Computational study of the influence of biomechanical forces on the shape of GBM

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GlimS — Glioma mass-effect Simulator

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Glioma

Gliomas are the **most frequent** (70 %) **malignant primary brain tumors** in adults [1], with Glioblastoma multiformae (GBM) being the **most frequent** and **malignant** sub-type (grade IV). These tumors **grow rapidly**, **infiltrate** the healthy brain and form a necrotic core of high cell density which is often accompanied by **compression and displacement** of the surrounding tissue. This so-called **"mass-effect"** leads to a multitude of **pressure-related symptoms**, from headache and nausea to coma or death due to herniation. Standard treatment involves surgical resection of the bulk tumor to reduce symptoms of mass-effect, followed by a combination of chemo- and/or radiation therapy. **Long-term prognosis** for GBM remains **poor** with median overall survival between 1 y to 2 y [1].
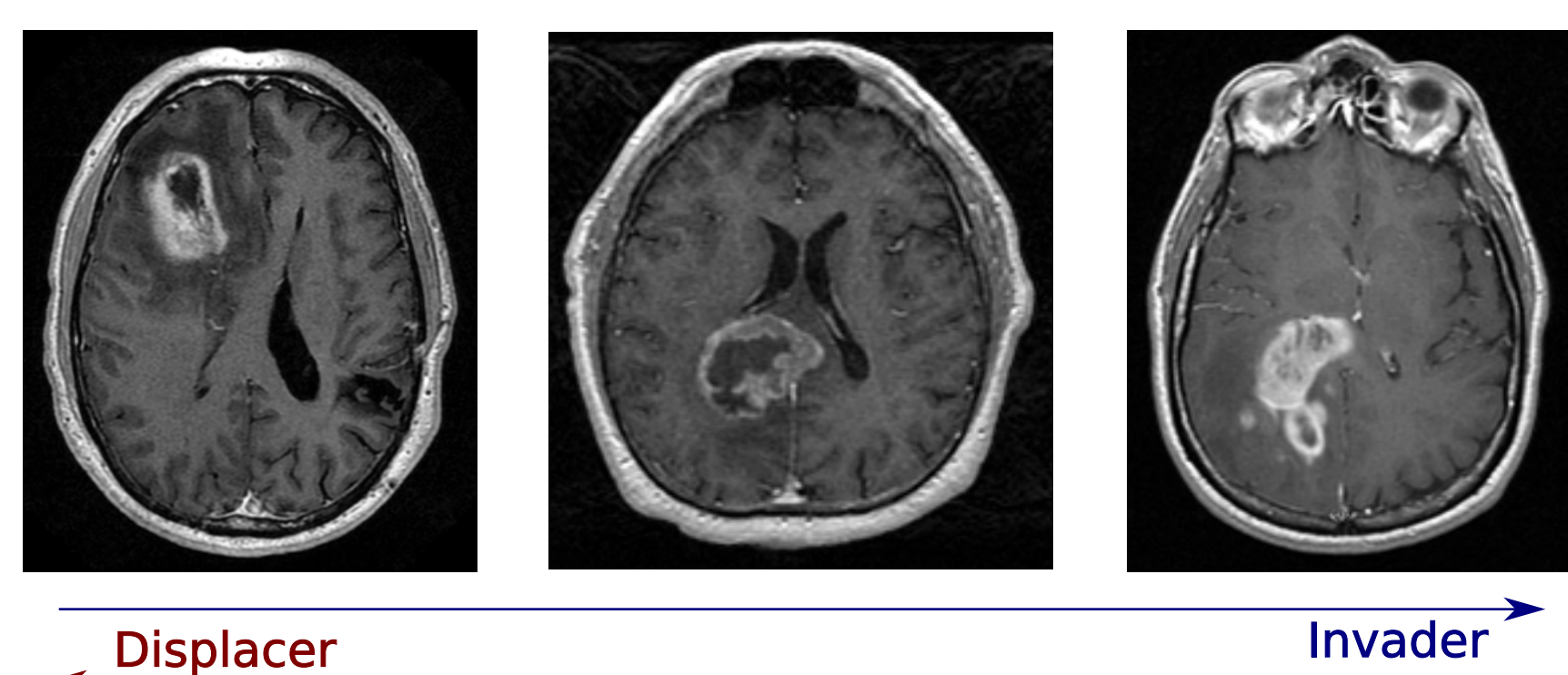

Figure 1: GBMs of different degrees of displaciveness, MRI images from [2].

Displacer ← → Invader

Importance of Tumor Mass-Effect

GBMs present with a **range of mechanical growth phenotypes**, from predominantly invasive tumours without notable mass-effect to strongly displacing lesions that induce higher mechanical stresses and result in healthy-tissue deformation, midline shift or herniation. **Biomechanical forces shape the tumour micro-environment**, affecting cell proliferation and invasive or metastatic potential. Tissue compression may result in reduced blood perfusion and cell motility, and reduced outward growth/expansion observed in areas of high stress. In addition to their implications on the biophysical level, **biomechanical factors are relevant for clinical decision making** as they may affect treatment response and outcome.

Mathematical Models of Glioma Growth

Different types of mathematical models (discrete, continuous, hybrid) on different spatio-temporal scales have been employed to improve the understanding of GBM and to optimize treatment approaches [3]. Modeling of the invasion dynamics of glioma received particular attention due to its immediate clinical importance, whereas their **mass-effect remains less studied**. Deformation of brain structures due to tumour growth has been investigated mainly in the context of image registration methods for atlas-based segmentation. Few models consider both tumour invasion and mass effect in a realistic 3D model of the human brain.

Objective

1. Development of **personalisable models** for simulation of **tumour invasion** and **mass effect**
2. Statistical evaluation in comparative numerical study:
   Can simple model reproduce characteristics of realistic pathologies?
   - growth patterns (shape of visible & microscopic tumor)
   - tumor-induced pressure

Materials & Methods

Mathematical Model & Implementation

Cell proliferation & healthy tissue invasion Reaction-Diffusion (RD) model with logistic growth:

$$\frac{\partial c}{\partial t} = \nabla \cdot (D\, \nabla c) + \rho\, c\, (1 - c)$$

with normalized cancer cell concentration $c = c(\boldsymbol{r}, t)$, diffusion constant $D = D(\boldsymbol{r})$ and proliferation rate ρ.

Mass-Effect Linear-elastic material model with Poisson ratio ν and Young's modulus E

Coupling Increasing tumour cell concentration leads to growth-related strains $\hat{\boldsymbol{\epsilon}}^{\mathrm{g}} = \lambda\, c\, \mathbb{1}$ in the tissue.

Implemetation "Coupled thermal-stress analysis" in Abaqus (Dassault Systèmes), solved using Finite Element Method (FEM)

Data

- **Image data** & **tumour segmentations** of 20 high-grade glioma patients from BraTS 2013 segmentation challenge.
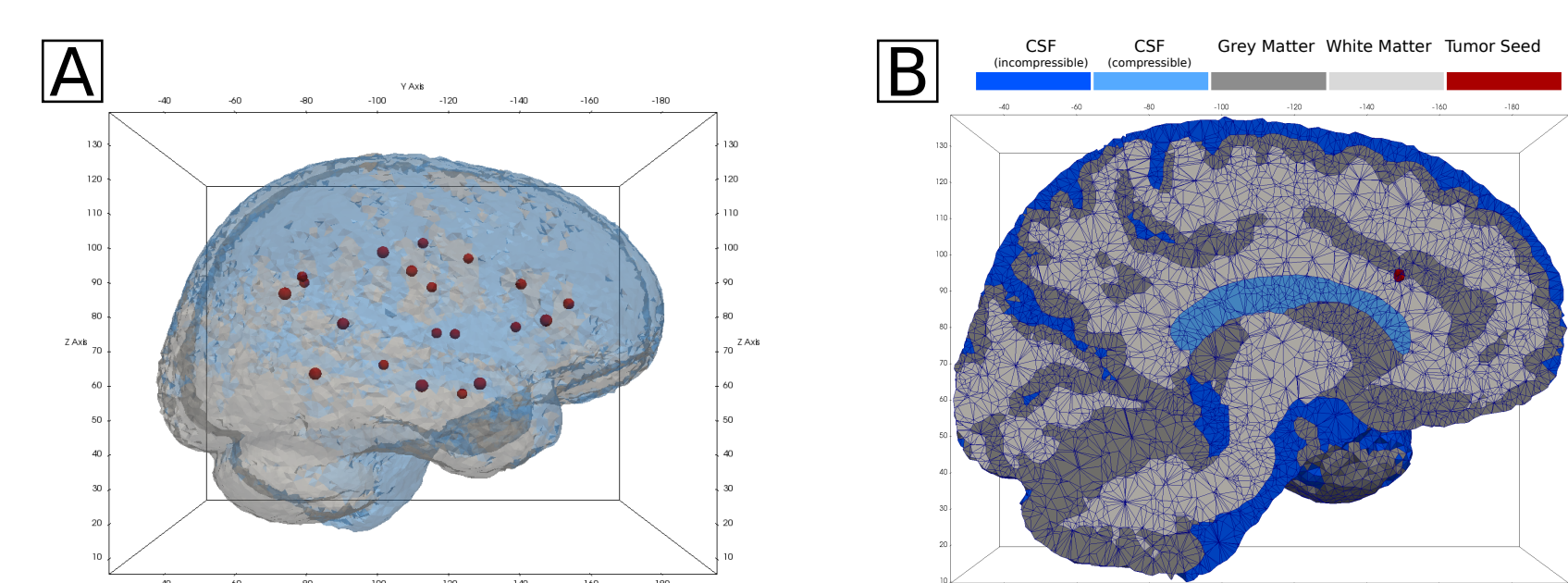- SRI24 **atlas of normal human brain anatomy** [4].

Figure 2: Overview of seed positions within healthy brain atlas (A), cross-section of FEM mesh for exemplary seeding scenario (B).

Parameter Assumptions

Literature-derived parameter values

D/ρ	ρ [1/d]	D_{avg} [mm²/d]	D_G [mm²/d]	D_W [mm²/d]
low	0.082	0.053	0.020	0.101
medium	0.046	0.058	0.022	0.110
high	0.037	0.105	0.040	0.200

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

Table 1: Values of RD parameters ρ, D derived from clinical study data [5–8], by D/ρ category.

Table 2: Mechanical material properties similar to [9].

Maximum volumetric "growth" of 15 %: $\lambda = 0.15$ [10]

Boundary conditions no flux across surface, nodes constrained

Parametric Study

- Tumor growth **simulation for each seed location** and D/ρ
- Comparison of simulated and actual tumour at imaged volume
- Evaluation of mechanical impact caused by tumor

Figure 3: Param. study: Tumor evolution in function of seed location and D/ρ.

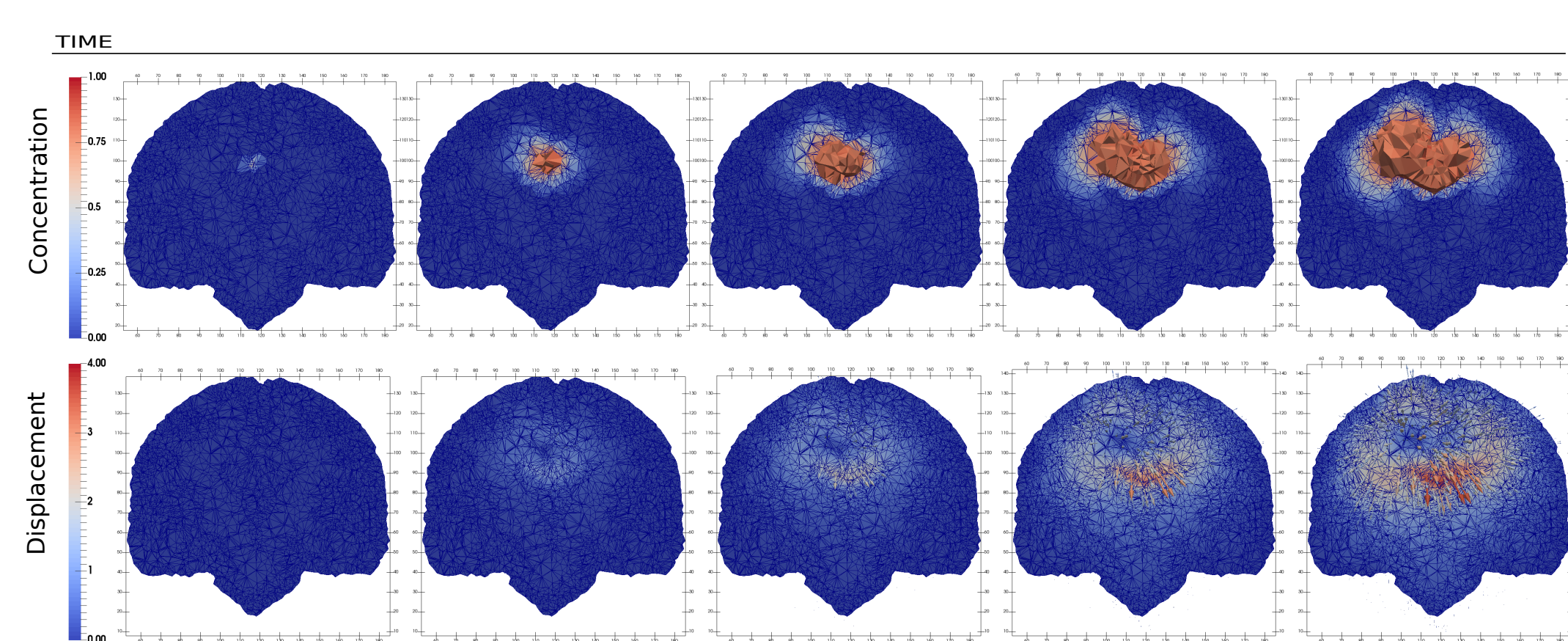## Results

Simulated Tumor Evolution

Figure 4: Evolution of tumor cell concentration and resulting tissue displacement.

Mechanical Impact

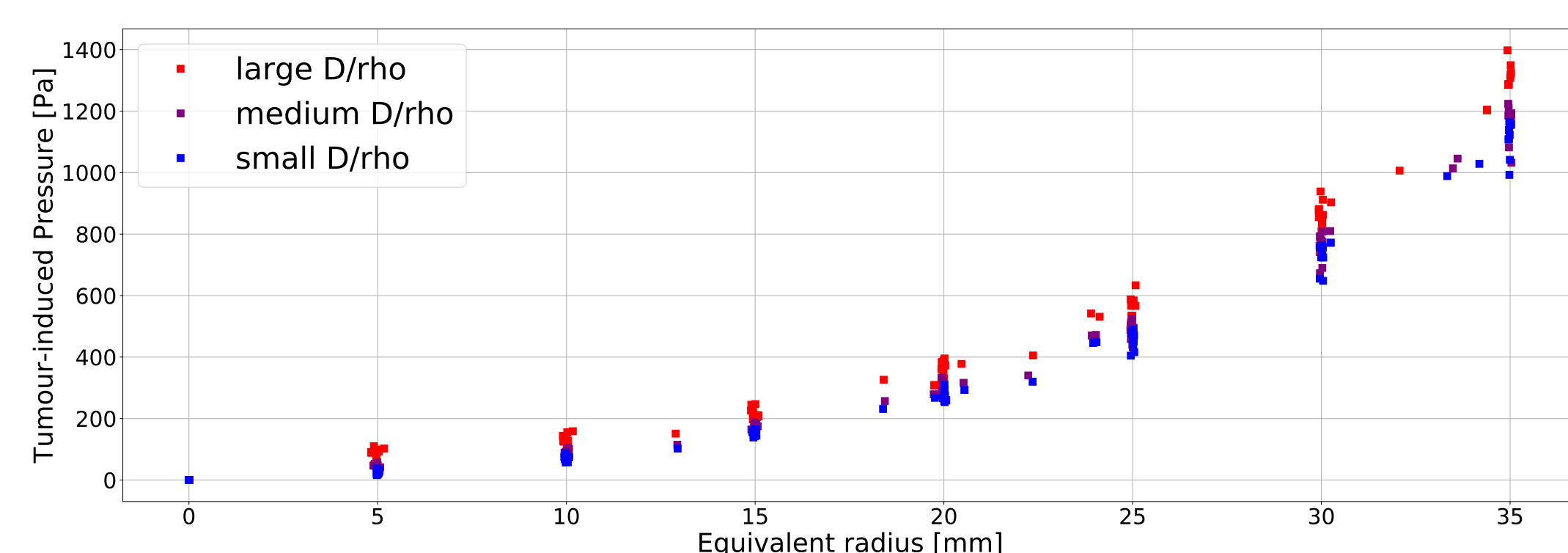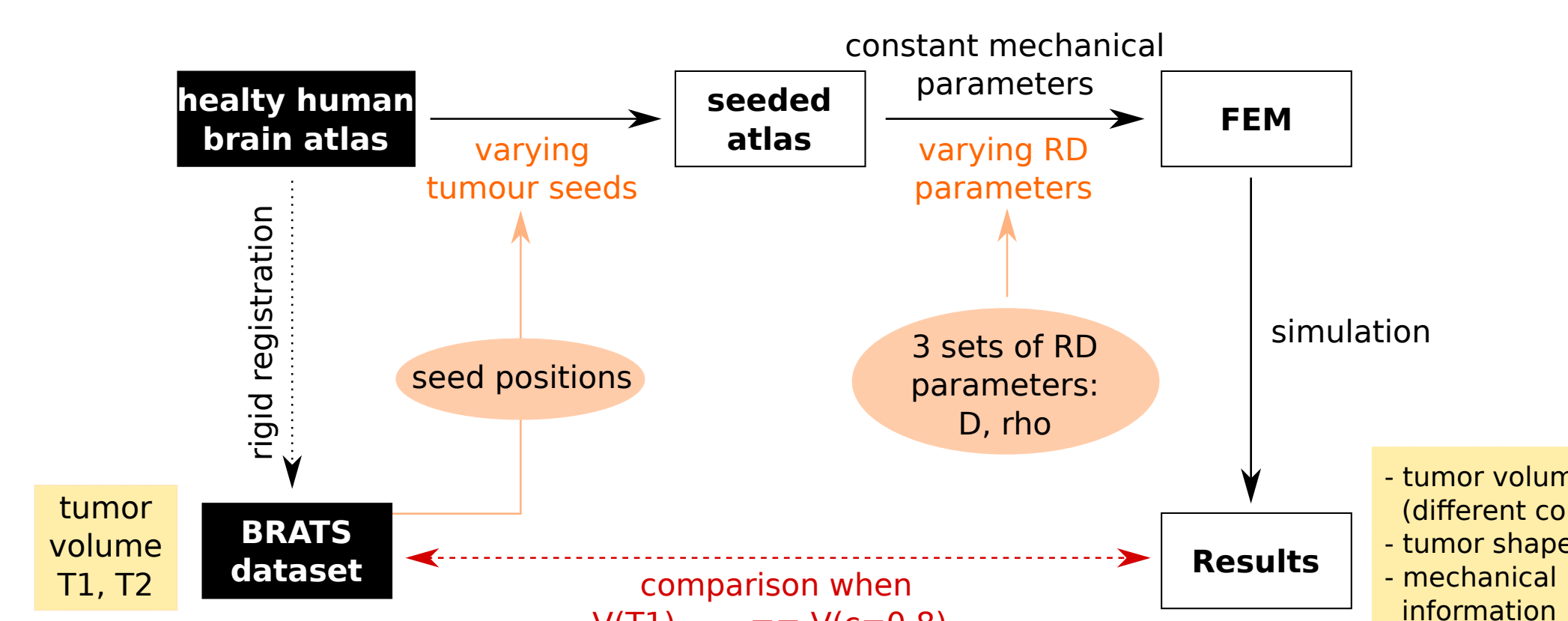
Figure 5: Pressure on skull due to tumor mass-effect: 1.0 kPa to 1.4 kPa at fatal tumour burden (3.5 cm equivalent radius [5]).

Simulated vs Actual Tumor Shape

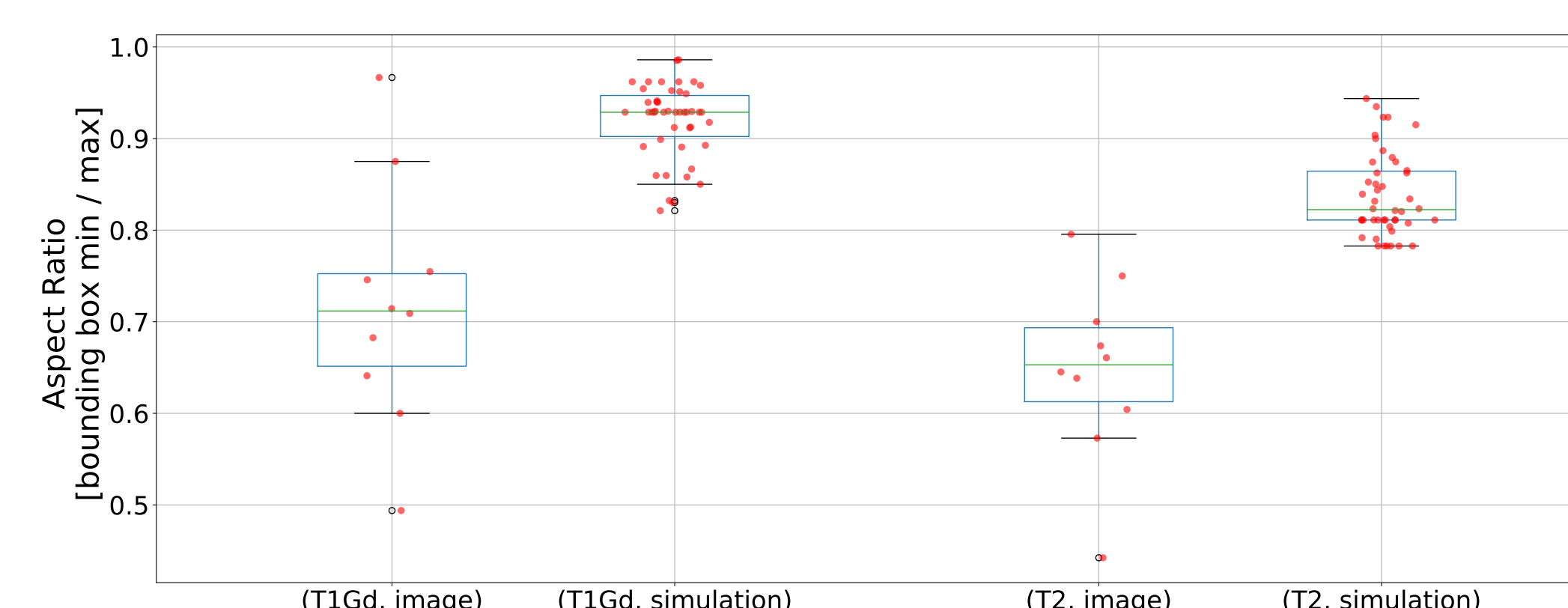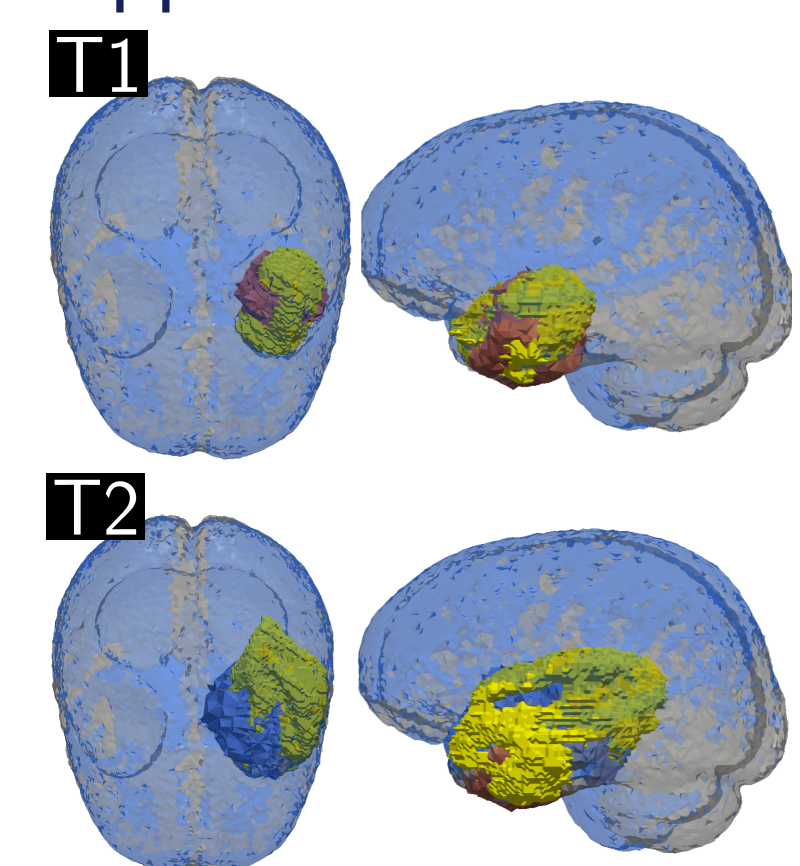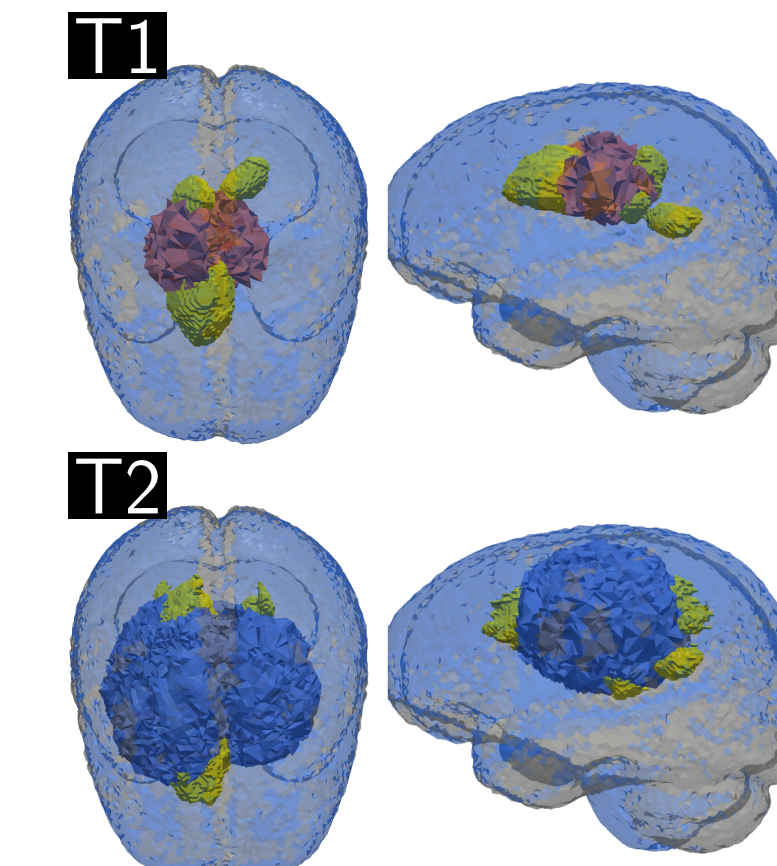Tumor "aspect ratio" as **measure for asymmetry**

Figure 6: Aspect ratio of simulated vs. actual tumor for different imaging modalities (cell concentration thresholds): T1Gd ($c = 0.80$), T2 ($c = 0.16$).

Approximate Match   No Match

Summary & Discussion

A **personalisable** mechanically-coupled RD **model of glioma growth** has been developed, including a processing pipeline for FEM model creation, simulation & analysis. Simulations yield **realistic tumor volumes** and **estimates of the mechanical impact** of the growing tumor. However, statistical evaluation of tumor shape showed the **simulated tumors** to be **more symmetric than** the corresponding **real lesions**.

Likely explanations for this mismatch are linked to **limitations of the current model** which assumes isotropic tissue properties, a linear elastic material model of brain tissue and does not account for vascularisation. Furthermore, the comparative study between observed and simulated tumors relies on the observed center-of-mass position as seed location. Tumors were grown in a healthy reference geometry of the human brain and with average tumor characteristics (ρ, D, E, ν) rather than personalized geometry and parameter values.

Outlook

This study underlines the **importance of tissue anisotropy for Glioma simulation** which will be accounted for in future studies: Previous studies based on RD models have found information from Diffusion-Tensor-Imaging (DTI) indicative for the preferred directionality of tumor cell migration. DTI allows to map out the principal orientations of axons in white matter. As material properties have been shown to depend on the relative direction of loading with respect to fiber orientation, this structural anisotropy is also critical for the mechanical behavior of the tissue.

Further Information

GlimS project website:

www.glims.ch

Selected References

[1] D. Ricard et al. "Primary Brain Tumours in Adults". *The Lancet* 379.9830 (05/2012), pp. 1984–1996.

[2] L. Scarpace et al. *Radiology Data from The Cancer Genome Atlas Glioblastoma Multiforme [TCGA-GBM] collection*. 2016.

[3] H. Hatzikirou et al. "Mathematical Modelling of Glioblastoma Tumour Development: A Review". *Math. Models Methods Appl. Sci.* 15.11 (2005), pp. 1779–1794.

[4] T. Rohlfing et al. "The SRI24 Multichannel Atlas of Normal Adult Human Brain Structure". *Hum Brain Mapp* 31.5 (12/16/2009), pp. 798–819.

[5] K. R. Swanson et al. "Velocity of Radial Expansion of Contrast-Enhancing Gliomas and the Effectiveness of Radiotherapy in Individual Patients: A Proof of Principle". *Clinical Oncology* 20.4 (05/2008), pp. 301–308.

[6] C. H. Wang et al. "Prognostic Significance of Growth Kinetics in Newly Diagnosed Glioblastomas Revealed by Combining Serial Imaging with a Novel Biomathematical Model". *Cancer Res* 69.23 (12/01/2009), pp. 9133–9140.

[7] M. D. Szeto et al. "Quantitative Metrics of Net Proliferation and Invasion Link Biological Aggressiveness Assessed by MRI with Hypoxia Assessed by FMISO-PET in Newly Diagnosed Glioblastomas". *Cancer Res* 69.10 (05/15/2009), pp. 4502–4509.

[8] R. Rockne et al. "Predicting the Efficacy of Radiotherapy in Individual Glioblastoma Patients *in Vivo*: A Mathematical Modeling Approach". *Phys. Med. Biol.* 55.12 (06/21/2010), pp. 3271–3285.

[9] A. Wittek et al. "Patient-Specific Non-Linear Finite Element Modelling for Predicting Soft Organ Deformation in Real-Time; Application to Non-Rigid Neuroimage Registration". *Progress in Biophysics and Molecular Biology*. Special Issue on Biomechanical Modelling of Soft Tissue Motion 103 (2-3 12/2010), pp. 292–303.

[10] A. Mohamed and C. Davatzikos. "Finite Element Modeling of Brain Tumor Mass-Effect from 3D Medical Images". *Medical Image Computing and Computer-Assisted Intervention–MICCAI 2005*. Lecture Notes in Computer Science 3749. Springer, 2005, pp. 400–408.