An integrated hybrid agent-based – differential equation model framework for solid tumor growth

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We introduce a hybrid agent-based – differential equation model framework to simulate the interactions of cancer cells with each other and their respective local environment during solid tumor growth. Cellular kinetics and cell-cell interactions are modeled using a cellular automaton approach. Cells live on a lattice where each grid point can only be occupied by one cell at any time. Cells have an internal clock, or a cell cycle, which determines the time until cells can divide and give birth to a new cell – subject to available neighboring space. Additionally, cells can migrate into adjacent vacant lattice points in random directions mimicking Brownian cell motion. Using wetlab experimental data, the rules of cell kinetics and interactions can be parameterized and validated.

In addition to competition for space on the cellular level, cells interact with their local environment. Cells consume oxygen and nutrients that diffuse in from nearby blood vessels. Malignant accumulation of cells creates local areas of food deprivation and thus an unfavorable environment prompting direct migration up nutrient gradients. The concentration of oxygen and nutrients as well as their production, diffusion and consumption is modeled using partial differential equations. Numerical approximation of the partial derivatives occurs on a discretized continuous layer mapped onto the cellular automaton lattice. The two layers with different lattice sizes are interlinked, as cells explore local oxygen concentrations and gradients and consume available nutrients. The spatial and temporal scales of the hybrid model need to be separated and appropriately integrated as molecular diffusion occurs on multiple orders of magnitude faster than cell migration and proliferation.

The continuous differential equation layer can readily be adapted to model and analyze alternative environmental tumor growth modulation mechanisms such cytotoxic immune reagent concentration or tumor cell-secreted chemorepellent gradients that guide directed cell dispersal.

We discuss an appropriate visualization approach to simultaneously present cell locations and phenotypes, as well as continuous agent concentrations and gradients.