

## Modeling tumor blood vessel dynamics

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In wound healing, there is an influx of immature, angiogenic blood vessels that rapidly provide blood flow to the damaged tissue. The resulting, initial network is not very efficient, because it has not been subjected to the normal remodeling processes that lead to the well-organized, optimal networks of adult tissue. During resolution of wound healing, endothelial cells in the immature networks respond to blood forces, re-organizing locally to optimize the network globally. Some segments dilate, while others are pruned, and eventually, a stable configuration is reached which is then supported and maintained by perivascular cells. In contrast, tumor blood vessels are chronically immature, probably due to the high levels of VEGF in the microenvironment (VEGF is initially high in wounds, but decreases during resolution). Interestingly, many anti-VEGF therapies can cause maturation or stabilization of tumor blood vessels through a process resembling adaptive remodeling of networks in wounds. Unfortunately this effect is temporary, and very little is known about how it affects the distribution of blood flow and the transport of nutrients and drugs into the tumor. In general, remodeling depends on blood shear forces, transvascular pressure as well as growth factors such as VEGF.

We are developing a mathematical model that incorporates: 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 mathematical framework, guided by multi-parameter intravital imaging of tumor vessel structure and function, will help us understand why normalization therapy is sometimes ineffective, and may suggest alternative strategies.