Title: Multi-cell Agent-based Simulations of Vascular Tissue Patterning

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Abstract:

The adult vasculature grows and adapts (remodels) in response to spatially and temporally heterogeneous mechanical and biochemical stimuli, and these processes can have a profound effect on a tissue's ability to survive an ischemic insult or heal a wound, for example. Vascular remodeling occurs in both the microcirculation, during angiogenesis and arteriogenesis, and in large vessels during atherosclerotic lesion development. The remodeling process is orchestrated by a complex cascade of biomechanical and biochemical signals and cellular behaviors, which give rise to altered vascular structures at the tissue level. To study how the actions and interactions of cells with one another and with their environment result in emergent tissue-level patterning phenomena, we have employed agent-based modeling (ABM) to compute vascular cell and vascular-associated cell behaviors in space and time in response to environmental signals, such as growth factors, extracellular matrix interactions, and hemodynamic forces. An empirically-derived rule set dictates how cells will 'behave' in certain settings, and the individualized behaviors of thousands of cells in the simulation give rise to the aggregate tissue patterning response: the growth of new microvessels (angiogenesis), the maturation of existing microvessels (arterialization), or the accumulation and distribution of inflammatory cells in the tissue (atherosclerotic lesion development), for example. We have applied the ABM approach to study how the addition of exogenous growth factors affects angiogenesis, the origin of new smooth muscle cells and pericytes during arteriogenesis, and how hemodynamic forces impact monocyte adhesion. A central aspect of this approach is its intimate pairing with *in vivo* experimental work. In this way the ABM informs the experiments by facilitating systematic and efficient hypothesis testing, and the experimental work informs the computational model by providing independent validation of the predictions and rule set. The long-term goals of this combined approach are to expedite the discovery of fundamental mechanisms underlying vascular remodeling, enable faster and more effective drug discovery, and aid in the design of regenerative medicine strategies targeted at the cardiovascular system.