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Tumor Blood Vessel Dynamics

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"Normalization" of tumor blood vessels has shown promise to improve the efficacy of chemotherapeutics. In theory, anti-angiogenic drugs targeting endothelial VEGF signaling can improve vessel network structure and function, enhancing the transport of subsequent cytotoxic drugs to cancer cells. In practice, the effects are unpredictable, with varying levels of success. The predominant effects of anti-VEGF therapies are decreased vessel leakiness (hydraulic conductivity), decreased vessel diameters and pruning of the immature vessel network. It is thought that each of these can influence perfusion of the vessel network, inducing flow in regions that were previously sluggish or stagnant. Unfortunately, when anti-VEGF therapies affect vessel structure and function, the changes are dynamic and overlapping in time, and it has been difficult to identify a consistent and predictable normalization "window" during which perfusion and subsequent drug delivery is optimal. This is largely due to the non-linearity in the system, and the inability to distinguish the effects of decreased vessel leakiness from those due to network structural changes in clinical trials or animal studies. We have developed a mathematical model to calculate blood flow in complex tumor networks imaged by two-photon microscopy. The model incorporates the necessary and sufficient components for addressing the problem of normalization of tumor vasculature: i) lattice-Boltzmann calculations of the full flow field within the vasculature and within the tissue, ii) diffusion and convection of soluble species such as oxygen or drugs within vessels and the tissue domain, iii) distinct and spatially-resolved vessel hydraulic conductivities and permeabilities for each species, iv) erythrocyte particles advecting in the flow and delivering oxygen with real oxygen release kinetics, v) shear stress-mediated vascular remodeling. This model, guided by multi-parameter intravital imaging of tumor vessel structure and function, provides a tool for identifying the structural and functional determinants of tumor vessel normalization.