Characterization of Biomechanical Tumor Growth Phenotypes from Clinical MR Imaging

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1. Introduction

Tumor growth is the result of a chain of processes that lead to uninhibited cell division and loss of normal tissue homeostasis. Cancer cells may infiltrate and replace normal tissue, or form a macroscopic "mass" that displaces other tissue structures. This tissue-displacing potential of macroscopic tumors is termed "mass-effect". Glioblastoma (GBM), the most frequent malignant brain tumor in adults, exhibits both infiltrative and displacive growth characteristics.

Physical forces arising from tumor growth can contribute to tumor progression and generate mechanical stresses in the tumor as well as in the surrounding tissues. In brain tumors, elevated solid stress causes neuronal loss and neurological dysfunction [2], and increased tumor mass-effect is associated to poor prognosis in Glioblastoma (GBM) patients [3].

These findings suggest that a tumor's propensity to displace healthy tissue provides information about its tumor micro-environment of potentially predictive value for treatment and outcome. However, most previous clinically motivated mathematical brain tumor models, e.g. [4], focused on the tumors' invasive growth characteristics, without taking into account their mass-effect.

We have previously investigated a simple mathematical model of mechanically-coupled tumor growth and showed that the parameters of this model can be estimated reliably from noisy synthetic data [1]. Here we report its application for estimating patient-specific tumor growth characteristics from clinical MR imaging data (n = 13) and discuss potential applications of personalized biomechanical brain tumor growth models.

2. Methods

As clinical reference we used publicly available single-timepoint pre-operative MR-imaging datasets of 13 patients from the Ivy Glioblastoma Atlas Project (Ivy GAP[1]). Each dataset was segmented into regions corresponding to T1-contrast enhancing tumor (*T1*), T2/FLAIR enhancing (*T2*) and lateral ventricles (*LV*) using the automatic segmentation software BraTumIA[2] and subsequent manual post-processing. For each case, a patient-specific "healthy" reference brain was created by affine registration of a normal-brain atlas to the T1-weighted MR image of the respective tumor-bearing brain.

parameter	min	max	step	units
WM diffusivity D_{WM}	0.10	0.80	0.05	$\frac{mm^2}{day}$
proliferation rate ρ	0.10	0.10	n.a.	$\frac{1}{day}$
mech. coupling λ	0.10	1.00	0.10	
growth time t	0	200	1	

Table 1: Parameter sampling grid for optimization. We assumed $D_{WM} = 5 \cdot D_{GM}$.

To estimate patient-specific tumor growth characteristics for these cases, we extended the 2D single-species mechanically-coupled reaction-diffusion model presented in [1] to 3D. In brief, the mathematical model describes invasive tumor growth as a reaction-diffusion process with tumor cell density c(x), diffusion coefficient D(x) and logistic growth proliferation rate ρ. The growth domain is modeled as a linear elastic continuum consisting of different brain tissues (white matter, grey matter, cerebro-spinal fluid) with their respective material properties. Simulation of the tumor's tissue-displacing mass-effect assumes a linear coupling between local tumor cell density and growth-induced strain ϵ^{growth} with mechanical coupling parameter λ: $\epsilon^{growth} = \lambda\, c\, \mathbb{I}$.

To allow for higher flexibility in the choice of optimization cost function compared to [1], we used a grid search approach, Table 1, for identifying the optimal parameter-set for each of the patient cases. Quality of model fit was quantified by the dice overlap between patient segmentation and model predictions for *T1*, *T2* and *LV* structures. Parameter selection was based on the maximum combined (*T1-T2-LV*) dice coefficient, computed as the average of *T1*, *T2* and *LV* dice.

3. Results and discussion

We identified patient-specific growth parameters $\{D/\rho, \lambda, t\}$ resulting in *T1-T2-LV* dice coefficients between 0.49 – 0.67 across all patients, and *T1* dice coefficients ranging between 0.54 – 0.85. Although, optimization was performed using *T1-T2-LV* dice, the selected parameter combinations approximate the actual *T1* tumor volume very well (R^2 = 0.97), Fig. 1 (A).

Figure 1 (B) compares patient image and optimal simulation results in a central tumor slice of three pa-

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[1] http://doi.org/10.7937/K9/TCIA.2016.XLwaN6nL

[2] https://www.nitrc.org/docman/?group_id=817

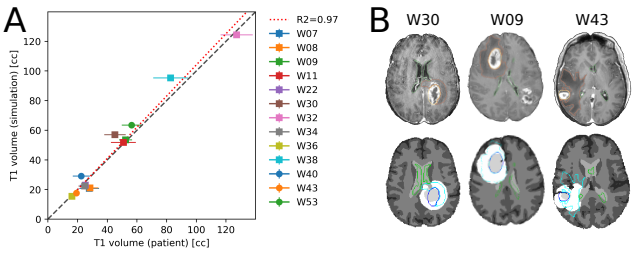

Figure 1: (A) Estimated vs actual T1 tumor volume. (B) Comparison of patient image and model fit in central tumor slice of cases with highest (W30), intermediate (W09) and lowest (W43) dice overlap.

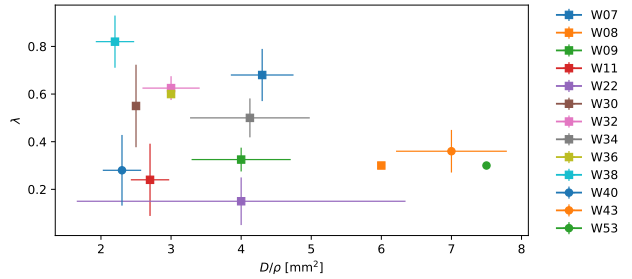

Figure 2: Estimated tumor characteristics D/ρ and λ. Errorbars indicate the standard deviation of parameter distributions that yield highest 0.5% of dice estimates.

tient cases corresponding to the highest (W30), intermediate (W09) and lowest (W43) *T1-T2-LV* dice coefficient. In general, the model provides a very good fit to the *T1* tumor and is able to reproduce regularly shaped *T2* imaging contours. As expected, given its simplicity, the model performs less well on very irregular shaped contours as in W43.

We used *LV* dice to introduce a measure of tumor-induced normal-tissue deformation in the optimization cost function. Although, perfect match between simulated and actual patient ventricles is rarely achieved, the effect of tumor-induced mechanical compression in and out-of-plane can be clearly observed in cases W30 and W09. This confirms that the proposed model and parameter optimization capture the global biomechanical impact of the growing tumor at least partially.

Figure 2 characterizes the included tumors by their *invasive* (D/ρ) and *displacive* (λ) characteristics: Tumors with higher (lower) D/ρ display a more invasive (nodular) phenotype, tumors with higher (lower) λ display a stronger (weaker) displacive behavior.

Most mechanically-coupled model-based tumor growth approaches have been studied in the context of automated brain tumor image segmentation, but without exploiting their potential for growth characterization. Patient-specific biomechanical tumor growth models allow tumors to be characterized along multiple growth dimensions, such as their *invasive* (D/ρ) and *displacive* (λ) potential, Fig. 2, which may provide markers of tumor biology. For example, D/ρ has been shown predictive of a tumor's isocitrate dehydrogenase 1 (IDH1) mutation status. Studies such as [2, 3] indicate a similar predictive potential for a model-based measure of tumor displaciveness, but this remains to be confirmed in higher-numbered studies that include additional clinical and biological data.

Biomechanically-coupled growth models also provide access to the distribution of tumor-induced mechanical stresses in the tumor and in normal brain. This information, correlated to functional brain areas, may be relevant for treatment planning and assessment. Its incorporation in tumor growth models has already been shown to yield more accurate predictions of growth and treatment effect.

4. Conclusion

This study demonstrates feasibility of characterizing invasive and displacive GBM growth attributes from single time-point clinical MR imaging. The mechanical properties of brain tissue have been well characterized and multiple approaches exist to incorporate tumor growth in a biomechanical modeling framework. Here we assessed one of the simplest and most common type of mechanically coupled growth model with regard to its ability to fit tumor geometry and ventricle shape of 13 human GBM cases. We plan to investigate the clinical utility of this model by benchmarking against specific use-cases that will also drive future model improvement and development.

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