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Mathematical modeling of brain glioma growth using modified reaction–diffusion equation on brain MR images

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ABSTRACT

In this paper, a modified reaction–diffusion model is proposed for modeling the diffusion of brain glioma cells. Unlike the other models, a weighted parameter is introduced, which balances the diffusion coefficient of the grey and white matters. Anisotropic characteristics of the model are represented. A local region similarity measure (local Bhattacharyya distance) determines the weighted parameter. Experimental results demonstrate the effectiveness and accuracy of the modified reaction diffusion equation with a weighted parameter for real brain glioma MR images.

1. Introduction

Brain gliomas account for about 50% of all primary brain tumors [1]. With the advent of magnetic resonance imaging (MRI) technology, more gliomas have been detected earlier, and more geometric patterns of gliomas have also been provided. Unlike most other tumors, glioma are generally diffuse and invasive intracranial neoplasms. There are no obvious boundaries between the normal brain tissue and gliomas. Currently, glioma surgery relies mainly on experience, often without complete resection. The residual gliomas reproduce easily after operation. Therefore, mathematical modeling has been used as a theoretical framework to describe the diffuse and invasive nature of gliomas. The true boundaries of gliomas can be determined more precisely to guide the research of glioma operation.

The models of brain glioma can be grouped into two classes: image-based modeling and reaction–diffusion model of glioma cells. Image-based models include models that concentrate on the migration of tumor cells and their invasive processes, and models that consider the mechanical mass effect of the lesion and their imprint on surrounding tissues. The existing problem is the estimation of model parameters in image-based modeling, and there are few studies addressing this problem. Hogea et al. [2] propose a framework for modeling glioma growth and the mechanical impact on the surrounding brain tissue. An Eulerian continuum approach is applied that results in a system of nonlinear partial differential equations (PDE). Some unknown parameters are estimated via PDE constrained optimization. Konukoglu et al. [3] propose a parameter estimation method that use time series of medical images for reaction–diffusion tumor growth models. A modified anisotropic Eikonal model is used to formulate the motion of tumor. This method estimates the patient specific parameters of the proposed model using the images of the patient taken at successive time instances. The proposed model formulates the evolution of the tumor delineation visible. The evolution of the tumor delineation visible remains consistent with the information available. Almost all glioma models are formulated by the reaction–diffusion equation, and the diffusivity is a constant. Swanson et al. [4] provides an equation to quantify the net proliferation rate of invasive cells. The model expands to include heterogeneous brain tissue with different motilities of glioma cells in gray and white matter. The equation can be formulated as rate of change of tumor cell concentration over time = net diffusion of tumor cells + net proliferation of tumor cells. Painter and Hillen [5] propose a method that uses diffusion tensor imaging data to predict the anisotropic pathways of invasion. The nonuniform growth of brain gliomas can be handled appropriately. Islem et al. [6] propose a tumor growth parameters estimation method. The tumor source location and the diffusive ratio between white and grey matter are estimated from a single time point image of nonswollen brain tumor. This method is applied to low-grade gliomas. Recently, Ellingson et al. [7] propose a high order diffusion tensor model, which estimates errors associated with diffusion tensor imaging for complex microstructure.

In this paper, we consider the different diffusivity of glioma cells in the white and grey matter, and propose a new automatic setting weighted parameter model, which controls automatically diffusivity of glioma cells in different regions. Diffusive gliomas infiltrate into the neighboring tissues. The study [8] shows that

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although gliomas grow from white matter, but they can infiltrate into grey matter as well. However, the rate of the growth in grey matter is lower. In the proposed model, we introduce the local Bhattacharyya distance, which mainly determines the similarity of two different local regions. The means and standard deviations are considered in the Bhattacharya distance. However, only one factor is considered in the other distance metrics, such as Euclidean distance, Minkowski distance. The accuracy using the Bhattacharya distance is better than the other distance metrics. The local Bhattacharyya distance can control the diffusive rate between the white and grey matter, instead of estimating the constant speed of glioma cell growth in different regions, respectively. In the experiments, a series of real brain glioma MR images are employed for evaluating the performance of the proposed method. The experimental results demonstrate that the proposed model can show the diffusion and invasion of brain glioma cells accurately.

The remainder of this paper is organized as follows: In Section 2, the proposed model is presented. The simulation results are shown in Section 3. Finally, this paper is summarized in Section 4.

2. The mathematical model

Let $u(x,t)$ be the number of glioma cells at any position x and time t. The diffusion and invasion equation can be written mathematically as a reaction–diffusion equation [9]:

$$\frac{du}{dt} = \nabla \cdot (D\nabla u) + \mathcal{R}(x,t) \tag{1}$$

where D denotes the diffusion coefficient of glioma cells in brain tissue. $\mathcal{R}(x,t)$ is the proliferation function, which represents the change of glioma cells invading normal tissue. The deficiency of this model is that the diffusive coefficient D is a constant. The different diffusive speeds between the white and grey matter are not represented accurately.

Due to this limitation, some anisotropic reaction–diffusion equations are proposed. In [10], D is constructed as an anisotropic tensor taking into account two different phenomena: differential motility of tumor cells in different tissues and directional preference of tumor cell diffusion in the white matter. D is directly obtained from the diffusion tensor MRI, and can be represented as follows:

$$D(x) = \begin{cases} d_g I, & x \in \text{gray matter} \\ d_w D_{water}, & x \in \text{white matter} \end{cases} \tag{2}$$

where tumor cells are assumed to diffuse isotropically in the grey matter with a rate d_g and diffuse along the fiber tracts in the white matter proportional to the diffusion tensor of the water molecules D_{water} through a coefficient d_w. D_{water} is obtained from the diffusion tensor MR image and normalized such that the highest diffusion rate in the brain would be 1. As the diffusion of the white matter is estimated from the diffusion tensor of the water molecules D_{water}, this model can have more error.

In this paper, we proposed a modified reaction–diffusion equation to simulate the diffusion and invasion of glioma cells. The diffusion tensor of the water molecules D_{water} is not considered in the proposed model, and we consider directly the diffusion of the white and grey matters. Our model is detailed as follows.

2.1. Modeling

Let $\Omega \subset \mathbb{R}^2$ is a $2D$ image space. We assume that the image domain can be partitioned into two regions. These two regions can be represented as the regions outside and inside the zero level set of ϕ, i.e., $\Omega_1 = \{\phi > 0\}$ and $\Omega_2 = \{\phi < 0\}$, where $\phi : \Omega \to \mathbb{R}$ is an auxiliary function. The boundaries between two different regions are defined as the zero level set of ϕ implicitly.

To account for spatial heterogeneity of the brain tissue, we assume that the diffusion coefficient D is a function of the spatial variable x differentiating regions of grey and white matters. The reaction–diffusion system can be written mathematically as

$$\frac{du}{dt} = \omega \nabla \cdot (D_g \nabla u) + (1-\omega)\nabla \cdot (D_w \nabla u) + \mathcal{R}(x,t) \tag{3}$$

$$D_g \nabla u \cdot \vec{n} = 0, x \in \partial\Omega_g, \tag{4}$$

$$D_w \nabla u \cdot \vec{n} = 0, x \in \partial\Omega_w, \tag{5}$$

where ω is a weighted variable parameter to reflect the similarity between the grey and white matters. How to set the parameter is addressed as follows. Ω is the brain MR image domain, $\partial\Omega_g$ represents the boundaries of the grey matter and $\partial\Omega_w$ represents the boundaries of the white matter. D_g is the diffusion coefficient of the grey matter. D_w is the diffusion coefficient of the white matter. $\mathcal{R}(x,t)$ is the proliferation function.

In Eq. (3), the proliferation function $\mathcal{R}(x,t)$ is often chosen as [4]

$$\mathcal{R}(x,t) = \rho u\left(1 - \frac{u}{k}\right) \tag{6}$$

where ρ is the proliferation coefficient. Cells throughout the tumor are assumed to proliferate at a constant rate ρ until they reach a limiting density k. k is a constant.

2.2. Parameter estimation

Parameter estimation in realistic mathematical models is crucial. In this section, we propose a local region method to compute the parameter ω. For each point x in the image domain Ω, we consider a circular neighborhood with a small radius γ, which is defined as

$$\mathcal{O}_x \triangleq \{y : |x-y| \le \gamma\}. \tag{7}$$

Let $\{\Omega\}_{i=1}^N$ denote a set of disjoint image regions, such that $\Omega = \bigcup_{i=1}^N \Omega_i$, $\Omega_i \cap \Omega_j = \varnothing$, $\forall i \neq j$, where N refers to the number of regions. Fig. 1 presents an image consisting of three regions: Ω_1, Ω_2, and Ω_3.

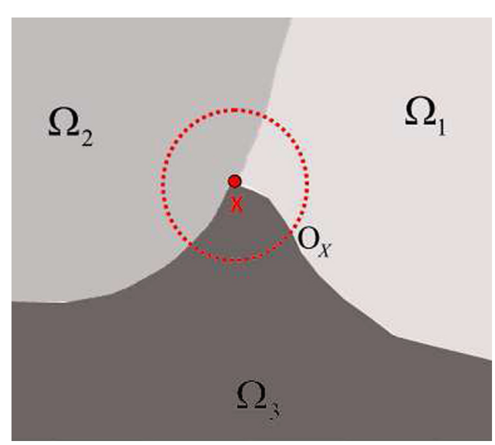

Fig. 1. Graphical representation of a local region. The dashed red circle denotes the circular neighborhood of x, $\mathcal{O}_x$. Ω_1, Ω_2 and Ω_3 denote a set of disjoint image regions. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this article.)