

A 3D Computer Model to Map Modifications in Cellular Metabolism into Different Tumor Phenotypes

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In this work we propose an approach for studying tumor development as an iterative process that searches for the minimum set of modifications in cell metabolism that would lead healthy tissue to develop an invasive tumor.

There are many models in the literature describing putative steps necessary for a homogenous population of healthy epithelial cells to generate an invasive tumor, however these studies do not account for the cellular metabolic modifications that drive and support cancer development and progression (hyperplasia, high aerobic glycolysis and acid resistance).

We propose an integrated process for discovering the minimal sets of modifications in cellular processes that lead tumors to become invasive (growth of tumoral tissue, invasion of normal epithelial cells and basement membrane).

The development of tumors such as Ductal Carcinoma In Situ (DCIS) is a complex process where a genetically heterogeneous population of tumoral cells is submitted to selective pressure in a dynamic environment. Here, we represent DCIS as a 3D computer model based on a tubular structure of 40 x 40 cells dimension (diameter x length), composed of endothelial cells, basement membrane and a layer of normal epithelial cells (Figure 1).

One region of this layer of healthy cells is chosen to be mutation prone, meaning that these cells have a higher than normal mutation rate due to environmental changes such as chronic inflammation or a mutation in DNA repair mechanisms. This will lead to appearance of different phenotypes - a process that will ultimately lead to evolution of a malignant population.

Each individual cell was built with algorithms to perform duplication or apoptosis, and three metabolic pathways: Glycolysis, TCA cycle, and pentose phosphate cycle. These cells were therefore programmed to duplicate, die, metabolize glucose and oxygen and generate ATP and excrete lactate. In order to account for dynamics in different time scales, the model is simulated in three levels: the first one being the reaction-diffusion of chemical species, the second is the metabolism of each cell and the last level is the cell duplication.

Within this model, one simulation is performed for each set of phenotypic modifications in tumoral cells and the set of modified cells that have successfully achieved invasiveness are selected. For each of these sub-populations the search moves one step further and details the reactions composing that pathway in search for the minimum set of enzymes that might be responsible the modifications in the phenotype previously observed. This drill-down process proceeds until reaching the genes responsible for the synthesis of the proteins that catalyze or regulate these metabolic reactions. Finally, the candidate genes found are compared to oncogenes known in literature and assessed experimentally for validation of the model.

This approach may improve understanding the intricate factors behind the development of tumors as well as test for treatments such as modification of acidity, oxygen and other substrates in the tumor microenvironment.

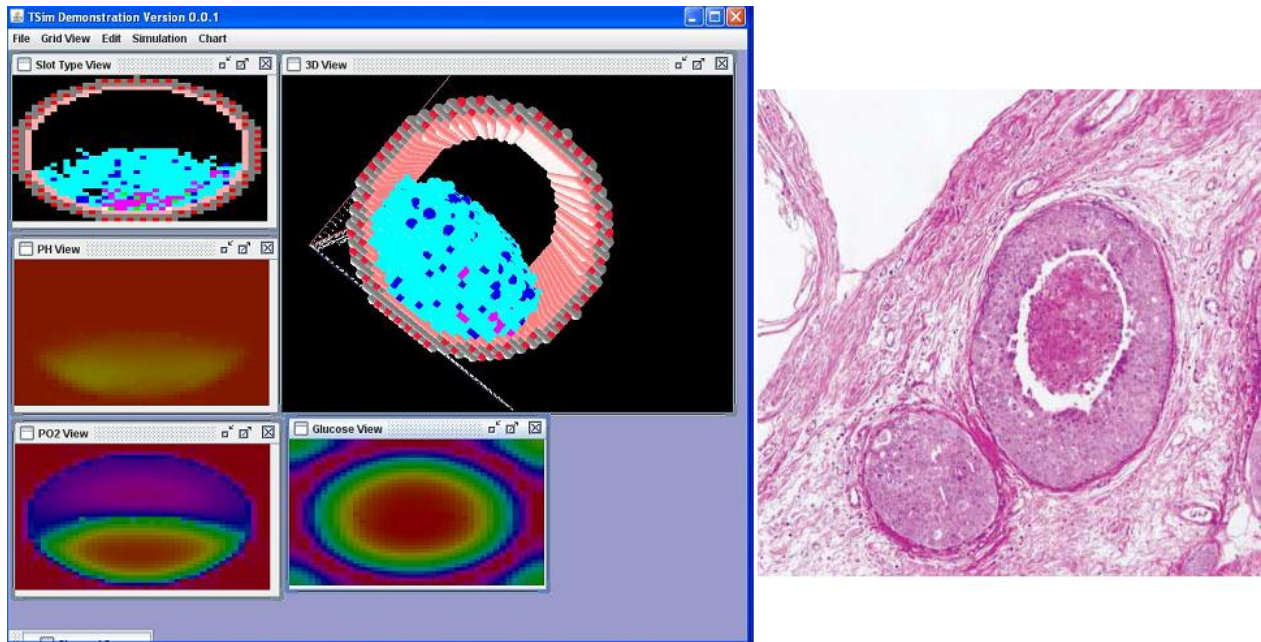


Figure 1: On the left, a snapshot of the simulation of a tumor developing in an epithelial duct (3D view on top right) and a 2D view of a transversal slice of the model showing the PH, oxygen and glucose concentration gradients. In the 3D view, red dots are blood vessels, gray represent the basement membrane, pink are healthy epithelial cells and the others are tumoral cells with different phenotypes. On the right, histology of DCIS shows the expansion of tumor cells within the duct (from Gatenby and Gilles, 2004).