Adaptation-driven Models of Cancer Invasion: Experimental Parameterization and Validation.

Vito Quaranta
Vanderbilt Integrative Cancer Biology Center, Nashville, TN
vito.quaranta@vanderbilt.edu

Abstract

Within the NCI Integrative Cancer Biology Program, our Center focuses on cell scale models of cancer invasion. In the Evolutionary Hybrid Cellular Automata (EHCA) model, each cell is a grid point containing a neural network linking genotype to phenotype. The grid represents tumor microenvironment (mE) with oxygen level controlled by a partial differential equation. At cell doublings, the neural network is copied to daughter cells with an error probability, to capture phenotypic adaptation in cancer progression. The Immersed Boundary Cell (mCell) model represents cells as 2D deformable objects bounded by linear spring nets (plasma membranes) studded with discrete receptors controlling growth, division, death or polarisation. The mE is represented as physical forces. In mCell, cells build realistic epithelial structures (acini, ducts) that capture invasion dynamics if perturbed by cancerous cells. The Hybrid Discrete-Continuum (HDC) model represents tumor growth in a one-cell thick 2D slice. The mE contains extracellular matrix, oxygen and matrix degrading proteases controlled by continuous reaction-diffusion equations, while tumor cells are discrete individuals on single lattice points, containing predefined random aggregates of traits (e.g., proliferation, death, motility rates). HDC examines effects on tumor morphology of cell adaptation to mE. We parameterize these models with homogeneous datasets from a platform breast epithelial cell, MCFIOA, and its invasive variants. Data include oxygen consumption, proliferation, survival, matrix-degrading enzyme secretion, growth patterns in 3D. High-throughput data collection is being developed for EHCA model parameterization. mCell, tuned with 2D and 3D growth data, is being tested for ability to predict receptor value ranges that lead to invasive morphology of epithelial structures. Parameterized simulations of HDC confirm its prediction that invasion requires competition between cell phenotypes with distinct adaptive value. For empyrical validation, we developed an Island Invasion Assay that closely mimics the spatial 2D arrangement of HDC tumor slices. Preliminary results support HDC predictions: invasion (fingering) occurs when competing phenotypes adapt to stressful mE conditions. For in vivo validation, we are performing orthotopic versus subcutaneous mouse xenografts of MCFIOA tumorigenic variants. In line with ICBP goals, this mathematical oncology

strategy closely integrates experimental biologists with physical scientists. It should produce novel insights in cancer by theory-driven experimentation and experiment-driven theory.

References

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