

# From Molecule to Morphology: A Multi-Scale Cell-Based Model of Angiogenesis

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**Short Abstract** — We introduce a novel multi-scale cell-based model of tumor-induced angiogenesis and present results from numerical simulations that elucidate some mechanisms controlling vascular formation in the context of pro- and anti-angiogenesis treatment strategies. In particular, we investigate how extracellular matrix topology influences cell migration and vascular structure, and the relationship between external stimuli, cell phenotype, and vascular morphology. This model is the first to simulate branching, anastomosis (loop formation), and the brush border effect without prescribing any rules for the formation of such complex structures.

**Keywords** — Multi-scale model, tumor-induced angiogenesis, molecular signaling, cellular dynamics, tissue morphology.

## I. PURPOSE

TUMOR-INDUCED angiogenesis, which is the formation of new blood vessels from existing vasculature in response to chemical signals from a tumor, is a crucial step in cancer invasion and metastasis. Although the sequential steps involved in tumor-induced angiogenesis are well known, the interplay between the biochemical and biomechanical mechanisms (e.g., cell-cell and cell-matrix interactions, and intracellular signaling pathways) that affect angiogenesis is largely unresolved. We have developed a novel multi-scale cell-based model of tumor-induced angiogenesis that integrates different modeling techniques and interfaces multiple time and length scales [1,2]. We present results from numerical simulations that elucidate some mechanisms controlling vascular formation in the context of pro- and anti-angiogenesis treatment strategies. In particular, we investigate how the topology of the extracellular matrix influences cell migration and vascular structure [3], and the relationship between external stimuli, cell phenotype, and vascular morphology [1,4]. This model is the first to simulate emergent vessel branching, anastomosis, and the brush border effect. These macroscale structures arise as a result of microscale behavior without any rules prescribing the formation of such complex structures.

Our two-dimensional multi-scale model integrates dynamics at the tissue, cellular, and molecular scales. At the tissue scale, we use a partial differential equation model to

describe diffusion, uptake, and half-life decay of tumor-secreted pro-angiogenic factor (VEGF). At the cellular level, a discrete lattice Monte Carlo model based on system-energy reduction (the cellular Potts model) considers endothelial cell migration, growth, division, cellular adhesion, and the evolving structure of the stroma. At the molecular scale, we employ a Boolean signal transduction network of the cross-talk between the RTK (VEGF), integrin, and cadherin receptors. Key features of this integrated systems multi-scale biophysical model include: (1) linking processes occurring on multiple time scales, (2) controlling processes at the level of the individual cell, (3) using physical constraints and energy minimization to capture emergent behaviors without prescribing phenomenological rules, and (4) quantifying morphological details that are not currently possible to capture with continuous models alone. We employ this multi-scale model for a more in-depth exploration of the molecular level mechanisms mediating capillary sprout formation.

## II. CONCLUSION

Our multi-scale model framework translates and synthesizes a large body of compartmentalized research on a complex biological system, from protein to whole tissue, and motivates an integrated systems approach for bridging multiple time and length scales applicable to a vast majority of other multi-scale biological systems. Our investigations are meant to inform and advance efforts to develop new approaches for treating cancer and other angiogenesis-dependent diseases.

## REFERENCES

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