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Numerical analysis of a cell dwarfism model

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ABSTRACT

In this work, we study numerically a model which describes cell dwarfism. It consists in a pure initial value problem for a first order partial differential equation, that can be applied to the description of the evolution of diseases as thalassemia. We design two numerical methods that prevent the use of the characteristic curve $x = 0$, and derive their optimal rates of convergence. Numerical experiments are also reported in order to demonstrate the predicted accuracy of the schemes. Finally, a comparison study on their efficiency is presented.

1. Introduction

We analyze, from a numerical point of view, a cell population balance model (CPBM) in which cells are distinguished by their individual size. CPBM were introduced in the early 1960s within the framework of particle dynamics in chemical and cellular contexts [1–3]. From a formal point of view, CPBM can be defined as the balance equation that accounts for the various processes that change the number of cells in a population. In general, it takes the form of a first-order integro-partial differential equation, along with boundary and initial condition. From a theoretical point of view, mathematical treatment of linear CPBMs has been developed since the early 1980s [4–6], where the study of the well-posedness, the convergence towards an asymptotically *stable-size distribution* and the stability analysis were made. In the case of a nonlinear model, the theoretical properties of existence and uniqueness of solutions have been addressed in [5].

The CPBM that we consider in this paper is based upon the model developed by Diekmann et al. [4], where cell-size is used to distinguish individuals in the population. We use the version presented in [7],

$$u_t(x,t) + (x\,u(x,t))_x = (\nu(x) - \mu(x) - b(x))\,u(x,t) + 4\,b(2x)\,u(2x,t), \quad 0 < x < 1,\ t > 0, \tag{1.1}$$

$$u(x,0) = \varphi(x), \quad 0 < x \leq 1, \tag{1.2}$$

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where the population of cells is described by a density function $u(x,t)$, t represents time and x measure the cell-size. Functions μ, b and ν explain different processes which take place within the population. In this model, cells grow exponentially, $x'(t) = x(t)$, as in a petri dish experiment, and die with death rate $\mu(x)$ depending on cellular size. With respect to the division process, we have considered a division in which the mother cell splits into two equal cells [4]. Note that the exponential growth introduces the unavailability of a boundary condition at size $x = 0$, thus cell renewal is introduced through the division $b(x)$ and immigration $\nu(x)$ rates. If we deal with a closed system (petri dish), it is usual to consider $\nu(x) = 0$, however other biologically significant systems are not closed, for example the blood production system which needs to replace the red blood cells daily in order to regulate the blood cells count (stem cell regulation). We want to point out that a proper combination of growth, division and mortality rates would introduce a natural maximum cell size [8], otherwise we could fix it as one (normalized) and we would consider that larger cells may only grow and die. As in [7], we assume μ and b are both positive, uniformly continuous functions on $(0, 1)$, with support in the interval $[0, 1]$ and $\nu(x)$ is a nonnegative, uniformly continuous function bounded above in the interval $[0, 1]$. We also assume that the environment is unlimited and all possible nonlinear mechanisms are ignored. Function φ is the initial state of the population density.

The usual CPBM, as developed in [4], assumes that a cell does not divide until it reaches a minimal cell size $a > 0$, which generates a minimal cellular size $a/2$. However, model (1.1)– (1.2) allows a cell of any size in the interval $(0, 1]$ to divide. Therefore, the minimal cellular size is $a = 0$. Although the idea of a cell with zero size is biologically unrealistic, we use it as the limiting value to describe an abnormality in the cellular division process: the production of unfunctional "dwarf" cells. These kind of cells are observed in a group of inherit blood disorders that affect the body's ability to produce hemoglobin and red blood cells: thalassemia. These hereditary blood disorders (anemias) are one of the most common human genetic abnormalities known and they are prevalent in tropical and subtropical world regions where malaria is still epidemic. Major α-thalassemia disorder (*hydrops fetalis*) has a high lethality rate and it has become an important public health problem due to population migrations. Besides, carriers of (minor) α-thalassaemia are found at high frequencies and they are usually asymptomatics. The disorders are caused by the absence or decreased production of the α chain of hemoglobin. In healthy persons, the synthesis of α and β-globin chains is finely balanced during terminal erythroid differentiation, giving rise to red blood cells of consistent size (reflected in the mean corpuscular volume (MCV)) and hemoglobin content (mean corpuscular hemoglobin (MCH)). Thus, minor forms of thalassemia are associated with smaller red blood cells than normal, a condition known as microcytosis which are only distinguishable through MCV. Finally, these diseases also can be associated with other blood disorders as the myelodysplastic syndrome [9–11].

Some theoretical properties of the model (1.1)– (1.2) were developed in [7]. In that work, the author addressed the existence and uniqueness of generalized solutions and their stability and unstability. On the one hand, he established the conditions on the data functions bounds to obtain a strongly stable solution, that biologically shows the extinction of the population. On the other hand, he proposed the data functions properties that leads to the topological transitivity of the different cellular generations. It includes the erratic behavior customarily associated with chaos. Such an issue has been subsequently refined in [12,13] and references therein.

These theoretical properties can 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 an information. In the case of general structured population models, many numerical methods have been proposed to solve them (see [14,15] and references therein). With respect to the study of CPBMs, different techniques have been used for both symmetric and asymmetric division rates (see [8,16–18] and the references therein). However, all of them are proposed for the solution of models with a minimal cell division size, and it is very important to design numerical schemes specially adapted to the features of this particular CPBM. For this model, there is an expression of the generalized solution but this formula does not possess an easy computational form, even in simple situations [7].

In this work, we present and analyze two first-order procedures: a natural grid method and an upwind scheme which are specially adapted to obtain the solution to the problem (1.1)– (1.2).

In Section 2 we describe the proposed numerical methods. In Section 3 we analyze their convergence to the exact solution and, in Section 4, we carry out a representative numerical simulation, including a comparison of the efficiency of the methods.

2. Numerical methods

We will introduce two numerical methods of first order adapted to different peculiarities of this particular model. On one hand, note that there is a characteristic curve at $x = 0$. Therefore, we avoid to use this "unknown" information into our numerical schemes. On the other hand, the solution of the problem is only first-order continuously differentiable, therefore we elude higher order methods. The first proposal is based on the integration along the characteristic curves, the other one consists on a finite difference method connected to an upwind technique.

2.1. Natural grid method (NGM)

This numerical integration is based on the discretization of the solution along the characteristic curves. Therefore, we define $\mu^*(x) = 1 + \mu(x) + b(x) - \nu(x)$ and rewrite (1.1) as

$$u_t(x,t) + x\,u_x(x,t) = -\mu^*(x)\,u(x,t) + 4\,b(2x)\,u(2x,t), \tag{2.1}$$