A MECHANICAL AND COMPUTATIONAL MODEL FOR PATIENT-SPECIFIC BRAIN TUMOUR GROWTH

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OUTLINE OF THE PROJECT

We develop a mathematical model to study the growth of Glioblastoma Multiforme, which is a very aggressive type of brain cancer. Using the well-established framework of Continuum Mechanics, our model is able to describe the proliferation of the tumour and to account for its mechanical impact on the surrounding healthy tissue and for the anisotropy of the brain. Moreover, patient-specific data reconstructed from medical imaging are included in our simulations, in order to reproduce the brain environment *in silico* as realistically as possible. The computational meshes based on medical data are reconstructed using dedicated C++ and Python libraries, while numerical simulations of the model are performed using the Python-based interface FEniCS.

Keywords: Glioblastoma Multiforme, mathematical modeling, cancer growth, patient-specific data, medical imaging.

GLIOBLASTOMA MULTIFORME

- Glioblastoma Multiforme (GBM) is a highly aggressive and malignant type of brain tumour, which is able to deeply invade the surrounding tissue.

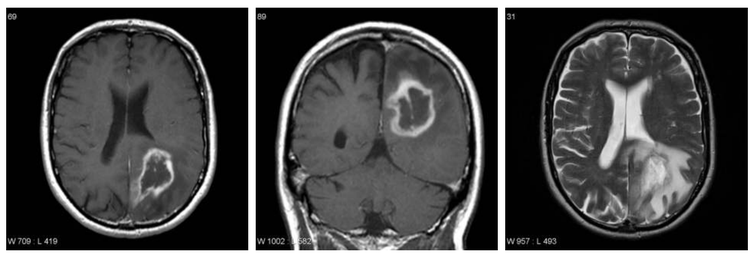
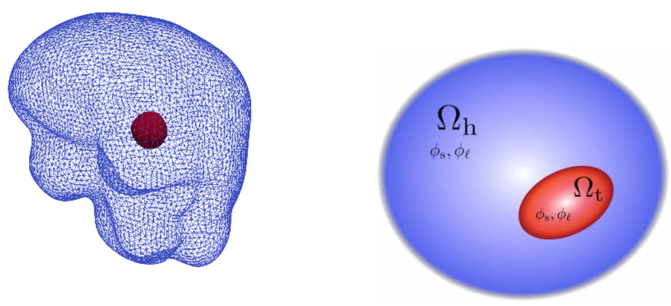


Figure 1: Magnetic Resonance Imaging of Glioblastoma.

- Even with a complete treatment (neurosurgery, chemotherapy and radiotherapy) the median survival time is about 10-16 months.
- Mathematical models and simulations can provide powerful tools to support decisions from physicians.
- It is clinically important to evaluate the *mechanical impact* of GBM on the soft healthy tissue, to realistically reproduce its proliferation inside the brain.

BRAIN MODELING

- We consider the brain as a closed, saturated biphasic mixture, comprising a solid and a fluid phase.
  - Solid phase: healthy and diseased cells $\rightarrow \phi_s$, $\mathbf{u}_s$ $\mathbf{v}_s$
  - Fluid phase: interstitial brain fluid, blood and nutrients $\rightarrow \phi_\ell$, $\mathbf{v}_\ell$
- The region occupied by the tumour $\Omega_t(t)$ is separated from the host tissue $\Omega_h(t)$ by a steep mollification of an indicator function H_{Ω_t}.
- This approach allows to distinguish the proliferating tumour from the rest of the tissue, accounting for the porous nature of the brain.



- Coherently with experimental results, we model brain tissue as a nonlinear elastic soft material.
- The anisotropy due to the presence of nerve fibers does not influence the mechanical response, but only the diffusion of substances and fluid movement inside the brain.

MATHEMATICAL MODEL

- Variables of the model:
  - ϕ_s, ϕ_ℓ: volume fractions of solid and fluid phase;
  - $\mathbf{u}_s$: displacement of the solid phase;
  - p: fluid pressure;
  - c_n: nutrients concentration.
- Mass balance equations:

$$\partial_t \phi_s + \nabla \cdot (\phi_s \mathbf{v}_s) = \Gamma_s(\phi_s, c_n, \Sigma)\, H_{\Omega_t}\,,$$

$$\partial_t \phi_\ell + \nabla \cdot (\phi_\ell \mathbf{v}_\ell) = -\Gamma_s(\phi_s, c_n, \Sigma)\, H_{\Omega_t},$$

$$\phi_\ell \partial_t c_n + \phi_\ell \mathbf{v}_\ell \cdot \nabla c_n = \nabla \cdot (\phi_\ell \mathbb{D} \nabla c_n) + G(\phi_s, \phi_\ell, c_n)\,,$$

$$G(\phi_s, \phi_\ell, c_n) = \left[-\zeta \phi_\ell \phi_s c_n + S_n \phi_\ell (1 - c_n)\right] H_{\Omega_t}\,,$$

$$\phi_\ell + \phi_s = 1\,.$$

- Momentum balance equations:

$$\phi_\ell(\mathbf{v}_\ell - \mathbf{v}_s) = -\frac{\mathbb{K}(J_e)}{\mu}\nabla p\,, \qquad -\nabla p + \nabla \cdot \mathbb{T}_s = \mathbf{0}\,.$$

- Constitutive equations:

$$\widehat{\mathcal{W}}_{sn}(\overline{\mathbb{C}}_e) = \frac{1}{2}\mu_1\left(\mathrm{I}_{\overline{\mathbb{C}}_e} - 3\right) + \frac{1}{2}\mu_2\left(\mathrm{II}_{\overline{\mathbb{C}}_e} - 3\right)\,, \quad \overline{\mathbb{C}}_e := J_e^{-2/3}\mathbb{C}_e,$$

$$\mu_\alpha = \begin{cases} \mu_{\alpha t}, & x \in \Omega_t \\ \mu_{\alpha h}, & x \in \Omega_h \end{cases}\,, \qquad \mathbb{T}_s = 2J_e^{-1}\mathbb{F}_e \frac{\partial \widehat{\mathcal{W}}_{sn}}{\partial \mathbb{C}_e}\mathbb{F}_e^T$$

$$\mathbb{K}(J_e) = k(J_e)\,\mathbb{A}\,,$$

$$\Gamma_s(\phi_s, c_n, \Sigma) = \nu \phi_s(\phi_{max} - \phi_s)(c_n - c_0)_+ \left(1 - \frac{\delta_1 \Sigma}{\Sigma + \delta_2}\right),$$

$$\Sigma := \left(-\frac{1}{3}\mathrm{tr}(\mathbb{T}_s)\right)_+\,.$$

- The function Σ describes tumour growth inhibition due to compression.
- The tensor of preferential directions $\mathbb{A}$ and the diffusion tensor $\mathbb{D}$ are reconstructed from medical imaging data.

PATIENT-SPECIFIC DATA

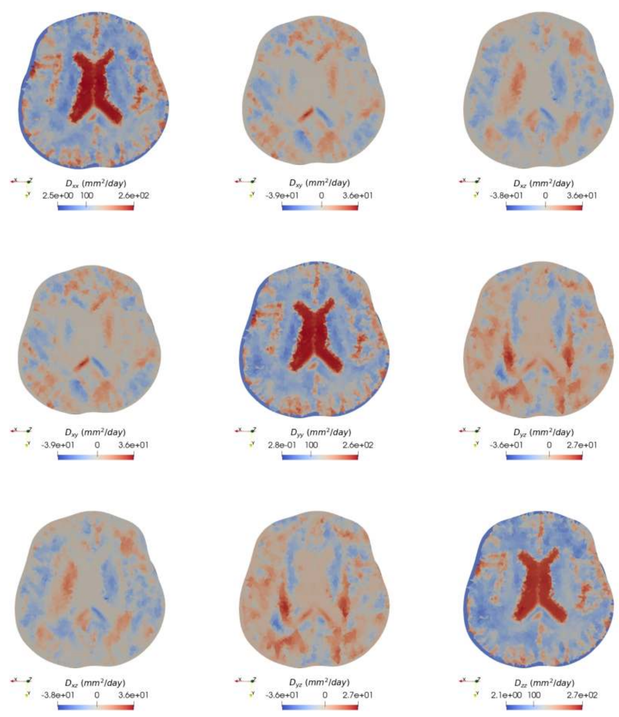
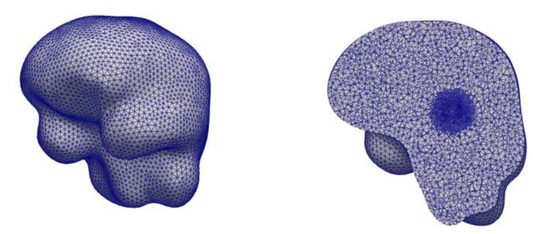


Table 1: Components of the diffusion tensor $\mathbb{D}$ reconstructed from imaging data, sliced along a plane. The highest values for diffusion coefficients are coloured in red.

- Patient-specific data are incorporated into the model by computationally building the tensors $\mathbb{D}$ and $\mathbb{A}$.
- Starting from Diffusion Tensor Imaging or Magnetic Resonance Imaging data, a mesh for each independent component of the tensors is built.

IMPLEMENTATION

- We derive a weak formulation of the mathematical model, in order to solve it using the Finite Element Method.
- Spatial discretization of all the equations using $\mathbb{P}_1$ tetrahedral elements.
- For medical imaging processing, segmentation and alignment, the software libraries FSL, VTMK and the ANIMA toolbox are employed.
- The computational mesh is built using imaging data, so as to work on a realistic brain geometry. It is also properly refined in the tumour region: all these operations are carried out using the C++ library TetGen.



- The code then is implemented using the open source platform FEniCS $\rightarrow$ high-level Python interface for solving PDEs using the Finite Element Method.

NUMERICAL RESULTS

- First case: no inhibition due to stress and compression, the tumour is free to proliferate.
- The amount of unnatural displacement induced by the growth of GBM is about 3.3 mm.
- Evident anisotropy: the growth is not uniform along all directions.

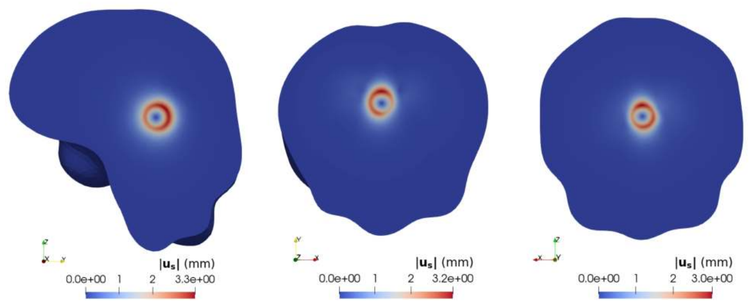


Figure 2: Displacement magnitude after 45 days of simulation, no inhibition case.

- Second case: stress-inhibited. Compression slows down the growth of the tumour, as in experiments.
- The displacement is about a half of the previous case.

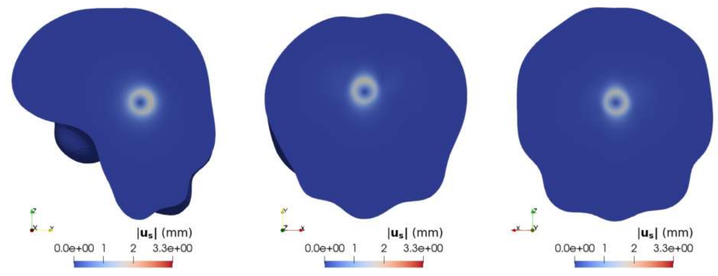


Figure 3: Displacement magnitude after 45 days of simulation, stess-inhibited case.

- The evolution of the tumour volume in time is strongly affected by the amount of compression and stress.

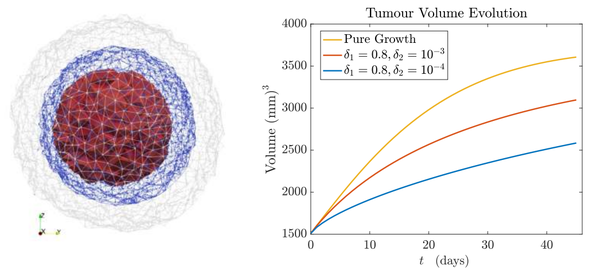


Figure 4: Left: initial tumour volume (red), pure growth case (grey), inhibited case (blue). Right: evolution of tumour volume in time.

REFERENCES

[1] M.C. Colombo et al. Towards the personalized treatment of glioblastoma: integrating patient-specific clinical data in a continuous mechanical model. *PLoS ONE*, 2015.

[2] A. Agosti et al. A personalized mathematical tool for neuro-oncology: A clinical case study. *IJNLM*, 2018.

CONCLUSIONS & FUTURE DEVELOPMENTS

The main purpose of this work is to make a step forward in Glioblastoma Multiforme growth modeling, by proposing a mechanical model able to account for elastic deformations of brain tissue and to computationally include patient-specific data. Possible future developments may include a validation of the model and the simulations of resection, together with the subsequent reorganization of the healthy tissue.