj}}{\beta^j\prod_{s=1}^{j}(\beta^{rs}-1)}d_{0,0},$$
$$d_{k,j}=\frac{-1}{(\alpha^{rk}\beta^{rj}-1)}(\alpha^{r-1}d_{k-1,j}+\beta^{r-1}jd_{k,j-1})$$

for $k,j\in\mathbb{N}$, and $d_{0,0}$ is chosen so that $\int_0^\infty(y/x^2)\,dx=1$. The analysis used by Suebcharoen et al. [19] can be employed to prove the uniqueness and positivity of the solution y, and the analysis of Zaidi et al. [27] can be mimicked to establish the convergence of (3.13).

3.3. Unimodality Zaidi et al. [28] determined the solution ψ to equation (1.10) for the constant-coefficients case $G(x)=g$, $B(x)=b$, $b>0, g>0$, as a certain Dirichlet series. They also established the unimodality of ψ (see Figure 1). The unimodality of the solution y to equation (3.4) does not follow from the unimodality of ψ. Certain arguments valid in the analysis of unimodality of ψ break down in the case of unimodality of y. Here, we show that y is unimodal (see Figure 2). Note that the conditions (1.8) and (1.9) and the smoothness of y imply that y must have at least one positive maximum. To prove that y is unimodal, we suppose on the contrary that y is a positive solution to equation (3.4) that is not unimodal. Let m and M be the largest values of x at which y has a minimum and a maximum, respectively. We refer to these as the last local minimum and last local maximum, respectively. Since

$$y(m)>0,\quad y(M)>0\quad\text{and}\quad y'(m)=0=y'(M),$$

equation (3.4) implies that

$$y(m)=\alpha^{r-1}y(\alpha m)+\beta^{r-1}y(\beta m)\tag{3.14}$$

and

$$y(M)=\alpha^{r-1}y(\alpha M)+\beta^{r-1}y(\beta M).\tag{3.15}$$

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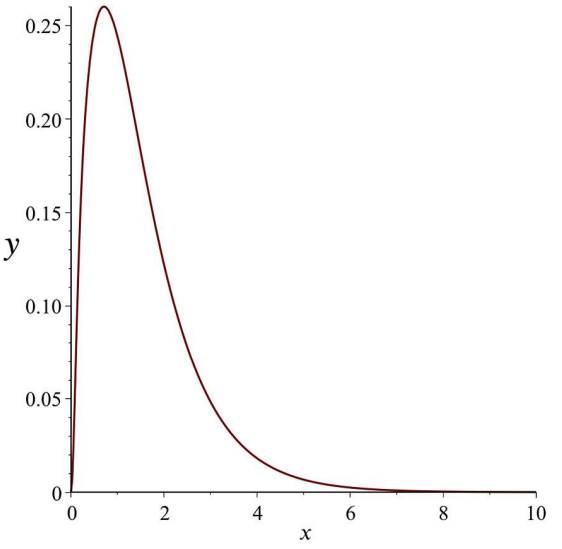


FIGURE 1. The solution to equation (1.10) for the constant-coefficients case. Here, $g = 1$, $b = 1$, $\alpha = 3$, $\beta = 3/2$ and $r = 2$.

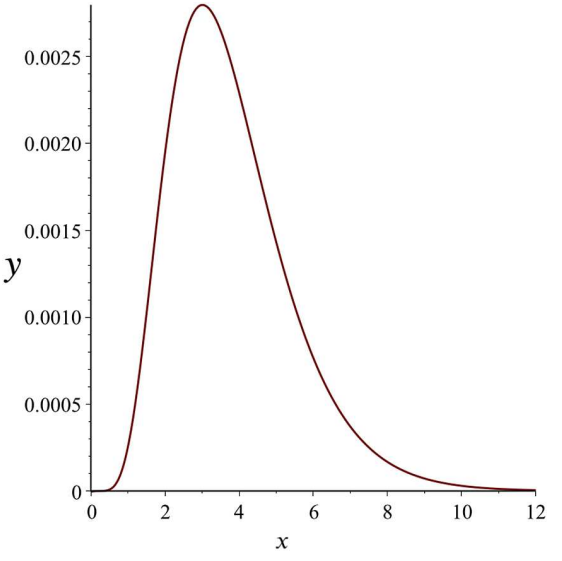


FIGURE 2. The solution to (3.4) given by (3.13) for $g = 1$, $b = 1$, $\alpha = 3$, $\beta = 3/2$ and $r = 0.5$.

We first establish unimodality of y for $0 < r < 1$. To establish this, we first show that $y(\alpha m)$ and $y(\beta m)$ cannot be greater than $y(\alpha M)$ and $y(\beta M)$, respectively. To prove this, we suppose on the contrary that

$$y(\alpha m) > y(\alpha M) \quad \text{and} \quad y(\beta m) > y(\beta M).$$

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Equation (3.15) implies that

$$\begin{aligned} y(M) &= \alpha^{r-1} y(\alpha M) + \beta^{r-1} y(\beta M) \\ &< \alpha^{r-1} y(\alpha m) + \beta^{r-1} y(\beta m), \end{aligned}$$

which, using (3.14), yields

$$y(M) < y(m).$$

This contradicts the fact that m and M are the last local minimum and the last local maximum, respectively.

We now show that if $y(\alpha m)$ is greater than $y(\alpha M)$, then $y(\beta m)$ cannot be less than $y(\beta M)$. To establish this, we assume on the contrary that

$$\begin{aligned} y(\alpha m) &> y(\alpha M), \\ y(\beta m) &< y(\beta M). \end{aligned} \tag{3.16}$$

Now $\beta m < \beta M$ and y is decreasing after M; hence,

$$m < \beta m < M < \beta M,$$

so that

$$y(\beta m) > y(m). \tag{3.17}$$

Equation (3.15) and inequality (3.16) give

$$\begin{aligned} y(M) &= \alpha^{r-1} y(\alpha M) + \beta^{r-1} y(\beta M) \\ &< \alpha^{r-1} y(\alpha m) + \beta^{r-1} y(\beta M). \end{aligned} \tag{3.18}$$

Adding and subtracting $\beta^{r-1} y(\beta m)$ to inequality (3.18) yields

$$y(M) < \alpha^{r-1} y(\alpha m) + \beta^{r-1} y(\beta M) + \beta^{r-1} y(\beta m) - \beta^{r-1} y(\beta m),$$

which, using (3.14), yields

$$y(M) - y(m) < \beta^{r-1} [y(\beta M) - y(\beta m)] \tag{3.19}$$

and, since $0 < r < 1$ and $\beta > 1$, $\beta^{r-1} < 1$, inequalities (3.19) and (3.17) imply that

$$\begin{aligned} y(M) - y(m) &< y(\beta M) - y(\beta m) \\ &< y(\beta M) - y(m), \end{aligned}$$

so that

$$y(M) < y(\beta M).$$

This contradicts the fact that M is the last local maximum.

Finally, we show that $y(\beta m)$ and $y(\alpha m)$ cannot be less than $y(\beta M)$ and $y(\alpha M)$, respectively. To prove this, we suppose on the contrary that

$$y(\alpha m) < y(\alpha M) \tag{3.20}$$

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and

$$y(\beta m) < y(\beta M). \tag{3.21}$$

Since y is decreasing after the last local maximum, inequalities (3.20) and (3.21) imply that

$$m < \beta m < \alpha m < M,$$

so that

$$y(\beta m) > y(m), \tag{3.22}$$
$$y(\alpha m) > y(m). \tag{3.23}$$

Equation (3.14) and inequalities (3.22) and (3.23) imply that

$$\begin{aligned} y(m) &= \alpha^{r-1} y(\alpha m) + \beta^{r-1} y(\beta m) \\ &> \alpha^{r-1} y(m) + \beta^{r-1} y(m). \end{aligned}$$

Consequently,

$$[1 - (\alpha^{r-1} + \beta^{r-1})] y(m) > 0. \tag{3.24}$$

For $0 < r < 1$ such that $\alpha^{r-1} + \beta^{r-1} \geq 1$, inequality (3.24) yields a contradiction since $y(m) > 0$. However, for $0 < r < 1$ such that $\alpha^{r-1} + \beta^{r-1} < 1$, inequality (3.24) holds, but then equation (3.15), inequalities (3.20) and (3.21), and the fact that y is decreasing after the last local maximum give

$$\begin{aligned} y(M) &= \alpha^{r-1} y(\alpha M) + \beta^{r-1} y(\beta M) \\ &< \alpha^{r-1} y(M) + \beta^{r-1} y(M) \\ &< (\alpha^{r-1} + \beta^{r-1}) y(M). \end{aligned}$$

Also, since $\alpha^{r-1} + \beta^{r-1} < 1$, the above inequality implies that

$$y(M) < 0,$$

which contradicts the fact that y is positive. This shows that y is unimodal for $0 < r < 1$.

We now establish the unimodality of y for $r \geq 1$. Since $r \geq 1$ and $\alpha > 2 > \beta > 1$, equation (3.14) implies that

$$y(m) > y(\alpha m) \tag{3.25}$$

and

$$y(m) > y(\beta m). \tag{3.26}$$

Inequalities (3.25) and (3.26) imply that

$$m < M < \beta m < \alpha m \tag{3.27}$$

and, since y is decreasing after M, (3.27) implies that

$$y(\alpha m) > y(\alpha M) \tag{3.28}$$

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and

$$y(\beta m) > y(\beta M). \tag{3.29}$$

Equation (3.15) and inequalities (3.28) and (3.29) yield

$$\begin{aligned} y(M) &= \alpha^{r-1} y(\alpha M) + \beta^{r-1} y(\beta M) \\ &< \alpha^{r-1} y(\alpha m) + \beta^{r-1} y(\beta m), \end{aligned}$$

which, using (3.14), gives

$$y(M) < y(m).$$

This contradicts the fact that m and M are the last local minimum and the last local maximum, respectively.

This shows that y is unimodal for all $r > 0$ and for all $\alpha > 2 > \beta > 1$.

4. Conclusions

The separable solutions usually correspond to the long-time asymptotic solutions to the cell-growth model, at least for constant coefficients. A key feature is that the number density of cells attains a certain "constant", positive, unimodal shape for large time for any initial distribution. We find certain values of λ that do not yield such a shape. We then consider the cell-growth equation for exponential rate of division and linear growth rate and find separable solutions to the problem. The unique solution to this equation is a double Dirichlet series, which is positive and convergent. Although the solution technique involving the transformations is limited to this specific case, it can be used as a guide for equations involving more general coefficients and higher order derivatives. The eigenvalue problems such as (1.10), for more general coefficients, remain to be investigated. This will be the work for future papers.

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