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A mathematical model of tumor hypoxia targeting in cancer treatment and its numerical simulation

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ABSTRACT

Solid tumor includes the areas where oxygen concentration is very low called hypoxia, often in the surrounding areas of necrosis. Hypoxic cells in these areas are resistant to chemotherapy and radiation therapy. The presence of hypoxia and necrosis enables tumor-selective treatment, including hypoxia-activated prodrugs, tumor hypoxia-specific gene therapy and tumor-targeting bacterial therapy. This article deals with the mathematical formulation of tumor hypoxia-targeting by introducing a decay parameter of oxygen in the model given by Kolobov et al. (2009) and Avila et al. (2013). The well-posedness of the governing partial differential equations and numerical simulation are provided. For the purpose of numerical simulations, the conforming Q_1 finite element method for space discretization and second-order diagonally implicit fractional step θ-scheme for temporal discretization are used. The effect of oxygen on hypoxia, necrotic region decay and the maximum age of growing tumor cells are computed and illustrated graphically. It is observed that the distribution of nutrients in tissues have substantial effect on tumor growth rate and structure.

1. Introduction

Cancer or rapid creation of abnormal/tumor cells that grow beyond their usual boundaries are among the leading causes of morbidity and mortality worldwide [1]. Therefore, advanced countries have allocated a large amount of research funding for the development of new methods and drugs to treat cancer. Due to availability of early identification tools and prodrugs techniques, the chances of successful cancer treatment has increased [2]. The formation of capillaries and new blood vessels from the existing vasculogenic network is referred to as angiogenesis [3]. The link between angiogenesis and tumor growth was first postulated in 1971 [4] and subsequently numerous studies have demonstrated that without the process of angiogenesis, growth of a tumor is restricted due to a limitation of oxygen and other nutrients derived from the blood supply [5,6]. Since tumor cells require a greater blood supply, for oxygen and other nutrients, their growth is limited to a certain size. Therefore, in order to grow beyond a certain size, tumors need to induce an angiogenic response from the blood vessels proximal to the tumor micro-environment [7,8]. Hypoxic conditions (transient hypoxic stress) in the core of the developing tumor and the resultant expression of hypoxia inducible factors (HIFs) in tumor cells are potent mediators

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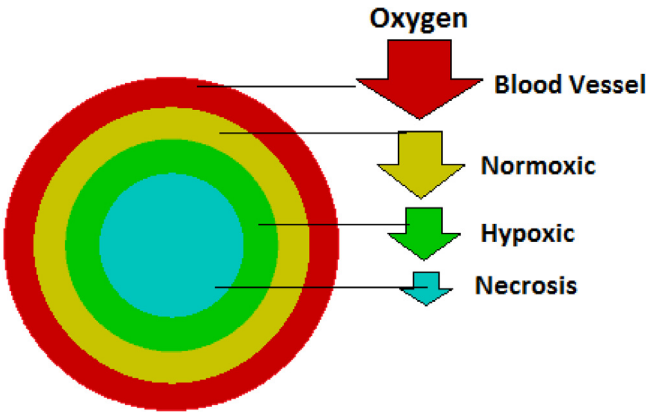

Fig. 1. Different stages of tumor growth depending on oxygen concentration.

of angiogenesis [9] which is required for blood and nutrients supply to proliferating cells. As the proliferating tumor cells consume most of available oxygen in the vicinity of normal cells, this decreased in oxygen tension may be harmful for its survival later and causes the tumor hypoxia. However, some cells can survive even under poorly oxygenated (hypoxic) conditions [2] as shown in Fig. 1. It is well-established that hypoxic tumor cells are resistant to radiation therapy [10,11], but the clinical impact of hypoxic tumor cells extends beyond the treatment of localized primary tumors with ionizing radiation. Hypoxic tumor cells promote tumor progression and metastasis through a variety of direct and indirect mechanisms, and hypoxic tumor cells, therefore, represent a significant impediment to successful cancer therapy [10–12]. Therefore, the study of hypoxic tumor cells has significant impact in cancer treatment [13].

In comparison to molecular biology, cell biology and anti-cancer drugs research, the contribution of mathematics for cancer treatment is relatively low [13–15]. A mathematical model of tumor growth is a mathematical expression of the growth of abnormal cells over time [16]. Since, estimation of number of cancer cells in a tumorous region, cells migration and position as a function of time is a challenging task both in applied sciences and cancer biology. So, different mathematical strategies are developed for tumor growth and cancer treatment. For example, in Ref. [17], several simple differential equations are illustrated to describe the tumor growth and anti-tumor treatments. Particularly, in the case of an invasive tumor growth, the kinetics of nutrients concentration and cell density is given by a system of reaction–diffusion equations [18]. Some qualitative analysis and numerical simulations of the cancer models are given in [19–21]. Particularly in Ref. [21], A.V. Kolobov et al., have proposed a mathematical model for the study of invasive tumor growth and have provided a traveling wave solution. The aim of this work is to extend the work done by A.V. Kolobov by considering the oxygen decay parameter to target tumor hypoxia in cancer therapy. The governing equations are numerically solved by finite element method using the PDELab [22,23], which is an open source software based on Distributed and Unified Numerics Environment (DUNE) [24]. PDELab has been used for solving problems with many applications of elliptic, parabolic and hyperbolic partial differential equations.

2. Mathematical model

Tumors are regarded as a colony of live and dead cells surrounded by normal tissues. The live tumor cells possess mobility, divide at a constant rate, and begin to die due to lack of nutrients. Although cells division and mobility require a large variety of nutrients, this model assumes only the lack of oxygen (i.e. nutrients) to determine the death of malignant cells [21]. It also assumes that oxygen consumption by normal non-proliferating cells is negligibly small when compared with actively dividing tumor cells [25]. Since tumor cells are self-sufficient in growth signals and divide more rapidly than normal cells so that their oxygen consumption is comparatively more than the non-proliferating (normal) cells [26,27]. Since oxygen is vital for metabolism, growth and division of cells, greater number of cells required more oxygen. Further assumptions are considered that the surrounding normal tissue does not hinder tumor cell movement and proliferation [28–30]. Therefore, the model given in [21] is based on the live cells with density "c" which divide at constant rate β and randomly move (diffuse) with constant coefficient D_c, die at low oxygen concentration "s" at a rate of cell death $P(s)$. Since oxygen is essential for the growth of the tumor cells, its distribution is determined by the diffusion constant coefficient D_s and nutrient (oxygen) consumption rate by live tumor cells, factor of μ.

Since decay of oxygen causes tumor hypoxia, in which portions of the tumor have significantly low oxygen concentrations is linked with more aggressive tumor behavior and poorer prognosis [31,32] and resistance to radiation therapy. So the decay of oxygen is considered as a factor of ρ in the model proposed by Kolobov et al. [21], which has significant effects in cancer growth.

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