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Second-order numerical integration of a size-structured cell population model with asymmetric division

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Abstract— In this work we present a second-order numerical method, based on the integration along the characteristic curves, for the approximation of the solution to a population model describing the evolution of a size-structured cell population with asymmetric division. This method is used to approximate the stable size distribution of the model.

Keywords: Size-structured population, cell population models, asymmetric division, numerical methods, characteristics method.

1 Introduction

Structured population models describe the evolution of a population by means of the individuals' vital properties (growth, fertility, mortality, etc.) which depend on individual physiological characteristics (structuring variables such as age or size). Structured models in cell populations dynamics were considered for the first time in the sixties (see, for example, [6, 9]). However, this subject has been developed rapidly [14, 10, 15].

When reproduction occurs by fission it seems appropriate to take into account the size of individuals (by which we mean any relevant quantity, like weight, satisfying a physical conservation law).

One of the most important issues in the modelization is whether or not exists a stable size distribution, and many efforts were directed towards describing the most general models will still exhibit a stable type distribution property [5].

Here we consider a model for the growth of a size-structured cell population reproducing by fission into two daughter cells based on that one proposed by Ramkrishna [16].

In general, physiologically structured population models are difficult to solve. Although theoretical properties of the models such as existence, uniqueness, smoothness of solutions, long-time behaviour (with the study of steady states and their stability) could be studied without a solution expression, the knowledge of their qualitative or quantitative behaviour 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 [1, 2] and references therein). In the case of cell population balance models different techniques have been used (see, for example, the works of Mantzaris et al. [11, 12, 13]).

In this work we present a second-order characteristics method, based on the numerical scheme developed and analyzed in [4] 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.

2 The model

We consider a nonnegative minimum cell-size x_m and a maximal size, normalized to 1, at which point every cell might divide or die. We suppose the cell does not divide until it reaches a minimal size a, so $0 \le x_m \le a < 1$. We also assume that the environment is unlimited and all possible nonlinear mechanisms are ignored.

The problem is given by a conservation law

(1)
$$u_t(x,t) + (g(x)\,u(x,t))_x = -\mu(x)\,u(x,t) - b(x)\,u(x,t) + 2\int_x^1 b(s)\,P(x,s)u(s,t)\,ds, \qquad x_m < x < 1,\ t > 0,$$

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a boundary condition

$$u\left(x_m,t\right)=0,\quad t>0, \tag{2}$$

and an initial size distribution

$$u(x,0)=\varphi(x),\quad x_m\leq x\leq 1. \tag{3}$$

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 and we assume that the size of any individual varies according to the following ordinary differential equation

$$\frac{dx}{dt}=g(x). \tag{4}$$

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 depend on the size x (the internal structuring variable). 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. It satisfies the following conditions:

$$\int_{x_m}^{1}P(x,y)\,dx=1,\qquad P(x,y)=P(y-x,y),\qquad P(x,y)=0,\quad x\geq y. \tag{5}$$

In an extreme case, if two daughter cells from a a mother cell are always identical (equal fission), the partitioning function reduces to the Dirac delta function $P(x,y)=\delta(x-y/2)$, obtaining the model proposed by Diekmann et al. [8].

In accordance with 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 $\lim_{x\to 1}\int_{x_m}^{x}\frac{ds}{g(s)}=+\infty$. Note that if g is a continuous function defined in $[x_m,1]$ then this hypothesis implies that $g(1)=0$. Moreover, the solution to the problem must satisfy $u(1,t)=0$, $t>0$, because we suppose that initially there are no cells of maximum size [7].

3 Numerical method

In [3], a useful first-order scheme was proposed to obtain the solution to a generalization of (1)-(3) when the vital functions involved in the problem depends 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 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 (1)-(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 [4], we developed a novel 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 $x(t)=x(t;t_*,x_*)$ the characteristic curve of the equation (1) which takes the value x_* at the time instant t_*. It is the solution to the following initial value problem

$$\begin{cases}\dfrac{d}{dt}x(t)=g(x(t)),\quad t>t_*,\\ x(t_*)=x_*.\end{cases} \tag{6}$$

In this way, the solution to (1) is given by

$$\begin{aligned}u(x(t),t)=\;& u(x_*,t_*)\,\mathrm{e}^{-\int_{t_*}^{t}\mu^*(x(\tau))\,d\tau}\\ &+2\int_{t_*}^{t}\Big[\mathrm{e}^{-\int_{\tau}^{t}\mu^*(x(s))ds}\int_{x(\tau)}^{1}b(\sigma)P(x(\tau),\sigma)u(\sigma,\tau)d\sigma\Big]d\tau,\\ &\qquad\qquad t\geq t_*.\end{aligned} \tag{7}$$

Note that, in this new layout, we have to solve two types of problems: the integration of the equation that defines the characteristic curves (6) and the solution to equations (7) which provides the solution to the problem along the characteristics. We use discretization procedures in order to solve them.

We consider the numerical integration of model (1)-(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 (6) which provides the grid on the space variable (size) of the method. 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* [1]. In this work, we approximate such a grid by using a second-order scheme for the numerical integration of (6): the modified Euler method providing

$$\begin{aligned}&x_0=\tfrac{a}{2},\\ &x_{j+1}=x_j+\tfrac{k}{2}\,\left(g(x_j)+g(x_j+kg(x_j))\right),\ 0\leq j\leq J-1.\end{aligned}$$

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 [1] 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 $u_j^n = u(x_j, t^n)$, $0 \le j \le J+1$, $0 \le n \le N$, 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 (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 (7). For $0 \le n \le N-1$,

(8)
$$U_{j+1}^{n+1} = \mathrm{e}^{-\frac{k}{2}(\mu^*(x_j)+\mu^*(x_{j+1}))}\left(U_j^n + k\mathcal{Q}_k^j(\mathbf{b}\cdot\mathbf{P}^j\cdot\mathbf{U}^n)\right) + k\,\mathcal{Q}_k^{j+1}(\mathbf{b}\cdot\mathbf{P}^{j+1}\cdot\mathbf{U}^{n+1}), \quad j = 0,\ldots,J-1.$$

In the previous expression, $\mathcal{Q}_k^l(\mathbf{V})$ represents a quadrature rule to approximate the integral over the interval $[x_l, 1]$, $0 \le l \le J$ of the function with grid values $\mathbf{V} = [V_0, \ldots, V_{J+1}]$. In this work, we consider the composite trapezoidal quadrature rule, that is

$$\mathcal{Q}_k^l(\mathbf{V}) = \sum_{j=l}^{J} \frac{x_{j+1}-x_j}{2}\left(V_j + V_{j+1}\right).$$

Notations $\mathbf{b}$, $\mathbf{P}^l$ 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. Finally, products $\mathbf{b}\cdot\mathbf{P}^l\cdot\mathbf{U}^m$, $0 \le l \le J$, $0 \le m \le N$ must be interpreted component-wise. Obviously, the approximating values at the minimum and maximum sizes are

(9)
$$U_0^{n+1} = U_{J+1}^{n+1} = 0.$$

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 (9), then U_{j+1}^{n+1} from $J-1$ to 0 using (8), and finally U_0^{n+1} using (9)), it results in an explicit procedure. The reason is that the right hand side values in (8) corresponding to the time t^{n+1} are either zero or previously computed.

4 Numerical experiments

We have checked experimentally the numerical method. Here we present the results obtaining with one of the test problems presented in [3] in order to study its stable size distribution $u^*(x)$.

Note that

(10)
$$u(x,t) \approx C\,\mathrm{e}^{\sigma\,t}\,u^*(x), \qquad \int_{x_m}^{1} u^*(x)\,dx = 1,$$

where σ is the Malthusian parameter (intrinsic rate of natural increase). Both $u^*(x)$ and σ do not depend on the initial condition and only the constant C depends on φ. In [8], for the equal fission case, Diekmann et al. proved the existence of a stable size distribution if $g(2x) < 2\,g(x)$. Here we compute an approximation to the stable size distribution by using the numerical solution obtained with the numerical method.

From (10) we can write

(11)
$$\frac{u(x,t)}{\int_{x_m}^{1} u(x,t)\,dx} \approx u^*(x).$$

So, from the numerical solution computed by (8)-(9), and approximating the integral on the left hand size of (11) by means of the compite trapezoidal rule, we can describe the evolution of the frequency of the cell volume distribution, which approaches the stable size distributions as

(12)
$$\frac{U_j^n}{\mathcal{Q}_k^0(\mathbf{U}^n)} \approx U_j^*.$$

In the simulation we consider the minimum cell-size $x_m = 0$, and the minimum size at which a cell divides as $a = \frac{1}{4}$. We suppose that there is no cellular death, therefore $\mu(x) = 0$, and we choose the size-specific growth rate as $g(x) = 0.1\,(1-x)$. The size-specific division rate function is

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

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 [14]. In this case

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

and $\lambda = \frac{81920}{3159}$. As in [3], the partitioning function is taken as

$$P(x,y) = \frac{1}{\beta(40,40)}\frac{1}{y}\left(\frac{x}{y}\right)^{39}\left(1 - \frac{x}{y}\right)^{39},$$

where $\beta(x,y)$ is the classical Euler beta function. Finally, we have considered different initial conditions, but we present the results obtained in this simulation with

$$\varphi(x) = \begin{cases} 0, \text{ if } \quad x \in \left[0, \frac{1}{8}\right], \\ \left(x - \frac{1}{8}\right)^3 (1-x)^3, \text{if} \quad x \in \left[\frac{1}{8}, 1\right]. \end{cases}$$

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 (12). For the step-size $k = 0.01$ we obtain the stable size distribution presented in Figure 1, and the value of the Malthusian parameter $\sigma = 0.061519$. The computed value C associated to the grid restriction of the initial data φ is $C = 0.002695$.

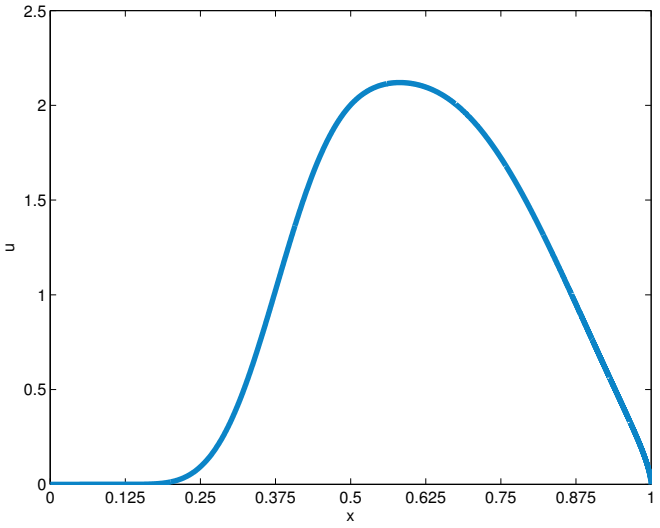

Figure 1: Numerical stable size distribution. $T = 200$.

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