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An adjoint-based method for a linear mechanically-coupled tumor model: Application to estimate the spatial variation of murine glioma growth based on diffusion weighted magnetic resonance imaging

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Abstract

We present an efficient numerical method to quantify the spatial variation of glioma growth based on subject-specific medical images using a mechanically-coupled tumor model. The method is illustrated in a murine model of glioma in which we consider the tumor as a growing elastic mass that continuously deforms the surrounding healthy-appearing brain tissue. As an inverse parameter identification problem, we quantify the volumetric growth of glioma and the growth component of deformation by fitting the model predicted cell density to the cell density estimated using the diffusion-weighted magnetic resonance imaging (DW-MRI) data. Numerically, we developed an adjoint-based approach to solve the optimization problem. Results on a set of experimentally measured, *in vivo* rat glioma data indicate good agreement between the fitted and measured tumor area and suggest a wide variation of in-plane glioma growth with the growth-induced Jacobian ranging from 1.0 to 6.0.

Keywords

glioma growth; mechanically-coupled; inverse problem; finite element; adjoint-state method; mass effect

1. Introduction

Tumor growth is a complex phenomenon affected by a series of multi-scale processes such as nutrient transport, cell-cell signaling and cellular interaction with the extracellular matrices [1]. It is also known that tumor cells display genetic heterogeneity and undergo constant mutations over time [2]. These biochemi-physical and genetic processes lead to varying intratumoral growth rate in both time and space. Clinically, tumor growth rates are often estimated from the observation of tumor sizes at multiple time points [3]. For this

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purpose, empirical models (e.g., logistic or Gompertzian growth [4]) were developed to describe the evolution of tumor sizes with average growth rate obtained by fitting to the observation. However, these empirical models are neither able to quantify the spatial variation of tumor growth nor to provide insights into the underlying biological mechanisms. This calls for a biophysical model that accounts for tumor development in space. When combined with quantitative medical imaging techniques, such biophysical models can potentially be used to quantify the spatial growth of tumor in a similar way as we estimate the average tumor growth rate [5].

In clinical oncology, medical imaging is a valuable tool used from early detection of tumors to post-treatment surveillance for recurring tumors. Recent developments in quantitative medical imaging methods have advanced to a point where properties relevant to tumor growth and function can be assessed non-invasively, in 3D, at several time points throughout the growth and treatment of tumors. Methods such as diffusion weighted magnetic resonance imaging (DW-MRI) or dynamic contrast enhanced MRI (DCE-MRI) can provide serial estimates of tumor cell density [6, 7] or tissue perfusion and plasma volume fraction [8], respectively. We [9, 10, 11, 12, 13] and others [14, 15, 16, 17] have investigated incorporating non-invasive imaging measurements into predictive biophysical models of tumor growth. Previously, we have used cell density maps estimated from DW-MRI to calibrate and apply reaction-diffusion based models to breast [10, 18] and brain [11, 13] cancers. In this paper, we will introduce and demonstrate a novel mechanically focused biophysical model of tumor growth, and then integrate this model with DW-MRI data to quantify the spatial variation of growth in a murine model of glioma.

Comprising more than 50% of primary brain tumors, glioma is an active subject for mathematical modeling [19]. Recently, there have been many efforts trying to incorporate the effect of solid stresses on glioma growth. This is due to a number of reasons including 1) the large deformation of surrounding healthy-appearing brain tissues (the so called, "mass effect") often caused by glioma development, and 2) the ability of solid stresses to directly or indirectly affect tumor growth. Indeed, *in vitro* experiments have demonstrated that solid stresses inhibit cell growth and induce apoptosis [20, 21, 22, 23]. Also, high intratumoral compression is known to cause collapse of blood vessels, leading to reduced delivery of both treatment and nutrients [24, 25].

Many mechanically-coupled models for avascular gliomas use reaction-diffusion equations to describe the proliferation and invasion of tumor cells, as well as model the mechanical impact of tumor development on the surrounding brain tissue as a pressure-like body force field [10, 11, 17, 26, 27, 28]. The classical reaction-diffusion model is often extended to include multiple species (e.g., normal cells, proliferative cells, quiescent cells, or other tissue components like the extracellular matrix, [29]) each of which occupies some volume fraction of the space and evolves with other constituents in an either coupled or decoupled manner [30, 31]. Another continuum model treats the tumor as a special case of a growing tissue [32, 33, 34, 35, 36], in which growth is characterized by volume change across the solid tumor [37]. Due to nonuniform growth, adjacent tumor volumes may not "fit together" in the Euclidean space as new material is created. Such incompatibility in deformation is remedied, in the finite growth theory, by introducing the notion of "multiplicative decomposition"

which splits the total deformation into a growth and an elastic component [32, 38]; for simplicity, remodeling is not considered [36]. In particular, the growth component characterizes the expansion of tumor volume in the absence of external stresses while the elastic component enforces the compatibility of deformation. Different from reaction-diffusion based models, the mass effect of the tumor is introduced automatically *via* the continuity condition on the interface between the tumor and surrounding brain tissue (i.e., force and displacement are continuous across the interface); hence, no additional assumption is necessary. In the assumption that the elastic component of the tumor constitutive behavior is Neo-Hookean, Stylianopoulos *et al.* successfully applied a solid growth model to predict tumor morphology in their “opening angle” experiments [39]. Finally, we note that while the solid growth model may not apply for malignant tumors that actively infiltrate into the surrounding environment, it is suitable for some tumor cell lines (e.g., the C6 glioma cells that are studied in this contribution) that are known to have a limited diffusive component and are generally considered as a growing mass-like object [40].

One of the challenges in image-driven tumor modeling is to calibrate model parameters from the data types routinely available from medical images [9, 12]. One approach is to consider the challenge as an inverse parameter identification problem [5, 12, 17, 41]; indeed, in the context of glioma modeling, there have been many such efforts. Hoge *et al.* [17] first applied an adjoint-based algorithm to efficiently solve the associated optimization problem. Their numerical method was further extended to include second-order (Hessian) information in the numerical optimization [42]. For stochastic models with random model parameters, the Markov chain Monte Carlo method has been applied to calibrate the posterior distribution of model parameters using Bayesian inference [43]. Other applications with reaction-diffusion based models that are more focused on clinical implications can be found in [5, 13, 44]. On the contrary, relatively few studies have considered the solid growth model (i.e. the second model type described in the previous paragraph). In this contribution, we present an efficient adjoint-based algorithm to solve a deterministic optimization problem for the (linearized) solid growth model in which the model parameters are correlated to the volumetric growth across the tumor. This is achieved by introducing adjoint variables to efficiently minimize the sum squared difference between the model’s estimate of tumor cell density and the cell density estimated by DW-MRI. In the present study, magnetic resonance imaging data is acquired during the course of tumor growth in a rat brain seeded with C6 glioma cells. By solving the inverse problem, we are able to quantify the spatial variation of tumor growth in a noninvasive way. This paper is organized as follows. Section 2 introduces the mechanically coupled growth model and the forward problem as well as the formulation of the inverse problem and the adjoint-based algorithm. Section 3 includes a validation of the algorithm on a 2D benchmark problem and presents results on the *in vivo* rat brain tumor data. The discussion and concluding remarks are provided in section 4.

2. Problem formulation

2.1. Growth model

We model the tumor as an elastic continuum with a growing mass ¹ in which growth is characterized by changes in local volume and density that can be either growth-induced or

stress-induced. In particular, the growth-induced volume and density change of a small section of tumor (i.e. the “element”) is defined as the volume and density of the element when the external elastic stress is released (e.g., by excising the element from the tumor mass). When the element is within the mass, there is an additional contribution due to the elastic stresses; the actual deformation of the element is a combination of growth-induced deformation and deformation caused by elasticity. This relation is reflected, in the finite growth theory, by the so-called multiplicative decomposition in which the overall deformation gradient is decomposed into the product of a growth component and an elastic component [33, 34]. In practice, the growth component is dictated by a user-selected empirical law [33, 34, 45], while the elastic component is determined such that compatibility of the overall deformation and force equilibrium are satisfied. While the finite growth theory is fully nonlinear, in this effort we instead focus on a linearized growth model [27] and use it to formulate the boundary value problem that describes the mass effect of tumor growth. The major assumptions of the linearized model are that: 1) the growth and elastic deformation are additive, and 2) the elastic responses of both tumor and healthy appearing brain tissue are linearly elastic. Although the linearized growth model is based on the linearity assumption, it is shown in Appendix A that it is a reasonable approximation to the finite growth theory even under substantial volumetric tumor growth. In particular, it is shown that the percentage error of tumor size and cell density calculated by the linearized growth model is less than 8% for the range of volumetric growth in our experimental data in section 3.2.

Figure 1 shows a 2D, T_2 -weighted, axial image of a rat head (left) and a closer view of the brain (right) in which the boundary value problem is formulated. Briefly, the boundary value problem is based on the force equilibrium in the tumor (Ω_T) and surrounding healthy appearing brain tissue (Ω_B) as the tumor grows in volume. On the interface between the tumor and brain tissue, continuity of displacement and traction forces are assumed. While on the rigid skull (Ω), no displacement of the material is allowed. For a description of the experimental details, interested readers are referred to [11, 13].

The governing equations and the constitutive relations for the tumor are summarized in the following [27]:

$$\nabla \cdot \sigma = 0, \quad (1)$$

$$\varepsilon = \frac{1}{2}(\nabla \mathbf{u} + \nabla^T \mathbf{u}), \quad (2)$$

$$\sigma = 2\mu_T(\varepsilon - \mathcal{E}) + \lambda_T \text{tr}(\varepsilon - \mathcal{E}) \mathbf{I} \quad (3)$$

¹Unless otherwise specified, the term “growth” refers to either case when the mass of tumor increases (positive growth) or decreases (negative growth).

where σ , ε , $\mathbf{u}$ are the stress, (total) strain, and displacement, respectively, of the tumor, $\mathcal{G}$ is the growth-induced strain, $\varepsilon - \mathcal{G}$ is the elastic component of the strain, μ_T and λ_T are the Lamé parameters and $\mathbf{I}$ is the identity matrix. When tumor growth is locally isotropic, we can write $\mathcal{G} = \frac{1}{3}g\mathbf{I}$ where $g = \text{tr}(\mathcal{G})$ is the trace of $1 + \frac{1}{3}g$ characterizes the growth-induced stretch ratio in each direction. Accordingly, the Jacobian of the growth-induced deformation, J_g , defined as the determinant of $\mathbf{I} + \mathcal{G}$, is given by $J_g = (1 + \frac{1}{3}g)^3$. For isotropic growth, according to (3), the constitutive relations for both the tumor and brain tissue are:

$$\sigma = \begin{cases} 2\mu_T\varepsilon + (\lambda_T\text{tr}(\varepsilon) - gK_T)\mathbf{I} & \text{in } \Omega_T \\ 2\mu_B\varepsilon + \lambda_B\text{tr}(\varepsilon)\mathbf{I} & \text{in } \Omega_B \end{cases} \quad (4)$$

in which μ_B and λ_B are the Lamé parameters of the brain tissue and K_T is the bulk modulus of the tumor. Note, here $g = g(\mathbf{X}, t)$ is non-vanishing only when a material point $\mathbf{X}$ belongs to the tumor area; for the healthy appearing brain tissue, $g \equiv 0$ always vanishes. As a result, no new volume is produced in Ω_B . Finally, the boundary conditions on the rigid skull Ω and the tumor-brain interface S are:

$$\mathbf{u}|_{\partial\Omega} = 0 \quad (5)$$

$$\mathbf{u}_T|_S = \mathbf{u}_B|_S \quad (6)$$

$$\sigma_T|_S \cdot \mathbf{n} = \sigma_B|_S \cdot \mathbf{n} \quad (7)$$

where the subscripts T and B indicate the tumor or the healthy-appearing brain tissue and $\mathbf{n}$ is the outward normal vector to the interface S .

Given the distribution of $g(\mathbf{X}, t)$, the solution to the above boundary value problem can be determined by the principle of virtual work [46]:

$$\int_{\Omega_T} \sigma : \delta\varepsilon dV^0 + \int_{\Omega_B} \sigma : \delta\varepsilon dV^0 = 0 \quad (8)$$

in which $\delta\varepsilon = \frac{1}{2}(\nabla\delta\mathbf{u} + \nabla^T\delta\mathbf{u})$ is virtual strain corresponding to the compatible virtual displacement $\delta\mathbf{u}$; i.e. $\delta\mathbf{u}|_{\Omega} = 0$, and the symbol $:$ represents double contraction of two tensors (sum of component-wise multiplication). The left hand side of (8), denote as $\mathcal{A}(\mathbf{u}, \delta\mathbf{u}; g)$, is the internal virtual work done by the virtual displacement on the current stress state. According to the constitutive relation (4), we have

$$\begin{aligned} \mathcal{A}(\mathbf{u}, \delta \mathbf{u}; g) = & \int_{\Omega_T} \left[\mu_T (\nabla \mathbf{u} + \nabla^T \mathbf{u}) : \nabla \delta \mathbf{u} + (\lambda_T \text{tr}(\nabla \mathbf{u}) - g K_T) \text{tr}(\nabla \delta \mathbf{u}) \right] dV^0 \quad (9) \\ & + \int_{\Omega_B} \left[\mu_B (\nabla \mathbf{u} + \nabla^T \mathbf{u}) : \nabla \delta \mathbf{u} + \lambda_B \text{tr}(\nabla \mathbf{u}) \text{tr}(\nabla \delta \mathbf{u}) \right] dV^0 \end{aligned}$$

where the two terms represent the virtual energy in the tumor and brain tissue, respectively. The solution to (8) defines the map of deformation $\mathcal{M}: \mathbf{X} \mapsto \mathbf{x}$, which maps the initial position of a material point $\mathbf{X}$ to its deformed position $\mathbf{x} = \mathbf{X} + \mathbf{u}(\mathbf{X})$. Naturally, $\mathcal{M}$ depends on the distribution $g(\mathbf{X})$.

Now let $c^0(\mathbf{X})$ denote the initial cell density of the tumor. According to conservation of mass, the tumor cell density after growth is given by

$$\hat{c}(\mathbf{x}) = c^0(\mathbf{X}) \frac{J_g}{J}, \quad (10)$$

where $J = \det(\mathbf{I} + \nabla \mathbf{xu})$ is the total Jacobian. Here, we've assumed that growth takes place in a density-preserving manner [34]; that is, in the absence of elastic stresses, the cell density is preserved during growth according to $\hat{c}(\mathbf{X}) = c^0(\mathbf{X})$. Note, in a complete growth theory, one also needs to characterize the rate change of volumetric growth as a function of, for example, strain, stress and nutrient concentration [27]. However, since in our case the volumetric growth is to be determined from subject-specific imaging data by solving an inverse problem (see section 2.2), we do not specify an evolution law for the growth-induced deformation.

2.2. Inverse problem

To quantify the volumetric growth of the glioma, we compare the predicted tumor cell density $\hat{c}(\mathbf{x})$ with the tumor cell density measured at the second time point $c(\mathbf{x})$. Both c and the initial cell density c^0 are estimated by DWMRI, which is a non-invasive imaging method that uses the diffusion of water molecules to generate contrast in MR images and can be used to estimate the apparent diffusion coefficient (ADC) in the region of interest on a voxel basis [47]. The ADC values are correlated with the cell density inside the tumor [6, 7, 11, 48], which we use to calculate c^0 and c at both time points by

$$c(\mathbf{x}, t) = \vartheta_{\max} \frac{ADC_w - ADC(\mathbf{x}, t)}{ADC_w - ADC_{\min}} \quad (11)$$

where $\vartheta_{\max}$ is the tumor cell carrying capacity for an imaging voxel representing the physical limitation to the number of cells that can fit within an imaging voxel assuming spherical tumor cells with a packing density of 0.7405 [49] and an average cell volume of

$908 \mu\text{m}^3$ [50], ADC_w is the ADC of free water at 37°C ($2.5 \times 10^{-3} \text{mm}^2/\text{s}$) [47], $ADC_{\min}$ is the minimum ADC value which corresponds to the voxel with the largest number of cells and $ADC(\mathbf{x}, t)$ is the ADC measurement at position $\mathbf{x}$ and time t . For the healthy appearing brain tissues, both c^0 and c are set to zero. Specifically, we aim to solve the following regularized optimization problem:

$$g^*(\mathbf{X}) = \arg \min_{g(\mathbf{X})} \left\{ \int_{\Omega_t} (\hat{c}(\mathbf{x}(\mathbf{X})) - c(\mathbf{x}))^2 dV + \alpha \int_{\Omega_T} (g(\mathbf{X}) - g_0(\mathbf{X}))^2 dV^0 \right. \\ \left. + \beta \int_{\Omega_T} \|\nabla g(\mathbf{X}) - \nabla g_0(\mathbf{X})\|_2^2 dV^0 \right\}, \quad (12)$$

in which $\Omega_t \equiv \mathcal{M}(\Omega)$ is the deformed configuration of the brain, g^0 is a reference distribution of growth, α and β are regularization parameters penalizing the L_2 norm of g and its gradient, respectively. Note, g^0 is chosen based on our prior knowledge of growth of the tumor. In the numerical calculation in section 3, we always assume that $g^0 \equiv 0$. Denote the objective function in (12) as $h(\mathbf{u}(\mathbf{X}), g(\mathbf{X}))$. Since $\mathbf{u}$ is determined provided that g is known, the objective is simply a functional of the model parameter g . However, instead of solving the unconstrained optimization problem, we consider it as a PDE-constrained optimization problem. This way allows us to calculate the gradient of the objective more efficiently by using the adjoint-state method.

2.2.1. Adjoint-state method—In this section, we introduce an adjoint-based approach to efficiently compute the gradient of the objective function with respect to g [51, 52]. This is achieved by defining a Lagrangian that combines the objective function with the total virtual work (9) of the tumor-brain system. According to the method of Lagrange multipliers, the extrema of the objective function are critical points of the Lagrangian. Numerically, this leads to an efficient way to compute the gradient since we avoid direct computation of the derivative of $\mathbf{u}$ with respect to the model parameters. In the following, we first introduce the formula to compute the gradient given the adjoint displacement, and then formulate the adjoint-state equation that determines the adjoint displacement. Due to discontinuity of the target cellularity c , the right hand side of the adjoint-state equation involves a special term of surface integral (see more discussion in (37) and (39)).

The aforementioned Lagrangian $\mathcal{L}$ is defined as:

$$\mathcal{L}(\tilde{\mathbf{u}}, \delta\tilde{\mathbf{u}}, g) = h(\tilde{\mathbf{u}}, g) - \mathcal{A}(\tilde{\mathbf{u}}, \delta\tilde{\mathbf{u}}; g), \quad (13)$$

in which the virtual displacement $\delta\tilde{\mathbf{u}}$ plays the role of the Lagrange multiplier. When $\tilde{\mathbf{u}} = \mathbf{u}(g)$ is a solution to the forward problem (8), we have $\mathcal{L}(\mathbf{u}, \delta\tilde{\mathbf{u}}, g) = h(\mathbf{u}(g), g)$ to be held for any compatible $\delta\tilde{\mathbf{u}}$ that satisfies $\delta\tilde{\mathbf{u}}|_{\Omega} = 0$. From the chain rule, the gradient of the objective function is given by

$$\frac{\partial h(\mathbf{u}(g), g)}{\partial g} = \frac{\partial \mathcal{L}(\mathbf{u}, \delta \tilde{\mathbf{u}}, g)}{\partial \tilde{\mathbf{u}}} \frac{\partial \mathbf{u}}{\partial g} + \frac{\partial \mathcal{L}(\mathbf{u}, \delta \tilde{\mathbf{u}}, g)}{\partial g}. \quad (14)$$

To avoid direct computation of $\frac{\partial \mathbf{u}}{\partial g}$, we choose $\delta \tilde{\mathbf{u}} = \delta \mathbf{u}$ such that $\frac{\partial \mathcal{L}(\mathbf{u}, \delta \mathbf{u}, g)}{\partial \tilde{\mathbf{u}}} = 0$, or equivalently,

$$\frac{\partial \mathcal{L}(\mathbf{u}, \delta \mathbf{u}, g)}{\partial \tilde{\mathbf{u}}}[\Delta \mathbf{u}] \equiv \frac{\partial h(\mathbf{u}, g)}{\partial \tilde{\mathbf{u}}}[\Delta \mathbf{u}] - \frac{\partial}{\partial \tilde{\mathbf{u}}} \mathcal{A}(\mathbf{u}, \delta \mathbf{u}; g)[\Delta \mathbf{u}] = 0 \quad (15)$$

for any test function $\mathbf{u}$ that satisfies $\mathbf{u}/\Omega = 0$. Here,

$$\frac{\partial \mathcal{P}(\mathbf{u})}{\partial \tilde{\mathbf{u}}}[\Delta \mathbf{u}] \triangleq \lim_{\varepsilon \rightarrow 0} \frac{d}{d\varepsilon} [\mathcal{P}(\mathbf{u} + \varepsilon \Delta \mathbf{u}) - \mathcal{P}(\mathbf{u})] \quad (16)$$

denotes the directional derivative of a functional $\mathcal{P}$. (15) is known as the adjoint-state equation of the forward problem and $\delta \mathbf{u}$ is the adjoint displacement. Notice that, by definition,

$$\frac{\partial}{\partial \tilde{\mathbf{u}}} \mathcal{A}(\mathbf{u}, \delta \mathbf{u}; g)[\Delta \mathbf{u}] = \mathcal{A}(\delta \mathbf{u}, \Delta \mathbf{u}; 0) \quad (17)$$

is the homogenized internal virtual work in the absence of growth, which we denote as $\mathcal{A}_0(\delta \mathbf{u}, \mathbf{u})$, the adjoint-state equation (15) becomes:

$$\mathcal{A}_0(\delta \mathbf{u}, \Delta \mathbf{u}) = \frac{\partial h(\mathbf{u}, g)}{\partial \tilde{\mathbf{u}}}[\Delta \mathbf{u}]. \quad (18)$$

Here, g is fixed in calculating the directional derivative on the right-hand side. With the adjoint displacement $\delta \mathbf{u}$, the sensitivity of the objective upon perturbation in the direction of g can be obtained from (14) as:

$$\begin{aligned} \frac{\partial h(\mathbf{u}(g), g)}{\partial g}[\Delta g] &= \frac{\mathcal{L}(\mathbf{u}, \delta \mathbf{u}, g)}{\partial g}[\Delta g] \\ &= \frac{\partial h(\mathbf{u}, g)}{\partial g}[\Delta g] - \frac{\partial}{\partial g} \mathcal{A}(\mathbf{u}, \delta \mathbf{u}; g)[\Delta g]. \end{aligned} \quad (19)$$

The first term, denoted as J_1 , arises from taking the partial derivative of the objective with respect to g while keeping $\mathbf{u}$ fixed. The second term, denoted as J_2 , is the contribution from the adjoint displacement. In particular, according to (9) and (12), we have

$$J_1 = \frac{\partial}{\partial g} \left[\int_{\Omega'} (\hat{c}(\mathbf{x}(\mathbf{X})) - c(\mathbf{x}))^2 dV \right] [\Delta g] + 2\alpha \int_{\Omega_T} (g - g_0) \Delta g dV^0 \quad (20)$$

$$+ 2\beta \int_{\Omega_T} (\nabla g - \nabla g_0) \cdot \nabla (\Delta g) dV^0,$$

$$J_2 = \int_{\Omega_T} K_T \text{tr}(\nabla_{\mathbf{X}} \delta \mathbf{u}(\mathbf{X})) \Delta g(\mathbf{X}) dV^0. \quad (21)$$

To further simplify J_1 , we transform the objective function h (ignoring the regularization terms) onto the undeformed configuration:

$$\int_{\Omega'} (\hat{c}(\mathbf{x}(\mathbf{X})) - c(\mathbf{x}))^2 dV = \int_{\Omega} (\hat{c}_r(\mathbf{X}, \mathbf{u}) - c_r(\mathbf{X}, \mathbf{u}))^2 J dV^0 \quad (22)$$

where

$$\hat{c}_r(\mathbf{X}, \mathbf{u}) = c^0(\mathbf{X}) \frac{J_g(\mathbf{X})}{J(\mathbf{u})}, \quad (23)$$

$$c_r(\mathbf{X}, \mathbf{u}) = c(\mathbf{X} + \mathbf{u}(\mathbf{X})) \quad (24)$$

are the pull-back of the predicted and target cellularity on the undeformed configuration. Accordingly, the first term in (20) becomes

$$\begin{aligned} \frac{\partial}{\partial g} \left[\int_{\Omega'} (\hat{c} - c)^2 dV \right] [\Delta g] &= \int_{\Omega} \frac{\partial}{\partial g} (\hat{c}_r - c_r)^2 [\Delta g] J dV^0 \quad (25) \\ &= \int_{\Omega} 2(\hat{c}_r - c_r) c^0 \frac{\partial}{\partial g} J_g [\Delta g] dV^0 \end{aligned}$$

in which

$$\frac{\partial}{\partial g} J_g [\Delta g] = J_g \frac{\Delta g}{1 + \frac{1}{3}g}. \quad (26)$$

Similarly, the right-hand side of the adjoint-state equation (18) can be split into three terms, which we denote as I, II and III, respectively:

$$\frac{\partial h(\mathbf{u}, g)}{\partial \tilde{\mathbf{u}}}[\Delta \mathbf{u}] = \text{I} + \text{II} + \text{III} \quad (27)$$

$$\text{I} = 2 \int_{\Omega} (\hat{c}_r - c_r) \frac{\partial \hat{c}_r}{\partial \tilde{\mathbf{u}}}[\Delta \mathbf{u}] J dV^0 \quad (28)$$

$$\text{II} = -2 \int_{\Omega} (\hat{c}_r - c_r) \frac{\partial c_r}{\partial \tilde{\mathbf{u}}}[\Delta \mathbf{u}] J dV^0 \quad (29)$$

$$\text{III} = \int_{\Omega} (\hat{c}_r - c_r)^2 \frac{\partial J}{\partial \tilde{\mathbf{u}}}[\Delta \mathbf{u}] dV^0. \quad (30)$$

From (23), we have

$$\frac{\partial \hat{c}_r}{\partial \tilde{\mathbf{u}}}[\Delta \mathbf{u}] = -\frac{\hat{c}_r}{J} \frac{\partial J}{\partial \tilde{\mathbf{u}}}[\Delta \mathbf{u}], \quad (31)$$

which calculates the sensitivity of the cellularity after tumor growth upon perturbation of displacement while growth is fixed. With (31) and noticing that

$$\frac{\partial J}{\partial \tilde{\mathbf{u}}}[\Delta \mathbf{u}] = J \operatorname{tr} \left((\mathbf{I} + \nabla_{\mathbf{X}} \mathbf{u})^{-1} \nabla_{\mathbf{X}}(\Delta \mathbf{u}) \right), \quad (32)$$

one can combine the terms I and III into:

$$\text{I} + \text{III} = \int_{\Omega} (-\hat{c}_r^2 + c_r^2) \frac{\partial \hat{c}_r}{\partial \tilde{\mathbf{u}}}[\Delta \mathbf{u}] dV^0, \quad (33)$$

and integrate them using standard finite element method. On the other hand, from (24), we obtain the sensitivity of the target cellularity in the following expression:

$$\frac{\partial c_r}{\partial \mathbf{u}}[\Delta \mathbf{u}] = \nabla_{\mathbf{x}} c|_{\mathbf{x} + \mathbf{u}} \cdot \Delta \mathbf{u}. \quad (34)$$

Note, since c is discontinuous across the boundary of the target tumor volume, $\nabla_{\mathbf{x}} c$ is not well defined on the boundary in the classic sense. Denote $D = \Omega_T^{\text{target}}$ as the target tumor volume and its boundary $S = \partial D$. Formally we can rewrite Π as:

$$\Pi = -2 \int_{\Omega} (\hat{c}_r - c_r) \nabla_{\mathbf{x}} c|_{\mathbf{x} + \mathbf{u}} \cdot \Delta \mathbf{u} dV^0 \quad (35)$$

$$= -2 \int_{\Omega^t} (\hat{c} - c) \nabla_{\mathbf{x}} (\check{c} \mathbb{1}_{\mathbf{x} \in D}) \cdot \Delta \mathbf{u} dV \quad (36)$$

$$= -2 \int_D (\hat{c} - c) \nabla_{\mathbf{x}} c \cdot \Delta \mathbf{u} dV - 2 \int_{\Omega^t} (\hat{c} - c) \check{c} \Delta \mathbf{u} \cdot \nabla_{\mathbf{x}} \mathbb{1}_{\mathbf{x} \in D} dV, \quad (37)$$

where $\check{c}$ is any smooth extension of c on the entire domain such that $\check{c}|_D = c|_D$ and $\mathbf{u}(\mathcal{M}^{-1}(\mathbf{x}))$ is the push-forward of the test function on the deformed configuration. Briefly, (36) first transforms the integral onto the undeformed configuration and then (37) uses the product rule to split $\nabla_{\mathbf{x}} (\check{c} \mathbb{1}_{\mathbf{x} \in D})$ into two terms. According to Appendix B, the second term that involves integrating the derivative of the indicator function over the deformed domain further reduces to

$$-2 \int_{\Omega^t} (\hat{c} - c) \check{c} \Delta \mathbf{u} \cdot \nabla_{\mathbf{x}} \mathbb{1}_{\mathbf{x} \in D} dV = \int_S (2\hat{c} - c) c \Delta \mathbf{u}_{\perp} dA, \quad (38)$$

in which $\mathbf{u}_{\perp}$ is the normal component of $\mathbf{u}(\mathbf{x})$ on S . That is, $\mathbf{u}|_S = \mathbf{u}_{\parallel} + \mathbf{u}_{\perp}$ where $\mathbf{e}_{\parallel}$ and $\mathbf{e}_{\perp}$ are the unit tangent and outward normal vectors to S , respectively. Combining (37) and (38), we reach

$$\Pi = -2 \int_D (\hat{c} - c) \nabla_{\mathbf{x}} c \cdot \Delta \mathbf{u} dV + \int_S (2\hat{c} - c) c \Delta \mathbf{u}_{\perp} dA, \quad (39)$$

which can now be integrated using standard finite element method.

Finally, we comment that the computational cost to determine the adjoint displacement $\delta \mathbf{u}$ from (18) is on the same order as solving for $\mathbf{u}$. Indeed, the bilinear form in the adjoint state equation is the homogenized version of that in the forward problem (8). After $\delta \mathbf{u}$ is determined, as is shown in (19) to (21), the cost for computing the gradient of the objective function reduces to evaluating multiple integrals. Despite the complexity of these integrals, this approach is still much more efficient compared to the finite-difference-based direct method. In the direct method, one calculates the gradient by perturbing each degree of freedom and hence the number of times needed to solve the forward problem is proportional to the number of degrees of freedom, which is very costly for a moderately refined mesh. This is also our major motivation to develop the adjoint based method.

2.2.2. Optimization scheme—Denote P_i as the finite element patch that consists of all tumor elements sharing the i^{th} degree of freedom (see Fig. 2). The average sensitivity of h upon unit perturbation of the i^{th} degree of freedom can be computed *via*

$$(\bar{\mathbf{J}})_i = \frac{1}{\text{vol}(P_i)} \frac{\partial h(\mathbf{u}(g), g)}{\partial g} [\Phi_i(\mathbf{X})], \quad (40)$$

where Φ_i is the finite element base corresponding to the i^{th} degree of freedom.

Figure 3 shows the flow chart of the optimization scheme. At each iteration, the adjoint displacement $\delta \mathbf{u}$ and the solution to the forward problem $\mathbf{u}$ are first computed given the current growth distribution g , which are then used to determine the average sensitivity for each degree of freedom by (40). After the average sensitivity is determined, we use the steepest descent method to update the growth distribution *via*

$$g_i^{(k+1)} = g_i^{(k)} - \gamma (\bar{\mathbf{J}})_i \quad (41)$$

until the maximum allowable iteration N is reached. Here, γ is the prescribed step size.

The algorithm was implemented with libMesh, a C++ finite element library that supports arbitrary unstructured discretizations [53]. In the implementation, two sets of finite element meshes (first order, triangular) are used (generated in Gmsh [54]). The mesh used to discretize the initial cell density c^0 is the major mesh on which the degrees of freedom of the growth distribution g are defined. While the mesh for the target cell density c is secondary and only used to evaluate the surface integral (38); see more details in Appendix C.2. For the experimental data discussed in section 3.2, c^0 and c were constructed using the voxel data composing the magnetic resonance images. For elements across multiple voxels, the cell densities are obtained *via* interpolation.

3. Results

In section 2, tumor growth is assumed to be isotropic in all spatial dimensions. If growth is restricted to occur only in the x - y plane, the growth-induced strain tensor becomes

$$\mathcal{G} = \begin{pmatrix} \frac{1}{2}g & 0 & 0 \\ 0 & \frac{1}{2}g & 0 \\ 0 & 0 & 0 \end{pmatrix} \quad (42)$$

where g still represents the trace of $\mathcal{G}$. If plane strain deformation is further assumed (see Appendix D), the boundary value problem reduces to a 2D problem for which one simply needs to replace K_T by $\lambda_T + \mu_T$ in (4), (9) and (21). In addition, since $J_g = (1 + \frac{1}{2}g)^2$, (26) becomes

$$\frac{\partial}{\partial g} J_g[\Delta g] = J_g \frac{\Delta g}{1 + \frac{1}{2}g}. \quad (43)$$

All other equations remain unchanged. In the following section, we validate our numerical approach on a 2D toy problem (plane strain + in-plane growth) that mimics tumor growth in the brain. Without introducing ambiguities, we do not differentiate 3D quantities from their 2D counterparts. For example, in the validation problem, $\mathbf{u}$ denotes the two dimensional vector of in-plane displacement and σ denotes the in-plane components of the 3D stress tensor.

3.1. Numerical validation

Consider a 2D circular domain as is shown in Fig. 4. The middle region ($r' < R_T$) represents the initial tumor area at t_1 and the surrounding region ($R_T < r' < R_B$) represents the brain tissue which is fixed at the outer boundary ($r' = R_B$). To be consistent with *in vivo* experiments [55, 56], both the healthy brain and tumor tissues are assumed to be compressible with Poisson's ratios ν_B and ν_T equal to 0.45 and initially in the stress-free state. In the figure, the boundary of the deformed tumor estimated by the model is indicated by the dashed circle with radius R_T^t , while the measured tumor area at t_2 is indicated by the solid circle with radius R . Hence, the two plots represent the scenarios when the model under-estimates (left, condition I) or over-estimates (right, condition II) the tumor size, respectively.

In the condition of extremely soft brain tissue (i.e., $\mu_B \ll \mu_T$), the growth-induced stress is negligible when volumetric growth $g(\mathbf{X}) \equiv \bar{g}$ is uniform in Ω_T . Indeed, due to radial symmetry, the tumor displacement for the problem is given by $\mathbf{u}(\mathbf{X}) = \frac{\bar{g}}{2} r' \hat{\mathbf{r}}$ in which r' denotes the distance of the undeformed position $\mathbf{X}$ to the origin and $\hat{\mathbf{r}}$ is the unit vector in the

(outward) radial direction. Thus, $\nabla \mathbf{u} = \varepsilon = \frac{\bar{g}}{2} \mathbf{I}$ and $J = J_g = (1 + \frac{\bar{g}}{2})^2$. According to (D.7), the Cauchy stress $\boldsymbol{\sigma} = 0$ vanishes inside the tumor. Since $\mu_B \ll \mu_T$, the stress inside the brain tissue is also negligible. To facilitate the analysis, we assume that the measured cell densities c^0 and c are uniform and the same at both time points. Specifically, let c^0 and c be given by

$$c^0(\mathbf{X}) = c_o, r' < R_T \quad (44)$$

$$c(\mathbf{x}) = c_o, r < R, \quad (45)$$

where c_o is the prescribed cell density and r denotes the distance of the deformed position $\mathbf{x}$ to the origin. According to (10), the predicted cellularity $\hat{c}$ at t_2 is also uniform and equals the prescribed cell density across the deformed tumor area. As a result, the objective function (12) follows a simple expression for both conditions:

$$h(\mathbf{u}) = 2\pi \left| \int_{R_T}^R c_o^2 r dr \right|. \quad (46)$$

Here, we've assumed that both regularization coefficients vanish; i.e., $\alpha = \beta = 0$.

The right hand side of the adjoint state equation (18) can be derived analytically by considering the perturbed solution $\mathbf{u}_\varepsilon = \mathbf{u} + \varepsilon \mathbf{u}$ while fixing $g(\mathbf{X}) \equiv \bar{g}$ as constant. Due to radial symmetry, only perturbation in the radial direction needs to be considered. In addition, since $\mu_B \ll \mu_T$, one can set the test function $\mathbf{u}$ to zero in Ω_B . Overall, we denote $\mathbf{u} = f_1(r) \hat{\mathbf{r}}$ in which f_1 is a continuous function that vanishes on the interval $[R_T, R_B]$. According to Appendix E, the adjoint state equation for the 2D problem ($\mu_B \ll \mu_T$) is given by

$$\mathcal{A}_0(\delta \mathbf{u}, f_1 \hat{\mathbf{r}}) = -2\pi c_o^2 \left(\frac{\bar{g}}{2} + 1 \right) R_T f_1(R_T) \quad (47)$$

for condition I and

$$\mathcal{A}_0(\delta \mathbf{u}, f_1 \hat{\mathbf{r}}) = -2\pi c_o^2 \left(\frac{\bar{g}}{2} + 1 \right) f_1(R_T) R_T + 4\pi c_o^2 \left(\frac{\bar{g}}{2} + 1 \right) f_1(R') R' \quad (48)$$

for condition II where $R' = R/(1 + \frac{\bar{g}}{2})$ is the pull-back of position R in the undeformed configuration.

In Fig. 5, we compare the numerically calculated adjoint displacement against the analytic solutions to (47) and (48) (see (E.10) and (E.19)) under various conditions. In the validation, $R_T = \frac{1}{3}R_B = 1$ and the finite element mesh consists of 26802 first order 2D triangular elements, approximately one third of which are tumor elements (see Fig. 4). The elements in the brain tissue are denser at the center of the domain with typical element size near the boundary about twice the size at the center. In the left plot of Fig. 5, the target radius of the tumor at t_2 is fixed to be $R = 1.5$ while the value of $\bar{g}$ is varied. On the right, $\bar{g} = 0$ is fixed while R is varied. As is shown in both plots, the numerically calculated adjoint displacement (red circles) agrees very well with the analytic solution (black lines). Note, when $R > R_T^t \equiv (1 + \frac{\bar{g}}{2})R_T$, the adjoint displacement is independent of R ; see (47) and Appendix E. Hence, the same profile is expected as $R > 1$ on the right plot.

3.1.1. Numerical results—Figure 6 shows the optimization result for three cases with different assigned stiffness values of the brain tissue: $\mu_B = 2\mu_T$ (black), $\mu_B = \mu_T$ (red) and $\mu_B \ll \mu_T$ (blue). In the calculation, $R = 1.5$ and a uniform initial guess of $g^{(0)}(\mathbf{X}) \equiv 1.8$ in Ω_T are used. The regularization parameters and the step size are given by $\alpha = \beta = 0.01$ and $\gamma = 1$, respectively. To the left, the circled and dashed curves plot for each case the logarithm of the objective function with and without the regularization terms, respectively. To the right, statistics of the growth distribution $g(\mathbf{X})$ are shown in which the mean and standard deviation of the error bars are defined by

$$\text{mean}(g) = \frac{1}{\text{vol}(\Omega_T)} \int_{\Omega_T} g(\mathbf{X}) dV^0, \quad (49)$$

$$\text{std}(g) = \sqrt{\frac{1}{\text{vol}(\Omega_T)} \int_{\Omega_T} (g(\mathbf{X}) - \text{mean}(g))^2 dV^0}. \quad (50)$$

For all three cases, the converged growth distribution is close to a uniform distribution. In particular, the largest standard deviation of $g(\mathbf{X})$ among the three cases is approximately 0.037 when $\mu_B = \mu_T$. When $\mu_B \ll \mu_T$, $g(\mathbf{X})$ converges to $g(\mathbf{X}) \equiv 1$, which agrees with the theory. Indeed, notice that $\mathbf{u} = \frac{\bar{g}}{2} r \hat{\mathbf{r}}$ gives the elastic solution under uniform tumor growth in a soft brain tissue, the objective function (46) vanishes given that $g \equiv 1$ and is hence minimized. When $\mu_B = \mu_T$, the initial (left) and converged (right) growth distributions after 500 iterations are shown in Fig. 7 (rendered in Paraview [57]). The initial guess overestimates the target tumor size (red circle) at t_2 . After optimization, the model predicted tumor size is close to the target size with a mean value of growth distribution converging to approximately around 1.24. Compared to the initial guess, the volume of tumor elements is smaller and the brain tissue near the interface between the tumor and brain tissue is less compressed (see the inserts).

The radius of the model predicted tumor size at convergence R_{T*}^t (left) as well as the mean value of the growth distribution $g_*(\mathbf{X})$ (right) are further shown in Fig. 8 as a function of μ_B/μ_T under different regularization conditions. For all conditions, the tumor size converges to the target radius (i.e., $R = 1.5$) when μ_B/μ_T is below a critical value, which coincides with a linear increase of mean tumor growth. Notice that, the average tumor cell density at convergence can be estimated, according to (10), by

$$\hat{c}_* \approx c_o \left(\frac{1 + \text{mean}(g_*)/2}{R_{T*}^t/R_T} \right)^2. \quad (51)$$

Hence, below the critical point the average tumor cell density increases with increasing μ_B/μ_T . For example, for the three cases in Fig. 6 (i.e., $\mu_B/\mu_T = 0, 1, 2$ and $\alpha = \beta = 0.01$), the converged tumor sizes are all equal to the target tumor size (also see Fig. 7) but the converged tumor cell density is the highest when $\mu_B/\mu_T = 2$ and the lowest when $\mu_B/\mu_T = 0$. Above the critical value, the converged tumor size and mean tumor growth decrease monotonically. Further calculations indicate that the average tumor cell density also decreases (see Fig. F.1 in Appendix F). These results suggest a balance between model predicted tumor area and tumor cell density in the optimization. In particular, when stiffness of the brain tissue is low, the optimal growth distribution tends to match the target tumor area by increasing the tumor cell density. When stiffness of the brain tissue increases, this strategy is not favored since matching the tumor size leads to significant error in cell density. Instead, a different strategy is favored to predict a less accurate tumor area while keeping the average tumor cell density close to the target value c_o .

When more regularization is introduced, both tumor size and mean tumor growth, as expected, converge to a lower value at a particular stiffness ratio and the critical point is also shifted toward the left. Figure 9 further shows the L-curves for the optimization. The x axis is the converged value of the objective function displayed in log scale and the y axis is the mean tumor growth which serves as a measure of the norm of growth distribution. Each curve, from left to right, connects points with different regularization conditions ($\alpha = \beta = 0, 0.01, 0.1, 0.5$) for a particular stiffness ratio μ_B/μ_T . Note, the curves for $\mu_B/\mu_T = 2$ are very close to each other and hard to recognize clearly. The L-curves indicate that the converged value of the objective increases with regularization while the norm of the growth distribution decreases. Additionally, the L-curves are steeper as μ_B/μ_T increases suggesting a stronger influence of regularization on the model parameters. Due to the physical confinement on tumor growth, the norm of $g(\mathbf{X})$ is naturally bounded from above; consequently, we do not see the typical L-shape in the curves.

3.2. Experimental data

We applied our algorithm on a set of experimentally measured *in vivo* rat glioma data. Figure 10 displays a set of T_2 -weighted spin echo magnetic resonance images (left column) and the corresponding cell density maps (right column) for a slice through the center of the tumor. The MRI data is acquired 10, 12 and 14 days after the rat was inoculated

intracranially with C6 rat glioma cells [11, 13]. Based on the maps of tumor cell density, we aim to obtain the optimal distribution of tumor growth, $g_*(\mathbf{X})$, from day 10 to day 12 and day 10 to day 14, respectively. In particular, we used the voxel map of cell density at day 10 to define c^0 , the initial tumor cell density, and used the measured cell density at day 12 or day 14 to define c , the target density at the second time point. Calculation is performed in the imaging plane assuming plane strain deformation and in-plane, isotropic tumor growth (see Appendix D). The tumor and brain tissue consist of approximately 3000 and 33000, respectively, 2D linear finite elements with typical dimension of a tumor element about one-fifth of a voxel. To avoid discontinuity, c^0 and c are interpolated for elements that sit across multiple voxels. Heterogeneity of material properties is neglected; we assign uniform elastic moduli $\mu_B = 0.42 \text{ kPa}$, $\nu_B = 0.45$ for the healthy-appearing brain tissue, and $\mu_T = 2.1 \text{ kPa}$, $\nu_T = 0.45$ for the tumor [55, 56]. Finally, the regularization coefficients are chosen, according to the L-curves, to be $\alpha = 1$, $\beta = 0$ (for more details, see Fig. F.2 in Appendix F).

The results of the algorithm are shown in Fig. 11. The left column plots the initial (in yellow) and target (in red) tumor areas for each case and the right column plots the contours of $J_g = \left(1 + \frac{g_*}{2}\right)^2$, the converged Jacobian of in-plane volumetric growth, on the deformed configuration for isolines $J_g = 1.0, 2.0, \dots, 6.0$. For both time points, there is significant variation of tumor growth in space, ranging approximately from 1.0 to 6.0. At day 12, volumetric growth is large at the top and bottom part of the tumor and small on the sides ($J_g \sim 1.0$). However, due to growth at the center of the tumor, we still observe some displacement in the horizontal direction. At day 14, the region with the maximum volumetric growth is shifted to the lower-right corner. This agrees with the change in tumor shapes from day 12 to day 14. Also, we notice that the deformed tumor shape provides a good fit of the measured tumor area. This is consistent with our previous discussion on the test case since the brain tissue is relatively soft compared to the tumor. More quantitatively, the relative symmetric difference (i.e., the percentage error of tumor area that is either fitted but not measured or measured but not fitted) is approximately 8% and 14% on days 12 and 14, respectively. Finally, we note that the converged tumor shape and growth distribution are not significantly affected by mesh refinement; see Fig. F.3 in Appendix F.

4. Discussion

In this contribution, we developed an adjoint-based method for a linear mechanically-coupled tumor model to estimate the nonuniform growth of C6 murine gliomas based on DW-MRI data. This is achieved by solving an inverse problem that minimizes the squared L^2 -difference between the cell densities estimated by the tumor model and the DW-MRI data. In particular, the algorithm takes the cellularity maps measured at two instants as input and calculates the optimal distribution of tumor growth. Given the cell density at the initial time point, the model estimated cell density is determined by solving a boundary value problem in the rat brain in which we characterize the glioma as a growing elastic solid. To solve the inverse problem more efficiently, we approximated the finite growth model *via* linearization. This allows us to use adjoint variables to optimize the objective function in a way much more efficient than the finite-difference-based direct method. We validated our numerical approach on a 2D test problem and applied the method to a set of MRI data of a

rat brain tumor. Results indicate good agreement of tumor shapes between measurement and prediction with relative symmetric difference being less than 15%.

Our work fits into the philosophy of image-driven tumor modeling [5, 12]; i.e., to use quantitative imaging data as inputs to biophysical tumor models to evaluate and predict the state of tumor development. In typical framework of image-driven modeling, one first calibrates model parameters from patient-specific medical images at earlier time points and then uses the calibrated model to predict the future state of the tumor [9]. Practically, the first step often involves solving an inverse problem in a high or even infinite dimensional parameter space. This prohibits the use of finite-difference-based direct method and calls for more efficient optimization methods such as the adjoint-state method. In the context of glioma development, our effort is the first to apply the adjoint-state method to the solid growth model in which tumor growth is characterized by a continuous function representing local volumetric growth. As opposed to reaction-diffusion type models, the solid growth model is suitable for tumors (e.g., C6 glioma tumor) with limited diffusivity. By solving the inverse problem, we are able to estimate the nonuniform volumetric growth across the tumor in a noninvasive way. Significantly, this approach does not require to optimize extra parameters given that the elastic moduli of the tumor and brain tissue are known. If the growth model is to be used to predict future state of the tumor, on the other hand, additional biophysical laws are necessary to describe the rate of local tumor growth (e.g., as a function of nutrient, stress, and strain) [27, 45] and hence more patient-specific parameters may be included. In more sophisticated tumor models, growth may also be coupled to access to nutrients, and can be affected by parameters related to (for example) cell-ECM adhesion, ECM remodeling, and porosity [36]. We acknowledge that these important features are not considered in our, more simplistic, model; however, our goal here is not to build a sophisticated tumor growth model, rather it is to build a model that can be calibrated using *in vivo* imaging data that can be acquired in a routine fashion. This makes it challenging to inform all the parameters that are present in a more comprehensive tumor model [12]. Furthermore, the underlying biological phenomena is only observed by standard morphology based imaging measures *via* their effects on the local volume change, a practice adopted in many solid growth models [33, 58, 59]. Such a relation allows us to quantify the volumetric growth of gliomas by solving an inverse problem – which is constrained by the experimentally measured *in vivo* data – without making assumptions about the underlying quantities. We note that other groups have offered elegant and extensive investigations of the underlying tissue mechanical properties; see, for example, references [33, 58, 36, 59] for more details on modeling growth-induced volume change in the tumor.

Despite the novelty of this work, there is much room for improvement in both modeling and computation. For example, in formulation of the forward problem, we used a simple linearized solid growth model with constant stiffness across the tumor and brain tissue and assumed plane strain deformation in analysis of the experimental data. These can be improved by considering the finite growth model and perform a full calculation in 3D with different mechanical properties assigned to different anatomical structures of the brain. In addition, we made the assumption that tumor growth is density-preserving, which shall be verified by experiments. Computationally, a fixed step size is used in the steepest descent method. More efficiently, one can choose the step size adaptively *via* (for example) the

Barzilai-Borwein or the backtrack line search method [60, 61]. Although adjoint-based method is efficient for our linearized growth model, it is to be noted that it may not be suitable for more complicated tumor models. To extend the adjoint-based method to the finite growth model, one can refer to the discussion in [62] for more details.

We also used a linear transformation of ADC to estimate tumor cellularity $c(\mathbf{x}, t)$. This is based off correlations between histological estimates of cellularity or cell density and the MRI measured ADC in human brain tumors ([63], $r = 0.77$, $p = 0.007$), breast cancer ([64], $r = 0.54$, $p < 0.01$), pediatric lesions ([65], $r = 0.73$, $p < 0.001$), small animal models of breast cancer ([7], $r > 0.57$, $p = 0.03$), and *in vitro* studies [6]. However, it is known that there is a level of ambiguity in the source of changes in ADC as many other factors (cell membrane permeability [66], cell size, and tissue tortuosity [67]) can also effect the ADC. The approach in this study, however, is a first order approximation of the cellularity and future work should investigate how to eliminate some of the ambiguity in these measurements.

5. Conclusion

We developed a noninvasive method for quantification of the volumetric growth in gliomas based on diffusion weighted magnetic resonance imaging data. Our results on simulated and experimentally measured rat data indicate that our adjoint-based method can efficiently solve the associated inverse problem compared to the finite-difference-based approach and effectively estimate the spatial variation of *in vivo* tumor growth.

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Appendix

A. Validation of the linearized model

Figure A.1.

2D test geometry. The “tumor” (in blue) is located at the center of the domain with radius $R_T = \frac{1}{10}R_B$. The outer boundary of the surrounding “brain tissue” (in yellow) is fixed.

We consider a 2D toy problem on the circular geometry as is shown in Fig. A.1. The domain consists of a growing “tumor” (in blue) at the center and the surrounding “brain tissue” (in

yellow) which is fixed on the outer boundary. We compare several quantities of interest using both the finite and linearized models as the tumor volume increases. In both models, the brain tissue is treated as a compressible isotropic material and the tumor as a uniformly growing elastic solid.

In the finite model, the brain tissue is assumed to be a hyperelastaic material of NeoHookean-type with the strain energy density per reference volume given by:

$$W_B(\mathbf{F}) = \frac{\mu_B}{2} (I_1 - 3 - 2 \ln J) + \frac{\lambda_B}{2} (\ln J)^2 \quad (\text{A.1})$$

where $\mathbf{F}$ is the deformation gradient, μ_B , λ_B are the Lamé parameters, I_1 is the first invariance of the right Cauchy-Green deformation tensor $\mathbf{F}^T \mathbf{F}$ and $J = \det \mathbf{F}$ is the Jacobian of deformation. Accordingly, the Cauchy stress in the brain tissue is

$$\sigma_B = \frac{\mu_B}{J} (\mathbf{b} - \mathbf{I}) + \frac{\lambda_B}{J} \ln J \mathbf{I} \quad (\text{A.2})$$

where $\mathbf{b} = \mathbf{F} \mathbf{F}^T$ is the left Cauchy-Green tensor and $\mathbf{I}$ is the identity matrix. The deformation gradient of the tumor, according to the finite growth theory, is decomposed into two multiplicative components, i.e. $\mathbf{F} = \mathbf{F}^e \mathbf{F}^g$ where $\mathbf{F}^e$ and $\mathbf{F}^g$ are due to elasticity and growth, respectively. In particular, we consider the scenario when $\mathbf{F}^g = \theta \mathbf{I}$ is isotropic and uniform in the tumor. Here, θ characterizes the growth-induced stretch ratio and relates to the growth-induced Jacobian of deformation by $J_g = \det \mathbf{F}^g = \theta^2$. Finally, we assume that the elastic part of the tumor constitutive behavior is also NeoHookean, i.e. the strain energy density and Cauchy stress are:

$$W_T(\mathbf{F}) = \frac{\mu_T}{2} (I_1^e - 3 - 2 \ln J^e) + \frac{\lambda_T}{2} (\ln J^e)^2 \quad (\text{A.3})$$

and

$$\sigma_T = \frac{\mu_T}{J} (\mathbf{b}^e - \mathbf{I}) + \frac{\lambda_T}{J} \ln J^e \mathbf{I} \quad (\text{A.4})$$

in which the superscript e indicates quantities relating to the elastic deformation and μ_T , λ_T are the Lamé parameters of the tumor. Given the growth-induced stretch ratio θ of the tumor, the 2D nonlinear boundary value problem is solved using the open source finite element library FEniCS [68] by minimizing the total potential energy

$$\Pi = \int_{\Omega_T} W_T(\mathbf{F}) d\mathbf{X} + \int_{\Omega_B} W_B(\mathbf{F}) d\mathbf{X}. \quad (\text{A.5})$$

Details of the linearized model can be found in section 2; see (1) to (7). In particular, we assume that growth is isotropic and only allowed in the plane. As a result, the growth-induced Jacobian $J_g = (1 + \frac{1}{2}g)^2$ and hence g is simply related to θ by $1 + \frac{1}{2}g = \theta$. Given the value of g , we determine the solution $\mathbf{u}$ to the linearized problem using the principle of virtual energy (8) from which the Jacobian of total deformation and Cauchy stress in the tumor are given by:

$$J = \det (\mathbf{I} + \nabla \mathbf{u}) \text{ and } \quad (\text{A.6})$$

$$\sigma_T = 2\mu_T \varepsilon + (\lambda_T \text{tr}(\varepsilon) - gK_T) \mathbf{I}. \quad (\text{A.7})$$

Note, since plane strain is not assumed, the constant K_T in A.7 is not replaced by $\lambda_T + \mu_T$; also see Appendix D.

Figure A.2 and A.3 plot the total stretch ratio ($\sqrt{J}$), the ratio of growth-induced Jacobian to the total Jacobian (J_g/J) and the radial component of the normalized Cauchy stress (σ_T^{rr}/μ_T) at the center of the tumor as a function of θ for $\mu_B/\mu_T = 0.2, 1, 2$. Since growth is uniform, the tumor deformation is simply a linear expansion. As a result, $\sqrt{J} = R_T^t/R_T$ indicates the ratio of deformed tumor radius to its initial radius. Additionally, according to (10), $J_g/J = \hat{c}/c^0$, and hence it reflects the ratio of cell density before and after growth. Finally, due to radial symmetry, the stress state in the tumor is isotropic and uniform, thus fully characterized by the radial component of the Cauchy stress at the center of the tumor. Overall, the results indicate that the linearized model (red, dashed) is a reasonable approximation to the finite models (black, solid) in calculating the tumor size and cell density (see Fig. A.2) but less accurate in stress (see Fig. A.3). In particular, when brain tissue is relatively soft compared to the tumor, i.e. $\mu_B/\mu_T = 0.2$, the relative errors of the linearized model in the tumor size and cell density are less than 2% for θ below 2.0. This corresponds to $J_g \approx 4.0$ which accounts for the range of volumetric growth in the most of tumor area for our experimental data; see Fig. 11. At $J_g = 7$, the relative percentage error increases to about 8%. When $\mu_B/\mu_T = 1$ or 2, the linearized model is a good approximation with 10% error as the growth-induced stretch ratio is below 4.2 and 3.4, respectively. For all three stiffness ratios, we notice that the linearized model is not very accurate in calculating the Cauchy stress. For this reason, no stress calculation is provided in this manuscript.

Figure A.2.

Total stretch ratio (top: $\sqrt{J}$) and the ratio of growth-induced Jacobian to the total Jacobian (bottom: J/J_g) as a function of the growth-induced stretch ratio (θ) for the linearized (red, dashed) and finite (black, solid) models. The linearized model achieves a better approximation to the finite model as the brain tissue is relatively soft compared to the tumor.

Figure A.3.

The radial component of the normalized Cauchy stress (σ_T^{rr}/μ_T) at the center of the tumor as a function of the growth-induced stretch ratio (θ) for the linearized (red, dashed) and finite (black, solid) models. The linearized model does not provide a good approximation to the Cauchy stress.

B. Theorem

The right hand side of the adjoint-state equation (27) involves integrating the derivative of the indicator function over the domain. For a d -dimensional continuous vector field $\mathbf{f}(\mathbf{x})$, it is known [69] that

$$\int_{R^d} \nabla_{\mathbf{x}} \mathbb{1}_{\mathbf{x} \in D} \cdot \mathbf{f}(\mathbf{x}) d\mathbf{x} = - \oint_{\partial D} \mathbf{f}(\beta) \cdot \mathbf{e}_{\perp} d\beta, \quad (\text{B.1})$$

where $\mathbf{e}_{\perp}$ is the unit outward normal to the boundary. In more general [70], when $\mathbf{f}$ is allowed to have discontinuity across the boundary D , (B.1) can be extended to

$$\int_{R^d} \nabla_{\mathbf{x}} \mathbb{1}_{\mathbf{x} \in D} \cdot \mathbf{f}(\mathbf{x}) d\mathbf{x} = - \oint_{\partial D} \frac{g_+(\beta) + g_-(\beta)}{2} d\beta, \quad (\text{B.2})$$

where

$$\lim_{\mathbf{y} \rightarrow \mathbf{x}, \mathbf{y} \notin D} \mathbf{f}(\mathbf{y}) \cdot \mathbf{e}_\perp = g_+(\mathbf{x}) \quad (\text{B.3})$$

$$\lim_{\mathbf{y} \rightarrow \mathbf{x}, \mathbf{y} \in D} \mathbf{f}(\mathbf{y}) \cdot \mathbf{e}_\perp = g_-(\mathbf{x}) \quad (\text{B.4})$$

in which $\mathbf{y}$ approaches $\mathbf{x} \in \partial D$ from the exterior and interior of D , respectively. To derive (38) in the formulation of the adjoint method, we simply choose

$$\mathbf{f} = -2(\hat{c} - c)\check{c}\Delta\hat{\mathbf{u}}. \quad (\text{B.5})$$

Noticing that $\hat{c}$ is a smooth extension of c and $c|_{\Omega-D} = 0$, we have

$$\lim_{\mathbf{y} \rightarrow \mathbf{x}, \mathbf{y} \notin D} \mathbf{f}(\mathbf{y}) \cdot \mathbf{e}_\perp = -2(\hat{c} - 0)c\Delta\hat{\mathbf{u}}_\perp, \quad (\text{B.6})$$

$$\lim_{\mathbf{y} \rightarrow \mathbf{x}, \mathbf{y} \in D} \mathbf{f}(\mathbf{y}) \cdot \mathbf{e}_\perp = -2(\hat{c} - c)c\Delta\hat{\mathbf{u}}_\perp. \quad (\text{B.7})$$

and therefore, according to (B.2),

$$-2 \int_{\Omega^t} (\hat{c} - c)\check{c}\Delta\hat{\mathbf{u}} \cdot \nabla_{\mathbf{x}} \mathbb{1}_{\mathbf{x} \in D} dV = \int_S (2\hat{c} - c)c\Delta\hat{\mathbf{u}}_\perp dA. \quad (\text{B.8})$$

C. Numerical schemes

C.1 Objective function

Figure C.1.

Illustration of different measures of tumor cell density. c^0 is initial cell density of the undeformed tumor element Ω_e (highlighted in the left panel). $\hat{c}$ and c are the predicted and target cell densities, respectively, of the deformed element Ω_e^t (highlighted in the right panel).

According to the growth model, the total amount of tumor cells in an element before and after growth are

$$N_c^0(\Omega_e) = \int_{\Omega_e} c^0(\mathbf{X}) dV^0, \quad (\text{C.1})$$

$$\hat{N}_c(\Omega_e^t) = \int_{\Omega_e^t} \hat{c}(\mathbf{x}) dV = \int_{\Omega_e} c^0(\mathbf{X}) J_g dV^0, \quad (\text{C.2})$$

where Ω_e^t denotes the deformed element after growth. Here, the second equality of (C.2) is not derived from the substitution rule but from the model assumption that tumor growth is density-preserving. That is, if the elastic stress on an infinitesimal tumor section dV is released (e.g., by excising the section from the rest of the tumor), the section has the same cell density as it had before growth occurs [34]. Since there is no elastic deformation, the volume of the excised section is, by definition, given by $J_g dV^0$. Notice that the number of tumor cells is the same whether the section is excised or not. The number of tumor cells in the section after growth is hence $c^0 J_g dV^0$ which leads to (C.2).

Likewise, the target total amount of cells in Ω_e^t (as measured at the second time point) is

$$N_c(\Omega_e^t) = \int_{\Omega_e^t} c(\mathbf{x}) dV. \quad (\text{C.3})$$

Accordingly, the initial, predicted and target average tumor cell densities in the element are

$$\overline{c^0(\Omega_e)} = \frac{N_c^0(\Omega_e)}{\text{vol}(\Omega_e)}, \quad (\text{C.4})$$

$$\overline{\hat{c}(\Omega_e^t)} = \frac{\hat{N}_c(\Omega_e^t)}{\text{vol}(\Omega_e^t)}, \quad (\text{C.5})$$

$$\overline{c(\Omega_e^t)} = \frac{N_c(\Omega_e^t)}{\text{vol}(\Omega_e^t)}. \quad (\text{C.6})$$

With the above notations, we can approximate the first term of the objective function (12) as

$$\int_{\Omega^t} (\hat{c}(\mathbf{X} + \mathbf{u}) - c(\mathbf{x}))^2 dV \approx \sum_{e \in \Omega^t} \left(\overline{\hat{c}(\Omega_e^t)} - \overline{c(\Omega_e^t)} \right)^2 \text{vol}(\Omega_e^t). \quad (\text{C.7})$$

Integration of the regularization terms follows the standard finite element method.

C.2 Adjoint displacement

To determine the adjoint displacement $\delta \mathbf{u}$, one needs to approximate $\frac{\partial h(\mathbf{u}, g)}{\partial \tilde{\mathbf{u}}}[\Delta \mathbf{u}]$ in the adjoint-state equation (18). From (27) to (32), we first have that

$$\text{I} + \text{III} = \sum_{e \in \Omega} \int_{\Omega_e} (-\hat{c}_r^2 + c_r^2) \frac{1}{J} \frac{\partial J}{\partial \tilde{\mathbf{u}}}[\Delta \mathbf{u}] dV^0 \quad (\text{C.8})$$

$$= \sum_{e \in \Omega^t} \int_{\Omega_e^t} (-\hat{c}^2 + c^2) \frac{1}{J} \frac{\partial J}{\partial \tilde{\mathbf{u}}}[\Delta \mathbf{u}] dV \quad (\text{C.9})$$

$$\approx \sum_{e \in \Omega^t} \left(-\overline{\hat{c}^2(\Omega_e^t)} + \overline{c^2(\Omega_e^t)} \right) \int_{\Omega_e^t} \frac{1}{J} \frac{\partial J}{\partial \tilde{\mathbf{u}}}[\Delta \mathbf{u}] dV \quad (\text{C.10})$$

$$= \sum_{e \in \Omega^t} \left(-\overline{\hat{c}^2(\Omega_e^t)} + \overline{c^2(\Omega_e^t)} \right) \int_{\Omega_e^t} \frac{\partial J}{\partial \tilde{\mathbf{u}}}[\Delta \mathbf{u}] dV^0. \quad (\text{C.11})$$

By definition,

$$\int_{\Omega_e^t} \frac{\partial J}{\partial \tilde{\mathbf{u}}}[\Delta \mathbf{u}] dV^0 \approx \frac{\text{vol}(\tilde{\Omega}_e^t) - \text{vol}(\Omega_e^t)}{\Delta \varepsilon}, \quad (\text{C.12})$$

where $\tilde{\Omega}_e^t = \tilde{\mathcal{M}}(\Omega_e)$ is the deformed element after perturbation. Here, $\tilde{\mathcal{M}}: \mathbf{X} \mapsto \tilde{\mathbf{x}}$ is the perturbed map of deformation in which $\tilde{\mathbf{x}} = \mathbf{X} + \mathbf{u} + \varepsilon \mathbf{u}$. Let $\Delta \mathbf{u}|_{\Omega_e} = \sum_{i=1}^{N_e} W_i \Phi_i(\mathbf{X})$ be the finite element discretization on Ω_e in which N_e is the number of degrees of freedom in the element. Since $\frac{\partial J}{\partial \mathbf{u}}[\Delta \mathbf{u}]$ is linear with respect to $\mathbf{u}$ (see (32)), (C.11) leads to that

$$\text{I} + \text{III} \approx \sum_{e \in \Omega^t} \sum_{i=1}^{N_e} W_i \left[\left(-\overline{\hat{c}^2(\Omega_e^t)} + \overline{c^2(\Omega_e^t)} \right) \int_{\Omega_e} \frac{\partial J}{\partial \mathbf{u}}[\Phi_i] dV^0 \right]. \quad (\text{C.13})$$

Next, according to (39), we have

$$\text{II} = -2 \sum_{\Omega_e^t \subset D} \int_{\Omega_e^t} (\hat{c} - c) \nabla_{\mathbf{x}} c \cdot \Delta \mathbf{u} dV + \sum_{S_e \subset S} \int_{S_e} (2\hat{c} - c) c \Delta \mathbf{u} \cdot \mathbf{n} dA. \quad (\text{C.14})$$

Here, D is the target tumor volume (measured at t_2) and $S = \partial D$ is the boundary of D . Let $\Delta \mathbf{u}|_{\Omega_e^t} = \sum_{i=1}^{N_e} W_i \tilde{\Phi}_i(\mathbf{x})$ and $\Delta \mathbf{u}|_{S_e} = \sum_{i=1}^{\tilde{N}_e} \tilde{W}_i \tilde{\Psi}_i(\mathbf{x})$ be the finite element discretization of the test function on elements $\Omega_e^t \subset D$ and $S_e \subset S$, respectively. Here, $\tilde{\Phi}_i(\mathbf{x}) = \Phi_i(\tilde{\mathcal{M}}^{-1}(\mathbf{x}))$ and $\tilde{N}_e$ denotes the number of degrees of freedom in the surface element S_e . Since the degrees of freedom of S_e usually do not coincide with the deformed finite element mesh $\{\Omega_e^t\}$, we introduce the transforming coefficients $\{k_{ij}^e\}$ for each degree of freedom in S_e such that

$$\tilde{W}_i = \sum_{j=1}^{N_s} k_{ij}^e W_j. \quad (\text{C.15})$$

Here, N_s is the total number of degrees of freedom of $\{\Omega_e^t\}$. With (C.14) and (C.15), the final discretization scheme of II is hence given by

$$\Pi = -2 \sum_{\Omega_e^t \subset D} \sum_{i=1}^{N_e} W_i \int_{\Omega_e^t} (\hat{c} - c) \nabla_{\mathbf{x}} c \cdot \tilde{\Phi}_i dV + \sum_{S_e \subset S} \sum_{i=1}^{\tilde{N}_e} \sum_{j=1}^{N_s} k_{ij}^e W_j \int_{S_e} (2\hat{c} - c) c \tilde{\Psi}_i \cdot \mathbf{n} dA. \quad (\text{C.16})$$

C.3 Sensitivity

To calculate the sensitivity of the objective function upon perturbation (40), we notice that from (25),

$$\frac{\partial}{\partial g} \left[\int_{\Omega^t} (\hat{c} - c)^2 dV \right] [\Delta g] \quad (\text{C.17})$$

$$= 2 \int_{\Omega} (\hat{c}_r - c_r) c^0 \frac{\partial}{\partial g} J_g [\Delta g] dV^0 \quad (\text{C.18})$$

$$= 2 \int_{\Omega} [(\hat{c}_r - c_r) \hat{c}_r J] \left[\frac{1}{J_g} \frac{\partial}{\partial g} J_g [\Delta g] \right] dV^0 \quad (\text{C.19})$$

$$\approx 2 \sum_{e \in \Omega^t} \frac{1}{\text{vol}(\Omega_e)} \int_{\Omega_e^t} (\hat{c} - c) \hat{c} dV \int_{\Omega_e} \frac{1}{J_g} \frac{\partial}{\partial g} J_g [\Delta g] dV^0 \quad (\text{C.20})$$

$$\approx 2 \sum_{e \in \Omega^t} \left(\overline{\hat{c}(\Omega_e^t)} - \overline{c(\Omega_e^t)} \right) \overline{\hat{c}(\Omega_e^t)} \frac{\text{vol}(\Omega_e^t)}{\text{vol}(\Omega_e)} \int_{\Omega_e} \frac{1}{J_g} \frac{\partial}{\partial g} J_g [\Delta g] dV^0. \quad (\text{C.21})$$

For isotropic growth in 3D, the integrand in (C.21) is given by

$$\frac{1}{J_g} \frac{\partial}{\partial g} J_g [\Delta g] = \frac{\Delta g}{1 + \frac{1}{3}g}. \quad (\text{C.22})$$

(C.22) as well as other terms in (20) and (21) can be integrated using the standard finite element method.

D. Plane strain case

When plane strain deformation is assumed (i.e., $\varepsilon_{3i} = 0$, $i = 1, 2, 3$), the constitutive equations (4) becomes

$$\tilde{\sigma} = \begin{cases} 2\mu_T \tilde{\varepsilon} + (\lambda_T \text{tr}(\tilde{\varepsilon}) - gK_T) \tilde{\mathbf{I}} & \text{in } \tilde{\Omega}_T \\ 2\mu_B \tilde{\varepsilon} + \lambda_B \text{tr}(\tilde{\varepsilon}) \tilde{\mathbf{I}} & \text{in } \tilde{\Omega}_B \end{cases} \quad (\text{D.1})$$

$$\sigma_{31} = \sigma_{32} = 0 \quad (\text{D.2})$$

$$\sigma_{33} = \begin{cases} \lambda_T \text{tr}(\tilde{\varepsilon}) - gK_T & \text{in } \tilde{\Omega}_T \\ \lambda_B \text{tr}(\tilde{\varepsilon}) & \text{in } \tilde{\Omega}_B \end{cases} \quad (\text{D.3})$$

Here, $\tilde{\Omega}_T$ and $\tilde{\Omega}_B$ represent the 2D projections of the tumor and brain volumes and $\sim$ denotes the in-plane components of a 3×3 tensor. Accordingly, the equation of force equilibrium (1) leads to

$$\tilde{\nabla} \cdot \tilde{\sigma} = 0 \quad \text{and} \quad (\text{D.4})$$

$$\sigma_{33} = \sigma_{33}(x_1, x_2). \quad (\text{D.5})$$

Note, (D.1) still assumes 3D isotropic growth in all directions. If only in-plane growth is allowed

$$\mathcal{G} = \begin{pmatrix} \frac{1}{2}g & 0 & 0 \\ 0 & \frac{1}{2}g & 0 \\ 0 & 0 & 0 \end{pmatrix}, \quad (\text{D.6})$$

then (4) becomes

$$\tilde{\sigma} = \begin{cases} 2\mu_T \tilde{\varepsilon} + (\lambda_T \text{tr}(\tilde{\varepsilon}) - (\mu_T + \lambda_T)g) \tilde{\mathbf{I}} & \text{in } \tilde{\Omega}_T \\ 2\mu_B \tilde{\varepsilon} + \lambda_B \text{tr}(\tilde{\varepsilon}) \tilde{\mathbf{I}} & \text{in } \tilde{\Omega}_B \end{cases} \quad (\text{D.7})$$

$$\sigma_{31} = \sigma_{32} = 0 \quad (\text{D.8})$$

$$\sigma_{33} = \begin{cases} \lambda_T \text{tr}(\tilde{\varepsilon}) - g\lambda_T & \text{in } \tilde{\Omega}_T \\ \lambda_B \text{tr}(\tilde{\varepsilon}) & \text{in } \tilde{\Omega}_B \end{cases} \quad (\text{D.9})$$

while (D.4) and (D.5) remain the same. From (D.4) and (D.7), one can determine the in-plane deformation when plane strain and in-plane growth are assumed.

For simplicity, the symbol $\sim$ is omitted in section 3.

E. Validation problem

Here, we derive the adjoint displacement analytically for the 2D test problem in section 3.1.

It is assumed that the brain tissue is very soft compared to the tumor; i.e., $\mu_B \ll \mu_T$.

According to the identities

$$\nabla(f\hat{\mathbf{r}}) = \begin{pmatrix} \frac{df}{dr} \cos^2 \theta + \frac{f}{r} \sin^2 \theta & \left(\frac{df}{dr} - \frac{f}{r}\right) \sin \theta \cos \theta \\ \left(\frac{df}{dr} - \frac{f}{r}\right) \sin \theta \cos \theta & \frac{df}{dr} \sin^2 \theta + \frac{f}{r} \cos^2 \theta \end{pmatrix} E_x E_y \quad (\text{E.1})$$

$$\nabla \cdot (f\hat{\mathbf{r}}) = \frac{df}{dr} + \frac{f}{r}, \quad \det(\mathbf{I} + \nabla(f\hat{\mathbf{r}})) = \left(\frac{f}{r} + 1\right) \left(\frac{df}{dr} + 1\right) \quad (\text{E.2})$$

there is

$$J_\varepsilon = \det(\mathbf{I} + \nabla \mathbf{u}_\varepsilon) = J \left(1 + \varepsilon \frac{\frac{f_1}{r'} + \frac{df_1}{dr'}}{\frac{g}{2} + 1} \right) + o(\varepsilon), \quad (\text{E.3})$$

$$\hat{c}_\varepsilon = c^0 \frac{J_g}{J_\varepsilon} = c_o \left(1 - \varepsilon \frac{\frac{f_1}{r'} + \frac{df_1}{dr'}}{\frac{\bar{g}}{2} + 1} \right) + o(\varepsilon). \quad (\text{E.4})$$

Here $\mathbf{u}_\varepsilon = \left(\frac{\bar{g}}{2} r' + \varepsilon f_1(r') \right) \hat{\mathbf{r}}$ is the perturbed displacement. Let R_T^{ε} be the radius of the tumor under the perturbed deformation $\mathcal{M}_\varepsilon : \mathbf{X} \mapsto \mathbf{x}_\varepsilon$, $\mathbf{x}_\varepsilon = \mathbf{X} + \mathbf{u}_\varepsilon$.

Condition I. $R_T^t < R$.

As ε is sufficiently small, the perturbed objective function is

$$h(\mathbf{u}_\varepsilon) = 2\pi \left[\int_0^{R_T^{\varepsilon}} + \int_{R_T^{\varepsilon}}^R \right] (\hat{c}_\varepsilon(r) - c(r))^2 r dr \triangleq X_\varepsilon + Y_\varepsilon \quad (\text{E.5})$$

in which

$$X_\varepsilon = 2\pi \int_0^{R_T} (\hat{c}_{\varepsilon}(r') - c_o)^2 J_\varepsilon r' dr' \sim o(\varepsilon), \text{ where } r' \mapsto r \quad (\text{E.6})$$

$$Y_\varepsilon = 2\pi \int_{R_T^{\varepsilon}}^R c_o^2 r dr = \pi c_o^2 (R^2 - (R_T^{\varepsilon})^2). \quad (\text{E.7})$$

Since $R_T^{\varepsilon} = \left(\frac{\bar{g}}{2} + 1 \right) R_T + \varepsilon f_1(R_T)$, therefore,

$$\frac{\partial h(\mathbf{u})}{\partial \mathbf{u}}[f_1 \hat{\mathbf{r}}] = -2\pi c_o^2 \left(\frac{\bar{g}}{2} + 1 \right) R_T f_1(R_T). \quad (\text{E.8})$$

Hence, (18) becomes

$$\mathcal{A}_0(\delta \mathbf{u}, f_1 \hat{\mathbf{r}}) = -2\pi c_o^2 \left(\frac{\bar{g}}{2} + 1 \right) R_T f_1(R_T), \forall f_1. \quad (\text{E.9})$$

According to the principle of virtual work, this is equivalent to exerting a uniform pressure p on the boundary of the tumor at $r' = R_T$ with $p = c_o^2 \left(\frac{\bar{g}}{2} + 1 \right)$. The adjoint displacement is thus

$$\delta \mathbf{u} = f_2 \hat{\mathbf{r}}, f_2(r') = -\frac{p}{2\mu_T + \lambda_T} r', 0 \leq r' \leq R_T. \quad (\text{E.10})$$

Note, $\delta \mathbf{u}$ is independent of R as $R > R_T^t$.

Condition II. $R_T^{te} > R$.

Let R'_ε be the material point at the initial configuration corresponding to the position $r = R$ under the perturbed deformation $\mathcal{M}_\varepsilon$, i.e. $\mathcal{M}_\varepsilon(R'_\varepsilon) = R$. By definition,

$$R'_\varepsilon + \left(\frac{\bar{g}}{2} R'_\varepsilon + \varepsilon f_1(R'_\varepsilon) \right) = R = R' + \frac{\bar{g}}{2} R' \quad (\text{E.11})$$

and hence

$$R'_\varepsilon = R' - \frac{f_1(R')}{\frac{\bar{g}}{2} + 1} \varepsilon + o(\varepsilon). \quad (\text{E.12})$$

The perturbed objective function is therefore

$$h(\mathbf{u}_\varepsilon) = 2\pi \left[\int_0^R + \int_R^{R_T^{te}} \right] (\hat{c}_\varepsilon(r) - c(r))^2 r dr \triangleq X_\varepsilon + Y_\varepsilon \quad (\text{E.13})$$

in which

$$X_\varepsilon = 2\pi \int_0^{R'_\varepsilon} (\hat{c}_{r\varepsilon}(r') - c_o)^2 J_\varepsilon r' dr' \sim o(\varepsilon) \quad (\text{E.14})$$

$$Y_\varepsilon = 2\pi \int_{R'_\varepsilon}^{R_T} \hat{c}_{r\varepsilon}(r')^2 J_\varepsilon r' dr'. \quad (\text{E.15})$$

After simplification, we have

$$Y_\varepsilon = Y - 2\pi\varepsilon \int_{R'}^{R_T} c_o^2 \frac{\frac{f_1}{r'} + \frac{f_1}{dr'}}{\frac{\bar{g}}{2} + 1} J r' dr' + 2\pi\varepsilon c_o^2 \left(\frac{\bar{g}}{2} + 1\right) f_1(R') R' + o(\varepsilon) \quad (\text{E.16})$$

$$= Y - 2\pi\varepsilon c_o^2 \left(\frac{\bar{g}}{2} + 1\right) f_1(R_T) R_T + 4\pi\varepsilon c_o^2 \left(\frac{\bar{g}}{2} + 1\right) f_1(R') R' + o(\varepsilon). \quad (\text{E.17})$$

Accordingly, (18) leads to

$$\mathcal{A}_0(\delta \mathbf{u}, f_1 \hat{\mathbf{r}}) = -2\pi c_o^2 \left(\frac{\bar{g}}{2} + 1\right) f_1(R_T) R_T + 4\pi c_o^2 \left(\frac{\bar{g}}{2} + 1\right) f_1(R') R', \forall f_1. \quad (\text{E.18})$$

Similarly, this is equivalent to exerting a uniform pressure p on the boundary of the initial tumor area at $b = R_T$ with $p_b = c_o^2 \left(\frac{\bar{g}}{2} + 1\right)$ and an outward pressure at $a = R'$ with $p_a = 2c_o^2 \left(\frac{\bar{g}}{2} + 1\right)$. The adjoint displacement $\delta \mathbf{u} = f_2 \hat{\mathbf{r}}$ is thus given by

$$f_2(r') = \begin{cases} \frac{p_2}{2} \frac{1}{\mu_T + \lambda_T} r', & 0 \leq r' < R', \\ \frac{(1 + \nu_T) a^2 b^2}{E_T (b^2 - a^2)} \left(\frac{p_1 - p_b}{r'} + (1 - 2\nu_T) \frac{p_1 a^2 - p_b b^2}{a^2 b^2} r' \right), & R' \leq r' \leq R_T. \end{cases} \quad (\text{E.19})$$

where

$$p_2 = \frac{(1 - 2\nu_T) a^2 + \nu_T b^2}{(1 - \nu_T) b^2} c_o^2 \left(\frac{\bar{g}}{2} + 1\right) \quad (\text{E.20})$$

$$p_1 = p_a - p_2. \quad (\text{E.21})$$

F. Additional figures

Figure F.1.

The ratio of average tumor cell density at convergence to the initial density $\hat{c}_*/c_0$ as a function of μ_B/μ_T for section 3.1.1 (red circle: $\alpha = \beta = 0$, black circle: $\alpha = \beta = 0.01$, red square: $\alpha = \beta = 0.1$, black square: $\alpha = \beta = 0.5$). Also see (51) and Fig. 8. The initial guess is $g^{(0)} \equiv 1.8$ in Ω_T . Parameters: $c_0 = 1$, $\nu_B = \nu_T = 0.45$, $\gamma = 1$.

Figure F.2.

L-curves for the experimental data in section 3.2 (red: t_1 to t_2 , black: t_1 to t_3). The y axis is the mean of converged growth distribution and the x axis is the value of objective function with (solid curves) and without (dashed curves) regularization. From left to right, each curve connect points with four sets of regularization coefficients: $\alpha = 0, 0.1, 0.5, 1, 5$ and $\beta = 0$. The highlighted points mark the parameters ($\alpha = 1, \beta = 0$) used in Fig. 11 which achieves good balance between smoothness of the growth distribution and minimization of the misfit in cellularity.

Figure F.3.

Illustration of mesh independence of the numerical method. The top six panels display the model predicted shape and converged Jacobians of the volumetric growth, J_g , for the tumor area for three mesh refinements. From left to right, the number of tumor elements is 3000 (coarse), 6000 (medium), 8000 (refined), respectively. In all calculations, $\alpha = 1$, $\beta = 0$ are used, and isolines indicate $J_g = 1.0, 3.0$ and 5.0 , respectively. The bottom figure displays the error bars and standard deviation of the converged growth distributions, g , (see (49) and (50)) for the three different mesh sizes depicted in the top panel. Both panels demonstrate that the tumor shape and growth distribution are not significantly affected by mesh refinement.

Figure 1.

T_2 -weighted spin echo MRI data of the head (left) and a zoomed in image of the brain (right, enclosed by the black curve) of a rat with an implanted C6 glioma (red outlined). The tumor, brain tissue, and the skull are denoted as Ω_T, Ω_B and Ω , respectively.

Figure 2.
Finite element patch for the i^{th} degree of freedom.

Figure 3.

Flow chart of the optimization algorithm. Input: the measured cellularity maps at the two time points $c^0(\mathbf{X})$ and $c(\mathbf{x})$. Output: the optimal growth distribution g^* and predicted cellularity $\hat{c}^*$. $g^{(0)}$ represents the initial distribution of growth. At each iteration, the displacement $\mathbf{u}$ and the adjoint displacement $\delta\mathbf{u}$ are computed by solving (8) and (18). The average sensitivity of the objective upon perturbation of each degree of freedom is then obtained from (27) and (40) and used to update the growth distribution g via the steepest descent method.

Figure 4.

Geometry for the 2D test problem mimicking a uniformly growing tumor (blue) at the center of a circular domain. In both plots, the initial radius of the tumor R_T is one third of the radius of the domain R_B . The red circle represents the target tumor boundary at the second time point (radius = R) and the blue dashed circle represents the deformed tumor boundary predicted by the model (radius = R'_T). Left: $R > R'_T$ (condition I); right: $R < R'_T$ (condition II).

On the domain boundary, zero displacement is prescribed. On the interface between the tumor and brain tissue, continuity of displacement and traction force is enforced.

Figure 5.

Comparison of the numerically calculated adjoint displacement (red circles) with the analytic solution (black lines) in the radial direction. Left: the amount of uniform growth in the tumor $\bar{g}$ is varied while the target tumor radius $R = 1.5$ is kept the same. Right: the target tumor radius R is varied while the same growth distribution $\bar{g} = 0$ is used. In both plots, $c_o = 1$, $\mu_B \ll \mu_T = 1$, $\nu_B = \nu_T = 0.45$. The highlighted cases indicate good agreement between the numeric calculation and the analytic solutions.

Figure 6.

Effect of brain tissue stiffness on optimization. Left: logarithm of the objective function as $\mu_B = 2\mu_T$ (black), $\mu_B = \mu_T$ (red) and $\mu_B \ll \mu_T$ (blue) at different iterations. The circled and dashed lines plot the objective function (12) with and without regularization, respectively. Right: evolution of the growth distribution during optimization. The circles and error bars represent the mean and standard deviation of $g(\mathbf{X})$ across the tumor at each iteration (see definition in (49) and (50); for clarity of the figures, the number of iterations are downsampled). The initial guess of the growth distribution is given by $g^{(0)}(\mathbf{X}) \equiv 1.8$. Other parameters are: $c_o = 1$, $\mu_T = 1$, $\nu_B = \nu_T = 0.45$, $\alpha = \beta = 0.01$, $\gamma = 1$. When the shear modulus of the healthy brain tissue increases, the mean value of the volumetric growth increases.

Figure 7.

The initial (left) and converged (right) growth distribution g as $\mu_B = \mu_T$ plotted on the initial and deformed meshes (see the inserts for a zoomed-in view). The blue circle in the middle indicates the initial tumor boundary, while the red circle indicates the tumor boundary at the later time point. The colored field visualizes the distribution of $g(\mathbf{X})$, which is identically zero outside the tumor area. At the convergent step, the growth distribution is close to a uniform distribution.

Figure 8.

The converged tumor radius R_{T*}^t (left) and mean value of the growth distribution $g_*(\mathbf{X})$ (right) as a function of μ_B/μ_T (red circle: $\alpha = \beta = 0$, black circle: $\alpha = \beta = 0.01$, red square: $\alpha = \beta = 0.1$, black square: $\alpha = \beta = 0.5$). The initial guess is $g^{(0)} \equiv 1.8$ in Ω_T . Other parameters are: $c_o = 1$, $\nu_B = \nu_T = 0.45$, $\gamma = 1$.

Figure 9.

L-curves for varying stiffness ratio μ_B/μ_T . On each curve, regularization parameters are $\alpha = \beta = 0, 0.01, 0.1, 0.5$ from left to right. Since the norm of $g(\mathbf{X})$ is naturally bounded from above, we do not see the typical L-shape in the curves.

Figure 10.

Left: T_2 -weighted MRI of the central slice of the tumor in the rat's brain imaged days 10, 12 and 14 after tumor cell injection. Right: The cell density per voxel in the tumor area estimated by DW-MRI. The voxel size is 0.25 mm in the x and y directions and 1 mm in the z direction.

Figure 11.

Left column: The initial (enclosed by the yellow curve) and target (in red) tumor areas.

Right column: the fitted tumor area (enclosed by the black curve) and isolines of the converged Jacobian of volumetric growth J_g . The top row compares data from day 10 to day 12 and the bottom row from day 10 to day 14. At day 12, the region with the highest growth is at the top and bottom parts of the tumor. At day 14, this region shifts to the lower-right corner of the tumor.