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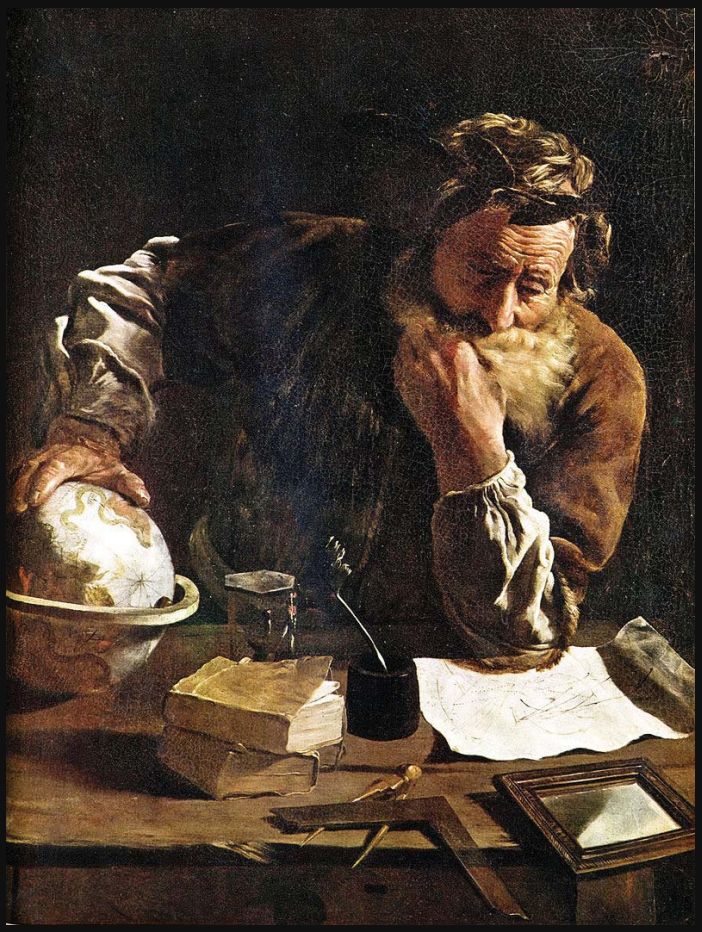

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Natural grid numerical methods revisited in cell population balance models with asymmetric division

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Abstract

We introduce and analyze a numerical method based on the integration along characteristics curves with the use of the *natural grid*. It is employed to obtain the solution to a cell population balance model structured by the cell size and with assymetric division rate.

Key words: population balance models, cell population dynamics, numerical methods, natural grid

1 Extended abstract

Cell population balance models were introduced in the early sixties and quickly experimented a great progress. The first efforts that can be associated with the concepts of population balance equations (PBE) were carried out within the framework of particle dynamics in chemical and cellular contexts [14, 4]. On the one hand, Randolph [14] formulates a generic population balance model (PBM) based on the generalized mechanical framework. This model is concerned about particles growth, aggregation and breakage, among others. On the other hand, Bell and Anderson [4] develop a cell population balance model in parallel. It is based on the cells growth and the probabilities of division and death of cells. In such a model, they consider two different state variables, cell-age and cell-volume, because of the different nature of reaccions, for instance involving DNA or ATP. In such a work, the division of an individual mother cell is considered to be into equally sized daughter cells. Later, Ramkrishna [12] adopts the generalized continuum mechanics concepts in [14] to derive a general PBE. He uses statistical concepts such as probability and expectancy to derive a set of equations in which age and cell mass are the descriptors of the cells state,

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even though they may only indirectly be indicators of the cell metabolism, and reflect the influences of other biochemical substances. The division (or breakage birth) term employed in is more general than in [4]. From a formal point of view, cell PBMs typically consist of a PBE along with boundary and initial conditions as well as other coupled equations describing cell division probability and intensity, partitioning cell content upon division probability, stage transitions and, in the case of chemically structured models, cellular kinetics. PBE can be defined as the balance equation that accounts for the various processes that change the number of cells in a population and takes the form of first-order partial integro-differential equation, while supplementary equations, coupled in a non-linear way, are tipically ordinary integro-differential equations.

From a theoretical point of view, mathematical treatment of linear cell PBM has been developed since the early eighties. The study of the well-posedness of the size-structured problem with division into equally sized daughter cells and its convergence towards an asymptotically *stable-type size distribution* was made in [5]. The PBM model proposed by Ramkrishna was studied similarly in [6]. In the case of nonlinear models, where the vital rates, sources and sinks depends explicitly on the environment, the theoretical properties of existence and uniqueness of solutions are also needed [6]. A general survey of the main mathematical problems solved and the principal techniques employed in this context is given in [9, 8, 3, 10].

In spite of this early development, nowadays population balance modeling is an area of increasing aplications and is currently used to describe quite different issues. Ramkrishna [13] did investigate biological populations as well as numerous studies of chemical engineering problems had been reported. These problems demostrate the wide applicability of the PBM modeling framework and suggest that many potential applications remain unexplored.

The practical application of cell PBM is not easy due to the fact that owing to their complex mathematical nature (first-order partial integro-differential equations, sometimes coupled in a nonlinear way with ordinary integro-differential equations). The development of numerical algorithms for the accurate approximation of their solution is a challenging task. In the last twenty years, several studies have addressed their numerical solution with different techniques: analytical solutions based on a successive generations approach in the case of simple single-cell growth expresions, classical finite difference schemes, finite element or spectral methods or the use of the integration along the characteristics (see [1] and references there in). However, the analysis of most of these numerical proposals is not finished yet and a convergence theorem to the theoretical solution has been provided only in a few of them [2]. This theoretical issue will lead to a variety of algorithms that may be used to efficiently obtain accurate solutions of these models and hence facilitate their use.

Here we consider a simple PBM where the evolution of a cell population is structured by only one state variable (the cell size) where cells reproduction is by fission into different

daughter cells [11]. Cell size is an attractive parameter due to the relative ease and precision with which it can be measured because the instrumentation for obtaining it has improved considerably. The model that arises due to this simplification is still useful in order to analyze and understand the cell population dynamics.

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 $0 \leq x_m \leq a < 1$. We also assume that the environment is unlimited and all possible nonlinear mechanisms are ignored. The problem is given by the PBE

$$u_t(x,t) + (g(x)\,u(x,t))_x = -\mu(x)\,u(x,t) - b(x)\,u(x,t) + 2\int_x^1 b(s)\,P(x,s)u(s,t)\,ds, \quad (1)$$

$x_m < x < 1$, $t > 0$, a boundary condition

$$u\,(x_m,t) = 0, \quad t > 0, \quad (2)$$

and an initial size distribution

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

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

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

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:

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

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

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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.

We will propose and analyze a characteristic curves scheme which employs a suitable invariant, nonuniform grid on the space variable, usually called *the natural grid*, as it was considered in [7]. This grid is quite interesting because its invariance allows us to study, at least experimentally, the long time behaviour of the cell population. We will provide numerical experiments which confirm the predicted accuracy of the numerical scheme.

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