Is the reaction-diffusion equation an accurate model of C6 glioma growth?

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TARGET AUDIENCE: Those studying 1) brain tumor development, and 2) mathematical modeling of tumor growth.

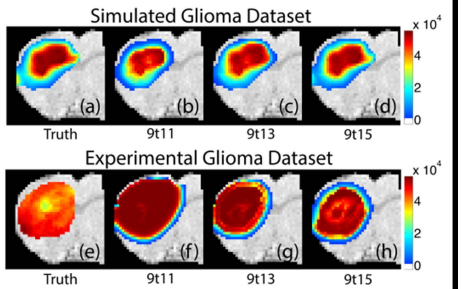
PURPOSE: Mathematical models of tumor growth typically require measurements that are difficult to obtain non-invasively. However, there have been recent efforts using quantitative imaging data to drive mathematical models of tumor growth[1]. One common model for glioma growth is the reaction-diffusion equation; however, it is not well-known how accurate this model is at predicting glioma growth *in vivo*. In this effort, we first determine the data acquisition strategies needed to allow for accurate estimation of the model parameters, and then test the accuracy of this model in predicting *in vivo* tumor growth using diffusion weighed MRI data.

METHODS: *Theory* Eq. [1] is a reaction-diffusion equation that describes the temporal change in tumor cell number (N_{TC}) with diffusion (D) and logistic growth (k, proliferation rate, θ, carrying capacity). In our formulation, k is assigned voxel wise, whereas white and gray matter maps are used to assign D.

$$\frac{\partial N_{TC}(\bar{x},t)}{\partial t} = \nabla \bullet [D(\bar{x})\nabla N_{TC}(\bar{x},t)] + k(\bar{x})N_{TC}(\bar{x},t)\left(1 - \frac{N_{TC}(\bar{x},t)}{\theta}\right) \quad \textbf{[1]}$$

Simulations To determine the necessary data acquisition strategies, simulated tumors described by Eq. [1] were seeded within a rat brain domain and evaluated on days 9, 11, 13, 15 and 17 post "implantation". D_{white}, D_{gray}, and k were estimated by fitting Eq. [1] voxel wise to the data using a Levenberg-Marquardt approach. These estimated parameters were then used to run Eq. [1] forward to predict tumor evolution. The effect of the sampling range on the day 17 prediction was assessed by comparing predicted tumor growth from parameters estimated using days 9 through 11 (9t11), 9 through 13 (9t13), and 9 through 15 (9t15). The agreement between the predicted and observed tumor growth at the final time point was assessed at the ROI (percent error in total cell number and volume) and the voxel (concordance correlation coefficient (CCC)) levels.

Experimental To assess the accuracy of Eq. [1] in describing *in vivo* glioma growth, data were collected from a Sprague-Dawley rat with a C6 glioma. The rat was imaged with DW-MRI *via* standard methods on days 9, 11, 13, 15, and 17 post-tumor cell implantation. Cell number was estimated from ADC maps as previously described[2]. D and k were estimated just as in the simulations and agreement between predicted and observed tumor growth was again assessed at the ROI and voxel levels.



The first panel (a) in the top row shows the true data at day 17, while the remaining three panels present the results of predicting the day 17 data using three combinations of earlier measurements. The bottom row presents analogous data for the experimental setting. While the approach is computationally sound (top row), Eq. [1] does not capture the relevant biology (bottom).

RESULTS: *Simulations* Panel (a) in the figure shows the true tumor cell distribution at the final time point (i.e., day 17), while panels (b-d) show the predicted growths from parameters estimated with the data obtained from days 9t11, 9t13, and 9t15. As indicated by the Table, increasing the number of observation points to estimate the parameters improves accuracy in estimating tumor volume and total cell number (ROI level predictions) and an increase in voxel CCC (voxel level prediction).

Experimental Panel (e) shows the true tumor cell distribution observed on day 17, while panels (f-h) show the predicted growths from the parameters estimated with the data obtained from days 9t11, 9t13, and 9t15. It is clear, that the predicted growths poorly predict the distribution observed on day 17. While accuracy still increases with the addition of more points, the CCC for experimental data (0.21) is lower than the simulated dataset (0.96) when days 9t15 are used. ROI level error for the experimental dataset was similar to the error observed for the simulated dataset.

TABLE	Simulated Dataset		
	9t11	9t13	9t15
Percent Error in Final Tumor Volume	40.00	18.40	15.80
Percent Error in Final Total Cell Number	42.7	16.7	16.5
Final Voxel CCC	0.66	0.94	0.96
	Experimental Dataset		
Percent Error in Final Tumor Volume	42.35	29.29	20.78
Percent Error in Final Total Cell Number	48.28	28.23	26.28
Final Voxel CCC	0.09	0.14	0.21

DISCUSSION: The errors in final tumor volume and total cell number suggest that Eq. [1] may accurately describe the bulk growth of gliomas such as the expansion rate and the total tumor proliferation rate. However, the poor voxel CCC for the experimental data suggests Eq. [1] is an incomplete description of *in vivo* glioma growth and that adjustments are needed to make it more accurate. One approach to improve this model is to use a dynamic proliferation/death term which changes, for example, due to cell density, distance from the tumor periphery, or vascularity; such measurements are available from imaging data.

CONCLUSION: The simulation study suggests that it is possible to accurately estimate parameters from Eq. [1] and then use those parameters to accurately predict future growth—provided Eq. [1] accurately describes the underlying biology. Using the same approach for the experimental data, Eq. [1] provides good predictions of ROI growth, but poor agreement at the voxel level. Thus, Eq. [1] is not a complete description of growth in the C6 model.

REFERENCES:1)Yankeelov TE. *ISRN Biomathem*. 2012; pii: 287394. 2) Atuegwu NC, *et al*. *Phys Med Biology*. 2010;55:2429-49.

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