A Mathematical Model of GL261-Luc2 Glioma Growth in Mice

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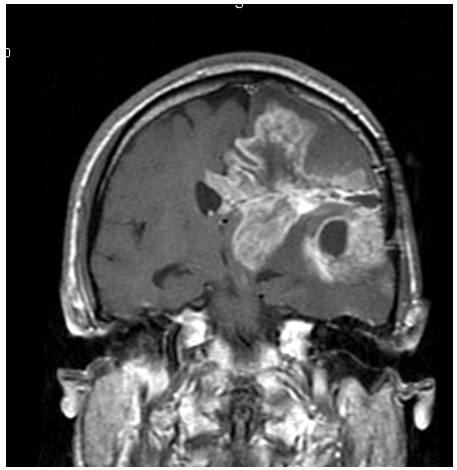
Outline

1. Introduction
2. Experimental Work
3. Mathematical Model
4. Results

Introduction: Glioblastoma Multiforme (GBM)

- 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
- MR (magnetic resonance) imaging only shows some of tumor

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



Sagittal cross-section of human brain with GBM

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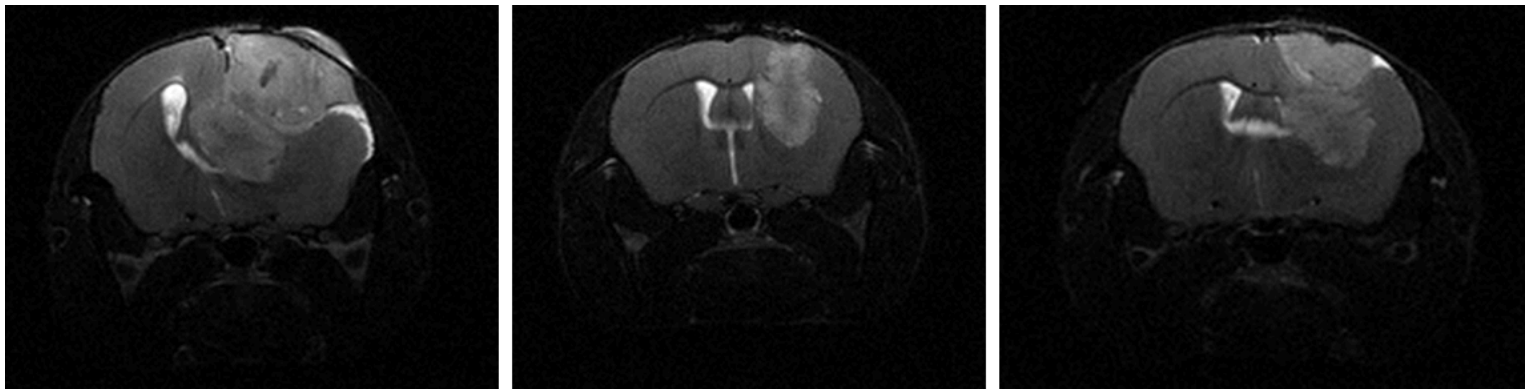
Introduction: *In vivo* Experimental Data

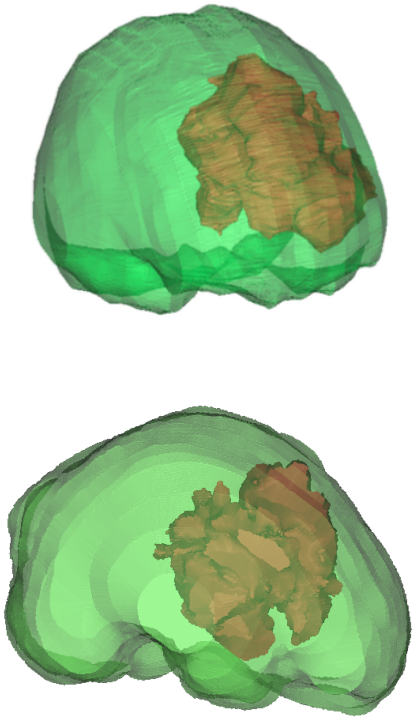
- 5 immune-competent mice were cranially injected with GL261 cell line
- Mice were imaged using MR 5 times (day 11, 15, 18, 22, 25)
- Mice were euthanized on day 26 brains harvested for histology



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



Human brain volume generated from MR images

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Mathematical Equation

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

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

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

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 (50% max)

- 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 Distance and use FMINSEARCH (Nelder-Mead)

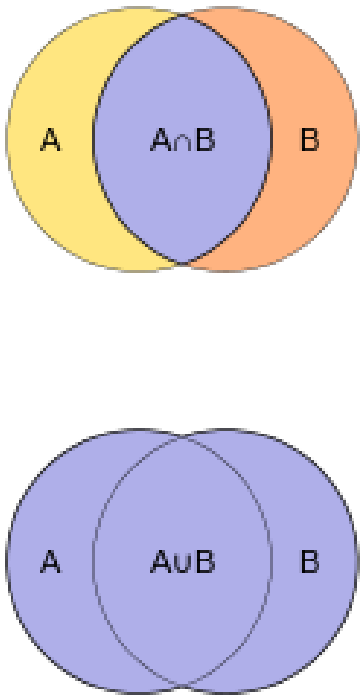
$$\text{error} = \frac{1}{n}\sum_{k=1}^{n}\left(1 - \frac{\text{data} \cap \text{simulation}}{\text{data} \cup \text{simulation}}\right)$$

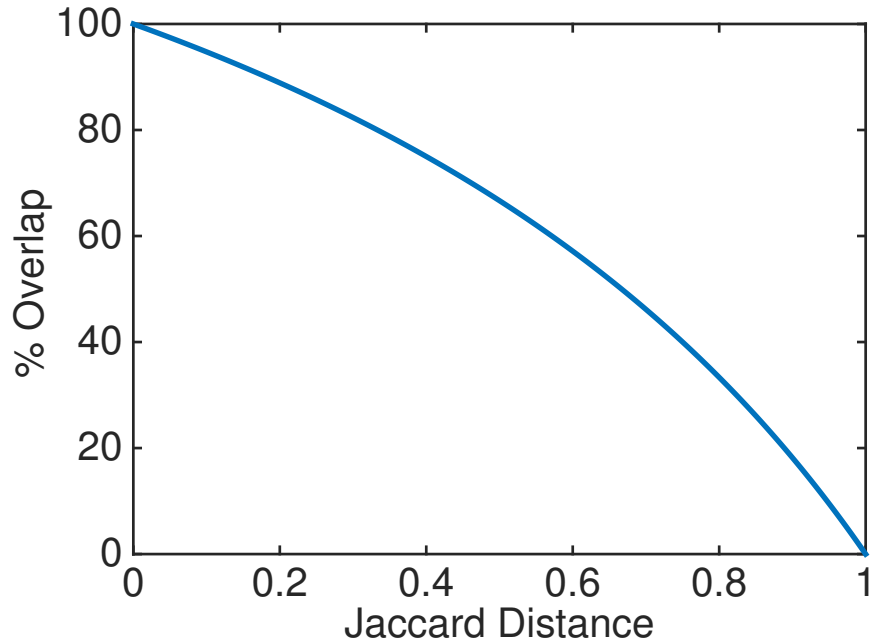
where k represent the time points we have data for.

Jaccard Distance

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

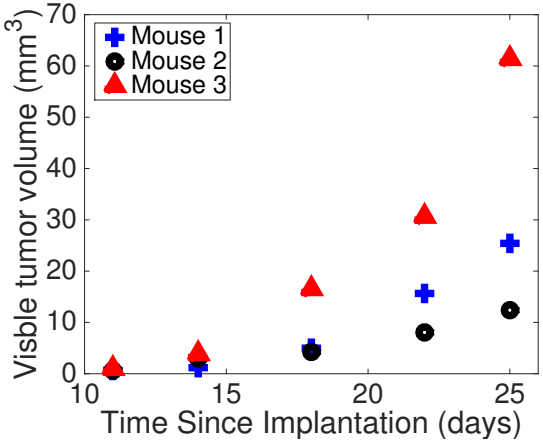
where data is visible tumor on MRI and simulation is above 16% carrying capacity





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.



- 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.

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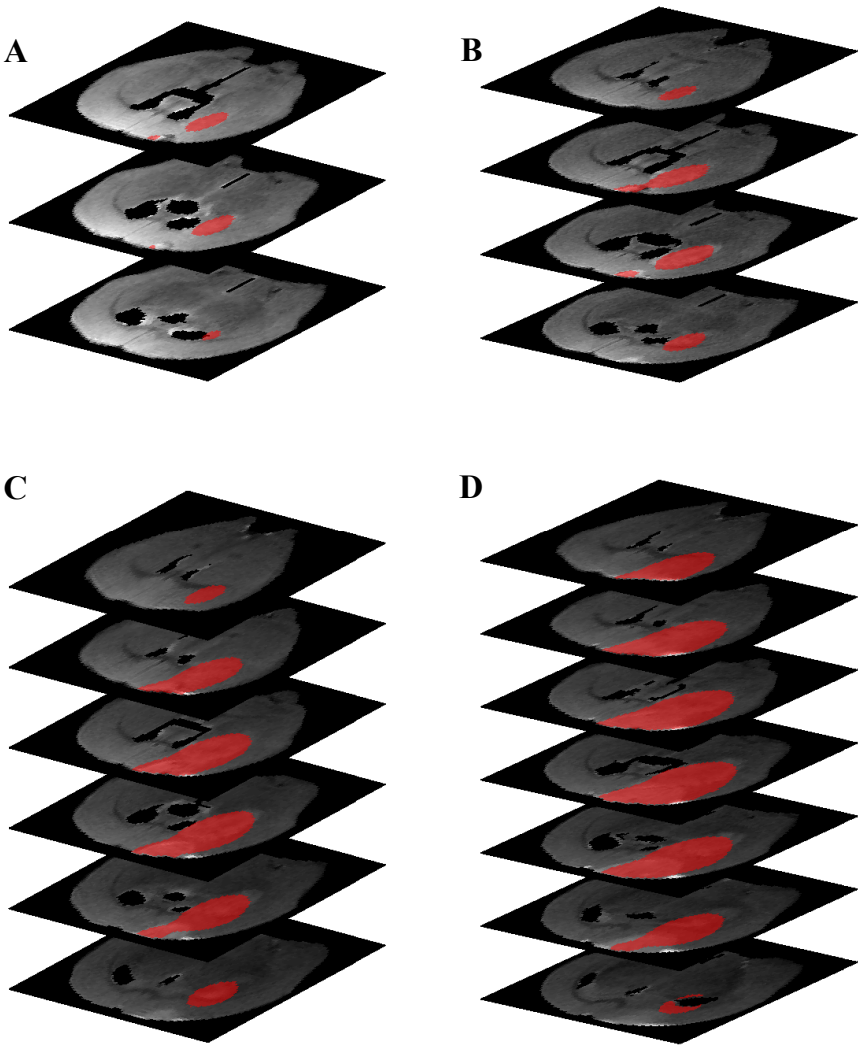
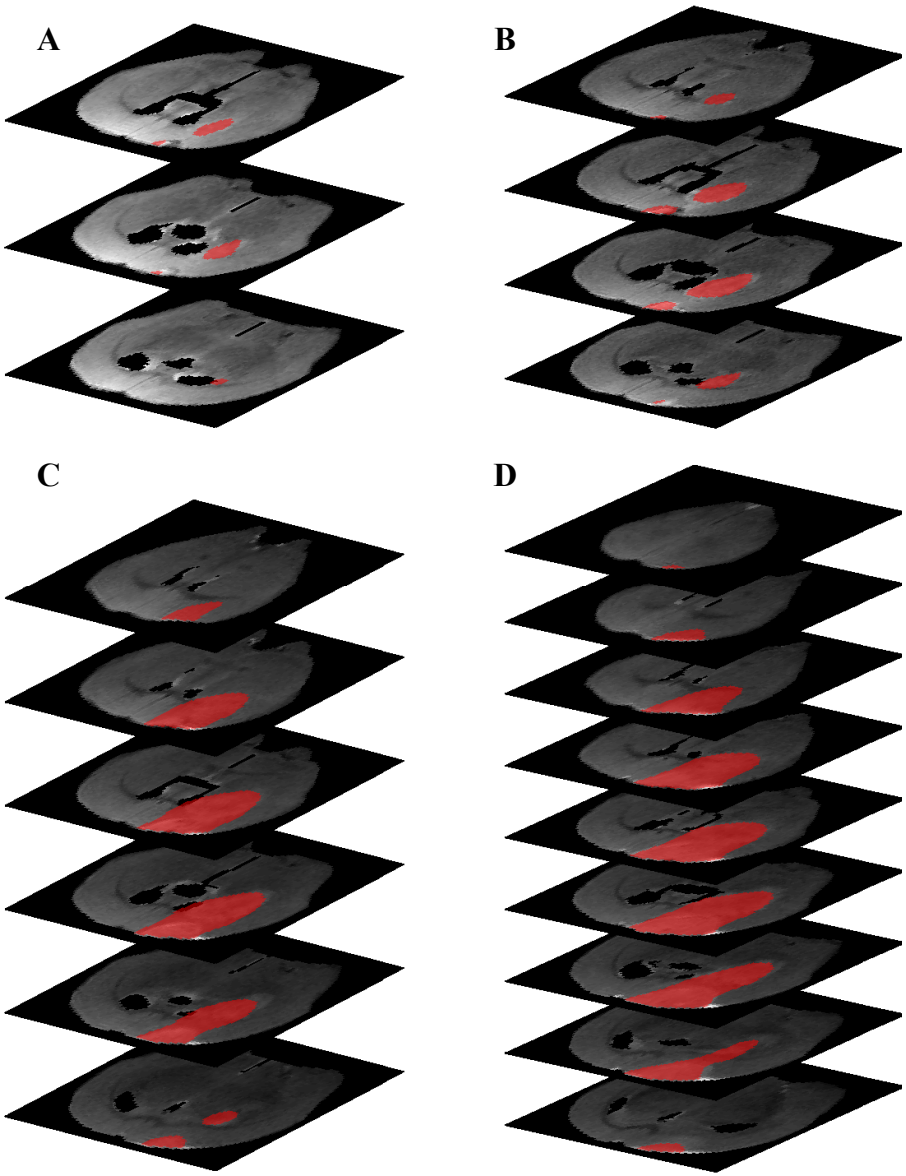
Results For Representative Mouse – Hypothesis 1



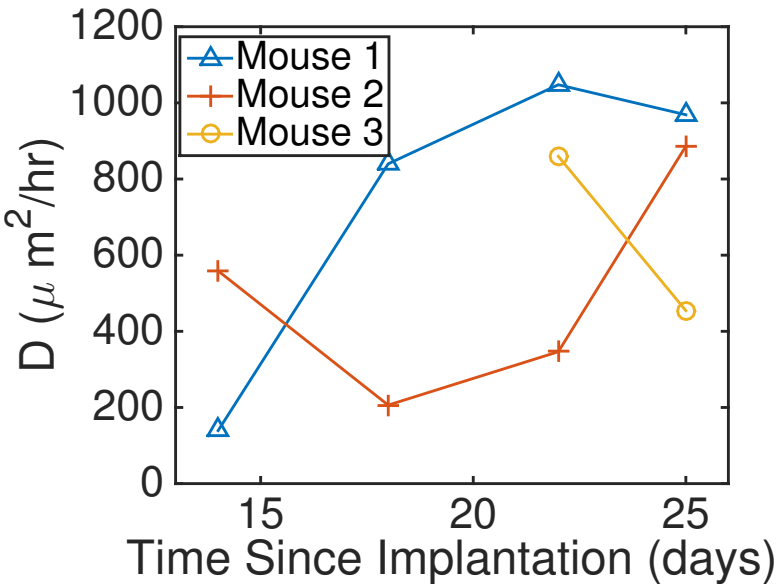
- D:
  413.77 $(\mu\mathbf{m}^2/\mathbf{h})$
- ρ:
  0.0188 $(\mathbf{h}^{-1})$
- Jaccard Distance:
  0.4524
- Percentage Overlap:
  70.8%

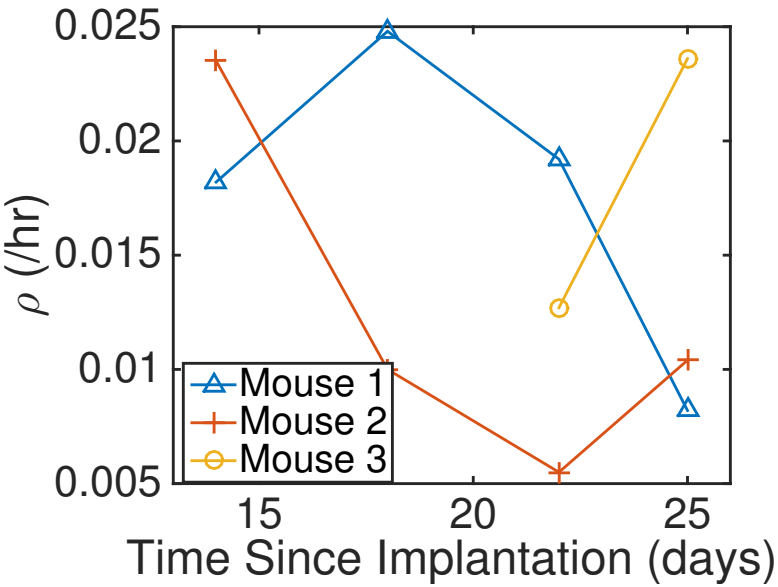
Results For Representative Mouse – Hypothesis 2



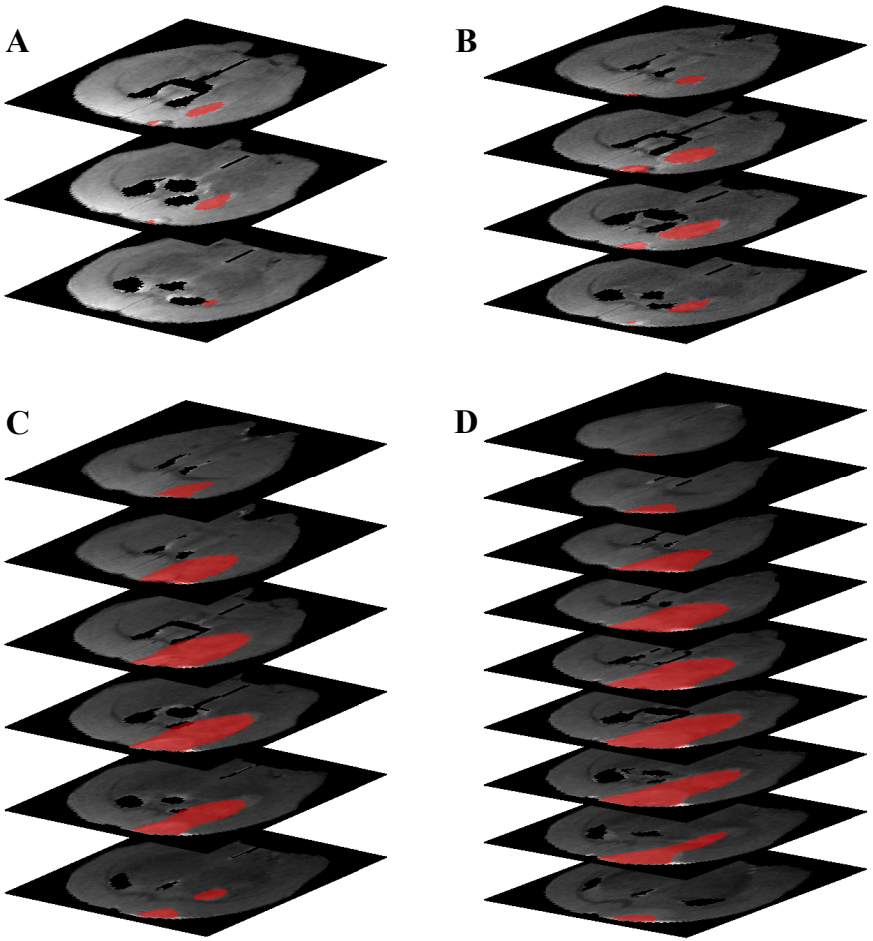
- $D(s)$:
  139.24 $(\mu\mathbf{m}^2/\mathbf{h})$
  839.93 $(\mu\mathbf{m}^2/\mathbf{h})$
  1047.6 $(\mu\mathbf{m}^2/\mathbf{h})$
  968.75 $(\mu\mathbf{m}^2/\mathbf{h})$
- ρ:
  0.0182 $(\mathbf{h}^{-1})$
  0.0248 $(\mathbf{h}^{-1})$
  0.0192 $(\mathbf{h}^{-1})$
  0.0082 $(\mathbf{h}^{-1})$
- Jaccard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

Parameter Variance through Time



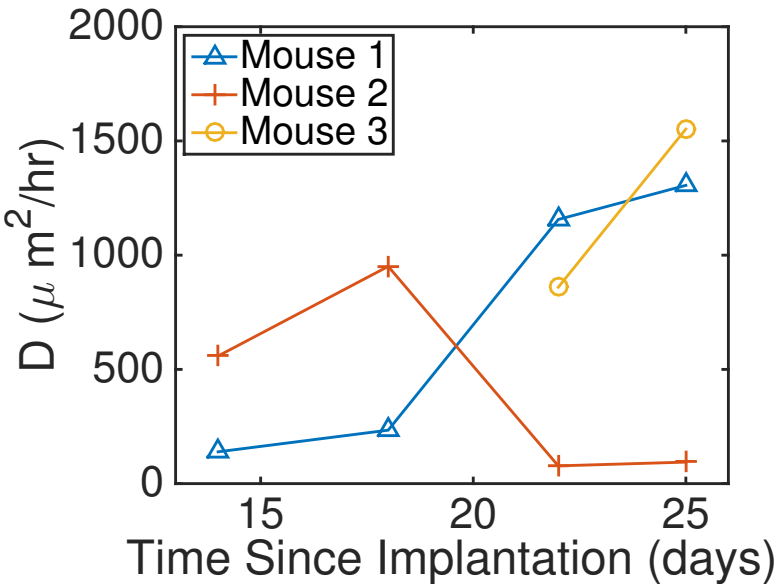


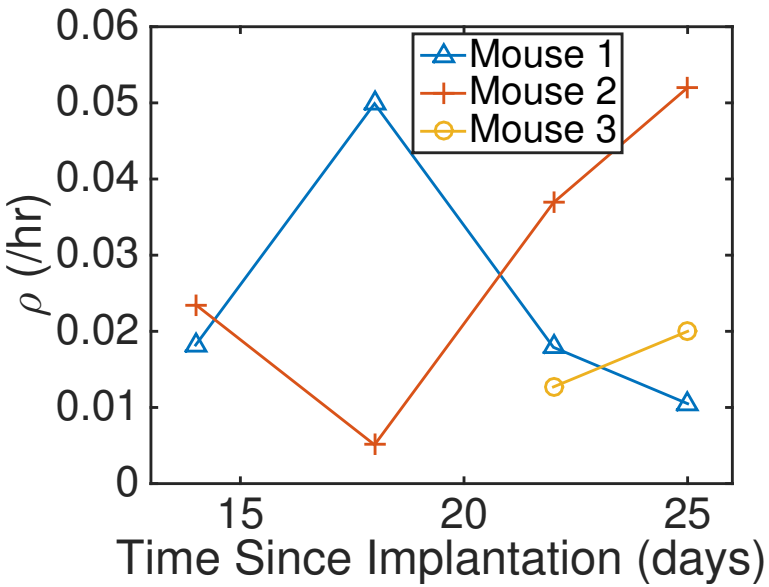
Results For Representative Mouse – Hypothesis 3



- $D(s)$:
  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%

Parameter Variance through Time



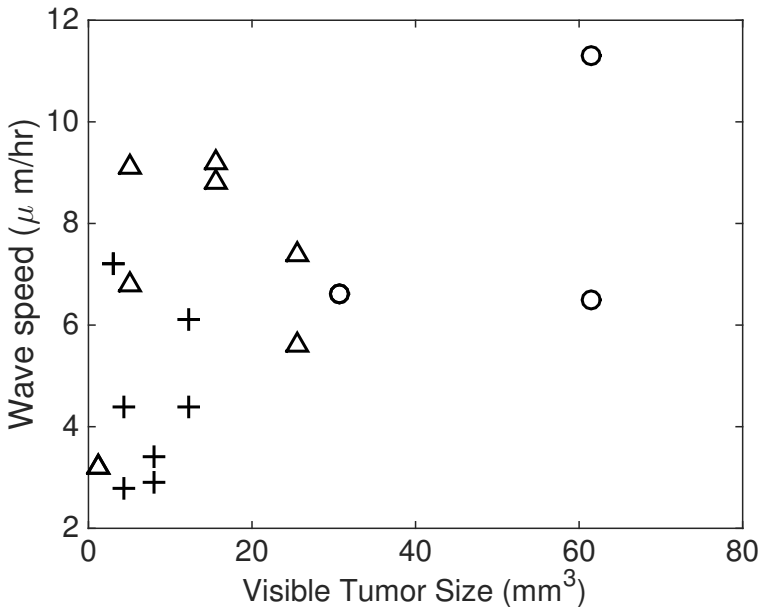


Remaining Information

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

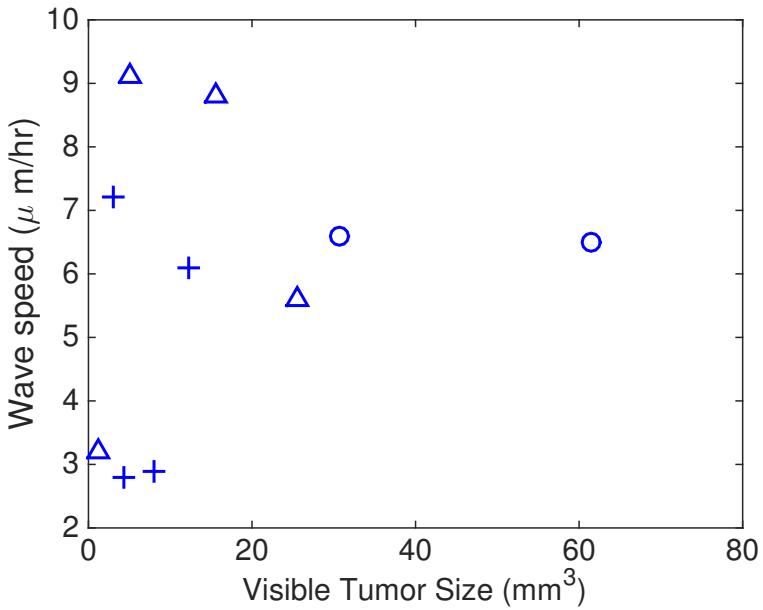
Recall for reaction-diffusion equation, the minimum wave speed is $c_{\text{min}} = 2\sqrt{D\rho}$. Examining the wave speeds for our simulations:



Estimated wave speeds for various tumor volumes. Mouse 1: triangles; Mouse 2 plusses; Mouse 3 circles.

Wave Speed

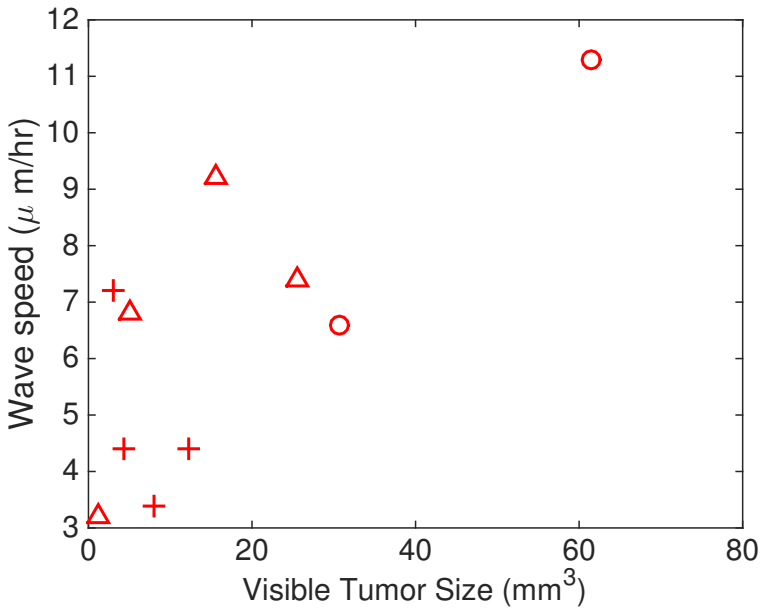
When we examine Hypothesis 2 only (shown in blue), we see no clear correlation between tumor volume and wave speed:



Estimated wave speeds for various tumor volumes under Hypothesis 2. Mouse 1: triangles; Mouse 2 plusses; Mouse 3 circles.

Wave Speed

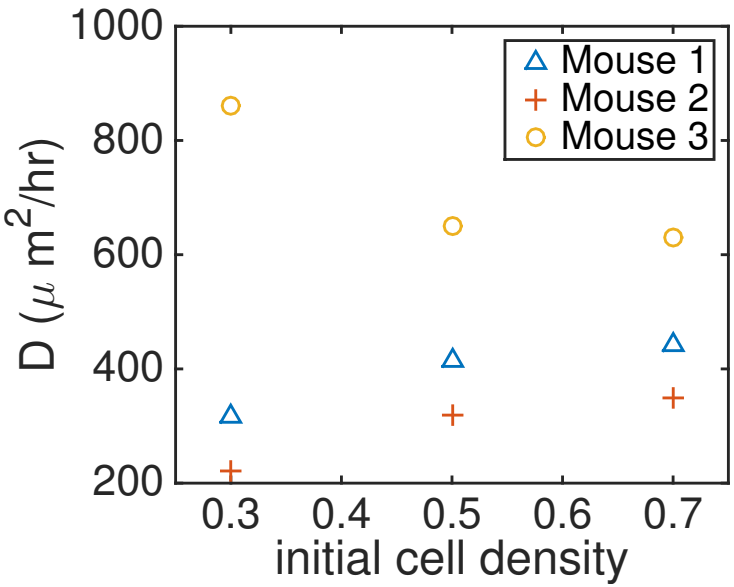
When we examine Hypothesis 3 only (shown in red), we see correlation between tumor volume and wave speed

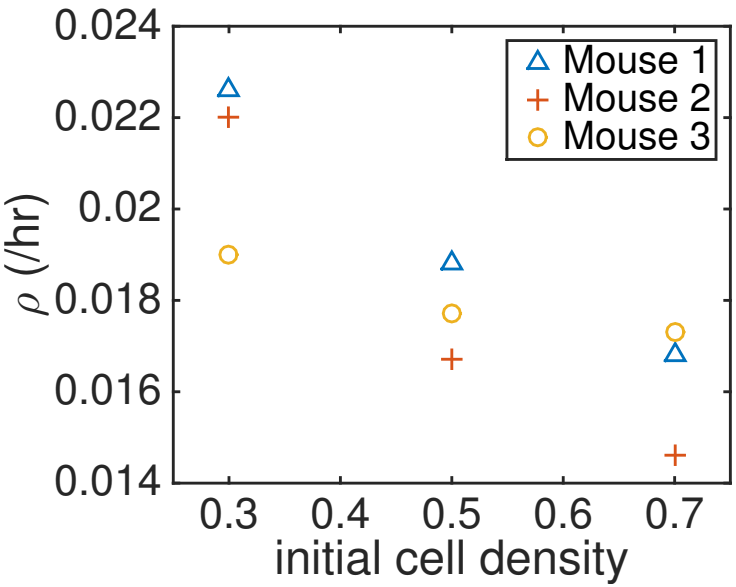


Estimated wave speeds for various tumor volumes under Hypothesis 3. Mouse 1: triangles; Mouse 2 plusses; Mouse 3 circles.

Initial Condition

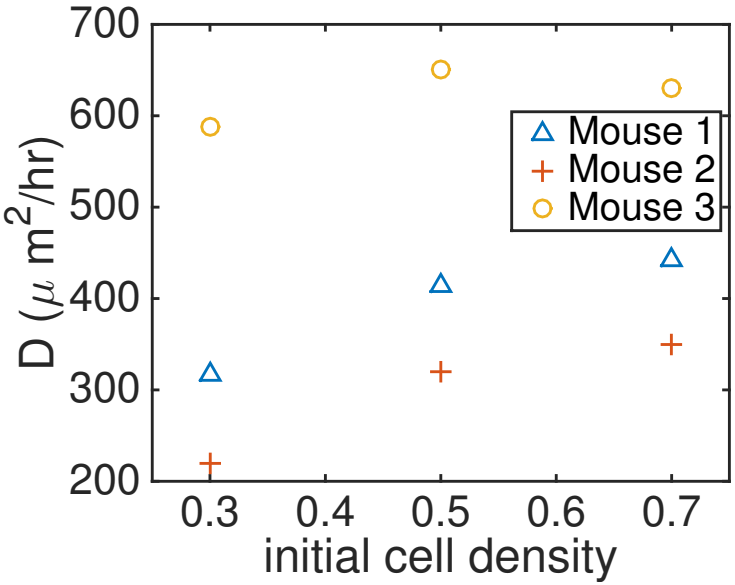
Initial Conditions a great source of uncertainty

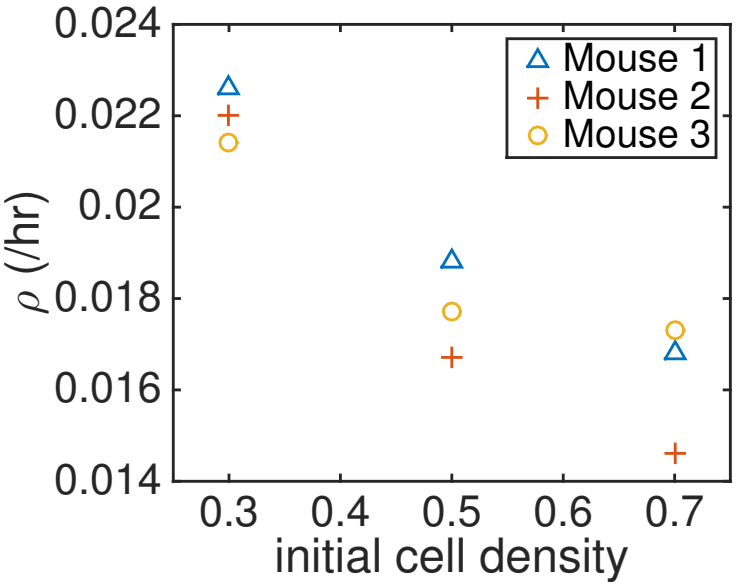




Mouse 1 and 2 have wave speeds within 5% of one another for all initial conditions, Mouse 3 22%

Initial Condition





Mouse 1 and 2 and 3 have wave speeds within 8% of one another for all initial conditions

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

Co-Author Acknowledgement and Thanks

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  - Qingwei Liu
  - Gregory Turner

Further Directions

- Confidence of parameter estimations
- Can we predict a future MRI?
- Incorporating more complexity into the model
- 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