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A second-order numerical method for a cell population model with asymmetric division

O. Angulo [a,*], J.C. López-Marcos [b], M.A. López-Marcos [b]

[a] Departamento de Matemática Aplicada e IMUVA, ETSIT, Universidad de Valladolid, Pso. Belén 5, 47011 Valladolid, Spain

[b] Departamento de Matemática Aplicada e IMUVA, Facultad de Ciencias, Universidad de Valladolid, Pso. Belén 7, 47011 Valladolid, Spain

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Population balance models represent an accurate and general way of describing the complicated dynamics of cell growth. In this paper we study the numerical integration of a model for the evolution of a size-structured cell population with asymmetric division. We present and analyze a novel and efficient second-order numerical method based on the integration along the characteristic curves. We prove the optimal rate of convergence of the scheme and we ratify it by numerical simulation. Finally, we show that the numerical scheme serves as a valuable tool in order to approximate the stable size distribution of the model.

1. Introduction

In the framework of the continuum modeling of cell kinetics, cell population balance models have become the most important theoretical tool for describing the proliferation of cells taking place in a cell culture. These ones can be included in the so-called structured population models which describe the evolution of a population by means of the vital properties of individuals (growth, fertility, mortality, division, etc.). Such intrinsic physiological state rates depend on individual characteristics (such as age or size) which structure the population. Cell population balance models were considered for the first time in the sixties (see, for example, [1,2]) and were developed rapidly [3–5]. In recent years, they have evolved towards more complicated models: several structuring variables, various populations (describing, for example, proliferating and quiescent cells or the different stages in a cell-cycle), nonlinear problems (with the consumption of a limited extracellular medium), inverse problems to compute the vital functions [6–9].

When reproduction occurs by fission it seems appropriate to take into account the size of individuals (by which we mean any relevant quantity, like mass, volume, weight, protein or DNA content, etc.). In this work, we suppose that cells are only distinguished in terms of this physiological characteristic. The model that arises due to this simplification is still useful in order to analyze and understand the cell population dynamics. Cell size varies over time, and maturation can be simulated

* Corresponding author. Tel.: +34 983 423000(Ext: 5835); fax: +34 983 423661.
E-mail addresses: oscar@mat.uva.es (O. Angulo), lopezmar@mac.uva.es (J.C. López-Marcos), malm@mac.uva.es (M.A. López-Marcos).

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assuming its increase with the cell-life cycle. To be precise, we consider the cell population balance model proposed by Ramkrishna [10] which considers reproduction by fission into two daughter cells with different size.

Theoretical properties of the models such as existence, uniqueness, smoothness of solutions, long-time behavior (with the study of steady states and their stability) could be studied without a solution expression. However, the knowledge of their qualitative or quantitative behavior in a more tangible way is sometimes necessary. Therefore, numerical methods provide a valuable tool to obtain such information. In the case of general structured population models, many numerical methods have been proposed to solve them (see [11,12] and references therein). In the case of cell population balance models different techniques have been used (see [13] and the references therein). However, it is very important to design numerical schemes specially adapted to the characteristics of cell population balance models.

Moreover, one of the most important issues in the modelization is whether or not a stable size distribution exists, and many efforts were directed towards describing the most general models which still exhibit a stable type distribution property [14].

In this work we present a second-order characteristics method, based on the numerical scheme developed and analyzed in [13] for the symmetric division case. It is based on the discretization of the integral representation of the solution to the problem along the characteristic curves. Second-order methods maintain a good compromise between the required smoothness of the vital functions based on realistic biological data and the efficiency of the numerical schemes.

In Section 2 we introduce the model and Section 3 is devoted to the description of the proposed numerical method. In Section 4 we analyze the convergence of the numerical scheme, and in Section 5 we carry out a representative numerical simulation, including the approximation of the stable size distribution of the model.

2. The model

We consider a nonnegative minimum cell-size $x_{\min}$ and a maximal size, normalized to 1, at which point every cell might divide or die, so $0 \le x_{\min} < 1$. We also assume that the environment is unlimited and all possible nonlinear mechanisms are ignored.

The problem is given by a conservation law

$$u_t(x,t) + (g(x)\,u(x,t))_x = -\mu(x)\,u(x,t) - b(x)\,u(x,t) + 2\int_x^1 b(s)\,P(x,s)u(s,t)\,ds,$$
$$x_{\min} < x < 1,\ t > 0, \tag{2.1}$$

a boundary condition

$$u\,(x_{\min},t) = 0, \quad t > 0, \tag{2.2}$$

and an initial size distribution

$$u(x,0) = \varphi(x), \quad x_{\min} \le x \le 1. \tag{2.3}$$

The independent variables x and t represent size and time, respectively. The dependent variable $u(x,t)$ is the size-specific density of cells with size x at time t. The size of any individual varies according to the following ordinary differential equation

$$\frac{dx}{dt} = g(x).$$

The nonnegative functions g, μ and b represent the growth, mortality and division rate, respectively. These are usually called the vital functions and define the life history of the individuals. Note that all of them only depend on the size x (the internal structuring variable). In this case, we also assume that $g(x) > 0$ for $x < 1$.

The dispersion of sizes at division amongst the two daughter cells (unequal division) is defined in terms of the partitioning function $P(x,y)$, a probability density function which gives the distribution of the size of a daughter-cell x when the size of the mother is equal to y. Thus $\int_{x_1}^{x_2} P(x,y)\,dx$ gives the probability for a daughter cell to have size in the interval (x_1,x_2) knowing that the mother had the size y. Such a distribution verifies the following conditions:

$$\int_{x_{\min}}^1 P(x,y)\,dx = 1, \qquad P(x,y) = P(y-x,y), \qquad P(x,y) = 0, \quad x \ge y.$$

In an extreme case, if two daughter cells from a mother cell are always identical (equal fission), the partitioning function reduces to the Dirac delta function $P(x,y) = \delta(x - y/2)$, leading to the model proposed by Diekmann et al. [15].

In accordance with the accepted biological point of view, there exists a maximum size. This means that cells will divide or die with probability one before reaching it. To this end, if μ and b are positive and bounded functions, we consider a growth function, introduced by Von Bertalanffy, satisfying $\lim_{x\to 1} \int_{x_{\min}}^{x} \frac{ds}{g(s)} = +\infty$. Note that if g is a continuous function defined in $[x_{\min}, 1]$ then this hypothesis implies that $g(1) = 0$. Thus, the solution to the problem will satisfy $u(1,t) = 0$, $t > 0$, so we suppose that initially there are no cells of maximum size [16].

3. Numerical method

In [17], a useful first-order scheme was proposed to obtain the solution to a generalization of (2.1)–(2.3) when the vital functions involved in the problem depend on an abiotic environment that changes with time. The method proposed in that work was based on the discretization of the ordinary differential equations that satisfies the solution along the characteristic curves. It is known that a low-order of convergence would produce a lack of efficiency which could be reduced with higher order methods. However, the smoothness of the solution to (2.1)–(2.3) is not as high as these last schemes demand. Thus, second-order methods present a good balance: they enhance the efficiency even with a lack of regular data.

In [13], we developed a novel second-order characteristics method based on the discretization of the integral representation of the solution to the problem along the characteristic curves for the equal fission model. Here we present an adaptation of this method to the more general asymmetric division case.

Therefore, we define $\mu^*(x) = g'(x) + \mu(x) + b(x)$ and denote by $x(t; t_*, x_*)$ the characteristic curve of Eq. (2.1) which takes the value x_* at the time instant t_*. It is the solution to the initial value problem

$$\begin{cases} \dfrac{d}{dt} x(t; t_*, x_*) = g(x(t; t_*, x_*)), \quad t > t_*, \\ x(t_*; t_*, x_*) = x_*. \end{cases} \tag{3.1}$$

In this way, the solution to (2.1) along a characteristic curve is given by

$$u(x(t; t_*, x_*), t) = u(x_*, t_*) \exp\left\{ -\int_{t_*}^{t} \mu^*(x(\tau; t_*, x_*))\, d\tau \right\}$$
$$+ 2\int_{t_*}^{t} \left[\exp\left\{ -\int_{\tau}^{t} \mu^*(x(s; t_*, x_*))\, ds \right\} \int_{x(\tau; t_*, x_*)}^{1} b(\sigma) P(x(\tau; t_*, x_*), \sigma) u(\sigma, \tau) d\sigma \right] d\tau, \quad t \geq t_*. \tag{3.2}$$

Note that, in this new layout, we have to solve two types of problems: the integration of the equation which defines the characteristic curves (3.1) and the solution to Eqs. (3.2) which provides the solution to the problem along those characteristics. We use discretization procedures in order to solve them.

We consider the numerical integration of model (2.1)–(2.3) along the time interval $[0, T]$. Thus, given a positive integer N, we define $k = \frac{T}{N}$ and introduce the discrete time levels $t^n = n\,k$, $0 \leq n \leq N$. We begin with the integration of (3.1) which provides the grid of the method on the cell-size variable. This grid is nonuniform and invariant with time because the growth rate function is, explicitly, independent of the time variable. However, note that it depends on time implicitly conditioned on cell size. It is usually called the *natural grid* [11]. In this work, we approximate such a grid by using a second-order scheme for the numerical integration of (3.1): the modified Euler method providing

$$\begin{aligned} &x_0 = x_{\min}, \\ &x_{j+1} = x_j + \frac{k}{2}\left(g(x_j) + g(x_j + k g(x_j)) \right), \quad 0 \leq j \leq J-1. \end{aligned} \tag{3.3}$$

Integer J represents the index of the last grid point computed at the size interval and is chosen in order to satisfy the condition $K_0\,k < 1 - x_J \leq K_1\,k$, with K_0 and K_1 suitable constants (we refer to [11] for further details). Note that the points (x_j, t_n) and (x_{j+1}, t_{n+1}), $0 \leq j \leq J-1$, $0 \leq n \leq N-1$, belong to the same numerical characteristic curve. Finally, we fix the last grid point $x_{J+1} = 1$.

Then, denoting $u_j^n = u(x_j, t^n)$, $0 \leq j \leq J+1$, $0 \leq n \leq N$, let U_j^n be a numerical approximation to u_j^n. We propose a one-step method in order to obtain it. Therefore, starting from an approximation to the initial data (2.3) of the problem, for example, the grid restriction of the function φ, the numerical solution at a new time level is described in terms of the previous one. Such a general step is obtained by means of the following second-order discretization of (3.2). For $0 \leq n \leq N-1$,

$$U_{j+1}^{n+1} = \exp\left\{ -\frac{k}{2}\left(\mu^*(x_j) + \mu^*(x_{j+1}) \right) \right\} \left(U_j^n + k\,\mathcal{Q}_k^j(\mathbf{b}\cdot\mathbf{P}^j\cdot\mathbf{U}^n) \right) + k\,\mathcal{Q}_k^{j+1}(\mathbf{b}\cdot\mathbf{P}^{j+1}\cdot\mathbf{U}^{n+1}), \quad 0 \leq j \leq J-1. \tag{3.4}$$

In the previous expression, $\mathcal{Q}_k^l(\mathbf{V})$ represents a quadrature rule to approximate the integral over the interval $[x_l, 1]$, $0 \leq l \leq J$ of the function with grid values $\mathbf{V} = [V_0, \ldots, V_{J+1}]$. In this case $\mathbf{b}$, $\mathbf{P}^l$ and $\mathbf{U}^m$, represent the vectors with components $[b(x_0), \ldots, b(x_{J+1})]$, $[P(x_l, x_0), \ldots, P(x_l, x_{J+1})]$ and $[U_0^m, \ldots, U_{J+1}^m]$, respectively, and products $\mathbf{b}\cdot\mathbf{P}^l\cdot\mathbf{U}^m$, $0 \leq l \leq J$, $0 \leq m \leq N$ must be interpreted component-wise. Here, a second order quadrature formula is appropriate. However, it should be noted that the magnitude of J is not determined with respect to k. So, in order to decrease the computational effort, it is useful to consider a quadrature rule over a suitable subgrid $\{x_{j_m}\}_{m=0}^{M+1}$, of the grid defined by (3.3), with $M = O(k^{-1})$ nodes. To this end, we construct a subgrid $\{x_{j_m}\}_{m=0}^{M+1}$ such that $x_{j_0} = 0$, $x_{j_{M+1}} = 1$, and

$$C_0\,k \leq x_{j_{l+1}} - x_{j_l} \leq C_1\,k, \quad 0 \leq l \leq M,$$

where C_0 and C_1 are positive constants irrespective of k (for more details we refer to [11]). Finally, for this problem, we propose the following composite trapezoidal quadrature rule on the previous subgrid, modified in the first subinterval by means of the rectangle formula

$$\mathcal{Q}_k^l(\mathbf{V}) = (x_{j_{m_l}} - x_l)\, V_{j_{m_l}} + \sum_{m=m_l}^{M} \frac{x_{j_{m+1}} - x_{j_m}}{2} \left(V_{j_m} + V_{j_{m+1}}\right), \tag{3.5}$$

where $x_{j_{m_l}}$ is the first node of the subgrid satisfying $x_{j_m} \geq x_l$.

Obviously, the approximating values at the minimum and maximum sizes are

$$U_0^{n+1} = U_{J+1}^{n+1} = 0. \tag{3.6}$$

The numerical procedure seems to be implicit. However, if we compute the approximations at the new time level t^{n+1} downwards (that is, first U_{J+1}^{n+1} using (3.6), then U_{j+1}^{n+1} from $J-1$ to 0 using (3.4), and finally U_0^{n+1} using (3.6) again), it results in an explicit procedure. The reason is that the right hand side values in (3.4) corresponding to the time t^{n+1} are either zero or previously computed.

4. Convergence analysis

In this section, we carry out the convergence analysis of the scheme. It is based on the property of consistency of the method.

If u is the solution to problem (2.1)–(2.3), we define

$$\mathbf{u}^n = (u_0^n, u_1^n, \ldots, u_{J+1}^n), \qquad u_j^n = u(x_j, t^n), \quad 0 \leq j \leq J+1,\ 0 \leq n \leq N.$$

The *local discretization error*, $\boldsymbol{\tau}^{n+1} = (\tau_0^{n+1}, \tau_1^{n+1}, \ldots, \tau_{J+1}^{n+1})$, $0 \leq n \leq N-1$ is given by

$$\begin{aligned} \tau_{j+1}^{n+1} &= \frac{1}{k}\left(u_{j+1}^{n+1} - \exp\left\{-\frac{k}{2}\left(\mu^*(x_j) + \mu^*(x_{j+1})\right)\right\}\left(u_j^n + k\,\mathcal{Q}_k^j(\mathbf{b}\cdot\mathbf{P}^j\cdot\mathbf{u}^n)\right) - k\,\mathcal{Q}_k^{j+1}(\mathbf{b}\cdot\mathbf{P}^{j+1}\cdot\mathbf{u}^{n+1})\right), \\ &\quad 0 \leq j \leq J-1, \\ \tau_0^{n+1} &= \tau_{J+1}^{n+1} = 0. \end{aligned} \tag{4.1}$$

For a vector $\mathbf{v} = (v_0, v_1, \ldots, v_{J+1})$, we denote by $\|\mathbf{v}\|_\infty$ its maximum norm.

From now on, C will denote a positive constant which is independent of k, $n\,(0 \leq n \leq N)$ and $j\,(0 \leq j \leq J+1)$; C possibly has different values in different places.

Lemma 1. *Let g be three times continuously differentiable, functions μ, $b\cdot P$ and u be two times continuously differentiable. Then, as $k \to 0$, the following estimates hold*

$$\|\boldsymbol{\tau}^{n+1}\|_\infty = O(k^2), \quad 0 \leq n \leq N-1. \tag{4.2}$$

Proof. From (4.1), we obtain

$$\begin{aligned} |\tau_{j+1}^{n+1}| \leq{}& \frac{1}{k}\left|u_{j+1}^{n+1} - u\left(x\left(t^{n+1}; t^n, x_j\right), t^{n+1}\right)\right| + \frac{1}{k}\left|u\left(x\left(t^{n+1}; t^n, x_j\right), t^{n+1}\right) - k\,\mathcal{Q}_k^{j+1}(\mathbf{b}\cdot\mathbf{P}^{j+1}\cdot\mathbf{u}^{n+1})\right. \\ &\left. - \exp\left\{-\frac{k}{2}\left(\mu^*(x_j) + \mu^*(x_{j+1})\right)\right\}\left(u_j^n + k\,\mathcal{Q}_k^j(\mathbf{b}\cdot\mathbf{P}^j\cdot\mathbf{u}^n)\right)\right|, \end{aligned} \tag{4.3}$$

$0 \leq j \leq J-1, 0 \leq n \leq N-1$.

With respect to the first term on the right-hand side of (4.3), assuming the smoothness of u and g and taking into account that the numerical grid is computed by the modified Euler method, we conclude that

$$\left|u_{j+1}^{n+1} - u\left(x\left(t^{n+1}; t^n, x_j\right), t^{n+1}\right)\right| \leq C\,k^3. \tag{4.4}$$

On the other hand, if we observe the second term on the right-hand side of (4.3), the formula (3.2) allows us to write

$$\begin{aligned} &\left|u\left(x\left(t^{n+1}; t^n, x_j\right), t^{n+1}\right) - k\,\mathcal{Q}_k^{j+1}(\mathbf{b}\cdot\mathbf{P}^{j+1}\cdot\mathbf{u}^{n+1}) - \exp\left\{-\frac{k}{2}\left(\mu^*(x_j) + \mu^*(x_{j+1})\right)\right\}\left(u_j^n + k\,\mathcal{Q}_k^j(\mathbf{b}\cdot\mathbf{P}^j\cdot\mathbf{u}^n)\right)\right| \\ &\quad \leq \left|u_j^n\right|\left|\exp\left\{-\int_{t^n}^{t^{n+1}} \mu^*\left(x\left(\tau; t^n, x_j\right)\right)\,d\tau\right\} - \exp\left\{-\frac{k}{2}\left(\mu^*(x_j) + \mu^*(x_{j+1})\right)\right\}\right| \end{aligned}$$

$$+\left|2\int_{t^n}^{t^{n+1}}\exp\left\{-\int_{\tau}^{t^{n+1}}\mu^*\left(x\left(s;t^n,x_j\right)\right)\,ds\right\}\left(\int_{x(\tau;t^n,x_j)}^{1}b(\sigma)\,P(x(\tau;t^n,x_j),\sigma)\,u(\sigma,\tau)\,d\sigma\right)d\tau\right.$$
$$\left.-k\left(\exp\left\{-\frac{k}{2}\left(\mu^*\left(x_j\right)+\mu^*\left(x_{j+1}\right)\right)\right\}\mathcal{Q}_k^j(\mathbf{b}\cdot\mathbf{P}^j\cdot\mathbf{u}^n)+\mathcal{Q}_k^{j+1}(\mathbf{b}\cdot\mathbf{P}^{j+1}\cdot\mathbf{u}^{n+1})\right)\right|. \tag{4.5}$$

Thus, we use the regularity of functions μ, $b\cdot P$ and g, the convergence properties of the trapezoidal quadrature rule and the modified Euler method to obtain

$$\begin{aligned}
&\left|\exp\left\{-\int_{t^n}^{t^{n+1}}\mu^*\left(x\left(\tau;t^n,x_j\right)\right)\,d\tau\right\}-\exp\left\{-\frac{k}{2}\left(\mu^*\left(x_j\right)+\mu^*\left(x_{j+1}\right)\right)\right\}\right|\\
&\le\left|\exp\left\{-\int_{t^n}^{t^{n+1}}\mu^*\left(x\left(\tau;t^n,x_j\right)\right)\,d\tau\right\}-\exp\left\{-\frac{k}{2}\left(\mu^*\left(x_j\right)+\mu^*\left(x\left(t^{n+1};t^n,x_j\right)\right)\right)\right\}\right|\\
&\quad+\exp\left\{-\frac{k}{2}\mu^*\left(x_j\right)\right\}\left|\exp\left\{-\frac{k}{2}\mu^*\left(x\left(t^{n+1};t^n,x_j\right)\right)\right\}-\exp\left\{-\frac{k}{2}\mu^*\left(x_{j+1}\right)\right\}\right|\\
&\le C\,\left(k^3+k\left|\mu^*\left(x\left(t^{n+1};t^n,x_j\right)\right)-\mu^*\left(x_{j+1}\right)\right|\right)\\
&\le C\,k^3.
\end{aligned}\tag{4.6}$$

Next, we bound the second part on the right-hand side of (4.5) as

$$\begin{aligned}
&\left|2\int_{t^n}^{t^{n+1}}\exp\left\{-\int_{\tau}^{t^{n+1}}\mu^*\left(x\left(s;t^n,x_j\right)\right)\,ds\right\}\left(\int_{x(\tau;t^n,x_j)}^{1}b(\sigma)\,P(x(\tau;t^n,x_j),\sigma)\,u(\sigma,\tau)\,d\sigma\right)d\tau\right.\\
&\quad\left.-k\left(\exp\left\{-\frac{k}{2}\left(\mu^*\left(x_j\right)+\mu^*\left(x_{j+1}\right)\right)\right\}\mathcal{Q}_k^j(\mathbf{b}\cdot\mathbf{P}^j\cdot\mathbf{u}^n)+\mathcal{Q}_k^{j+1}(\mathbf{b}\cdot\mathbf{P}^{j+1}\cdot\mathbf{u}^{n+1})\right)\right|\\
&\le 2\left|\int_{t^n}^{t^{n+1}}\exp\left\{-\int_{\tau}^{t^{n+1}}\mu^*\left(x\left(s;t^n,x_j\right)\right)\,ds\right\}\left(\int_{x(\tau;t^n,x_j)}^{1}b(\sigma)\,P(x(\tau;t^n,x_j),\sigma)\,u(\sigma,\tau)\,d\sigma\right)d\tau\right.\\
&\quad-\frac{k}{2}\left(\exp\left\{-\int_{t^n}^{t^{n+1}}\mu^*\left(x\left(s;t^n,x_j\right)\right)\,ds\right\}\left(\int_{x_j}^{1}b(\sigma)\,P(x_j,\sigma)\,u(\sigma,t^n)\,d\sigma\right)\right.\\
&\quad\left.\left.+\int_{x(t^{n+1};t^n,x_j)}^{1}b(\sigma)\,P(x(t^{n+1};t^n,x_j),\sigma)\,u(\sigma,t^{n+1})\,d\sigma\right)\right|\\
&\quad+k\left|\exp\left\{-\int_{t^n}^{t^{n+1}}\mu^*\left(x\left(s;t^n,x_j\right)\right)\,ds\right\}\left(\int_{x_j}^{1}b(\sigma)\,P(x_j,\sigma)\,u(\sigma,t^n)\,d\sigma\right)\right.\\
&\quad\left.-\exp\left\{-\frac{k}{2}\left(\mu^*\left(x_j\right)+\mu^*\left(x_{j+1}\right)\right)\right\}\mathcal{Q}_k^j(\mathbf{b}\cdot\mathbf{P}^j\cdot\mathbf{u}^n)\right|\\
&\quad+k\left|\int_{x(t^{n+1};t^n,x_j)}^{1}b(\sigma)\,P(x(t^{n+1};t^n,x_j),\sigma)\,u(\sigma,t^{n+1})\,d\sigma-\mathcal{Q}_k^{j+1}(\mathbf{b}\cdot\mathbf{P}^j\cdot\mathbf{u}^{n+1})\right|.
\end{aligned}\tag{4.7}$$

The use of the trapezoidal quadrature rule results in the first term on the right-hand side of (4.7) being $O(k^3)$. With respect to the second term on the right-hand side of (4.7), we have

$$\begin{aligned}
&\left|\exp\left\{-\int_{t^n}^{t^{n+1}}\mu^*\left(x\left(s;t^n,x_j\right)\right)\,ds\right\}\left(\int_{x_j}^{1}b(\sigma)\,P(x_j,\sigma)\,u(\sigma,t^n)\,d\sigma\right)\right.\\
&\quad\left.-\exp\left\{-\frac{k}{2}\left(\mu^*\left(x_j\right)+\mu^*\left(x_{j+1}\right)\right)\right\}\mathcal{Q}_k^j(\mathbf{b}\cdot\mathbf{P}^j\cdot\mathbf{u}^n)\right|\\
&\le\left|\exp\left\{-\int_{t^n}^{t^{n+1}}\mu^*\left(x\left(s;t^n,x_j\right)\right)\,ds\right\}-\exp\left\{-\frac{k}{2}\left(\mu^*\left(x_j\right)+\mu^*\left(x_{j+1}\right)\right)\right\}\right|\left|\int_{x_j}^{1}b(\sigma)\,P(x_j,\sigma)\,u(\sigma,t^n)\,d\sigma\right|\\
&\quad+\exp\left\{-\frac{k}{2}\left(\mu^*\left(x_j\right)+\mu^*\left(x_{j+1}\right)\right)\right\}\left|\int_{x_j}^{1}b(\sigma)\,P(x_j,\sigma)\,u(\sigma,t^n)\,d\sigma-\mathcal{Q}_k^j(\mathbf{b}\cdot\mathbf{P}^j\cdot\mathbf{u}^n)\right|.
\end{aligned}$$

Thus, taking into account the assumed regularity of the vital functions and solution, the second order convergence of the composite quadrature rule (3.5), and (4.6), we conclude that the previous term is $O(k^2)$.

Finally, we bound the third term on the right-hand side of (4.7) as follows

$$
\begin{aligned}
&\left| \int_{x(t^{n+1};t^n,x_j)}^{1} b(\sigma)\, P(x(t^{n+1};t^n,x_j),\sigma)\, u(\sigma,t^{n+1})\, d\sigma - \mathcal{Q}_k^{j+1}(\mathbf{b}\cdot\mathbf{P}^j\cdot\mathbf{u}^{n+1}) \right| \\
&\le \left| \int_{x(t^{n+1};t^n,x_j)}^{x_{j+1}} b(\sigma)\, P(x(t^{n+1};t^n,x_j),\sigma)\, u(\sigma,t^{n+1})\, d\sigma \right| \\
&\quad + \left| \int_{x_{j+1}}^{1} b(\sigma)\, \big(P(x(t^{n+1};t^n,x_j),\sigma) - P(x_{j+1},\sigma)\big)\, u(\sigma,t^{n+1})\, d\sigma \right| \\
&\quad + \left| \int_{x_{j+1}}^{1} b(\sigma)\, P(x_{j+1},\sigma)\, u(\sigma,t^{n+1})\, d\sigma - \mathcal{Q}_k^{j+1}(\mathbf{b}\cdot\mathbf{P}^{j+1}\cdot\mathbf{u}^{n+1}) \right|.
\end{aligned}
$$

And, we can conclude, as previously shown, that this term is $O(k^2)$.

Thus, we can settle for the left term on (4.7)

$$
\begin{aligned}
&\Bigg| 2\int_{t^n}^{t^{n+1}} \exp\left\{-\int_{\tau}^{t^{n+1}} \mu^*\left(x\left(s;t^n,x_j\right)\right)\, ds\right\} \left(\int_{x(\tau;t^n,x_j)}^{1} b(\sigma)\, P(x(\tau;t^n,x_j),\sigma)\, u(\sigma,\tau)\, d\sigma\right) d\tau \\
&\quad - k\left(\exp\left\{-\frac{k}{2}\left(\mu^*\left(x_j\right)+\mu^*\left(x_{j+1}\right)\right)\right\} \mathcal{Q}_k^{j}(\mathbf{b}\cdot\mathbf{P}^j\cdot\mathbf{u}^n) + \mathcal{Q}_k^{j+1}(\mathbf{b}\cdot\mathbf{P}^{j+1}\cdot\mathbf{u}^{n+1})\right)\Bigg| \\
&\le C\,k^3,
\end{aligned}
\tag{4.8}
$$

and from (4.6), we observe that the right-hand side of (4.5) is $O(k^3)$. The substitution of this bound and (4.4) in (4.3) produces the estimate (4.2). ∎

In the following result, we prove the convergence of the numerical method. We denote the error produced by the numerical approximation as

$$\mathbf{E}^n = (E_0^n,\ldots,E_J^n,E_{J+1}^n), \qquad E_j^n = u_j^n - U_j^n, \quad 0 \le j \le J+1,$$

$0 \le n \le N$, (remember that u_j^n are the nodal values of the theoretical solution and U_j^n are the numerical approximations obtained by means of the numerical method).

Theorem 2. *Under the hypotheses of Lemma 1, if $\|\mathbf{E}^0\|_\infty = O(k^2)$, as $k \to 0$, then*

$$\|\mathbf{E}^n\|_\infty = O(k^2), \quad 0 \le n \le N,$$

as $k \to 0$.

Proof. From Eqs. (4.1) and (3.4), we have

$$E_{j+1}^{n+1} = \exp\left\{-\frac{k}{2}\left(\mu^*\left(x_j\right)+\mu^*\left(x_{j+1}\right)\right)\right\}\left(E_j^n + k\,\mathcal{Q}_k^j(\mathbf{b}\cdot\mathbf{P}^j\cdot\mathbf{E}^n)\right) + k\,\mathcal{Q}_k^{j+1}(\mathbf{b}\cdot\mathbf{P}^{j+1}\cdot\mathbf{E}^{n+1}) + k\,\tau_{j+1}^{n+1},$$

$0 \le j \le J-1$, $0 \le n \le N-1$.

Then, taking into account the smoothness properties of the functions μ^* and b we arrive at,

$$|E_{j+1}^{n+1}| \le (1+C\,k)\ |E_j^n| + C\,k\,\left(\|\mathbf{E}^n\|_\infty + \|\mathbf{E}^{n+1}\|_\infty\right) + k\,|\tau_{j+1}^{n+1}|,$$

$0 \le j \le J-1$, $0 \le n \le N-1$, and then

$$\|\mathbf{E}^{n+1}\|_\infty \le (1+C\,k)\ \|\mathbf{E}^n\|_\infty + C\,k\,\|\mathbf{E}^{n+1}\|_\infty + k\,\|\boldsymbol{\tau}^{n+1}\|_\infty.$$

$0 \le n \le N-1$. Then, by means of the discrete Gronwall's lemma, we arrive at

$$\|\mathbf{E}^n\|_\infty \le C\left\{\|\mathbf{E}^0\|_\infty + \sum_{l=1}^{n} k\,\|\boldsymbol{\tau}^l\|_\infty\right\},$$

Q3 $1 \le n \le N$, and using (4.2) the estimate holds. ∎

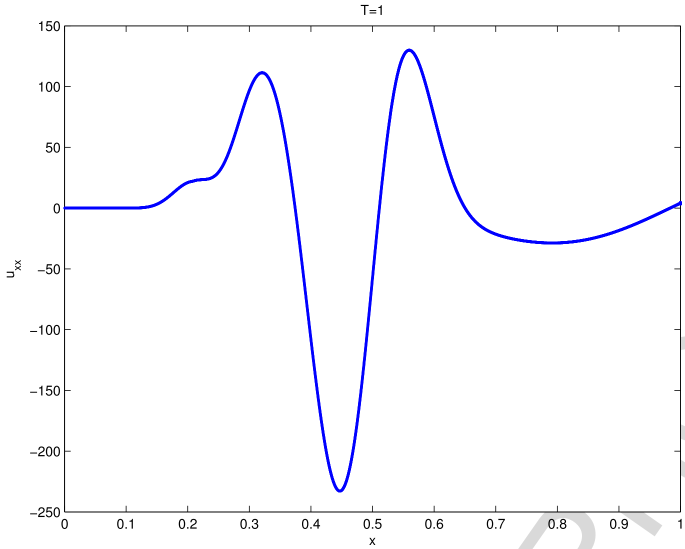

Fig. 1. Test Problem 1. Approximated second derivative of u.

5. Numerical experiments

We have checked experimentally the numerical method. In order to incorporate a more realistic behavior, we introduce a minimum size a at which cells divide, $x_{\min} \leq a < 1$. So, we assume that the division rate b vanishes at the interval $[x_{\min}, a]$.

Test problem 1. The following experiment shows the optimal rate of convergence obtained with the numerical method. It mirrors a similar one introduced in [13] for the symmetric division case.

We take $x_{\min} = 0$, and $a = \frac{1}{4}$. We also suppose that there is no cellular death ($\mu(x) = 0$), and we choose the size-specific growth rate as $g(x) = 0.1\,(1 - x)$. We take the size-specific division rate function

$$b(x) = b_1 \left(x - \frac{1}{4} \right)^3, \quad \frac{1}{4} \leq x \leq 1,$$

(coefficient b_1 is chosen in order to assure that the maximum value of $b(x)$ is 1). In order to avoid discontinuities caused by an incompatible initial condition, we take φ satisfying $\varphi(0) = \varphi'(0) = \varphi''(0) = 0$. In this experiment, we opt for

$$\varphi(x) = \begin{cases} 0, & \text{if } x \in \left[0, \dfrac{1}{8}\right], \\ \varphi_1 \left(x - \dfrac{1}{8} \right)^3 (1 - x), & \text{if } x \in \left[\dfrac{1}{8}, 1\right], \end{cases} \tag{5.9}$$

(coefficient φ_1 is chosen in order to assure that the maximum value of $\varphi(x)$ is 1). Note that this is similar to the third test problem in [13] for the symmetric division case (we assume that initially there are no cells under $\frac{1}{8}$). Taking into account the special structure of the equal fission model, there existed numerical difficulties in the numerical simulation due to the lack of smoothness in the solution to the problem: we did not observe the optimal rate of convergence in the numerical approximation. However, as we will see, this test does not provide a remarkable situation in the asymmetric division case.

With respect to the partitioning function, as in [17], we take

$$P(x, y) = \begin{cases} \dfrac{1}{\beta(40, 40)} \dfrac{1}{y} \left(\dfrac{x}{y} \right)^{39} \left(1 - \dfrac{x}{y} \right)^{39}, & \text{if } x < y, \\ 0, & \text{if } x \geq y, \end{cases} \tag{5.10}$$

where $\beta(x, y)$ is the classical Euler beta function.

We do not know the analytical solution to the problem therefore, in order to compare, we take the computed approximation with a sufficiently small value of the size step k as the exact solution. In the experiment we compute such a solution at the final time $T = 1$ with $k^* = 4.8828125\text{e}{-4}$. If we analyze the (approximated) second derivative of the computed solution, we observe in Fig. 1 the required regularity in the hypothesis of the convergence result (as we previously mention, this behavior differs from that of the symmetric division case [13]).

In Table 1 we present the results obtained with the method for different values of the step size. For each k, we compare at the final time T the computed numerical solution $\mathbf{U}_k^N$, with the representation of the solution corresponding to k^* at the

Table 1
Test problem 1. Error and numerical convergence order. $T = 1$.

k	Error	Order
5e−1	1.808892e−2	
2.5e−1	5.061369e−3	1.8
1.25e−1	1.252221e−3	2.0
6.25e−2	3.161828e−4	2.1
3.125e−2	8.003949e−5	2.1
1.5625e−2	1.985401e−5	2.0

coarsest grid obtained with k, $\mathbf{U}^N_{k*}$. Therefore, the second column shows the maximum error at the final time with different step sizes; that is

$$e_k = \|\mathbf{U}^N_k - \mathbf{U}^N_{k*}\|_\infty.$$

The third column shows the numerical order of convergence, which we compute with the formula

$$s = \frac{\log(e_{2\,k}/e_k)}{\log(2)}.$$

Results in Table 1 clearly confirm the expected second-order of convergence.

Test problem 2. Now we present the results obtained in order to study the emerging stable size distribution. For the equal fission case, Diekmann et al. [15], proved the existence of a stable size distribution assuming a certain condition of the growth function: $g(2x) < 2\,g(x)$. For the unequal division case, in [17] we have observed the appearance of such asynchronous exponential growth: that is, in the course of time,

$$u(x,t) \approx C\,e^{\sigma\,t}\,u^*(x), \qquad \int_{x_{\min}}^1 u^*(x)\,dx = 1, \tag{5.11}$$

where σ is the Malthusian parameter (intrinsic rate of natural increase), and $u^*(x)$ the stable size distribution. Both $u^*(x)$ and σ do not depend on the initial condition and only the constant C depends on φ.

From (5.11) we can write

$$\frac{u(x,t)}{\int_{x_{\min}}^1 u(x,t)\,dx} \approx u^*(x). \tag{5.12}$$

Then, we can compute an approximation to the stable size distribution by using the numerical solution obtained with the numerical method in the following way: from the numerical solution computed by (3.4)–(3.6), and approximating the integral on the left hand size of (5.12) by means of the composite trapezoidal rule, we can describe the evolution of the frequency of the cell volume distribution which approaches the stable size distributions as

$$\frac{U^n_j}{\mathcal{Q}^0_k(\mathbf{U}^n)} \approx U^*_j. \tag{5.13}$$

The following simulation reproduces one of the experiments presented in [17]. As in the previous test, we consider the minimum cell-size $x_{\min} = 0$, and the minimum size at which a cell divides as $a = \frac{1}{4}$. Again, we choose the mortality rate $\mu(x) = 0$ (there is no cellular death), and the size-specific growth rate $g(x) = 0.1\,(1-x)$. However, this time we use the size-specific division rate function

$$b(x) = \begin{cases} 0, & \text{if } x \in \left[0, \dfrac{1}{4}\right], \\ g(x)\,\dfrac{\phi_b(x)}{1 - \int_{1/4}^x \phi_b(s)\,ds}, & \text{if } x \in \left[\dfrac{1}{4}, 1\right], \end{cases}$$

where we have considered that each cell has a stochastically predetermined size at which fission has to occur, which is given by a probability density ϕ_b [4]. In this case

$$\phi_b(x) = \lambda \begin{cases} \left(x - \dfrac{1}{4}\right)^3, & \text{if } x \in \left[\dfrac{1}{4}, \dfrac{5}{8}\right], \\ \dfrac{459}{4096} - \dfrac{9}{4}\left(x - \dfrac{13}{16}\right)^2 + 16\left(x - \dfrac{13}{16}\right)^4, & \text{if } x \in \left[\dfrac{5}{8}, 1\right], \end{cases}$$

and $\lambda = \frac{81920}{3159}$. On the other hand, we consider the same partitioning function as in the previous test (5.10). Finally, we have checked with various initial conditions, but here we present the results obtained with (5.9).

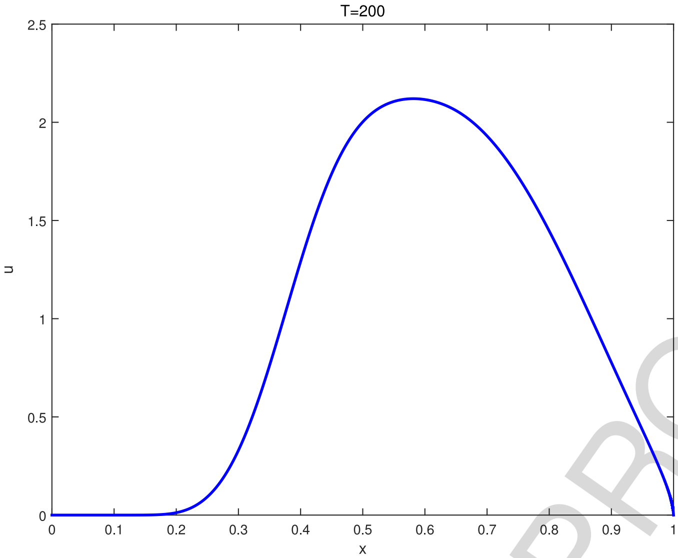

Fig. 2. Test problem 2. Numerical stable size distribution u^*.

We have carried out an extensive numerical experimentation with different final-times T and step-sizes k. We observe that $T = 200$ produces a sufficiently long time simulation in order to provide the stable size distribution by means of (5.13). For the step-size $k = 0.01$ we obtain the stable size distribution presented in Fig. 2, the value of the Malthusian parameter $\sigma = 0.061519$, and the computed value $C = 0.440209$ associated to the grid restriction of the initial data φ.

6. Conclusions

The study of cell populations by means of the use of structured population models, and their numerical simulation, are current and important topics. In this work we consider a size-structured population balance model describing the dynamics of a cell population when the reproduction process takes place by division into two unequal parts. The analytical solution of this problem is difficult to attain in a general situation and numerical approximations are necessary. There are few numerical methods adapted to this problem, and the theoretical studies that would validate them are rare. So it is crucial to design and analyze innovative numerical procedures.

In this study we have proposed a new and efficient numerical method in order to attain the solution to this model. It is an extension of the one given in [13] for the even case, which could be seen as a particular model when the partitioning function is a Dirac delta. The uneven model seems to be more realistic and it does not introduce a lack of smoothness in the solution. However, the birth term in the equation involves an integral term that must be approximated by means of a suitable quadrature rule. This issue requires a more expensive, slower and harder numerical integration. However, we have improved the efficiency of the numerical procedure by using a suitable subgrid of the natural grid in the quadrature rule.

We have carried out a demonstration of the second-order convergence of the approximate solution to the exact one under suitable smoothness hypotheses of the vital functions and the exact solution, and we have corroborated this optimal rate experimentally.

Finally, this numerical method is revealed as a valuable tool for the analysis and approximation of the stable size distribution of the model.

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