

## Investigating the limitations of the reaction-diffusion equation for predicting *in vivo* tumor growth

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**Introduction and Methods.** The reaction-diffusion equation has been used extensively to model brain tumor growth. However, previous efforts have not used *in vivo* imaging data to estimate the parameters within this model (i.e., tumor cell diffusion and proliferation), and then use those parameters to predict future tumor status. Towards this end an *in silico* tumor, seeded within a rat brain domain and “grown” for ten days as dictated by the reaction-diffusion equation, was used to test the accuracy of parameters estimated from three imaging time points. This parameter set was then used to predict subsequent tumor growth. The predicted and observed tumor growths were compared at the whole tumor level (error in total volume, Dice similarity coefficient) and at the voxel level (concordance correlation coefficient (CCC)). We then performed the analogous study *in vivo* with rats (n=6) with C6 gliomas imaged with diffusion-weighted MRI (DW-MRI). A preliminary study was also performed in glioma patients (n=4) treated with Bevacizumab and serially imaged with DW-MRI.

**Results.** The *in silico* experiments resulted in less than 10% error for predictions up to five days into the future and high Dice (>0.87) and CCC values (>0.85). The *in vivo* rat experiments, resulted in greater than 10% error in all tumor volume predictions, though, these predictions did have good Dice values (>0.68). The predicted tumor cell numbers at the voxel level were poorly correlated with actual data with CCCs less than 0.30 for all predictions. For the glioma patients, tumor growth predicted two weeks into the future resulted in 16% (+/- 5.1%) error in tumor volume predictions with a high Dice value of 0.89 (+/- 0.04). Similar, to the results of the *in vivo* rat study, predictions of tumor cell number at the voxel level had low correlation with experimentally measured data with a CCC of 0.44 (+/- 0.25).

**Conclusion.** The results of the *in silico* study suggest that with appropriate image data it is possible to invert the reaction-diffusion equation to accurately estimate model parameters, and then use those parameters to generate accurate whole tumor and voxel level predictions. Using the same methodology for the *in vivo* rat study and the glioma patient study, however, resulted in good descriptions of whole tumor level properties, but poorly described the distribution of tumor cells. This suggests the

reaction-diffusion equation is an incomplete description of *in vivo* glioma growth.