Image-driven modeling of cellular microenvironment habitats in a pre-clinical model of glioma

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Introduction: Gliomas are an invasive cancer affecting the cells that support and protect neurons with less than a 33% 5-year survival across all stages[1]. Variability in treatment efficacy between (and within) tumors is influenced by heterogeneity in tumor vasculature and cell density. One way to characterize this heterogeneity is with quantitative magnetic resonance imaging (MRI) data that measures tumor perfusion and cell density and with hierarchical clustering to identify distinct physiological tumor habitats. In this study, we apply hierarchical clustering to identify three habitats from longitudinal MRI data obtained from a murine model of glioma. Our objective is to use these clusters to inform a mathematical model that will predict growth patterns based on initial tumor composition.

Materials and Methods: We analyzed MRI data of Wistar rats (N = 8) injected with C6 glioma cells that were imaged up to 10 times over a 14-day span. The rats were imaged at each time point with diffusion-weighted and dynamic contrast-enhanced MRI to calculate the apparent diffusion coefficient (*ADC*), transfer rate from vascular to tissue space (K^{trans}), the volume fraction of tissue information (v_e), and transfer rate of contrast agent back into the vasculature (K^{trans}/v_e). Tumor regions of interest were manually segmented on dynamic contrast-enhanced MRI. The quantitative imaging features from the last time point of each rat were used to define three clusters or habitats *via* hierarchical clustering. We then applied the trained cluster centroids to identify tumor habits in the remaining imaging time points. The observed longitudinal habitat data was used to fit the proliferation (g_1, g_2; see Figure 1A) and transition (α, β, γ_1, γ_2) parameters of a set of coupled ordinary differential equations (ODE). Model performance was assessed by calculating the Pearson correlation coefficient (PCC) between the measured and model estimated volumes for each habitat.

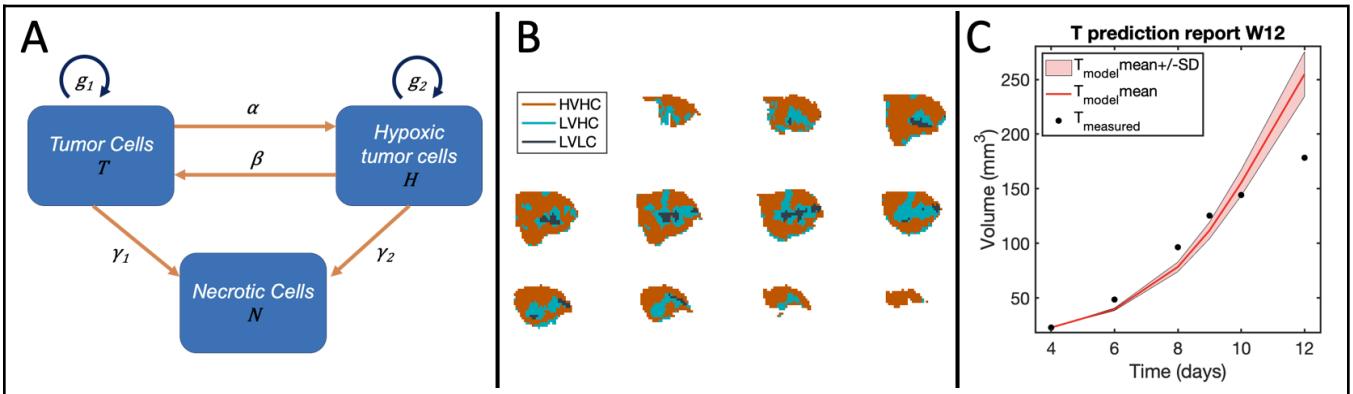

Figure 1: Quantifying and Modeling Tumor Habitats. A) Inter- and intra-habitat behaviors guiding the ODE model. **B)** MRI slices depicting mapped clustered habitats at the last time point for an illustrative rat. **C)** A plot of actual normoxic cluster volume and model predicted normoxic volume over time.

Results and Discussion: By analyzing the quantitative MRI data averages for each cluster, we have identified three tumor habitats: high vasculature high cellularity (HVHC), low vasculature high cellularity (LVHC), and low vasculature low cellularity (LVLC). This characterization aligns with normoxic, hypoxic/stressed, and necrotic tumor cells, respectively. The proposed clusters were confirmed visually (Figure 1B) and through a multiregional spatial interaction matrix analysis (which assesses if the habitats are spatially colocalized). The predictions of the ODE model with trained parameters (Figure 1C) displayed a modest to strong correlation with experimental observations in this cohort (PCC = 0.61 - 0.85).

Conclusion: We used MRI to identify habitats reflecting different cellular states within a tumor that correlated accurately to expected tumor physiology. With the success of our predictive model of glioma habitat progression, patterns of tumor heterogeneity can be used to predict tumor evolution in between MRI scans.

Acknowledgments: NSF 1757885, CPRIT 160005, NIH U01CA174706, R01CA186193, and R01CA226258

References: 1. "Cancer of the Brain and Other Nervous System - Cancer Stat Facts." *SEER*, https://seer.cancer.gov/statfacts/html/brain.html.