Image-based Parameter Optimization of a mechanically-coupled Brain Tumor Growth Model

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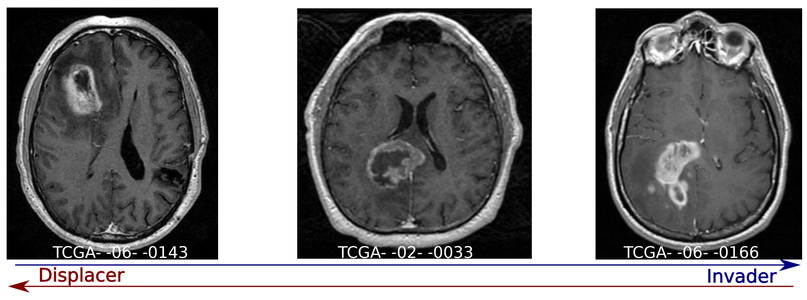
Glioblastoma

Glioblastoma multiforme (GBM) is the most frequent malignant brain tumor in adults. It presents with **varying degree of mass-effect**, 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** [1] and thus affect tumor evolution and treatment response.



Simulation Framework

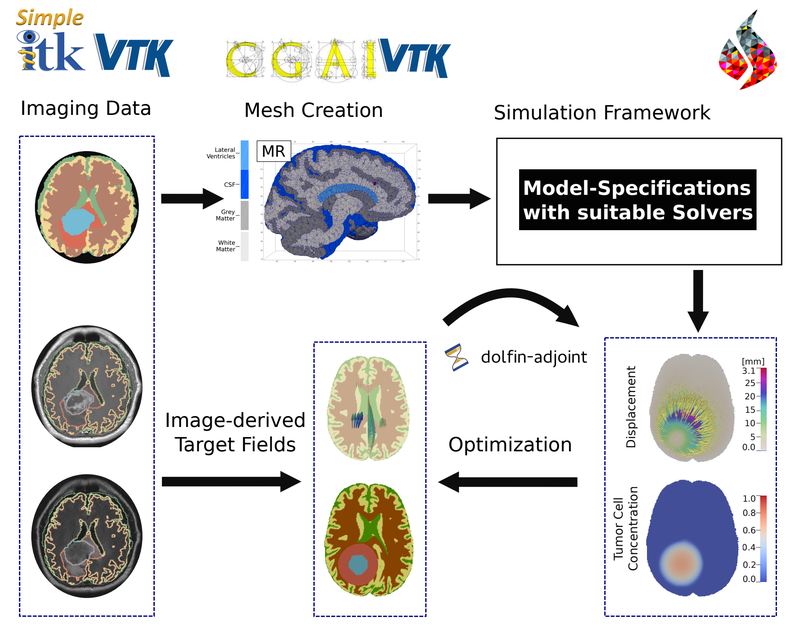
Can different GBM "growth phenotypes" be distinguished by mathematical modeling?

Developing open-source framework for image-based simulation of macroscopic tumor growth and mechanical impact, to

- Estimate patient-specific growth parameters for cohorts of patients.
- Evaluate and compare different model specifications to identify best-fitting model.

Design considerations:

- Support for simulations in 2D & 3D
- Adaptable to different model specifications
- Efficient approach to inverse problem
- High-level language



Forward Model

Mathematical Model

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

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

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

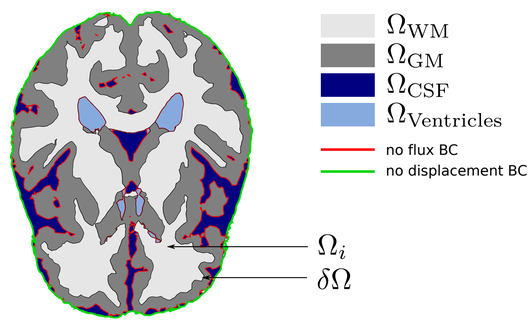
Mass-Effect based on **linear constitutive relationship** between stress $\hat{\boldsymbol{\sigma}}(\boldsymbol{u})$ and strain $\hat{\boldsymbol{\epsilon}}(\boldsymbol{u})$:

$$\hat{\boldsymbol{\sigma}}(\boldsymbol{u}) = \hat{\boldsymbol{E}} \ : \hat{\boldsymbol{\epsilon}}(\boldsymbol{u})$$
$$\hat{\boldsymbol{\epsilon}}(\boldsymbol{u}) = \frac{1}{2}\left(\boldsymbol{\nabla} \cdot \boldsymbol{u} + (\boldsymbol{\nabla} \cdot \boldsymbol{u})^{\mathsf{T}} \right)$$

Presence of tumor cells assumed to result in **tumor-induced strains** with **coupling** strength $\hat{\boldsymbol{\lambda}}$:

$$\hat{\boldsymbol{\epsilon}}^{\text{growth}}(c) = \hat{\boldsymbol{\lambda}}\, c \ .$$

Simulation Domain & Parameters



All parameters currently assumed **isotropic**.

Growth parameters:

cell motility $\hat{\boldsymbol{D}}$: D_{GM}, D_{WM}
proliferation ρ: ρ_{GM}, ρ_{WM}
coupling $\hat{\boldsymbol{\lambda}}$: $\lambda_{\text{GM}} = \lambda_{\text{WM}} = \lambda$

Mechanical properties:

Young's modulus E: E_{Ω_i}
Poisson ratio ν: ν_{Ω_i}

Inverse Problem

PDE-constrained Optimization

Find model parameters $\boldsymbol{p}$ that minimize a given optimization functional $f(\boldsymbol{\phi}, \boldsymbol{p})$ under the PDE constraint $g(\boldsymbol{\phi}, \boldsymbol{p}) = 0$, where $\boldsymbol{\phi}$ are the statevariables.
The adjoint method provides an efficient approach for computing the gradient $\frac{df}{d\boldsymbol{p}}$.
We use FENICS-adjoint [2] for deriving the adjoint equations.

General optimization functional for observation time point k with estimates of tumor cell concentration $c_k^*(\boldsymbol{r})$ and tissue deformation $\boldsymbol{u}_k^*(\boldsymbol{r})$:

$$J = \|c(\boldsymbol{r}, t_k) - c_k^*(\boldsymbol{r})\|_2^2 + \|\boldsymbol{u}(\boldsymbol{r}, t_k) - \boldsymbol{u}_k^*(\boldsymbol{r}_l)\|_2^2$$

Optimization on Synthetic Data

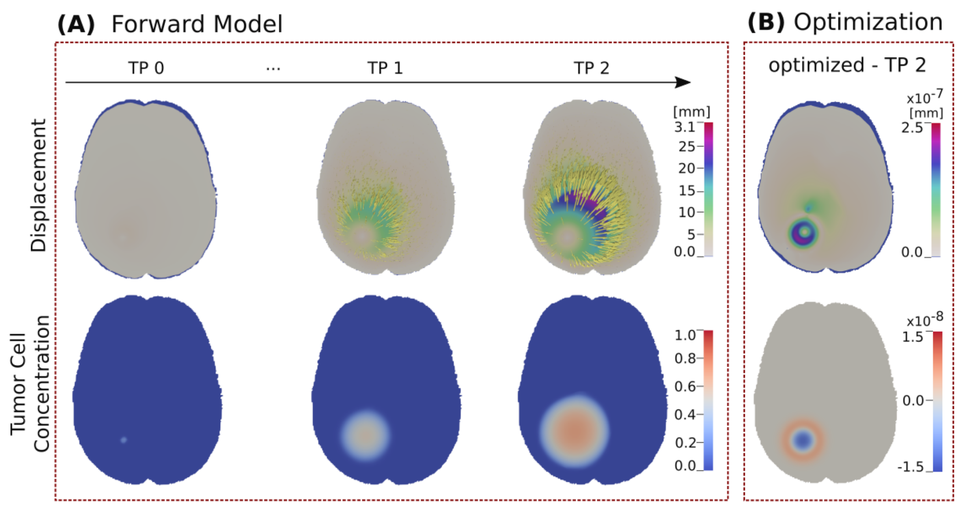
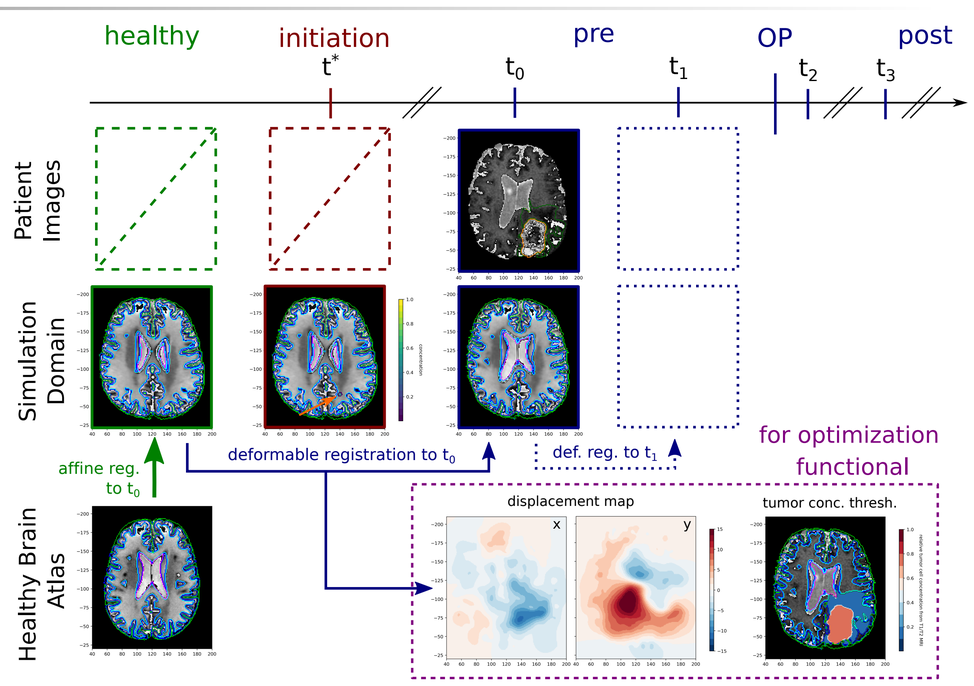


Image-derivable Information for Patient-specific Optimization

The patient's normal (non-tumor bearing) anatomy is typically unknown.
We approximate the **healthy patient-specific anatomy** by **affine registration** of an atlas (MR and tissue labels) to the first imaging time point.

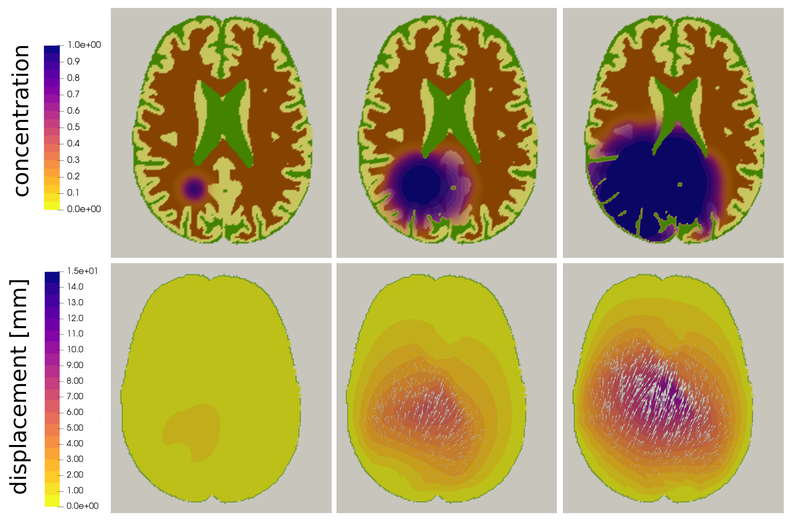
From this configuration, **tumor-induced displacements** are estimated by **deformable registration** [3].

Approximate **tumor cell distribution** is inferred from surrogate information:
anatomical MR: tumor segmentation and **imaging thresholds** for T1, T2-weighted MR
functional MR: tumor **cellularity** from diffusion-weighted imaging.



Status & Results

Forward model implemented for 2D & 3D, tested in 2D.



Adjoint optimization tested for parameters across domains. Achieves reliable simultaneous estimation of at least 2 growth parameters $\{(D, \rho), (D, \lambda), (\rho, \lambda)\}$ on synthetic data.

Image-derivable information compatible with optimization approach.

Next Steps

Evaluation of **parameter estimation approach on patient-data**.

Evaluation of image-based initialisation using time-series data from rodent study where normal and tumor-bearing states are known.

Explore **different model specifications**, particularly

- stress-modulated diffusivity / cell motility
- isotropic Ogden material model [4]

Further Information

Software will be available on project website soon!

GlimS
Glioma mass-effect Simulator

www.glims.ch

Selected References

[1] R. K. Jain et al. "The Role of Mechanical Forces in Tumor Growth and Therapy". In: *Annu. Rev. Biomed. Eng.* 16.1 (07/11/2014), pp. 321–346.
[2] P. Farrell et al. "Automated Derivation of the Adjoint of High-Level Transient Finite Element Programs". In: *SIAM Journal on Scientific Computing* 35.4 (2013), pp. C369–C393.
[3] *Advanced Normalization Tools (ANTs)*. https://github.com/ANTsX/ANTs.
[4] S. Budday et al. "Mechanical Characterization of Human Brain Tissue". In: *Acta Biomaterialia* 48 (01/2017), pp. 319–340.
[5] D. Abler et al. "Evaluation of a Mechanically Coupled Reaction–Diffusion Model for Macroscopic Brain Tumor Growth". In: *Computer Methods in Biomechanics and Biomedical Engineering*. Ed. by A. Gefen et al. Cham: Springer International Publishing, 2018, pp. 57–64.
[6] C. Hogea et al. "An Image-Driven Parameter Estimation Problem for a Reaction–diffusion Glioma Growth Model with Mass Effects". In: *Journal of Mathematical Biology* 56.6 (06/2008), pp. 793–825.
[7] A. Gholami et al. "An Inverse Problem Formulation for Parameter Estimation of a Reaction–diffusion Model of Low Grade Gliomas". In: *J. Math. Biol.* 72 (1-2 01/2016), pp. 409–433.
[8] M. S. Alnæs et al. "The FEniCS Project Version 1.5". In: *Archive of Numerical Software* 3.100 (2015).

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