Data-Motivated Models of *in vitro* Glioblastoma Growth

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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 compare and contrast a single density-dependent diffusion equation to model the behavior of both proliferation and migration with a two-population model for proliferative and migratory cells. We begin analysis of the models to determine existence of traveling wave solutions. Both models are compared with well-known in vitro experimental data.

Background

- Stein et. al [1] performed experiments to track in vitro glioblastoma sphere growth
- Stepien et. al l [2] created density dependent diffusion model, matching experimental data better than Stein et al's two-equation model

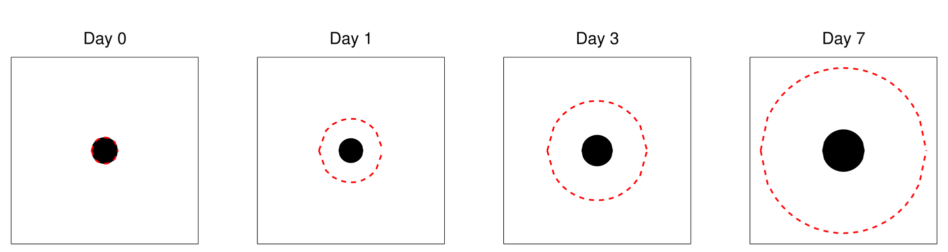

Figure : Radii of the proliferating (black) and migratory (red) cells for the experiment from Stein et al.l [1] on days 0, 1, 3, and 7. Domain is 3 mm by 3 mm.

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

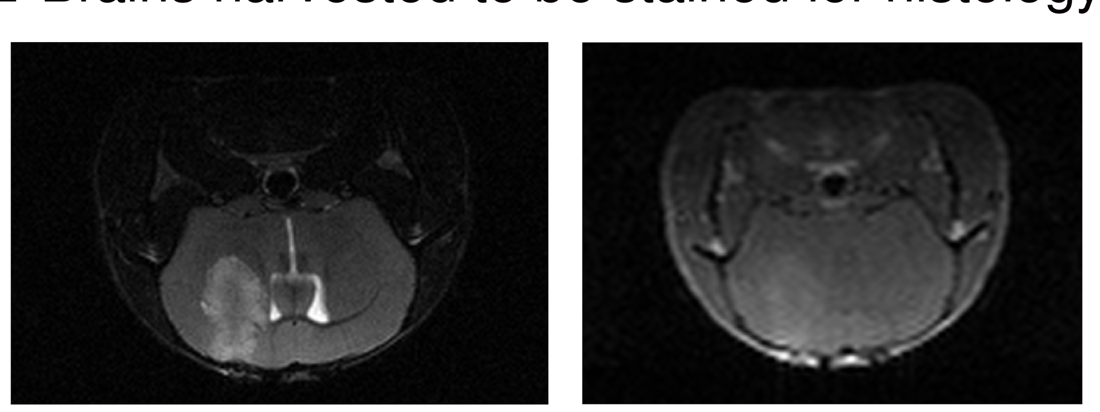

Figure : MR images from day 25 for the second mouse in cohort 3 from the same location in the brain. On the left is the T2-weighted image, on the right T1-weighted post contrast image. The tumor is visible in both images.

Model Equations

- Stepien et. al [2] density-dependent diffusion equation

$$\frac{\partial T}{\partial t} = \underbrace{\nabla\cdot(D(T)\nabla T)}_{\text{density-dependent diffusion}} + \underbrace{gT\left(1-\frac{T}{T_{\text{max}}}\right)}_{\text{logistic growth}} - \underbrace{\text{sgn}(x)\nu_i\nabla\cdot T}_{\text{taxis}}, \qquad D(T) = D_1 - \frac{D_2T^n}{a^n+T^n} \quad (1)$$

- $D_1, D_2, g, v_i, u_{\text{max}}, a, n > 0$, $D_1 > D_2$
- $T =$ total number of cancerous cells ($T = M + P$)
- As cell density increases, diffusion constant decreases
- Low cell-density areas increase diffusion to simulate single-cell migration

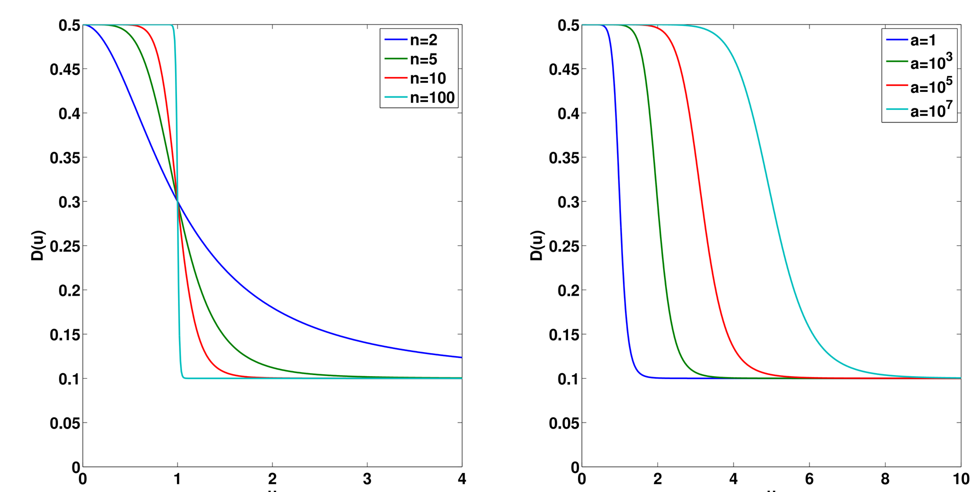

Figure : Density-dependent diffusion function, $D(T)$

- 2 Equation Model

$$\frac{\partial M}{\partial t} = \underbrace{D_1\nabla^2 M}_{\text{diffusion}} + \underbrace{\epsilon k\frac{T^2}{T^2+K_M^2}P}_{\text{switch from proliferating to migrating}} - \underbrace{k\frac{T^2}{T^2+K_M^2}M}_{\text{switch from migrating to proliferating}} - \underbrace{\mu M}_{\text{death}}$$

$$\frac{\partial P}{\partial t} = \underbrace{gP\left(1-\frac{T}{T_{\text{max}}}\right)}_{\text{logistic growth}} - \underbrace{\epsilon k\frac{T^2}{T^2+K_M^2}P}_{\text{switch from proliferating to migrating}} + \underbrace{k\frac{T^2}{T^2+K_M^2}M}_{\text{switch from migrating to proliferating}} \quad (2)$$

- P represents population of proliferating cells
- M represents population of migrating cells

Simulation Results

- Use fminsearch to minimize error function

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

with $N+M$ the total number of data points (21), and q the number of free parameters (6)

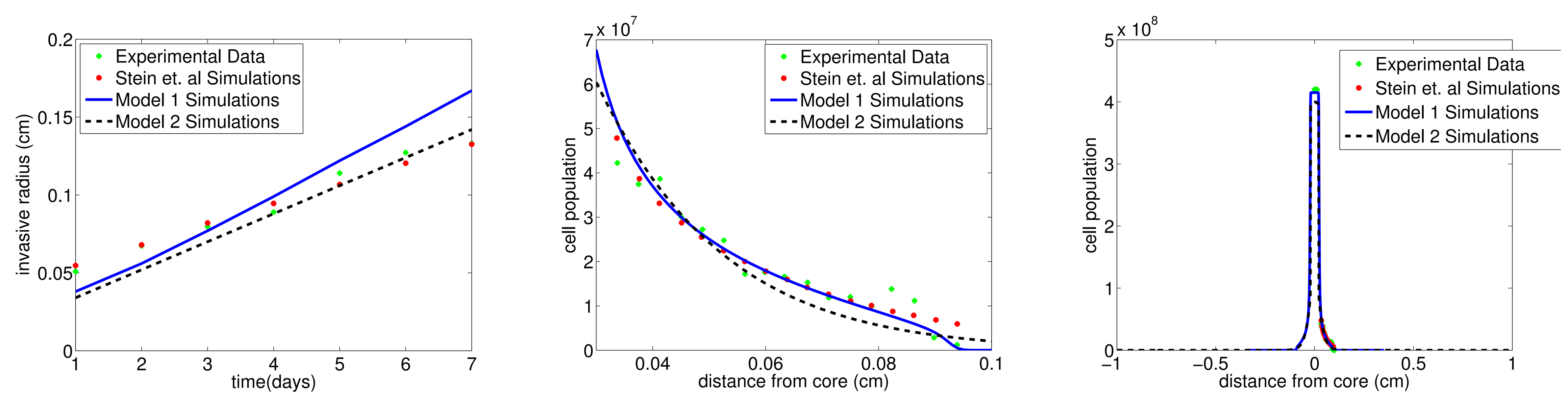

Figure : Numerical solution of the density-dependent diffusion glioblastoma model (1) the two equation model (2) optimized using error function (3) compared to experimental data from Stein et al. [1] and their simulations.

- Model (1), has 1/2 error for Stein et al, the two equation model (2) has error approximately on the order of Stein et al

Traveling Wave Solutions

- Model 1
  Traveling wave solution of Model 1 exists if and only if $k \geq k_{\text{min}} = 2\sqrt{D_1 g} + v$ is satisfied.
  - With optimized parameters, theoretical $k_{\text{min}} = 0.003345$ cm/day, but simulations $k = 0.02255$ cm/day
  - Why the discrepancy?

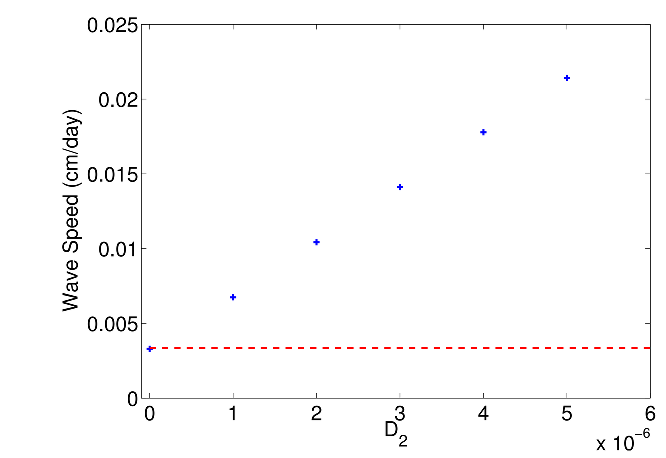

Figure : The observed simulated wave speed when varying parameter D_2. k_{min} is the red dashed line.

- Model 2
  - Traditional wave speed analysis gives $k_{\text{min}} = \sqrt{\frac{rg^2D_1}{g+\mu}}$
  - Observe many differing wave speed front shapes varying ϵ:

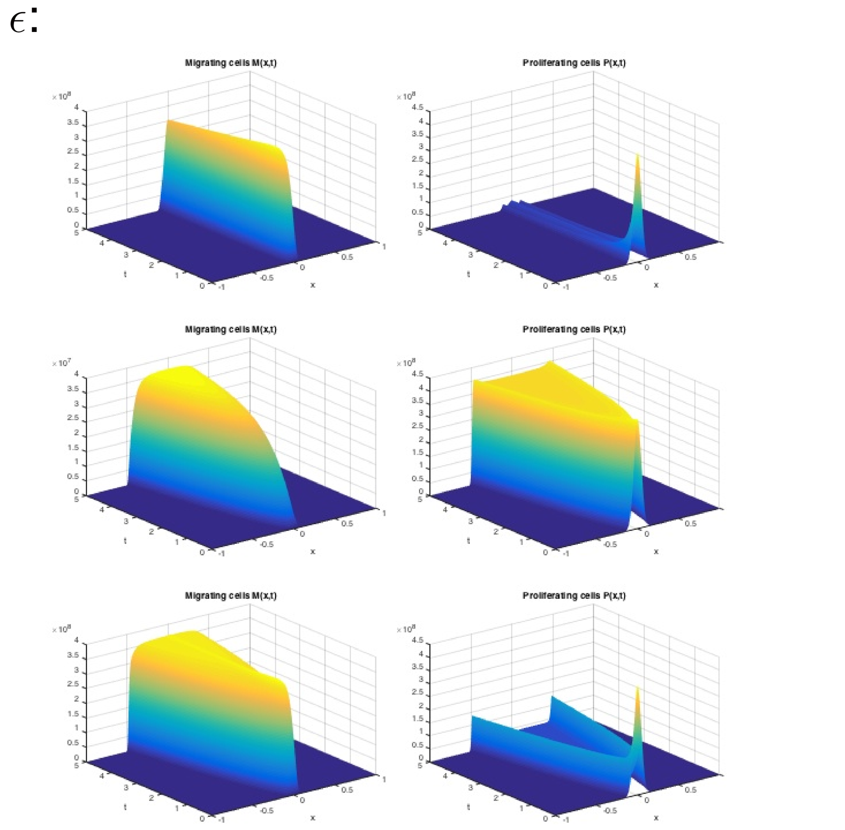

Figure : Varying parameters gives many different shapes of wave fronts, showing analysis not enough

Conclusions and Further Directions

- Compared single density-dependent diffusion model for glioblastoma multiform tumor growth with two-equation model using *in vitro* experimental data
- Future work includes applying both models to *in vivo* data
- Determine discrepancy between simulated and theoretical wave speeds for Model 1
- Determine analytical expression for theoretical wave speed for Model 2

[1] Stein, Andrew M., et al. "A mathematical model of glioblastoma tumor spheroid invasion in a three-dimensional in vitro experiment." Biophysical journal 92.1 (2007): 356-365.
[2] Stepien, Tracy L., Erica M. Rutter, and Yang Kuang. "A Data-Motivated Density-Dependent Diffusion Model of *in vitro* Glioblastoma Growth. Mathematical Biosciences and Engineering. *In press*"
[3] Swanson, K. R., R. C. Rostomily, and E. C. Alvord. "A mathematical modelling tool for predicting survival of individual patients following resection of glioblastoma: a proof of principle." British journal of cancer 98.1 (2008): 113-119."

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