Modeling Tumor Growth Biomechanics — Approaches, Challenges & Opportunities

Daniel Abler[1, 2], Philippe Büchler[1], Russell Rockne[2]

[1]University of Bern, ARTORG Center for Biomedical Engineering Research, Computational Bioengineering; [2]City of Hope, Department of Computational and Quantitative Medicine, Mathematical Oncology

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.

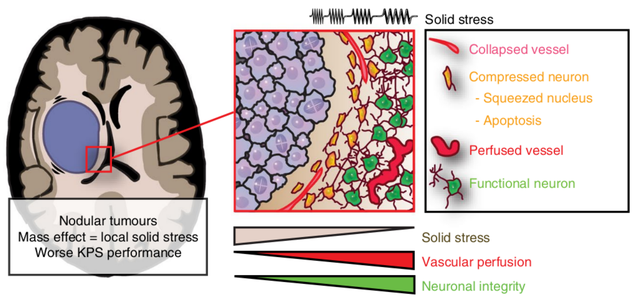

Figure 1: Tumor-induced solid stress and physiological consequences. Adapted from [2].

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.

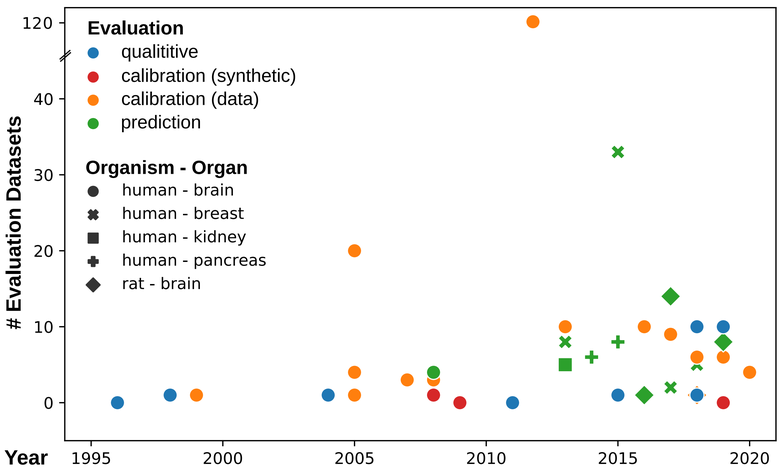

Figure 2: Overview of mechanically-coupled tumor growth models, and their degree of evaluation.

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 $\hat{\boldsymbol{\epsilon}}$ [relative deformation] and stress $\hat{\boldsymbol{\sigma}}$ $[F/L^2]$ 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 $\boldsymbol{u}$ and bodyforce $\boldsymbol{f}$ $[F/L^3]$:

$$\boldsymbol{\nabla} \cdot \hat{\boldsymbol{\sigma}}(\boldsymbol{u}) + \boldsymbol{f}(\boldsymbol{x}) = 0\,. \tag{1}$$

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 $p_{\mathsf{T}}(c) = \tilde{\lambda}\, c$ or force $\boldsymbol{f}_{\mathsf{T}} = \tilde{\lambda}\, \boldsymbol{\nabla} c$:**
  Several choices for the coupling $\tilde{\lambda}$ are employed, of the general form
  $$\tilde{\lambda} = \lambda\, f(c, \kappa_i)\,, \tag{2}$$
  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 $\hat{\boldsymbol{\epsilon}}_g = \hat{\boldsymbol{\lambda}}\, c$:**
  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 $\hat{\boldsymbol{\epsilon}}_{tot} = \hat{\boldsymbol{\epsilon}}_e + \hat{\boldsymbol{\epsilon}}_g$. Isotropic growth under this assumption is frequently modeled by a unit-free linear coupling coefficient λ:
  $$\hat{\boldsymbol{\lambda}} = \lambda\, \mathbb{I}\,. \tag{3}$$

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]
  $$D = D_0\, \exp^{-\gamma\, \sigma_{\mathsf{VM}}} \tag{4}$$
- Exponential **damping of growth rate** by van-mises stress [5]
  $$\rho = \rho_0\, \exp^{-\gamma\, \sigma_{\mathsf{VM}}} \tag{5}$$

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 pressue/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.

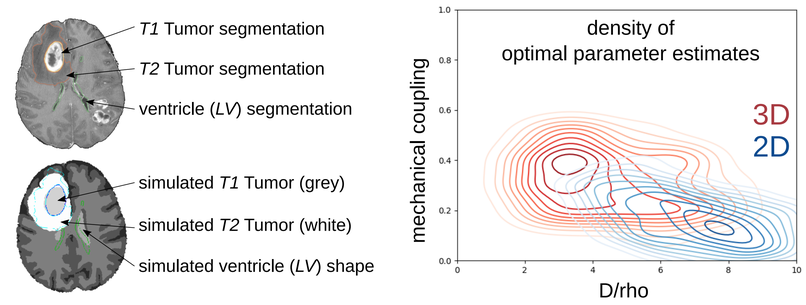

Figure 3: Top left: 2D slice of MR patient image with tumor and ventricle segmentation. Bottom left: Simulated (primary) tumor and ventricle deformation based on best parameter estimate. Right: density distribution of best parameter estimates inferred from 2D / 3D clinical images.

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

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 (2014), pp. 321–346.
[2] G. Seano et al. "Solid Stress in Brain Tumours Causes Neuronal Loss and Neurological Dysfunction and Can Be Reversed by Lithium." en. In: *Nature Biomedical Engineering* (2019).
[3] T. C. Steed et al. "Quantification of Glioblastoma Mass Effect by Lateral Ventricle Displacement." In: *Scientific Reports* 8.1 (2018).
[4] J. A. Weis et al. "Predicting the Response of Breast Cancer to Neoadjuvant Therapy Using a Mechanically Coupled Reaction-Diffusion Model." en. In: *Cancer Research* 75.22 (2015), pp. 4697–4707.
[5] E. A. B. F. Lima et al. "Selection, Calibration, and Validation of Models of Tumor Growth." en. In: *Mathematical Models and Methods in Applied Sciences* 26.12 (2016), pp. 2341–2368.
[6] A. M. Jarrett et al. "Incorporating Drug Delivery into an Imaging-Driven, Mechanics-Coupled Reaction Diffusion Model for Predicting the Response of Breast Cancer to Neoadjuvant Chemotherapy: Theory and Preliminary Clinical Results." In: *Physics in Medicine & Biology* 63.10 (2018), p. 105015.
[7] D. A. Hormuth et al. "A Mechanically Coupled ReactionDiffusion Model That Incorporates Intra-Tumoural Heterogeneity to Predict *in Vivo* Glioma Growth." en. In: *Journal of The Royal Society Interface* 14.128 (2017), p. 20161010.
[8] O. Clatz et al. "Realistic Simulation of the 3-D Growth of Brain Tumors in MR Images Coupling Diffusion with Biomechanical Deformation." In: *IEEE Transactions on Medical Imaging* 24.10 (2005), pp. 1334–1346.
[9] C. Hogea et al. "A Robust Framework for Soft Tissue Simulations with Application to Modeling Brain Tumor Mass Effect in 3D MR Images." In: *Physics in Medicine and Biology* 52.23 (2007), pp. 6893–6908.
[10] A. Gooya et al. "GLISTR: Glioma Image Segmentation and Registration." In: *IEEE Transactions on Medical Imaging* 31.10 (2012), pp. 1941–1954.
[11] D. Abler et al. "Towards Model-Based Characterization of Biomechanical Tumor Growth Phenotypes." In: *Mathematical and Computational Oncology*. Ed. by G. Bebis et al. Vol. 11826. Cham: Springer International Publishing, 2019, pp. 75–86.
[12] S. Subramanian et al. "Multiatlas Calibration of Biophysical Brain Tumor Growth Models with Mass Effect." In: *arXiv:2006.09932 [physics, q-bio]* (2020).
[13] X. Chen et al. "Kidney Tumor Growth Prediction by Coupling Reaction-Diffusion and Biomechanical Model." In: *IEEE Transactions on Biomedical Engineering* 60.1 (2013), pp. 169–173.

The research leading to these results has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement No 600841 and from European Unions Horizon 2020 research and innovation programme under the Marie Skodowska-Curie grant agreement No 753878.

Contact:
daniel.abler@artorg.unibe.ch