Second-order numerical integration of a size-structured cell population model with equal fission

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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 equal fission. This method is used to approximate the stable size distribution of the model.

Keywords: Size-structured population, cell population models, equal fission, 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 identical daughters proposed by Diekmann et al. [8].

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, developed and analyzed in [4], 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

In the size-structured cell population model proposed by Diekmann et al. [8], the reproduction is given by the fission of the cell in two equal parts. In this model, cell does not divide until it reaches a minimal size $a > 0$. This means that there is a positive minimum cell-size $\frac{a}{2}$. On the other hand, there must be a maximal size, normalized to 1, at which point every cell might divide or die. It is also supposed that the environment is unlimited and all possible nonlinear mechanisms are ignored.

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The problem is given by a conservation law

(1)
$$u_t(x,t) + (g(x)\,u(x,t))_x = -\mu(x)\,u(x,t)$$

$$-b(x)\,u(x,t) + 4\,b(2\,x)\,u(2\,x,t),\ \frac{a}{2} < x < 1,\ t > 0,$$

a boundary condition

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

and an initial size distribution

(3)
$$u(x, 0) = \varphi(x), \quad \frac{a}{2} \le x \le 1.$$

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

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

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 depend on the size x (the internal structuring variable). Here, we should note that the term $4\,b(2\,x)\,u(2\,x,t)$ is interpreted as zero whenever $x \ge \frac{1}{2}$. We perform this feature with the use of functions u and b extended with the value zero on the interval $[1, 2]$. Condition (2) reflects that cells with a size less than $\frac{a}{2}$ cannot exist and is a consequence of the fact that cells only divide after the minimal size $a > 0$.

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 $\lim_{x \to 1} \int_{a/2}^{x} \frac{ds}{g(s)} = +\infty$. Note that if g is a continuous function defined in $\left[\frac{a}{2}, 1\right]$ 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], two useful first-order schemes were proposed to obtain the solution to (1)-(3). 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 develop a novel characteristics method based on the discretization of the integral representation of the solution to the problem along the characteristic curves. This procedure was previously used in [3] for this problem, obtaining a valuable first-order method, but now, in order to obtain a second-order scheme, we consider a different discretization of the integral representation to the solution.

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

(5)
$$\begin{cases} \dfrac{d}{dt}x(t) = g(x(t)), & t > t_*, \\ x(t_*) = x_*. \end{cases}$$

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

(6)
$$u(x(t), t) = u(x_*, t_*)\,\mathrm{e}^{-\int_{t_*}^{t} \mu^*(x(\tau))\,d\tau}$$

$$+ 4\int_{t_*}^{t} \mathrm{e}^{-\int_{\tau}^{t} \mu^*(x(s))ds} b(2x(\tau))u(2x(\tau), \tau)d\tau,\ t \ge t_*.$$

Note that, in this new layout, we have to solve two types of problems: the integration of the equation that defines the characteristic curves (5) and the solution to equations (6) 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 $t^n = n\,k$, $0 \le n \le N$. We begin with the integration of (5) 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 (5): the modified Euler method providing

$$x_0 = \frac{a}{2},$$

$$x_{j+1} = x_j + \frac{k}{2}\left(g(x_j) + g(x_j + kg(x_j))\right),\ 0 \le j \le J - 1.$$

Integer J represents the index of the last grid point computed at the size interval and is chosen in order to satisfy the condition $1 - x_J \le K\,k$, with K a suitable constant (we refer to [1] for further details). Note that the points (x_j, t_n) and (x_{j+1}, t_{n+1}), $0 \le j \le J - 1$, $0 \le n \le N - 1$, 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 (6). For $0 \leq n \leq N - 1$,

(7)
$$U_{j+1}^{n+1} = e^{-\frac{k}{2}(\mu^*(x_j) + \mu^*(x_{j+1}))} \left(U_j^n + 2\,k\,b(2\,x_j)\,\bar{U}_{2\cdot j}^n \right)$$
$$+ 2\,k\,b(2\,x_{j+1})\,\bar{U}_{2\cdot(j+1)}^{n+1}, \quad j = 0, \ldots, J-1.$$

In the previous expression, $\bar{U}_{2\cdot j}^n$ and $\bar{U}_{2\cdot(j+1)}^{n+1}$, represent approximations to the solutions at sizes $2\,x_j$ and $2\,x_{j+1}$ (not included in the discrete grid), and times t^n and t^{n+1}, respectively. So, in order to keep the second order, we compute them by linear interpolation based on the nearest grid points. More precisely, for the computation of $\bar{U}_{2\cdot l}^m$, approximation to the solution at $2\,x_l$, and time t^m, first we look for the index M so that $x_{M-1} < 2\,x_l \leq x_M$. Thus:

$$\bar{U}_{2\cdot l}^m = \begin{cases} U_{M-1}^m + \frac{U_M^m - U_{M-1}^m}{x_M - x_{M-1}}(2\,x_l - x_{M-1}), & \text{if} \quad 2\,x_l < 1, \\ 0, & \text{if} \quad 2\,x_l \geq 1. \end{cases}$$

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

(8)
$$U_0^{n+1} = U_{J+1}^{n+1} = 0.$$

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 (8), then U_{j+1}^{n+1} from $J-1$ to 0 using (7), and finally U_0^{n+1} using (8)), it results in an explicit procedure. The reason is that the right hand side values in (7) corresponding to the time t^{n+1} are either zero or previously computed.

Assuming that the vital function g, μ and b and the solution u are sufficiently smooth, we show the second-order convergence of the numerical method [4].

4 Numerical experiments

In [4] we shown the robustness of the numerical method (7)-(8) in different situations. 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

(9)
$$u(x,t) \approx C\,e^{\sigma\,t}\,u^*(x), \qquad \int_{a/2}^1 u^*(x)\,dx = 1,$$

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], 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 (9) we can write

(10)
$$\frac{u(x,t)}{\int_{a/2}^1 u(x,t)\,dx} \approx u^*(x).$$

So, from the numerical solution computed by (7)-(8), and approximating the integral on the left hand size of (10) 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

(11)
$$\frac{U_j^n}{\sum_{j=0}^J \frac{x_{j+1} - x_j}{2}\left(U_j^n + U_{j+1}^n\right)} \approx U_j^*.$$

In the simulation we consider 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

$$b(x) = \begin{cases} 0, & \text{if} \quad x \in \left[\frac{1}{8}, \frac{1}{4}\right], \\[2mm] g(x)\,\dfrac{\phi_b(x)}{1 - \int_{1/4}^x \phi_b(s)\,ds}, & \text{if} \quad x \in \left[\frac{1}{4}, 1\right], \end{cases}$$

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

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

and $\lambda = \frac{81920}{3159}$. Finally, we have considered different initial conditions, but we present the results obtained in this simulation with $\varphi(x) = \left(x - \frac{1}{8}\right)^3 (1-x)^3$.

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 (11). For the step-size $k = 0.01$ we obtain the stable size distribution presented in Figure 1, and the value of the Malthusian parameter $\sigma = 0.061392$. The computed value C associated to the grid restriction of the initial data φ is $C = 0.002694$.
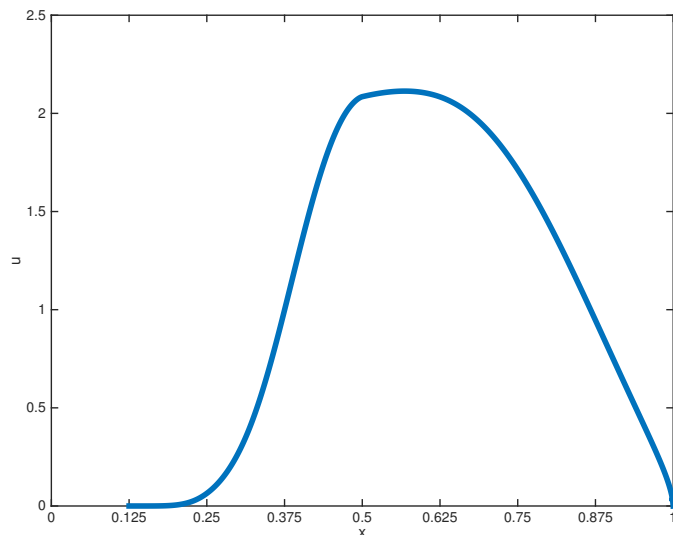
Figure 1: Numerical stable size distribution. $T = 200$.

Acknowledgements

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