A Data-Validated Density-Dependent Diffusion Model of Glioblastoma Growth

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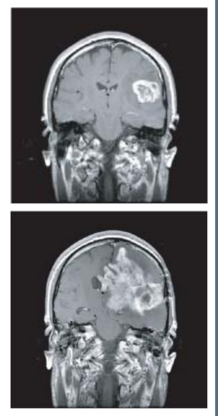
Abstract

Glioblastoma multiforme is an aggressive brain cancer that is extremely fatal. It is characterized by both proliferation and large amounts of migration, which contributes to the difficulty of treatment. Previous models of this type of cancer growth often include two separate equations to model proliferation or migration. We propose a single equation which uses density-dependent diffusion to capture the behavior of both proliferation and migration. We analyze the model to determine the existence of traveling wave solutions. To prove the viability of the density-dependent diffusion function chosen, we compare our model with well-known in vitro experimental data.

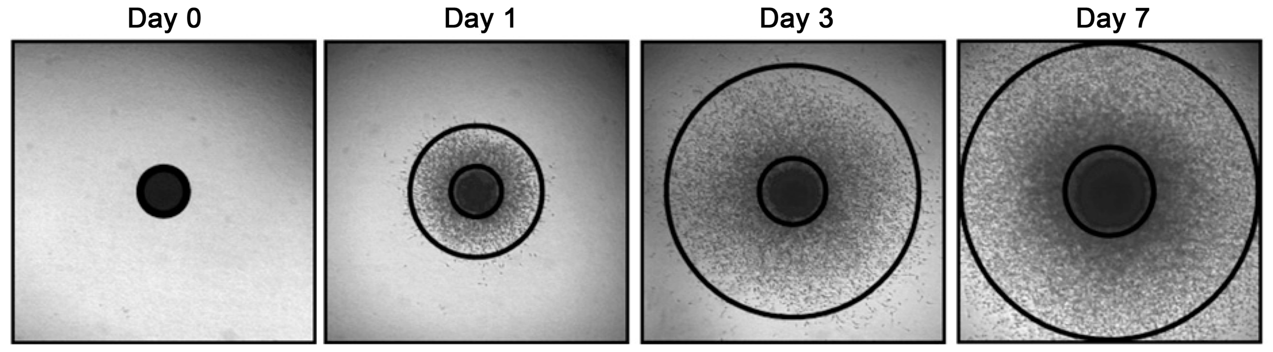
Glioblastoma Multiforme (GBM)

- GBM is a deadly primary brain tumor characterized by intense proliferation and diffusive migration
- More than 12,500 new cases diagnosed annually in the US
- Median survival time for recurrent GBM with treatment is 9–15 months



Experimental Data and Previous Modeling

- Stein et al. [Biophys. J., 92 (2007), 356–365] performed experiments to track in vitro glioblastoma sphere growth



- Created landmark model which separated migratory/invasive and proliferative cells

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

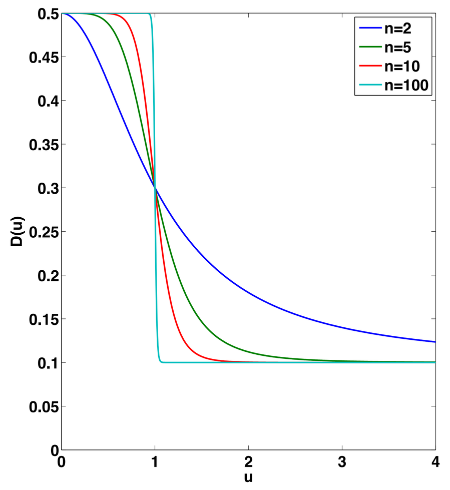
Model Formulation and Diffusion Function

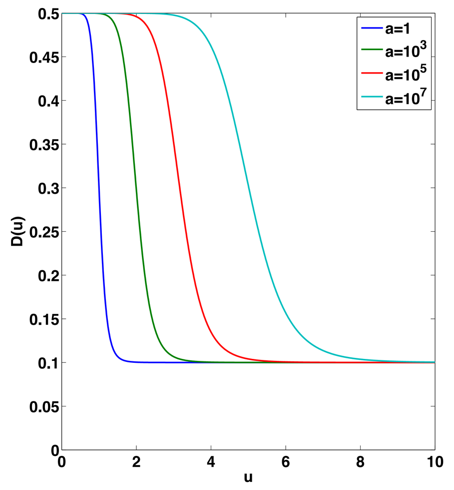
- Replace cell shedding term with density-dependent diffusion
- Invasive cells (low density) diffuse more than proliferative cells (high density)

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

Assumptions:

- $D_1, a, n > 0$
- $D_2 < 0$
- $|D_1| > |D_2|$





Model Equations

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

Parameters

- g = proliferation rate
- ν_i = radially biased component of cell motility
- $u_{\max}$ = carrying capacity density $= 4.2\times 10^8\,\text{cells/cm}^3$

Boundary conditions

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

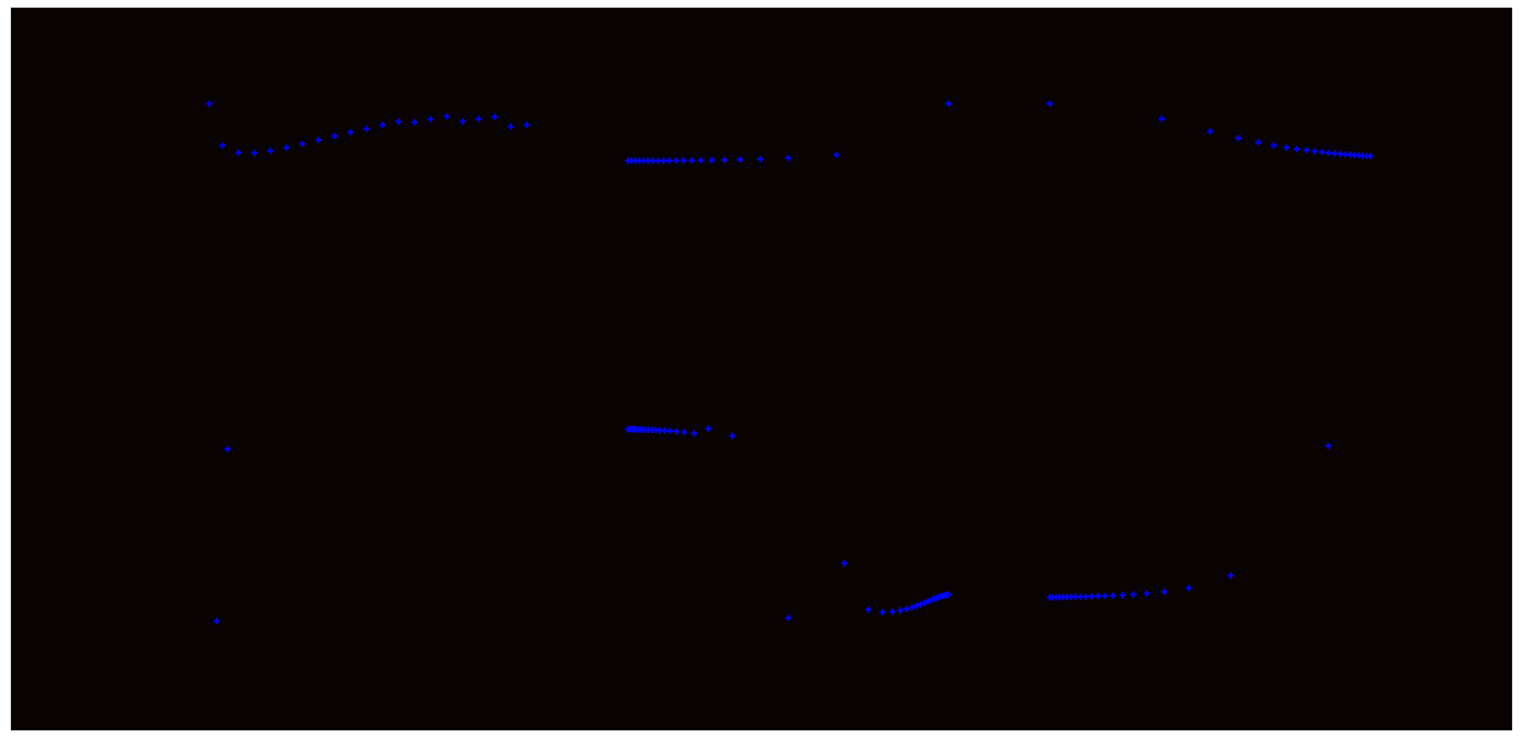
Initial condition

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

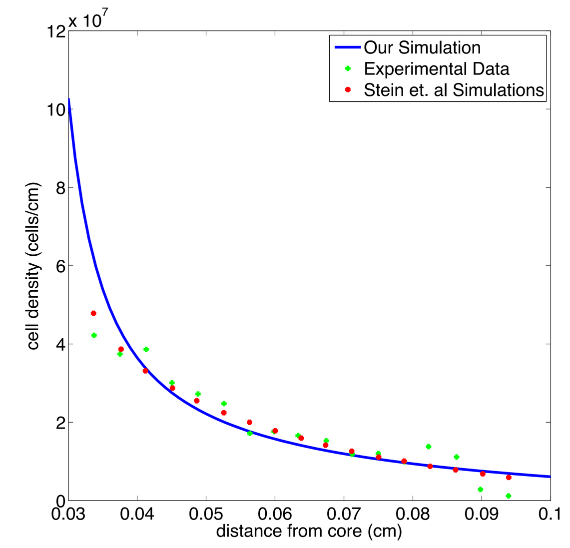
$$u(x,0) = \begin{cases} u_{\max}, & \|x\| \le 210\mu\text{m} \\ 0, & \text{elsewhere} \end{cases}$$

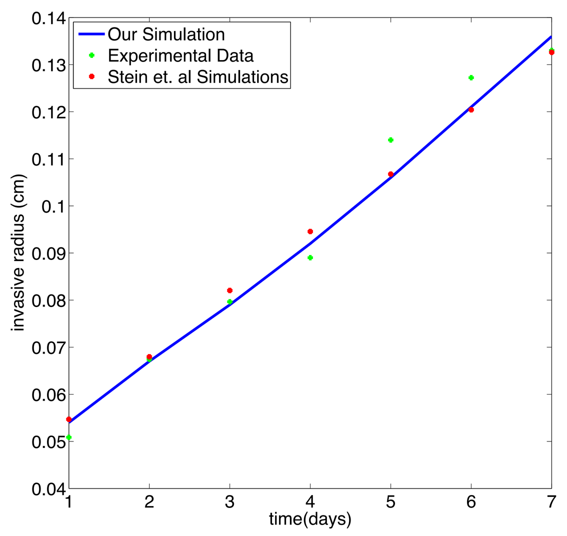
Parameter Sensitivity

- Error function based on both density profile and invasive radius
- When $D_1 >> |D_2|$ ($D_1 = 10^{-2}, D_2 = -10^{-4}$)
  - a, n insensitive
  - $D(u)$ can be approximated by the constant D_1
- If $D_1 \approx -D_2$ ($D_1 = 10^{-4}, D_2 = -9.99\times 10^{-5}$)
  - all parameters sensitive
  - $D(u)$ for small u $\approx 100D(u)$ for large u



Parameter Optimization





$$D_1 = 0.000983095750583$$
$$D_2 = -0.000983095750371$$
$$a = 10^{16.700522320628068}$$
$$n = 2.505019359789113$$
$$g = 0.203565511543623$$
$$\nu_i = 9.6\times 10^{-14}$$

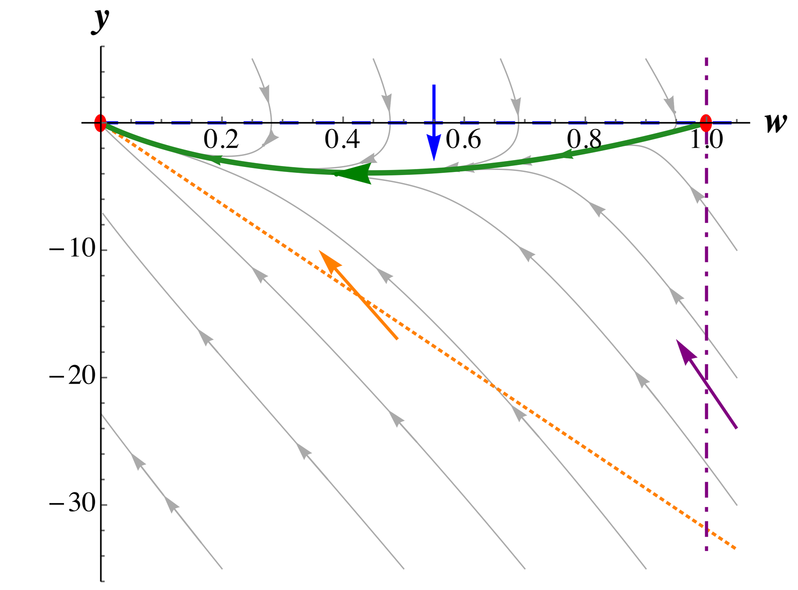
Analytical Traveling Wave Solutions

- Seek a solution of the form $u(x,t) = w(x-kt),\ \ k\ge 0$
- Nondimensionalize and reduce PDE to a system of ODEs

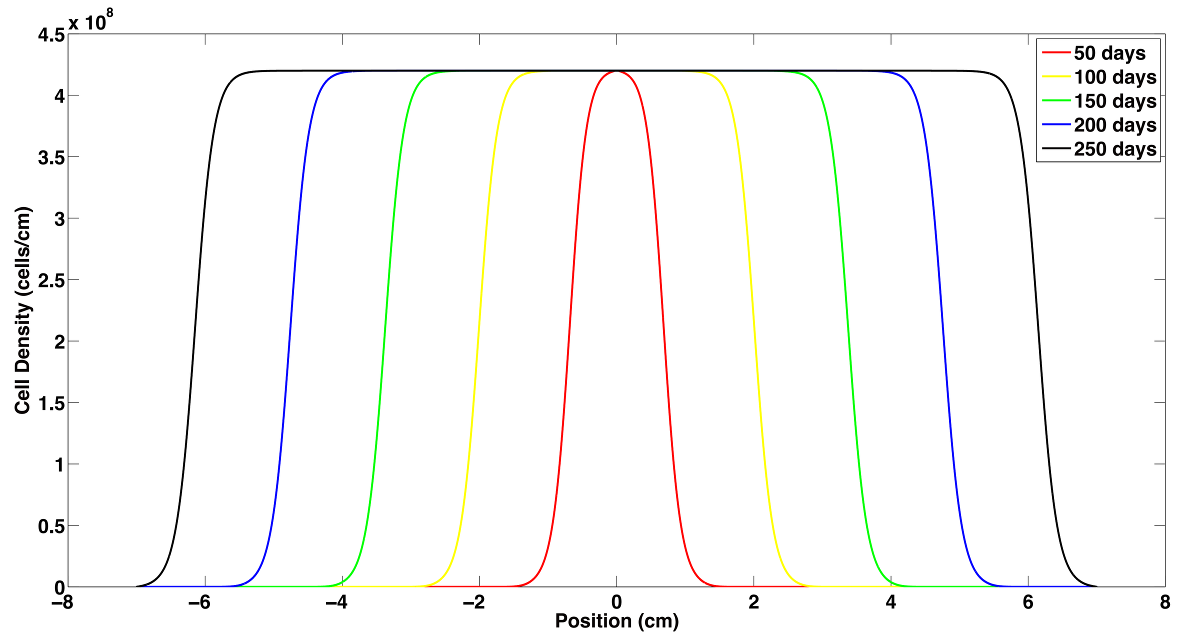
$$w' = y$$
$$y' = \frac{-1}{D(w)}\left(\left(k - \frac{\nu_i}{\sqrt{g}}\right)y + D'(w)y^2 + w(1-w)\right)$$

  with boundary conditions $w(z) \xrightarrow{x\to-\infty} 1$ and $w(z) \xrightarrow{x\to\infty} 0$
- Minimum wave speed (dimensionalized)

$$k \ge k_{\text{min}} = 2\sqrt{D_1 g} + \nu_i$$



Numerical Traveling Wave Solutions



- MATLAB's `polyfit` used to estimate speed of traveling wave
- Analytical $k_{\text{min}} \approx 0.0282931$ cm/day and the numerical wave speed $k = 0.0278428$ cm/day

Conclusions

- Modeled both migratory/invasive cells and proliferative cells for glioblastoma multiforme tumor growth with one equation.
- Effect of density-dependent diffusion more prevalent than haptotaxis.
- Future work includes applying model to in vivo data.

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