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Subject-specific Brain Tumor Growth Modelling via An Efficient Bayesian Inference Framework

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Abstract

An accurate prediction of brain tumor progression is crucial for optimized treatment of the tumors. Gliomas are primarily treated by combining surgery, external beam radiotherapy, and chemotherapy. Among them, radiotherapy is a non-invasive and effective therapy, and an understanding of tumor growth will allow better therapy planning. In particular, estimating parameters associated with tumor growth, such as the diffusion coefficient and proliferation rate, is crucial to accurately characterize physiology of tumor growth and to develop predictive models of tumor infiltration and recurrence. Accurate parameter estimation, however, is a challenging task due to inaccurate tumor boundaries and the approximation of the tumor growth model. Here, we introduce a Bayesian framework for a subject-specific tumor growth model that estimates the tumor parameters effectively. This is achieved by using an improved elliptical slice sampling method based on an adaptive sample region. Experimental results on clinical data demonstrate that the proposed method provides a higher acceptance rate, while preserving the parameter estimation accuracy, compared with other state-of-the-art methods such as Metropolis-Hastings and elliptical slice sampling without any modification. Our approach has the potential to provide a method to individualize therapy, thereby offering an optimized treatment.

Keywords

Gliomas; Tumor Growth Model; Elliptical Slice Sampling

1. INTRODUCTION

Gliomas are the most common primary brain tumors which arise from a glial cell of the central nervous system.¹ In particular, survival in patients with high-grade brain gliomas

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remains limited with a median patient survival of about 16 months. Gliomas differ from other tumors in that they grow infiltratively into the brain parenchyma rather than growing extra-axially by pushing outward.² Despite different treatment regimes, such as surgical removal, radiotherapy, and chemotherapy, treatment of these tumors remains one of the most challenging tasks as infiltrating tumor cells spread beyond the radiographic margins of the tumor visible through medical imaging, such as Magnetic Resonance Imaging (MRI). Localized treatments are dependent on the radiographically obvious tumor, often guessing at the spatial extent of tumor infiltration by using current radiologic reading practices. Excessive and unnecessary over-estimation of disease extension results in an increase in radiation exposure and an associated toxicity risk. On the other hand, under-estimation is generally less of a risk due to generous empiric margins used, but it can lead to reduced local tumor control. To address this, we propose an efficient tumor growth model to estimate the infiltration of tumors as well as to predict the tissue that is likely to exhibit the fastest tumor recurrence, which will aid in offering an optimized treatment.

A tumor growth model usually consists of two biological factors—i.e., the proliferation and the infiltration of the tumors, which can be described using the reaction-diffusion equation.^{3–6} The reaction is typically modelled as a logistic growth for the proliferation and the diffusion describes the infiltration. Accurate parameter estimation is a challenging task due to inaccurate tumor boundaries and the approximation of the tumor growth model. Several attempts have been made to estimate the parameters of tumor growth model to date. Some early works^{3, 4} have focused on tumor growth velocity, as the asymptotic velocity of tumor growth can be determined from the parameters associated with tumor growth. In recent developments, Konukoglu et al.⁵ proposed a parameter estimation approach by using both tumor delineation and tumor growth velocity. In addition, Lê et al.⁶ presented a Bayesian framework for the parameter estimation, effectively dealing with the lack of time-series tumor information, uncertainty of tumor boundary, and the tumor model approximation. In that work, Hamiltonian Markov chain Monte Carlo (MCMC) sampling was used to obtain a sequence of random samples from a target density function. Our work is inspired by both of these approaches and we incorporated a more efficient way to achieve the goal.

In most Bayesian models, exact posterior inference is intractable and therefore approximate inference techniques are preferred to obtain the parameters.⁷ There are two main categories of approaches to find the solution from Bayesian models. The first group of approaches is to use deterministic approaches such as the Laplace approximation, Expectation Propagation, and Variational Bayes. These approaches provide fast and analytical posterior approximations, yet may cause significant bias that may lead to incorrect parameter estimation. The second group of approaches is to use stochastic sampling approaches such as MCMC, where MCMC represents the target posterior with samples. While these approaches provide asymptotically exact solutions, the techniques under this category can be slow, as they require extensive tuning. Additionally, they perform poorly when the variables used in the tumor growth model are highly correlated. Among MCMC methods, elliptical slice sampling (ESS) is a generic method for posterior inference with models that have a Gaussian prior. In this work, in order to improve the efficiency of the posterior inference in ESS and to disambiguate the two parameters (i.e., the proliferation and infiltration) in the tumor growth model, we propose to use ESS with a marginal region for candidate samples,

defined by using the relationship between the parameters and tumor growth speed to yield efficient and accurate tumor parameter estimation results. Our approach improves the acceptance rate, while preserving the parameter estimation accuracy of ESS. We apply the proposed algorithm to synthetic and clinical MR data to demonstrate the validity of the proposed method and its improved efficiency compared with other alternatives such as Metropolis-Hastings and elliptical slice sampling without any modification.

2. METHODS

2.1 Tumor growth model

For the tumor growth model, we adopt a diffusion-reaction equation including two terms of proliferation of tumor cells and invasion into surrounding tissue. By using the normalized tumor cell density, the model can be expressed as

$$\frac{\partial c}{\partial t} = \nabla \cdot (\mathbf{D} \nabla c) + \rho c(1 - c), \quad (1)$$

where $c(\mathbf{x}, t)$ denotes the tumor cell density, t represents the time variable, and ∇ denotes the gradient operator. The reaction term, $\rho c(1 - c)$, represents the proliferation model using proliferation rate ρ . In the diffusion term, $\mathbf{D}(\cdot)$ denotes the diffusion tensor of a 3-by-3 symmetric positive definite matrix describing the local anisotropic diffusion, which can be written as

$$\mathbf{D}(\mathbf{x}) = \begin{cases} d_g \mathbf{I}(\mathbf{x}) & \mathbf{x} \in \text{gray matter} \\ d_w \mathbf{D}_{\text{water}}(\mathbf{x}) & \mathbf{x} \in \text{white matter.} \end{cases} \quad (2)$$

Here $\mathbf{I}(\cdot)$ is the 3-by-3 identity matrix, $\mathbf{D}_{\text{water}}(\cdot)$ is the diffusion tensor of water molecules at $\mathbf{x}$, and d_g and d_w denote the diffusion rates in gray and white matter, respectively. The ratio of d_w to d_g is set to 100 as in,² because gliomas diffuse faster in white matter than gray matter. In addition, to set the boundary condition, the Neumann boundary condition is adopted, namely $\mathbf{D}_{\text{water}} \nabla c \cdot \mathbf{n}_b = 0$ only for $\mathbf{x}$ on the boundary of the brain, where $\mathbf{n}_b$ denotes the surface normal. Since a tumor density image is difficult to obtain directly from an MR image, the initial condition of tumor density is determined via the tumor density extrapolation from tumor delineation as in.⁸ To evolve tumors based on a tumor growth model, an operator splitting method and the Crank-Nicolson method are used to solve Eq. (1).

2.2 Personalization of tumor growth model

Algorithm 1

Our region-adaptive sampling based on ESS

Input : Initial state $\mathbf{f}$, a routine that samples from $\mathcal{N}(\boldsymbol{\mu}, \boldsymbol{\Sigma})$, log-likelihood function $\log L$, the number of samples to be accepted N , and sample region Ω

Output : Sequence of accepted samples $\mathbf{S}$

```

1 Initialize:  $n \leftarrow 0$ ,  $\mathbf{g} \leftarrow \mathbf{f}$ 
2 repeat
3   Choose  $\boldsymbol{\nu} \sim \mathcal{N}(\boldsymbol{\mu}, \boldsymbol{\Sigma})$  to define ellipse.
4   Determine log-likelihood threshold value:
       $u \sim \text{Uniform}[0, 1]$ 
       $\log y \leftarrow \log L(\mathbf{g}) + \log u$ 

5   Draw an initial proposal:  $\theta \sim \text{Uniform}[0, 2\pi]$ 
6   Define a bracket:  $[\theta_{\min}, \theta_{\max}] \leftarrow [\theta - 2\pi, \theta]$ 
7    $\mathbf{g}' \leftarrow \mathbf{g} \cos \theta + \boldsymbol{\nu} \sin \theta$ 
8   if  $\mathbf{g}' \notin \Omega$  then
9     Shrink the bracket and try a new point:
10    if  $\theta < 0$  then  $\theta_{\min} \leftarrow \theta$  else
11
12     $\theta_{\max} \leftarrow \theta$ 
13     $\theta \sim \text{Uniform}[\theta_{\min}, \theta_{\max}]$  GoTo 7
14  else
15    Evaluate  $\log L(\mathbf{g}')$ .
16    if  $\log L(\mathbf{g}') \leq \log y$  then
17      GoTo 9 ▷ Reject
18    else
19      Add  $\mathbf{g}'$  to  $\mathbf{S}$ . ▷ Accept
20       $n \leftarrow n + 1$  and  $\mathbf{g} \leftarrow \mathbf{g}'$ 
21    end
22  end
23 until  $n = N$ 
24 Return  $\mathbf{S}$ 

```

To personalize the tumor growth model, we estimate its parameters using tumor images for two different time points obtained from the same subject. The posterior of tumor growth model parameters in the Bayesian framework⁶ can then be expressed as

$$P(\boldsymbol{\Theta} \mid y_{t_1}, y_{t_2}) \propto P(y_{t_1}, y_{t_2} \mid \boldsymbol{\Theta})P(\boldsymbol{\Theta}), \quad (3)$$

where $\boldsymbol{\Theta} = (\rho, d_w)$, y_t is the tumor density image at time t , and t_1 and t_2 denote the time points of the first and second examinations, respectively. In Eq. (3), we assume that prior $P(\boldsymbol{\Theta})$ follows a Gaussian distribution, and the likelihood can be modelled as

$$P(y_{t_1}, y_{t_2} \mid \boldsymbol{\Theta}) \propto \exp \left(-\mathcal{D}(\phi(u), \phi(y_{t_2}))^2 / \sigma^2 \right), \quad (4)$$

where $\phi(\cdot)$ denotes a boundary function of tumor density that is determined using a threshold value, and $\mathcal{D}$ denotes the Hausdorff average distance. Note that the parameter σ is determined from the noise level. To obtain the posterior density of the parameters, we first obtain a sequence of random samples from the posterior by using the ESS method,⁷ and then perform kernel density estimation.

2.3 Adaptive region based sampling

In this work, we opt to improve the ESS in approximating the posterior via the tumor physiology. The overall algorithm is shown above. The two parameters under consideration are inversely proportional given constant tumor growth speed. Note in Eq. (1) that an asymptotic tumor growth speed can be determined as

$$v = 2\sqrt{n'Dn\rho}, \quad (5)$$

where n denotes the direction of tumor growth.⁵ Utilizing this relationship, we adaptively define a region for candidate samples, where the region can be determined by using a central straight line and its two marginal lines in the log domain of the parameters. To determine the lines, the likelihood is evaluated on sparse-grid points, and Gaussian fitting is performed in the log domain of the parameters. The central line is then determined as the major axis of the fitted Gaussian function. The marginal lines are determined as two lines parallel to the central line with a marginal distance. Here, the marginal distance is selected as $4\sigma_{minor}$ where σ_{minor} denotes the standard deviation of the fitted Gaussian function along the minor axis. This sampling scheme is incorporated into ESS.⁷

3. EXPERIMENTAL RESULTS

One synthetic and three *in vivo* human data were used to validate our method. The detection threshold of tumor density was set to 16% for both the synthetic data and clinical T2-FLAIR images.^{3, 6} We performed Gaussian fitting on the likelihood of sparse-grid points of the two parameters without correlation assumption, and then adopted the mean and 3 times the standard deviation of the fitting function as the prior mean and standard deviation for each parameter. Meanwhile, σ of the likelihood in Eq. (4) was manually tuned empirically for each dataset. We compared the acceptance rate of our approach with those of ESS without any modification and Metropolis-Hastings (MH).⁷

3.1 Synthetic data

As for the synthetic data, an atlas-based brain image was adopted along with its diffusion tensor with a resolution of $1 \times 1 \text{ mm}^2$. Initializing a single voxel as a tumor cell in the brain image, we simulated a tumor growth using d_w of $0.05 \text{ mm}^2/\text{days}$ and ρ of 0.05 days^{-1} . Figure 1(a) shows that the posterior result obtained from the proposed method was quite similar to that from ESS, even though the samples drawn from the proposed method are limited to a marginal region of candidate samples. Meanwhile, as shown in Figure 2(a), the acceptance rate of the proposed method was higher than those of ESS and MH.

3.2 Clinical data

In order to estimate the parameters in the *in vivo* human data, we used three datasets of two T2-FLAIR images at different time points, as shown in Figure 3. For each set of images, we first performed rigid registration from the second time point image to the first time point image. Meanwhile, manual segmentation was performed for the tumor, gray matter, white

matter, cerebrospinal fluid (CSF), and ventricles on the T2-FLAIR images, and diffusion tensor is reconstructed using the diffusion weighted MR images of the same subject. Using the segmentation and the reconstructed diffusion tensor, we extrapolated the tumor density based on the given parameters and the tumor delineation, followed by evolving the tumor until the second time point. The time differences between the first and second time points for patients 1, 2, and 3 are 60, 55, and 55 days, respectively. Figures 4(a–c) show tumor segments at the second time point that are superimposed on the segmented image of the first time point, and Figures 4(d–f) show simulated tumor segments using the peaks of the posterior results obtained through our method. It is noted in Figures 2(b–d) that the proposed method provided higher acceptance rates than the other sampling methods, while the estimated posterior for the proposed method is comparable to that of ESS. To further quantify the accuracy of the estimated posteriors, Dice coefficients of simulated tumors obtained using different sampling methods are compared in Figure 2, where all sampling methods provided similar Dice coefficients for patient datasets. This confirms the accuracy of our method is satisfactory, which is similar to other methods.

4. CONCLUSION

In this paper, we have presented a Bayesian framework using an improved ESS method for a subject-specific tumor growth model to estimate the tumor parameters effectively. Experimental results on synthetic and *in vivo* human data showed that the proposed method yielded higher acceptance rate, while preserving the parameter estimation accuracy. Our approach has the potential to provide a method to account for anisotropic growth patterns of gliomas, therefore offering a tool to make target delineation more objective and automated.

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Figure 1.

Posterior contours determined for synthetic and patient data. The first and second rows are determined from ESS and the proposed method, respectively.

Figure 2.

Acceptance rates and Dice coefficients obtained from each sampling method for both synthetic and *in vivo* human data. 1, 2 and 3 represent MH sampling, ESS, and the proposed method, respectively.

Figure 3. T2-FLAIR images for (a) patient 1, (b) patient 2, and (c) patient 3, obtained at two different time points, t_1 (first row) and t_2 (second row)

Figure 4.

Comparison of tumor segments (red regions) at t_2 . Red regions in (a–c) are the tumor segments determined from three patient datasets and the ones in (d–f) are the simulated tumor segments determined from the peaks of the posterior.