

Multiscale Model of Tumor Growth

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The microenvironment inside a tumor is extremely complex and adaptive, involving spatial and temporal variations in nutrient and waste gradients, cellular physiology, metabolism, the expression patterns of genes and proteins, as well as the malignant progression. The Multicellular tumor spheroid system has been a primary example of in vitro models of tumor microenvironment, and has provided numerous insights into tumor dynamics and progression.

We develop a multiscale model to study spheroid tumor growth. At the subcellular level, our model includes a protein expression network that controls the possibility for cell cycle arrest. At the cellular level, our model is a hybrid model of cellular dynamics (lattice Monte Carlo) and reaction-diffusion subcellular of chemicals (PDEs). This integrated subcellular and cellular model provides a realistic representation of both structure and dynamics over a large range of time and length scales.

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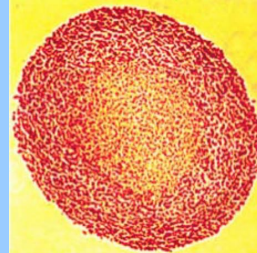
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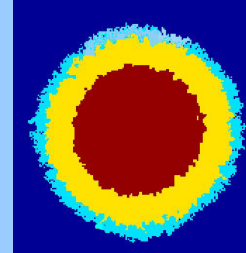
Multicellular Tumor Spheroid

- In vitro** avascular tumor model
- Exhibits many characteristics of solid tumors
 - differentiation between proliferating and quiescent cells
 - development of necrosis
 - immunity to radiation
- Develops in precisely controlled microenvironment
 - Allows for easy access to rich data
- Three stages of growth:
 - initial phase* (exponential growth)
 - layering phase* (growth rate decrease)
 - plateau phase* (constant size)

Tumor Cross Sections



EMT6/R₀ spheroid



simulated spheroid

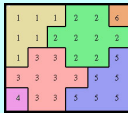
Multiscale Cellular Model

Multiscale Model

- Cellular level
 - cell growth, mitosis, mutations, chemical reaction diffusion of metabolites and factors, cell shedding, and necrosis
- Subcellular Level
 - Probabilistic Boolean protein regulatory network

Hybrid Model

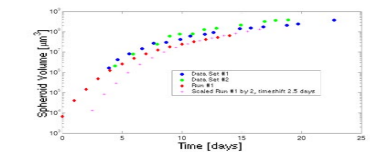
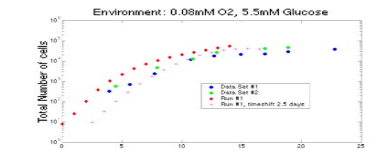
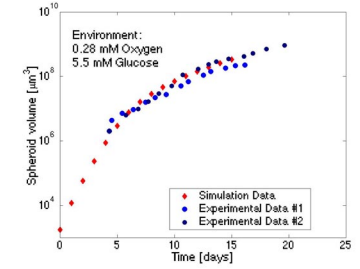
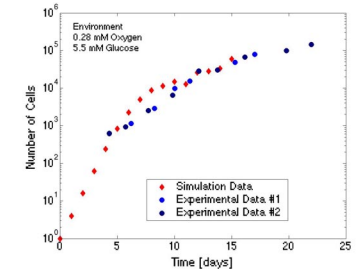
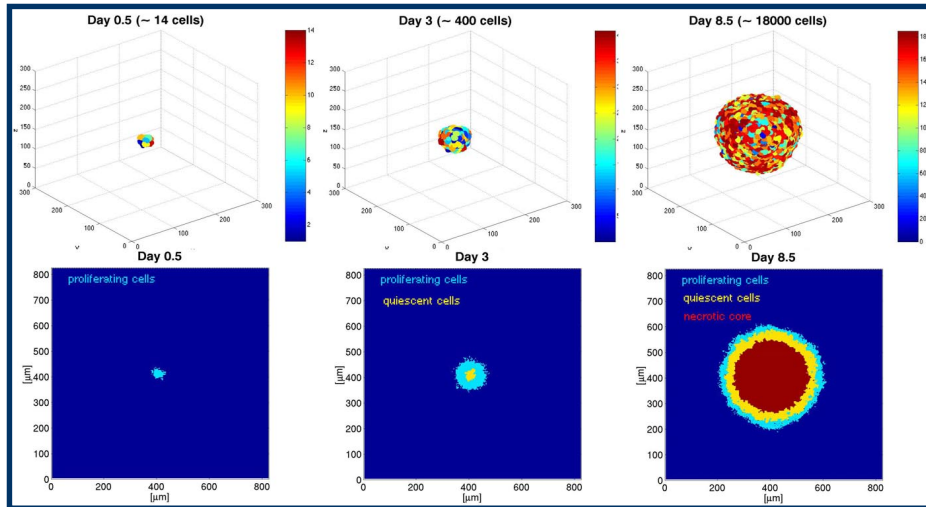
- Discrete Lattice Monte Carlo model for cells
- Minimization of total energy
- Continuous reaction-diffusion for metabolites and growth and inhibitory factors
 - Implicit solver for partial differential equations
 - Boolean Network for protein expressions



Algorithm



- Initialization consists of:
 - allocating space on grid
 - reading in parameters
 - positioning cells



Total Energy

$$H = \sum_{sites} J_{\tau(s)\tau(s')} (1 - \delta_{s,s'}) + \lambda_s \sum_{cells} [v_s - V^T s]^2 + \sum_{sites} \mu \cdot C$$

Surface energy

Volume energy

Chemical energy

Chemical Reaction Diffusion

$$\frac{\partial C_{o_2}}{\partial t} = D_{o_2} \nabla^2 C_{o_2} - a(x, y, z)$$

$$\frac{\partial C_x}{\partial t} = D_x \nabla^2 C_x - b(x, y, z)$$

$$\frac{\partial C_{n_2}}{\partial t} = D_n \nabla^2 C_n + c(x, y, z)$$

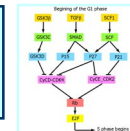
$$\frac{\partial C_{gl}}{\partial t} = D_{gl} \nabla^2 C_{gl} - e(x, y, z)$$

$$\frac{\partial C_{ab}}{\partial t} = D_a \nabla^2 C_a + f(x, y, z)$$

Constant Boundary Conditions

Protein Regulatory Network

- Proteins are either on or off
- Protein expression controls transition between G1 and S phase
- Protein expression is controlled by concentration of growth and inhibitory factors



Summary

- Results of our model show good match with experimental data
 - Cell cycle phase
 - Number of proliferating, quiescent, and necrotic cells
 - Tumor Volume
 - General tumor physiology
- Further work
 - Adding angiogenesis
 - Create a more realistic protein regulatory network