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An algorithm for partial functional differential equations modeling tumor growth

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ABSTRACT

We introduce a parallel algorithm for the numerical simulation of the growth of human tumor cells in time-varying environments and their response to therapy. The behavior of the cell populations is described by a system of delay partial differential equations with time-dependent coefficients. We construct the new algorithm by developing a time-splitting technique in which the entire problem is split into independent tasks assigned to arbitrary numbers of processors chosen in light of available resources. We present the results of a series of numerical experiments, which confirm the efficiency of the algorithm and exhibit a substantial decrease in computational time thus providing an effective means for fast clinical, case-by-case applications of tumor invasion simulations and possible treatment.

1. Introduction

The past decades have marked significant progress in the understanding and modeling of cancer growth from the nano-scale and micro-scale to the morphologies observed at the centimeter-scale. Of increasing importance has been the development and evaluation of effective possible treatment options—an area of priority that continues to concern many. Nevertheless, significant challenges continue to surface in the multi-scale modeling of cancer and the effectiveness of treatment, the attainment of numerical solutions and validation of mathematical models against clinical and experimental data [1]. One of these stems from the fact that it is often difficult, if not prohibitively expensive from the clinical and experimental perspective, to generate data reproducibly over a broad enough range of all parameters involved to understand cancer progression though clinical studies and experimentation alone [2]. It is here where the reproducibility of predictive mathematical modeling on all scales and the efficiency of associated computational algorithms can facilitate a route toward patient-specific prediction and therapy [2].

The interactions between cancer cells and the host immune system intricately affect the development of the disease starting from the smallest scales. Mathematical kinetic theory has been frequently used to model these scales of tumor progression dynamics throughout various parts of the literature, including [3–9]. Of these, Bellomo and Forni [3] initiated this type of approach to understand cellular interactions and cancer growth within an environment with an active immune system. Macroscopic equations have also been derived from thermostatted kinetic equations through the use of an asymptotic limit method in [10], in which the magnitude of the activity of the complex biological system changes as a result of conservative interactions with close-by particles as well as due to proliferative and destructive processes. The effects on biological tissue have also been studied through the development of macroscopic models that have been derived from an underlying statistical mechanics viewpoint in [11–13]. The link between different scales intrinsic to a problem, such as the

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micro-scale of the kinetics of tissue invasion and its macroscopic description, remains one of the major challenges in the mathematical modeling of complex systems to date. It has been shown in [14] that under certain conditions, these two modeling approaches for tissue invasion lead to equivalent formulations.

Modeling efforts concerning tumor growth with and without therapy have also been validated against available experimental and clinical data in interdisciplinary studies such as [15], where in vitro experimental data has been used to examine flow cytometry profiles [16,17], where in vivo laboratory data has been utilized to validate a mouse model and [18,19], where clinical data has been used to estimate the model parameters of a model of human tumor growth. Each of these studies involve a series of direct numerical simulations, and in the case of clinical data, makes use of large data sets requiring large amounts of patient-specific simulations. Computational efficiency and reducing required run time, therefore, remains a main area of interest in such interdisciplinary pursuits as well as in the development of patient-specific prediction and treatment options.

This paper is devoted to mathematical modeling of the behavior of cell populations in vivo under the influence of anticancer therapy (such as radiotherapy or chemotherapy) and induced apoptosis. The model equations involve time delay terms and are proposed in [15] in an effort to develop strategies for decreasing resistance to therapy. Different cancer patients react differently to anticancer therapies and the respective mathematical model parameters depend specifically on the individual patient for whom anticancer therapies are to be employed. The model parameters may be estimated in line with the principles adopted by [15] with the help of individual material obtained at surgery or medical examination and intensive numerical simulations. Such computation must be conducted in real time and it is the purpose of this paper to introduce a parallel algorithm to minimize the computational time required to solve the model equations, through the use of parallel computing environments.

The structured model [15] is based on DNA content and has been validated against DNA content by using flow cytometry and a human melanoma cell line. Flow cytometry analysis is commonly used (e.g. [20]) to find efficient drug therapies in cancer treatment. The results presented in [15] show a correlation between predicted and clinical data from DNA-based flow cytometry. The method of flow cytometry is used in the subsequent paper [21] to analyze mitotic arrest with cell death, where the model equations are applied to another human cancer cell line in order to predict the effect of drugs on tumor cells. However, applications to a broader variety of cell lines across patients are inhibited by the computationally intensive process of determining the model parameters and we address this issue in the present paper. The algorithm that we derive is based on the principles simulated in [22] and developed theoretically in [23]. The previously developed algorithm, investigated in [22], [23], differs from the new algorithm in that the new algorithm applies to a wider class of problems; namely, those that involve time-dependent coefficients.

The paper is organized as follows. The delay partial differential equations modeling tumor growth are presented in Section 2. The generalized numerical algorithm for the model equations is introduced in Section 3. Results of numerical experiments are presented in Section 4 and Section 5 presents concluding remarks and future directions.

2. Delay partial differential equations modeling tumor growth

In this section, we investigate a mathematical model that describes the growth of human tumor cells as well as their response to therapy. As cancer cells and surrounding healthy tissues, such as those of specimens from animals and patients treated in vivo, undergo cell death, these cells become a part of a complex and highly regulated process referred to as apoptosis. Despite its complexity, the process can typically be readily recognized histologically regardless of the type of species, cell, or tissue, and regardless of whether the affected cells are normal or affected by the growth of cancer [24]. Apoptosis marks itself by changes to resulting DNA profiles within the stages of the cell cycle.

The following model

$$\begin{cases} \dfrac{\partial G_1(x,t)}{\partial t} &= 4b(t)\,M(2x,t) \;-\; \big(k_1(t)+\mu_{G_1}(t)\big)\,G_1(x,t), \\ \dfrac{\partial S(x,t)}{\partial t} &= \varepsilon(t)\,\dfrac{\partial^2 S(x,t)}{\partial x^2} \;-\; \mu_S(t)\,S(x,t) - g(t)\dfrac{\partial S(x,t)}{\partial x} \;+\; k_1(t)\,G_1(x,t) - I(x,t;T_S), \\ \dfrac{\partial G_2(x,t)}{\partial t} &= I(x,t;T_S) \;-\; \big(k_2(t)+\mu_{G_2}(t)\big)\,G_2(x,t), \\ \dfrac{\partial M(x,t)}{\partial t} &= k_2(t)\,G_2(x,t) \;-\; b(t)\,M(x,t) - \;\mu_M(t)\,M(x,t), \end{cases} \tag{2.1}$$

was introduced in [15] to describe the dynamics between the cells in the G_1, S, G_2 and M-phases of the cell division cycle. Here, x represents the dimensionless relative DNA content, t represents time, and $G_1(x,t)$, $S(x,t)$, $G_2(x,t)$, $M(x,t)$ stand for the densities of cells in these corresponding phases. In general, the model parameters are functions of time. Specifically, $\mu_{G_1}(t)$, $\mu_S(t)$, $\mu_{G_2}(t)$, $\mu_M(t)$ are the death rates of cells in the phases indicated by the subscripts, $k_1(t)$ is the transition rate from the G_1-phase to the S-phase, $k_2(t)$ is the transition rate from the G_2-phase to the M-phase, $\varepsilon(t)$ is the dispersion coefficient, $g(t)$ is the average growth rate of DNA in the S-phase, and $b(t)$ is the rate at which a cell in the M-phase divides into two daughter cells.