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Application of fixed point-collocation method for solving an optimal control problem of a parabolic–hyperbolic free boundary problem modeling the growth of tumor with drug application

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ABSTRACT

In this paper, employing a fixed point-collocation method, we solve an optimal control problem for a model of tumor growth with drug application. This model is a free boundary problem and consists of five time-dependent partial differential equations including three different first-order hyperbolic equations describing the evolution of cells and two second-order parabolic equations describing the diffusion of nutrient and drug concentration. In the mentioned optimal control problem, the concentration of nutrient and drug is controlled using some control variables in order to destroy the tumor cells. In this study, applying the fixed point method, we construct a sequence converging to the solution of the optimal control problem. In each step of the fixed point iteration, the problem changes to a linear one and the parabolic equations are solved using the collocation method. The stability of the method is also proved. Some examples are considered to illustrate the efficiency of method.

1. Introduction

In the past three decades, a significant number of researchers have been interested in studying and analyzing optimal control problems for practical models especially ones formulated by partial differential equations according to the medical concepts. One of the most remarkable models, which needs to be controlled for treatment purposes, is tumor growth model. There is considerable literature that study optimal control for mathematical model of tumor growth, owing to the importance of destroying cancer tumors and due to the fact that tumor growth may depend on several factors (such as the concentration of drug and nutrient) and may be sustained or diminished by controlling these factors properly. For instance, the authors of [1] studied optimal control for a model [2] of tissue invasion by solid tumors. Also, Calzada et al. [3] investigated optimal control for a free boundary tumor growth model that is a slight simplification of the model proposed by Greenspan [4,5] and Byrne and Chaplain [6]. In [6], a reaction–diffusion model for a spherically symmetric, nonnecrotic tumor was presented. In investigation [7], the authors have studied a distributed optimal control problem for a model of tumor growth. They have obtained the necessary optimality conditions in terms of a variational inequality. In another one [8], the techniques of optimal control are employed to an ordinary differential equation model of tumor growth. Using a numerical relaxation algorithm, the necessary conditions of Pontryagin's minimum principle are solved. The authors of [9] have studied the treatment of cancer that processed by combining radio and anti-angiogenic therapy, which is aimed to minimize the size of cancer by

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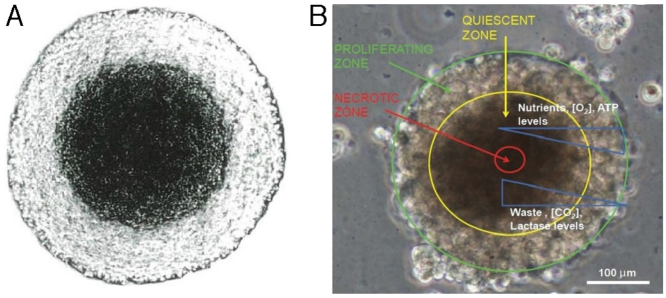

Fig. 1. Unstained equatorial cryosection of 10 μm thickness through a WiDr human colon adenocarcinoma spheroid as visualized by a phase contrast microscope (bar, 250 μm) [14] (A). The inner necrotic core is surrounded by a layer of quiescent cells, which, in turn, is surrounded by a layer of viable cells [15]; Pathophysiological gradients in a 3D tumor spheroid [16] (B).

adding control variables, which control radiation dose and dosage of anti-angiogenic agent. An ordinary differential equation model is considered in this research. In [10], nonlinear optimization for a tumor model is investigated. In this work a PDE model based on the theory of the change of the pH of the environment is considered. The authors of [11], have studied two optimal controls for a free boundary problem modeling tumor growth with drug application considered in [12]. They have controlled the concentration of nutrient and drug on the boundary and inside the tumor to destroy the tumor cells. The necessary conditions employing the tangent-normal cone techniques are obtained. Also, using the Ekeland variational principle, the existence and uniqueness of optimal control for each optimal control problem are proved. The model presented in [12] is a multicellular tumor spheroid model with drug application, which includes two parabolic, three hyperbolic, and an ordinary differential equation. It should be noticed that three types of cells: proliferative cells, quiescent cells, and dead cells are then considered in this model because of the fact that low concentration of glucose and oxygen in the inner regions of spheroids may contribute to the formation of many types of cell subpopulations including quiescent, hypoxic, anoxic, and necrotic cells [13] (see Fig. 1). Evolution of cells is described by three first-order hyperbolic equations. Furthermore, diffusion of nutrient (e.g., oxygen and glucose) and drug concentration is described by two second-order parabolic equations.

Numerical methods for optimal control have been a field of active research for the last few decades. There are many applications of the collocation method in the literature for solving optimal control problems. For instance, in [17], the authors studied wavelet collocation method for optimal control problems. They also solved examples of two kinds of optimal control problems, continuous and discrete. In [18], Tiesler et al. studied the use of stochastic collocation for the solution of optimal control problems with stochastic partial differential equations constraints.

In this paper, using fixed point-collocation method, we have solved an optimal control problem presented in our last paper [11] in which a partial differential equation model of tumor growth, which is a system of six coupled equations including five PDEs (two parabolic equations and three hyperbolic equations) and one ODE describing the radius of tumor, is considered. In the optimal control problem, we have considered four control variables and six terms in the cost function and we have avoided simplification to have more reliable problem. We added two control variables to the model of tumor growth with drug application to reduce the concentration of nutrient, which results in the starving of tumor cells. Also, the concentration of drug on the boundary and inside the tumor is controlled using two control variables to increase the concentration of drug, which results in increasing the death rate of tumor cells. We proved the optimal control problem has unique control variables and obtained them in terms of the adjoint states. Our main strategies and contributions are briefly highlighted as follows:

- Applying the fixed point method, we have constructed a sequence, which converges to the exact solution of optimal control problem. In each step of fixed point iteration, the problem has changed to a linear one.
- In all steps of the fixed point iteration, using collocation method, the parabolic equations ((67)–(68) and (73)–(74)) are solved and the convergence of collocation method is studied (see Lemmas 4.1 and 4.2).
- In each step, the hyperbolic equations ((69)–(71) and (75)–(77)) are changed to ordinary differential equations using characteristic equation.
- We have proved the constructed sequence converges to the exact solution of problem (see Theorem 4.3) and by the use of the constructed sequence, the stability of method is proved (see Theorem 4.4).
- Some illustrative numerical examples are employed showing the efficiency of the presented method.

The organization of paper is as follows. In Section 2, a free boundary problem modeling tumor growth with drug application is presented. In Section 3, we introduce the optimal control problem. The necessary condition and the existence and uniqueness of optimal control together with the adjoint equations, which are instrumental in introducing the necessary condition and proving the existence and uniqueness of optimal control, are presented in Section 3.1. Convergence and stability of fixed point-collocation method for solving the optimal control problem are studied in Section 4. In Section 5, some numerical experiments are provided. In Section 6, conclusions are given. Some lemmas and theorems, which have been used in the mathematical analysis throughout the paper, besides the proofs of some theorems, are provided in Appendix.

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