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A detailed numerical treatment of the boundary conditions imposed by the skull on a diffusion–reaction model of glioma tumor growth. Clinical validation aspects

Stavroula G. Giatili, Georgios S. Stamatakos *

In Silico Oncology Group, Laboratory of Microwave and Fiber Optics, Institute of Communication and Computer Systems, National Technical University of Athens 9, Iroon Polytechniou, Zografos GR-157 80, Greece

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ABSTRACT

The study of the diffusive behavior of glioma tumor growth is an active field of biomedical research with considerable therapeutic implications. An important aspect of the corresponding computational problem is the mathematical handling of boundary conditions. This paper aims at providing an explicit and thorough numerical formulation of the adiabatic Neumann boundary conditions imposed by the skull on the diffusive growth of gliomas and in particular on glioblastoma multiforme (GBM). Additionally, a detailed exposition of the numerical solution process for a homogeneous approximation of glioma invasion using the Crank–Nicolson technique in conjunction with the Conjugate Gradient system solver is provided. The entire mathematical and numerical treatment is also in principle applicable to mathematically similar physical, chemical and biological phenomena. A comparison of the numerical solution for the special case of pure diffusion in the absence of boundary conditions or equivalently in the presence of adiabatic boundaries placed in infinity with its analytical counterpart is presented. Numerical simulations for various adiabatic boundary geometries and non zero net tumor growth rate support the validity of the corresponding mathematical treatment. Through numerical experimentation on a set of real brain imaging data, a simulated tumor has shown to satisfy the expected macroscopic behavior of glioblastoma multiforme including the adiabatic behavior of the skull. The paper concludes with a number of remarks pertaining to both the biological problem addressed and the more generic diffusion–reaction context.

1. Introduction

The generic diffusion–reaction equation is applicable to a wide spectrum of physical, chemical and biomedical phenomena. In the context of cancer biology and oncology, diffusion has been regarded as one of the fundamental phenomena governing tumor invasion into neighboring normal tissues. Glioblastoma multiforme (GBM), a highly aggressive brain tumor, is a classical example of a highly invasive tumor. GBM cell diffusion in the brain is a reasonable first approximation of the migration of glioma cells along structures such as the basement membranes of blood vessels or the glial limitans externa that contain extracellular matrix (ECM) proteins. Frequently, invasive glioma cells are also found to migrate along myelinated fiber tracts of white matter. Due to its markedly diffusive character, a significant component of the tumor cannot be delineated based on standard tomographic imaging techniques (CT, MRI, PET etc). This constitutes an important limitation

* Corresponding author.
E-mail addresses: giatili@mail.ntua.gr, stgiatili@gmail.com, giatili@otenet.gr (S.G. Giatili), gestam@central.ntua.gr (G.S. Stamatakos).

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to the optimal design of both surgical excision and therapeutic irradiation of the tumor. In order to partly alleviate the problem, mathematical modeling of diffusive tumor growth has been proposed. To this end a number of diffusion based models dealing primarily with the morphology of tumor growth have been developed [1–15].

An early study proposing a reaction–diffusion framework for the modeling of tumor growth in patients with glioma has been published by Cruywagen et al. [16] and Woodward et al. [17]. The effect of treatment has been included as a negative reaction term. Tumor cell invasion has been assumed isotropic, following homogeneous diffusion that is characterized by a global scalar diffusion coefficient. The prototypical modeling study of Burgess et al. [18] stipulates that glioma growth results from an interplay between cell diffusion and cell proliferation. The authors have introduced a simple model for glioma growth based on cell proliferation, cell loss, cell death and cell diffusion starting with an initial tumor lump. Their assumptions are spherical symmetry, homogeneous diffusion and exponential growth. It is noted that in order to facilitate focusing on the cell diffusion phenomena several models assume, either explicitly or implicitly, a mean angiogenesis potential characterizing the entire brain. Inadequate angiogenesis and poorly functioning neovascularization are taken into account indirectly through the consideration of a tumor cell loss rate which along with the tumor cell division rate produce the net tumor growth rate.

A number of publications deal with the macroscopic mechanical deformations of the brain imposed by various agents such as neurosurgery or the macroscopic volume effect of brain tumors [19]. Although such approaches usually ignore tumor cell diffusion within the brain, they may be combined with diffusion based modeling techniques dealing with glioma invasion in order to provide a more comprehensive quantitative perception of the related composite phenomena.

It should be noted, however, that a tumor growth modeling approach based exclusively on the continuous and/or finitized form of the diffusion–reaction equation has a limited potential to efficiently address the complexities of the treatment response phenomena in the multiscale context. The latter include *inter alia* the existence and dynamics of different proliferation potential cell categories (stem cells, limited mitotic potential cells, differentiated cells), different cell cycle phases (G1, S, G2, M), differing radiosensitivities and chemosensitivities, different times spent within each cell-cycle phase etc. Particularly efficient methods to mathematically describe and simulate tumor response to treatment have been based on the consideration of discrete entities and discrete events [20–24]. Therefore, in the future a more comprehensive model addressing both glioma invasion and response to complex treatment modalities could emerge by combining the continuous with the discrete mathematics approach mentioned so far.

For a biologically meaningful and computationally reliable diffusion based solution to the problem of diffusive clinical tumor growth and in particular glioma progression, a careful boundary condition handling is a *sine qua non* prerequisite. However, to the best of the authors' knowledge no explicit treatment of the numerical application of boundary conditions in this context has appeared in the literature as yet. The latter is also in contrast with the importance of a careful handling of the boundary conditions between bone and soft issue which has been demonstrated in a number of cases in the neurosurgery setting. Therefore, the aim of this paper is to outline a detailed numerical handling of the boundary conditions imposed by the presence of the skull in the case of gliomas and in particular of glioblastoma multiforme.

According to the diffusion–reaction based approach the tumor is considered a spatiotemporal distribution of continuous cell density which follows the general diffusion–reaction law [25]. The macroscopic formulation of diffusion, leads to a partial parabolic differential equation. A single tumor cell may constitute the initial tumor within a three-dimensional medium. Tumor growth can be expressed by the following statement [26,27]:

$$\begin{aligned}\text{Rate of change of tumor cell population} = {} & \text{diffusion(motility)of tumor cells} + \text{net proliferation of tumor cells} \\ & - \text{loss of tumor cells due to treatment.}\end{aligned}$$

In the case of glioma, the simulated region of interest may include part of the skull. The latter acts as an adiabatic boundary for the diffusion of the brain tumor, precluding migration beyond it. As a result, the mathematical treatment of the biophysical processes taking place in the vicinity of anatomic boundaries must satisfy specific constraints. Zero flux boundary conditions have to be applied on the anatomic boundaries of the skull surface. Thus if Ω is the brain domain on which the diffusion equation is to be solved the previous statement can be symbolically formulated through the following differential equation [1]:

$$\left\{\begin{array}{c} \frac{\partial c(\vec{x},t)}{\partial t} = \nabla\cdot(D\nabla c(\vec{x},t)) + \rho c(\vec{x},t) - G(t)c(\vec{x},t) \text{ in } \Omega \\ c(\vec{x},0) = f(\vec{x}), \quad \text{initial condition} \\ \hat{n}\cdot D\nabla c(\vec{x},t) = 0 \text{ on } \partial\Omega, \quad \text{boundary condition} \end{array}\right\}. \tag{1}$$

The variable c denotes the cell concentration at any spatial point defined by the position vector $\vec{x}$ and time t. The parameter D denotes the diffusion coefficient and represents the active motility of tumor cells. The term ρ represents the net rate of tumor growth including proliferation, loss and death, $\hat{n}$ is the unit vector normal to the boundary $\partial\Omega$ of the domain Ω and $f(\vec{x})$ is a known function that defines the initial spatial distribution of malignant cells. The term $G(t)$ accounts for the temporal profile of treatment and as a first facilitating approximation $G(t) = k$ may be assumed constant. The latter may crudely model a continuous administration of radiation e.g. through special radioisotope based implants. A more realistic assumption is to assign $G(t)$ different values for different time intervals reflecting various chemotherapeutic and/or radiotherapeutic schedules. The simulation domain R of which Ω is a subdomain is defined as: