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Modelling growth and treatment dynamics in PDGF-driven glioblastoma: how heterogeneity manifests across scales

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Glioblastoma multiforme (GBM) is a rare brain cancer with a median survival of only around 15 months. Intratumoural heterogeneity and extensive infiltration into the brain tissue contribute to poor prognosis and probable recurrence. Predicting the timing of post-treatment recurrence is often limited if using only MRI imaging measurements, as a diverse range of treatment outcomes can result from similar pre-treatment growth dynamics. To better understand the diversity in recurrence, we analyze multiscale data from an ex vivo rat model during progression to inform an agent-based computational model to quantify how heterogeneity in proliferation and invasion affects both the bulk and individual scale tumour metrics following treatment.

The rat experiment is a model of platelet-derived growth factor (PDGF) driven GBM. The production of PDGF by cells allows both autocrine and paracrine stimulated proliferation and migration to drive growth. PDGF in the tissue environment also stimulates and recruits normal progenitor cells. Throughout this experiment, bulk tumour size was recorded via MRI, and single cell tracks were analyzed to quantify proliferation and migration spatially. Guided by this data, we built an agent-based model within the gray-white brain tissue context. We fit the model to the growth data alone using a hybrid genetic algorithm approach, and then fit individual cell proliferation and migration distributions.

We find parameter sets that define a suite of fits, which describe similar bulk scale growth dynamics with widely different underlying phenotypes that tend to be more proliferative, more migratory, or more driven by growth-factor dynamics. A more limited set of parameters fits the individual scale dynamics, with heterogeneity predicted to be both an intrinsic feature and driven by the environment. Application of an anti-proliferative treatment on these heterogeneous tumours reduces tumour size, but leads to recurrence of a less proliferative tumour. An anti-migratory treatment is seen to have little effect on growth dynamics, but selects for more proliferative phenotypes. The changes that occur at the imaging scale down to the single cell level lead to a better understanding how the evolutionary impact of treatment on GBM can inform treatment regimens.

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