Computational Methods and Results for Structured Multiscale Models of Tumor Invasion

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Outline

Goal of this Work

Develop a computational framework for models that link the spatial dynamics of sufficiently large invasive tumors (continuous representation) to smaller scale processes such as the cell cycle and mutations

Potential application: some chemotherapies target cells in certain stages of the cell cycle, and treatment can result in changes to the population genetics of a tumor (drug resistance)

Goal of this Talk

Argue that

- using physiological structure such as age or size to represent certain traits of individuals (such as position in the cell division cycle) is a useful upscaling of these traits for use in a fully continuous model
- moving-grid Galerkin methods are the way to go to handle the numerical issues induced by age structure

The Anderson Model

The model in this paper is a translation to fully continuous equations of the hybrid discrete-continuous (HDC) model of A.R.A. Anderson, *Math. Med. Biol. IMA*, pp. 163-186, 2005.

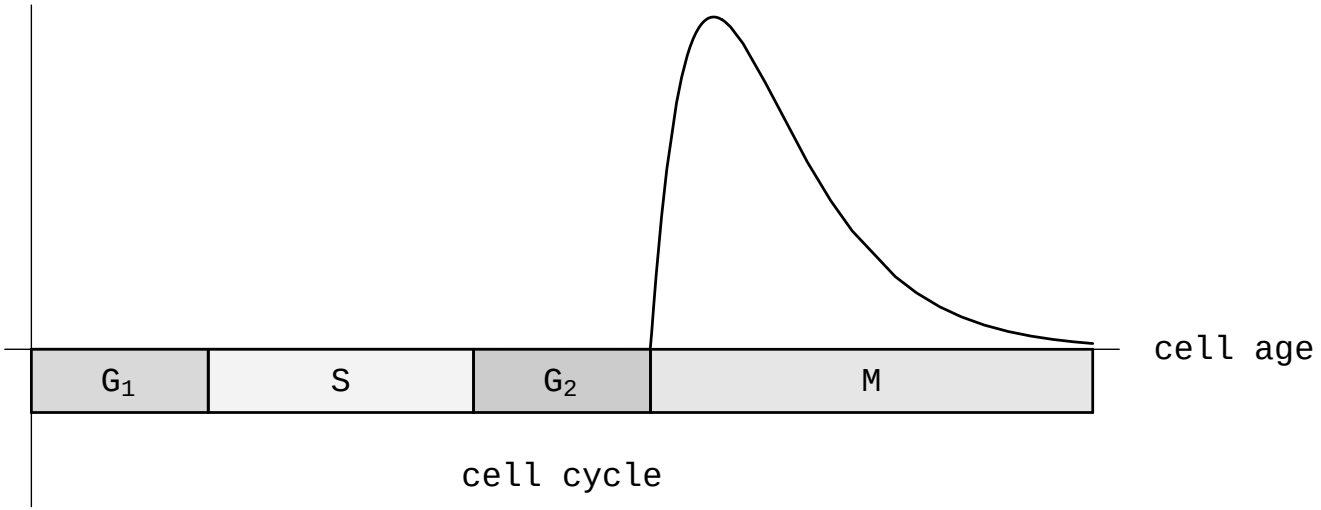
Multiscale-ness

Components at the molecular, cellular (using age or size variables), and tissue levels. Different physical scales induce different time scales into the problem.

Tumor invasion differs from typical multiscale problems: smaller physical scales also have faster time scales – homogenization or upscaling.

Relationship is inverted. Smaller physical scales have progressively slower time scales: mutation events occur on a slower time scale than cell growth and progression through the cell cycle, which occurs on a slower time scale than diffusion and haptotaxis.

Age Represents the Cell Cycle



pdf of cell ages at division (the function θ in the model)

Idea goes back to George I. Bell in 1968. Current version is Glenn Webb's from 1989.

Vasculature

We make a "mean-field" assumption that the surrounding tissue is the source of the vasculature

Future work may include an explicit vascular network

Model Species

$p_i(x, a, s, t)$ = density of proliferating tumor cells of type i, at position x, age a, and size s at time t

$i = 0$ corresponds to a mutated type p53 gene, and $i = 1, 2, \ldots, n$ corresponds to a linear sequence of mutated genotypes of increasing aggressiveness

$q_i(x, a, s, t)$ = density of quiescent cells of type i

Model Species

$f(x,t)$ = surrounding tissue macromolecule (MM) concentration at position x at time t

$m(x,t)$ = matrix degradative enzyme (MDE) concentration

$c(x,t)$ = oxygen concentration

Model Species

$P(x,t) = \sum_{i=0}^{n} \int_0^{a_M} \int_{s_m}^{s_M} p_i(x,a,s,t)\, ds\, da =$ the total population density in x of proliferating cells of all types at time t

$Q(x,t) = \sum_{i=0}^{n} \int_0^{a_M} \int_{s_m}^{s_M} q_i(x,a,s,t)\, ds\, da =$ the total population density of quiescent cells of all types

$N(x,t) = P(x,t) + Q(x,t) =$ total tumor population density in x of all cell types at time t

Proliferating-Cell Equations

$$\frac{\partial}{\partial t}p_i(x,a,s,t) = \underbrace{-\frac{\partial}{\partial a}p_i(x,a,s,t)}_{\text{cell aging}} \underbrace{-\frac{\partial}{\partial s}(\kappa_i(a,s,c,N(x,t))p_i(x,a,s,t))}_{\text{cell growth}}$$
$$\underbrace{+\nabla\cdot(D_{p_i}\nabla p_i(x,a,s,t))}_{\text{diffusion}} \underbrace{-\chi_i\nabla\cdot(p_i\nabla f(x,t))}_{\text{haptotaxis}}$$
$$\underbrace{-\rho_i(x,a,s,c)p_i}_{\text{cell death from insuffi cient oxygen}} \underbrace{-\theta_i(x,a,s,c)p_i}_{\text{division with suffi cient oxygen}}$$
$$\underbrace{-\sigma_i(x,a,s,c,N(x,t))p_i}_{\text{exit to quiescence}} \underbrace{+\tau_i(x,a,s,c)q_i(x,a,s,t)}_{\text{entry from quiescence}}$$

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Proliferating-Cell "Birth"

$$\underbrace{p_i(x,0,s,t)}_{\text{newborn type } i \text{ cells}} = 4(1-\psi_i)\underbrace{\int_0^{a_M} \theta_i(x,a,2s,c)p_i(x,a,2s,t)\,da}_{\text{type } i \text{ cell division}},$$

$$+\ 4\psi_{i-1}\underbrace{\int_0^{a_M} \theta_{i-1}(x,a,2s,c)p_{i-1}(x,a,2s,t)\,da}_{\text{type } i-1 \text{ cell division}}$$

4 ?!?

$$2 \int_{s_m}^{s_M} \int_0^{a_M} k(s,u)\, \theta_i(x,a,u,c,N(x,t))\, p_i(x,a,u,t)\, da\, du$$

$$= 2 \int_{s_m}^{s_M} \int_0^{a_M} \delta(s-\hat{u})\, \theta_i(x,a,2\hat{u},c,N(x,t))\, p_i(x,a,2\hat{u},t)\, da\, (2d\hat{u})$$

$$= 4 \int_0^{a_M} \theta_i(x,a,2s,c,N(x,t))\, p_i(x,a,2s,t)\, da.$$

Quiescent-Cell Equations

$$\frac{\partial}{\partial t} q_i(x,a,s,t) = \underbrace{-\frac{\partial}{\partial a} q_i(x,a,s,t)}_{\text{cell aging}} + \underbrace{\sigma_i(x,a,s,c,N(x,t))p_i}_{\text{entry from proliferation}} - \underbrace{\tau_i(x,a,s,c)q_i}_{\text{exit to proliferation}}$$

Quiescent-cell populations are "born" from proliferating cells of the same mutation class

Chemical Species

per Anderson 2005, we have

$$\frac{\partial}{\partial t} f(x,t) = -\underbrace{\delta m(x,t) f(x,t)}_{\text{degradation}}$$

$$\frac{\partial}{\partial t} m(x,t) = \underbrace{D_m \nabla^2 m(x,t)}_{\text{diffusion}} + \underbrace{\mu P(x,t)}_{\text{production}} - \underbrace{\lambda m(x,t)}_{\text{decay}}$$

$$\frac{\partial}{\partial t} c(x,t) = \underbrace{D_c \nabla^2 c(x,t)}_{\text{diffusion}} + \underbrace{\beta f(x,t)}_{\text{production}} - \underbrace{\gamma P(x,t)}_{\text{uptake}} - \underbrace{\alpha c(x,t)}_{\text{decay}}$$

Simplifi ed Model

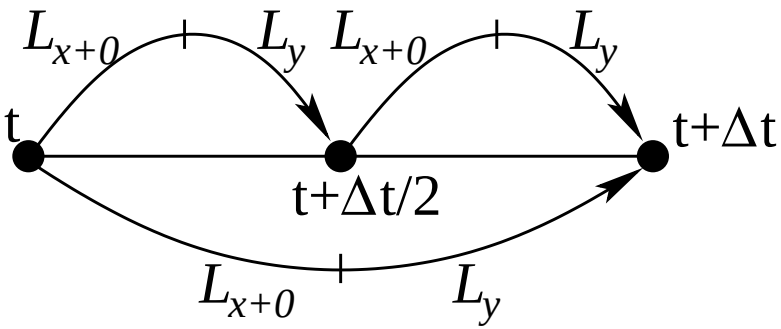
We

- ignore size structure
- use only one genotype/phenotype class
- consider only two spatial dimensions

The system then has four independent variables: age, time, and two in space

Computational Methodology

1. A moving-grid Galerkin method in age reduces the age- and space-structured PDE's to a system of parabolic equations (decoupled by lagging total populations)
2. An ADI method splits the elliptic operators into 1D operators
3. We embed the ADI method in a step-doubling method for the time integration



Age Method

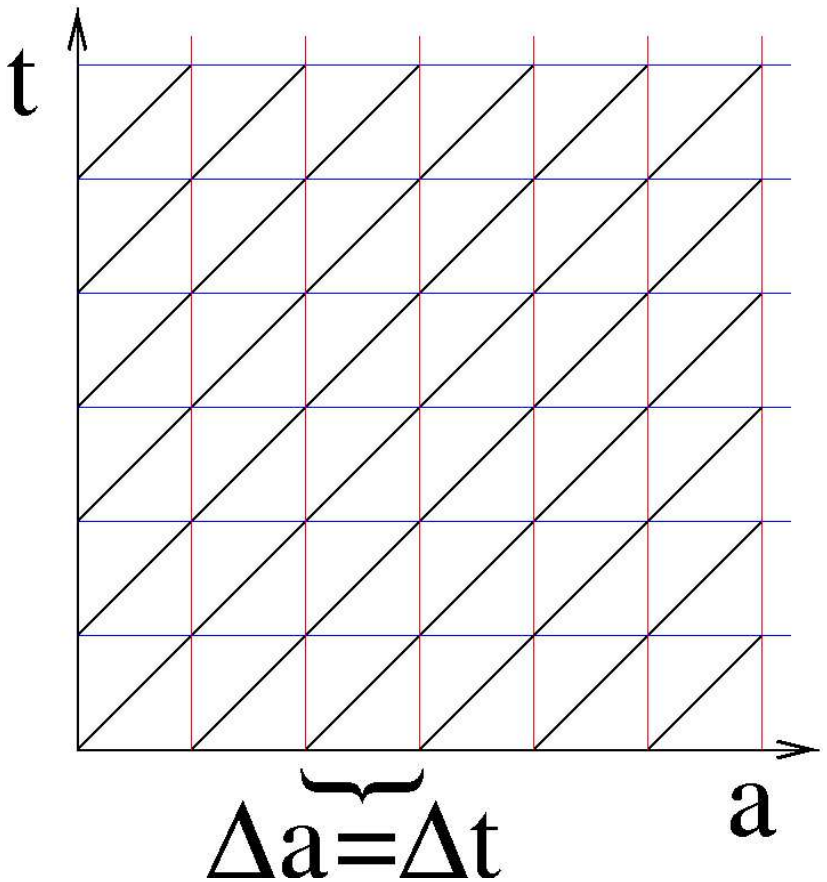
Previous Methods:
Integrate in the age–time plane along characteristic lines

Use a fixed age grid

Problem:
This requires our age and time steps to be equal and constant,
$\Delta a = \Delta t = \text{const}$

This is inefficient in practice

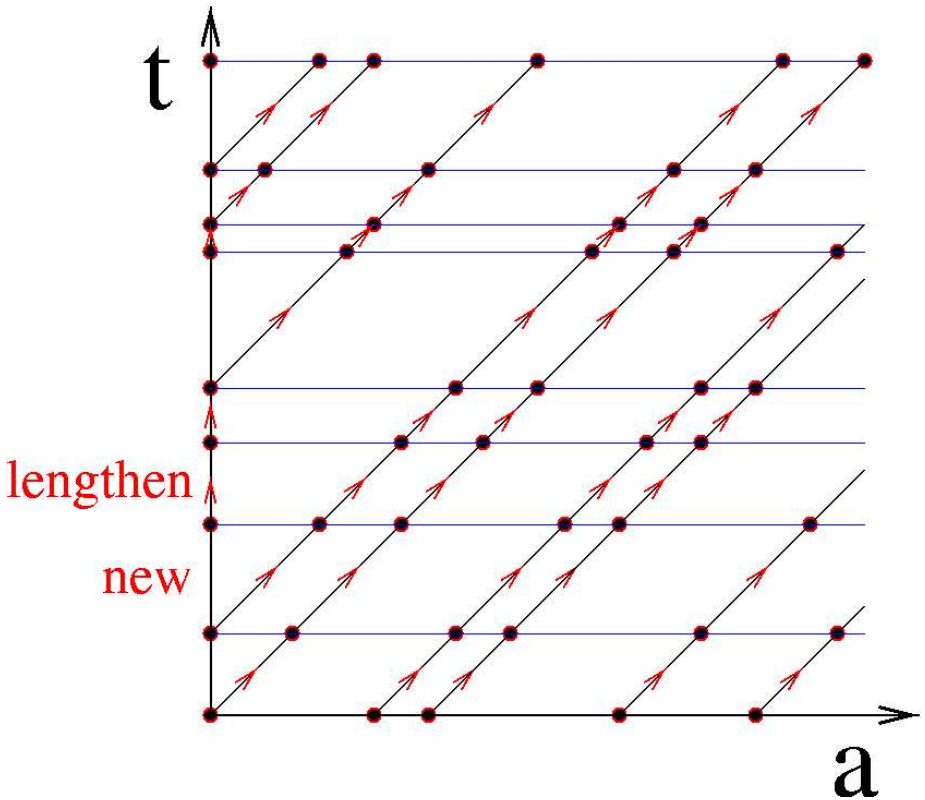
Fixed Age Grid



Moving Age Grid

Decouple age and time

Do not explicitly approximate age derivative



Notions of a cohort

Discretizations correspond to different notions of aging and what constitutes a cohort

Static discretization corresponds to the situation when an individual becomes “older” - and changes cohorts - on their birthday

Ex: the cohort of 35 year olds

In the moving discretization, individuals do not change cohorts - the cohort ages

Ex: Class of ’89

Increasing Birth Interval

Ignore death and diffusion. Over a time step Δt, we have a conservation law:

$$\Delta a_{\text{new}} U_{\text{new}} = \Delta a_{\text{old}} U_{\text{old}} + \Delta t\, b$$

Note $\Delta a_{\text{new}} = \Delta a_{\text{old}} + \Delta t$:

$$\Delta a_{\text{old}} (U_{\text{new}} - U_{\text{old}}) + \Delta t U_{\text{new}} = \Delta t\, b$$

Then

$$\frac{U_{\text{new}} - U_{\text{old}}}{\Delta t} = \frac{b - U_{\text{new}}}{\Delta a_{\text{old}}}$$

The term in red is the penalty term for the lengthening of the first interval

Galerkin Method

From this notion of a cohort, we can create a Galerkin finite element method

We use a subspace in age that moves along the characteristic curves, $da/dt = 1$

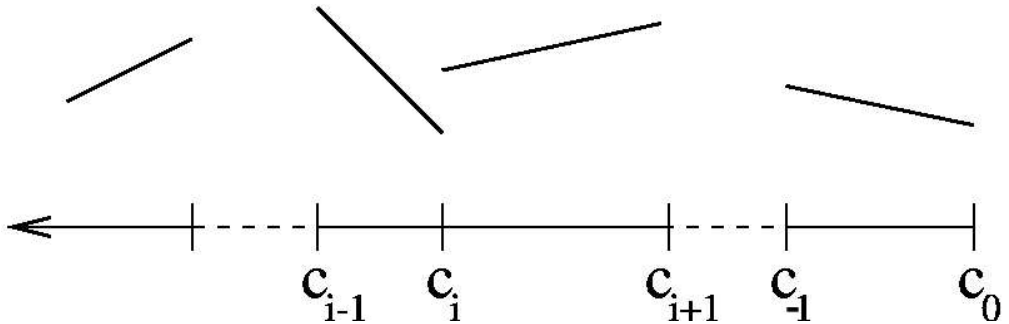
Taking the variational form in age of the model equations, and restricting solutions to functions that live in the age space, results in a separate time- and space-dependent PDE for each age group, which in turn can be discretized and solved on computer (in parallel for each age group)

Age Space

Finite dimensional subspace in age that moves along the characteristic curves, $da/dt = 1$:

$$\mathcal{A}(t) = \left\{ \varphi \in L^2(\mathbb{R}^+) : \varphi(\cdot) = \psi(\cdot - t)\big|_{\mathbb{R}^+},\ \psi \in \mathcal{C} \right\}$$

$\mathcal{C}$ = space of all discont. piecewise continuous polynomials of order q over a fixed partition $\mathcal{J}$ of $(-\infty, a_M]$



Discontinuous Galerkin Methods

The moving-grid Galerkin method is a discontinuous Galerkin method of sorts (we use discontinuous piecewise polynomials as the approximation space in age), but has an important additional property:

The movement of the grid computes the age transport – there is no error from discretizing the derivative in age, nor from integrating the jump discontinuities as would be done in a standard discontinuous Galerkin method (other than in the first interval)

The error in the solution comes "solely" from the approximation error

Convergence of the Age Method

BPA (SINUM 2000) proved second order convergence for the piecewise constant case (density within a cohort is uniform) for the general model

BPA and Todd F. Dupont (SINUM 2002) have shown convergence for general spaces of discontinuous piecewise polynomials including one extra power of superconvergence

Convergence of Step-Doubling

BPA and Todd F. Dupont (Math. Comp. 2005) showed second-order convergence in time of step-doubling – with variable time steps – for parabolic problems.

A freely available software toolkit, BuGS, implements step-doubling for systems of PDE's with at most one time derivative and one space variable (up to two derivatives in space).

Comment on Parameters

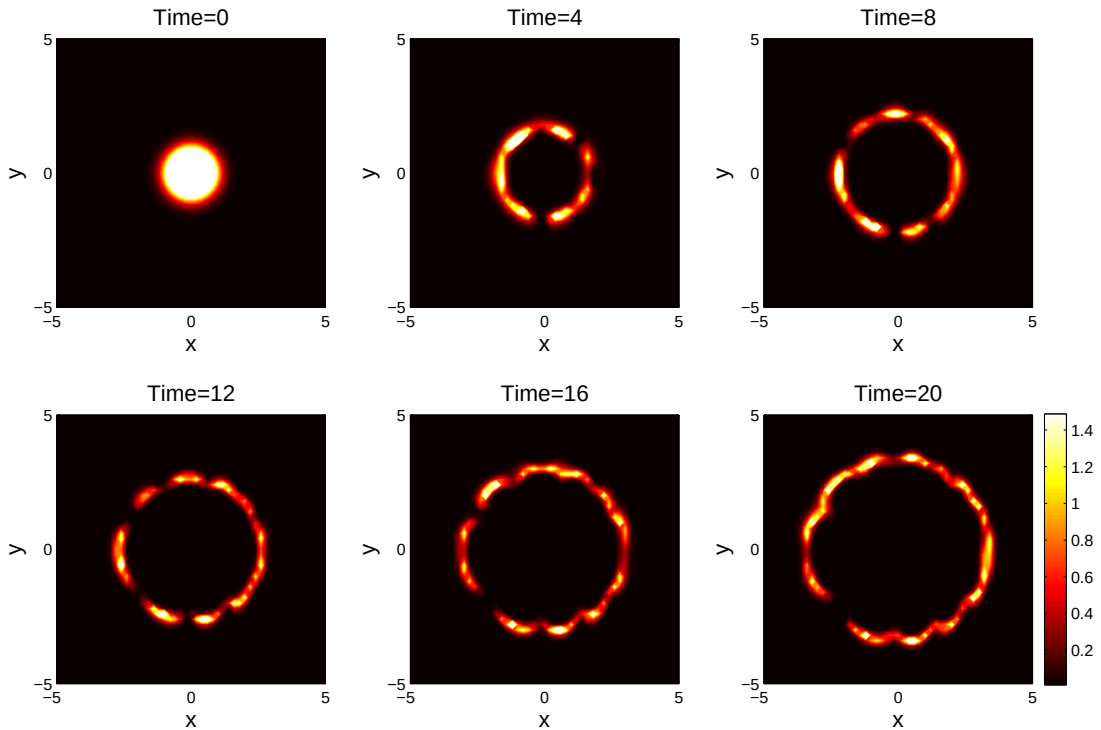
The 22 parameters/functional forms were chosen for illustrative purposes and/or based on those in Anderson, *Math. Med. Biol.*, 2005

Current work includes getting better biologically justified numbers

One goal was to strain the software:

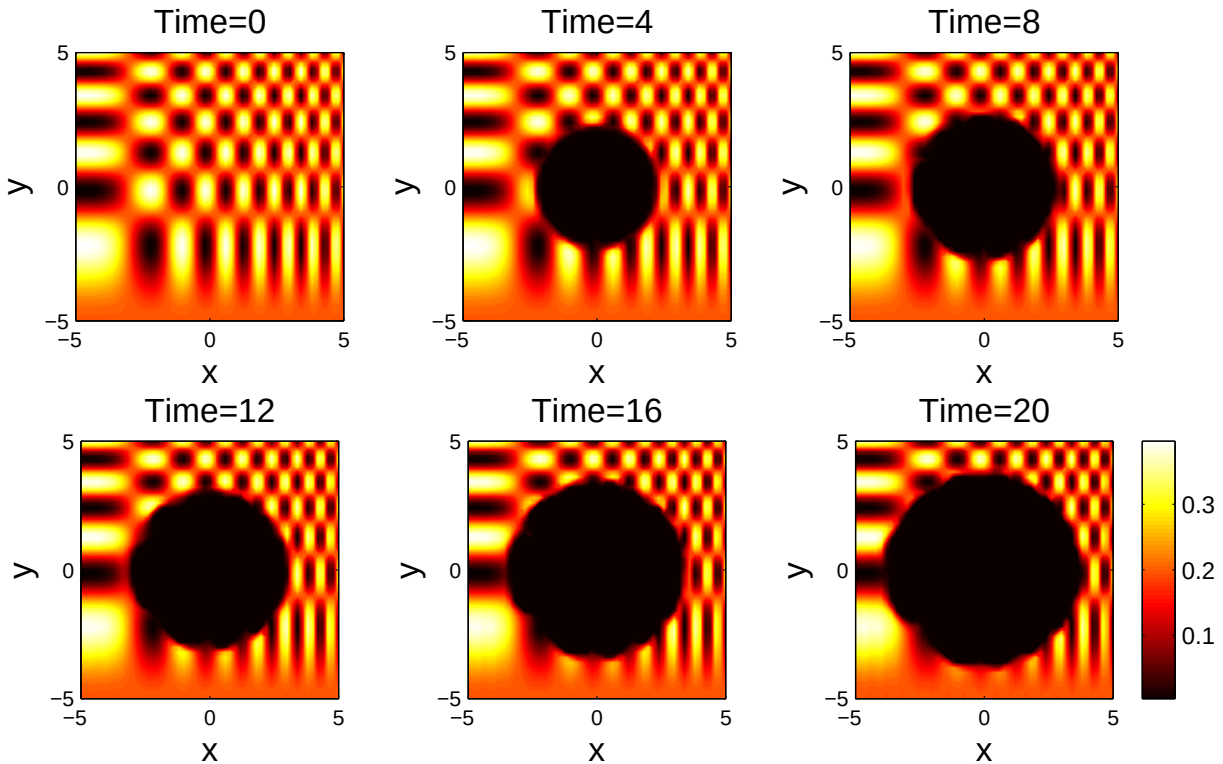
- Steep gradients/haptotaxis
- Stiffness in the ODE system

Computational Results



Proliferating-cell density profiles

Computational Results



Matrix molecule density profiles

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Conclusions

Although the current models require much work before they are relevant to understanding any aspect of cancer biology, the computational and modeling framework we have developed should allow us to incorporate new ideas relatively quickly

Model Refi nements

Current work:

- parameters
- arrest aging in quiescent cells for no-size model since age is used as a proxy for size (source/sink terms in PDE's no longer within same age interval in code)
- explicit necrotic cell population
- refine density dependence of haptotaxis term

Also need to begin incorporating chemotherapy into the model

General Physiological Structure

Currently developing methods for:

- cell size as in the general model
- continuous representations of different phenotypes/genotypes

Other Biological Systems

Structured Multiscale Modeling and Simulation is relevant to:

- *Proteus mirabilis* swarm-colony development (movement via degenerate diffusion)
- Biofilm (at IPAM with Isaac Klapper, movement via Darcy flow)
- Forests (seed movement via dispersal kernels)

Details of this talk can be found in

Ayati, Webb, and Anderson, “Computational Methods and Results for Structured Multiscale Models of Tumor Invasion,” *Multiscale Model. Simul.,* **5**(1), 2006, pp. 1–20