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Multiscale model of tumor-derived capillary-like network formation

Solid tumors must recruit and form new blood vessels for maintenance, growth and detachments of metastases [1]. Vascularization is thus a pivotal switch in cancer malignancy and an accurate analysis of its driving processes is a big issue for the development of pharmacological treatments, giving rise to multiple experimental models. In particular, *tubulogenic* assays have demonstrated that tumor-derived endothelial cells (TECs), cultured in Matrigel (a commercial gelatinous protein mixture acting as basement membrane matrix), are able to autonomously organize in a connected network, which mimics an in vivo capillary plexus [3]. Such a process is promoted by the activity of the soluble peptide vascular endothelial growth factor (VEGF, [2]) as well as by the induced intracellular calcium signals [5]. We here propose and discuss a multilevel hybrid model which reproduces the main features of the experimental system: it incorporates a continuous model of the microscopic VEGF-induced calcium-dependent regulatory cascades, and a discrete mesoscopic Cellular Potts Model (CPM, [4]) describing the phenomenological evolution of the single cells. The two components are unified and interfaced, and produce a multiscale framework characterized by a constant flux of information from finer to coarser levels: in particular, the molecular sub-cellular events realistically regulate the mesoscopic biophysical properties, behaviors and interactions of the simulated TECs. The model results are in good agreement with the analysis performed in published experimental data, allowing to identify the key mechanisms of network formation as well as to characterize its topological properties [7]. Moreover, by varying important model parameters, we are able to simulate some pharmacological interventions that are currently in use, confirming their efficiency, and, more interestingly, to propose some new therapeutic approaches, that are counter intuitive but potentially effective [6].

References

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