A Hybrid Multiscale Tumor Growth Model

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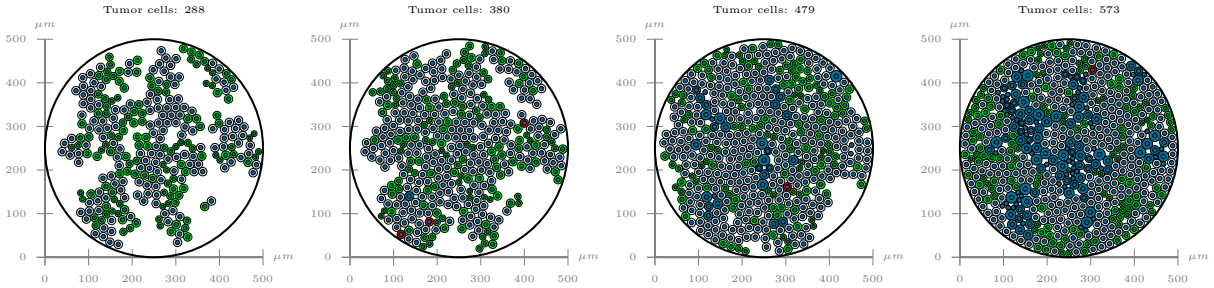
We integrate different modeling approaches in a hybrid multiscale model of avascular tumor growth. At the cell level, an agent-based model is used to describe normal and tumor cell dynamics, with the former kept in a state of homeostasis and the latter differentiated by quiescent, proliferative, apoptotic, hypoxic, and necrotic states. Various cell transitions are governed by local densities of nutrients and growth factors. Phenotypic transitions are mainly deterministic, although the transitions to apoptotic and to proliferative states are stochastic. In particular, changes within the molecular network at the sub-cellular scale controls proliferative advantages in response to microenvironment stimuli. Cell movement is driven by the balance of a variety of forces according to Newton's second law. The nutrient and growth factors dispersions are modeled through macroscale diffusion models characterized by partial differential equations. At the sub-cellular scale, the epidermal growth factor pathway (which is directly correlated with cellular proliferation, differentiation, and survival) is modeled through a system of nonlinear ordinary differential equations based on chemical kinetics which is naturally integrated to each cell (agent).

Our hybrid model is built in a modular way, enabling the systematic investigation of the role of different mechanisms (at multiple scales) on tumor progression. This strategy allows the representation of several different experimental scenarios. If necessary, one can remove some of the modules from the simulation (e.g., the modules responsible for the healthy cells and the signaling pathway) and still be able to simulate the interactions between the tumor cells with different phenotypes and nutrient evolution (see Figure 1). Computational simulations are presented to demonstrate that the model can reproduce complex mechanisms of tumor dynamics.



(a) 5 hours **(b)** 6 hours **(c)** 7 hours **(d)** 8 hours

Figure 1: Agent-based model of the tumor cell growth in a two-dimensional domain. The different colors represent tumor cells with different phenotypes: green indicates tumor cells going through proliferation, quiescent cells are light blue, apoptotic cells are red, and necrotic cells are dark blue.

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