CHARACTERIZING BIOMECHANICAL TUMOR GROWTH

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Tumor Mass-Effect in GBM

Glioblastoma (GBM) is the most frequent malignant brain tumor in adults. Its rapid invasive growth can cause healthy-tissue deformation, so-called tumor *mass-effect*, resulting in midline shift or herniation. Solid stress in brain tumors leads to neuronal loss and neurological dysfunction [1], and elevated tumor mass-effect is associated to poor prognosis in GBM patients [2]. Despite presentation with similar imaging volumes, GBM can cause varying amounts of tissue deformation [2]. To investigate the relation between growth characteristics, mass-effect and manifestation on clinical imaging, we are developing a framework for characterizing mechanically-coupled GBM growth.

Mathematical Models of GBM Growth

Our model [3] captures the dominant aspects of macroscopic GBM growth: *Invasive growth* of GBM is modelled phenomenologically as a reaction-diffusion process with normalized cancer cell concentration $c(x,t)$, diffusion tensor $\widehat{\boldsymbol{D}}(x)$, and logistic growth with proliferation rate ρ(x):

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

To simulate the *tissue-displacing mass-effect* of the growing tumor, the domain is modeled as elastic continuum in which the actual deformation $\boldsymbol{u}(x,t)$ of a tissue element is given by the combination of growth-induced strains $\hat{\boldsymbol{\varepsilon}}^{growth}$ and strains associated with the elastic response of the tissue. We assume a linear constitutive relation between mechanical stress and strain, as well as isotropic material properties. Additionally, we postulate a linear coupling between tumor concentration and growth-induced strain with isotropic coupling strength λ:

$$\hat{\boldsymbol{\varepsilon}}^{growth}(c) = \hat{\boldsymbol{\lambda}}\, c = \lambda\, \mathbb{I}\, c \qquad (2)$$

PDE-constrained Optimization Problem

The problem of identifying growth parameters (D, ρ, λ), can be framed as a PDE-constrained optimization problem in which we seek the set of parameters $\boldsymbol{p_{opt}}$ that minimize an objective functional of the form

$$J = \|c(\boldsymbol{x}, t_k) - c_k^*(\boldsymbol{x})\| + \|\boldsymbol{u}(\boldsymbol{x}, t_k) - \boldsymbol{u}_k^*(\boldsymbol{x})\| \qquad (3)$$

where $c_k^*(\boldsymbol{x})$ and $\boldsymbol{u}_k^*(\boldsymbol{x})$ are estimates of tumor cell concentration and tissue displacement fields at observation time point k. Simulated tumor cell concentration $c(\boldsymbol{x}, t_k)$ and tissue deformation $\boldsymbol{u}(\boldsymbol{x}, t_k)$ fields at the corresponding simulation time step t_k are constrained by the forward model of tumor growth.

We use the adjoint method to efficiently find solutions to the optimization problem for multiple model parameters $\boldsymbol{p}$. The mechanically-coupled reaction diffusion model is implemented in *FEniCS* [4], a finite-element library, and uses the *dolfin-adjoint* [5] library for deriving and solving the adjoint equations.

Parameter Estimation

Fig. 1 illustrates forward simulation and parameter estimation in a 2D model of the human brain with separate subdomains for white matter (WM), grey matter (GM), and cerebrospinal fluid (CSF) and distinct isotropic growth $\boldsymbol{p} = \{D_{WM}, D_{GM}, \rho_{WM}, \rho_{GM}, \lambda\}$ and mechanical tissue parameters. Using the objective functional Eq. (3) with concentration and displacement fields from the final time point of the forward simulation as optimization target, we recovered the parameters of the forward simulation by adjoint optimization. Differences between target (based on $\boldsymbol{p}$) and estimated growth configuration (based on $\boldsymbol{p}_{opt}$) are of order 10^{-5}.

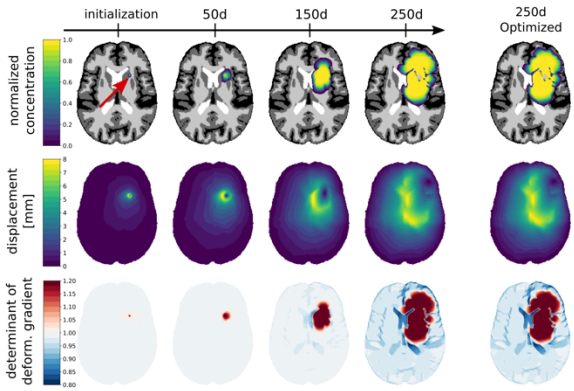

Figure 1: Left: Tumor evolution from seed (red arrow) with reference growth parameters $\boldsymbol{p}$. Right: Predicted growth configuration based on $\boldsymbol{p_{opt}}$ from adjoint optimization.

Application to Clinical Imaging Data

The current developments focus on evaluating the performance of this approach in 3D, and in the presence of noisy and partial observations. Strategy and feasibility for characterizing GBM growth phenotypes from clinical imaging will be discussed.

References

1. Seano et al, Nat Biomed Eng, 2019.
2. Steed et al, Sci. Rep, 8 (1):2827, 2017.
3. Abler et al, In: Gefen, Weihs (eds) Computer Methods in Biomechanics and Biomedical Engineering, 57-64, 2018
4. M. Alnæs et al, "The FEniCS Project Version 1.5"
5. Farrell et al, SIAM J. Sci. Comput, 35 (4):C369–C393, 2013.

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