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BIOMECHANICAL MODELING OF TUMOR GROWTH: ITS RELEVANCE TO GLIOMA RESEARCH

ANTHONY J. PALOCAREN AND CORINA S. DRAPACA

Abstract. In 2009 the US National Center for Health Statistics showed that cancer is close to becoming the deadliest disease of modern times. Recent years have seen unprecedented advancements in medicine that have contributed to a substantial decrease in the death rates of some serious diseases such as heart disease, stroke, influenza and pneumonia. However, with cancer, equivalent scientific and technological advances have yet to be achieved. Theoretical models capable of explaining the fundamental mechanisms of tumor growth and making reliable predictions are urgently needed. These models can contribute considerably to the design of optimal, personalized therapies that will not only maximize treatment outcomes but also reduce health care costs. Recently [25] we have proposed a non-invasive way of classifying gliomas, primary brain tumors, based on their stiffness. The model uses image mass spectra of proteins present in gliomas and shows that the Young's modulus of a high grade glioma is at least 10kPa higher than the Young's modulus of a low grade glioma. In this paper we will use this model to investigate the effect of mechanics on the growth of gliomas. The proposed mechano-growth model is a non-linear evolution differential equation which is solved analytically using the Adomian method. The time evolution is represented in two ways: (1) using a classical first-order derivative, and (2) using a fractional order derivative. Our results show that the fractional order model captures a very interesting temporal multi-scale effect of tumor transition from low grade (benign) to high grade (malignant) glioma when a certain threshold of mechanical strain is reached in the tissue. For comparison, we also reproduce the results we presented in [25] when linearization is used to solve the evolution equations analytically.

Key words. Tumor Mechano-Growth, Adomian Method, Glioma Stiffness.

1. Introduction

In the spring of 2009, the New York Times published data from the National Center for Health Statistics showing that cancer is close to becoming the deadliest disease of modern times [3]. Recent advancements seen in medicine have contributed to a substantial decrease in the death rates of some serious diseases such as heart disease, stroke, influenza and pneumonia. However, in the case of cancer, equivalent scientific and technological advances have yet to be achieved. The annual cancer death rate currently stands at about 200 deaths a year per 100,000 people of all ages and about 1,000 deaths per 100,000 people over the age of 65 [4]. Although a steady increase in diagnoses and survival has been seen over the past sixty years, the treatment of deadly cancers has not improved and thus the cancer death rate has hardly changed. In particular, gliomas are primary brain tumors that, at high grades, are among the deadliest cancers. For instance, a European study published in 2005 showed that around 65% of adults with low grade astrocytoma (a type of glioma) lived for at least 5 years without any tumor growth during that time. However, low grade gliomas in adults may come back or change into high grade gliomas after some time. On the other hand, although more than 30% of brain tumors in children are gliomas, these are usually low grade (benign) and once removed do not recur. More than 87% of children, diagnosed with gliomas, survive

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for more than 5 years post surgery and over 83% will live for more than 10 years [4].

In order to advance our understanding of the fundamental mechanisms underlying tumor growth, we need to develop appropriate mathematical models able to predict evolutionary patterns in diseased tissues as well as recovery after treatment. Such models can contribute considerably to the design of optimal, personalized therapies that will not only maximize treatment outcomes but also reduce health care costs. The last few decades have seen extensive progress in mathematical modeling of solid tumor growth that has provided insight into the understanding of some experimental and clinical data. Most models are either discrete cell-based or continuum models (see some recent reviews in [5, 6, 7, 8, 9]). For example, some models of brain cancer are given in [10, 11, 12]. Modeling has also shown that tumor morphology can be used as a predictor of invasiveness [5, 13, 14, 15, 16]. In [17, 18, 19], the authors proposed cell-cell adhesion and external nutrient concentration as parameters controlling the stability of three-dimensional multi-cellular spheroids. While Greenspan [24] considered necrotic tumors in the avascular stage, where growth is regulated only by nutrient diffusion through the surrounding micro-environment, Byrne and Chaplain [17] modeled non-necrotic tumors where nutrient is supplied through the surrounding vascularized environment. During avascular growth, tumor cells receive oxygen, nutrients and growth factors via diffusion through the host tissue. This phase can be investigated by *in vitro* experiments where cancer cells are cultured in a three dimensional geometry [20, 21, 22, 5]. These experiments show that cancer cells self organize into multi-cellular spheroidal colonies due to cell-cell adhesion in which the outer layer of cells tends to expand and grow while the interior cells die due to lack of nutrients. All the continuum models of tumors are based on reaction-diffusion equations describing the evolution of tumor cell density, extracellular matrix, matrix degrading enzymes, and concentrations of cell substrates such as glucose, oxygen, and growth factors and inhibitors. Different constitutive laws have been employed to describe the deformation and stress fields of tissues. For example, the Darcy model, which models fluid flow through a porous medium, was used in [24, 13, 17, 26], while the Stokes' law of fluids was studied in [27]. Both models were investigated in [28, 29, 30]. Other continuum models have used constitutive laws for (visco-) elastic solids to predict the growth of tumors [23]. More details on such models are given in [7].

The main challenge in using these mathematical models for predicting tumor growth in patients is finding the appropriate model parameters. The clinical evaluation of patients required to determine these parameters must be safe and minimally invasive. An example of a non-invasive technology, that may greatly assist in this endeavor, is imaging elastography. Imaging elastography combines information about mechanical wave propagation through tissues together with advances in medical imaging to diagnose tumors based on their stiffness. This *palpation through imaging* process is based on the well-known fact that tumors tend to be stiffer than the surrounding healthy tissue. In order to improve the outcomes of this novel technology, we recently [25] proposed a non-invasive way of classifying gliomas based on their stiffness. The model uses image mass spectra of proteins present in gliomas and assumes that: 1) the relative intensities of proteins given by the image mass spectroscopy are proportional to the corresponding concentrations, and 2) the Young's modulus of a tissue is proportional to the concentrations of proteins present in that tissue. The results in [25] show that we can differentiate, for example, between low and high grade gliomas based on their stiffness, a high grade