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Proteolytic control of the mechanical switch leading to in vitro morphogenesis of capillary-like networks: a theoretical analysis

In vivo morphogenesis of capillary networks, or angiogenesis, is closely mimicked by in vitro models of endothelial cells (ECs) cultured on extracellular matrices, such as fibrin biogels with tunable stiffness. Indeed, under specific microenvironmental conditions, randomly seeded ECs self-organize into capillary-like structures (CLS). Traction forces exerted by ECs affect the initiation and progression of the biogel patterning and remodeling. Considering the well-documented mechanosensitivity of endothelial cells, and especially the suggested role of secreted matrix metalloproteinases, we develop and analyze a mathematical model of this morphogenetic process which is able to reproduce several qualitative and quantitative features of our in vitro experiments. The results of the theoretical analysis show how CLS result from an autobaric-driven instability and appear for a well-defined critical traction force that is a function of the proteolytic ECs response to extracellular stresses. This model also provides a basis for a theoretical analysis of the anisotropic mechanical sensing of ECs and its functional inter-dependence with ECs migration and CLS formation. We additionally illustrate how the simulated model behaviors contribute to define a model-driven data acquisition framework that is necessary to increase our understanding of angiogenesis both in physiological and pathological contexts.