Glioma Forecasting Using Mathematical Models
ASU AM^2 REU 2021
Patrick Hoover, Agustin Garcia Flores, Ashley Nichols

I. Introduction

Glioblastoma Multiforme (GBM) is an aggressive brain cancer that frequently moves location throughout the brain to acquire access to nutrients. GBM greatly damages the brain to the extent that even with treatments, patients tend to have a low survival rate. The goal of this project is to give doctors and patients a way to predict the diffusion and growth of GBM for patient counseling and treatment purposes by using Magnetic Resonance Imaging scans (MRIs) and Partial Differential Equations (PDEs).

II. Background

The human brain consists of three main parts: white matter, cerebrospinal fluid (CSF), and gray matter. White matter consists of the axon tracts (Mercadante & Tadi, 2020) and cerebrospinal fluid acts to surround the brain from trauma and removes waste in the extracellular matrix surrounding the brain (U.S. National, 2020). Gray matter consists of neurons and glial cells, where GBM is commonly seen, though GBM is also found infecting hormonal glial cells for neurons (Davis, 2016).

Treating brain cancers such as GBM is difficult due to GBM's close proximity to eloquent areas of the brain. Reduced bodily function, such as loss of motor skills, loss of sight, and changes in personality, can develop if a significant quantity of brain margin is removed during resection surgeries (Aldape et al, 2019). GBM is usually ineffective to chemotherapy drugs due to the blood brain barrier blocking substances from reaching the brain. This makes having a simulation technology to predict the growth and diffusion of the tumor essential in giving patients accurate counseling on their treatment options.

In the context of this problem, GBM is understood to have both growth and diffusion properties. The Harris-Kuang Model was the main model used this summer for simulations.

To prepare the MRI scans for simulation, each scan was first preprocessed, which consists of three major parts: organizing the files, clearing the scans of any bias field signal from an MRI, and coregistering the scans and creating new ones. Clean file organization is achieved by running a MATLAB code that names each of the files using the same naming convention. Each scan is then entered into 3D Slicer, a software used for biomedical and imaging research, to filter the scans and get rid of any signal corruption from the MRI machine. Additional MATLAB SPM12 (Statistical Parametric Mapping) code is then run to coregister each scan, reduce the dimensions of the scans for less time-consuming simulations, and to create a new Native Brain scan for each scan.

The Native Brain scan is a layout of the white matter, gray matter, and CSF in the scans of each patient. Further segmentations were done by hand to identify a general region where three regions of the brain tumor were indicated based on MRI scans: edema, enhancing rim, and core. These three regions of the tumor indicated where cancer cells were present within the brain of the patients, although core signified dead cancer cells.

III. Body

i. Agave parameters

The simulation model for these GBM tumors contained different base parameters that could be modified. The model differentiates between two types of conditions brain cells may undergo: proliferation and quiescence. Proliferation occurs when cells are actively dividing to make new cells, whereas quiescent cells are cells that stop cell division-either being necrotic (dead) or hypoxic (alive but lacking oxygen). These cell types can have different parameters that simulate the spread of tumor growth in patients. The simulation model allows for a diffusion and growth of these different cell types to provide both a simulated spread and accumulation of tumor cells within the brain. The simulation time could also be adjusted, accounting for the correct amount of days that were taken between each of the brain scans. All of these aspects of the simulation model were edited and simulated through Agave, a High-Performing Computing (HPC) cluster.

ii. Patient 48

One of the patients the researchers evaluated was patient 48. Patient 48 has a significantly sized resection cavity in the right lower region of the patient's brain (the temporal lobe). According to the Brain Tumour Charity, some of the symptoms that the patient might experience are: having difficulties with hearing, speaking, and identifying and categorizing objects. *Figure 1.1* shows a plain scan 1 for patient 48. *Figure 1.2* shows our segmentation of scan 1. For the Agave prediction of scan 2 the researchers continued using the Harris-Kuang model [*Equation 1.1*] and the basic set of parameters; the proliferating and quiescent cell population was kept at the initial rates of the program. Scan 2 took place 68 days after scan 1 and was put into the Agave program and simulated for the same length of time. After running the Harris-Kuang and running the file through MATLAB visualization code the researchers were able to produce *Figure 1.3*. As a comparison, a segmentation of scan 2 [*Figure 1.4*] can be used to compare what the actual segmentation should appear to be. While comparing the two figures, although the model is not completely accurate, it provides a very good prediction of the overall shape of the tumor. The Agave program predicted the tumor to grow rapidly towards the lower region of the resection cavity, however that did not occur as seen in *Figure 1.4*. This is just one example of when the Harris-Kuang Model was able to provide a solid prediction.

iii. Patient 15

Patient 15's first scan [*Figure 1.5* and *Figure 1.6*] shows a small area of high intensity in the bottom right corner of the brain. Using the Harris-Kuang Model to simulate 56 days of tumor progression, the progress of the tumor growth and diffusion produced a circular-

looking mass in the bottom right corner of the brain [*Figure 1.7*]. Comparing this with the actual growth of the tumor in scan 2 [*Figure 1.8*] reveals the simulation does not look like the actual growth of the tumor. This could be due to an incorrect classification of white and gray matter using SPM12 during the preprocessing steps.

iv. Patient 38

Patient 38's scans were also simulated and predicted using the Harris-Kuang model. Scan 2 [*Figure 1.9* and *Figure 1.10*] shows a resection cavity to the right of the tumor. Similar to patient 48, the tumor lies within the temporal lobe, leading to similar symptoms for the patient. The difference between the scan 2 [Figure 1.10] and scan 3 [Figure 1.12] is a timeframe of 56 days. The Harris-Kuang model was modified and the rate of diffusion of proliferating enhancing rim cells was decreased. The growth rate of proliferating enhancing rim was also decreased to improve the prediction presented by the simulation, as seen in *Figure 1.11*.

v. Patient 40

Using the same values for the diffusion and growth rate as with patient 38, patient 40 was also simulated using the Harris-Kuang modified model. The timeframe between patient 40's scan 1 [*Figure 1.13* and *Figure 1.14*] and scan 2 [*Figure 1.16*] was 31 days. Applying the modified Harris-Kuang model, the researchers wanted to observe if an increase in similarity was seen between the segmentation and predicted model. As seen in *Figure 1.15*, the predicted model did correlate with scan 2 of patient 40 [*Figure 1.16*]. The correlation suggests that the modified version of the model with lower rates of diffusion and growth rates of enhancing rim may be more biologically correct for predicting brain tumors. However, more testing would be needed to conclude if this modified model is considered accurate.

IV. Results

Using a very basic image subtraction technique allowed the researchers to produce percentages showing how much the simulation scans overlapped with the actual scans. The percentage was calculated in this manner:

$$\frac{Number\ of\ nonzero\ cells\ where\ the\ images\ intersected}{Total\ number\ of\ nonzero\ cells}$$

The results for each patient were as follows:

Patient	Rim Agreement	Core Agreement
Patient 48	9.75%	0%
Patient 15	14.39%	5.22%
Patient 38	26.47%	2.96%
Patient 40	35.60%	43.21%

Table 1: Image Subtraction Results

There are limitations to these results because the nonzero cells do not take into account the cell density at each voxel and simply consider an area to be “Rim” (proliferating cells) or “Core” (quiescent cells) based on the intensity at each region. A better way of determining the agreement percentage for each simulation may take into account the overall high intensity diameter rather than the individual section of the “Rim” and “Core”. This is meant to be a very basic way of determining the agreement between the two scans so simulation parameters can be adjusted accordingly, and future work could include finding a better way of comparing the two scans.

V. Future Work

The future work of this project is to continue to run the Agave program in order to find a set of parameters that best fits the growth of a GBM tumor. The researchers in this project are currently using a very crude and basic model of the tumors. After ensuring the accuracy of the math and simulations, the researchers can expand the equations to include more input from neuroscientists and create even more accurate predictions. Once a good set of parameters is found they must then be tested on different scans and different patients to see if they are also applicable elsewhere. This requires a lot of manual labor and a good interpretation of the information. It will consist of many trial and error simulations, but once a reasonable set of parameters is established this will be useful with other patients.

VI. Conclusion

The simulations show promising possibilities of more accurate results. However, more research would need to be done to justify these claims by simulating multiple scans from different patients. More simulations for subsequent scans of one particular patient would also need to be evaluated as well. The current methodology seems stable as a general workflow, but future work is needed to facilitate the production of better simulation results and the betterment of the biological factors of these scans.

VII. Acknowledgments

Thank you to Duane Harris, Dr. Kostelich, Dr. Preul, and Dr. Mignucci for their input during this REU. Thank you also to the National Science Foundation and to the Arizona Biomedical Research Commission for sponsoring our program.

References

Aldape, K., Brindle, K.M., Chesler, L. *et al.* Challenges to curing primary brain tumours. *Nat Rev Clin Oncol* 16, 509–520 (2019). https://doi.org/10.1038/s41571-019-0177-5

Davis, M. E. (2016). Glioblastoma: Overview of Disease and Treatment. *Clinical journal of oncology nursing*, *20*(5 Suppl), S2–S8. https://doi.org/10.1188/16.CJON.S1.2-8

Fisher, R.A. The wave of advance of advantageous genes, *Annals of Eugenics*, 7 (1937), 355–3

Han, L.F., Eikenberry, S., He, C.H., Johnson, L., Preul, M.C., Kostelich, E.J., Kuang, Y. *Patient specific parameter estimates of glioblastoma multiforme growth dynamics from a model with explicit birth and death rates*. Math Biosci Eng. 2019 Jun 11;16(5):5307-5323. doi: 10.3934/mbe.2019265. PMID: 31499714; PMCID: PMC7304543

Juntu J., Sijbers J., Van Dyck D., Gielen J. (2005) *Bias Field Correction for MRI Images*. In: Kurzyński M., Puchała E., Woźniak M., żołnierek A. (eds) *Computer Recognition Systems*. Advances in Soft Computing, vol 30. Springer, Berlin, Heidelberg. https://doi.org/10.1007/3-540-32390-2_64

Kostelich, E.J., Harris, D. *Comparing the Predictive Capability of Glioma Growth Models*. October 1, 2020.

Mercadante, A.A., Tadi, P. (2020, July 31). Neuroanatomy, Gray Matter. *StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing*. Retrieved July 10, 2021, from https://www.ncbi.nlm.nih.gov/books/NBK553239/.

The Brain Tumour Charity. (n.d.). *Symptoms based on brain tumour location: The Brain Tumour Charity*. Symptoms based on brain tumour location. https://www.thebraintumourcharity.org/brain-tumour-signs-symptoms/brain-tumour-location-symptoms/.

U.S. National Library of Medicine. (2020, November 30). *Cerebrospinal Fluid (CSF) Analysis*. MedlinePlus. https://medlineplus.gov/lab-tests/cerebrospinal-fluid-csf-analysis/.

Equations

Equation 1.1: Harris-Kuang Model

$$\frac{\partial p}{\partial t} = \nabla * (D \nabla p) + \rho g(p+q)p - k\delta(p+q)p$$

$$\frac{\partial q}{\partial t} = k\delta(p+q)p$$

$$n = p + q$$

Figures

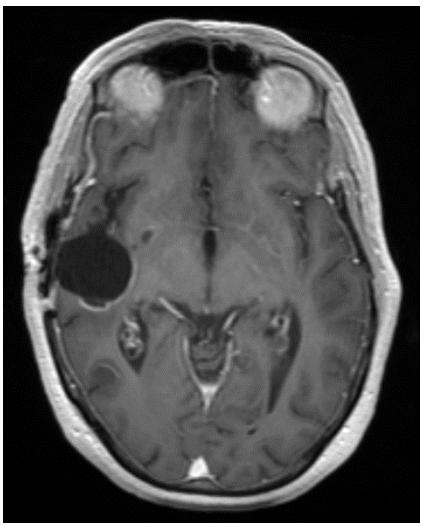

Figure 1.1: Pt 48 Scan 1

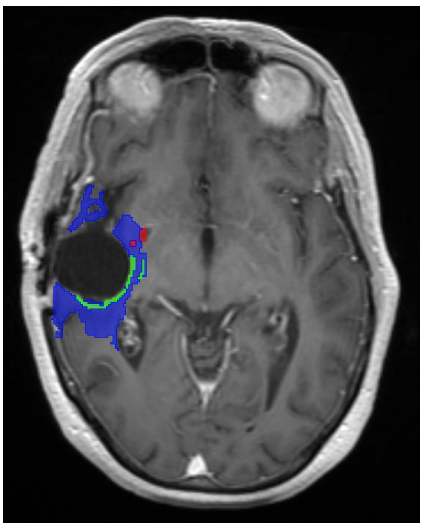

Figure 1.2: Pt 48 Scan 1 Segmentation

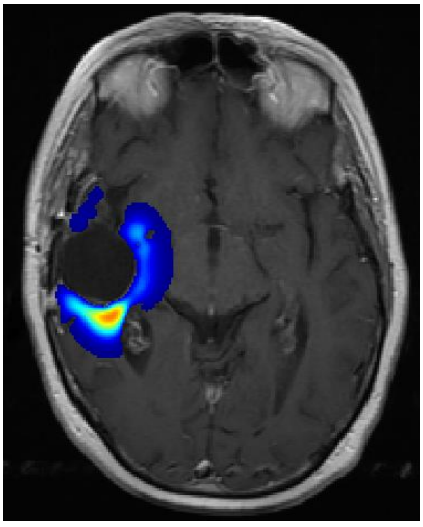

Figure 1.3: Pt 48 Harris-Kuang Model

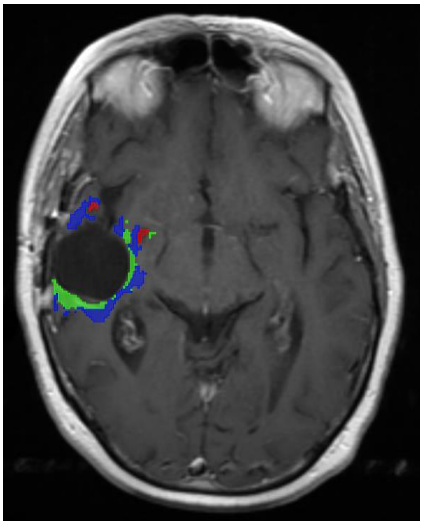

Figure 1.4: Pt 48 Scan 2 Segmentation

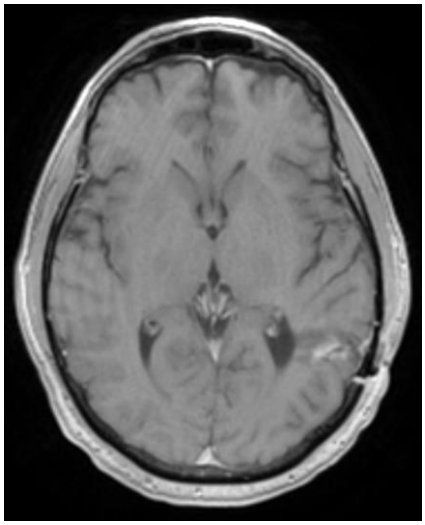

Figure 1.5: Pt 15 Scan 1

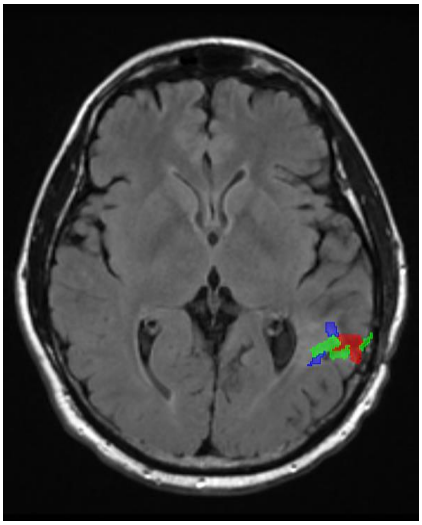

Figure 1.6: Pt 15 Scan 1 Segmentation

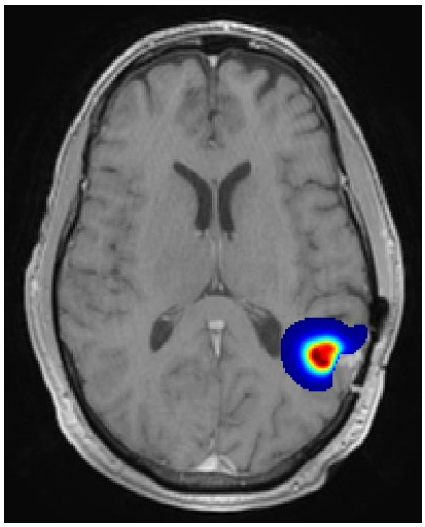

Figure 1.7: Pt 15 Harris-Kuang Model

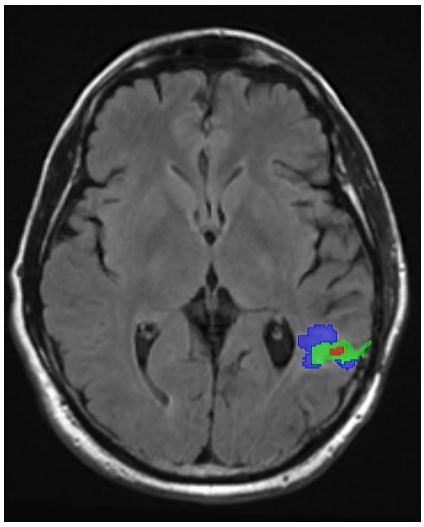

Figure 1.8: Pt 15 Scan 2 Segmentation

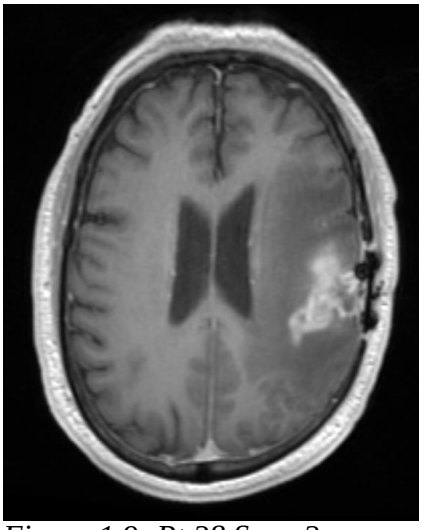

Figure 1.9: Pt 38 Scan 2

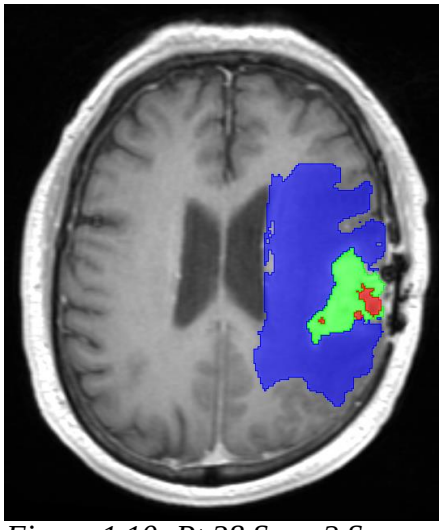

Figure 1.10: Pt 38 Scan 2 Segmentation

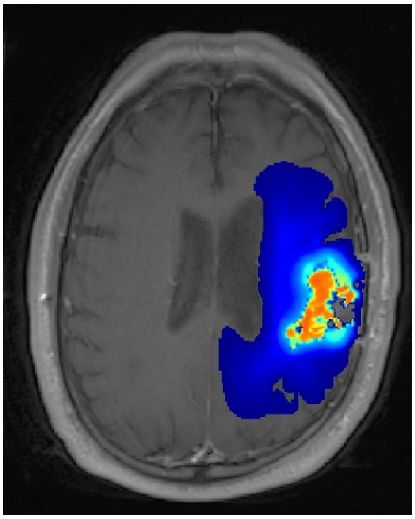

Figure 1.11: Pt 38 Scan 2 Modified Harris-Kuang Model

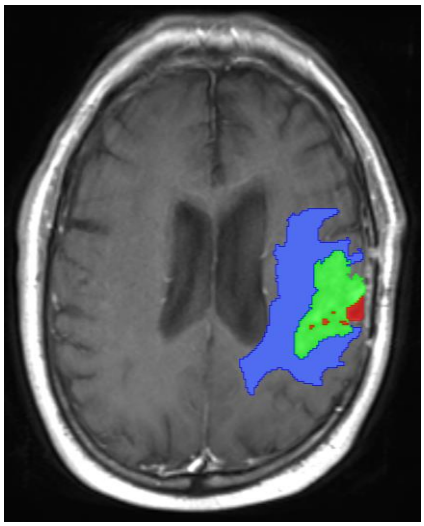

Figure 1.12: Pt 38 Scan 3 Segmentation

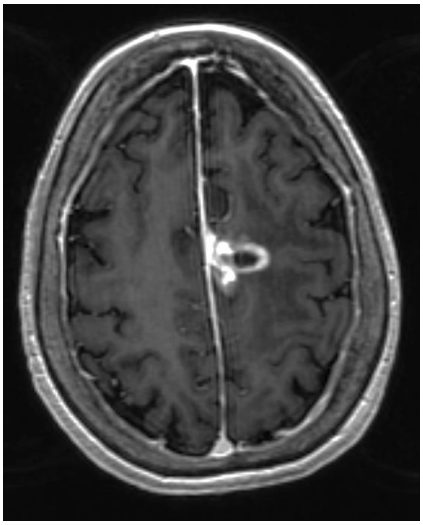

Figure 1.13: Pt 40 Scan 1

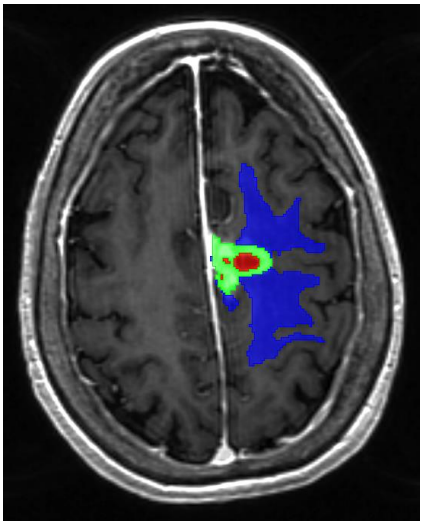

Figure 1.14: Pt 40 Scan 1 Segmentation

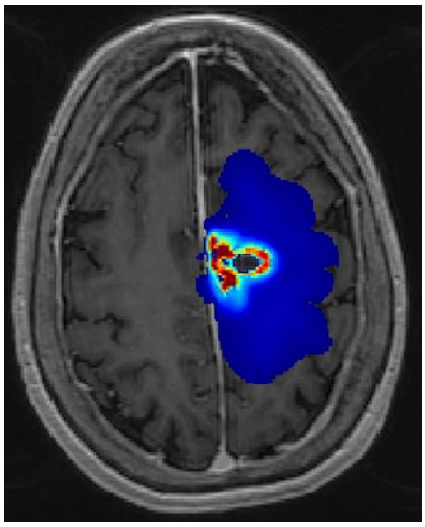

Figure 1.15: Pt 40 Scan 1 Modified Harris-Kuang Model

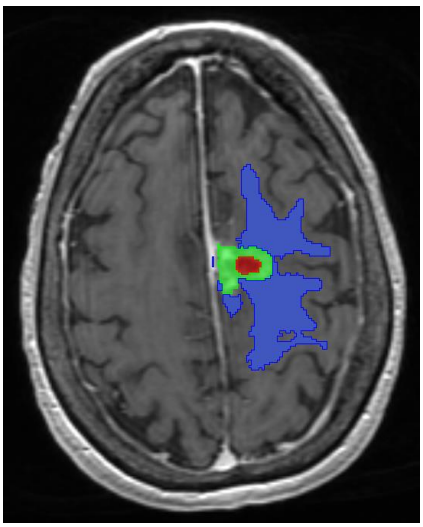

Figure 1.16: Pt 40 Scan 2 Segmentation