Modeling Avascular Tumor Growth

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Abstract

We have developed a cellular model to study mechanisms behind the early stage of tumor development. Most of the relevant experimental data came from in vitro tumor models such as multicellular tumor spheroids that exhibit most of the properties of avascular spherical tumors. An avascular spherical tumor grows into a layered structure consisting of a necrotic core, a quiescent layer, which consists of living cells arrested mainly in G1 phase due to stressful environment, and the outermost proliferating layer of cells.

Multicellular Tumor Spheroid

- MTS is an *in vitro* tumor model
- Used to assay tumor growth, reaction to the treatments, cell signaling, etc.
- Distinct phases in the growth of MTS:
  - initial phase (exponential growth)
  - layering phase
  - plateau phase

Model

- Extended large-Q Potts model in 3D
- Lattice Monte Carlo model coupled with continuous reaction-diffusion chemical dynamics
- Includes all important processes in a tumor cell growth ((cell-environment interactions, intercellular adhesion, mitosis and cell growth, mutations, nutrient and waste chemical dynamics, geometry and structure of cells)

Total Energy

Total energy of the cell aggregate:

$$H = \sum_{sites} J_{\tau(s)\tau(s')}(1-\delta_{s,s'}) + \lambda_v \sum_{cells} [v_s - V_s]^2$$

S - cell identification number
$\tau(S)$ - cell type (proliferating, quiescent, or necrotic)
$J_{\tau(S)\tau(S')}$ - coupling energy between cell types $\tau(S)$ and $\tau(S')$
λ_v - elasticity
v_s - cell Volume
V_s - target Volume

Chemical Reaction-Diffusion Dynamics

$$\frac{\partial C_{O_2}}{\partial t} = D_{O_2}\nabla^2 C_{O_2} - a(x,y,z) \qquad (C_{O_2} = C^0_{O_2} \text{ at boundary})$$

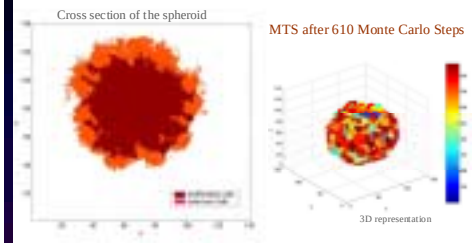
$$\frac{\partial C_n}{\partial t} = D_n\nabla^2 C_n - b(x,y,z) \qquad (C_n = C^0_n \text{ at boundary})$$

$$\frac{\partial C_w}{\partial t} = D_w\nabla^2 C_w + c(x,y,z) \qquad (C_w = 0 \text{ at boundary})$$

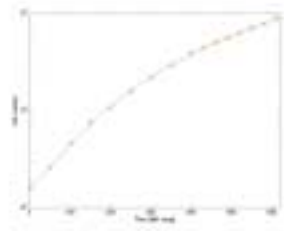
D_{O2}, D_n, D_w – diffusion constants for oxygen, nutrients, and waste, respectively
a, b, c – consumption/production rate of oxygen, nutrients and waste, respectively, of cell occupying site (x,y,z)
$c = F(a, b)$

Results:

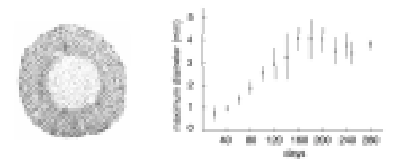
Early Tumor Growth



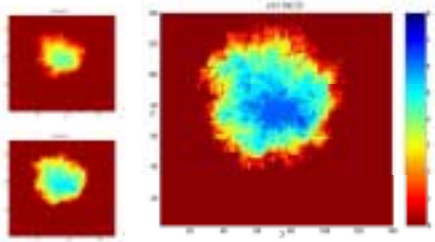
Number of Cells versus Time



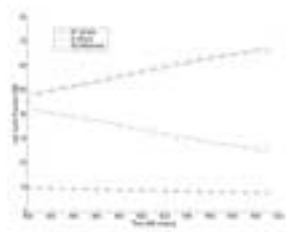
MTS experiments



Metabolic Waste Distribution



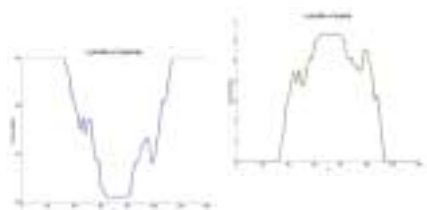
Cell Cycle Fraction



Future work

- Detailed comparison to the existing spheroid experimental data
- Extending model to describe *vascular* tumors by introducing *angiogenesis*
- *Chemotaxis*
- Development of continuous cellular model?
  - combining continuous and discrete model in a unique integrated cellular model

Chemical Profiles



Summary

- At early stage of MTS development, exponential growth of the aggregate was obtained. This is consistent with experiments.
- Nutrient deficit/waste production could cause quiescence
- Metabolic waste production has larger influence on cell cycle dynamics at early stage of tumor growth
- Plateau phase, that starts with onset of necrosis will occur in near future

References

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