IEEE Access
Multidisciplinary | Rapid Review | Open Access Journal

Received March 19, 2018, accepted May 9, 2018, date of publication May 22, 2018, date of current version June 26, 2018.

Digital Object Identifier 10.1109/ACCESS.2018.2839681

Macroscopic Cerebral Tumor Growth Modeling From Medical Images: A Review

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This work was supported in part by the National Natural Science Foundation of China under Grant 81571758, Grant 81771922, and Grant 61501305, in part by the National Key Research and Develop Program under Grant 2016YFC0104703, in part by the National Natural Science Foundation of Guangdong Province under Grant 2017A030313377 and Grant 2016A030313047, in part by the Shenzhen Peacock Plan under Grant KQTD20160531112051497, and in part by the Shenzhen Key Basic Research Project under Grant JCYJ20170818142347251 and Grant JCYJ20170818094109846.

ABSTRACT Mathematical models have been ubiquitously employed in various applications. One of these applications that arose in the past few decades is cerebral tumor growth modeling. Simultaneously, medical imaging techniques, such as magnetic resonance imaging, computed tomography, and positron emission tomography, have witnessed great developments and become the primary clinical procedure in tumors diagnosis and detection. Studying tumor growth via mathematical models from medical images is an important application that is believed to play significant role in cancer treatment by predicting tumor evolution, quantifying the response to therapy, and the effective treatment planning of chemotherapy and/or radiotherapy. In this paper, we focus on the macroscopic growth modeling of brain tumors, mainly glioma, and highlight the current achievements in the state-of-the-art methods. In addition, we discuss some challenges and perspectives on this research that can further promote the research of this field.

INDEX TERMS Mathematical modeling, cerebral tumors, glioma growth, macroscopic models, diffusive model, biomechanical model, chemotherapy, radiotherapy.

I. INTRODUCTION

Human brain is the most complicated organ in the body that acts as the center of the nervous system. The average weight of adult human brain is about 1.2–1.4 kg of a very soft, jelly like matter and it consists, basically, of neurons, blood vessels, and glial cells [1]. Roughly estimated, human brain consists of 100 billion cells [2]. Each brain cell is connected to around 10,000 other cells, which equals about 1000 trillion connections inside the brain [3]. With this complex structure, any small damage or interruption of cells' functions may result in very serious consequences.

The word ''tumor'' is derived from the Latin word ''*tumor*'' which means swelling and recently it is called lesion. Brain tumors or intracranial neoplasms are abnormal and uncontrolled growth of cells in the central nervous system (CNS) that affect the brain functioning. Basically, brain tumors can be classified either by place of origin or by the degree of aggressiveness. Tumors that originally grow and remain in the brain are known as primary tumors while those begin elsewhere and spread to the brain are known as secondary (metastatic) tumors.

According to the degree of aggressiveness, brain tumors can be cancerous (malignant) or noncancerous (benign). Benign brain tumors grow slowly and rarely invade the surrounding tissues, therefore, they are less life threatening. They usually have visible and clear borders which make them easy in surgical resection. On the other hand, malignant brain tumors grow very fast and invade the healthy brain tissues which make quick medical intervention very urgent. However, these types of tumors have unclear borders that make surgical resection very difficult. Although brain tumors are not very common compared with other types of cancer,

e.g. lung and breast, they are among the most fatal cancers with high mortality rate [4].

The most common primary malignant brain tumor is known as glioma. It arises from the glial cells (from the Greek word "*glue*") which support and nourish the brain. Glioma accounts for 30% of all brain and CNS tumors and 80% of all malignant brain tumors [5]. Based on the type of the glial cells, gliomas mainly include astrocytoma, oligodendroglioma, and ependymoma (Fig. 1a). According to their locations in the brain, the other common primary brain tumors are gliomas, meningioma, pituitary adenomas, and vestibular schwannoma [6]. Fig. 1 shows the physiological and anatomical characteristics of brain tumors [6].

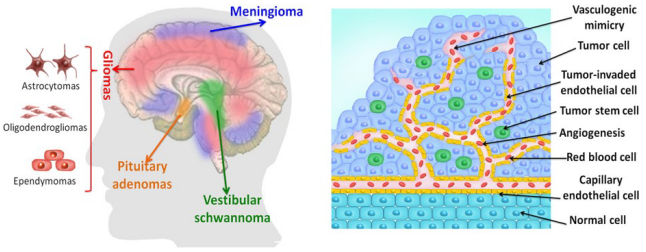


FIGURE 1. Physiological and anatomical characteristics of brain tumor [6]. (a) The glial cells involved and primary brain tumors. (b) Cells associated with the brain tumor tissue.

Gliomas vary in histological and biological features from low to high grades. The most known and accepted grading of gliomas are made by the World Health Organization (WHO) which divides glioma according to the degree of malignancy and other factors to four grades from I to IV [7]. Grades I and II, known as low grade glioma (LGG), tend to be less malignant and slow-growing. These tumors account for about 25% of all gliomas patients that may survive for many years (3–8) and have a good quality of life during that period [8]. However, LGG are vulnerable to transformation to grade III and IV after variable period of time. In study on transformation of LGG in 2011 [9], it was observed that 60% of patients with LGG were progressed to high grade ones.

On the other hand, grades III and IV, known as high grade glioma (HGG), are highly malignant tumors that eventually lead to death. Grade III includes: anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic oligoastrocytoma, and anaplastic ependymoma while grade IV is known as gliomblastoma multiforme (GBM). The HGG, particularly GBM, grows very fast and invades surrounding tissue. In most cases, HGG exhibits a necrotic core surrounded by edema that exerts pressure on surrounding brain tissues causing local mass effect (deformation). Unlike LGG, the prognosis of HGG is very poor and, mostly, subject to recur after treatment with average survival time of 1 year [10].

Brain tumors can be diagnosed by symptoms or some other medical tests. However, medical imaging remains the standard method to detect, examine, and diagnose brain tumors. Such imaging techniques include magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), computed tomography (CT), and positron emission tomography (PET), each has its favorable uses and benefits.

MRI is an imaging technique based on the principles of nuclear magnetic resonance and can be anatomical, diffusion, or functional. The anatomical and diffusion MRI are commonly used when studying tumor growth modeling while functional MRI, to the best of our knowledge, plays no major role in tumor growth modeling and there is no such study reports this. Anatomical MRI provides different information based on the applied radio frequency and the contrast agent (gadolinium) injected into the subject during the imaging process. Basically, there are 4 different sequences of the anatomical MRI: T1-weighted, T1Gd (T1-weighted with gadolinium), T2-weighted, and fluid attenuated inversion recovery (FLAIR) images where the appearance of the tumor regions and brain tissues differs accordingly. Fig. 2 shows different appearances of brain tissues and glioma regions in T1, T1Gd, T2, and FLAIR MR images.

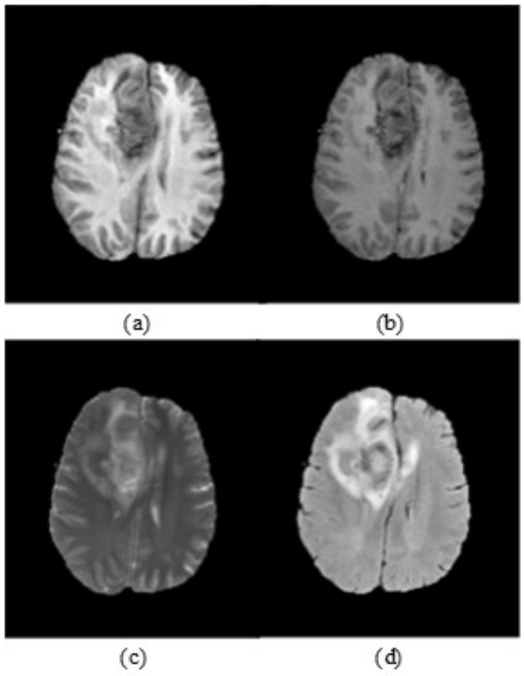


FIGURE 2. The appearance of glioma in MR images (axial slices). (a) T1-weighted image, (b) T1Gd image, (c) T2-weighted image, and (d) FLAIR image.

On the other hand, DTI is another MRI protocol that is relatively new imaging technique proposed in the mid of nineties of the last century by Basser *et al.* [11], [12]. The main concept of DTI is that, water molecules diffuse in different directions along the tissues depending on their type, integrity, architecture, and presence of barriers, thus, giving information about their orientation and quantitative anisotropy [13]. The diffusion is less restricted along the axon and tends to be anisotropic in white matter (WM) whereas in gray matter (GM) it is usually less anisotropic and unrestricted in all directions (isotropic) in the cerebrospinal

fluid (CSF) [14], [15]. Such information is of great importance for tumor growth modeling, especially, for the diffusive gliomas.

For isotropic diffusion, normal diffusion MRI represented by one scalar parameter would be sufficient. However, the anisotropic diffusion needs a tensor to fully describe the molecular mobility in each direction and the correlation between them. Tensor is represented by a 3×3 symmetric matrix, thus, one must collect diffusion weighted imaging (DWI) scans with several gradient directions (at least six directions are necessary) along with an image acquired without diffusion weighting (called b0) [16]. DTI can provide a plenty of information that can be widely used in many applications [14], [16]–[19]. The most beneficial parameters that can be used in studying tumor growth modeling are mean diffusivity, fractional anisotropy, relative anisotropy, and volume ratio.

In fact, MRI and DTI are not the only imaging modalities used to study tumor growth modeling but they are the most important and common ones. However, other imaging techniques can be used to provide different information of interest such as CT and PET [20]–[22].

Since late nineties of last century, the research of tumor growth modeling became very active on both brain tumor and other tumors as well. Although some interesting reviews are already existing [23]–[35], they are either obsolete, focus on biological aspects, or even non-comprehensive. In this paper, we review recent publications from the literature and classify different approaches to highlight the current achievements and challenges of the different tumor growth models. In particular, we will review the diffusive models, mechanical models, customization of the diffusive model parameters, treatments efficacies on tumor growth modeling, mathematical solutions, and finally the relation between tumor growth models and different applications, specifically, segmentation and registration. Finally, we give some discussions and perspectives on the future of tumor growth modelling for further research.

The rest of this review is structured as follows. Section II represents the different classifications of tumor growth models. Section III is dedicated to the different treatments and their efficacies on tumor growth modeling. Sections IV and V discusses the customization of growth model parameters and the mathematical solutions of the diffusive models. The relationships between segmentation, registration, and growth models are given in Section VI. Finally, discussions and perspectives followed by conclusion are summarized in Sections VII and VIII, respectively.

II. TUMOR GROWTH CLASSIFICATION

Tumor growth can be studied using three different strategies: *in vivo*, *in vitro*, and *in silico*. *In vivo*, from Latin ''within the living'', concentrates on growth dynamics by observing the biological characteristics of a living organ and this mainly uses animals for such experiments. While *in vitro*, from Latin ''in glass'', focuses on experiments done in test tubes to observe only one thing rather than the whole organ. The in silico, from Latin ''*in silicon*'', refers to experiments that are simulated using machine with silicon semiconductors, which is basically computers in our case. These three strategies can be classified in different ways as microscopic (includes in vivo and in vitro) and macroscopic (for in silico) [36]. From another point of view, growth models can be classified into continuous, discrete, or hybrid [37]. Also, models can be classified according to image spaces used; atlas-based and patient-based. Here, we consider the microscopic and macroscopic strategy.

Microscopic models focus on the observations at microscopic level by describing the interactions between cells and chemical excretion, nutrition sources, oxygen, and surrounding blood vessels. Based on microscopic point of view, there are three different phases of growth which are: avascular, angiogenesis, and vascular growths, see [38]–[42] for more details. On the other hand, macroscopic models use complex mathematical models guided by medical images and histological slices to study the tumor growth which is our main focus in this review. The macroscopic models can be further divided into two different types: mechanical models which focus on the induced mass-effect of the tumor on the surrounding tissues and the diffusive models which focus on the invasion of the tumor cells into the surrounding tissues. Basic classification of the growth models is given in Fig. 3.

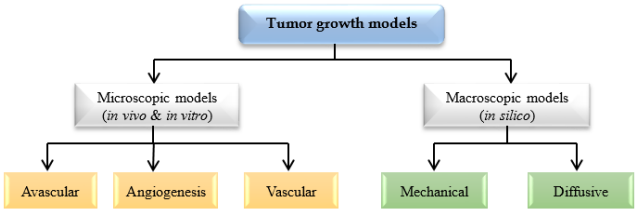


FIGURE 3. Basic classification of tumor growth models.

A. DIFFUSIVE MODELS

Majority of the published works on tumor growth modeling are classified as diffusive models. These models use the reaction diffusion (RD) formalism to describe the growth of tumors [43]–[45]. The RD model is widely used due to its simplicity and consistency with the biological tumor growth process. It describes the tumor growth, when there is no treatment administrated, with two terms: diffusion term that describes the invasion of tumor cells in the surrounding tissues ($\nabla \cdot (D\nabla u)$ in Eq. (1)) and proliferation term that describes the proliferation of tumor cells ($f(u, t)$ in Eq. (1)). The RD model can be represented by a system of semi-linear parabolic partial differential equation (PDE) with no-flux boundary condition which are defined as follows:

$$\frac{\partial u}{\partial t} = \nabla \cdot (D\nabla u) + f(u, t), \tag{1}$$

$$\gamma \cdot (D\nabla) u = 0, \tag{2}$$

where u is the tumor cell density, γ is normal direction, D is the tumor cell diffusion rate, and $f(u,t)$ is the proliferation term and mostly can be described by either exponential, Gompertz, or logistic terms [43] which are, respectively, defined as follows:

$$f(u,t) = \rho u, \tag{3}$$

$$f(u,t) = \rho u \, ln\left(\frac{1}{u}\right), \tag{4}$$

$$f(u,t) = \rho u\,(1-u). \tag{5}$$

In case of using logistic proliferation, which is very common, the RD model is known as Fisher Kolmogorov model [46]. Nevertheless, Murphy *et al.* [47] discussed other terms that can be used for tumor growth. They demonstrated the importance of careful consideration of model assumptions when developing mathematical models in cancer treatment planning. Interestingly, they found that there might be up to 12-fold change in the predicted outcomes and that the model that best fits experimental data might not be the model that best predicts future growth [47].

One of the earliest growth models was proposed in 1995 by Tracqui [48], [49] using RD model to isotropically (constant diffusion coefficient) simulate the spatio-temporal change of tumor cell concentration in 2D CT images. Tumor cells diffuse with different rates according to the surrounding tissues [50], faster in WM, slower in GM, and stops by CSF. Based on these facts, Swanson *et al.* [51], [52] used a spatial function $D(x)$ to represent the heterogeneity (not the anisotropy) of the diffusion coefficients in WM and GM guided by tissue segmentation of an anatomical atlas. The spatial function $D(x)$ is defined as follows:

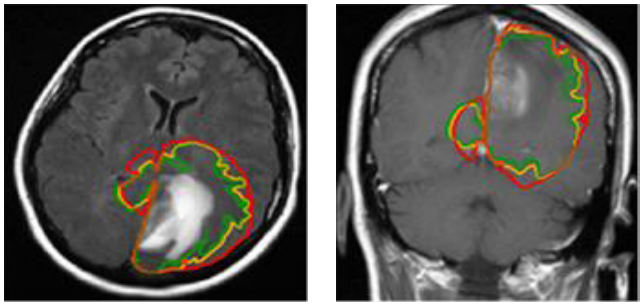
$$D(x) = \begin{cases} D_{WM} & for\ x \in WM \\ D_{GM} & for\ x \in GM \\ 0 & Otherwise \end{cases}. \tag{6}$$

Later, Yuan *et al.* [53] modified the RD equation by introducing a weighted parameter to balance the diffusion coefficient of the WM and GM. Local region similarity measure using normalized Bhattacharyya distance was estimated to determine the weighted parameter guided by level set function. Later, the same model was enhanced by including viscous stress tensor [54]. Motivated by the work of Yuan *et al.* [53], we proposed a content based modified RD model using a weighted parameter that measures the WM proportion in a small window [55]. The weighted parameter was used to promote the cells diffusivity to be higher in WM than GM without using tensor information from DTI.

Isotropic diffusion is not very precise and cannot accurately simulate the invasion of glioma growth, particularly in HGG [56]. Therefore, in this case, information provided by DTI will be very useful in guiding the anisotropic invasion of tumor cells. Earliest models that employed DTI were proposed in 2005 by Jbabdi *et al.* [56] and Clatz *et al.* [57]. They used DTI to assign anisotropic diffusion in WM having higher diffusion along the direction of fiber tracts by replacing $D(x)$ with $\bar{\boldsymbol{D}}(x)$ that is defined as follows:

$$\bar{\boldsymbol{D}}(x) = \begin{cases} D_{WM} D_{Water} & x \in WM \\ D_{GM} I & x \in GM, \end{cases} \tag{7}$$

where I is 3×3 identity matrix and D_{Water} is the normalized water diffusion tensor in the brain tissues measured by DTI. These two models can better predict the spiky nature of tumor shapes by controlling the ratio between diffusion coefficients in WM and GM, respectively. Fig. 4 shows the effect using different diffusion ratios [58]. Generally, the degree of anisotropy is totally dependent on the construction method of $\bar{\boldsymbol{D}}(x)$. Because of high anisotropy in most parts of the WM, the previous two approaches led to diffusivities that are much lower than gray diffusion in the directions orthogonal to the fibers. Moreover, the high ratios of anisotropy encountered in those two models are computationally expensive.



(a) (b)

FIGURE 4. Effect of using different diffusion ratios between WM and GM [58] (red, $D_{WM}/D_{GM} = 1$; yellow, $D_{WM}/D_{GM} = 10$; green $D_{WM}/D_{GM} = 100$).

DTI was also used by Painter and Hillen [59] to develop a mesoscopic model for glioma invasion based on the individual migration pathways of invading cells along the fiber tracts. Via scaling, they obtained a macroscopic model that allows to explore the overall growth of a tumor. The DTI information was included in the model by assuming that directional guidance along fiber tracts is described by a bimodal von Mises–Fisher distribution (it is the normal distribution on a unit sphere) and parameterized according to the directionality and degree of anisotropy in the diffusion tensors. Later, Engwer *et al.* [60] extended this model to explicitly include adhesion mechanisms between glioma cells and the extracellular matrix components which are associated to WM tracts. Recently, Swan *et al.* [61] also utilized the DTI anisotropic diffusion based on the model of Painter and Hillen [59] and proved that it can have slight improvement when compared to the proliferation model of Swanson *et al.* [51].

Although DTI provides a very useful information about the preferable directions of glioma growth, there are some tradeoffs when use it. In fact, processing DTI is expensive and mostly comes with low resolution which compromises the accuracy of the growth models. Therefore, Stretton *et al.* [62] investigated the importance of using DTI in

tumor growth modeling. They concluded that, refraining from DTI would be fine if the images are very coarse (low resolution) in condition that there is a very good WM segmentation in the areas surrounding the tumor. This conclusion is also applicable in case of LGGs as they slowly grow and tend to be isotropic. However, for the accurate growth modeling of HGG, DTI is indispensable due to the anisotropic and the spiky nature of these tumors.

The PDE system of the RD model can be approximated by travelling wave solution [63]. Because tumor boundary is the only measurable parameter from MR images and based on the assumption that for large times, Konukoglu *et al.* [36], [64] approximated the RD model using an anisotropic Eikonal equation. This equation is then solved by using a recursive fast marching algorithm [65]. Recently, the same model was used to simulate the virtual glioma growth pattern in expert-validated CSF segmentation of the MNI atlas [66] which proved that accurate segmentation of WM had an important role on the diffusive boundaries of glioma. Also, using the anisotropic Eikonal equation introduced by Konukoglu [64], Rekik *et al.* [67] proposed WM tumor diffusion tensor that can handle high anisotropy and complex shapes of the tumors using the following formulation:

$$\bar{\boldsymbol{D}}(x) = E(x)\left[diag\left(e_1(x) D_{WM}, D_{GM}, D_{GM}\right)\right] E^T(x), \quad (8)$$

where $E(x)$ is a matrix of sorted eigenvectors of $DTI(x)$ while $e_1(x)$ is the normalized largest eigenvalue of $DTI(x)$. An example that shows the effect of the new formulation of $\bar{\boldsymbol{D}}(x)$ on controlling the boundary spikiness and the anisotropic diffusion is shown in Fig 5.

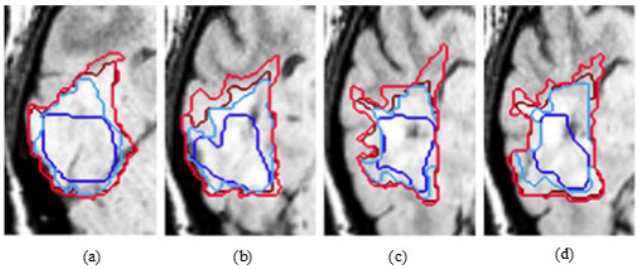


FIGURE 5. Examples show an anisotropic diffusions and boundary spikiness in 4 different axial slices (a), (b), (c), and (d) of a patient with 4 time point scans t_1 (dark blue), t_2 (light blue), t_3 (dark red), t_4 (light red) [67].

Roniotis *et al.* [68] exploited the spatial proportions of WM and GM extracted from brain atlas as well as the DTI information extracted from SRI24 atlas [69] to anisotropically simulate the tumor growth of HGG. They used different construction of the $\bar{\boldsymbol{D}}(x)$ as follows:

$$\bar{\boldsymbol{D}}(x) = D(x)\,\boldsymbol{W}(x), \quad (9)$$

where $\boldsymbol{W}(x)$ represents the contribution of each direction of the white fiber and it is calculated using:

$$\boldsymbol{W}(x) = \begin{bmatrix} w_x(x) & 0 & 0 \\ 0 & w_y(x) & 0 \\ 0 & 0 & w_z(x) \end{bmatrix}, \quad (10)$$

where $w_x(x)$, $w_y(x)$, and $w_z(x)$ are, respectively, the directional diffusion weight with values between 0 and 1.

B. MECHANICAL MODELS

As previously mentioned, mechanical models study the mechanical behavior of tumor growth and its effects on the surrounding tissues. Mechanical models contain two distinct formulations, one for the growth of the tumor while the other for bio-mechanical characteristics of the brain tissue. In these models, the mechanical interaction between the grown tumor and brain tissue has to include the viscosity and the elasticity of the brain material. One of the earliest mechanical models was proposed by Wasserman *et al.* [70] that considered brain tissue as a linear elastic material for which strain-stress relations could be given by generalized Hooke's law. In addition, an exponential growth term (Eq. 3) with fixed proliferation rate was used to simulate the tumor growth in 2D space using CT images.

Kyriacou *et al.* [71] characterized the brain tissues by nonlinear elastic materials that follow incompressible nonlinear elastic neo-Hookean model to overcome the linear stress-strain relation in the model of Wasserman *et al.* [70] and simulate large deformation. That model was also applied in 2D space and used simple proliferation term that made a uniform strain.

Based on the model of [71], Mohamed and Davatzikos [72] extended that model by considering the brain tissue as an isotropic and homogenous hyperelastic material. They used 3D finite element method (FEM) to simulate brain tumor mass-effect of both tumor and edema applied to 4 real cases. Their model was able to describe large deformation. Although this model yielded good simulation of tumor mass effect, it was based on many assumptions and computationally expensive. Hogea *et al.* [73], [74] reformulated the above two models within a general Eulerian framework using a level-set based method for the evolving tumor to improve their efficiency. This model was able to deal with complex geometries fast and in less expensive way. Simulation results from the above models are shown in Fig. 6.

Later, Gevertz *et al.* [75], employed cellular automaton algorithm to simulate spherically symmetric tumor growth and generalized the algorithm to incorporate the effects of tissue shape and structure. They demonstrated that, those models which do not account for tissue geometry and topology lead to false simulations about tumor spread, size, and shape. In addition, they showed that, the impact of organ-imposed confinement and heterogeneity of tissue on the tumor growth is greater when tumor grows close to the confining boundary.

Most recent biomechanical and hybrid models (Section II.C) make use of the continuum mechanics to study the volume expansion. For comprehensive review of the-state-of-the-art constitutive models, readers are referred to [76] and more details about the mechanical properties of brain tumors can be found in [77]. Since tumors grow over long time (days, months, or even years), in most of cases, the deformation is quite slow. Thus, static equilibrium

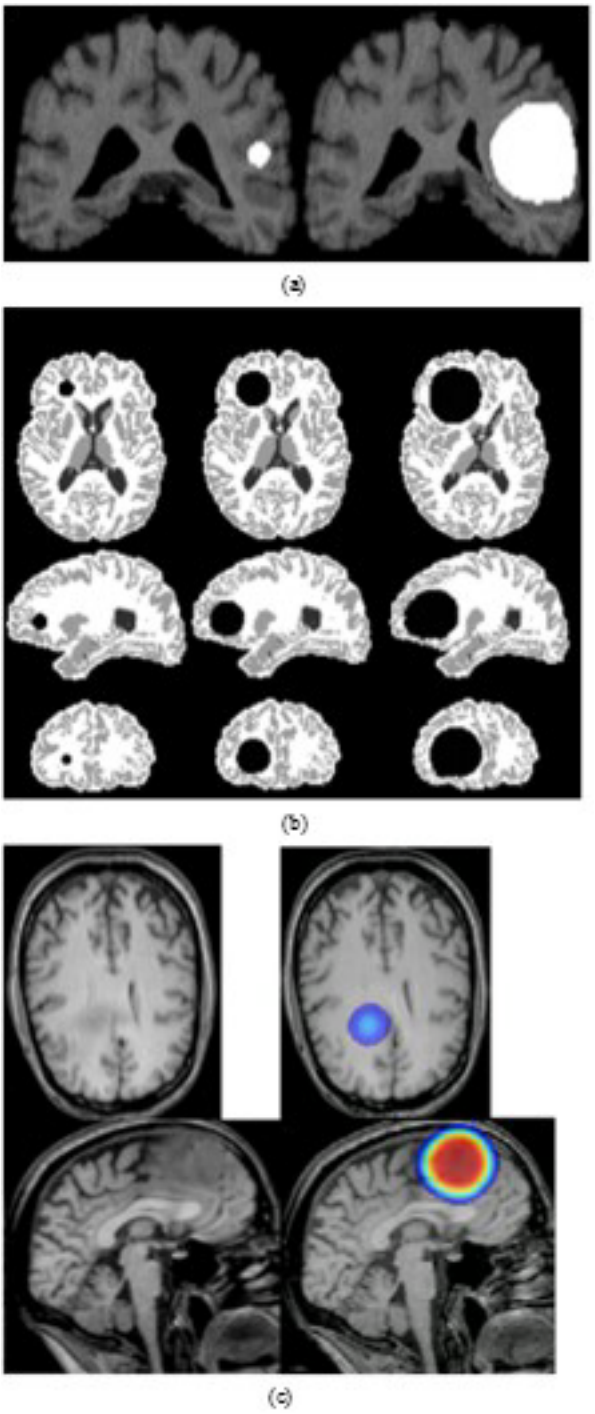


FIGURE 6. Simulation of tumor growth using different mechanical models (a) from [72], (b) from [74], and (c) from [73].

equation can be utilized for the displacement as follows [57]:

$$div(\sigma) + f_{ext} = 0, \tag{11}$$

where σ is the internal stress tensor and f_{ext} is the external force applied on the tissue and it can be defined as [78]:

$$f_{ext} = P.A.\varphi(n, \gamma), \tag{12}$$

where P is the pressure, A is the surface area, and $\varphi(n, \alpha)$ is the direction from the von Mises-Fisher distribution with mean direction n and concentration γ [78]. Following Clatz *et al.* [57], the relationship for the strain computation and the constitutive equation is:

$$\sigma = K \cdot \varepsilon, \tag{13}$$

$$\varepsilon = 0.5\left(\nabla u + \nabla u^T\right), \tag{14}$$

where K and ε represent the elasticity and strain tensors, respectively, while u represents the displacement.

C. HYBRID MODELS

Both mechanical and diffusive models can be combined together to have more realistic simulation of tumor growth. The hybrid models combine the RD and its boundary condition in Eqs. (1) and (2) with the biomechanical model given in Eqs. (11)-(16). The earliest trial was performed by Clatz *et al.* [57] to simulate tumor growth by coupling tumor diffusion and the biomechanical effect in one model that was solved by FEM. The biomechanical effect considered the brain as a linear viscoelastic material since the time scale of tumor growth was relatively large (6 months in that work). In their model, the mass effects of bulk tumor as well as edema were considered (tested only on one MR dataset). However, this model is susceptible to the discretization of FEM which sometimes gives error.

In a similar work, Chen *et al.* [79], coupled the RD model and linear mechanical model solved by FEM to simulate the kidney tumor growth. In this model, the parameters were estimated by the hybrid optimization parallel search package based on segmented tumor volumes from contrast enhanced CT images at different time points. Later, Liu *et al.* [80] presented patient specific tumor growth model that coupled both cell metabolism and mass effect from clinical CT and fluorodeoxyglucose - PET (FDG-PET) images. They used an inverse problem formalization as a coupled PDE constrained optimization problem solved by finite difference method to estimate the model parameters. However, their formulation is very complicated and may not fit the requirements of realistic models.

May *et al.* [81] established a multi-scale and multi-physics approach to simulate tumor growth, considering both the cellular and the macroscopic mechanical levels. Their composite model led to significant tumor shape corrections (about 20%) that were achieved through the utilization of environmental pressure information and the application of biomechanical principles. It was concluded from this study that the two models could be coupled in a self-consistent manner without any effect on each other.

Wong *et al.* [82] coupled the RD equation and the nonlinear biomechanics to predict the tumor growth of pancreatic neuroendocrine using FEM and to overcome the shortcomings of [57] and [79]. They fused physiological data of structural and functional images to improve the model customization. Furthermore, they adopted a derivative-free global

optimization algorithm to facilitate the model complexity and accommodate flexible choices of the objective functions.

Recently, three mathematical models of glioma growth were developed by Hormuth *et al.* [83], [84] to establish a framework for accurate prediction of changes in tumor volume as well as intra-tumoral heterogeneity. In the first model, tumor cell movement was described by coupling movement to tissue stress, leading to a mechanically coupled RD model. In the second model, intra-tumor heterogeneity was described by including a voxel-specific carrying capacity to the RD model. Eventually, the mechanically coupled and carrying capacity models were also combined in a third model. Experiments on 14 rats with glioma demonstrated that mechanical–biological effects were a necessary component for an efficient tumor growth modelling [83].

Very recently, Agosti *et al.* [85] developed diffuse-interface mathematical model based on mixture theory with continuous mechanical model and solved by FEM to predict the patient-specific evolution of GBM. This model also incorporated the effects of chemotherapy and radiotherapy.

III. GROWTH MODELLING WITH TREATMENTs

One of the most important motivations of studying tumor growth is therapy planning. Tumor growth models can incorporate the treatment effects into the model either to evaluate its efficacy or to tailor the therapy, for instance calculate the effective doses and fractions of specific therapy. Glioma treatment comes in one or more of the following ways: radiotherapy, chemotherapy, surgery, and targeted therapy (like antiangiogenic therapy). In fact, combinations of these methods are usually concurrently or adjuvantly used. Generally, the treatment effect can be included as a loss term in the RD model (Eq. (1)) to represent the number of the dead cells due to the treatment.

The majority of aforementioned models did not include the effect of treatments: neither chemotherapy nor radiotherapy. Radiotherapy is a common treatment therapy used to control tumor cells either by killing or damaging their proliferation and is given, mostly, post-surgery in different fractionation regimens according to many factors [86]. Linear quadratic (LQ) model [87] is the most widely used methodology to determine the effect of radiotherapy doses by estimating the probability of cells surviving due to dose of radiation. The LQ model has been successfully used with tumor growth models to simulate the efficacy and responses of radiotherapy [88]–[93]. Generally, the LQ estimates the probability of cell survival S after radiation dose is calculated by [87]:

$$S = e^{-\alpha d_i(u,t) - \beta d_i(u,t)^2}, \tag{15}$$

where $d_i(u,t)$ represents the radiation dose and α and β are the linear and quadratic radiobiology coefficients, respectively. The tumor cell loss is:

$$r(u,t,d_i) = \begin{cases} 0 & \textit{no radiotherapy} \\ 1 - S[\alpha, \beta, d_i(u,t)] & \textit{radiotherapy}. \end{cases} \tag{16}$$

Using Eq. (16), the final loss term due to radiotherapy $R(u,t)$ that has to be included as a negative term in Eq. (1) is written as follows:

$$R(u,t) = r(u,t,d_i).u(1-u). \tag{17}$$

Rockne *et al.* [88], [93] embedded the LQ model into RD model to predict and quantify the efficacy of radiotherapy with response to various therapy schedules and doses distributions. Later, Corwin *et al.* [90] extended this work and investigated generating patient-specific and biologically-guided radiotherapy dose plans. Roniotis *et al.* [89] simulated the radiotherapy effect in the RD equation using LQ model guided by DTI information extracted from the SRI24 atlas [69].

Knoukoglu *et al.* [94], [95] extended their previous work and proposed a different way to extrapolate the extents of the tumor invasions that is not visible in MR images. Their formulations aimed to create irradiation regions that take into account tumor growth dynamics rather than the conventionally used method of radiating 1.5-2.0 cm margin around the visible tumor bulk. Unkelbach *et al.* [58] used the RD model for the improvement and automation of target volume delineation for HGG. Their model considered the spatial growth patterns of tumor and the anatomical barriers. They concluded that, this approach is mainly useful for tumors located close to the falx and the corpus callosum. However, their model accuracy is totally dependent on an accurate segmentation of the brain tissues, particularly the anatomical barriers.

Different from LQ models, Pérez-García *et al.* [96], explored mathematical model based on the RD model and radiobiological facts to study the delay effects on radiotherapy. Their model predicted that, tumors with high proliferation will likely respond faster to radiotherapy than those with slower proliferation values. However, the regrowth is expected early in those tumors responding faster. Galochkina *et al.* [97] went further to evaluate the optimal radiotherapy fractionation for LGG in the standard protocol of 30 fractions using mathematical models. Their optimal results found minor deviations from the standard radiation fractionations (6 weeks treatment period) which approve the efficacy of the current fractionations of radiotherapy on LGG treatment.

Another commonly used formalism in radiotherapy is tumor control probability (TCP) model which is used to define the probability of how a prescribed dose of radiation eradicates or controls the tumor [98]–[102]. In fact, TCP is basically based on LQ model [98] and that is the reason that makes LQ model dominant in tumor growth models that consider the radiotherapy efficacy. On the other hand, to the best of our knowledge, there is no growth model in literature that used TCP model to incorporate radiotherapy efficacy.

The other treatment regimen is to use chemotherapy either as neoadjuvant, adjuvant, or concomitant. Chemotherapy acts on rapidly proliferating cells by interfering with the cell-cycle and other cell-cycle specific targets. It is also used to stop

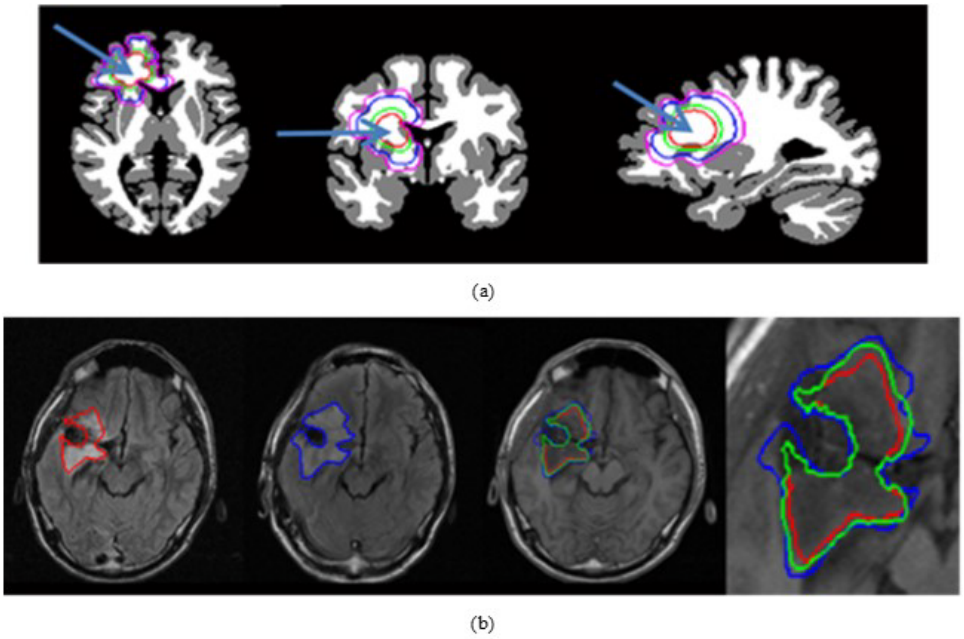


FIGURE 7. Effects of including chemotherapy and radiotherapy on the growth of LGG [108]. (a) Synthetic LGG growth from single point on MNI atlas. The red and blue contours represent the tumor boundaries for 1 and 2 years with treatment effect while the green and magenta contours are the corresponding boundaries without treatment. (b) Real LGG case; from left to right, T1 image, T2 image with manual delineation of tumor boundary in red and blue, simulated growth in green, and enlarged view simulated growth.

or slow down tumor growth and can either be administrated before, during, or after radiotherapy. Swanson *et al.* [103] introduced simple technique to incorporate homogenous and heterogeneous drug delivery of chemotherapy into tumor growth model. The loss term due to chemotherapy can be embedded into the RD model as a proportion of the tumor growth rate [46].

Later, Stamatakos *et al.* [104] modeled the effect of chemotherapy based on cellular automata to growth model where the effect of the chemotherapy was included as a damage to each cell independently. If that damage is large enough, this would yield cell apoptosis. However, their model used many parameters that cannot be observed from images which reduce the model significance for real applications. Further, Powathil *et al.* [105], [106] used log-kill model to represent the cell death caused by the chemotherapy as removing constant fraction of tumor cells at the time of administrating it. In addition, the same model included the radiotherapy effect using the LQ model. Another interesting work by Bogdańska *et al.* [107] proposed to build mathematical model that can incorporate the basic biological features of LGG growth and its response to chemotherapy. Their results showed that tumors had a shorter time to radiological response after chemotherapy treatment might be more aggressive in terms of proliferation potential.

Recently, we were also able to combine the radiotherapy and chemotherapy treatments with RD model. As previously mentioned, chemotherapy effect is commonly hypothesized to damage tumor cells to be proportional to the growth rate as log-kill term [105]. However, this is not precise as chemotherapy is usually delivered to the whole body and the absorption of drug by tissues can differ accordingly. In [108], we tackled this issue and related the heterogeneity of tissues with the absorption of the chemotherapy using our previously proposed weighted parameter that measures the WM proportion in small window [55]. In addition, the LQ model was also incorporated into the RD model to simulate the LGG growth. Fig. 7 shows 2 different experiment on the MNI atlas and a real LGG case. Later, we extended the previous model to include brain viscoelasticity using Maxwell-Weichert model with the RD model [109]. An example of the simulated results is shown in Fig. 8.

IV. CUSTOMIZATION OF THE GROWTH MODEL PARAMETERS

Every human being has some biometrics, e.g. finger print, iris, and voice tag, which are unique and exclusive only for him/her. Same applies also for brain structure and even brain tumors. There are more than 120 different types of brain and CNS tumors [110] each has different histology, diffusivity rate, aggressiveness level, and so on. Therefore, using same parameters of the growth model will not be precise. Growth parameters of diffusive models are mainly the diffusion coefficient (D) and the proliferation rate (ρ) given in Eq. (1). Customization of these two parameters to be patient-specific will have great impact on the accuracy and the whole model performance. To do so, one has to compare the model estimation with the visible abnormalities

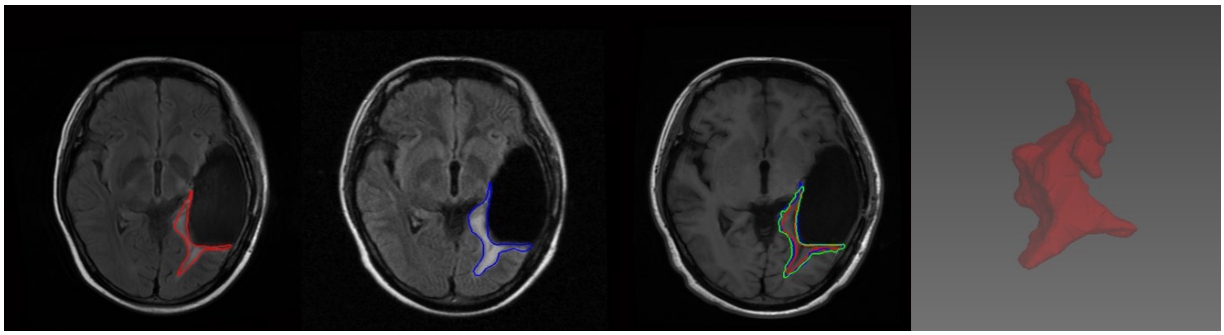


FIGURE 8. Simulation results of tumor growth in LGG subject [109]. From left to right, first and second scans with the red and blue contours representing the tumor boundaries, the simulated growth with green contour, and a constructed 3D view of the simulated tumor growth.

from at least 2 MR images acquired at different time points. Harpold *et al.* [25] described the customization of glioma growth using RD model and an exponential proliferation term. They presented the relationship between D and ρ of LGG and HGG cases collected up to 2007 by log-log graph as shown in Fig. 9. From Fig. 9, it can be noticed that LGGs appear in the bottom-left as these tumors are slowly growing with average velocity of 2 mm/year. In contrast, HGGs are in the top-right enclosed within a rectangle defined by D/ρ of 2 to 20 mm^2 and velocities of 10 to 200 mm/year.

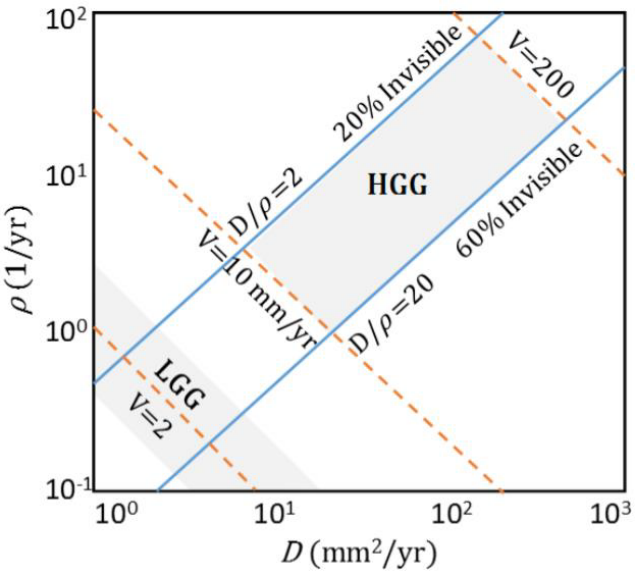


FIGURE 9. A log-log graph of D and ρ summarizing the distribution of HGG and LGG (reproduced from [25]).

Hogea *et al.* [73] considered the parameter customization as an inverse estimation to find the tumor growth model parameters based on the patient's MR images. They formulated and solved this using PDE-constrained optimization problem with first order information. However, their optimization problem is slow and limited only to 1D case. Recently, Gholami *et al.* [111] extended this work by using second order Hessian information for the numerical optimization instead of using only first order information and falling back to a derivative free optimization. This method was able to reconstruct the model parameter considering the anisotropy of the LGG with reduced computational cost. However, it was only applied to synthetic images with no demonstration on real MR images with tumors.

Konukoglu *et al.* [64] used the derivative-free optimization algorithm called bounded optimization by quadratic approximation to minimize the distance between the tumor segmentations observed from series of brain MR images and the output of the model. Their formulation was based on an Eikonal approximation of the RD model.

Based on the spherical asymptotic analysis, Corwin *et al.* [90] customized the RD model parameters by relating the asymptotic velocity and the invisibility index from two segmented time point MR images of the same patient. This customization was mainly targeted towards biological optimization of radiotherapy treatment of HGG.

Probabilistic approaches can also be used to customize the growth model parameters. Menze *et al.* [112] linked the physical process model with the statistical image observation model that enabled efficient estimation of the model parameters by Bayesian formulation. This model was based on the approximation of the posterior probabilities using sparse grids which was adopted via Markov Chain Monte Carlo sampling.

Lately, Lê *et al.* [113], [114] analyzed the uncertainty in the patient specific parameters of a tumor growth model by sampling the posterior probability of the parameters from MR images of the same patient. Their estimation was based on parallelized implementation of the RD model using lattice Boltzmann method and Gaussian process Hamiltonian Monte Carlo technique. To sum up, the most relevant growth models described above are given in Table 1.

V. MATHEMATICAL SOLUTION TO DIFFUSIVE MODELS

Tumor growth modeling usually results in a complex mathematical formulation using set nonlinear PDE. However, having a mathematical solution of such equation is not straightforward and has to be done very carefully as there is discretization in both time and the 3D space. In fact, studying such solutions have many independent research topics and

TABLE 1. Summary of most relevant tumor growth models.

Model	Brief description	Imaging - number of datasets used	Dimensions	Treatments effect	Parameters customization	Numerical solution - stability
Tracqui [48, 49]	Diffusive model, isotropic diffusion	CT - 1	2D	-	-	N/A
Swanson *et al.* [52]	Diffusive model, isotropic but heterogeneous diffusion	MRI - 1	2D	-	-	N/A
Yuan *et al.* [53]	Diffusive model, LGG, anisotropic diffusion	MRI - 12	2D	-	-	unstable
Elazab *et al.* [55]	Diffusive model, isotropic but heterogeneous diffusion	MRI - 1	3D	-	-	FDM - unstable
Yuan & Liu [54]	Diffusive model with viscous stress tensor, LGG, anisotropic diffusion	MRI - 10	2D	-	-	unstable
Jbabdi *et al.* [56]	Diffusive model, LGG, anisotropic diffusion	MRI, healthy DTI - 2	3D	-	-	FDM - unstable
Clatz *et al.* [57]	Diffusive model, biomechanical model, GBM, anisotropic diffusion	MRI, healthy DTI - 1	3D	-	-	FEM - uninvestigated
Konukoglu *et al.* [64]	Diffusive model using anisotropic Eikonal equation, GBM	MRI, DTI - 2	3D	-	Customized	Fast marching – uninvestigated
Painter and Hillen [59]	Diffusive model, predict the anisotropic pathways of tumor	MRI, DTI - 1	2D/3D	-	-	FDM – unstable
Amelot *et al.* [66]	Diffusive model using anisotropic Eikonal equation, expert-validated CSF segmentation	MNI MRI Atlas - 1	3D	-	-	Fast marching – uninvestigated
Rekik *et al.* [67]	Diffusive model using anisotropic Eikonal equation, LGG	MRI, DTI - 4	3D	-	Customized	Fast marching – uninvestigated
Roniotis *et al.* [68]	Diffusive model, HGG, anisotropic diffusion	MRI, SRI atlas - 1	3D	-	-	FDM - stable
Wasserman *et al.* [70]	Biomechanical model, linear elastic material	CT - 1	2D	-	-	FEM - uninvestigated
Kyriacou *et al.* [71]	Biomechanical model, nonlinear elastic neo-Hookean model	MRI - 2	2D	-	-	FEM - unstable
Mohamed *et al.* [72]	Biomechanical model, isotropic and homogenous hyperelastic material	MRI - 4 (1 human & 3 dogs)	3D	-	-	FEM - uninvestigated
Hogea *et al.* [73, 74]	Diffusive model, biomechanical model, Eulerian framework using a level-set method	MRI - 2	3D	-	Customized	Fictitious domain method - stable
Chen *et al.* [79]	Diffusive model and linear biomechanical model, kidney tumor growth	CT - 5	3D	-	Customized	FEM - uninvestigated
May *et al.* [81]	Biomechanical model, cellular level model	MRI atlas - 1	3D	-	-	FEM - uninvestigated
Liu *et al.* [80]	Reaction advection diffusion model with cell metabolic rate and mass effect, pancreatic tumor growth	CT, FDG-PET - 6	3D	-	Customized	FDM - uninvestigated
Wong *et al.* [82]	Diffusive model and hyperelastic biomechanical model, pancreatic neuroendocrine tumor growth	CT, PET - 8	3D	-	Customized	FEM - uninvestigated
Hormuth *et al.* [83]	Diffusive model, biomechanical model	MRI, DWI – 14(rats)		-	Customized	FDM - uninvestigated

TABLE 1. ***Continued.*** **Summary of most relevant tumor growth models.**

Rockne *et al.* [88, 93]	Diffusive model, LQ model, quantify the radiotherapy efficacy in GBM	MRI - 9	3D	Radiotherapy	Customized	FDM - uninvestigated
Roniotis *et al.* [89]	Diffusive model, LQ model, radiotherapy effect simulation	MRI, SRI atlas - 6	3D	Radiotherapy	-	FDM -stable
Corwin *et al.* [90]	Diffusive model, LQ model, biologically-guided radiotherapy dose plans in GBM	MRI, DTI - 9	3D	Radiotherapy	Customized	Crank-Nicolson method - uninvestigated
Knoukoglu *et al.* [94, 95]	Diffusive model using anisotropic Eikonal equation, extrapolate glioma invasion margin	MRI, DTI - 9	3D	Radiotherapy	-	Fast marching - uninvestigated
Unkelbach *et al.* [58]	Diffusive model, radiotherapy target volume delineation for HGG	MRI - 10	3D	Radiotherapy	-	Fast marching - uninvestigated
Swanson *et al.* [103]	Diffusive model, heterogeneous and homogenous effect of chemotherapy	MRI - 1	2D	Chemotherapy	-	N/A
Stamatakos *et al.* [104]	Cellular automata model, effect of chemotherapy treatment on solid tumor growth	MRI, PET - 1	3D	Chemotherapy	Customized	Monte Carlo simulation - uninvestigated
Powathil *et al.* [105]	Diffusive model, HGG, log-kill model, LQ model	MRI atlas - 1	2D	Chemotherapy-radiotherapy	-	FDM - unstable
Lê *et al.* [113, 114]	Diffusive model, analyze the uncertainty of the parameters by sampling their posterior probabilities	MRI, DTI - 7	3D	-	Customized	Lattice Boltzmann method - uninvestigated
Elazab *et al.* [108]	Diffusive model, heterogeneous and homogenous effect of chemotherapy, LQ model	MRI - 2	3D	Chemotherapy-radiotherapy	-	FDM – unstable
Rutter *et al.* [148]	Diffusive model, level set, LGG	MRI – 3(mice)	2D/3D	-	Customized	FDM – unstable
Elazab *et al.* [109]	Diffusive model, anisotropic and heterogeneous effect of chemotherapy, LQ model	MRI, DTI - 9	3D	Chemotherapy-radiotherapy	Customized	FDM - stable
Agosti *et al.* [85]	Diffusive and biomechanical models, anisotropic and heterogeneous on GBM	Reconstructed MRI, DTI – N/A	3D	Chemotherapy-radiotherapy	Partially customized	FEM - stable

has been studied extensively in the literature. Solving the RD model, mostly, comes in two different forms, FEM and finite difference method (FDM). Here, we just give a brief introduction about them and highlight some techniques that were proved to be suitable in the mathematical solution to the tumor growth model. However, for further reading readers can refer to [115]–[120].

FEM is a numerical methodology that is used to find approximate solutions to boundary constrained problems and tumor growth models. This method represents the brain as a structure of several elements connected together. The size of these elements is application dependent and reflects the complexity of this method, tetrahedron (element with 4 nodes) is sufficient for mass effect simulation in tumor growth models. FEM can handle the complex geometries and complex structures, therefore, it was used in the following models mechanical models [41], [71]–[74], [121], [122]. However, using FEM is computationally very expensive and small mistake can lead to a fatal problem.

On the other hand, FDM is a discretization method that approximates the solution to the PDE using derivatives. The most popular methods of FDM are: forward Euler, backward Euler, and Crank-Nicolson. These methods are easy to implement but the stability of their numerical solution is a challenge as they are discretized in 3D and the challenge becomes bigger when DTI is used. Therefore, the numerical solution of the RD model is at stake if the stability is not guaranteed. The leading work on the stability of the FDM was studied by Weickert [123] by providing different discretization techniques that makes the anisotropic diffusion unconditionally stable. Later, Mosayebi *et al.* [124] extended this work to investigate the stability of FDM on the mathematical tumor

growth models in 3D. Fig. 10 demonstrates the stability effect importance on the performance of the tumor growth models.

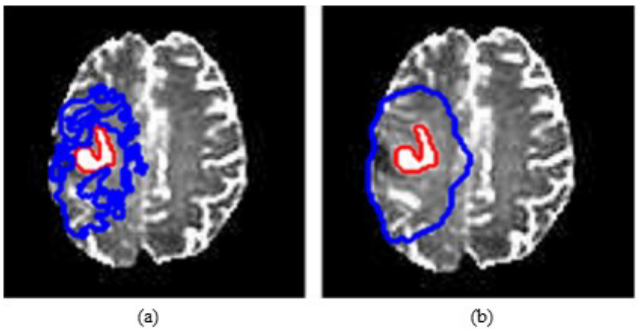


FIGURE 10. An example shows the stability effect on the performance of tumor growth models [124]. (a) Unstable solution, (b) Stable solution.

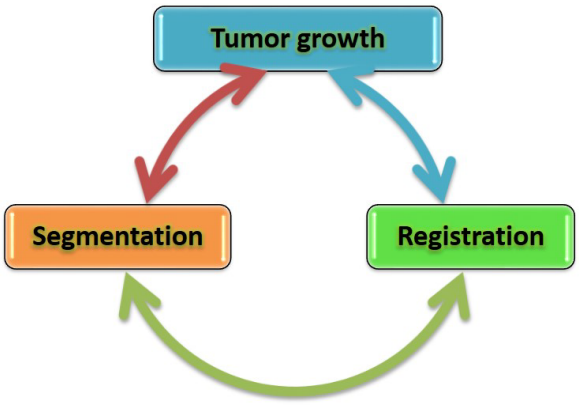


FIGURE 11. Relationship between tumor growth, segmentation, and registration.

Roniotis *et al.* [125], [126] presented mathematical solution for the RD model in 3D with different FDM schemes and FEM. Namely, forward Euler, the backward Euler, the Crank-Nicolson, and the θ-method were discussed in terms of accuracy, simulation time, and storage. The authors concluded that, FDM schemes are practically suitable solution for glioma growth models and are 10 times faster than FEM.

Özuğurlu [127] focused on handling the stability issues due to the discontinuity of the diffusion coefficient. He demonstrated that, using the correct finite difference scheme can overcome the stability issues by proposing two numerical methods, the implicit backward Euler and the Crank-Nicolson scheme, both in combination with Newton's method for solving the governing equations.

In our recent works [108], [109], we tried to solve the bottleneck challenge by employing the stable FDM proposed by Mosayebi *et al.* [124] while including the effects of both chemotherapy and/or radiotherapy, if any. In addition, the brain tissue viscoelasticity effect was included in the modified RD using Maxwell-Weickert approach.

VI. GROWTH MODELS, SEGMENTATION, AND REGISTRATION

Tumor growth is not a standalone procedure, instead, it has close relation to both segmentation and registration. On the one hand, both segmentation and registration are used as prerequisite steps in the growth models (Fig. 11). On the other hand, tumor growth can be used to aid segmentation and registration which are ubiquitous applications in medical image analysis and other applications as well [128]. Some interesting integrations between them are given below.

A. SEGMENTATION AND GROWTH MODEL

One cannot proceed in studying tumor growth before segmenting the tumor regions and the brain tissues. The former is mostly done manually or semiautomatic while the latter is done automatically. Since here we only discuss the relation between segmentation and growth modeling, readers are referred to the following comprehensive reviews on brain tumors and brain tissue segmentations [129]–[135]. Similarly, skull stripping is necessary for the no-flux boundary condition of the RD model (Eq. 2). On the other hand, tumor growth model can be used in tumor segmentation which is considered as very subjective and complicated task. Several studies were proposed to generate synthetic realistic MR images bearing tumors where there is known ground truth to be used for validation. However, realistically simulating the tumor and describing the effect of the tumor growth on the grayscales of the MR image are not straightforward.

Rexilius *et al.* [136] proposed one of the earliest models for generating a realistic brain tumor phantom. Their tumor model included three compartments: active tumor, necrotic core, and edema. The active tumor and the necrotic core were manually drawn on MR image of a healthy subject. A radial displacement model was used to simulate the displacement of the surrounding tissue assuming linear elastic material properties of WM and GM. The image intensities on the necrotic core were assigned using Gaussian noise where the edema was represented by an intensity fading with increasing distance to the active tumor.

Prastawa *et al.* [78] enhanced the model of Clatz *et al.* [57] for more 3D realistic generation of synthetic tumors and an improved appearance in the MR images. Furthermore, they introduced tensor model for the warping and destruction of WM fibers. Later, Cordier *et al.* [137] presented a generative model for the synthesis of multimodal medical images of pathological cases by using an iterative multi-atlas patch-based algorithm. Although the iterative nature of their method could synthesize more realistic images, this model is costly and extremely slow (in days).

B. REGISTRATION AND GROWTH MODEL

Registration is also a prerequisite step to align the acquired time-point images from single modality or multimodality to a common space before studying the tumor growth [138]. It makes it easy to track the changes of the anatomical tissues and sizes of the pathology. Registration of MR images with tumor to an anatomical atlas is of great interest in clinical

usage to track the effect of the lesion growth. However, this process is very challenging when lesion size is big which makes conventional registration methods inappropriate. Many methods were proposed to address the challenges related to image registration such as [139]–[144]. In this regard, tumor growth models can also be included in the registration process and improve the registration outcomes.

Kyriacou *et al.* [71] proposed a 2D atlas to patient registration based on tumor growth dynamics. They simulated the resection of the tumor allowing images to be registered to an atlas and obtain tumor-free images. Then, the tumor-free images with real images were used to estimate the parameters of the growth model. Finally, using the estimated parameters they performed the mechanical tumor growth inside the registered atlas to the final atlas to patient registration.

Mohamed *et al.* [145] took a statistical approach for the atlas to patient registration. They proposed statistical model on the deformation map created by applying a nonlinear elastic registration to align the atlas with patient image. Their statistical model used the space displacement fields and decomposed the deformation field on two orthogonal hyperplane, one for the tumor-induced deformation while the other for the inter-subject variability.

Gooya *et al.* [146] used multi-parametric imaging modalities for segmentations of various tissues, and then used supervised learning to compute the posterior probability map of membership to each tissue class. By simulating the tumor growth using RD model, similar maps were generated in the atlas. The expectation-maximization algorithm was used in the registration procedure to approximate the spatial transformation while tumor growth parameters were optimized.

Later, Gooya *et al.* [147] presented a generative approach for simultaneously registering a probabilistic atlas to the brain MR scans showing glioma and segmenting the scans into tumor and healthy tissues. Their method was based on the expectation maximization algorithm that incorporates a glioma growth model for atlas seeding. The seeded atlas was then registered to patient image to estimate the probabilities of various tissue labels.

VII. DISCUSSIONS AND PERSPECTIVES

From the above review, it is clear that, the challenges surrounding the tumor growth modeling research are many and there is still much to go. Almost each step involved in the tumor growth modeling can be an independent research topic. Therefore, much integrated efforts have to be exerted to have efficiently and widely applicable models rather than theoretical and simple computer simulations. Below, we elaborate the main challenges and give some perspectives for further research.

One of the earliest key points researchers consider when starting their research projects is the dataset availability. Unlike many segmentation and identification tasks that have publicly available datasets, studying tumor growth modeling suffers from dataset availability as, to the best of our knowledge, there is neither standard MR nor any modality dataset that can be used as benchmark for tumor growth modelling. In fact, having such dataset requires at least 2 time-point scans for the same subject within few months in case of LGG or few weeks in case of HGG. For HGG, after the first scan subjects usually go for surgery where tumor bulk is mostly resected which makes the second time-point scan meaningless for studying the tumor growth. In case of LGG, subjects likely have treatments in forms of chemotherapy, radiotherapy or/and surgery which makes it a bit easier to have multi-time points than HGG. However, these treatments may have potential effects on the quality of the MR images and thus become difficult to use them. This challenge is obvious in the previous works where we can find some studies only used 1 dataset [55], [57], [66], [81], [103], [105] or even 2 datasets [41], [64], [71], [73], [108]. Similarly, open sourcing in studying tumor growth modeling is very limited as there are very few studies with open source codes [78], [148].[1,2]

Realistic validation using an *in vivo* mechanism of the growth models is still a problem and hard to apply, except in rare studies on animals. Even though some *in vitro* experiments were conducted, one cannot assure that, such growth will match the exact dynamics and behaviors of the tumor *in vivo*. However, fusing information from different and advanced imaging techniques rather than depending on the conventional MRI and DTI may help to have more accurate and plausible tumor growth simulation. Such imaging techniques may include PET, magnetic resonance spectroscopy, and magnetic resonance elasticity imaging. Furthermore, exploring genomic information regarding disease-driving mutations and embedding it with multimodal images into growth models could lead to better results.

Another challenge which, to the best of our knowledge, remains unexplored is the linking between the microscopic dynamics and macroscopic parameters in modeling tumor growth especially when treatment is administrated. Such linking will be considerably useful to closely estimate the therapy efficacy and the possible plans for effective treatments. Meanwhile, the customization of model parameters shall also be adaptive during the growth simulation due to the effects of the chemotherapy and/or radiotherapy.

The ultimate goal of studying tumor growth modeling is to clinically use it to help predicting the tumor prognosis and response to treatment. However, model validation on sufficient number of datasets is very important to have sensitivity analysis of the model parameters. Another noteworthy point for clinical application, is the running time. As previously mentioned, processing several 3D images and solving higher order PDEs increase the complexity and the running time drastically (days in some models). This makes conventional numerical solutions of PDE less significant and opens new directions to find faster solutions and use parallel processing.

[1] https://www.nitrc.org/projects/tumorsim/
[2] https://github.com/banderie/murine-GL261-tumors

Finally, we aim that machine learning can play a role in tumor growth modeling. Although machine learning can be partially used indirectly in segmentation tasks associated with tumor growth, it is not directly used in the modeling process itself. Machine learning can be involved when multimodal imaging techniques and genomic information are used. Also, it can be utilized for validation but this is subject to datasets availability. However, deep learning algorithms, particularly, convolutional neural networks showed its favor in pancreatic tumor growth prediction [149], [150]. Yet, to the best of our knowledge, there is no such study that reports any deep learning algorithms in the cerebral tumor growth prediction or modeling as well as the incorporation of any clinical information.

VIII. CONCLUSIONS

In this review, we went through the different models in literature that focus on the macroscopic growth modeling of cerebral tumors. We recalled the diffusive and mechanical models and their basic concepts. We also highlighted the merits of those models to include the treatment effects in different ways to tailor therapies and evaluate their efficacies. We hope this review can help researchers to be aware of this research field and its importance to go through for further achievements.

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