Data-Validated Model of Glioblastoma Growth in Murine Brains

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Abstract

Glioblastoma multiforme is an extremely fatal aggressive brain cancer, characterized by both intense proliferation and excessive migration, contributing to the difficulty of treatment. We use a simple reaction-diffusion equation to model the natural variation observed between final tumor volumes for experimental data collected from murine brains. We examine three hypotheses for what might contribute to the natural variation within the mice: testing whether it is natural variance in growth or morphological.

Experimental Data

- 5 immune-competent mice injected with GL261 cell line
- MR acquisitions 5 times and euthanized on day 26 (T2w, T1w post, DWI)
- Brains harvested to be stained for histology

Figure : 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.

In vivo Simulations

Motivating Question: Can we predict the growth and spread of the tumor using the simple reaction diffusion equation:

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

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

Simulations consist of:

- CFD in 3D space, ode45 in time
- Synthetic T2w MR images constructed from 16% or higher of carrying capacity
- Initial condition assumes uniform 50% maximum density from first image captured on day 11

Parameter Optimization

- Motivated by very different final tumor size between mice: final tumor sizes range from 10 mm^3 to 60 mm^3
- hypotheses:
  1. Natural variance in parameters D and ρ between mice
  2. Morphological changes occur which change the individual values of D and ρ as the tumor changes in volume
  3. Difference in initial conditions, i.e. how many tumor cells stuck (to eliminate this threat, we use the first imaged time point as the initial condition)
- We optimize the parameters D and ρ individually for each mouse according to the Jaccard Index over the four remaining time point images:

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

Hypothesis 1

- We optimize the parameters D and ρ for each mouse using time point 1 as an initial condition and the error function above
- We compare the optimized parameters across the mice: do similar values of D and ρ generate varied tumor sizes?
- We can examine each time point to determine how well the simulation fits to the actual data
- Best fit for mouse 2 (pictured on right) was $D = 21.9078$ and $\rho = 7.8164$

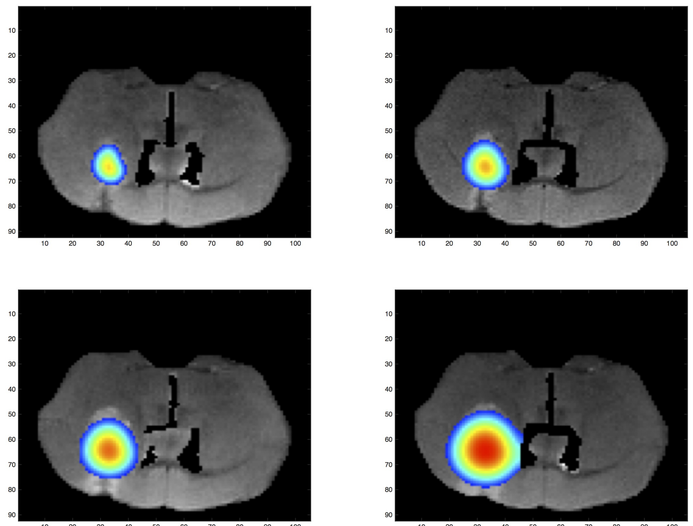

Figure : Examples of the best-fit simulation tumor (color) superimposed on the MR-generated image (black and white) for a series of time points for one mouse. Only examining one cross-section.

Hypothesis 2

- We minimize for each time segment for the mouse.
- We find the optimized D and ρ for time point 1 to time point 2, from time point 2 to time point 3, etc
- Comparing the Jaccard index determined by hypothesis 1 to hypothesis 2

Time Point	Optimized D	Optimized ρ	Error (Hyp 1)	Error (Hyp 2)
2	22.6484	20.4766	0.3999	0.4644
3	3.0234	20.9062	0.4899	0.3722
4	3.1844	22.3838	0.4412	0.2570
5	11.000	9.5000	0.4165	0.2895

Table : Table displaying errors for each hypothesis at each time point. Hypothesis 2 seems to generate smaller errors.

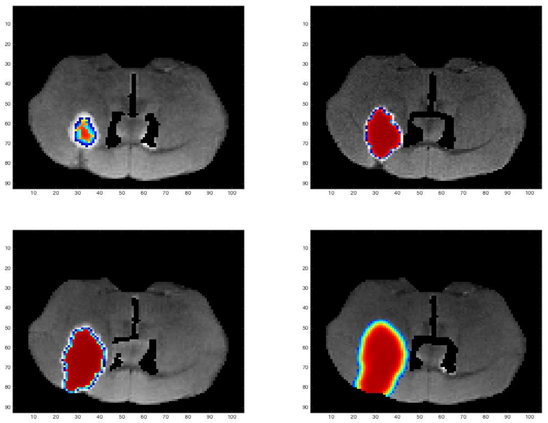

Figure : Best-fit simulations for the tumor (color) superimposed on the MR generated image (back and white) for individually optimized time points for each mouse

- We notice that the total error for hypothesis 2 (1.5631) is smaller than the total error generated by hypothesis 1 (1.7475).
- The best fit parameters change quite drastically from the beginning to the end.

We can categorize the 'steps' the tumor takes:

1. initial tumor has large diffusion and proliferation: resources are plentiful and the tumor is able to grow and spread with little resistance.
2. mid-tumor has much proliferation but less diffusion: perhaps angiogenesis is occurring, and tumor cells are staying put to access nutrients and proliferate.
3. late tumor has moderate diffusion and proliferation has decreased a lot: resources are scarce so proliferation is stunted and cells are forced to migrate in order to access nutrients

Conclusions and Further Directions

- Tested hypotheses for varying final tumor sizes for *in vivo* experimental data
- A simple parameterization of a simple model allows insights into possible morphological changes as tumor grows
- All mice must be tested as such to see if the trends hold true across all mice.
- Future work includes applying DTI data to *in vivo* model

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