Comparison of imaging-based measures of tumor mass-effect

Evidence from a computational study.

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

[1]Beckman Research Institute, City of Hope; [2]University of Bern

Aim

This study **characterizes image-derivable measures of tumor mass-effect** by their ability to capture a tumor's mechanical impact:

- We use a mathematical model to simulate tumor growth and tumor-induced "mass effect".
- For given simulation parameters and growth location, we compute two measures of mass-effect from anatomical deformation during the growth process.
- We evaluate the ability of these measures to explain the tumors mechanical impact, quantified by the tumor-induced pressure on the skull.

Tumor Mass Effect

Tumor growth results in displacement of normal tissue, known as "mass-effect". This displacement is a major cause of neurologic injury [1], with brain herniation being the leading cause of death in high-grade glioma patients in the end-of-life care [2]. Elevated tumor mass-effect is also associated to poor prognosis in GBM [3, 4]. While **biomechanical forces** are known to **affect tumor growth and evolution** [5], **tumor mass-effect** is **poorly quantified** in clinical practice.

This study compares "midline shift" and "lateral ventricle displacement" as quantitative measures of tumor mass effect.

Midline Shift (MLs)

Objective quantification of **brain midline shift (MLs)** has been studied primarily in the context of traumatic brain injury. Either the septum pellucidum (SP) or the pineal gland are typically used as anatomic reference [6].
Here, we define MLs as the **maximum in-plane displacement of the SP** from the "ideal midline" (iML). MLs can be estimated from 2D axial imaging slices.

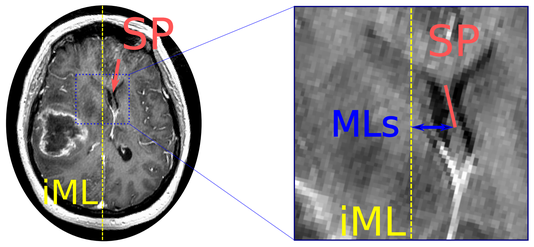


Figure 1: Midline shift (MLs) is often quantified by comparing the position of the septum pellucidum (SP) to an "ideal midline" (iML) assumed to be coplanar with the falx cerebri.

Lateral Ventricle Displacement (LVd)

"Lateral ventricle displacement" (LVd) [4] has recently been proposed as quantitative measure of tumor mass effect.
LVd is defined as the **distance between center-of-mass** (COM) **positions of** the **lateral ventricles** between an undeformed reference and the tumor-bearing anatomy. Quantification from imaging data involves image registration to estimate the patient-specific healthy reference state.

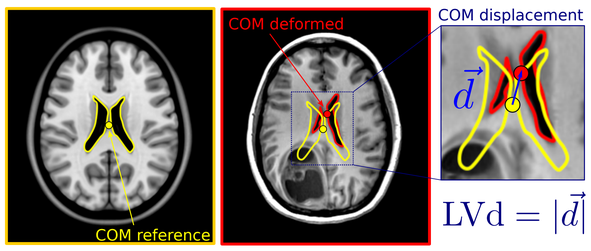


Figure 2: Lateral ventricle displacement (LVd) is distance between center of mass (COM) of (healthy) reference and tumor bearing configuration.

Computational Model

We used a computational model [7] to **simulate** the **macroscopic spatio-temporal evolution and mass-effect** of growing tumors. This enables us to control and objectively quantify "mass effect" for a range of simulation parameters and growth locations.

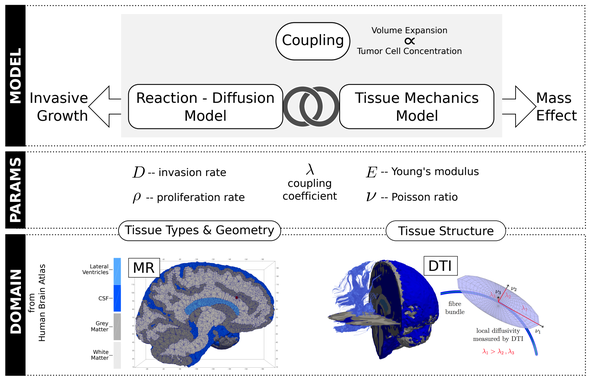


Figure 3: Mechanically-coupled Reaction-Diffusion Model.

Seed Locations

Tumors were seeded at **44 equidistant locations** in the right hemisphere of a 3D human brain atlas, fig. 4.

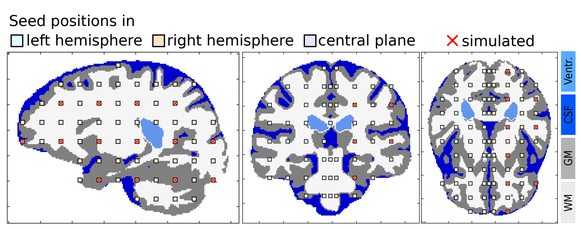


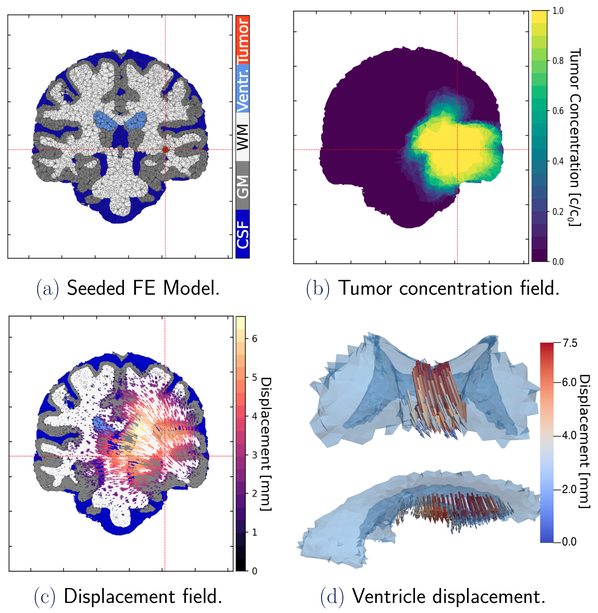
Figure 4: Equidistant seed positions (44 positions, 15 mm apart).

Simulation Parameters

- **Isotropic mechanical** and **growth properties** for tumor, brain white and grey matter. Linear elastic mechanical material model.
- Two levels of invasion rate D and proliferation rate ρ, corresponding to **diffuse** and **nodular growth**.
- Three levels of **mechanical coupling** strength $\lambda \in \{0.15, 0.30, 0.50\}$.

Growth Simulation

For each seed position and growth parametrization, a Finite Element Model was created (fig. 5a), and growth (fig. 5b) and tumor-induced displacements (fig. 5c) were simulated.



(a) Seeded FE Model. (b) Tumor concentration field. (c) Displacement field. (d) Ventricle displacement.

Figure 5: Simulated tumor growth and mass effect.

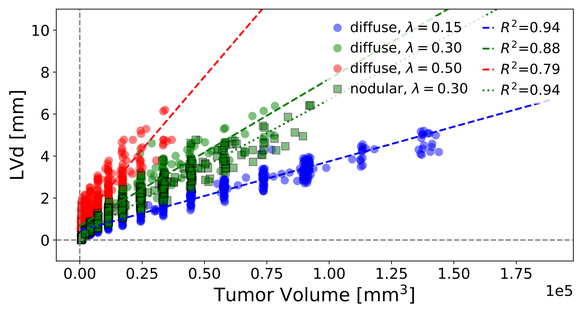
Comparison: LVd vs MLs

Simulation results were sampled at intervals of 2 mm equivalent tumor radius. **LVd**, **MLs**, **tumor volume**, **distance** between tumor center of mass and ventricles, and **tumor-induced pressure** were computed for each growth step, resulting in multiple data points for each combination of seed location and growth parameters.

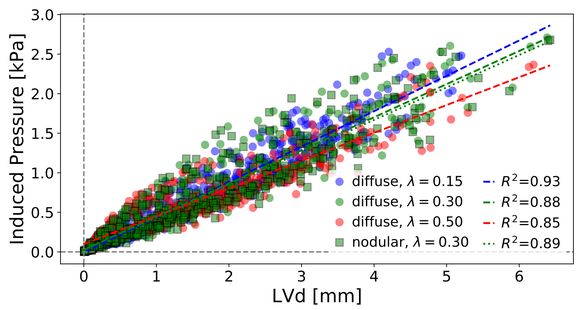
Figure 6a and fig. 7a compare the relation of LVd and MLs to tumor volume. Figure 6b and fig. 7b show tumor-induced pressure in function of LVd and MLs, respectively. Table 1 summarizes the findings from multiple regression analysis.

LVd

LVd is highly correlated with tumor volume, relatively insensitive to tumor position, and good predictor of tumor-induced pressure.



(a) LVd vs. tumor volume.

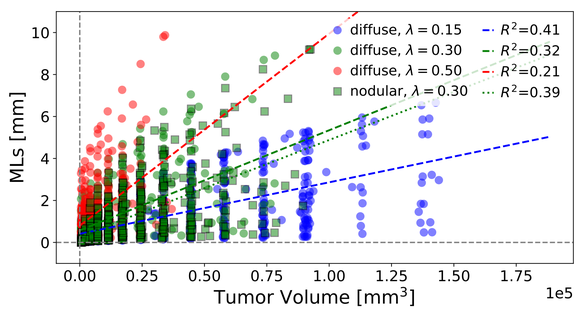


(b) Tumor-induced pressure vs. LVd.

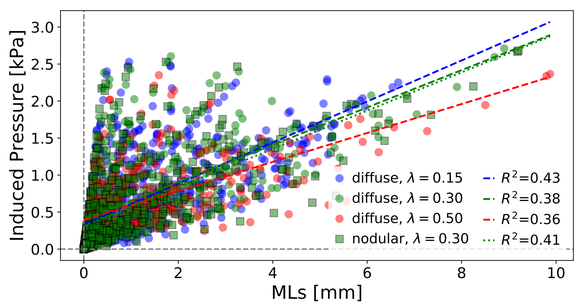
Figure 6: LVd vs. tumor size and tumor-induced pressure.

MLs

MLs varies considerably across different seed locations at same tumor volume. This leads to low predictive value of MLs for tumor-induced pressure.



(a) MLs vs. tumor volume.



(b) Tumor-induced pressure vs. MLs.

Figure 7: MLs vs. tumor size and tumor-induced pressure.

Dep. Variable	Independant Variables	R^2
LVd	volume, controls	0.76
LVd	volume, distance, controls	0.77
induced pressure	LVd, controls	0.89
induced pressure	LVd, volume, controls	0.92
induced pressure	LVd, volume, distance, controls	0.95
MLs	volume, controls	0.30
MLs	volume, distance, controls	0.33
induced pressure	MLs, controls	0.40
induced pressure	MLs, volume, controls	0.83
induced pressure	MLs, volume, distance, controls	0.85

Table 1: Proportion of variance in dependent variable explained by linear model of independent variables. "Distance" is the distance between center-of-mass position of the tumor to the lateral ventricles; "controls" correspond to different model parametrizations.

Summary

Computational model of tumor mass effect

- Enables investigation of tumor growth and mass-effect for multiple tumor locations.
- Gives direct access to image-derivable deformation metrics and hard-to-measure physiological quantities.

Compared MLs and LVd

- LVd insensitive to tumor location; highly correlated with tumor volume ($R^2 = 0.76$) and good predictor of tumor-induced pressure in this model ($R^2 = 0.89$).
- MLs very sensitive to tumor location, poor predictor of tumor-induced pressure ($R^2 = 0.40$)

Limitations

- Model not accounting for physiological mechanisms that regulate intra-cranial pressure and would result in non-linear relation between tumor volume and induced pressure.
- Study compares "actual" LVd and MLs. Uncertainty in LVd and MLs estimates when extracted from imaging data are not accounted for.

Ongoing and Future Work

- Include uncertainty estimates for image-based LVd, MLs estimates in analysis.
- Calibrate tumor growth model to range of observed LVd values.

Quantification of pre-surgical LVd for 30 GBM patients at **Poster TMIC-19**!

Project Information

GlimS
Glioma mass-effect Simulator

www.glims.ch

Selected References

[1] A. H. Ropper. "Lateral Displacement of the Brain and Level of Consciousness in Patients with an Acute Hemispheral Mass". In: *New England Journal of Medicine* 314.15 (04/10/1986), pp. 953–958.

[2] N. G. Burnet et al. "Years of Life Lost (YLL) from Cancer Is an Important Measure of Population Burden and Should Be Considered When Allocating Research Funds". In: *British Journal of Cancer* (01/11/2005).

[3] E. S. Gamburg et al. "The Prognostic Significance of Midline Shift at Presentation on Survival in Patients with Glioblastoma Multiforme". In: *Int. J. Radiat. Oncol.* 48.5 (12/2000), pp. 1359–1362.

[4] T. C. Steed et al. "Quantification of Glioblastoma Mass Effect by Lateral Ventricle Displacement". In: *Sci. Rep.* 8.1 (12/2018).

[5] R. K. Jain et al. "The Role of Mechanical Forces in Tumor Growth and Therapy". In: *Annu. Rev. Biomed. Eng.* 16.1 (07/11/2014), pp. 321–346.

[6] C.-C. Liao et al. "Brain Midline Shift Measurement and Its Automation: A Review of Techniques and Algorithms". In: *International Journal of Biomedical Imaging* 2018 (2018), pp. 1–13.

[7] D. Abler et al. "TMIC-09. Towards a framework for predictive mathematical modeling of the biomechanical forces causing brain tumor mass-effect". In: *Neuro-Oncology* 19.suppl 6 (2017), p. vi245.

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:
dabler@coh.org