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A note on the numerical approach for the reaction–diffusion problem to model the density of the tumor growth dynamics

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ABSTRACT

In this article, we numerically solve an equation modeling the evolution of the density of glioma in the brain—the most malignant form of brain tumor quantified in terms of net rates of proliferation and invasion. We employ a non-linear heterogeneous diffusion logistic density model. This model assumes that glioma cell invasion throughout the brain is a reaction–diffusion process and that the coefficient of diffusion can vary according to the gray and white matter composition of the brain at that location. The analysis provided in this article demonstrates that using the correct finite difference scheme can overcome the stability issues caused by the discontinuities of the diffusion coefficient. We also observe that at the steady-state these discontinuities vanish. To visualize and investigate numerically the behavior of the evolution of tumor concentration of the glioma, we calculated and plotted the number of tumor cells, the average mean radial distance, and the speed of the tumor cells along with charting the effects of net dispersal rate and net proliferation rate terms versus time for different center position values of Gaussian initial profile for each zone (gray and white matter tissues). We have proposed two numerical methods, the implicit backward Euler and the averaging in time and forward differences in space (the Crank–Nicolson scheme), both in combination with Newton's method for solving the governing equations. These methods are compared in terms of their performance in varying time-step and mesh-discretization. The Crank–Nicolson implicit method is shown to be the better choice to solve the equation.

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1. Introduction

Cancer is a complex disease which leads to the uncontrolled growth of abnormal cells, destruction of normal tissues and invasion of vital organs. Uncontrolled evolution of cells leads to tumor formation but the tumors can be benign and malignant. The distinction between benign and malignant tumors is based on many criteria: degree of differentiation, rate of growth, local invasion and metastatic ability (Prayson [1]).

Mathematical modeling of tumor growth by diffusion has been studied by many researchers (Clatz et al. [2], Cruywagen et al. [3], Glass [4], Rockne et al. [5], Tracqui et al. [6], and Woodward et al. [7]). Unfortunately these works did not consider the spatial heterogeneity of the brain tissue in terms of gray and white matter. Giese et al. [8] experimentally established the result that tumor cells moved faster in white matter than in gray matter. Swanson et al. [9] took into account the spatial heterogeneity of the brain tissue by defining the diffusion coefficient D as a function of the spatial variable differentiating regions of gray and white matter and observed that migration in white brain tissue was faster than in gray tissue.

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In a reaction–diffusion model, diffusion and proliferation are the main biological behaviors. This approach models tumor cell infiltration into the surrounding brain tissue. The proliferation is a function representing a reactive behavior and it simulates tumor cell growth and death (Murray [10]). In the literature, the problem of brain tumor growth has been formulated as a reaction–diffusion process, in which the rate of change of tumor cells is given by the net proliferation and diffusion of tumor cells (Bacaër [11], Drasdo [12], Hatzikirou et al. [13], Harpold [14], Mansuri [15], Murray [16], Swanson [17,18]). Swanson's thesis [17] is especially important because it encompasses both the mathematical and medical issues at work. Reaction–diffusion equations with logistic nonlinearity were introduced in the pioneering works of Fisher [19], and Kolmogorov, Petrovskii and Piskunov [20]. The latter model is known as the KPP equation.

Different kinds of cancerous growth such as exponential, logistic and Gompertz are detailed in Murray [16]. Population growth equations are commonly used for the proliferation rate $f(c)$ as summarized either as the exponential law

$$f(c) = \rho\, c(t, x)$$

or the Verhulst (or logistic) law

$$f(c) = \rho\, c(t, x)\left(1 - \frac{c(t, x)}{c_{\max}}\right)$$

or Gompertz law

$$f(c) = -\rho\, c(t, x) \ln\left(\frac{c(t, x)}{e^{k/d}}\right)$$

where ρ is the net proliferation rate in units day^{-1}, $c_{\max}$ represents the carrying capacity of the tissue, providing an upper limit on the number of tumor cells capable of occupying any cubic millimeter of brain, k is the growth rate of tumor and d is a density coefficient, and $e^{k/d}$ is the carrying capacity. Here, k gives an exponential increase when the tumor size $c(t, x)$ is small and d, the decay constant, damps out the growth rate when $c(t, x)$ is large.

The exponential growth is the simplest proliferation law and is suited for quantifying the growth of small tumors during a short period. Gompertz [21] showed that the growth, which was initially exponential, was later limited to an asymptotic rate. In the Gompertzian mode, tumors develop with a growth rate that decreases with the tumoral growth.

The estimation of parameters such as cell proliferation (ρ), diffusion coefficient D, and carrying capacity $c_{\max}$ is important in understanding the behavior of glioma. Since medical imaging techniques can detect regions containing tumor cells, but only if the number of cells are above some threshold (Konukoglu [22]), net rates of proliferation (ρ) and dispersal (diffusion coefficient) D have been estimated from features of pretreatment magnetic resonance (MR) images to predict tumor growth (Tracqui et al. [6], Swanson et al. [9], Powathil et al. [23], Swanson [18], Szeto et al. [24], Konukoglu et al. [25], Roniotis et al. [26]).

The two general numerical methods used to solve the reaction–diffusion equation in the context of tumor growth are finite elements and finite differences. Clatz et al. [27], Hogea et al. [28], and Rockne et al. [29] used finite-element methods to solve anisotropic diffusion equation. But, the finite difference scheme is easier to implement and the pixel structure of digital images provides a natural regular grid. However, the anisotropic diffusion equation is a complex second order partial differential equation (PDE) and simple finite difference is not appropriate. This second order PDE was reduced to simpler first order PDEs by using the concept of manifolds (Cobzas et al. [30] and Konukoglu et al. [25]). But the solution of the equation gives us tumor delineation area instead of the tumor cell density. Jbabdi et al. [31] used chain rule expansion to solve anisotropic diffusion equation, however, Mosayebi et al. [32] proved that chain rule expansion was unstable. In Roniotis [33], anisotropic heterogeneous diffusion case study, the abstract model used was non-linear. However, for their computation, the net cell proliferation rate function was zero which effectively rendered the model linear. They made a detailed error analysis in this linear case. Lolas [34] used finite difference methods to solve isotropic diffusion equation. An isotropic diffusion equation was first proposed by Swanson [17] in her Ph.D. thesis assuming the net growth of glioma cells was linear. Later, Swanson et al. [35], Roniotis et al. [26], Papadomanolaki and Saridakis [36] utilized the finite difference methods to solve heterogeneous version of this diffusion equation.

We should note that tumor environment is combination of many constituents, such as, different types of tumor cells, blood vessels, nutrients, immune system cells, healthy cells, among others. There are numerous researchers modeling the tumor evolution using complex models that have 4-, 6-, and 10-species. For instance, the model developed by Cristini et al. [37] depicted the evolution of the nutrients as a reaction–diffusion equation and delineated the mixture as being composed of tumor cells and water. As the model did not consider the dead cells as a separate constituent, when the cells inside the tumor died because of lack of oxygen, water occupied their original position, and the characteristic necrotic core was not represented. The model developed by Wise et al. [38] splits the tumor into viable and dead cells. This modification allowed the representation of cells dying inside the tumor due to lack of nutrients and oxygen.

The model developed by Hawkins-Daarud et al. [39] was a four-species tumor growth model, in which the extracellular water was divided into nutrient rich and nutrient poor parts. However, it did not reproduce the necrotic core inside the tumor. A universal hybrid 10-species tumor growth model of this general type was recently developed by Lima et al. [40], in which tumor cells were divided into proliferative, hypoxic (quiescent) and necrotic states: healthy cells, nutrient, tumor growth factor and endothelial cells all incorporated in the mixture. Following the work of Lima et al. [40], Lima et al. [41]

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