Mathematical Modeling of Glioblastoma Growth and Response to Treatment

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ABSTRACT
**TITLE:** Mathematical Modeling of Glioblastoma Growth and Response to Treatment

**PURPOSE:** Glioblastoma is a devastating disease with generally poor prognosis despite multimodal therapy. However, there is significant variability in individual patient outcomes. Thus, the goal of the current work is to use mathematical modeling in combination with serial MR imaging to personalize prognostication on a patient-by-patient level and to help develop individualized, optimized therapy.

**METHODS:** Mathematical modeling was done using a reaction-diffusion partial differential equation to account for glioblastoma cell diffusion as well as proliferation. To individualize the model for each patient, tumor-specific diffusion and proliferation parameters can be derived for each patient using contrast-enhanced T1 and T2 MR imaging from as few as two days. Subsequent projects, as detailed in the attached publications, focused on either (1) improving the accuracy of the model or (2) exploring applications of the model. With regards to improving the model’s accuracy, 3D-DTI data was incorporated to model anisotropic tumor growth in 3 dimensions. Additionally, the model was extended to incorporate the effect of tumor cell necrosis, which is an important component of glioblastoma growth and progression. With regards to applications, the model was used to describe the tumor cell concentration gradient beyond imaging boundaries, optimization of radiation therapy using the technique of genetic algorithms, and evaluation of the effect of the extent of surgical resection on patient survival.

**RESULTS:** There were several important results from this work, as detailed in the attached publications. Incorporation of 3D-DTI data was qualitatively demonstrated to more accurately reproduce tumor growth and response to radiation therapy than the more traditional, one-dimensional tumor model. Additionally, the current work demonstrated the ability to utilize initial tumor location as a personalized parameter in addition to the tumor-specific diffusion and proliferation parameters used in the model. The incorporation of necrosis into the 3D-DTI model was qualitatively and quantitatively demonstrated to reproduce tumor morphology more accurately than one-dimensional, isotropic tumor growth model as well as the 3D model without necrosis. With regards to model applications, it was found that tumors of the same size on MR imaging may have significantly different tumor cell concentration gradients below the threshold of imaging detection. Specifically, tumors with higher diffusion:proliferation ratios were found to have a greater amount of subthreshold disease burden and a greater spatial extent of tumor cells throughout the brain. The current work also demonstrated that the extent of resection required to improve patient outcomes depends on the tumor-specific proliferation coefficient.

**CONCLUSIONS:** The combination of mathematical modeling and serial MR imaging contributes to a more complete understanding of glioblastoma growth and response to treatments including surgical resection and radiation therapy. The ability to personalize the model to individual patients allows for more tailored therapy in order to optimize patient outcomes.
My Contribution

I served as the primary investigator for the work described above and, as such, was the first author on five of the six papers listed below. In order to accomplish this research, I forged collaborative relationships with several other individuals. As listed above, these include Dr. Patrick Wen, Dr. Whitney Pope, Dr. Benjamin Ellingson, Dr. Timothy Cloughesy, and Vishal Patel. The above research required several components and my contributions to the various components of this research are described below. Firstly, the mathematical model used for this research relies on a reaction-diffusion partial differential equation that incorporates tumor diffusion and proliferation. I was responsible for the understanding and use of these equations as well as the development of the bicompartmental mathematical model (publication 6) and the extension of our modeling capabilities to allow for 3-dimensional modeling using DTI data. Additionally, the personalization of this model to each patient relies on the ability to calculate tumor-specific coefficients for diffusion and proliferation that can then be used to simulate each individual patient’s tumor. For each patient, these parameters are calculated based on contrast-enhanced T1 and T2 MR imaging data from as few as two different time points. I was responsible for developing our group’s method for using the available MR data to derive these tumor-specific parameters. In order to do this, of course, imaging data for patients with glioma was required. Dr. Whitney Pope and Dr. Benjamin Ellingson were instrumental in acquiring this imaging, drawing from the available UCLA patient database. In order to actually implement the mathematical modeling, a significant amount of computer programming was necessary to be able to use the model to calculate tumor-specific proliferation and diffusion coefficients and to use the model to simulate the growth of tumor cells. I was responsible for all of the programming for the one-dimensional model as well as the programming of treatments such as surgical resection and radiation therapy for the one-dimensional as well as three-dimensional tumor model. Dr. Vishal Patel and I worked together on programming of the three-dimensional model. Dr. Patel programmed the incorporation of necrosis into the model. Additionally, Dr. Patel took primary responsibility for writing the manuscript that details the incorporation of necrosis in our model, entitled “Image-driven modeling of the proliferation and necrosis of glioblastoma multiforme”, as listed below. For the other publications listed below, I served as the primary author. Dr. Patrick Wen assisted with review and final preparation of the manuscript entitled, “A 3-dimensional DTI MRI-based model of GBM growth and response to radiation therapy”. Dr. Whitney Pope and Dr. Benjamin Ellingson assisted in the preparation of the manuscript, “Patient-specific characterization of the invasiveness and proliferation of low-grade gliomas using serial MR imaging and a mathematical model of tumor growth”.

Accompanying publications (full text of the publications to be found in the attached folder, titled “SIM Papers”)


5. Hathout L, Ellingson BM, Cloughesy TF, Pope WB. Patient-specific characterization of the invasiveness and proliferation of low-grade gliomas using serial MR imaging and a mathematical model of tumor growth. [https://www-spandidos-publications-com.ezp-prod1.hul.harvard.edu/or/33/6/2883](https://www-spandidos-publications-com.ezp-prod1.hul.harvard.edu/or/33/6/2883)