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Biphasic modeling of brain tumor biomechanics and response to radiation treatment

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Abstract

Biomechanical forces are central in tumor progression and response to treatment. This becomes more important in brain cancers where tumors are surrounded by tissues with different mechanical properties. Existing mathematical models ignore direct mechanical interactions of the tumor with the normal brain. Here, we developed a clinically relevant model, which predicts tumor growth accounting directly for mechanical interactions. A three-dimensional model of the gray and white matter and the cerebrospinal fluid was constructed from magnetic resonance images of a normal brain. Subsequently, a biphasic tissue growth theory for an initial tumor seed was employed, incorporating the effects of radiotherapy. Additionally, three different sets of brain tissue properties taken from the literature were used to investigate their effect on tumor growth. Results show the evolution of solid stress and interstitial fluid pressure within the tumor and the normal brain. Heterogeneous distribution of the solid stress exerted on the tumor resulted in a 35 % spatial variation in cancer cell proliferation. Interestingly, the model predicted that distant from the tumor, normal tissues still undergo significant deformations while it was found that intratumoral fluid pressure is elevated. Our predictions relate to clinical symptoms of brain cancers and present useful tools for therapy planning.

Keywords

mathematical modeling; image reconstruction; interstitial fluid pressure; solid stress; poro-elasticity

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Conflicts of Interest Declaration

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

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1 Introduction

Recent studies have highlighted the fact that not only biological factors but also biomechanical forces shape the tumor microenvironment and contribute to tumor progression and response to treatment (Jain et al., 2014). The growth of a solid tumor in the confined space of the host tissue causes the generation and build-up of forces within structural components of the tumor microenvironment (e.g., stromal and cancer cells, collagen, hyaluronic acid), owing to mechanical interactions between the tumor and the surrounding host tissue. These forces might hinder cancer cell proliferation, induce apoptosis and enhance the invasive and metastatic potential of cancer cells affecting directly tumor progression, but can also compress intratumoral blood vessels reducing perfusion and drug delivery (Helmlinger et al., 1997; Kaufman et al., 2005; Cheng et al., 2009; Demou, 2010; Stylianopoulos et al., 2012; Tse et al., 2012). Therefore, the contribution of biophysics to tumor growth, even though it is complex and pleiotropic, should be incorporated into a mathematical modeling framework. The need for incorporation of biomechanical interactions to tumor growth models becomes more crucial in the case of brain tumors, where cancer cells are surrounded by multiple tissues, such as gray and white matter, cerebrospinal fluid (CSF) and the skull, with material properties that vary considerably among them.

The majority of computational models that have been developed to date to predict brain tumor growth ignore mechanical forces. In most models, the rate of change of cancer cells is given by a diffusion-reaction equation of the general form $dc/dt = \nabla \cdot (D \nabla c) + \rho c$, where c is the cancer cell concentration, D is the “diffusion coefficient” of cells, and ρc describes the net rate of cancer cell growth (proliferation minus cell death) (Swanson et al., 2000; Swanson et al., 2003; Szeto et al., 2009; Unkelbach et al., 2014). The values of D are assumed to be different for the gray and white matter, while in more recent articles data from diffusion tensor imaging (DTI) and from water diffusivity in the brain have been employed to describe anisotropic invasion of glioma cells by constructing a diffusion tensor at each point of the brain (Jbabdi et al., 2005; Roniotis et al., 2012; Colombo et al., 2015). Recognizing the importance of mechanics in tumor progression, diffusion-reaction models have been further extended to account for the deformation of the normal brain due to biomechanical interactions with the tumor. In these models, a linear momentum balance is also solved along with the diffusion-reaction equation with the addition of an external body force to describe the contribution of tumor cells to the displacement of the normal brain (Wasserman et al., 1996; Clatz et al., 2005; Hoge et al., 2008; Zacharaki et al., 2008). The brain is assumed to consist only of a single solid phase (e.g., cells and extracellular proteins), whose mechanical response is modeled as linearly elastic or hyperelastic, and the external force is most often considered to be proportional to the negative gradient of the concentration of cancer cells. Therefore, in these models there are no direct mechanical interactions between the tumor and normal brain tissues, i.e., the tumor and the normal brain are not treated as two different computational domains with the former growing at the expense of the latter. Additionally, the brain mechanical behavior, as most biological tissues, is better described by a biphasic, poro-elastic model that accounts not only for the solid phase and its associated stresses, but also for the fluid phase and the interstitial fluid pressure

(Li et al., 2011; Li et al., 2013; Goriely et al., 2015). Consequently, multiphasic biomechanical models that account directly for mechanical interactions should be considered to be better suited than the already established models.

To this end, we developed a biphasic, biomechanical, computational model for the growth of brain tumors using principles from continuum mechanics. An existing biphasic, poro-elastic theory for soft biological tissues was implemented to take into account the solid and fluid phase of the tumor, and the gray and white matter (Mow et al., 1980; Roose et al., 2003; Voutouri et al., 2014b). The CSF was approximated as a biphasic material, as well. To model tumor growth, a methodology for tissue growth and remodeling based on the multiplicative decomposition of the deformation gradient tensor was employed (Rodriguez et al., 1994). According to our approach, magnetic resonance imaging (MRI) of a normal brain was used and a three-dimensional segmentation was performed that separated the different compartments of the brain, i.e., gray and white matter, and CSF. Subsequently, a small area in the brain was defined as the point of initiation of the tumor and a finite element model was generated, which consisted of four subdomains, namely the aforementioned three compartments plus the tumor. Simulations of tumor growth were performed and the deformation of the tissues as well as the developed solid stresses and interstitial fluid pressures were calculated within the tumor, at the tumor adjacent locations and in more distal parts of the brain. Furthermore, we incorporated into the model the effect of radiotherapy and simulated the tumor response after the delivery of a single dose of ionizing radiation. Finally, three different sets of brain material properties taken from the literature were implemented to study their effect on tumor growth and the resulting stresses and displacements. Using this detailed mathematical framework, the model predicted heterogeneous cancer cell proliferation owing to the heterogeneous distribution of solid stresses exerted on the cells from the surrounding normal brain. Interestingly, the model also predicted that distant from the tumor, normal tissues still undergo deformations while variation of brain material properties greatly affects the developed stresses and displacements both within the tumor and the healthy tissue.

2 Methods

2.1 MR Imaging and model extraction

Imaging of the brain of a healthy volunteer was performed on a clinical 1.5 T Philips Achieva MR scanner (Philips Healthcare, Amsterdam, Netherlands) employing the SENSE 16-channel head coil. In order to attain optimum contrast between the gray and white matter, a T1 weighted pulse sequence was used to scan a field of view of 256×256×93 mm with a repetition time of 7 ms and an echo time of 3 ms. The slice thickness and voxel size were set to 1 mm.

The acquired MR images (Fig. 1) were subsequently exported as a standard DICOM format and imported in ScanIP v. 6.0 software (Simpleware Ltd, Exeter, UK) for model extraction. Initially, a thresholding operation allowed the automatic segmentation of the gray and white matter and the CSF regions of the brain, followed by a manual refinement of the produced masks. Noise removal from the masks was performed using island removal and cavity filling operations, followed by 1-sigma Gaussian filtering to achieve smoothing (Fig. 1). Finally, a

fourth mask was manually created to act as the initial tumor seed located in the left parietal lobe of the brain. Such a methodology allowed the extraction of the three-dimensional masks presented in Fig. 1, which closely resemble the actual geometry of the scanned brain. Volume meshing (Fig. 2a) of the masks was achieved using the FE Free algorithm of Simpleware employing tetrahedral elements and the resulting mesh (Fig. 2b) was saved as a COMSOL Multiphysics (COMSOL, Inc., Burlington, MA, USA) mesh file.

To reduce the computational demands, we accounted only the part of the brain spanning from the occipital lobe until the brainstem in the antero-posterior direction, the right hemisphere until the mid-left ventricle in the right-left direction, and the parietal lobe until the cerebellum in the cranial-condyle direction (Fig. 2). The ensuing model included 42% of the initial brain geometry and consisted of 533,714 tetrahedral finite elements, resulting in 1,132,530 degrees of freedom.

2.2 Decomposition of the total deformation gradient tensor

The model was developed to account for the kinematics of the growth of a spherical tumor seed surrounded by healthy tissue based on the decomposition of the total deformation gradient tensor $\mathbf{F}$ (Skalak et al., 1996; Ambrosi et al., 2002):

$$\mathbf{F} = \mathbf{F}_e \mathbf{F}_g, \quad (1)$$

where $\mathbf{F}_e$ is the elastic component of $\mathbf{F}$ used to account for interactions with the normal tissue, and $\mathbf{F}_g$ was assumed to be an isotropic tensor that accounts for tumor growth due to cancer cell proliferation. The growth tensor $\mathbf{F}_g$ was defined by an associated growth stretch ratio λ_g as follows (Roose et al., 2003; Kim et al., 2011; Stylianopoulos et al., 2013; Mpekris et al., 2015):

$$\mathbf{F}_g = \lambda_g \mathbf{I}, \quad (2)$$

while the elastic component $\mathbf{F}_e$ is determined by rearranging Eq. (1).

2.3 Calculation of growth stretch ratio λ_g

The growth stretch ratio takes into account the effect of oxygen concentration along with the direct effect of solid stress on cell proliferation (Roose et al., 2003; Kim et al., 2011; MacLaurin et al., 2012; Voutouri et al., 2014b; Mpekris et al., 2015). In particular,

$$\frac{d\lambda_g}{dt} = \frac{1}{3} G (1 + \beta \bar{\sigma}) S_f \Phi^s (1 - \Phi^s) \lambda_g, \quad (3)$$

where $d\lambda_g/dt$ is the time derivative of the growth stretch ratio, $\bar{\sigma} = (\sigma_{rr}^s + \sigma_{\theta\theta}^s + \sigma_{\varphi\varphi}^s)/3$ is the average (bulk) of the solid Cauchy stress tensor $\boldsymbol{\sigma}^s$, β is a constant to describe the dependence of growth on solid stress and Φ^s is the volume fraction of the solid phase of the tumor. The term $(1 + \beta \bar{\sigma})$ is taken to be positive but less than unity when the bulk stress was

compressive, and set equal to unity when the bulk stress was tensile. This assumption is based on previous studies showing that tumor growth is inhibited by compressive stresses only (Helmlinger et al., 1997; Cheng et al., 2009). Additionally, G is a term used to describe the effect of oxygen on tumor growth in accordance with previous experimental observations (Casciari et al., 1992):

$$G = \frac{k_1 c_{ox}}{k_2 + c_{ox}}, \quad (4)$$

where c_{ox} is the oxygen concentration and k_1 , k_2 are growth rate constants, the values of which are listed in Table 1, along with all other constants used in this study. Finally, in Eq. (3), S_f denotes the fraction of cells that survive after the administration of a single cycle of ionizing radiation and it is used to account for the response of the tumor to radiation therapy.

2.4 Cell survival following ionizing radiation

The calculation of the survival fraction S_f of cancer cells post-irradiation is based on the linear-quadratic model (Steel, 1991) according to the following expression:

$$S_f = e^{ad - bd^2} \quad (5)$$

where a and b are constants depending on the irradiated cell lines and d is the radiation dose. In our study experimental data by Steel (Steel, 1991) were used to calculate the survival fraction of neuroblastoma cell lines following a dose (d) of 1.5 and 2 Gy. Such doses result in survival fractions of 20 and 10 % respectively. Additionally the knowledge of the oxygen concentration (described in Section 2.6 - Eq. 17) at the time of irradiation allowed the calculation of the oxygen partial pressure, used to estimate the oxygen enhancement ratio (i.e., the enhancement of the therapeutic effect of ionizing radiation in the presence of oxygen) as described in previous studies (Steel et al., 1989). The oxygen enhancement ratio (OER) was subsequently employed to adjust the aforementioned dose to achieve the same biological effect according to the following expression:

$$d_{oxygen} = \frac{d}{OER} \quad (6)$$

2.5 Biphasic formulation of the tumor's mechanical behavior

The continuity equations for the tumor's solid and fluid phases are given by the following expressions (Roose et al., 2003):

$$\frac{\partial \Phi^s}{\partial t} + \nabla \cdot (\Phi^s \mathbf{v}^s) = S^s \quad (7)$$

$$\frac{\partial \Phi^f}{\partial t} + \nabla \cdot (\Phi^f \mathbf{v}^f) = Q, \quad (8)$$

where Φ^f is the volume fraction of the fluid phase, and $\mathbf{v}^s, \mathbf{v}^f$ are the solid and fluid phase velocities, respectively. Furthermore, the growth stretch ratio and the creation/degradation rate of the solid phase S^s (assuming isotropic volumetric growth) are related according to the following expression (Ambrosi et al., 2002):

$$3 \frac{1}{\lambda_g} \frac{d\lambda_g}{dt} = S^s. \quad (9)$$

By combining Eqs. (3) and (9), it yields:

$$S^s = G(1 + \beta \bar{\sigma}) S_f \Phi^s (1 - \Phi^s). \quad (10)$$

The fluid source term Q is calculated by accounting for the flux entering the tumor from the tumor blood vessels and the fluid flux exiting the tumor from the lymphatic vessels as follows:

$$Q = L_p S_v (p_v - p_i) - L_{pl} S_{vl} (p_i - p_l), \quad (11)$$

where L_p, S_v and p_v are the hydraulic conductivity of the blood vessel wall, vascular density and vascular pressure, respectively, L_{pl}, S_{vl} and p_l are the corresponding quantities for lymphatic vessels, and p_i is the interstitial fluid pressure. In the case of healthy tissues the values of these parameters are assumed to be constant and listed in Table 1. For the tumor, the parameters L_p and S_v are assumed to increase linearly from the value of the healthy tissue to the value of the tumor (Table 1) to account for changes in vessel density and permeability due to tumor induced angiogenesis. Furthermore, the product $L_{pl} S_{vl}$ for the tumor is assumed to be zero because of the dysfunction of intratumoral lymphatic vessels starting from the early stages of carcinogenesis (Stylianopoulos et al., 2013). Finally, stress build-up during tumor growth can compress intratumoral blood vessels, leading to vessel collapse and increase in micro-vascular pressure (Stylianopoulos et al., 2013). However, this effect was not accounted in the model due to lack of experimental data for brain tumors.

Summation of Eqs. (7) and (8) and combination of the result with the conservation of matter results in the following mass balance expression:

$$\nabla \cdot (\Phi^s \mathbf{v}^s + \Phi^f \mathbf{v}^f) = Q + S^s, \quad (12)$$

where the fluid velocity $\mathbf{v}^f$ is given by Darcy's law (Byrne et al., 2003)

$$\Phi^f (\mathbf{v}^f - \mathbf{v}^s) = -k_{th} \nabla p_i \Rightarrow \mathbf{v}^f = \frac{-k_{th} \nabla p_i}{\Phi^f} + \mathbf{v}^s, \quad (13)$$

with k_{th} the hydraulic conductivity of the interstitial space (Stylianopoulos et al., 2008).

The biphasic theory for soft tissues (Mow et al., 1980) dictates that the total stress tensor $\boldsymbol{\sigma}_{tot}$ is the sum of the fluid phase stress tensor $\boldsymbol{\sigma}^f = -p_i \mathbf{I}$ and the solid phase stress tensor $\boldsymbol{\sigma}^s$, resulting in the following expression

$$\nabla \cdot \boldsymbol{\sigma}_{tot} = 0 \Rightarrow \nabla \cdot (\boldsymbol{\sigma}^s - p_i \mathbf{I}) = 0. \quad (14)$$

The Cauchy stress tensor of the solid phase $\boldsymbol{\sigma}^s$ is given by (Taber, 2008)

$$\boldsymbol{\sigma}^s = J_e^{-1} \mathbf{F}_e \frac{\partial W}{\partial \mathbf{F}_e^T}, \quad (15)$$

where $J_e = \det \mathbf{F}_e$ and W is the strain energy density function of the tissues. The compressible neo-Hookean constitutive equation was employed to describe the mechanical behavior of the normal brain and the tumor (Stylianopoulos et al., 2012; Ciarletta, 2013; Voutouri et al., 2014a) with a strain energy density function given by:

$$W_i = \frac{\mu_i}{2} (\bar{I}_1 - 3) + \frac{k_i}{2} (J_e - 1)^2, \quad (16)$$

where μ is the shear modulus and k the bulk modulus, and i = tumor, gray matter, white matter, whereas the CSF was assumed to be linear elastic (Li et al., 2011; Li et al., 2013). In order to account for the variability of the brain material properties found in the literature, three different simulation setups were implemented each one using a different set of the material properties 1 presented in Table 2.

At the interfaces between the different domains, COMSOL applies automatically the conditions for the continuity of the stresses and displacements. Symmetry boundary conditions for the pressure and the displacements were employed for the boundaries that were formed by reducing the size of the domain, while for the other boundaries a no-flux condition was employed for the 1 fluid and a no-displacement (i.e., fixed boundary) condition for the solid phase.

2.6 Oxygen concentration

Transport of oxygen is modeled taking into account the convection and diffusion mechanisms that deliver oxygen in the tissue, the oxygen entering the tissue from the blood vessels and the amount of oxygen consumed by cells (Roose et al., 2003; Kim et al., 2011; Mpekris et al., 2015), that is,

$$\frac{\partial c_{ox}}{\partial t} + \nabla \cdot (c_{ox} \mathbf{v}^f) = D \nabla^2 c_{ox} - \frac{A_{ox} c_{ox}}{c_{ox} + k_{ox}} S_f \Phi^s + P_{er} S_v (C_{iox} - c_{ox}), \quad (17)$$

where D is the diffusion coefficient of oxygen in the interstitial space, A_{ox} and k_{ox} are oxygen uptake parameters, P_{er} is the vascular permeability of oxygen that describes diffusion across the tumor vessel wall, and C_{iox} is the oxygen concentration in the vessels.

3 Results

Simulations were performed for different sets of material properties for the components of the healthy brain in order to investigate the dependence of tumor growth on the mechanical characteristics of the surrounding tissue (Table 2). Initially the simulation setup 1 was employed and a complete set of model predictions regarding tissue deformations, interstitial fluid pressure and solid stress evolution, cancer cell proliferation and response to radiotherapy are presented. Subsequently, in simulation setups 2 and 3 the healthy tissue material properties were altered and results for tumor growth and stress evolution are shown.

3.1 Spatial heterogeneity of intratumoral solid stress results in heterogeneous cancer cell proliferation

The mathematical model was solved in COMSOL allowing the initial 4 mm tumor seed to grow to 29 mm in diameter in the first run (material properties from (Basser, 1992)). Figure 3 presents the volume increase of the tumor as a function of the simulation steps. The curve shows the tumor of the first run to increase from 32 to 13256 mm³ in volume, with a marked reduction in the growth rate at the point when radiotherapy treatment is initiated at timestep 550, when compared to runs 1a (1.5 Gy dose) and 1b (2 Gy dose). Furthermore, tumor growth appears to be heterogeneous due to mechanical interactions with the structurally inhomogeneous surrounding environment. This effect is illustrated in Fig. 4 (top) where the computational domains are presented in the beginning, in the middle and at the final stages of the simulation along with the growth stretch ratios (Fig. 4, middle) for the corresponding times. The growth stretch ratios, which describe the rate of cancer cell proliferation minus death, exhibit a variation of up to 35 % within the tumor volume.

3.2 Deformations are significant for both the malignant and healthy tissue

Apart from the growth rate of the tumor, we are also interested in the displacements caused to the host tissue owing to tumor growth. The deformation of the host tissue can be observed in the domain representations of Fig. 4 (top) and in Supplementary Movie 1, where the deformation of the tumor's surrounding structures is apparent as the tumor grows. The tumor deformation ranged from 2.3 mm to 1.45 cm depending on the radial distance from the tumor center, whereas healthy vicinities proximal to the tumor exhibit displacements up to 1.2 cm. Displacement plots of the tumor and the normal brain during the last timestep of the simulation are presented in Fig. 5 (top) superimposed on MR anatomical images. These contour plots are presented over different mesh configurations since the plots related to the tumor are presented over the final/deformed mesh configuration, whereas the plots related to the healthy tissue are presented over the initial/reference mesh configuration. This enables

the better visualization of the distribution of the plotted quantities within the tumor (on the deformed configuration) and study which parts of the healthy brain are affected (in the reference mesh configuration). The plots demonstrate the deformation at the tumor periphery along with a 1 mm displacement at more distal healthy brain structures.

3.3 Interstitial fluid pressure and solid stress increase during tumor growth

A direct consequence of tumor growth and the accompanied deformation is the notable increase of the interstitial fluid pressure along with the generation of solid stresses within the tumor and in the host tissue. The interstitial fluid pressure increased from the normal value of 1.2 kPa to 6.4 kPa as a result of the increase in vessel permeability during tumor progression while the spatial distribution of the fluid pressure appears relatively homogeneous in the interior of the tumor reducing to normal tissue values at the periphery (Fig. 4, bottom).

Contrary to the interstitial pressure, the stress distributions appear inhomogeneous. Such distributions of the bulk stress superimposed on MR anatomic images is presented in Fig. 5 (bottom) for both the tumor (presented over the deformed mesh configuration) and the host tissue (presented over the reference configuration). The levels of solid stress developed in the normal brain ranged from 120 kPa at the boundary with the tumor, while more distal areas of the brain exhibited stresses of approximately 600 Pa. The compressive solid bulk stress increases at the center of the tumor reaching a maximum at 13 kPa. The evolution of solid stress and the interstitial fluid pressure at the centre of the tumor as a function of tumor's volume are presented in Figs. 6a,b.

3.4 Material properties of the healthy brain affect significantly tumor growth

The choice of material properties used to describe the brain tissue play an important role in tumor mechanics and growth. Such dependency is observed in Fig. 6c which depicts the volume of the tumor for the different simulation runs (Table 2). In timestep 550 the first run yields a tumor volume of 3090 mm³ while runs 2 and 3 yield a volume of 7312 mm³ and 4856 mm³ respectively. The calculated bulk stresses at this timestep were 12.6, 2.5 and 8.5 kPa respectively (Fig. 6a), while the corresponding values of the interstitial fluid pressure were found to be 5.6, 4.8 and 5.2 kPa (Fig. 6b).

4 Discussion

In the current study, a mathematical framework for the prediction of brain tumor growth was presented based on principles from continuum mechanics and taking into consideration the direct effects of solid stress and fluid pressure on cancer cell proliferation and response to treatment. This framework is general and as more knowledge is acquired about the behavior of glioma cells in response to mechanical forces, it can be incorporated into the model. Contrary to existing models that either ignore mechanics in brain tumor progression or account for them in an indirect way, our model explicitly incorporates mechanical interactions between the tumor and the normal brain. The computational demands of our approach are more strenuous than previous models, but it is well justified by the crucial role of the mechanical forces in tumor progression (Jain et al., 2014). Findings of this study that

could not have predicted with existing models are: a) the heterogeneous growth of the tumor owing to the heterogeneous solid stress distribution and the complicated and structurally inhomogeneous geometry of the human brain, b) the evolution of the interstitial fluid pressure during tumor progression and c) the deformations and stresses developed in the normal brain.

In the simulation setup the tumor was positioned at the parietal lobe which is a common location for tumor occurrence. The predictions are sensitive to the selected location due the ability of the model to account for the inhomogeneous environment encountered during tumor growth; however any location for the initial tumor seed could be simulated. Additionally the model predicted the normal brain deformation due to the growth of the tumor, which is clearly visible not only in areas adjacent to the tumor but also to more distal areas such as the brain midline, where a displacement of 1 mm and solid stress of 600 Pa were calculated at the final stages of the simulation. These predictions depend on the accurate characterization of the brain's material and structural inhomogeneities and their incorporation as different domains in the simulation setup. Additionally, the realistic consideration of the tumor as a space occupying lesion, which grows in the expense of the host tissue, further improves the accuracy of the results. It is noticeable that the predictions of the elevated solid stresses, pressures, and deformations within the brain, are the primary causes of the clinical symptoms experienced by the patients with brain tumors (Laws et al., 1993; Bradley, 2008).

Radiation therapy is intensively used in clinical practice to achieve tumor control and cure. It is therefore incorporated into the model and the effects of ionizing radiation were calculated. To increase accuracy of the results, the radiation dose delivered was adjusted to account for the oxygen concentration within the tumor allowing the model to predict the decline of tumor growth rate due to treatment.

The use of different brain material properties in runs 1, 2 and 3, resulted in a marked change of the tumor growth and the exhibited stresses and pressures. In run 2 where the elastic modulus and Poisson's ratio were reduced, compared to run 1, the tumor was able to grow larger since the developed stress was greatly reduced. Additionally, the tumor in run 3, also exhibited lower stress than in run 1, again resulting in higher tumor growth. In run 3, the lower stress is attributed to the reduced Poisson's ratio of the healthy tissue, rendering him more compressible than in run 1. Our results validate the models ability to account for tumor-healthy tissue interactions and their effect on tumor growth.

A number of simplifying assumptions were adopted in the study. A main assumption is related to the consideration of CSF as a poro-elastic material even though a simulation setup with fluid-structure interactions would be more appropriate, considering CSF as purely fluid, circulating around the brain and interacting with the solid tissue domains. Additionally, recent studies demonstrated that the mechanical properties of white matter do not exhibit an isotropic behavior and vary considerably due to the neurons lining in varying directions (Pervin et al., 2009; Kaster et al., 2011). However, assumptions similar to the ones adopted herein have been implemented in numerous studies in the past and have been shown to produce physiologically meaningful results (Basser, 1992; Kaczmarek et al., 1997; Li et al.,

2011; Li et al., 2013; Goriely et al., 2015). Our mathematical framework also employed a number of assumptions. The tumor was characterized as a compressible, neo-Hookean material with an isotropic proliferation, which is not always the case given the heterogeneity of malignant growths. However, such simplifications are frequently used and do not prevent the manifestation of heterogeneous growth patterns presented in this paper (Ambrosi et al., 2002; MacLaurin et al., 2012; Ciarletta, 2013).

The model implementation includes a number of parameters (Tables 1 and 2) the majority of which were retrieved independently from the pertinent literature. Nevertheless, parameters for which no data were found, they were chosen in such a way that model predictions were reasonable and physiologically relevant. Furthermore, the evolution of the presented results can be only related to the tumor volume or the simulation timestep due to the absence of data for the tumor growth rate, in terms of actual time, in the human brain. To enable direct comparison among different simulations the same value for the timestep was used. However, this limitation is not considered of great significance because treatment is immediately commenced upon tumor detection, as the delay of treatment initiation will result in deterioration of the ability to achieve tumor control (Fortin et al., 2002; Choan et al., 2005; Soyfer et al., 2014). In fact, a number of considerations rising during chemoradiation planning relate directly to quantities predicted by our model such as the interstitial fluid pressure, perfusion, and the stress exhibited in certain regions of interest, and not to the time evolution of growth (Sorensen et al., 2009; Sorensen et al., 2012).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Fig. 1.

(Top row; left to right) Coronal, axial and sagittal T1 weighted magnetic resonance slices of the imaged brain. (Second row) Corresponding extracted masks, after automatic threshold-based segmentation and manual refinement. (Third row) Resulting masks after cavity filling and island removal operations followed by (Bottom row) final masks after smoothing operations.

Fig. 2.

(a) (Left) Three-dimensional models of the white (purple color) and gray (green color) matter. (Right) Three-dimensional model showing a posterior view of both brain tissue domains, the cerebrospinal fluid (gold color) and the initial tumor seed (blue color). (b) Different orientations of the computational finite element mesh employed in the present study. The mesh consists of 533,714 tetrahedral elements.

Fig. 3.
Effect of radiation on tumor volume as a function of the simulation step in arbitrary units (A.U.) for runs 1, 1a (1.5 Gy) and 1b (2.0 Gy).

Fig. 4. (Top) Domain map showing the deformation of the healthy tissue as the tumor increases in size. (Middle) Growth stretch ratios at the interior of the tumor at the corresponding timesteps presented above. The stretch ratios exhibit inhomogeneous patterns therefore causing heterogeneous tumor growth. (Bottom) Interstitial fluid pressure contour plots for the same timesteps as in the Top and Middle panel.

Fig. 5. (Top) Displacement maps and (bottom) bulk stress maps superimposed on anatomical MR images for the tumor presented over the final deformed mesh configuration (left), and for the host tissue presented over the reference configuration (right).

Fig. 6.

(a) Bulk stress and (b) interstitial fluid pressure as a function of tumor volume at the center of the tumor presented for runs 1, 2 and 3. (c) Tumor volume as a function of the simulation step in arbitrary units (A.U.) for the three implemented material property sets.

Table 1

Values of the model parameters used in the simulations.

Parameter	Description	Domain	Value	Reference
k_{th}	Hydraulic conductivity	Gray matter	$6.71 \times 10^{-13} \text{ m}^2 \cdot \text{Pa}^{-1} \cdot \text{day}^{-1}$	(Li et al., 2011)
		White matter	$6.71 \times 10^{-11} \text{ m}^2 \cdot \text{Pa}^{-1} \cdot \text{day}^{-1}$	
		CSF	$1.21 \times 10^{-1} \text{ m}^2 \cdot \text{Pa}^{-1} \cdot \text{day}^{-1}$	
		Tumor	$6.5 \times 10^{-9} \text{ m}^2 \cdot \text{Pa}^{-1} \cdot \text{day}^{-1}$	
B	Growth stress dependence	Tumor	0.000025 Pa^{-1}	(Voutouri et al., 2014a)
C_{iox}	Initial oxygen concentration	All	$0.2 \text{ mol} \cdot \text{m}^{-3}$	(Casciari et al., 1992)
D	Oxygen diffusion coefficient	All	$1.55 \times 10^{-4} \text{ m}^2 \cdot \text{day}^{-1}$	(Kim et al., 2011)
A_{ox}	Oxygen uptake	All	$2,200 \text{ mol} \cdot \text{m}^{-3} \cdot \text{day}^{-1}$	(Casciari et al., 1992; Kim et al., 2011)
k_{ox}	Oxygen uptake	All	$0.00464 \text{ mol} \cdot \text{m}^{-3}$	(Casciari et al., 1992; Kim et al., 2011)
k_1	Growth rate parameter	Tumor	$10,000 \text{ day}^{-1}$	This Study
k_2	Growth rate parameter	Tumor	$0,0083 \text{ mol m}^{-3}$	(Casciari et al., 1992)
S_v	Vascular density	Brain, CSF	44.6 cm^{-1}	This study (Takano et al., 1996)
		Tumor	$44.6 - 96 \text{ cm}^{-1}$	
L_p	Hydraulic conductivity	Brain	$1.8 \times 10^{-7} \text{ cm/mmHg} \cdot \text{s}$	This Study (Baxter et al., 1989)
		Tumor	$1.8 - 2.8 \times 10^{-7} \text{ cm/mmHg} \cdot \text{s}$	
P_v	Vascular pressure	All	10000 Pa	(Czosnyka et al., 2004)
$L_{pt}S_v$		Brain	$0.0365 \text{ mmHg} \cdot \text{s}$	This Study
		Tumor	0	(Stylianopoulos et al., 2013)

Table 2

Values of the normal brain and tumor mechanical material properties employed in the simulations.

Domain	Reference	Run Number	Elastic Modulus (kPa)	Poisson's Ratio
Gray matter	(Basser, 1992)	1, 1a, 1b	5.96	0.49
	(Clatz et al., 2005)	2	0.694	0.40
	(Kaczmarek et al., 1997)	3	10.0	0.35
White matter	(Basser, 1992)	1, 1a, 1b	2.68	0.49
	(Clatz et al., 2005)	2	0.694	0.40
	(Kaczmarek et al., 1997)	3	10.0	0.35
CSF	(Li et al., 2013)	All runs	30	0.1
Tumor	(Basser, 1992)	All runs	35 kPa	0.45