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Research paper

Conciliating efficiency and dynamical consistency in the simulation of the effects of proliferation and motility of transforming growth factor β on cancer cells

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ABSTRACT

In this work, we provide some discretizations of a partial differential equation that generalizes the well-known Fisher's equation from population dynamics. The mathematical model of interest is a nonlinear diffusion-reaction equation that appears in the investigation of the proliferation and motility effect of transforming growth factor β on cancer cells. Only positive and bounded solutions are physically relevant in this context, and the discretizations that we provide in this manuscript are able to preserve both properties. One of the techniques is an implicit linear method that is motivated by previous approaches of the author. On the other hand, the second method is a novel explicit exponential technique which has the advantage of requiring less computational resources and less computer time. Similar qualitative results are obtained with both methods, but the latter one is able to handle finer grid meshes. Some qualitative and quantitative comparisons are carried out in support of the advantages of the exponential scheme. It is worthwhile to note that the explicit technique used in the present manuscript has the advantage over other exponential methodologies that it yields no singularities. In addition, the preservation of the properties of non-negativity and boundedness of both the solution and the total mass are distinctive features which are established analytically in this work. The numerical simulations on cancer growth obtained with the exponential method are found to be in good agreement with the experimental results available in the literature.

1. Introduction

The mathematical modeling of cancer growth is nowadays a rich area of research that has many fruitful avenues of investigation. Many mathematical systems have been proposed to describe the proliferation of cancer cells under various physical circumstances, and the models available in the literature range from the macroscopic perspective down to the cell-to-cell descriptions. To that effect, various approaches have been employed: from systems of coupled nonlinear ordinary or partial differential equations treating tumors as continuous entities [1–3] to fully discrete models in which each cell is handled as an individual agent in a complex chain [4–6]. In the continuous scenario, the models employed are derived using deterministic and/or stochastic approaches, while the discrete case has been developed mainly using automata and

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other models of theoretical computer sciences. The results under both approaches have proved to be qualitatively successful, though the mathematical investigation moves forward nowadays aiming at developing models that yield more accurate predictions and that consider more realistic scenarios.

It is important to point out that the continuous models of cancer growth (both deterministic and stochastic) become more complicated as more realistic features are taken into consideration [7,8]. Indeed, the systems of coupled partial differential equations become more complex as more physical factors and diffusion-reaction mechanisms are taken into account. As a consequence, the analytical determination of the exact solutions associated to physically meaningful initial conditions becomes a difficult task. In fact, in the best case scenario only suitable theorems on the existence and uniqueness of solutions of those mathematical systems may be derived under appropriate analytical constraints [9]. In view of these shortcomings, the design of reliable and fast computational techniques to approximate the solutions of those systems represents a viable alternative of solution. As we all know, this parallel numerical/computational approach opens another important avenue of research in the investigation of the dynamics of cancer growth which has produced many interesting reports [10,11].

From a numerical perspective, the literature gives account of many computational techniques to approximate solutions of coupled systems of partial differential equations describing the development of cancer tumors. In particular, the search for numerical techniques that optimize the computer resources and provide fast results is a topic of research that attracts a lot of attention in the area. This direction of investigation is entirely justified by the facts that the mathematical models for cancer growth may involve various complicated differential equations, and that the discrete domains must be partitioned in fine meshes in order to produce accurate outcomes. From this point of view, the explicit techniques would be highly desirable tools in order to obtain fast and computationally economic simulations of cancer growth. However, it is worthwhile pointing out that the design of numerical methods following the criterion of computational efficiency frequently ignores taking into account the mathematical properties of the solutions inherent to the continuous model [12,13]. For example, some partial differential equations that describe the growth of cancer involve the normalized density of cancer cells as one of the variables of interest [10,14], which is a positive quantity that is bounded from above by 1. From a physical point of view, one expects for a numerical technique to approximate the solutions of that model to be *dynamically consistent* with the model [15,16], that is, we expect that the properties of non-negativity and boundedness be preserved by the technique under known conditions on the computational and model parameters. Ideally, the rigorous scientist would require for a simulation tool to be both efficient and dynamically consistent with the problem under consideration, but the practice shows that both criteria are difficult to meet when it comes to complex continuous models.

The present work is motivated by various systems of partial differential equations that describe the growth of cancer. More precisely, the present work is motivated by partial differential equations in the dynamics of brain cancer [3,10] and the effects of proliferation and motility of transforming growth factor (TGF) β on cancer cells [14]. In all these cases, the models under consideration are extensions of the classical Fisher's equation of population dynamics [17,18], and all of them are physically interesting in the two-dimensional scenario in view of the applications to the dynamics of growth of tumors on human tissues. Moreover, the variable of interest in either case is the density of tumor cells at each point of the tissue, whence the properties of non-negativity and boundedness naturally arise. In view of these remarks, one is immediately led to ask whether it is possible to design an efficient and dynamically consistent technique to approximate the solutions of a generalized two-dimensional form of the equations investigated in [10,14]. More precisely, we are interested in developing numerical methods to approximate the solutions of those equations with the following characteristics:

1. The non-negativity and the boundedness of numerical approximations is preserved.
2. The method preserves the non-negativity and the boundedness of the total mass of the cancer tumor.
3. The technique is computationally fast.
4. The method is easy to implement in any computer language.
5. The computational implementation allows to employ fine grid meshes.

It is important to recall that some previous reports by the author have been devoted to the design of dynamically consistent techniques to approximate the solutions of various nonlinear systems [19–21]. Those methodologies are capable of preserving the non-negative and the bounded (and, in some cases, even the monotone) characters of approximations, however, all of them are linear and implicit techniques that require a tremendous amount of computer resources and simulation time. In our search for new efficient and dynamically consistent techniques, we turned our attention to a family of exponential finite-difference methods available in the literature [22,23]. Those techniques are explicit schemes which, unfortunately, present the disadvantage of not being able to handle solutions that are allowed to be equal to zero. This feature represents a major shortcoming in view that many studies on the growth of cancer cells consider initial profiles in which only a small number of grid points are inoculated with cancer cells. In the present manuscript, we report on a modification of those approaches in order to handle zero solutions. Using a modified version of the linear approach reported in [24] and some numerical results reported in the literature, we provide qualitative and quantitative comparisons in order to assess the validity of the modified exponential technique. As a conclusion of this manuscript, we provide a finite-difference method to approximate the solutions of partial differential equations describing the growth of cancer, which satisfies the properties on efficiency and dynamic consistency listed in the paragraph above.

The present work is organized as follows. In Section 2, we introduce the analytic nomenclature along with the model for the growth of cancer tumor that motivates this report. We provide therein an alternative representation of our model