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Metabolism: Integrating cellular and microenvironmental heterogeneity to drive tumor progression

Clinical and experimental evidence increasingly suggests that cellular and microenvironmental heterogeneity plays a significant role in tumor progression and response to treatment. Zones of hypoxia, acidosis, and necrosis in the tumor and surrounding tissue can exert selection pressure on a dynamic heterogeneous tumor population, driving the emergence of increasingly aggressive phenotypes. Critically, cellular metabolism acts as a key integrator between these cellular and microenvironmental components. In order to understand the complex interplay between these elements, we have developed a hybrid multi-scale mathematical model of tumor growth in a vascularized tissue. Cellular behavior, including proliferation, migration, death and signaling, are driven by microenvironmental conditions, mediated through cellular metabolism. A range of tumor phenotypes emerges due to selection by the heterogeneous microenvironment. The response of a tumor to treatment depends on the presence of different tumor phenotypes, as well as the local conditions. By tracking the multiple routes of tumor progression, we use the model to predict optimal treatment strategies that can block the most malignant routes.