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Simulating Brain Tumour Mass-Effect

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Glioblastoma (GBM) is the most frequent malignant brain tumour in adults [1]. Its growth is characterized by infiltration of surrounding healthy tissue, and the formation of a necrotic core. GBM presents with varying degree of mass-effect which results in healthy-tissue deformation, midline shift or herniation. Biomechanical forces, such as those resulting from displacive tumour growth, shape the tumour environment, contribute to tumour progression [2] and may affect treatment response and outcome.

To investigate the role of tumour mass-effect for tumour evolution, we have previously developed a mechanically-coupled reaction-diffusion model [3] that captures three dominant aspects of macroscopic GBM growth: (a) tumour cell proliferation, (b) the diffuse invasion of the growing tumour into surrounding healthy tissue, and (c) the resulting mass effect.

Here we present an implementation of this model in FENICS and first steps towards an image-based optimization approach, based on dolphin-adjoint [4], to estimate patient-specific parameters from clinical magnetic-resonance imaging (MRI).

Forward Problem We model the invasive growth of glioma phenomenologically as as a reaction-diffusion process:

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

with normalized cancer cell concentration $c\,(\boldsymbol{r}, t)$ and diffusion tensor $\hat{\boldsymbol{D}} = \hat{\boldsymbol{D}}\,(\boldsymbol{r})$. Tumour cell proliferation is assumed to follow logistic growth with proliferation rate ρ.

The tissue-displacing mass-effect of the growing tumour is introduced by linking the local concentration of tumour cells to a volumetric increase of the affected brain tissue. This volumetric increase is modeled by a growth-induced strain component $\hat{\boldsymbol{\epsilon}}^{\,\mathrm{growth}}(c\,)$, so that

$$\hat{\boldsymbol{\epsilon}}^{\,\mathrm{total}}(\boldsymbol{u}\,, c\,) = \hat{\boldsymbol{\epsilon}}^{\,\mathrm{elastic}}(\boldsymbol{u}\,) + \hat{\boldsymbol{\epsilon}}^{\,\mathrm{growth}}(c\,) \ , \tag{2}$$

where displacements $\boldsymbol{u}$ are obtained from solving the linear-momentum equilibrium equation.

Our current implementation assumes a linear constitutive relation between stress $\hat{\boldsymbol{\sigma}}\,(\boldsymbol{u}\,)$ and strain $\hat{\boldsymbol{\epsilon}}^{\,\mathrm{total}}(\boldsymbol{u}\,)$ and is limited to isotropic growth and tissue characteristics. The mechanical model is therefore fully characterised by Young's modulus E and Poisson ratio ν, and $\hat{\boldsymbol{D}} \equiv D\,\mathbb{1}$. Additionally, we assume a linear coupling between tumour cell concentration and growth-induced strain with isotropic coupling strength λ:

$$\hat{\boldsymbol{\epsilon}}^{\,\mathrm{growth}}(c\,) = \hat{\boldsymbol{\lambda}}\, c \ = \lambda\, \mathbb{1}\, c \ . \tag{3}$$

The simulation domain is composed of different components with distinct parameters D_i, E_i, ν_i for $i \in \{$white matter (WM), grey matter (GM), CSF, ventricles, tumour$\}$. Proliferation rate ρ takes a global value.

Tumour cells are prevented from crossing the interface between brain tissue (WM, GM, tumour) and cerebro-spinal fluid (CSF, ventricles) by imposing zero-flux von-Neuman boundary conditions. The displacement constraint imposed by the rigid skull is approximated by zero-displacement Dirichlet boundary conditions at the interface between skull and CSF.

We solved the fully coupled model in 2D using FENICS' MixedElement formulation. The simulation domain was defined by an atlas of healthy brain anatomy or patient-specific tumour segmentations derived from magnetic-resonance imaging (MRI), fig. 1 Tumour growth was initiated from a Gaussian initial tumour cell distribution $c\,(\boldsymbol{r}, t = 0)$.

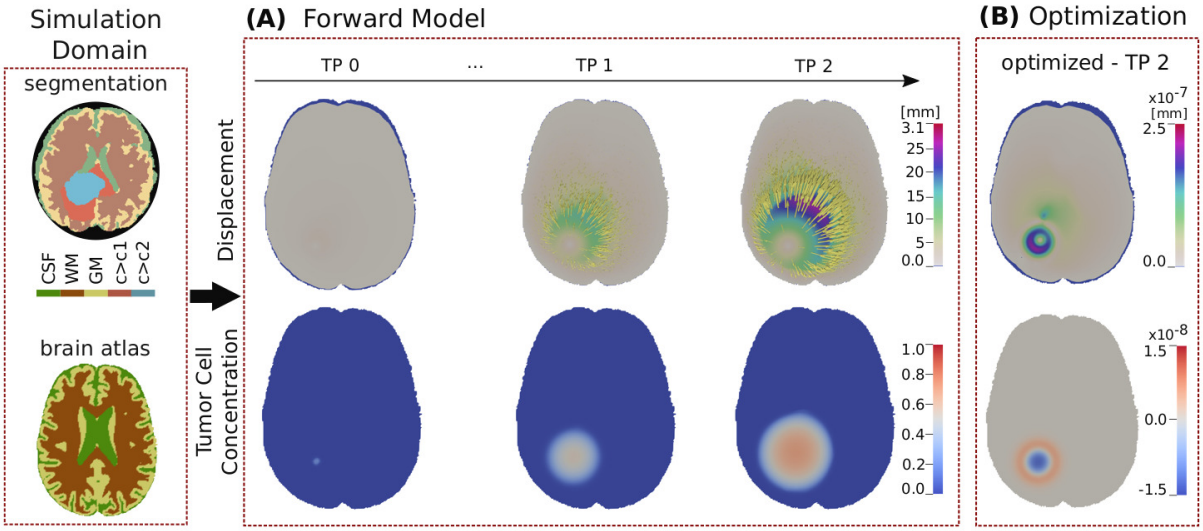

Figure 1: Solution of forward and inverse model over 2D brain atlas. (A) Tumour growth was initiated from Gaussian tumour cell distribution $c\,(\boldsymbol{r}, t = 0)$ (TP 0) and simulated until later time point (TP 2) for a set of patient-specific growth parameters (D, ρ, λ). The resulting synthetic data was used to estimate two (of three) growth parameters $\{(D, \rho), (D, \lambda), (\rho, \lambda)\}$ by solving the inverse problem. (B) shows the mismatch between solutions of the forward model using the original and the estimated parameter set, respectively.

Inverse Problem The inverse problem is formulated as a PDE constrained optimization problem that aims at minimizing the difference between observed and predicted tumour cell distribution and induced displacements. Solution of the inverse problem relies on the adjoint method and FENICS dolphin-adjoint [4].

We tested the parameter estimation approach on synthetic data generated by solving the forward problem on a brain atlas, fig. 1. We obtained satisfying results for simultaneous estimation of two parameters $\{(D, \rho), (D, \lambda), (\rho, \lambda)\}$ and predefined initial conditions.

Future Work We will focus on refining the parameter estimation approach to find optimal solutions of the inverse problem based on partial observations from MRI data, such as displacement fields estimated from healthy tissue deformation or threshold-based approximations of tumour cell distribution. We also plan to extend the code to support simulations in 3D.

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References

[1] Damien Ricard, Ahmed Idbaih, François Ducray, Marion Lahutte, Khê Hoang-Xuan, and Jean-Yves Delattre. Primary brain tumours in adults. *The Lancet*, 379(9830):1984–1996, May 2012.

[2] Rakesh K. Jain, John D. Martin, and Triantafyllos Stylianopoulos. The Role of Mechanical Forces in Tumor Growth and Therapy. *Annual Review of Biomedical Engineering*, 16(1):321–346, July 2014.

[3] Daniel Abler and Philippe Büchler. Evaluation of a Mechanically Coupled Reaction–Diffusion Model for Macroscopic Brain Tumor Growth. In Amit Gefen and Daphne Weihs, editors, *Computer Methods in Biomechanics and Biomedical Engineering*, pages 57–64. Springer International Publishing, Cham, 2018.

[4] P. E. Farrell, D. A. Ham, S. W. Funke, and M. E. Rognes. Automated Derivation of the Adjoint of High-Level Transient Finite Element Programs. *SIAM Journal on Scientific Computing*, 35(4):C369–C393, January 2013.