Using quantitative MR imaging to relate GBM mass effect to perfusion characteristics of the tumor micro-environment

Daniel Abler[1,2], Prativa Sahoo[1], Brennan Hall[3], Kathryn Kingsmore[4], Jennifer Munson[5], Philippe Büchler[2], Russell Rockne[1]

[1]Beckman Research Institute, City of Hope; [2]University of Bern; [3]Biola University; [4]University of Virginia; [5]Virginia Tech

City of Hope

UNIVERSITÄT BERN

Aim

This study investigates whether **tumor mass-effect** is **reflected in** measures of **tumor perfusion kinetics** and **interstitial fluid flow**.

- We quantified pre-operative tumor mass-effect on 30 GBM patients of the Ivy Glioblastoma Atlas Project (Ivy GAP [1]) and report its relation to tumor size, location and clinical outcome.
- We evaluated Dynamic-Contrast-Enhanced (DCE) MR Imaging for 9 cases to investigate the relation between tumor mass-effect, perfusion and interstitial fluid flow in the tumor.

Tumor Mass Effect

Tumor mass effect results from biomechanical forces that displace surrounding tissue during tumor growth. Biomechanical forces are known to affect tumor growth and evolution [2], and likewise, tumor growth drives physical changes in its micro-environment that affect tissue solid and fluid mechanics.

Elevated mass effect has been shown to be linked to poor outcome in GBM patients and to be associated with the expression of gene signatures consistent with proliferative growth phenotype [3]. Similarly, elevated interstitial fluid flow (IFF) has been shown to drive GBM invasion [4].

Lateral Ventricle Displacement (LVd)

This study uses "lateral ventricle displacement" (LVd) [3] 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.

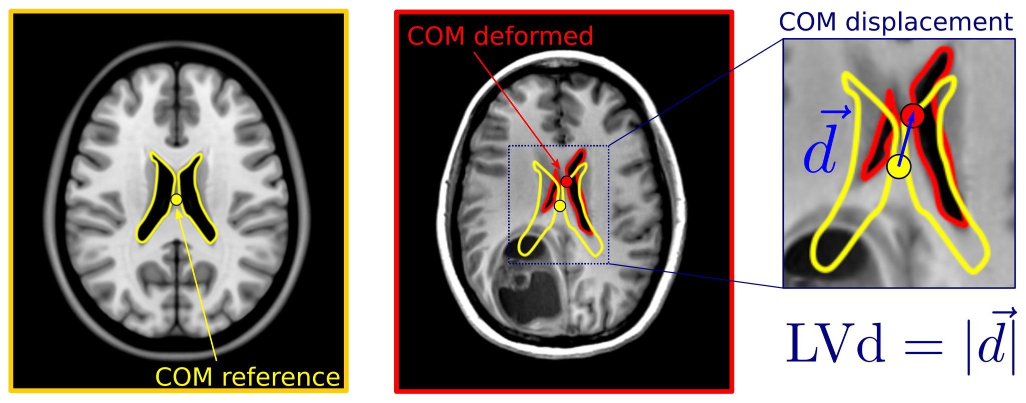


Figure 1: Lateral ventricle displacement (LVd) defined as distance between center of mass (COM) of (healthy) reference (yellow) and tumor bearing (red) configuration.

LVd Estimation from MR Images

We implemented a semi-automatic approach for estimating LVd from anatomic brain MR imaging data, based on image registration and following [3].

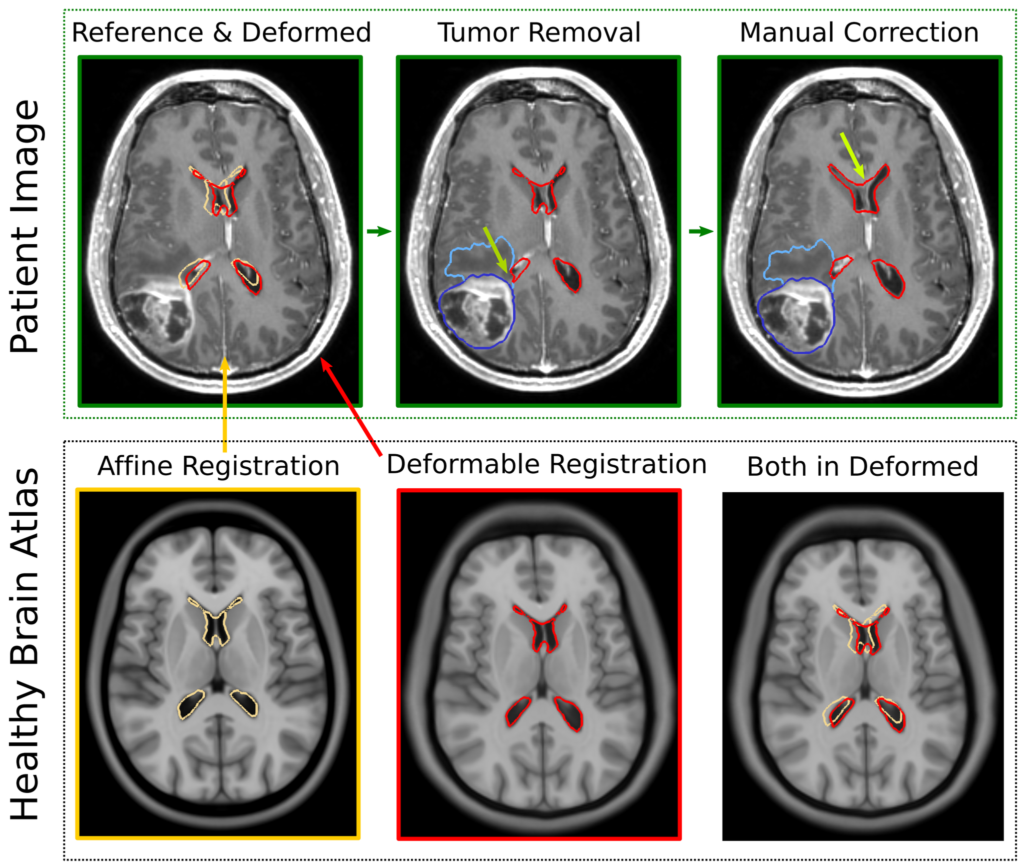


Figure 2: The patient's "healthy" anatomy is estimated by affine registration of a brain atlas to the patient's brain MRI. Deformed ventricles are segmented by deformable registration and subsequent manual correction. LVd is computed from the center-of-mass positions of reference and deformed ventricles.

LVd Estimation on Glioblastoma

The Ivy Glioblastoma Atlas Project (Ivy GAP [1]) provides matched imaging, ISH, RNA, gene expression and clinical data over the treatment course of 39 patients.

We estimated LVd from pre-surgical MR imaging datasets of 30 patients; 9 patients were excluded.

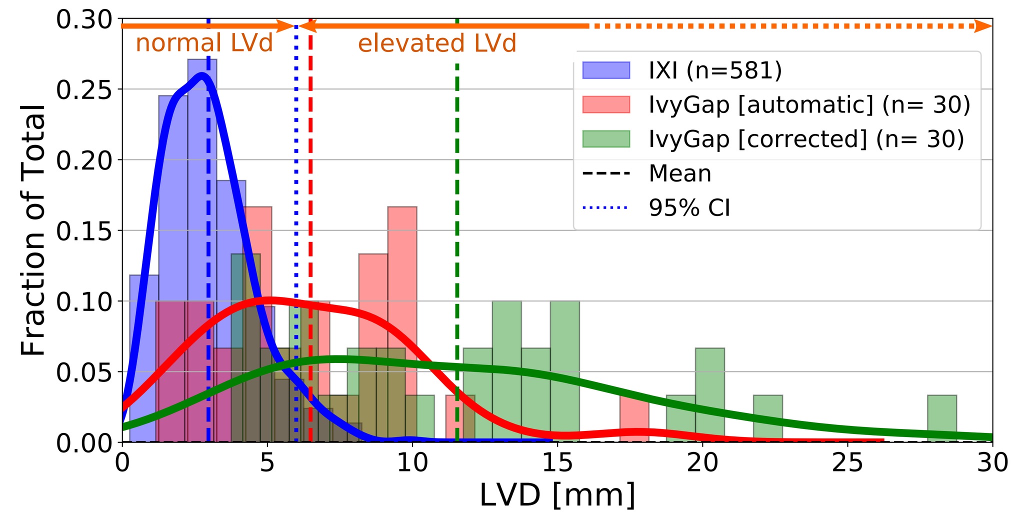
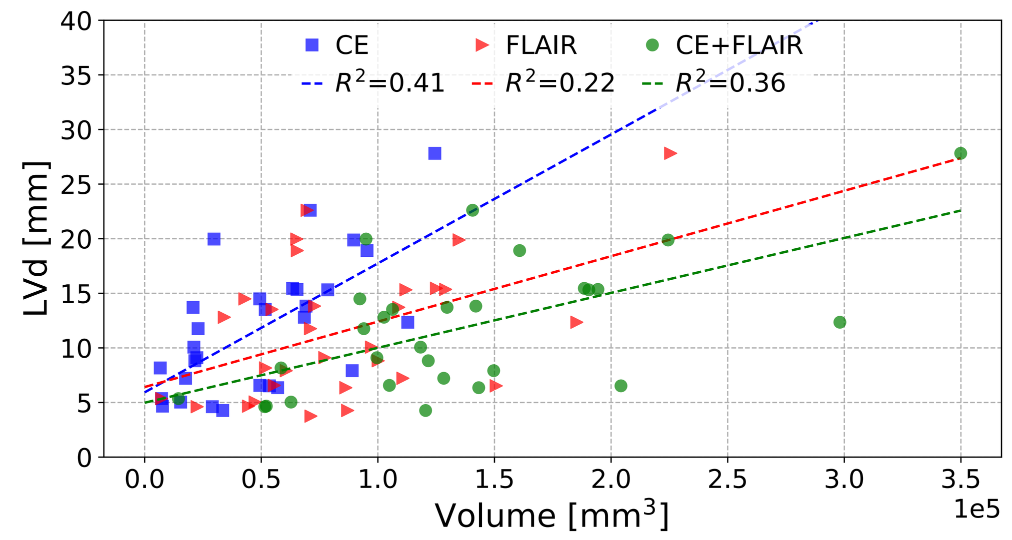


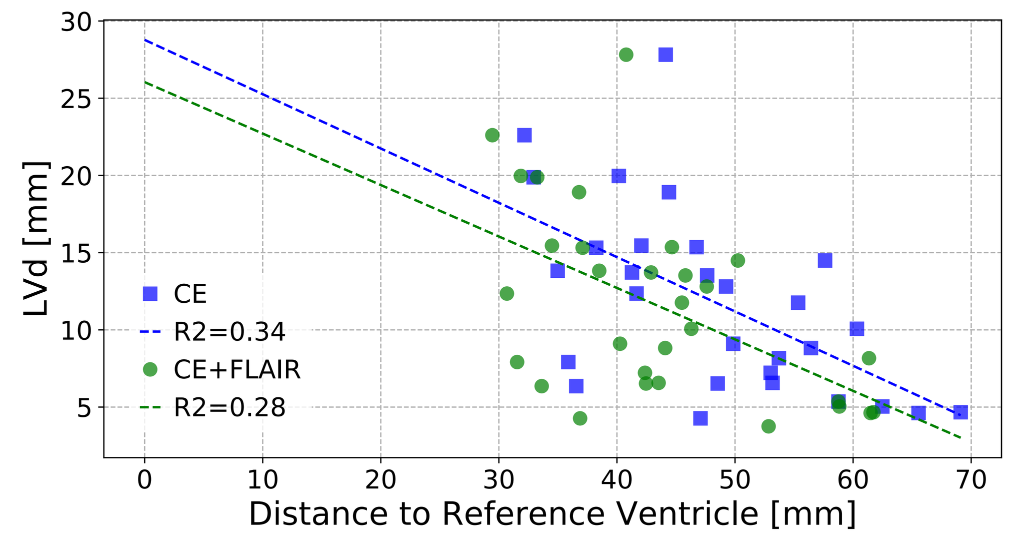
Figure 3: Distribution of estimated LVd magnitudes. To evaluate registration uncertainty across a wide range of anatomic shapes, the LVd estimation approach was additionally applied to a dataset of healthy brain anatomy (IXI [5]).

LVd vs. Tumor Size & Location

Tumor volume and location jointly explain about 40 % to 50 % of LVd variability.



(a) Increased tumor burden (e.g. contrast-enhancing (CE) volume) is associated with increase in LVd.



(b) Increased distance between tumor COM and ventricles is associated with decrease in LVd.

Figure 4: LVd vs. tumor size and location.

LVd vs. Survival

We find reduced survival in patients with elevated LVd pre-surgical (LVd >6 mm). However, neither tumor volume, nor LVd are significantly linked to survival.

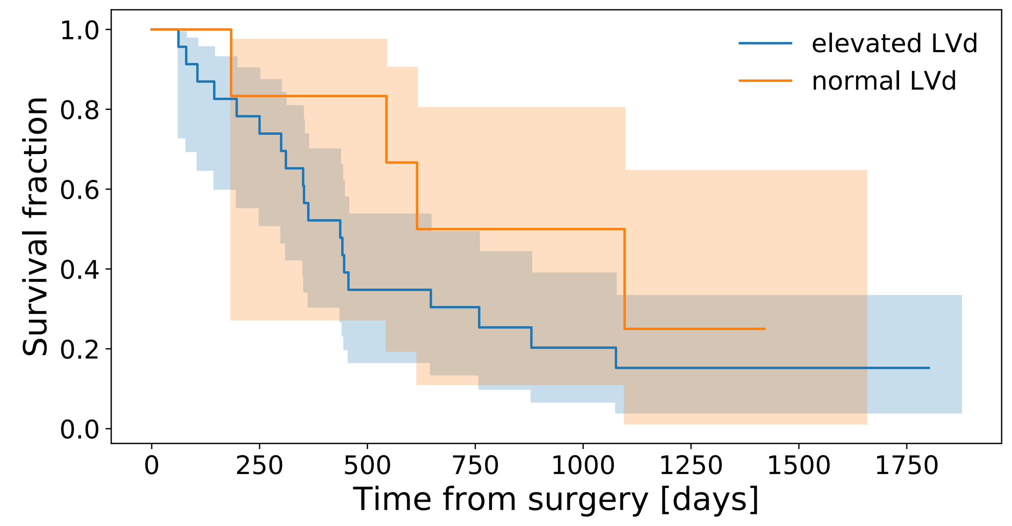
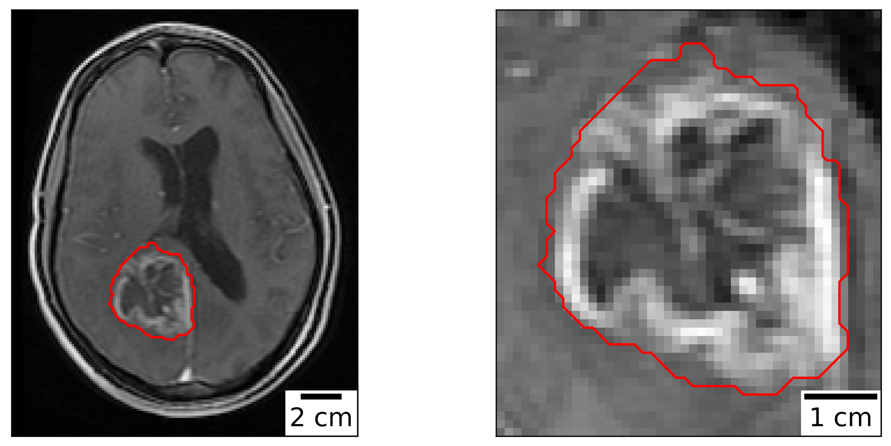


Figure 5: Kaplan Meier graph comparing survival of Ivy GAP patients with "normal" and "elevated" LVd. LVd is considered "elevated" when exceeding the 95% CI of the normal population (6 mm).

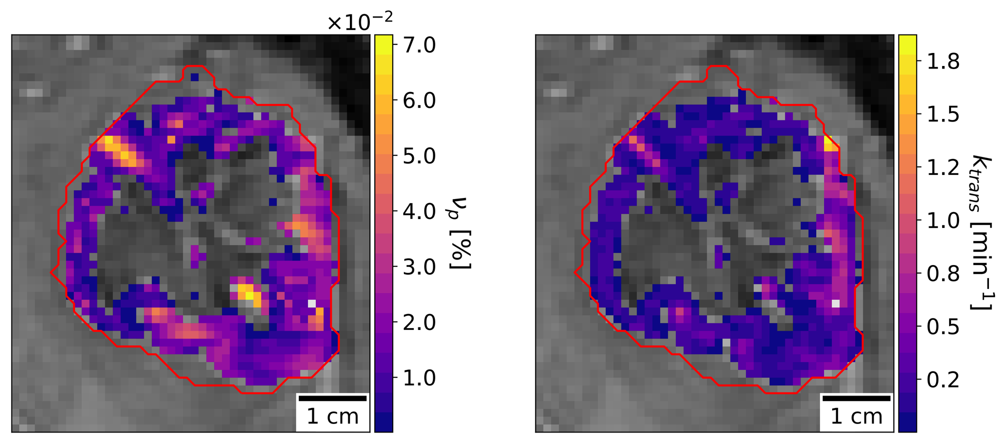
Quantitative MR Imaging

We computed blood perfusion kinetics [6] (3D) and interstitial fluid flow (IFF) [7] (2D) from 9 patients with pre-operative dynamic contrast enhanced (DCE) MR imaging.

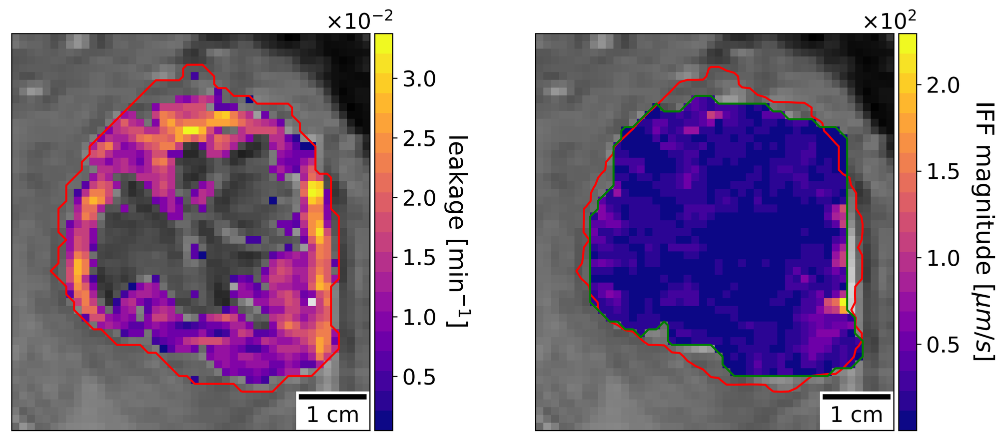


(a) Post-contrast T1 MRI. (b) Zoom on tumor region.

Figure 6: Axial slice of representative DCE MRI image. Region used for perfusion analysis indicated by red contour.



(a) Plasma volume fraction ν_p. (b) Transfer rate k_{trans}.

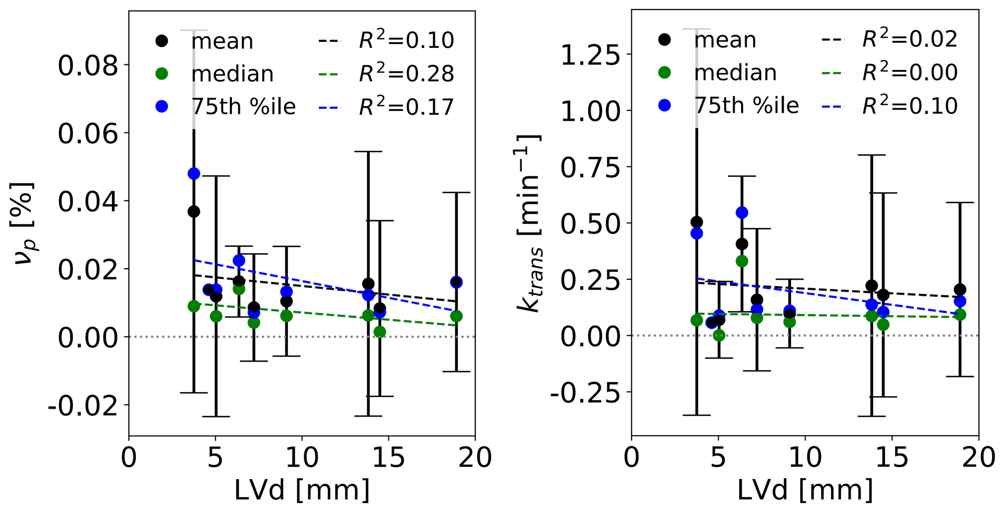


(c) Leakage. (d) IFF magnitude.

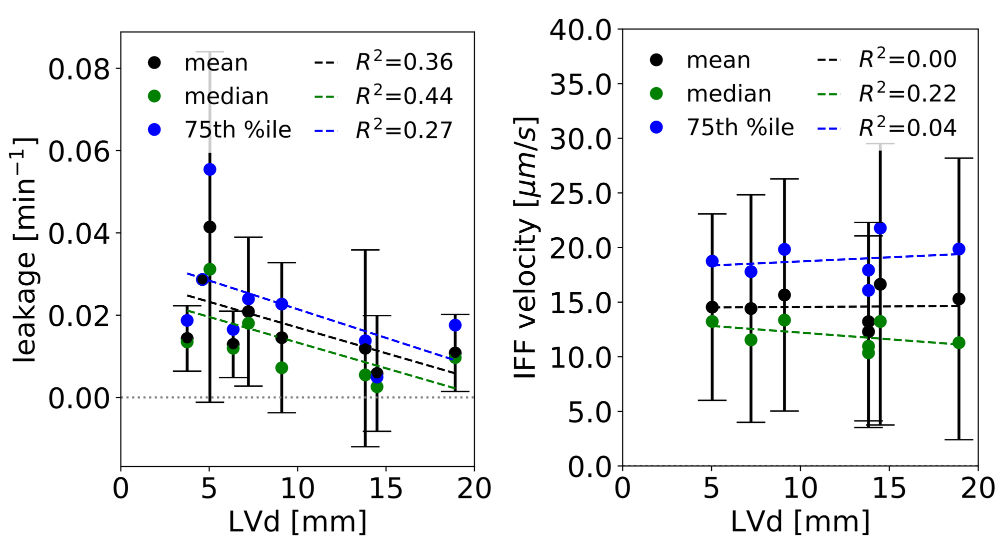
Figure 7: Representative parameter maps obtained from perfusion and IFF analysis. Parameters were estimated separately for each voxel of the tumor volume. For perfusion kinetic parameters (a b, c), only estimates with fit quality $R^2 > 0.80$ are shown.

Perfusion kinetics & IFF vs. LVd

Perfusion kinetic and IFF parameter estimates are highly heterogeneous across the tumor volume. Figure 8 shows the relation between summary statistics and LVd.



(a) Plasma volume fraction ν_p. (b) Transfer rate k_{trans}.



(c) Leakage. (d) IFF magnitude.

Figure 8: Perfusion kinetic parameters (a b, c, $R^2 > 0.95$) and interstitial fluid flow (d) in function of LVd. Black whiskers indicate the (symmetric) standard deviation around the mean of parameter estimates across all voxels.

Summary

Evaluated workflow for LVd estimation

- Analysis of healthy brain images indicates LVd estimation accuracy of 3.0 ± 1.5 mm.
- Uncertainty and LVd values for GBM patients similar to literature [3].

Analyzed pre-surgical LVd on Ivy Gap dataset

- LVd increases with tumor burden.
- However, patients can exhibit largely different LVd, despite similar tumor burden.
- Tumor volume and location only explain 40 % to 50 % of LVd variability.

Explored link between LVd and perfusion, IFF

- Perfusion kinetic and IFF parameter estimates are highly heterogeneous across the tumor volume.
- Decrease in mean, median *leakage* with increasing LVd (R^2 between 0.4 to 0.7, depending on fit quality selection criteria), fig. 8c.
- No consistent trend apparent for mean, median, maximum k_{trans}, *plasma volume fraction* ν_b, and magnitude of *interstitial fluid flow* velocity vs. LVd.

Limitations

- Small number of GBM cases: LVd ($n = 30$), IFF and perfusion kinetics ($n = 9$).
- IFF analysis currently restricted to 2D.
- No quality-of-fit metric for IFF data selection.

Ongoing and Future Work

Data Analysis

- Explore spatial heterogeneity in perfusion and IFF parameters; compare to apparent diffusion coefficient (ADC).
- Improve data selection criteria for IFF analysis.
- Investigate relation between LVd and biological data available in Ivy GAP.

Modeling & Simulation

- Use mathematical model to investigate robustness of LVd measure and its relation to observable and non-observable (or difficult to measure) quantities.
- Calibrate mathematical model to observed LVd values.

Computational study comparing measures of tumor mass effect at **Poster TMOD-15**!

Project Information

GlimS
Glioma mass-effect Simulator

www.glims.ch

Selected References

[1] N. Shah et al. *Data from Ivy GAP. The Cancer Imaging Archive.*. 2016.

[2] 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.

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

[4] K. M. Kingsmore et al. "Interstitial Flow Differentially Increases Patient-Derived Glioblastoma Stem Cell Invasion via CXCR4, CXCL12, and CD44-Mediated Mechanisms". In: *Integrative Biology* 8.12 (2016), pp. 1246–1260.

[5] *IXI (Information eXtraction from Images) dataset.*

[6] P. Sahoo et al. "Subcompartmentalization of Extracellular Extravascular Space (EES) into Permeability and Leaky Space with Local Arterial Input Function (AIF) Results in Improved Discrimination between High- and Low-Grade Glioma Using Dynamic Contrast-Enhanced (DCE) MRI: Leaky Tracer Kinetic Model". In: *Journal of Magnetic Resonance Imaging* 38.3 (09/2013), pp. 677–688.

[7] K. M. Kingsmore et al. "MRI Analysis to Map Interstitial Flow in the Brain Tumor Microenvironment". In: *APL Bioengineering* 2.3 (09/2018). bibtex*:Kingsmore_2018, p. 031905.

[8] K. Clark et al. "The Cancer Imaging Archive (TCIA): Maintaining and Operating a Public Information Repository". In: *J. Digit. Imaging* 26.6 (12/2013), pp. 1045–1057.

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