

Data driven mechanistic modeling of oxygen distribution and hypoxia profile in tumor microenvironment

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Hypoxia, a state of insufficient oxygen availability, is a hallmark of tumor microenvironment and affects multiple cellular pathways and contributes to tumor progression, invasiveness, angiogenesis, vasculogenic mimicry (D'Aguanno et al. 2021). Hypoxic tumor microenvironment promotes the activation of hypoxia-inducible factor (HIF), which mediates the expression of genes regulating metabolic pathways, pH regulation, DNA replication, protein synthesis and phenotypic switch from proliferative to invasive, resulting in intratumor heterogeneity, which hinders accurate diagnosis (D. S. Widmer et al. 2013, A. Tameemi et al., 2019). Moreover, hypoxia influences the response of cancer cells to various treatments, especially radiation therapy. Hence, presence of hypoxia is a clear indication of poor prognosis for patients with various cancer types including cutaneous melanoma, which is one of the most aggressive, complex, and heterogeneous cancers (B. Bedogni et al. 2009, T. Grzywa et al. 2017). Accurate assessments of oxygen and hypoxia distributions in the tumor microenvironment would be helpful for the prognostic evaluation and therapeutic options.

Although there are plenty of theoretical and computational models for the oxygen distribution in the literature for various tumors, the novelty of this work lies in incorporating theoretical hypotheses to the actual tumor samples and in addressing the corresponding issues. We propose mathematical and computational frameworks to understand and mimic the spatial heterogeneity of oxygen partial pressure distribution and resulting hypoxia in the microenvironment of melanoma and other tumor samples. In this order, we develop a mechanistic model for the prediction of oxygen gradients based on partial differential equation (PDE), whereby the production and distribution of oxygen depends on the underlying vasculature and on the architecture and geometry of the blood vessels. Knowing the oxygen concentration for a given domain, hypoxia is modeled through an explicit relation depending upon the oxygen. This mechanistic approach is supplemented by experimental data in the form of scans of Patient Derived Xenograft (PDX) of breast, ovarian and pancreatic as well as human melanoma tumors. The blood vessel and hypoxia are represented respectively by the immunohistochemical scans CD31 (cluster of differentiation 31, marking the presence of endothelial cells) and CA9 (carbonic anhydrase IX, regulated via HIF 1, is an intrinsic marker of tumor hypoxia) staining of these cancerous tissues. After necessary preprocessing of the data, these are used to estimate the model parameters and for the validation of the simulation results by utilizing an optimization process. Another aspect of this work is to compare the inclusion of 3D vasculature (artificial as well as reconstructed from tumor slices) with its 2D approximation as source of oxygen in the modeling process. As obtaining the necessary tumor slides as well as corresponding 3D reconstruction is not always feasible, having a framework to quantify this approximation inadequacy

and the difference of oxygen distribution and hypoxia profile are crucial. The goal is to develop a general framework which is applicable to most of the tumors to predict the hypoxia profile for a known blood vessel architecture.