

Physical forces & tumor growth

Rapid proliferation of cancer cells introduces strains in the tumor micro-environment which pushes against and deforms surrounding normal tissue. This leads to the accumulation of solid stress, mechanical forces between the solid components of the tissue. **Elevated solid stress** can drive tumors to **more aggressive phenotypes** and compromise therapeutic outcome [1]:

- Cell compression alters gene expression, and cellular behavior.
- Compression of blood and lymphatic vessels reduces delivery of oxygen, nutrients, and treatment agents.

Solid stress also affects healthy tissue. For example, it causes neuronal loss in brain tissue [2], and is linked to neurological deficits and reduced survival in patients with glioblastoma (GBM) [3], the most common malignant primary brain tumor in adults.

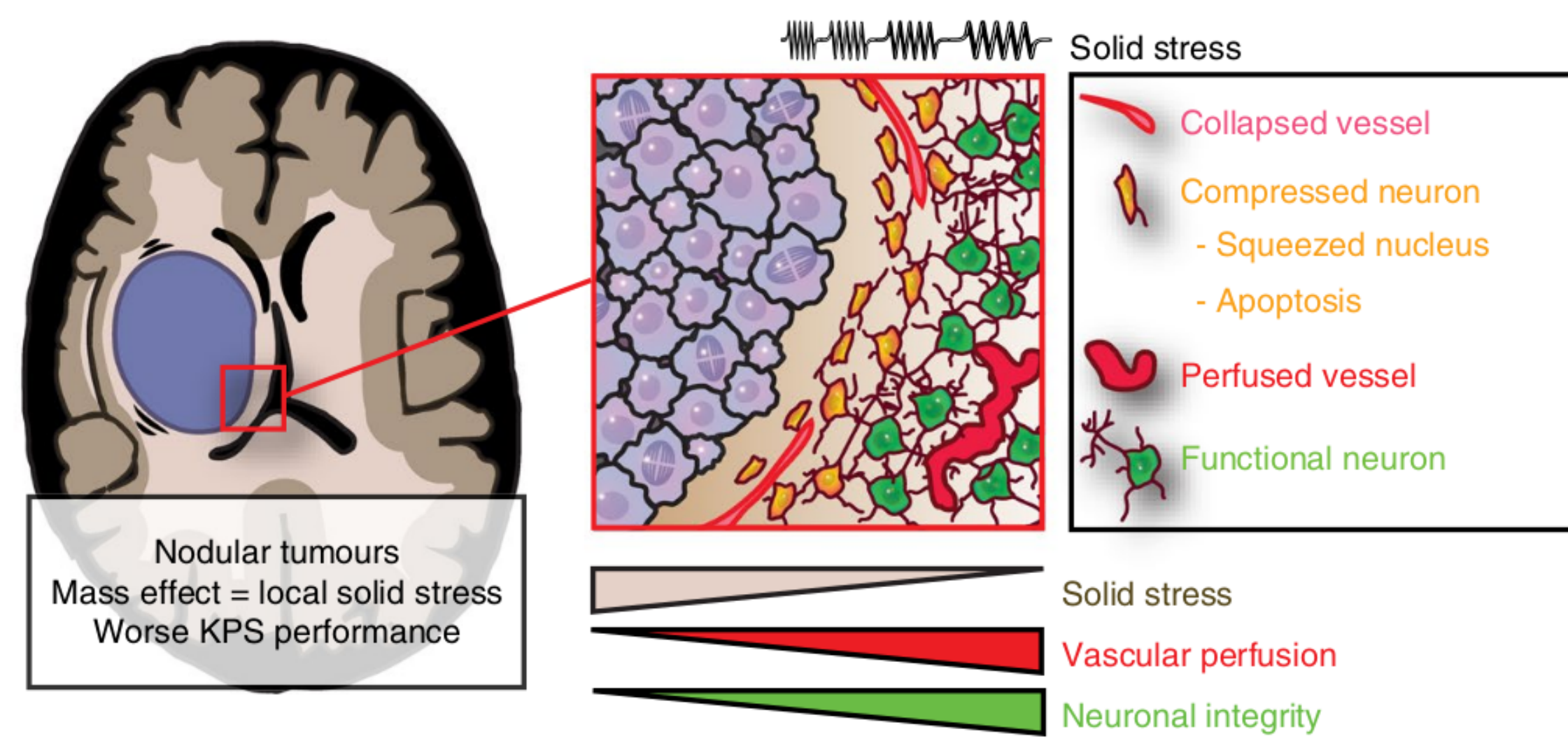


Figure 1: Tumor-induced solid stress and physiological consequences. Adapted from [2].

Mechanical solid stress in tumor growth models

We identified over 50 literature contributions of macroscopic spatial tumor growth models that include aspects of tumor-induced solid stress and their biological or physiological consequences. These studies represent a **wide range of modeling approaches and purposes**, as well as **evaluation strategies**.

Here we distinguish different approaches and extent of evaluation:

- **Qualitative:** Qualitative evaluation of model behavior.
- **Calibration (synthetic/data):** Quantitative target metric and optimization approach, tested against synthetic/real imaging data.
- **Prediction:** Model calibration and prediction against longitudinal data set.

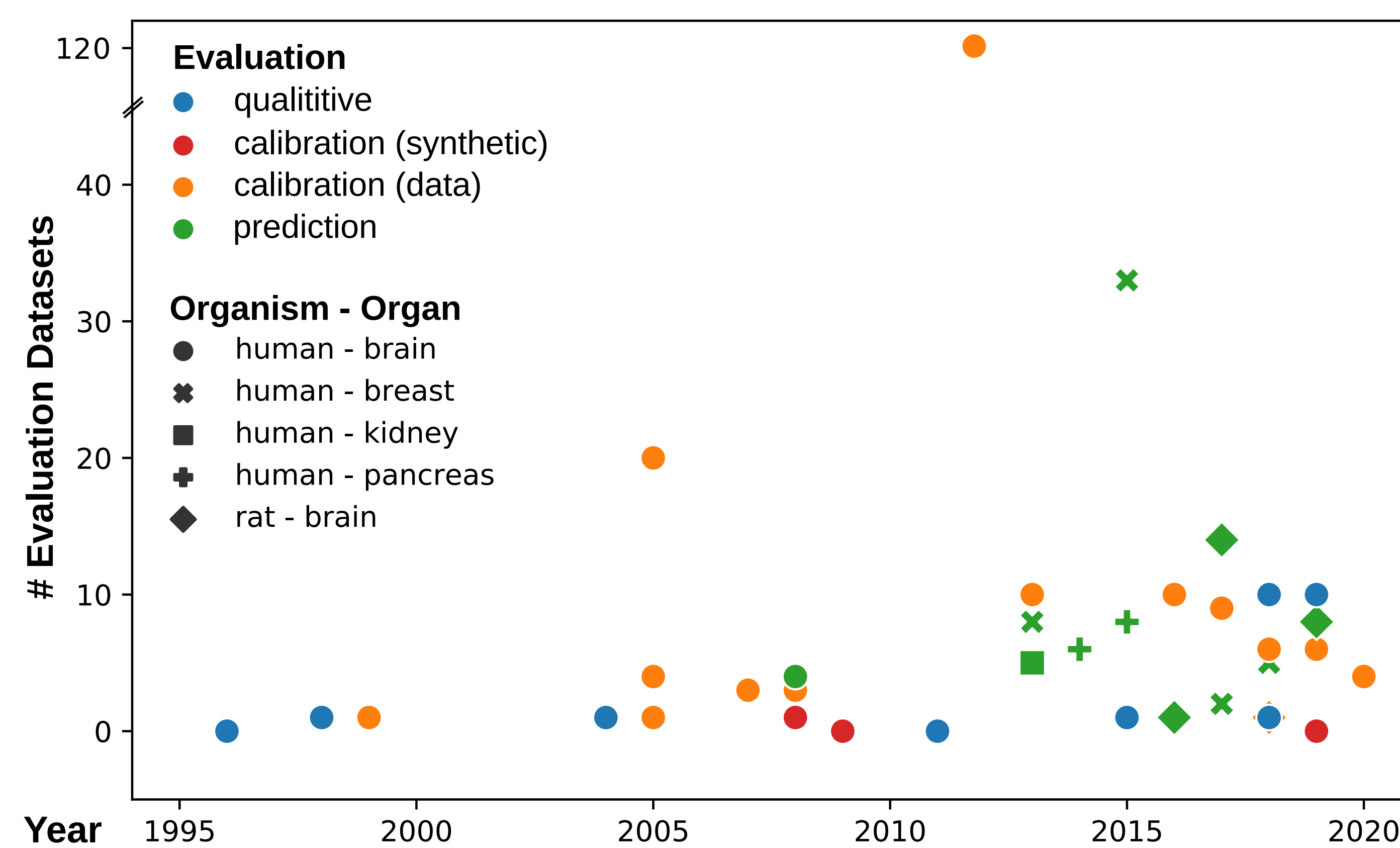


Figure 2: Overview of mechanically-coupled tumor growth models, and their degree of evaluation.

Continuum mechanics – Elasticity

When an elastic material is deformed, it experiences internal resistance to the deformation and restores its original shape when the deforming force is no longer applied. The elastic behavior of a material is described by the relation between strain $\hat{\epsilon}$ [relative deformation] and stress $\hat{\sigma}$ [F/L^2] and defined by empirically determined constitutive models. About **3/4 of reviewed models** are built on the assumption of **linear-elasticity**; the remaining cases use (non-linear) hyper-elastic stress-strain relationships, such as Neo-Hookean and Ogden models.

Linear-momentum equilibrium equation with displacement \mathbf{u} and bodyforce \mathbf{f} [F/L^3]:

$$\nabla \cdot \hat{\sigma}(\mathbf{u}) + \mathbf{f}(\mathbf{x}) = 0. \quad (1)$$

Modeling tumor-induced mechanical impact

Tumor growth affects the mechanical state of the tumor micro-environment. The constitutive equation of tumor growth (e.g. reaction-diffusion model) can be coupled to eq. (1) by relating tumor cell concentration c (density, fraction, number) to:

- **Tumor-induced pressure** $p_T(c) = \tilde{\lambda} c$ or **force** $\mathbf{f}_T = \tilde{\lambda} \nabla c$:
Several choices for the coupling $\tilde{\lambda}$ are employed, of the general form

$$\tilde{\lambda} = \lambda f(c, \kappa_i), \quad (2)$$

with linear coupling coefficient λ and (optional) (non-)linear function f . Assuming c to be unit-free, $\tilde{\lambda}$ has dimensions [F/L^2].

- **Tumor-induced strain** $\hat{\epsilon}_g = \tilde{\lambda} c$:

The deformation of a body can be decomposed into elastic and growth-induced components. Under the infinitesimal strain assumption used in linear elasticity, total strain can be decomposed as $\hat{\epsilon}_{tot} = \hat{\epsilon}_e + \hat{\epsilon}_g$. Isotropic growth under this assumption is frequently modeled by a unit-free linear coupling coefficient λ :

$$\hat{\lambda} = \lambda \mathbb{I}. \quad (3)$$

Modeling mechanical feedback on tumor growth.

Experimental observations that the mechanical state of the tumor micro-environment affects growth are introduced in reaction-diffusion based cancer growth models by:

- Exponential **damping of cell motility** by van-mises stress σ_{VM} , e.g. [4, 5, 6, 7]

$$D = D_0 \exp^{-\gamma \sigma_{VM}} \quad (4)$$

- Exponential **damping of growth rate** by van-mises stress [5]

$$\rho = \rho_0 \exp^{-\gamma \sigma_{VM}} \quad (5)$$

Benefits of modeling tissue/tumor mechanics.

Accounting for mechanical effects of tumor growth (with and without out feedback on growth mechanism) improves:

- **Approximation of tumor / healthy-tissue shape** (e.g. overlap measures): Ability to reproduce and capture tumor shape, and tumor-induced healthy tissue deformation. Typically performed against single time-point imaging and in context of image-registration and atlas-based segmentation, e.g. [8, 9, 10]. More recent work aims to characterize mechanical growth phenotypes by fitting mechanically-coupled growth models to patient imaging data [11, 12].
- **Prediction of tumor burden** (e.g. volume, tumor cell number): Slight improvement of predicted tumor volume when accounting for tumor-induced pressure/force by eq. (2) [13]. Mechanically constrained diffusivity, as in eq. (4), has been shown to improve prediction of global measures of tumor burden [4, 7, 6], such as total tumor cellularity.

Example Application: Characterization of GBM growth

Evaluation of mechanically-coupled GBM tumor growth model against single time-point clinical images. Characterization of GBM growth phenotypes.

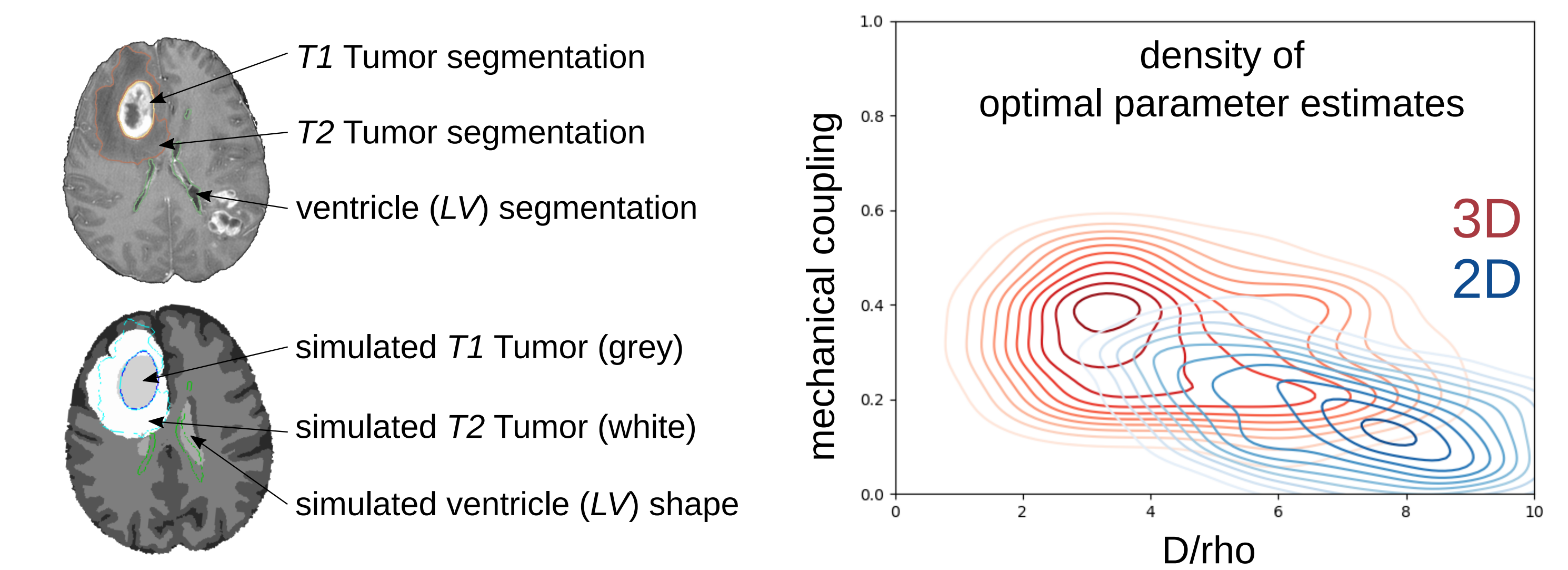


Figure 3: Top left: 2D slice of MR patient image with tumor and ventricle segmentation. Bottom left: Simulated (primary) tumor and ventricle deformation based on best parameter estimate. Right: density distribution of best parameter estimates inferred from 2D / 3D clinical images.

Challenges & Opportunities

- Additional modeling choices: constitutive mechanical model & parameters
- Mechanical boundary conditions often unclear (e.g. CSF pressure)
- Increased computational cost
- Data limitations (e.g. lack of “healthy” anatomical reference)
- Direct validation of predicted tumor-induced mechanical stresses very difficult.
- Ability of mechanically-coupled models to capture tumor/tissue shapes can likely be improved by more advanced growth models and (anisotropic) growth modulation.
- Information about tumor-induced deformation and mechanical stresses may further improve integration of multiparametric imaging data and prediction.

Project Information



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Selected References

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