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DYNAMICS OF A MODEL FOR BRAIN TUMORS REVEALS A SMALL WINDOW FOR THERAPEUTIC INTERVENTION

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Abstract. Glioblastomas are the most malignant and most common glioma, a type of primary brain tumor with the unfortunate ability to recur despite extensive treatment. Even with the advent of medical imaging technology during the last two decades, successful treatment of glioblastomas has remained elusive. It has become increasingly clear that, along with the proliferative potential of these neoplasms, it is the subclinically diffuse invasion of glioblastomas that primarily contributes to their resistance to treatment. In otherwords, the inevitable recurrence of these tumors is the result of diffusely invaded but invisible tumor cells peripheral to the abnormal signal on medical imaging and to the current limits of surgical, radiological and chemical treatments.

Mathematical modeling has presented itself as a viable tool for studying complex biological processes (Murray, 1993, 2002). We have developed a mathematical model that portrays the growth and extension of theoretical glioblastoma cells in a matrix that accurately describes the brain's anatomy to a resolution of 1 cu mm (Swanson, et al, 1999, 2000, 2002, 2003a, 2003b). The model assumes that only two factors need be considered for such predictions: net growth rate and infiltrative ability. The model has already provided illustrations of theoretical glioblastomas that not only closely resemble the MRIs (magnetic resonance imaging) of actual patients, but also show the distribution of the diffusely infiltrating cells.

1. **Introduction.** Glioblastomas are brain tumors that differ from most other tumors by their aggressive diffuse invasion of the surrounding normal tissue. This invasive nature contributes to their dismal 6 to 12 months prognosis (Nazzaro and

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Neuwelt, 1990). The remarkable continuing development of medical imaging has increased the ability to detect gliomas, but has not, to date, come close to sufficiently defining the extent of invasion of the tumor cells peripheral to the bulk tumor mass. So, it is not surprising that even extensive surgical resection or local irradiation of gliomas is followed by tumorous recurrence at or near the edge of the treatment region (Gaspar et al., 1992; Liang et al., 1998). As with a forest fire, it does little good to drop fire-fighters into the burned out center of the fire when the action is at the periphery.

Mathematical modeling of biomedical phenomena (Murray, 2003) can be extremely helpful in analyzing factors that may contribute to the complexity intrinsic to many diseases. Despite the complexity of gliomas, some of the basic components of this disease have been found. Based on present knowledge of the properties of gliomas, we developed a mathematical model to quantify the spatio-temporal proliferation and invasion dynamics of gliomas within anatomically accurate heterogeneous brain tissue in three spatial dimensions. The implications of this type of modeling would be of considerable interest not only to neuro-oncologists attempting to improve the treatment of gliomas, but also to those interested in the quantitative study of other diseases for which medical imaging plays a large role in the assessment of the disease (e.g. other cancers and developmental and degenerative diseases).

2. **Mathematical Model.** Our mathematical model defines the progression of gliomas beginning from a solid mass of about 1 cu mm, growing and diffusing (infiltrating) into the adjacent tissue. Although the initial models (Tracqui et al., 1995; Cruywagen et al., 1995; Woodward et al., 1996; Burgess et al., 1997) utilized essentially 2-dimensional homogeneous brain bounded only by the ventricles and arachnoid, the availability of the BrainWeb brain atlas database (Cocosco et al., 1997; Collins et al., 1998) lets us refine the gross anatomic boundaries of the human brain in three dimensions (Swanson et al., 2002). By defining a virtual human brain with the anatomical distribution of grey and white matter (the two primary tissue components of the brain) to a resolution of 1 cu mm, we can model the differential motility of glioma cells in grey or white matter to accommodate reports (Giese and Westphal, 1996) that such differences are biologically significant. Specifically, since glioma cells reportedly migrate more rapidly in white matter than in grey matter (Giese and Westphal, 1996; Silbergeld and Chicoine, 1997), we include the motility coefficient dependence on the local tissue composition.

The model expressed as a word equation is:

$$\begin{gathered}\text{rate of change of glioma cell density} = \\ \text{diffusion (motility) of glioma cells} + \\ \text{net growth of glioma cells.}\end{gathered}$$

with $c(\mathbf{x}, t)$ denoting the concentration of glioma cells at any position $\mathbf{x}$ and time t, this word equation can be written mathematically as:

$$\frac{\partial c}{\partial t} = \nabla \cdot (D(\mathbf{x})\nabla c) + \rho c, \tag{1}$$

where ρ is in units of per day and represents the net rate of growth of tumor cells, including proliferation, loss and death. In the equation, D is in units of cm^2/day and represents the diffusion coefficient of cells in brain tissue: $D(\mathbf{x}) = D_g$ is a constant for x in gray matter, $D(\mathbf{x}) = D_w$ is another constant for x in white matter. As noted above, the diffusion coefficent in white matter is larger then that

in grey matter: $D_w > D_g$. To complete the mathematical formulation of the model requires that we describe the initial state of the tumor. At time $t = 0$, we assume that there is a tiny solid mass containing approximately 20 generations of 10 μm cells, about 10^6 cells.

3. **Numerical Techniques.** Our model equation is parabolic so we expect to use an implicit numerical scheme. Two obvious choices are Backward Euler and Crank Nicolson methods. Both methods are well suited to (1). Although a Crank Nicolson scheme is more accurate, a Backward Euler scheme is more capable of resolving steep gradients and dealing with discontinuous data (Strikwerda, 1989) like that within our virtual brain.

There is one simple expression combining both the Backward Euler and Crank Nicolson schemes. Let v_n be a spatial vector of the numerical solution at time step n with temporal stepsize k. Let Φ be a discrete spatial differentiation operator.

$$(I - \theta k(\Phi(D\Phi) + \rho))\delta^n = k(\Phi(D\Phi) + \rho)v^n. \tag{2}$$

where for $\theta = \frac{1}{2}$ we have Crank Nicolson and for $\theta = 1$ we have Backward Euler. The numerical method (2) is (at least) first order accurate in space and time for $\frac{1}{2} \leq \theta \leq 1$. Neglecting the growth ρv_n [2] , the method (2) is unconditionally [3] stable.

Although we have only discussed the one dimensional case, the method (2) is easily extended to multiple dimensions. The method (2) involves solving $A\delta^n = b$ for δ^n and updating $v^{n+1} = v^n + \delta^n$. In three dimensions, the human brain simulations are on a 181 x 217 x 181 grid. The resulting matrix A is quite large and inverting it directly is impractical. As an alternative to a direct inversion method, we use interative methods. Since we used a symmetric formulation of the diffusion operator and despite the spatial heterogeneities in the coefficient D, the matrix we are inverting, A, is symmetric and positive-definite (Greenbaum, 1997). Such a matrix can be inverted iteratively using, for example, a Conjugate Gradient (CG) Method. Other iterative methods are also applicable but we chose CG.

4. **Results.** Assessing the true extent of gliomas is limited by the ability of present imaging technologies to resolve the low-density invasion of the normal appearing brain surrounding the bulk of the lesion. This limitation is emphasized in Figure 1 which shows the time evolution of the total number of tumor cells throughout the brain (solid-line) as well as the average radius of the MRI-detectable[4] portion of the lesion (dashed-line). For the first 500 days following initiation of the tumor, the standard clinical MRI is unable to detect the lesion. Despite significant growth of the total number of glioma cells invaded throughout the brain (solid-line), the tumor is detectable by MRI for less than 25% of it's total time course.

Figure 2 shows contour plots of the tumor cell density of the virtual glioma shown in Figure 1 at multiple timepoints following the initiation of the lesion at the asterisk. Note that the origin of the lesion (asterisk) is no longer in the geometric center of the virtual tumor due to the asymmetric diffusion in grey and white

[2]Clearly as $t \to \infty$, n blows up due to the growth term ρn, so in considering stability of our numerical scheme we neglect growth.

[3]for all $\mu = \frac{k}{h^2}$

[4]Magnetic resonance imaging, or MRI. Throughout, our use of the term MRI corresponds to T1-weighted, gadolinium-enhanced MRI, a stanard imaging protocol used to characterize the size of high-grade gliomas (glioblastomas).

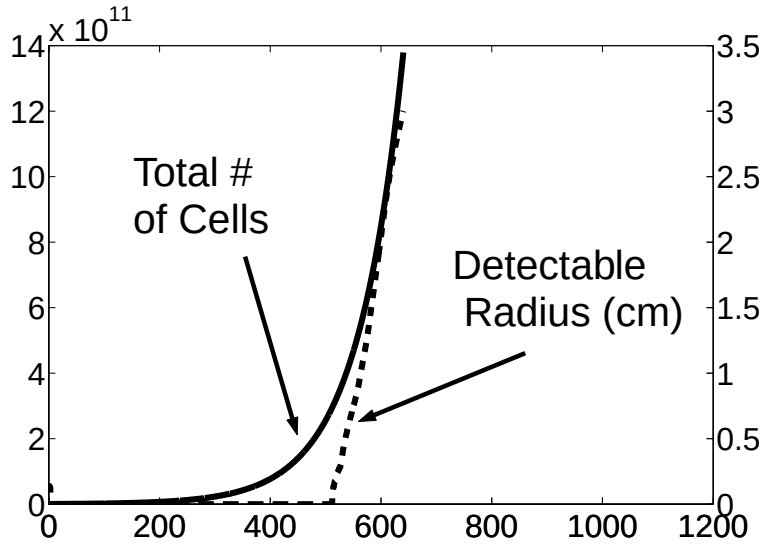

FIGURE 1. Time evolution of the total number of tumor cells throughout the brain (solid-line) as well as the average radius of the MRI detectable portion of the lesion (dashed-line).

matter. The concentration gradient of tumor cells is represented by concentric curves with each curve representing a certain cell density. The current standard threshold of detection approximating that of a gadolinium-enhanced T1-weighted MRI (solid black curve) is contrasted with a theoretical new technique 80 times more sensitive (lightest blue curve). Although the tumor is not detectable by MRI for at least the first 500 days, the tumor has already invaded significantly throughout the brain. Death is assumed to occur when the detectable lesion reaches a volume equivalent to a 3 cm in radius sphere.

Figures 1 and 2 combine to reflect the fundamental problem with gliomas: 1) diffuse invasion of the lesion is significant by the time the lesion is detected and 2) the window of opportunity for treatment following diagnosis is very small. These results reveal the true limitations of treatment. Since imaging technologies can not resolve the true extent of gliomas, accurate assessment of the lesion behavior following treatment is difficult, if not impossible, without the insight provided by mathematical modeling like that presented here. Additionally, the temporal window of opportunity following diagnosis of a glioma, is very small ($<$150 days) compared to the entire life cycle of the lesion (640 days).

Our model can be applied to an individual patient to calculate the two factors (proliferation and infiltrative potential) precisely enough to display the past, present and future distributions of tumor cell concentrations down to the individual cell, well beyond the "edge" of the tumor defined by current imaging. From the steepness of the gradient of glioma cells beyond the detectable tumor margin, the model provides information regarding the expected locations of potential recurrence, as well as the time scale on which we expect that regrowth to happen. These displays should provide guidance to surgeons, radiotherapists and neuro-oncologists as to where and when to expect recurrences. Not only should these predictions help them to define where to concentrate their respective treatments, but also comparison

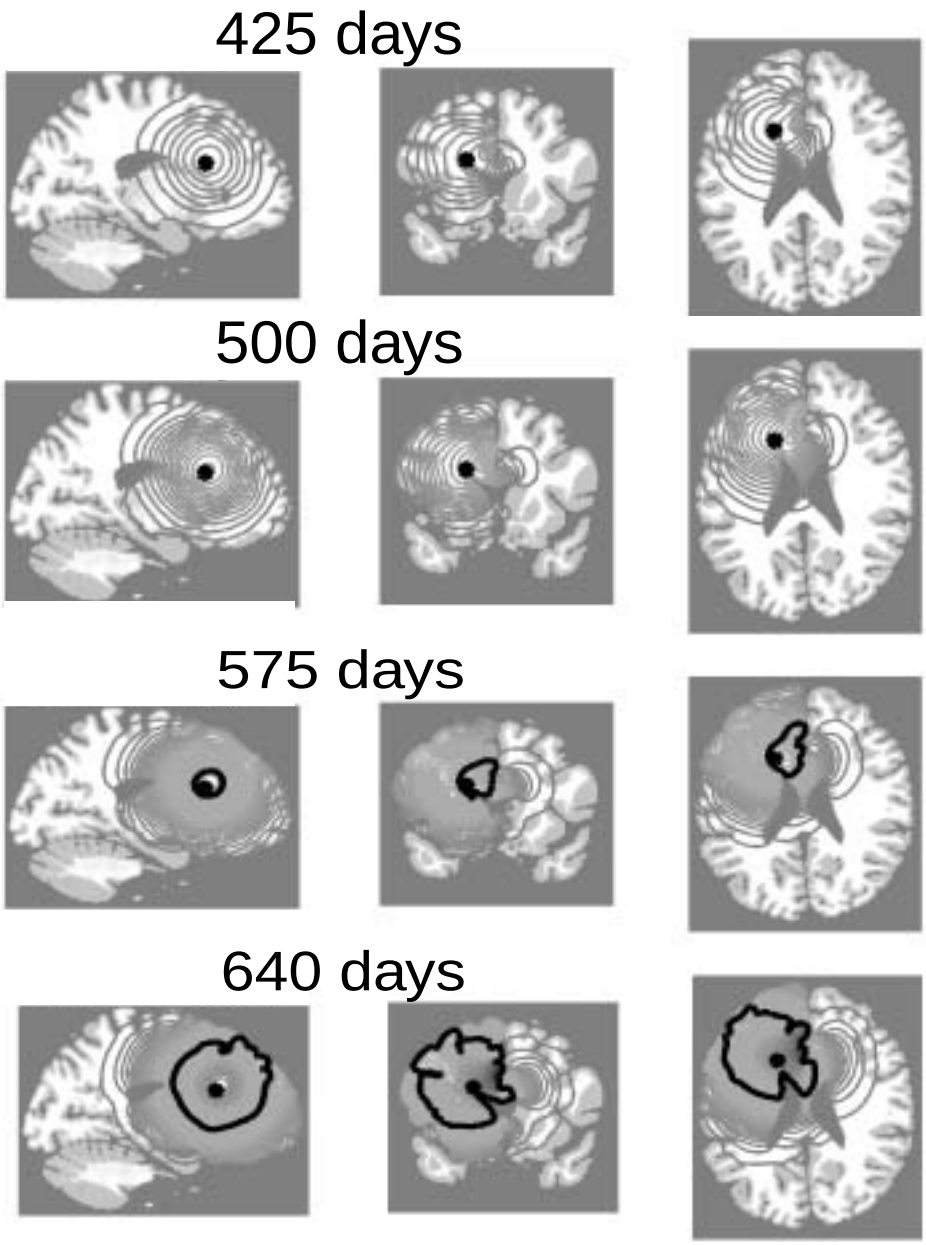

FIGURE 2. Contour plot of the tumor cell density of a virtual glioma at multiple time points following the initiation of the lesion at the asterisk. The images are cross-sections of the brain intersecting at the asterisk. The outermost contour corresponds to a detection threshold 80 times more sensitive than MRI technology (thick black curve).

of the actual and predicted times to recurrence should also help to ascertain the effectiveness of treatments in individual patients, thereby, avoiding the necessity to use large groups of patients and averages.

Our modeling approach establishes a new way of thinking about gliomas and has many applications, in the clinic as well as in the laboratory. Clearly, it is necessary to develop better treatment protocols that more directly address the diffuse nature of gliomas. However, since standard imaging technologies cannot define the diffusiveness of gliomas, there is essentially no means of assessing the efficacy of such a diffuse treatment regime without a quantitative model to interpret the available patient data. With our model for the basic biological mechanisms involved in brain tumor progression, limited patient data can be combined to develop a more thorough picture of the tumor's past history and future behavior.

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