Towards a Framework for Predictive Mathematical Modeling of the Biomechanical Forces causing Brain Tumor Mass-Effect

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Introduction

Glioblastoma multiforme (GBM) present with a **range of growth phenotypes** [1], from predominantly invasive tumors without notable "mass-effect" to strongly displacing lesions that induce high mechanical stresses resulting in healthy-tissue deformation, midline shift or herniation. **Biomechanical forces shape** the **tumor micro-environment** by compression of blood and lymphatic vessels, reducing blood perfusion and generating hypoxia [2].
We expect these forces to be **important for tumor evolution**, for the formation of distinct growth phenotypes and tumor shape.

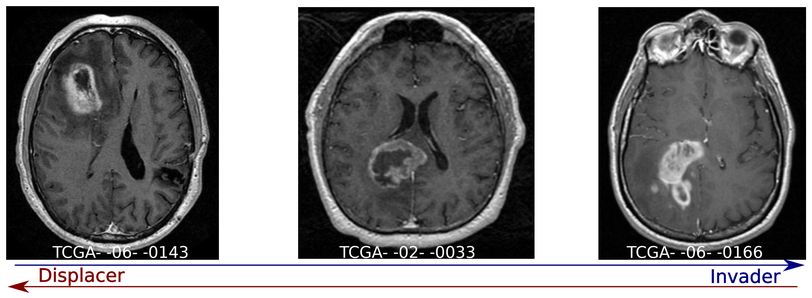


Figure 1: GBM growth phenotypes with varying degrees of mass-effect.

With the **aim to quantitatively characterize different growth phenotypes**, to better understand the role of mechanical forces in their formation and to **study possible implications for treatment**, we started developing a **framework for GBM growth simulation**:
Its underlying mathematical model accounts for the biomechanical stresses induced in the tissue and thus allows simulation of GBM's **invasive growth characteristics** as well as the **mass-effect** caused by the growing tumor.

A previous version of the framework [3] yielded realistic estimates of the mechanical impact of a growing tumor on intra-cranial pressure. However, it was limited to isotropic growth assumptions and failed to reproduce the asymmetric tumor shapes found in patient images.

Here we present an **extended version** of this model that accounts for the **anisotropic orientation of axons** in white matter using information from Diffusion-Tensor-Imaging (DTI). This **structural anisotropy** is known to **affect** the preferred **directionality** of **tumor cell migration** and the **mechanical behavior** of the tissue.

Parametric Simulation Study

Study Workflow

- ▶ Tumor growth simulation for
  - **multiple seed locations** derived from tumor segmentations,
  - **invasive** (large D/ρ) and **nodular** (small D/ρ) **growing tumors**,
  - **isotropic** and **anisotropic** model versions.
- ▶ **Comparison** of **simulated** to **actual tumor** at imaged volume.

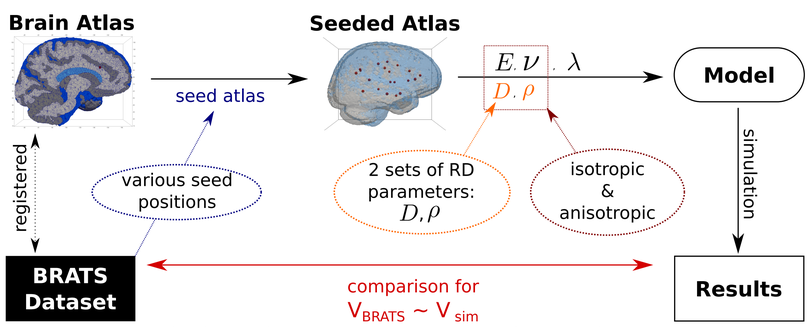


Figure 2: Parametric simulation study of tumor evolution, varying seed positions and RD parameters, with and without accounting for tissue anisotropy.

Parameter Assumptions

Literature-derived parameter values

▶ **Isotropic**, no account of tissue structure:

D/ρ	ρ [1/d]	D_G [mm²/d]	D_W [mm²/d]
low	0.082	0.020	0.101
high	0.037	0.040	0.200

(a) Reaction-Diffusion parameters ρ, D, derived from clinical study data [4–7], by D/ρ category.

Tissue	E [kPa]	ν
W/G Matter	3.0	0.45
Tumour	6.0	0.45
CSF (Ventricles)	1.0	0.30
CSF (other)	1.0	0.49

(b) Mechanical tissue properties [8].

Table 1: Parameter choices for isotropic model.

▶ **Anisotropic**, (transverse isotropic) White Matter structure:
- Grey Matter parameters as in isotropic case.
- Higher motility along fibres: $D_W^{\parallel} = D_W^{iso}$, $D_W^{\perp} = 0.01 \cdot D_W^{iso}$
- Stiffer (tensile) along fibres: $E_W^{\parallel} = 3 \cdot E_W^{\perp}$ (details in [9])

Maximum volumetric growth of 15 %: $\lambda = 0.15$ [10].
Boundary conditions constrain surface flux & nodes.
Atlas of normal human brain anatomy (SRI24) [11], MR & MR-DTI.
Image data of high-grade glioma patients from BraTS 2013.
Implementation via Finite Element Method (FEM). Calculations were performed on UBELIX, the HPC cluster at the University of Bern.

Simulated Tumor Evolution & Mechanical Impact

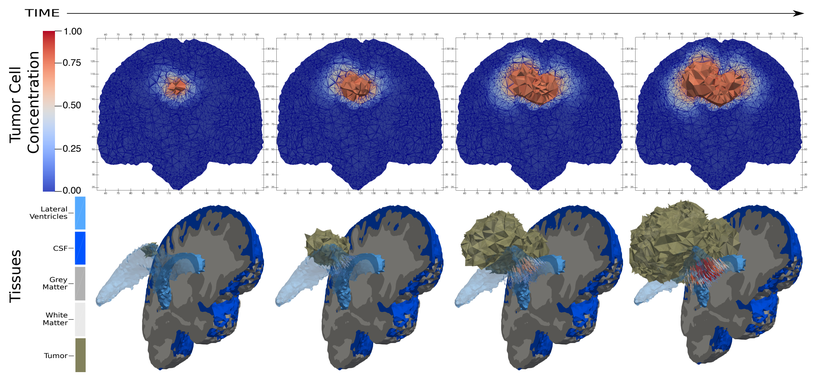
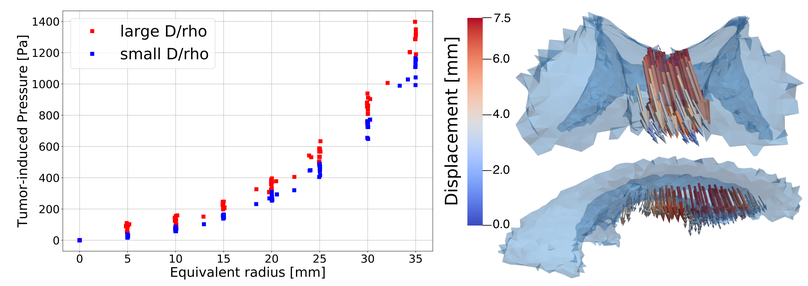


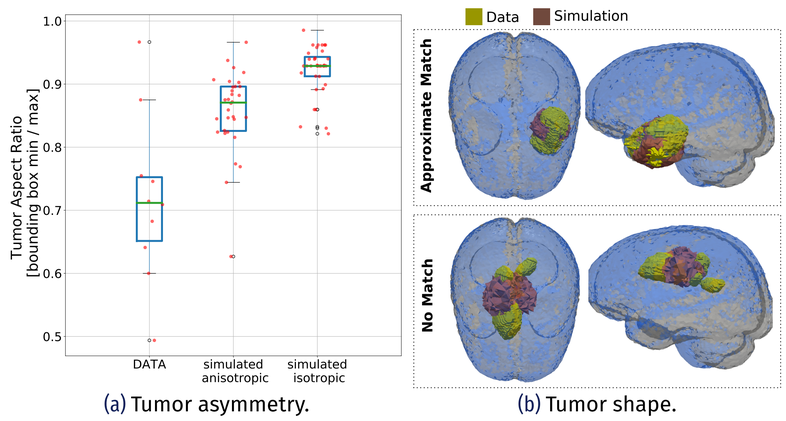
Figure 3: Simulated tumor evolution. Threshold for solid tumor $c > 0.8$.



(a) Tumor-induced pressure. (b) Midline deformation.

Figure 4: Simulated mechanical impact of growing tumor.

Tumor Shape



(a) Tumor asymmetry. (b) Tumor shape.

Figure 5: Comparison of tumor shape: simulated vs. observed in BRATS data set.

Mathematical Model

Cell proliferation and invasion are modeled as **reaction-diffusion** process; the simulation of the **mechanic interaction** relies on a linear-elastic material model. Both are **coupled** by relating local **tumor cell concentration** to the generation of **strains in** the **tissue**. The model accounts for multiple brain regions and incorporates information of structural tissue anisotropy.

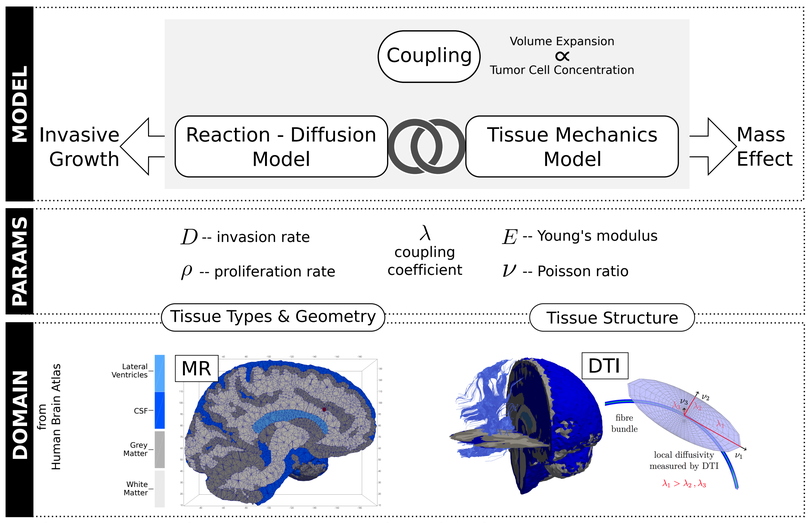


Figure 6: Mechanically-coupled Reaction-Diffusion Model: Structure & Inputs.

Summary & Discussion

The mathematical model captures invasive growth characteristics of GBM and the biomechanical stresses caused by tumor growth. Simulations yield **realistic tumor volumes** and **estimates of mechanical impact**. **Simulated tumor shapes** are **more symmetric than** the corresponding **real lesions**. **Accounting for brain tissue structure reduces symmetry** of simulated lesions on average, however, not to the level observed in GBM patient data.

▶ **Model & Study Limitations:**
- Parametrisation and growth domain **not personalized**.
- No account of vasculature and growth promoting/inhibiting factors in tumor micro-environment.
- Assumption of linear-elastic mechanical material model.

Outlook

Further model testing and development in animal study. Model personalization to enable **patient-specific characterization** of distinct "invasive" and "displacive" **growth phenotypes**.

Further Information

GlimS
Glioma mass-effect Simulator

www.glims.ch

Selected References

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The research leading to these results has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement No 600841 and from European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 753878.

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