Exploring Partial Differential Equation Models of Glioma Growth

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Partial Differential Equation Seminar
Arizona State University
March 25, 2016

Outline

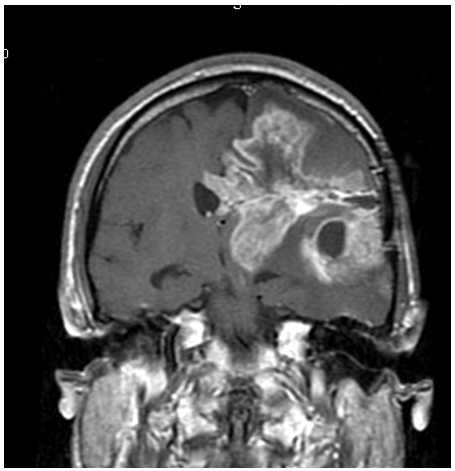
Introduction

- Cancer is a major health problem today, with an estimated 1.66 million new cancer cases and over 580,000 projected cancer deaths in the USA in 2015 [1]
- Mathematical models can be a helpful tool in understanding all stages of the disease, from growth to treatment
- As spatial structure is an important component of brain cancer, PDE's are often used. The models are:
  1. One equation PDE using density dependent diffusion, using *in vitro* data
  2. Two equation PDE using *in vitro* data
  3. Reaction-Diffusion PDE using *in vivo* data

Introduction: Glioblastoma

- Glioblastoma Multiforme (GBM) is a deadly primary brain tumor
- GBM is characterized by both high proliferation and diffusivity
- Mean Survival time with treatment is less than 15 months after detection
- Begins avascularaly, so early stages can be modeled by spheroids

- Symptoms include
  - hemorrhaging
  - nausea
  - vomiting
  - headaches
  - memory loss
  - seizures

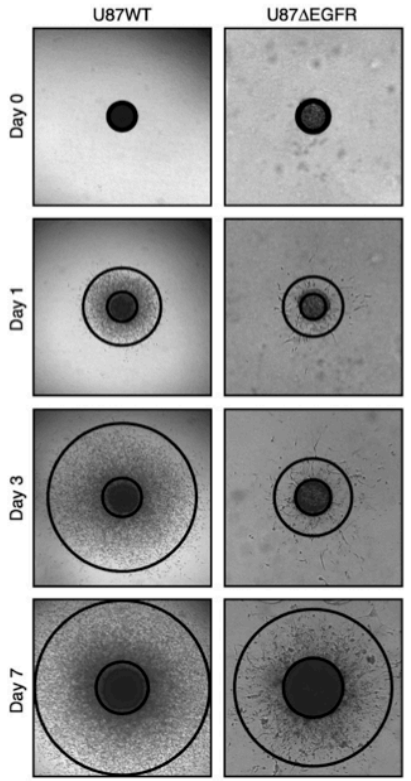


Sagittal cross-section of human brain with GBM

Outline

A Biological Introduction

- In 2007, Stein et. al performed cell line experiments on most common mutation of Epidermal Growth Factor Receptor gene (U87ΔEGFR) and wild-type EGFR (U87WT)
- This proved there are distinct behavioral differences between 'migrating' cells and 'proliferating cells'
- Wild type cells migrated more and mutated EGFR proliferated more
- Concluded that migrating and proliferating cells must be modeled separately: Go or Grow



Experimental images from several days with proliferating cell radius and migratory radius [2]

Stein et. al Mathematical Model

Governing behavior of migratory cells

$$\frac{\partial u_i(r,t)}{\partial t} = \underbrace{D\nabla^2 u_i}_{\text{diffusion}} + \underbrace{g u_i\left(1 - \frac{u_i}{u_{\max}}\right)}_{\text{logistic growth}} - \underbrace{v_i \nabla_r \cdot u_i}_{\text{taxis}} + \underbrace{s\delta(r - R(t))}_{\text{shed cells from core}}$$

$u_i(r,t)$	invasive/migratory cell population at position r and time t
D	diffusion constant $\quad O(10^{-4})$
g	growth rate $\quad O(0.1)$/day
$u_{\max}$	carrying capacity $\quad O(10^8)$
v_i	rate invasive cells move away from tumor core $\quad O(10^{-2})$
s	shed rate of tumor core $\quad O(10^5)$ cells/day
$R(t)$	radius of proliferating core at time t

Problematic numerically and analytically (how to simulate Dirac delta?)

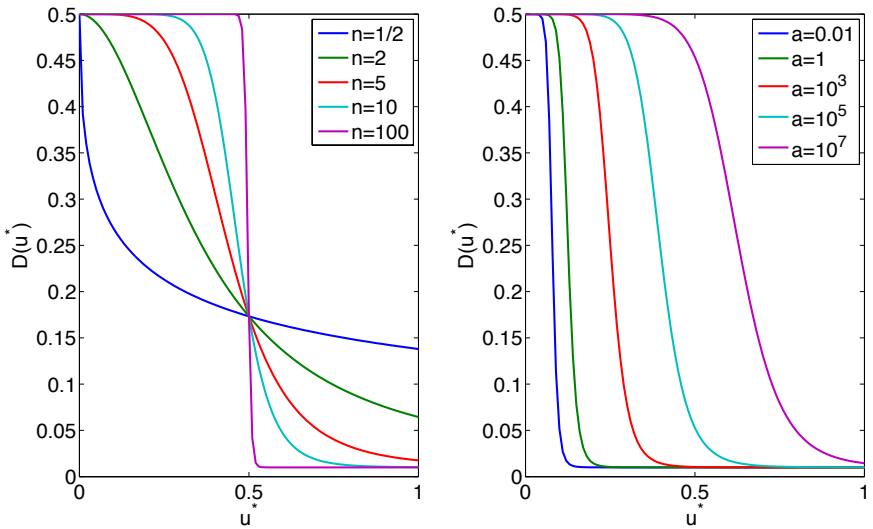
Biological and Mathematical Questions

- Biological Questions
  - Do we really need separate equations for the migratory cells and proliferating cells?
  - Is there really directed movement bias away from the proliferating core?
- Mathematical Questions
  - Can we create a biologically-driven model that fits the data better than the proposed 2-equation model?
  - Do our optimized parameters make biological sense?
  - Can we analyze the traveling wave solutions and corroborate the minimum wave speed computationally?

Density Dependent Diffusion

- Replace cell shedding term with density-dependent diffusion
- Invasive cells (low density) diffuse more than proliferative cells (high density)

$$D(u^*) = D_1 - \frac{D_2 (u^*)^n}{a^n + (u^*)^n}$$



Assumptions:

- $D_1,\ D_2,\ a,\ n > 0$
- $|D_1| > |D_2|$ to avoid numerical issues
- $u^* = \frac{u}{u_{\max}}$
  - Low densities correspond to high diffusion and higher densities correspond with lower diffusion

Density Dependent Diffusion Model

$$\frac{\partial u}{\partial t} = \underbrace{\nabla \cdot \left(D\left(\frac{u}{u_{\max}}\right) \nabla u \right)}_{\text{density-dependent diffusion}} + \underbrace{gu\left(1 - \frac{u}{u_{\max}}\right)}_{\text{logistic growth}} - \underbrace{\text{sgn}(x)\nu_i \nabla \cdot u}_{\text{taxis}},$$

Parameters

- All parameters non-negative
- $u_{\max}$ = carrying capacity density $= 4.2 \times 10^8 \, \text{cells/cm}^3$

Boundary conditions

- Far from the tumor, $u(x, t) = 0$

Initial condition

- Initial density profile based on experimental cell density data at Day 0:

$$u(x, 0) = \begin{cases} u_{\max}, & \|x\| \leq 210\mu\text{m} \\ 0, & \text{elsewhere} \end{cases}$$

Traveling Wave Speed

We begin by non–dimensionalizing the equation to get

$$\frac{\partial u}{\partial t} = D(u)\frac{\partial^2 u}{\partial x^2} + D'(u)\left(\frac{\partial u}{\partial x}\right)^2 - v\frac{\partial u}{\partial x} + u\,(1-u),$$

Our traveling wave solution is of the form

$$u(x,t) = w(x-ct) = w(z)$$

which we substitute into the above PDE:

$$w''(z) + \frac{1}{D(w(z))}\left((c-v)w'(z) + D'(w(z))(w'(z))^2 + w(z)(1-w(z))\right) = 0$$

Traveling Wave Speed cont'd

Rewriting this as a system of first-order differential equations

$$w' = y,$$
$$y' = -\frac{1}{D(w)}\left((c-v)y + D'(w)y^2 + w(1-w)\right)$$

We have two equilibria: (1,0), and (0,0).

For stability we examine Jacobian for $(1,0)$ first:

$$J(1,0) = \begin{pmatrix} 0 & 1 \\ \frac{1}{D(1)} & \frac{-(c-v)}{D(1)} \end{pmatrix}$$

$\det J(1,0) = \frac{-1}{D(1)} < 0$, so $(1,0)$ is a saddle point

Traveling Wave Speed cont'd

We examine Jacobian for $(0,0)$ for stability, assuming $c > v$:

$$J(0,0) = \begin{pmatrix} 0 & 1 \\ \frac{-1}{D(0)} & \frac{-(c-v)}{D(0)} \end{pmatrix},$$

$$\det J(0,0) = \frac{1}{D(0)} > 0$$

$$\tau J(0,0) = \frac{-(c-v)}{D(0)} < 0$$

$(0,0)$ is then either a stable node or a stable spiral. In order to have biologically relevant results, we cannot have a spiral, so we get the condition to be a stable node:

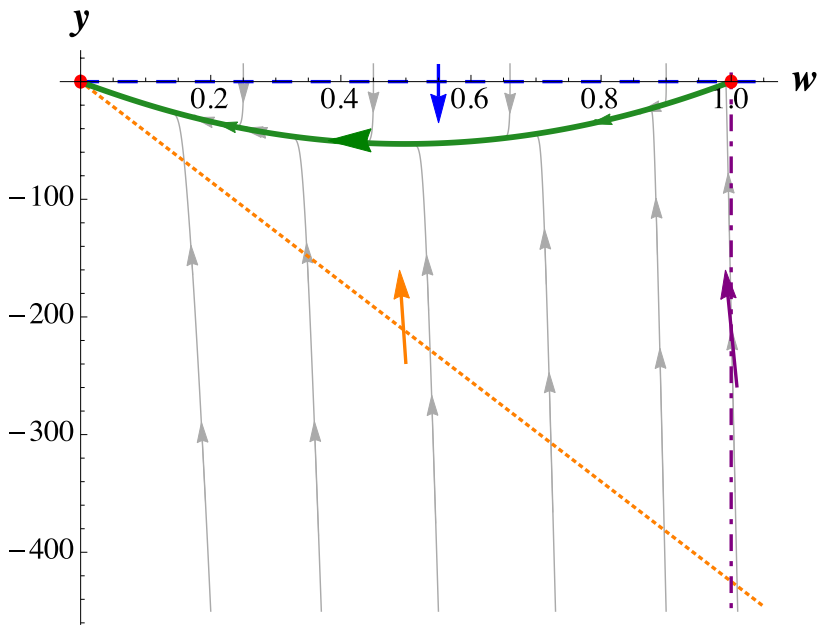
$$c \geq c_{\min} = 2\sqrt{D_1} + v, \quad \text{non-dimensional}$$

$$c \geq c_{\min} = 2\sqrt{D_1 g} + \nu_i, \quad \text{dimensional}$$

Wave Speed Analysis

Minimum wave speed (dimensionalized)

$$c \geq c_{\min} = 2\sqrt{D_1 g} + \nu_i$$



For full details on forming the trapping region, see Stepien et. al [3]

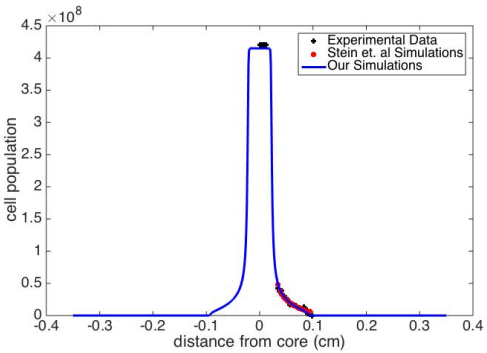
- Use fminsearch algorithm in MATLAB® to minimize the error function:

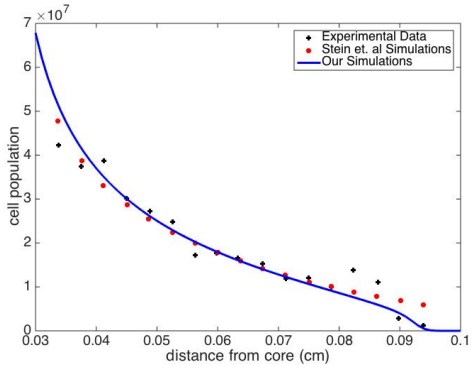
$$\text{err} = \frac{1}{(N+M)-q-1}\left[\sum_{t=1}^{N}\frac{|r_{\text{data}}(t)-r_{\text{simulation}}(t)|}{r_{\text{data}}(t)} + \sum_{i=1}^{M}\frac{|u_{\text{data}}(3,x_i)-u_{\text{simulation}}(3,x_i)|}{u_{\text{data}}(3,x_i)}\right]$$

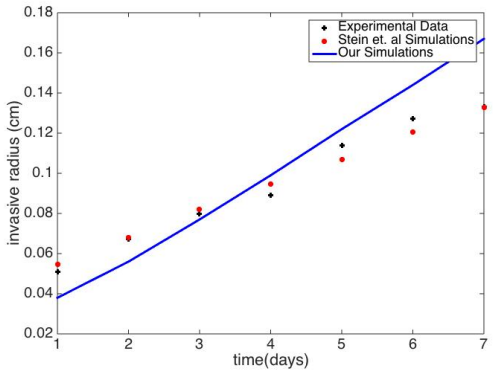
- $N+M$ represents total number of data points
- q is number of parameters being optimized

Optimization

- Started from various initial guesses
- Constrained to ensure parameters are non-negative







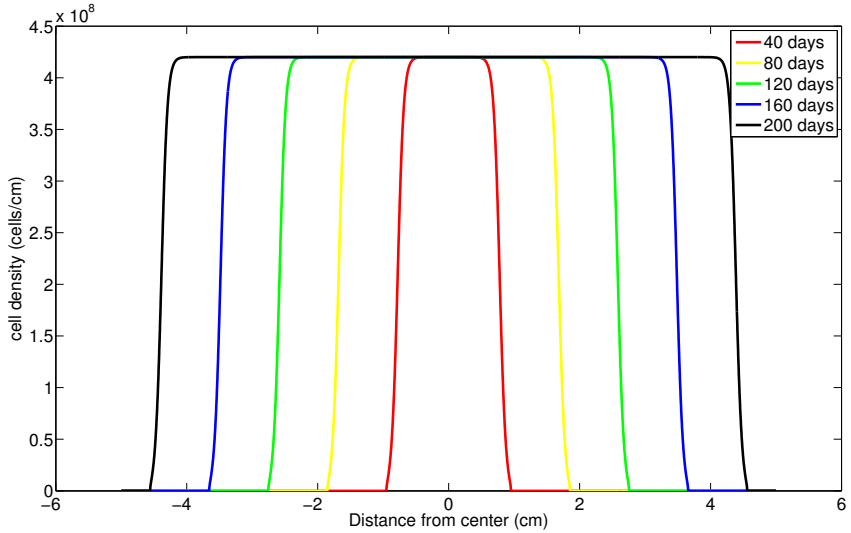
Numerical solution of our density-dependent diffusion GBM model with optimized parameter values compared to experimental data and simulations from Stein et al. [2]

$$D_1 = 5.5408 \times 10^{-6}\ \text{cm}^2/\text{day}, \quad D_2 = 5.3910 \times 10^{-6}\ \text{cm}^2/\text{day},$$

$$a = 0.021188\,\text{cells}/\text{cm}^3, \quad n = 1.2848,$$

$$g = 0.49120/\text{day}, \quad \nu_i = 4.6801 \times 10^{-5}\ \text{cm}/\text{day}$$

Traveling Wave Speed

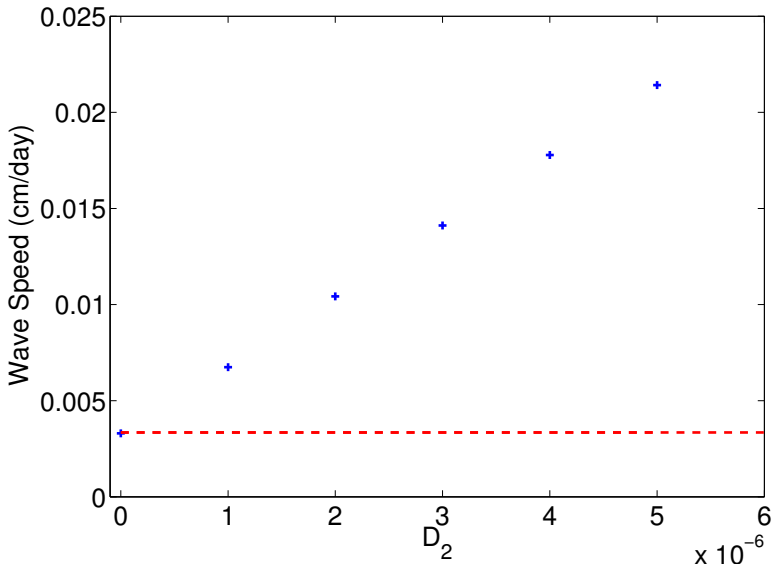


- Extended domain and time of simulation
- Track 10% of maximum through time and use polyfit to find wave speed

- Theoretical minimum wave speed $c_{\text{min}} \approx 0.003346$ cm/day, simulated wave speed $c = 0.02255$ cm/day
- Simulated wave speed is magnitudes larger than theoretical minimum wave speed
- Where does the discrepancy come from?

Traveling Wave Speed Cont'd

- Observable wave speed much larger than theoretical minimum wave speed
- Information is lost through the linearization process



- Observable wave speed appears to increase linearly through values of D_2
- When $D_2 = 0$, observable matches theoretical wave speed

Conclusions and Further Directions

- Conclusions
  - Created a density-dependent diffusion equation modeling *in vitro* growth of GBM
  - Sensitivity analysis revealed all parameters important
  - Optimized parameters to generate a fit better than the two-equation model
  - Compared theoretical minimum wave speed to observed wave speed
- Further Directions
  - Perform computational analysis to determine how each parameter affects observed wave speed.
  - How to accurately determine observed wave speed analytically
  - Stability of wave
  - Use density-dependent diffusion equation for *in vivo* modeling – is it accurate?

Outline

Model Formulation

We have two populations: Migrating cells, $M(x,t)$, and Proliferating Cells, $P(x,t)$) and $T = M + P$

$$\frac{\partial M}{\partial t} = \underbrace{D\nabla^2 M}_{\text{diffusion}} + \underbrace{\epsilon \frac{T^n}{T^n + K_M^n} P}_{\text{switch form prolif to mig}} - \underbrace{k \frac{K_P^n}{T^n + K_P^n} M}_{\text{switch form mig to prolif}} - \underbrace{\mu M}_{\text{death}}$$

$$\frac{\partial P}{\partial t} = \underbrace{gP\left(1 - \frac{T}{T_{\max}}\right)}_{\text{logistic growth}} - \underbrace{\epsilon \frac{T^n}{T^n + K_M^n} P}_{\text{switch form prolif to mig}} + \underbrace{k \frac{K_P^n}{T^n + K_P^n} M}_{\text{switch form mig to prolif}}$$

Boundary conditions and initial conditions

- Far from the tumor, $u(x,t) = 0$
- Initial density profile based on experimental cell density data at Day 0:

$$u(x,0) = \begin{cases} u_{\max}, & \|x\| \leq 210\mu\text{m} \\ 0, & \text{elsewhere} \end{cases}$$

Traveling Wave Solutions

We assume a traveling wave solution of the form:

$$M(x,t) = u(x-ct) = u(z)$$
$$P(x,t) = v(x-ct) = v(z)$$

where $c \geq 0$ is the speed of the traveling wave.

Substituting into our PDE, we get:

$$c\frac{du}{dz} + D\frac{d^2u}{dz^2} + \epsilon\frac{(u+v)^n}{(u+v)^n + K_M^n}v - k\frac{K_P^n}{(u+v)^n + K_P^n}u - \mu u = 0$$
$$c\frac{dv}{dz} + gv\left(1 - \frac{u+v}{T_{\max}}\right) - \epsilon\frac{(u+v)^n}{(u+v)^n + K_M^n}v + k\frac{K_P^n}{(u+v)^n + K_P^n}u = 0$$

Traveling Wave cont'd

We break into a system of 3 first-order ordinary differential equations:

$$u' = w$$

$$w' = -\frac{1}{D}\left[cw + \epsilon\frac{(u+v)^n}{(u+v)^n + K_M^n}v - k\frac{K_P^n}{(u+v)^n + K_P^n}u - \mu u\right]$$

$$v' = -\frac{1}{c}\left[gv\left(1 - \frac{u+v}{T_{\max}}\right) - \epsilon\frac{(u+v)^n}{(u+v)^n + K_M^n}v + k\frac{K_P^n}{(u+v)^n + K_P^n}u\right]$$

We can see that (0,0,0) is certainly an equilibrium, as well as some E^*

Traveling Wave cont'd

We examine the Jacobian for (0,0,0), which is where our previous model derived its minimum wave speed condition:

$$J(0,0,0) = \begin{pmatrix} 0 & 0 & 1 \\ -\frac{k}{c} & -\frac{g}{c} & 0 \\ \frac{k+\mu}{D} & 0 & -\frac{c}{D} \end{pmatrix},$$

Which has eigenvalues of:

$$\lambda_1 = -\frac{g}{c}$$

$$\lambda_2 = -\frac{1}{2}\left[\frac{c}{D} + \sqrt{\left(\frac{c}{D}\right)^2 + 4\left(\frac{k+\mu}{D}\right)}\right]$$

$$\lambda_2 = -\frac{1}{2}\left[\frac{c}{D} - \sqrt{\left(\frac{c}{D}\right)^2 + 4\left(\frac{k+\mu}{D}\right)}\right]$$

So (0,0,0,) is a saddle

Traveling Wave cont'd

E^*, the (at least one) other equilibrium is not so easy to solve for :

$$g\left(1-\frac{U+V}{T_{\max}}\right)V-\epsilon k\frac{(U+V)^n}{(U+V)^n+K_M^n}V+k\frac{K_P^n}{(U+V)^n+K_P^n}U=0$$

$$\epsilon k\frac{(U+V)^n}{(U+V)^n+K_M^n}V-k\frac{K_P^n}{(U+V)^n+K_P^n}U-\mu U=0$$

We can add the equations together to solve for U

$$U=\frac{g(T_{\max}-V)V}{\mu T_{\max}+gV} \tag{1}$$

But plugging back into the above to solve for V is problematic

Traveling Wave Solutions Cont'd

We assume ahead of the wave front:

$$u(z) = \hat{u}e^{-\theta z}$$
$$v(z) = \hat{v}e^{-\theta z}$$

Substituting into our PDE, we get:

$$-c\theta\hat{u} + D\theta^2\hat{u} + \epsilon\frac{(\hat{u}+\hat{v})^n e^{-n\theta z}}{(\hat{u}+\hat{v})^n e^{-n\theta z} + K_M^n}\hat{v} - k\frac{K_P^n}{(\hat{u}+\hat{v})^n e^{-n\theta z} + K_P^n}\hat{u} - \mu\hat{u} = 0$$
$$-c\theta\hat{v} + g\hat{v}\left(1 - \frac{(\hat{u}+\hat{v})e^{-n\theta z}}{T_{\max}}\right) - \epsilon\frac{(\hat{u}+\hat{v})^n e^{-n\theta z}}{(\hat{u}+\hat{v})^n e^{-n\theta z} + K_M^n}\hat{v} + k\frac{K_P^n}{(\hat{u}+\hat{v})^n e^{-n\theta z} + K_P^n}\hat{u} = 0$$

Traveling Wave Solutions Cont'd

Keeping only leading order terms:

$$-c\theta\hat{u} + D\theta^2\hat{u} - k\hat{u} - \mu\hat{u} = 0$$
$$-c\theta\hat{v} + g\hat{v} + k\hat{u} = 0$$

We solve the first equation for θ

$$\theta = \frac{1}{2}\left[\frac{c}{D} \pm \sqrt{\left(\frac{c}{D}\right)^2 + 4\left(\frac{k+\mu}{D}\right)}\right]$$

Traveling Wave Solutions Cont'd

Now we examine the second equation

$$c\theta\hat{v} = g\hat{v} + k\hat{u} = 0$$

And using the positive root of $\theta(c)$, since $\hat{u}, \hat{v} \geq 0$:

$$f(c) := c\theta(c) = g + k\frac{\hat{u}}{\hat{v}}$$

Since $\hat{u}, \hat{v} > 0$, and assuming migrating population is at most the same as proliferating population far from the tumor, we can state that $\frac{\hat{u}}{\hat{v}} \geq 0$ or

$$f(c) \geq g$$

Traveling Wave Solutions Cont'd

We see that $f(0) = 0$ and that $f'(c) > 0$ for $c > 0$, so there is a positive minimum wave speed c_m such that $f(c_m) = g$

$$f(c) = c\frac{1}{2}\left[\frac{c}{D} + \sqrt{\left(\frac{c}{D}\right)^2 + 4\left(\frac{k+\mu}{D}\right)}\right] = g$$

Solving for c we obtain

$$c_{m1} = g\sqrt{\frac{D}{g+k+\mu}}$$

This is our minimum wave speed of the tumor growth

Traveling Wave Solutions Cont'd

On the other hand, we can say that at most we expect an equal ratio of proliferating cells and migrating cells, meaning $\frac{\hat{u}}{\hat{v}} \approx 1$, or that migrating cells dominate proliferating cells away from the tumor $\frac{\hat{u}}{\hat{v}} \geq 1$ so there is a positive minimum wave speed c_m such that $f(c_m) = g + k$

$$f(c) = c\frac{1}{2}\left[\frac{c}{D} + \sqrt{\left(\frac{c}{D}\right)^2 + 4\left(\frac{k+\mu}{D}\right)}\right] = g + k$$

Solving for c we obtain

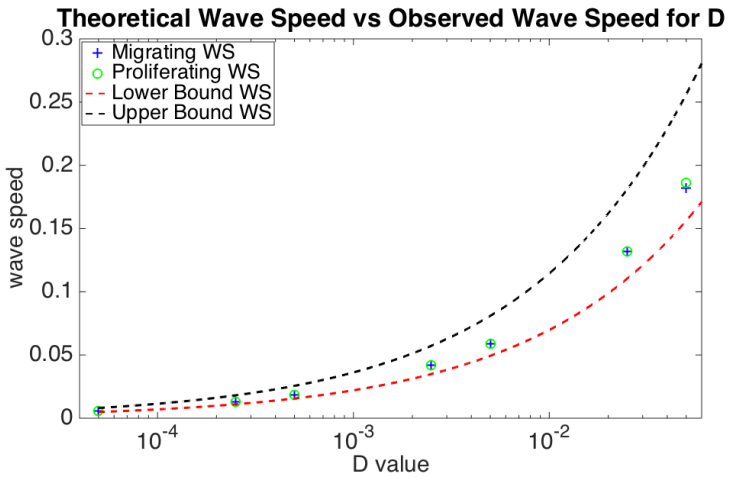
$$c_{m2} = (g+k)\sqrt{\frac{D}{g+2k+\mu}}$$

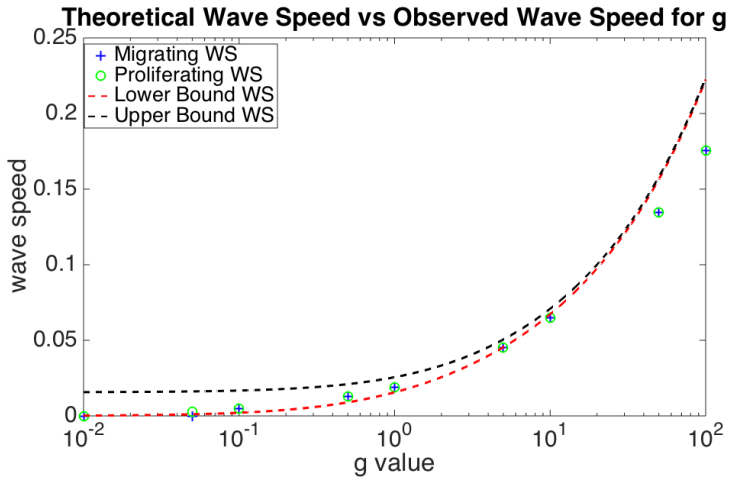
This is our minimum wave speed of the tumor growth

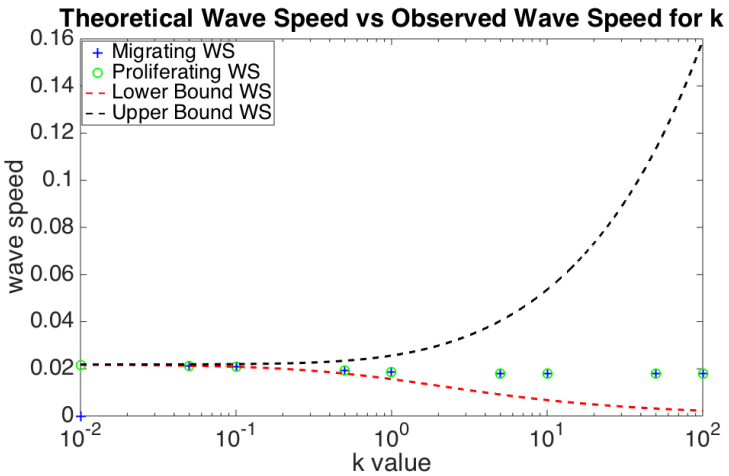
Simulations

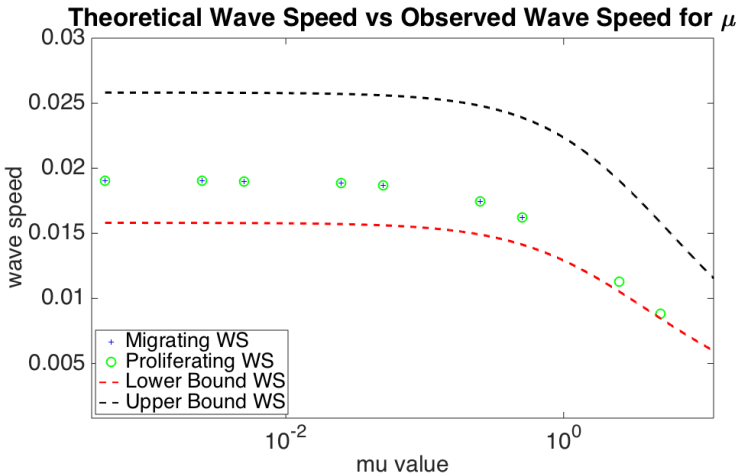
We expect the wave speed to follow:

$$c_{m1} = g\sqrt{\frac{D}{g+k+\mu}} \leq c_m \leq (g+k)\sqrt{\frac{D}{g+2k+\mu}} = c_{m2}$$



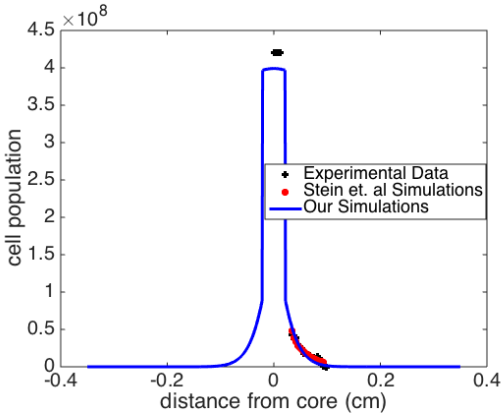


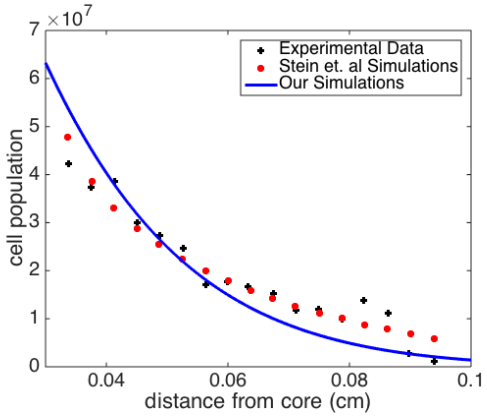


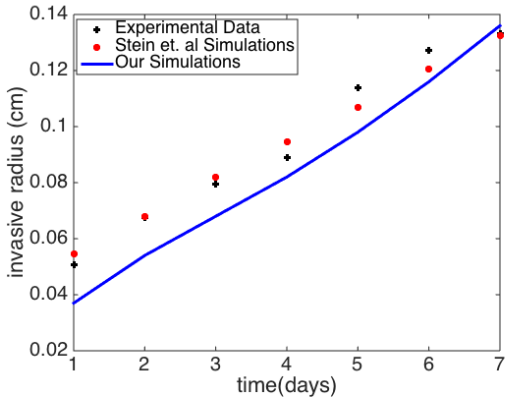


Optimization

- Constrained to ensure parameters are non-negative







Numerical solution of 2-equation GBM model with optimized parameter values compared to experimental data and simulations from Stein et al. [2]

$$D = 2.992 \times 10^{-4}\ \text{cm}^2/\text{day}, \quad g = 1.75/\text{day},$$
$$k = 0.02891, \quad \mu = 0.01456/\text{day},$$
$$K_M = 0.7559, \quad K_P = 1.4528 \times 10^{-5},$$
$$\epsilon = 0.2639$$

Fit is worse than the density-dependent diffusion model and on par with the Stein et. al fit

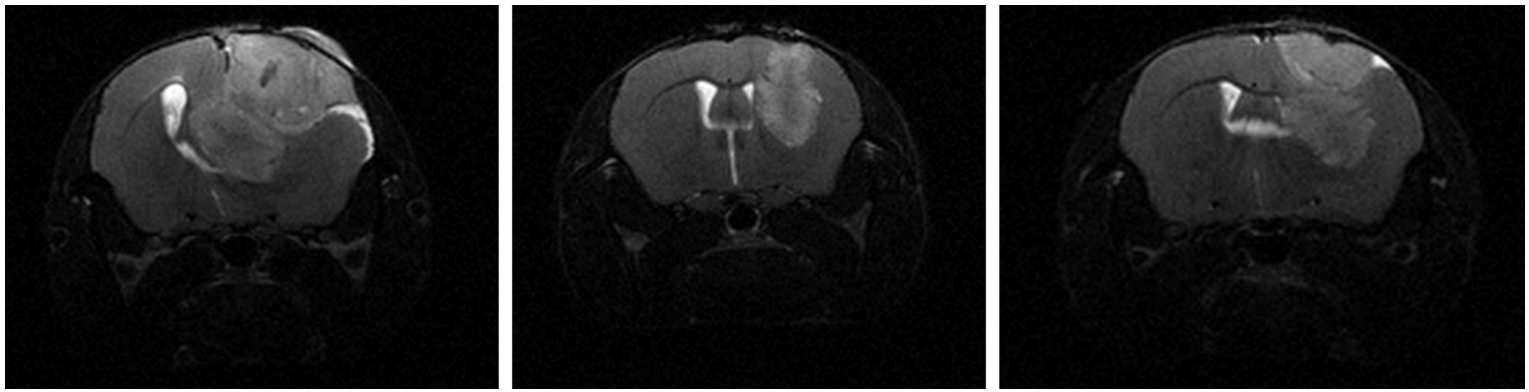
Conclusions and Further Directions

- Conclusions
  - Created a 2–equation modeling *in vitro* growth of GBM
  - Determined theoretical minimum wave speed
  - Optimized parameters to see that the two—equation model is inferior to the density-dependent diffusion at fitting the experimental data – maybe GBM should not be modeled with constant diffusion
  - Compared theoretical minimum wave speed(s) to observed wave speed
- Further Directions
  - Determine what $\frac{\hat{u}}{\hat{v}}$ is to figure out our c_m
  - Incorporate density-dependent diffusion equation in M
  - Use density-dependent diffusion equation for *in vivo* modeling – is it accurate?
  - Consider specialized cases such as $\mu = 0$

Outline

Introduction: *In vivo* Experimental Data

- 5 immune-competent mice were cranially injected with GL261 cell line
- Mice were imaged using MR 5 times (day 11, 15, 18, 22, 25)
- Mice were euthanized on day 26 brains harvested for histology



MR images from day 25 for all mice at the same location

Creation of Computational Domain

- Mimics® uses thresholding to generate rough segmentation of brain
- Edges smoothed by hand to ensure a computationally-friendly domain
- Each mouse is registered to their third time point using GeoMagic® to ensure computational domain remains consistent throughout simulation
- MATLAB® is used to apply the affine matrix from GeoMagic® to register all brains to their third time point geometry
- Uniform matrix saved with brain geometries

Mathematical Equation

$$\frac{\partial u}{\partial t}(\mathbf{x}, t) = \underbrace{D\nabla^2 u(\mathbf{x}, t)}_{\text{diffusion}} + \underbrace{\rho u(\mathbf{x}, t)\,(1 - u(\mathbf{x}, t))}_{\text{growth}}, \qquad \mathbf{x} \in \Omega$$

$$u(\mathbf{x}, t) = 0, \qquad \mathbf{x} \in \partial\Omega$$

$$u(\mathbf{x}, 0) = f(\mathbf{x}), \qquad \mathbf{x} \in \Omega$$

Where Ω is brain geometry with ventricles segmented out, $\partial\Omega$ is the boundary of the brain and ventricles, and $f(x)$ depends on the initial condition choice

- D represents diffusion coefficient
- ρ represents intrinsic growth rate of GL261

Computational Methods

- 3D finite difference model
- Spatial discretization is centered finite difference
- Ode45 used to step through time
- Code written as a MCTP project by Barrett Anderies
- To optimize the parameters ,we examine the error function based on the Jaccard Index

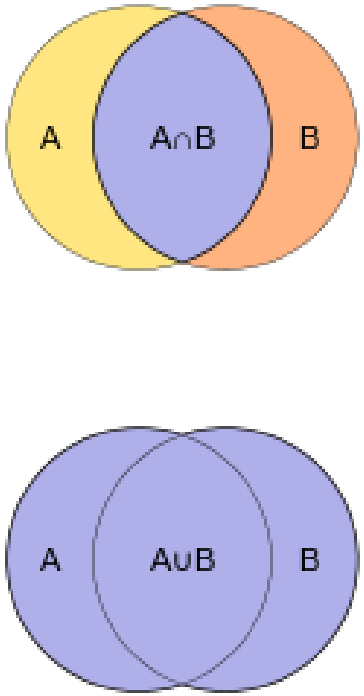
$$\text{error} = \sum_{k=1}^{4} \left(1 - \frac{\text{data} \cap \text{simulation}}{\text{data} \cup \text{simulation}} \right)$$

where k represent the time points we have data for.

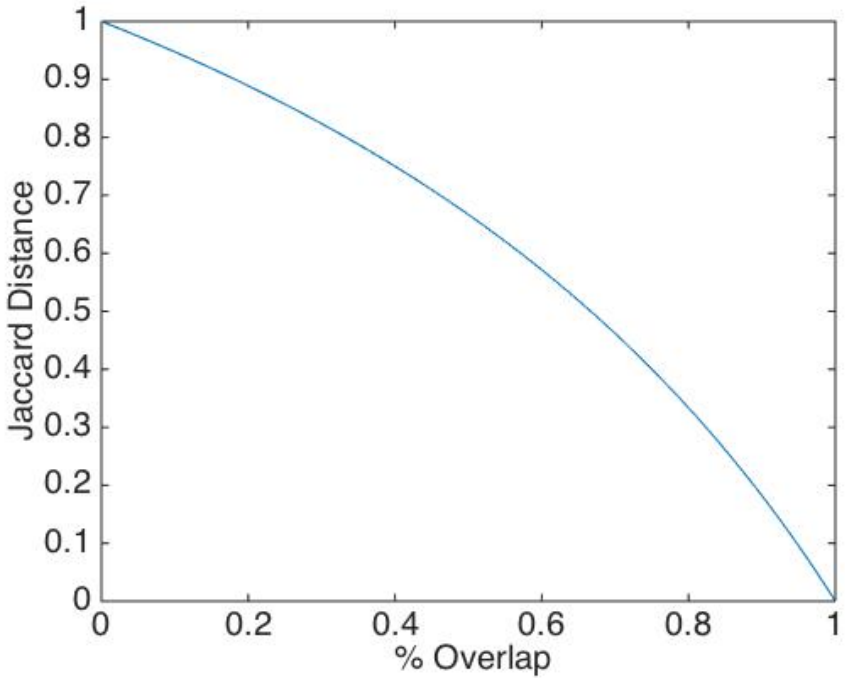
Jaccard Distance

The error function is based on the Jaccard distance:

$$\text{error} = \frac{1}{n}\sum_{k=1}^{n}\left(1 - \frac{\text{data} \cap \text{simulation}}{\text{data} \cup \text{simulation}}\right)$$



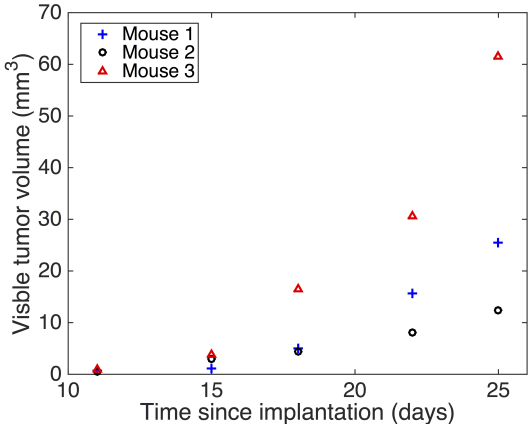
Union and intersection of overlapping sets



Graph displaying the Jaccard distance 'score' for various overlap values

Biological and Mathematical Questions

- Biological Question: Why such large variance in final tumor size between mice?
  1. Hypothesis 1 (H1): Natural variations in D and ρ account for the change
  2. Hypothesis 2 (H2): Morphological chages occur, meaning D and ρ should not be constant.
  3. Hypothesis 3 (H3): Short-term solutions changing D and ρ.



Total visible volume for each mouse at each time point

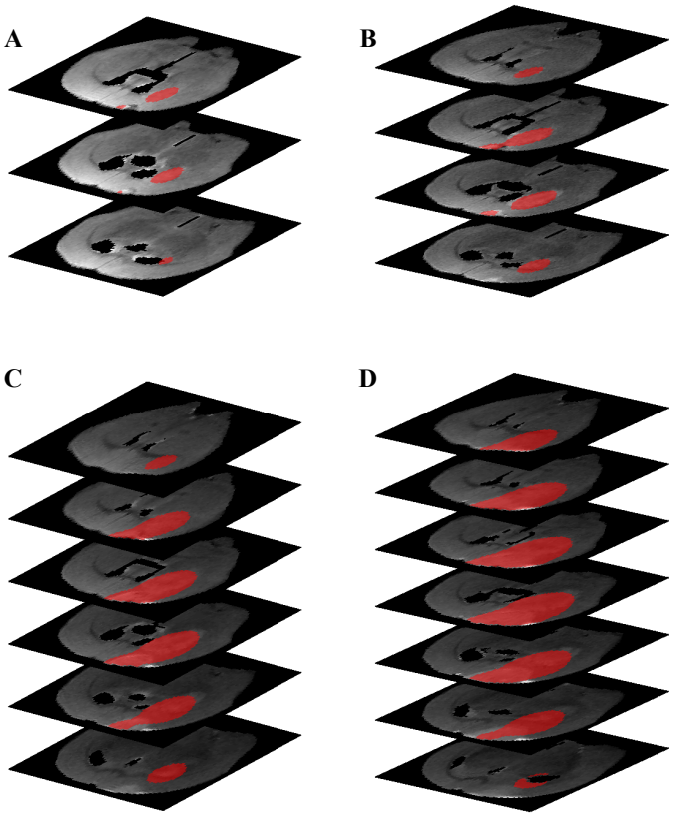
- Mathematical Questions
  - Can we use a simple model to test the above biological hypotheses?
  - Can we optimize to find biologically relevant parameters?

How to Test Hypotheses?

We need methods to test our hypotheses

1. Hypothesis 1: We simply optimize D and ρ over all times points for each mouse, using the Jaccard index at each time point.
2. Hypothesis 2: We optimize from previous optimized time point, i.e. we must optimize day 11 to day 14 first, then use the optimal simulated tumor to initialize day 14 to day 18.
3. Hypothesis 3: We optimize from MR-generated time point. At each new optimization, we use the MR image as initialization. i.e. for day 14 to day 18, we use MR image from day 14 as initialization.

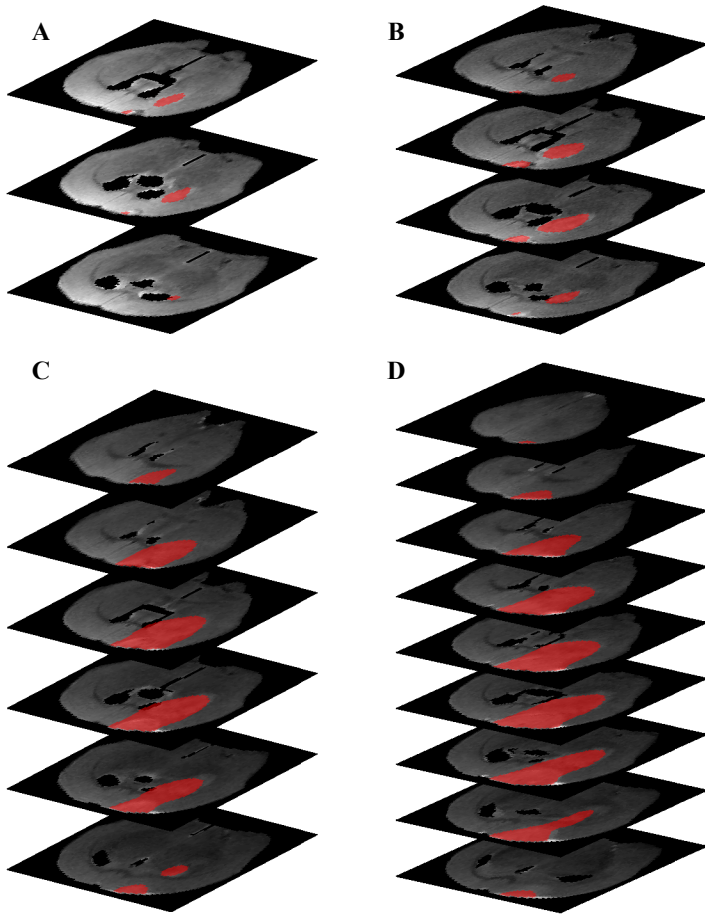
Results For Representative Mouse – Hypothesis 1



Simulated tumor (red) superimposed on MR images for Mouse 1 on (A) Day 15; (B) Day 18; (C) Day 22, and (D) Day 25 following implantation.

- D: 413.77 $(\mu \mathbf{m}^2/\mathbf{h})$
- ρ: 0.0188 $\mathbf{(h^{-1})}$
- Jaccard Distance: 0.4524
- Percentage Overlap: 70.8%

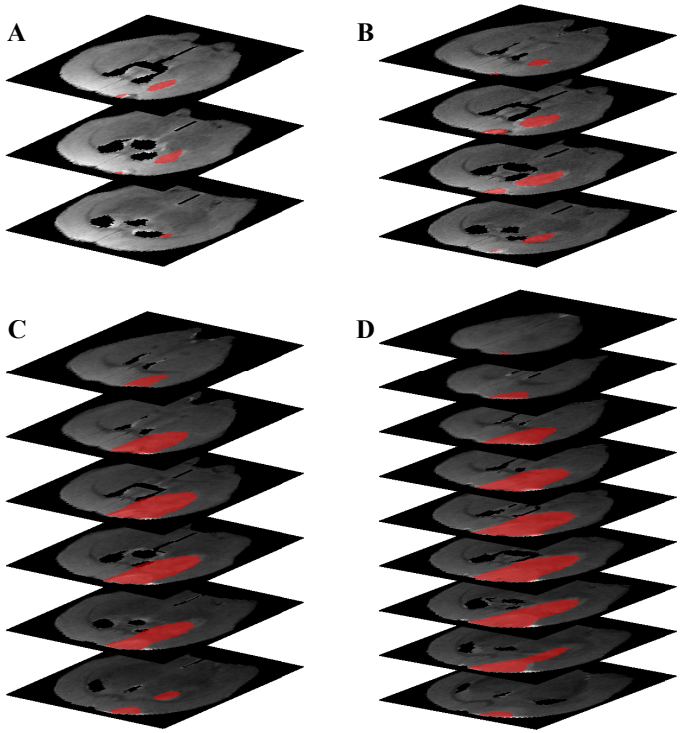
Results For Representative Mouse – Hypothesis 2



Simulated tumor (red) superimposed on MR images for Mouse 1 on (A) Day 15; (B) Day 18; (C) Day 22, and (D) Day 25 following implantation.

- $D(s)$:
  139.24 $(\mu \mathbf{m}^2/\mathbf{h})$
  839.93 $(\mu \mathbf{m}^2/\mathbf{h})$
  1047.6 $(\mu \mathbf{m}^2/\mathbf{h})$
  968.75 $(\mu \mathbf{m}^2/\mathbf{h})$
- ρ:
  0.0182 $(\mathbf{h}^{-1})$
  0.0248 $(\mathbf{h}^{-1})$
  0.0192 $(\mathbf{h}^{-1})$
  0.0082 $(\mathbf{h}^{-1})$
- Jaccard Distance:
  0.4365
- Percentage Overlap:
  72%

Results For Representative Mouse – Hypothesis 3



Simulated tumor (red) superimposed on MR images for Mouse 1 on (A) Day 15; (B) Day 18; (C) Day 22, and (D) Day 25 following implantation.

- $D(s)$:
  139.24 $(\mu \mathbf{m}^2/\mathbf{h})$
  233.97 $(\mu \mathbf{m}^2/\mathbf{h})$
  1156.2 $(\mu \mathbf{m}^2/\mathbf{h})$
  1305.6 $(\mu \mathbf{m}^2/\mathbf{h})$
- ρ:
  0.0182 $(\mathbf{h}^{-1})$
  0.0499 $(\mathbf{h}^{-1})$
  0.0178 $(\mathbf{h}^{-1})$
  0.0105 $(\mathbf{h}^{-1})$
- Jaccard Distance:
  0.3673
- Percentage Overlap:
  77%

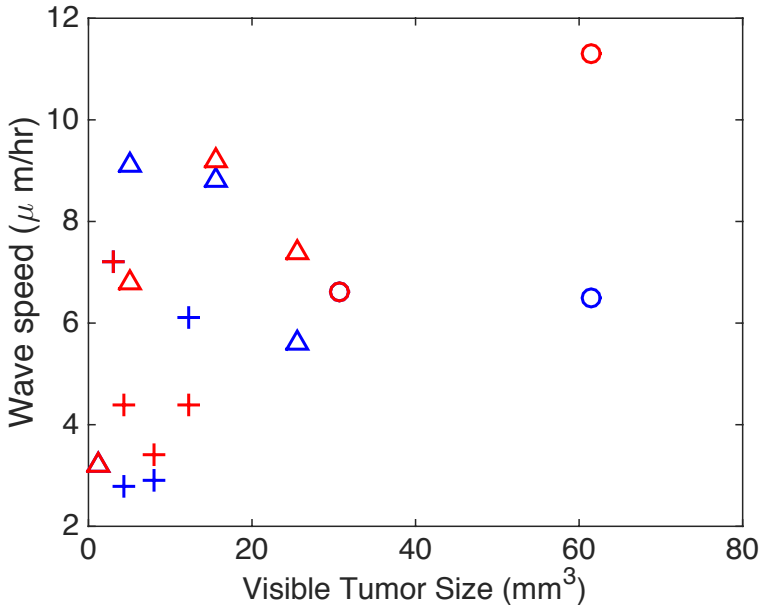
Remaining Information

Table : Values of estimated parameters for Mouse 2 and 3 and each hypothesis at each time point using the 3D finite difference method. Minimization is performed with respect to Jaccard distance

Mouse	Hypothesis	Time Point	D (μm^2/h)	ρ (h^{-1})	velocity $2\sqrt{D\rho}$ (μm/h)	Error	Overlap (%)
2	1	–	319.22	0.0167	4.6178	0.4528	70.7
	2	2	558.74	0.0235	7.2472	0.1151	70.1
		3	206.21	0.0100	2.8720	0.1067	72.9
		4	346.35	0.0055	2.7604	0.1042	73.7
		5	886.07	0.0104	6.0713	0.0979	75.6
	3	2	558.74	0.0235	7.2472	0.1151	70.1
		3	950.79	0.0051	4.4041	0.0846	79.6
		4	77.734	0.0369	3.3873	0.0621	85.8
		5	94.161	0.0520	4.4255	0.0643	85.2
3	1	–	651.17	0.0177	6.7899	0.2833	83.5
	2	4	859.70	0.0127	6.6085	0.1408	83.6
		5	454.29	0.0236	6.5487	0.1364	84.2
	3	4	859.704	0.0127	6.6085	0.1408	83.6
		5	1552.1	0.0200	11.1431	0.1027	88.6

Wave Speed

Recall for reaction-diffusion equation, the minimum wave speed is $c_{\text{min}} = 2\sqrt{D\rho}$. Examining the wave speeds for our simulations:



Estimated wave speeds for various tumor volumes. Red represents hypothesis 3, blue is hypothesis 2. Mouse 1: triangles; Mouse 2 plusses; Mouse 3 circles.

Conclusions and Further Directions

- Conclusions
  - Generated uniform grid from actual MR images
  - Used 3D finite difference code to fit simulated tumor to actual tumor
  - Tested hypotheses as to why the final tumor sizes are so different
  - Measured wave speeds which match other rat and human experimental data
- Further Directions
  - Incorporating more complexity into the model to achieve a better fit
  - Use more realistic diffusion (Diffusion Tensor Imaging)
  - Use histology to quantify relationship between visible tumor on MR image and carrying capacity/tumor density
  - Incorporate more realistic brain structure – mass effect via finite element method

Thanks

Special thanks must be given to

- From the SOMMS Dept:
  - Dr. Yang Kuang
  - Dr. Tracy Stepien
  - Dr. Eric Kostelich
  - Barrett Anderies
- From IPA Lab:
  - Dr. David Frakes
  - Jon Plasencia
- From Barrow Neurological Institute
  - Dr. Mark Preul
  - Dr. Adrienne Scheck
  - Dr. Eric Woolf

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