248c A 3d Algorithm Simulating Acid-Mediated Growth of Solid Tumors

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It has long been known that tumor cells, which are more tolerant of acidic extracellular environments than normal cells, preferentially convert glucose and other substrates to lactic acid even under aerobic conditions. This phenotypic change lowers the pH at the tumor edge by about 0.5 units and, thus, facilitates tumor invasion by killing normal cells and degrading ECM components. A quantitative understanding of this process will help us analyze the time course of tumor development and may lead to the development of more effective treatment strategies. We will present here the development of a model that simulates acid-mediated invasion of early-stage tumors in three-dimensional lattices. Our model solves the diffusion-reaction problems describing transport and uptake (or secretion) of glucose and H+ in a tissue consisting of normal cells, tumor cells and native capillary blood vessels. Appropriate boundary conditions are applied to describe the mass transfer at the tissue-capillary interface and an implicit-explicit finite difference method is employed to discretize the transient PDE's. The resulting sparse linear system is solved with a preconditioned GMRES method and the computed local concentrations of glucose and H+ are then used to determine the state of cells. For example, when the H+ level in the microenvironment of a normal cell exceeds some critical value, the cell dies and decomposes, making its position available for other cells (like tumor cells) to move in. Because of its large computational requirement, the 3D algorithm has been parallelized and run on computer clusters. A 3D capillary network generated from literature data is used first in our simulations. In order to study the effect of host vascularity on tumor growth, we also generate tree-like 3D capillary networks with adjustable overall vascularity using a bifurcating distributive algorithm. Our simulations produce tumor growth curves similar to those observed for both animal and human subjects. The predicted range of tumor cell acid production rate shows better agreement with experimental values than existing two-dimensional models. The growth rates of tumors are determined not only by the cell phenotype, but also by the local host vascularity, a finding that is consistent with clinical observations. Finally, our model can predict the universal existence of necrotic regions in large tumors.

Key words: tumor invasion, tumor necrosis, mathematical modeling, discrete algorithm, diffusion-reaction equation.