A Mathematical Model of GL261-Luc2 Glioma Growth in Mice

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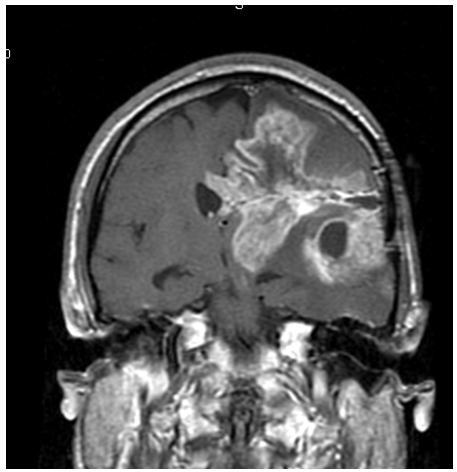
Outline

Introduction: Mathematical Oncology and Glioblastoma

- 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
- Mathematical models can be a helpful tool in understanding all stages of the disease, from growth to treatment
- Glioblastoma Multiforme (GBM) is a deadly primary brain tumor
- GBM is characterized by both high proliferation and diffusivity
- With treatment, mean survival from detection is < 15 months

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

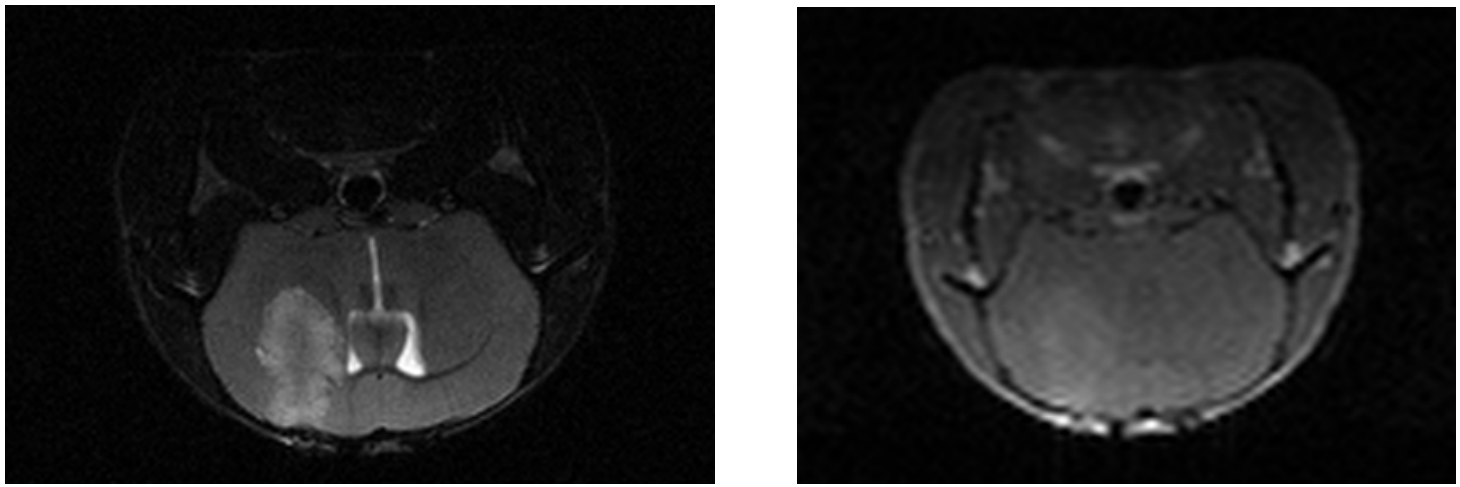


Sagittal cross-section of human brain with GBM

Outline

Introduction: *In vivo* Experimental Data

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



MR images from day 25 for the second mouse in cohort 3 from the same location in the brain. On the left is the T2-weighted image, on the right T1-weighted post contrast image. The tumor is visible in both images.

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

Outline

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 Distance

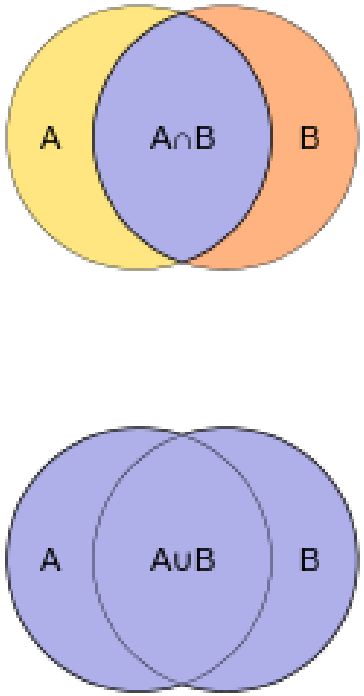
$$\text{error} = \frac{1}{n}\sum_{k=1}^{n}\left(1 - \frac{\text{data} \cap \text{simulation}}{\text{data} \cup \text{simulation}}\right)$$

where n represent the time points we have data for

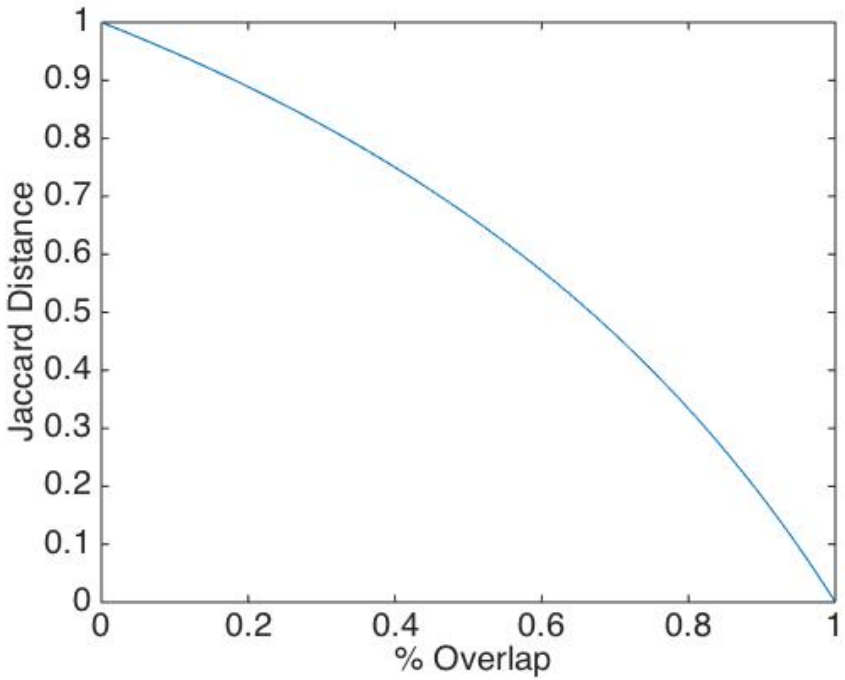
Jaccard Distance

The error function is based on the Jaccard distance:

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



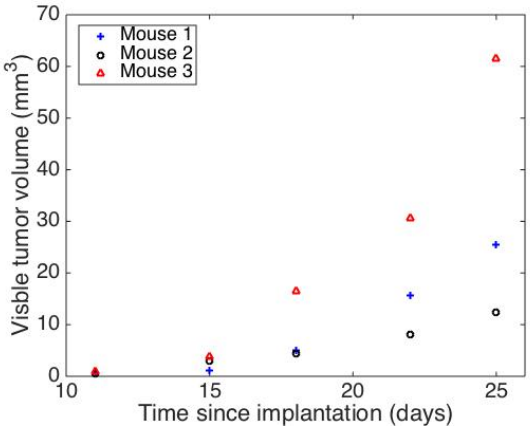
Union and intersection of overlapping sets



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?

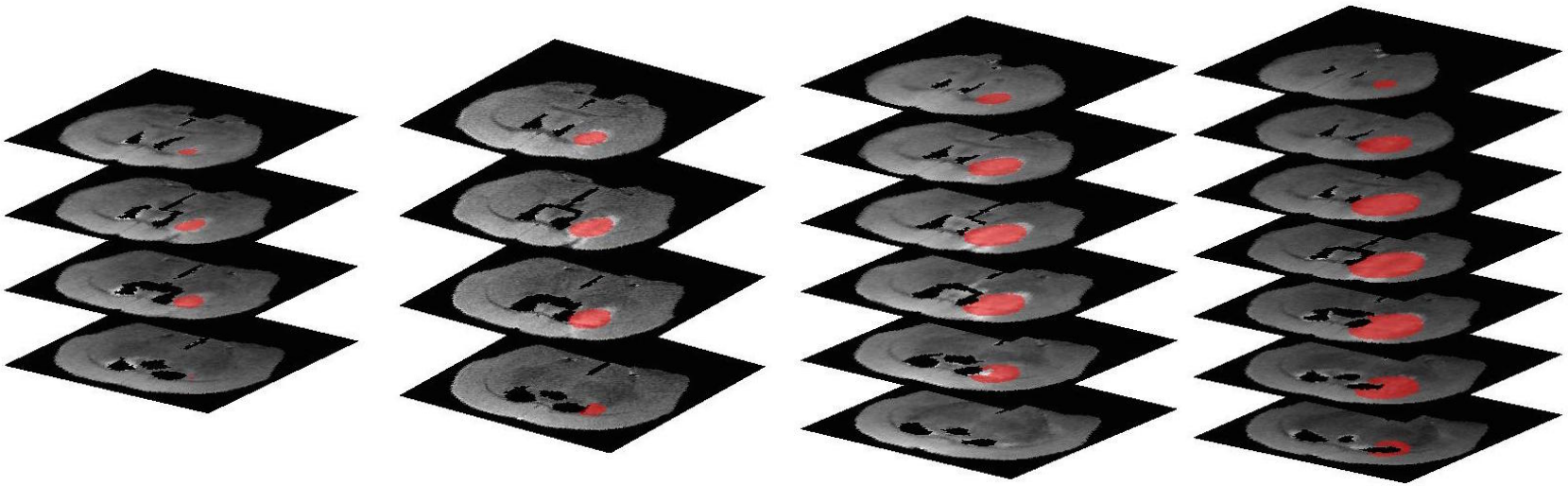
We need methods to test our hypotheses

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

Outline

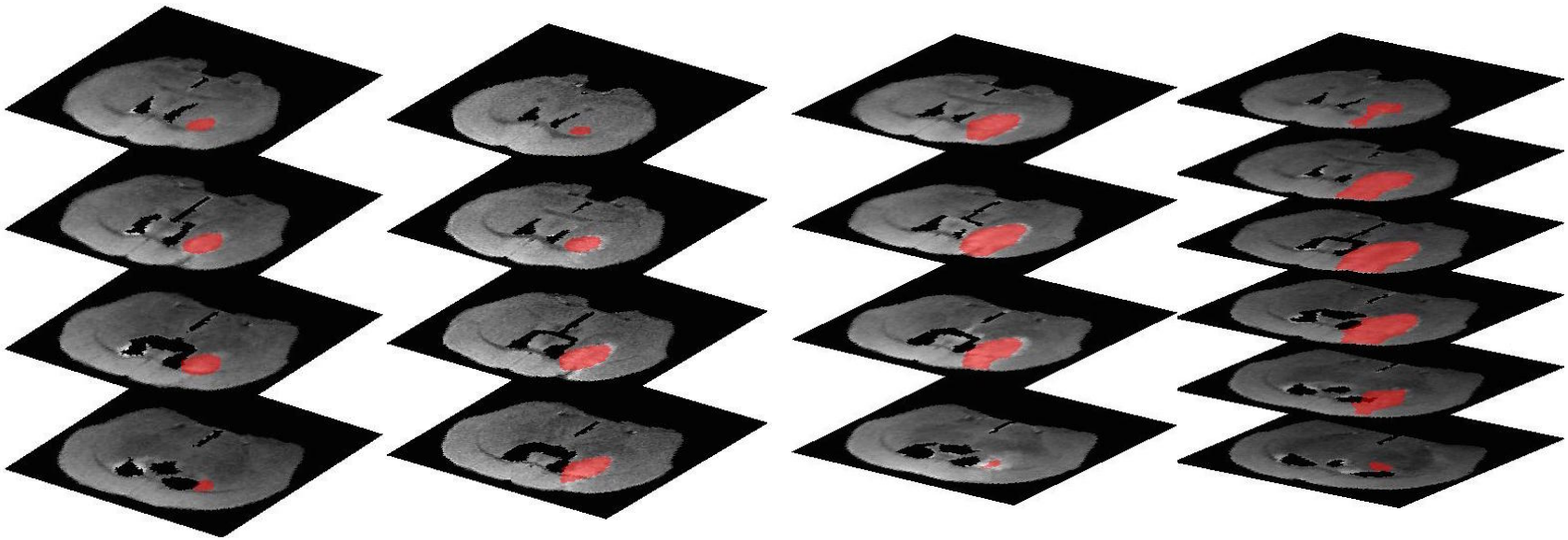
H1: Natural Variance in D and ρ

Error=0.4524, Overlap 70%



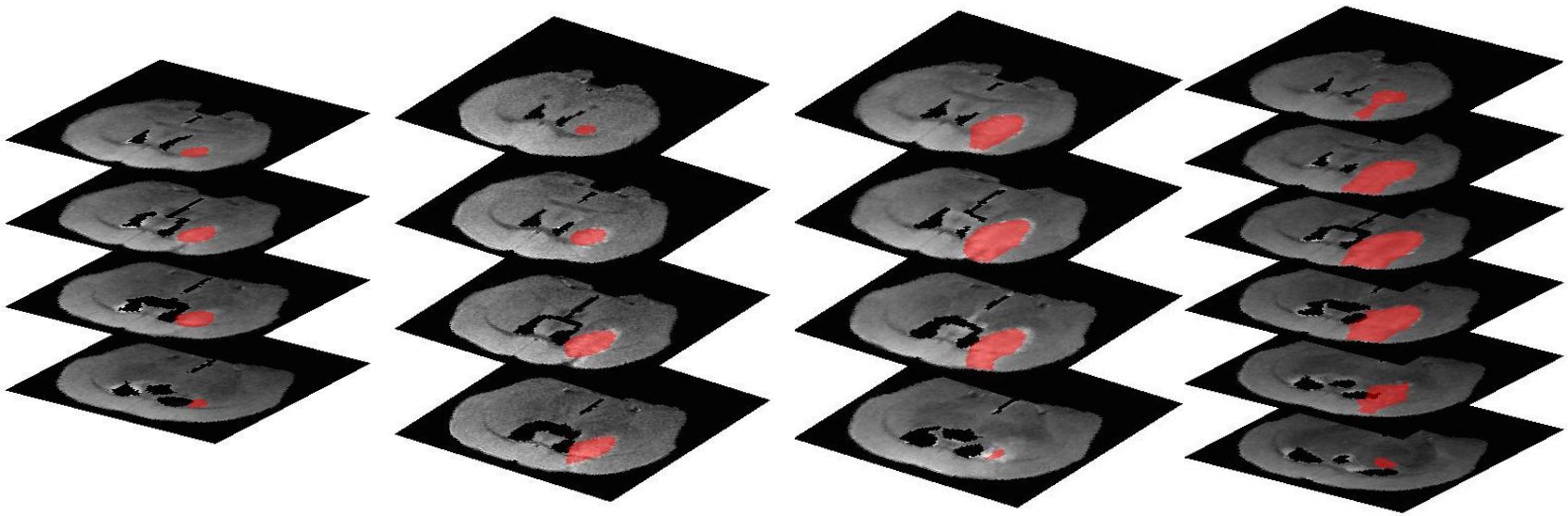
H2: Varying D and ρ from time step to time step

Error=0.4365, Overlap 72%



H3: D, ρ non-constant, short term simulations

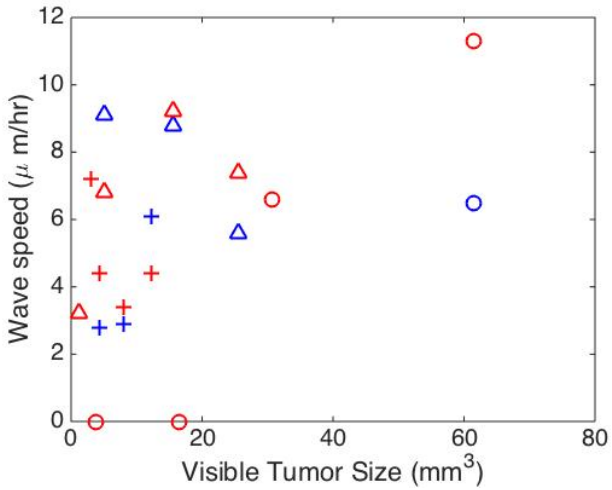
Error: 0.3673, Overlap 77 %



Remaining Information

Hypothesis	Time Point	D (μm^2/h)	ρ (h^{-1})	error
1	-	413.77	0.0188	0.4524
2	2	139.24	0.0182	0.1196
	3	839.93	0.0248	0.1191
	4	1047.6	0.0192	0.1029
	5	968.75	0.0082	0.0949
3	2	139.24	0.0182	0.1196
	3	233.97	0.0499	0.1145
	4	1156.2	0.0178	0.0688
	5	1305.6	0.0105	0.0644

Hypothesis	Time Point	D (μm^2/h)	ρ (h^{-1})	error
1	-	651.17	0.0177	0.2833
2	4	859.70	0.0127	0.1408
	5	454.29	0.0236	0.1364
3	4	859.704	0.0127	0.1408
	5	1552.1	0.0200	0.1027



Estimated wave speeds for various tumor volumes. Red represents hypothesis 3, blue is hypothesis 2. Different markers used for each mouse.

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
  - Discovered short-term fits were much more accurate
- 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

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