QUANTIFYING EFFICACY OF CHEMOTHERAPY OF BRAIN TUMORS WITH HOMOGENEOUS AND HETEROGENEOUS DRUG DELIVERY

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ABSTRACT

Gliomas are diffuse and invasive brain tumors with the nefarious ability to evade even seemingly draconian treatment measures. Here we introduce a simple mathematical model for drug delivery of chemotherapeutic agents to treat such a tumor. The model predicts that heterogeneity in drug delivery related to variability in vascular density throughout the brain results in an apparent tumor reduction based on imaging studies despite continual spread beyond the resolution of the imaging modality. We discuss a clinical example for which the model-predicted scenario is relevant. The analysis and results suggest an explanation for the clinical problem of the long-standing confounding observation of shrinkage of the lesion in certain areas of the brain with continued growth in other areas.

1. INTRODUCTION

Gliomas are diffuse and invasive neoplasms of the brain with a dismal prognosis of six to 12 months despite heroic treatment protocols including resection, radiation therapy and chemotherapy. Chemotherapies are particularly difficult to use for these brain tumors due to the diffuse invasion of the normal brain peripheral to the bulk lesion as well as the hindrance of drug delivery by the blood-brain-barrier (BBB). The BBB exists to maintain the chemical harmony of the delicate brain cells by maintaining tight junctions of the capillary network, thus hindering drug delivery to malignantly invaded tissue. If one is using a chemotherapeutic agent that can bypass the BBB, another level of complexity in the treatment of gliomas relates to heterogeneity in drug delivery to the various tissues of the brain. Here we will explore the effect of these heterogeneities on the efficacy of chemotherapies in the treatment of gliomas.

In this paper, we extend the previously described model (Murray, 2002; Swanson *et al*., 2002, 2000; Swanson, 1999) for brain tumor growth and invasion to reconsider the effects of chemotherapy on the spatio-temporal response of gliomas. We begin by studying the case of homogeneous drug delivery to the brain tissue. Next, we incorporate effects of heterogeneities in the vascular structure of the brain tissue to consider heterogeneous drug delivery. In this more biologically reasonable case of

heterogeneous drug delivery, we show an example of a patient for which the model-predicted behavior was observed.

2. PREVIOUS MODELS FOR BRAIN TUMOR GROWTH AND INVASION

The general approach for modeling gliomas has been to isolate two key characteristics of these brain tumors: proliferation and diffusion (Burgess *et al*., 1997; Cook *et al*., 1995; Cruywagen *et al*., 1995; Tracqui *et al*., 1995; Woodward *et al*., 1996): see Murray (2002) for a full discussion and review. The basic model can be written in words as:

$$\begin{aligned} &\text{Rate of change of glioma cells} = \\ &\text{Diffusion (motility) of glioma cells} + \\ &\text{Net proliferation of glioma cells.} \end{aligned} \tag{1}$$

Mathematically, the word equation (1) for untreated gliomas can be quantified as

$$\frac{\partial \bar{c}}{\partial \bar{t}} = \overline{\nabla} \cdot (\overline{D}(\bar{\mathbf{x}})\, \overline{\nabla} \bar{c}) + \rho \bar{c}, \tag{2}$$

where $\bar{c}(\bar{\mathbf{x}}, \bar{t})$ is the tumor cell density at location $\bar{\mathbf{x}}$ and time $\bar{t}$, $\overline{\nabla}$ is the spatial gradient operator, ρ is the net proliferation rate and $\overline{D}(\bar{\mathbf{x}})$ is the space-dependent diffusion coefficient representing the active motility of glioma cells. Clinical data show that exponential growth is a good description, hence the linear term $\rho\bar{c}$. Experimental observations that glioma cells migrate more quickly in the white matter than in the grey matter of the human brain are accounted for by taking the diffusion coefficient $\overline{D}(\bar{\mathbf{x}})$ to be a function of the spatial variable $\bar{\mathbf{x}}$ so that $\overline{D}(\bar{\mathbf{x}}) = D_W$, D_G in white and grey matter, respectively. The above model formulation is completed by boundary conditions imposing zero flux of cells at the brain boundaries: $\overline{\nabla}\bar{c} \cdot \mathbf{n} = 0$ where $\mathbf{n}$ is the unit normal to the domain boundary ∂B, as well as initial conditions defining the initial distribution of tumor cells at model time zero: $\bar{c}(\bar{\mathbf{x}}, 0) = \bar{f}(\bar{\mathbf{x}})$.

There has been one study that has previously considered chemotherapy in the context of the above general model, namely the work by Tracqui *et al.* (1995). They include the analysis of a patient that received multiple chemotherapeutic treatments during the last 12 months of the patient's life. Tracqui *et al.* (1995) highlighted the significance of a treatment-resistant subpopulation of tumor cells presumably responsible for the eventual death of the patient. In this paper we shall highlight the importance of another aspect of chemotherapies relating to the vascular structure of the brain by accounting for heterogeneity in drug delivery to these diffusely invaded regions.

3. HOMOGENEOUS DRUG DELIVERY

The Mathematical Model

We follow the basic brain tumor growth and invasion model structure of Swanson *et al.* (Swanson *et al*., 2000; Swanson, 1999) described above and then introduce

chemotherapy as a loss term. If $G(\bar{t})$ defines the temporal profile of the chemotherapy, then, assuming a loss proportional to the strength or amount of therapy at a given time (Kroll *et al*., 1996), we write the model as

$$\frac{\partial \bar{c}}{\partial \bar{t}} = \bar{\nabla} \cdot (\bar{D}(\bar{\mathbf{x}})\, \bar{\nabla} \bar{c}) + \rho \bar{c} - G(\bar{t})\bar{c} \tag{3}$$

for $\bar{t} > \bar{t}_c$: the time at which chemotherapy starts. Usually $G(\bar{t})$ is periodic, but more generally

$$G(\bar{t}) = \begin{cases} k, & \bar{t} \in \bar{T}_{\text{on}} - \text{chemotherapy on} \\ 0, & \bar{t} \in \bar{T}_{\text{off}} - \text{chemotherapy off} \end{cases}$$

where k is the effectiveness of the chemotherapy reaching the brain tissue. $\bar{T}_{on}$ and $\bar{T}_{\text{off}}$ are the set of times for which chemotherapy is on and off, respectively. We solve (3) subject to the initial conditions $\bar{c}(\bar{\mathbf{x}}, \bar{t}_c^{+}) = \bar{f}(\bar{\mathbf{x}})$, where $\bar{t}_c$ is the time the chemotherapy starts, and no-flux boundary conditions $\bar{\nabla} \bar{c} \cdot \mathbf{n} = 0$ on ∂B (the brain boundary).

Chemotherapy is usually administered periodically. Typically, a cycle of treatment consists of the administration of drugs for a period of time $\bar{t}_{\text{chemo}}$ followed by a waiting period $\bar{t}_{\text{wait}}$. The total time elapsed per cycle is then given by $\bar{t}_{\text{cycle}} = \bar{t}_{\text{chemo}} + \bar{t}_{\text{wait}}$. Assuming chemotherapy starts at $\bar{t} = \bar{t}_c$ then

$$\bar{T}_{\text{on}} = \left\{ [n\bar{t}_{\text{cycle}} + \bar{t}_{\text{c}},\ n\bar{t}_{\text{cycle}} + \bar{t}_{\text{chemo}} + \bar{t}_{\text{c}}),\quad n = 0,1,\ldots, N_{\text{cycles}} \right\},$$
$$\bar{T}_{\text{off}} = \left\{ [n\bar{t}_{\text{cycle}} + \bar{t}_{\text{chemo}} + \bar{t}_{\text{c}},\ (n+1)\bar{t}_{\text{cycle}} + \bar{t}_{\text{c}}),\quad n = 0,1,\ldots, N_{\text{cycles}} \right\}.$$

Introducing nondimensional variables (9) (see Appendix), the model becomes

$$\frac{\partial c}{\partial t} = \nabla \cdot (D(\mathbf{x})\, \nabla c) + (1 - G(t))c, \quad t > 0 \tag{4}$$

where

$$G(t) = \begin{cases} \dfrac{k}{\rho} = \beta, & t \in T_{\text{on}} - \text{chemotherapy on} \\ 0, & t \in T_{\text{off}} - \text{chemotherapy off} \end{cases}$$

and

$$T_{\text{on}} = \left\{ [nt_{\text{cycle}} + t_{\text{c}},\ nt_{\text{cycle}} + t_{\text{chemo}} + t_{\text{c}}),\quad n = 0,1,\ldots, N_{\text{cycles}} \right\},$$
$$T_{\text{off}} = \left\{ [nt_{\text{cycle}} + t_{\text{chemo}} + t_{\text{c}},\ (n+1)t_{\text{cycle}} + t_{\text{c}}),\quad n = 0,1,\ldots, N_{\text{cycles}} \right\}$$

where N_{cycles} is the number of cycles of chemotherapy administered and time is measured from t_{c}. The nondimensional diffusion coefficient is given by

$$D(\mathbf{x}) = \begin{cases} 1, & \mathbf{x} \in \text{White Matter} \\ \dfrac{D_G}{D_W} = \gamma, & \mathbf{x} \in \text{ Grey Matter} \end{cases}$$

where $\gamma > 1$.

Effectiveness of Chemotherapy

Solving (4) on a homogeneous infinite two-dimensional domain (see Appendix) gives the following distribution of cancer cells:

$$c(x, y, t) = \frac{\exp\left[t\,(1 - \langle G(t) \rangle) - \dfrac{r^2}{4t} \right]}{4\pi t}$$

where $r = \sqrt{x^2 + y^2}$ and we define the average value of $G(t)$ as

$$\langle G(t) \rangle = \frac{1}{t} \int_0^t G(\tau)\, d\tau.$$

The clinical determination of the effectiveness of chemotherapy treatment is directly linked to the decrease in the detectable size of the tumor. To quantify this we use the solution above for $c(x,y,t)$ to define the detectable tumor radius as a function of time. Assuming a threshold of detection c^* the detectable tumor radius, r^*, then satisfies

$$r^* = 2t \sqrt{1 - \langle G(t) \rangle - \frac{1}{t} \ln(4\pi t c^*)}$$

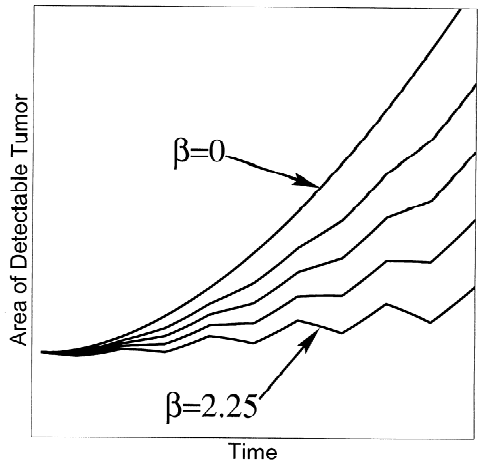

Figure 1. Time evolution of the area of the detectable tumor during chemotherapy of various strengths. The $\beta = 0$ curve represents no chemotherapy, while the $\beta = 2.25$ represents an effective chemotherapy regime. The negative slope regions correspond to the times during which chemotherapy is being administered.

In Figure 1 we plot the detectable area of the tumor as a function of time t. Note that even for fairly effective chemotherapies ($\beta = 2.25$), the tumor continues to grow. Interestingly, for short time the *detectable* area may go to zero but for large time the area will again increase. For large time, $\langle G(t) \rangle$ approaches its mean value over a single cycle: $\langle G(t) \rangle \to \dfrac{\beta\, t_{\text{chemo}}}{t_{\text{cycle}}}$ as $t \to \infty$ and the radius, r^* of the detectable tumor approaches

$$r^* \sim 2t\sqrt{1-\langle G(t)\rangle} \to 2t\sqrt{1-\frac{t_{\text{chemo}}}{t_{\text{cycle}}}\beta} \ .$$

Assuming that chemotherapy is administered for a very long period time, the effectiveness can then be approximated by the quantity: $E = \beta \frac{t_{\text{chemo}}}{t_{\text{cycle}}}$. If E is greater than 1, assuming that chemotherapy could be administered indefinitely and remain effective, then the detectable tumor (not the actual tumor based on this model) could be eliminated (and with no resistant subpopulations).

4. HETEROGENEOUS DRUG DELIVERY

The vascular structure is quite varied throughout the brain. In particular, the capillary density is approximately 3.3 times higher in grey matter than that in white matter (Blinkov and Glezer, 1968). Therefore, we expect the drug delivery to the white matter to be much less than that to grey matter. Additionally, since tumor cell motility is slower in grey matter than white matter, tumor cells spend more time in grey matter regions and are, therefore, exposed longer to the higher drug delivery.

Mathematical Model with Tissue Heterogeneity

To consider the implications of heterogeneity in diffusion and drug delivery, we reconsider the model equation (3) where the chemotherapy delivery, $G(\bar{\mathbf{x}}, \bar{t})$, is now a function of the spatial variable $\bar{\mathbf{x}}$:

$$\frac{\partial \bar{c}}{\partial \bar{t}} = \bar{\nabla} \cdot (\bar{D}(\bar{\mathbf{x}})\, \bar{\nabla}\bar{c}) + \rho \bar{c} - G(\bar{\mathbf{x}}, \bar{t})\bar{c} \tag{5}$$

and

$$G(\bar{\mathbf{x}}, \bar{t}) = \begin{cases} \begin{cases} k_W & \bar{\mathbf{x}} \in \text{White Matter} \\ k_G = \alpha\, k_W & \bar{\mathbf{x}} \in \text{Grey Matter} \end{cases} & \text{for } \bar{t} \in \bar{T}_{\text{on}} \\ 0 & \text{for } \bar{t} \in \bar{T}_{\text{off}} \end{cases}$$

where α is the ratio of drug delivery in grey matter to that in white matter. We assume that α is simply the ratio of the capillary densities in the two tissues: $\alpha \approx 3.5$. We solve (5) subject to the initial conditions $\bar{c}(\bar{\mathbf{x}}, \bar{t}_c^{+}) = \bar{f}(\bar{\mathbf{x}})$ and zero flux boundary conditions $\bar{\nabla}\bar{c} \cdot \mathbf{n} = 0$ on ∂B (the brain boundary).

Again introducing nondimensional variable (9) (see Appendix) the model (5) becomes

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

where $P(\mathbf{x},t)$ represents the effective net growth rate of the lesion at location $\mathbf{x}$ and time t. While chemotherapy is being administered, the net growth rate is:

$$P(\mathbf{x},t)=\begin{cases}1-\dfrac{k_W}{\rho}=1-\beta, & \text{for } \mathbf{x}\in \text{White Matter}\\ 1-\dfrac{k_G}{\rho}=1-\alpha\beta, & \text{for } \mathbf{x}\in \text{ Grey Matter}\end{cases}$$

and, while chemotherapy is not being administered, $P(\mathbf{x},t)=1$ for all spatial locations.

Clearly, if $k_W>\rho$, then $P(\mathbf{x},t)<0$ for all $\mathbf{x}$ and the chemotherapy is, at least marginally, effective. That is, at every spatial location, while chemotherapy is being administered, the tumor cell population is dying since the tumor proliferation rate is less then the death rate induced by the chemotherapy. The problem, of course, is that extinction of the tumor cell population would require essentially an infinite treatment time since the right hand side of (5) is linear in c. This is, of course, clinically impractical.

Effectiveness of Chemotherapy

One could imagine the situation of a marginally effective chemotherapy where $P(\mathbf{x},t)$ is small but greater than 0 for some $\mathbf{x}$ and less than 0 for other $\mathbf{x}$ values. Assume the chemotherapeutic drug delivery in white matter is sufficient to slow the tumor cell growth but not eliminate it: $k_W<\rho$. Due to the increased vascularity of the grey matter, this same treatment could result in the decay of the cancer cell population in grey matter: $k_G>\rho$. That is, the chemotherapy would be considered effective on the portion of tumor in the grey matter but not in white matter. The question remains, accounting for the heterogeneous diffusion of the cancerous cells in grey and white matter, would the chemotherapy be considered effective globally? Would the total cancer cell population decrease in size?

To answer this question, we reconsider the model equation. When chemotherapy is not being administered, the tumor cell population is, by definition, increasing. In other words, the trivial solution $c=0$ of (5) is unstable. We propose that a necessary condition for a chemotherapy treatment to be effective is that during treatment the size of the tumor cell population should be decreasing which implies that the trivial steady state $c=0$ of (5) must be stable. The steady state $c=0$ is not attained during the time course of treatment, but the tumor cell population is tending, at some rate, towards the extinction of the cancerous population; that is, the bulk effect is to decrease the tumor size. Ultimately, following the end of treatment, the tumor cell population begins to grow again but one hopes that the treatment has decreased the number of tumor cells significantly so as to delay progression of the tumor.

As mentioned above, the spatial distribution of grey and white matter in the brain is quite heterogeneous. Solutions of equation (5) are intractable for general spatial distributions of grey and white matter. We follow Shigesada and Kawasaki (1997), who studied periodic heterogeneity in an ecological context, and consider a simplified one-dimensional brain where the grey and white matter is interspersed in a periodic fashion. In particular, assume that all white and grey matter regions are of characteristic width l_W and l_G, respectively. The diffusion coefficient and net growth

rate have period $l = l_W + l_G$: $D(x+l) = D(x)$ and $P(x+l, t) = P(x, t)$ for all x and $t > 0$. Now

$$D(x) = \begin{cases} 1, & \text{for } nl < x < nl + l_W \\ \gamma, & \text{for } nl - l_G < x < nl \end{cases}$$

and

$$P(x, t) = \begin{cases} 1-\beta, & \text{for } nl < x < nl + l_W \\ 1-\alpha\beta, & \text{for } nl - l_G < x < nl \end{cases}.$$

Figure 2 shows *D(x)* and *P(x,t)* in such a situation.

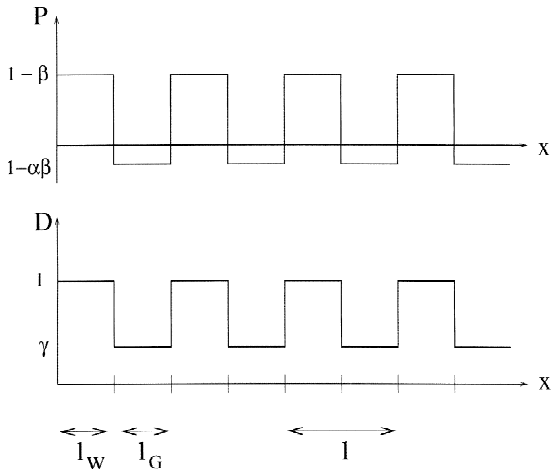

Figure 2. Diffusion coefficient *D(x)* and net growth rate *P(x,t)* in a one-dimensional periodic domain. Diffusion and growth are higher in the favourable white matter patches of width l_W than in the unfavourable grey matter patches.

The periodic grey and white distributions (domain) defined in Figure 2 could be considered a model for drug delivery to tumors located in the mixed grey and white matter regions of the brain between the cortex (grey matter) and the corpus callosum (white matter). During chemotherapy, we identify the white matter as favorable tissue for tumor growth and invasion while the grey matter is unfavorable.

We are interested in determining the stability of the trivial solution $c = 0$ of (5). If the trivial solution is stable during treatment, then the treatment is, at least minimally, effective. Stability of the trivial solution $c = 0$ indicates that the tumor is tending towards this case of tumor eradication while the treatment is being administered.

In the appendix we detail the process of obtaining the conditions for which the trivial solution $c = 0$ is stable and treatment is therefore considered effective. The minimum requirement for the chemotherapy treatment to be successful (effective) is

$$\tan\left(\frac{l_W\sqrt{1-\beta}}{2}\right) < \sqrt{\frac{\alpha\beta-1}{(1-\beta)\gamma}}\,\tanh\left(\frac{l_G}{2}\sqrt{\frac{\alpha\beta-1}{\gamma}}\right). \tag{6}$$

The relation (6) defines the parameter domain in which we can expect a given chemotherapeutic treatment to be effective. In particular, the length of the favorable white matter regions l_W is bounded

$$l_W < l_W^* = \frac{2}{\sqrt{1-\beta}} \arctan\left(\sqrt{\frac{\alpha\beta - 1}{\gamma(1-\beta)}} \tanh\left(\frac{l_G}{2} \sqrt{\frac{\alpha\beta - 1}{\gamma}} \right) \right) \tag{7}$$

for effective treatment. That is, there cannot be too much of the favorable white matter available for the cancer cells to migrate through, thus evading treatment. Figure 3 shows the regions of the l_W-l_G parameter space where chemotherapy is effective. Since

$$\lim_{l_G \to \infty} l_W^* = \frac{2}{\sqrt{1-\beta}} \arctan\left(\sqrt{\frac{\alpha\beta - 1}{\gamma(1-\beta)}} \right) \tag{8}$$

a necessary but not sufficient condition for the chemotherapy to be effective is

$$l_W < \frac{2}{\sqrt{1-\beta}} \arctan\left(\sqrt{\frac{\alpha\beta - 1}{\gamma(1-\beta)}} \right).$$

We can use the condition (7) to discuss the effectiveness of treatment in various regions of the brain. Near the cortex, where the grey matter regions are significantly larger than the white matter regions $l_G > l_W$, we expect the treatment to be most successful. However, as the tumor moves radially inward from the cortex, the characteristic white matter length increases until the threshold defined by (8) is reached and the treatment is not locally effective (see Figure 3).

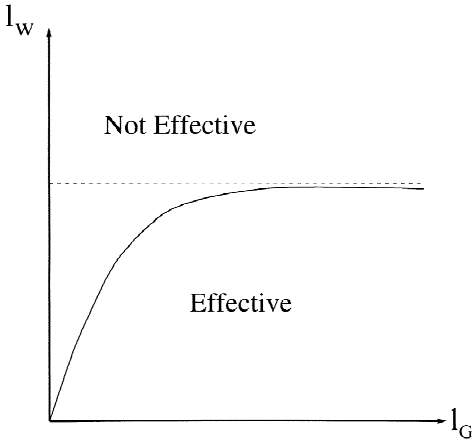

Figure 3. Parameter domain in l_W - l_G plane where chemotherapy is effective for the one-dimensional infinite periodic domain problem (6).

We now want to extend this result to the whole brain scale. In the cerebral hemispheres, the grey matter of the brain is primarily at the periphery near the cortex, while the white matter is in the interior. For this situation, we consider the problem on only a portion of the one-dimensional periodic domain defined in Figure 2. And we impose zero-flux boundary conditions

$$\frac{dc}{dx}\left(-\frac{l_G}{2} \right) = 0 = \frac{dc}{dx}\left(\frac{l_W + l_G}{2} \right).$$

The analysis follows as above and we obtain exactly the same condition (7) for effective treatment. The brain consists of about 60% grey matter and 40% white matter. Using these values to define characteristic lengths of the grey matter regions at the periphery and white matter region in the interior, and for the range of diffusion coefficients and growth rates we use in the model, treatment would be at least marginally effective.

Alternatively, while chemotherapy is being applied, the tumor cell concentration is decreasing near the periphery but increasing (albeit slowly) in the central white matter regions. This increase in white matter regions may be clinically undetectable if the concentration of cancer cells is sufficiently low in the white matter regions. Additionally, since the tumor cell motility is higher in white matter regions, it takes longer for a sufficiently high concentration of cancer cells to build up and be detectable on a CT scan. The bulk effect is that the chemotherapy is inducing a geographical redistribution of (a portion) of the cancer cell population. In fact, since chemotherapy treatments are often applied periodically over an extended length of time, the bulk tumor (in the grey matter) for which the treatment was intended may have decreased in size enough even to be undetectable with CT. However, a great deal of tumor cells may have infiltrated at undetectable levels into the white matter regions. We expect tumor recurrence to be common in white matter regions or at the junction between grey and white matter regions. The diffusion in the white matter might be too large to induce a detectable tumor but tumor cells slow down in grey matter regions and therefore can build up to detectable tumor concentrations.

The above analysis is essentially the same with logistic cell growth, $\rho\left(1-\frac{c}{K}\right)$, rather than the exponential growth, ρc, discussed here. The main difference is that when chemotherapy is off, the trivial solution $c = 0$ is unstable and the $c = K$ solution is stable and a traveling wave solution exists. When chemotherapy is on (and spatial heterogeneities are present), a traveling periodic wave can develop if the treatment is not sufficiently effective (the trivial solution remains unstable) (Shigesada and Kawasaki, 1997).

Simulation Example

Magnetic resonance imaging (MRI) is a standard tool for tracking the growth of brain tumors. Typically, the bulk lesion is associated with the gadolinium-enhanced T1-weighted imaging abnormality (that is, contrast-enhancing portion of the lesion). The portion of the lesion shown on T2-weighted imaging (consistently larger than the T1 signal) is often associated with diffuse tumor invasion and edema.

Here we consider a high-grade tumor located in the superior fronto-parietal region of the brain with chemotherapy applied. Figure 4 shows this tumor: a) at detection, b) after chemotherapy, and c) at recurrence. The left column of figures represents the model prediction of portion of the lesion observable on a gadolinium-enhanced T1-weighted MRI while the right column represents the T2-weighted MRI portion.

Based on the above discussion of the mathematical model for differential delivery of chemotherapy, we expect the bulk tumor in the grey matter regions near the cortex to decrease in size during the treatment. Assuming sufficiently effective treatment, the tumor may recur in the white matter regions (that is, corpus callosum due to its close

proximity to this virtual tumor). The simulated chemotherapy consists of five cycles separated by six weeks - the time elapsed between Figures 4a and b and Figures 4b and c is 30 weeks. Note that although the tumor recurs locally, it has continued to spread significantly into the white matter regions.

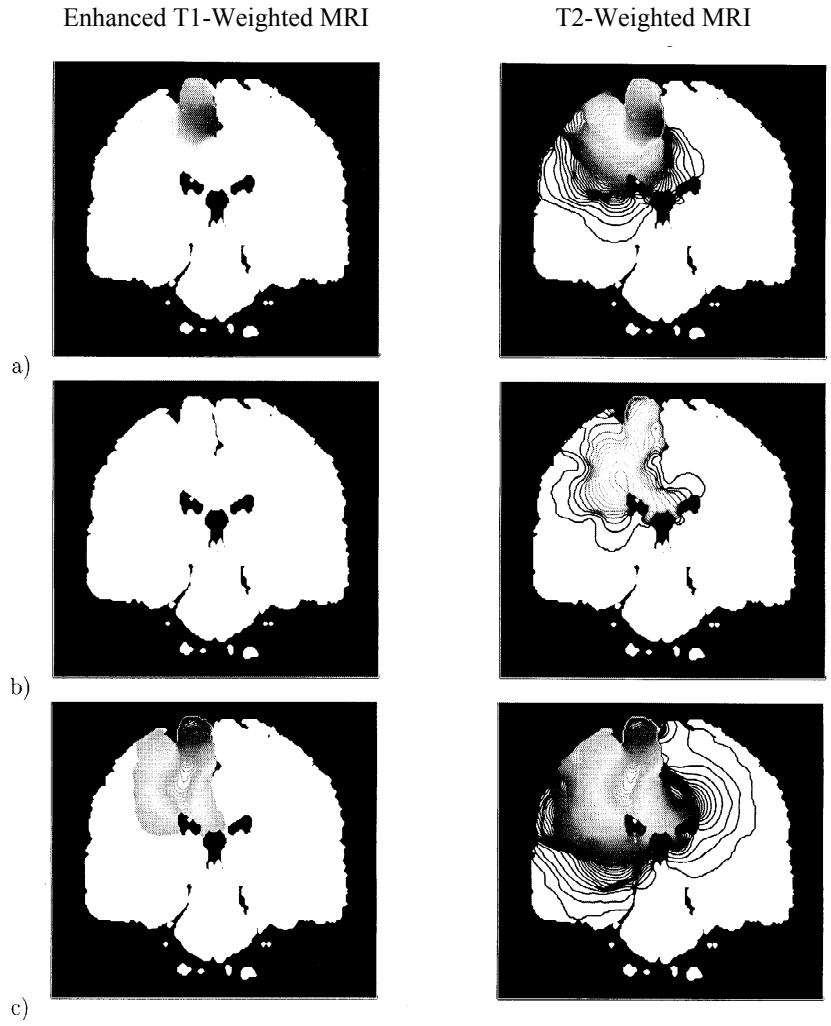

Figure 4. Superior frontal lobe tumor treated by chemotherapy: a) at detection; b) just after five cycles of chemotherapy (30 weeks after a)); c) recurrence following chemotherapy (30 weeks after b)). The T1-Weighted MRI reflects a higher cell density threshold of detection than the T2-Weighted MRI. T1 is the time required for the z component of magnetization to return to 63% of its original value following an excitation pulse. T2 is the time required for the transverse component to decay to 32% of its initial value. The practical difference is that T2 reveals water better, whereas T1 allows enhancement by gadolium to be visualized. Parameter values used for this simulation are tabulated in Table 1.

Table 1. Parameter values used in simulation displayed in Figure 4.

Parameter		Value Used	Units
Growth rate	ρ	0.012	1/day
Diffusion coefficient in grey matter	D_G	0.0013	cm^2/day
Diffusion coefficient in white matter	D_W	0.0065	cm^2/day
Strength of chemotherapy in grey matter	k_G	0.024	1/day
Strength of chemotherapy in white matter	k_W	0.084	1/day
Length of chemotherapy per cycle	t_{chemo}	15	days
Length of chemotherapy cycle	t_{cycle}	6	weeks
Number of cycles	N_{cycles}	5	

Clinical Example

Figure 5 shows a malignant brain tumor patient for which chemotherapy (treatment with a drug called Gleevec) resulted in the disappearance of the contrast-enhancing portion of the lesion located within the grey matter of the deep nuclei while the tumor continued to invade peripherally through the white matter corpus callosum during the same treatment. Figure 5a shows the patient's enhanced T1-weighted MRI before treatment and Figure 5b shows the resolution of the enhancing lesion located within the grey matter following three weeks of chemotherapy. Although the grey matter portion of the tumor disappears from the MRI, tumor progression is observable within the neighboring white matter of the corpus callosum.

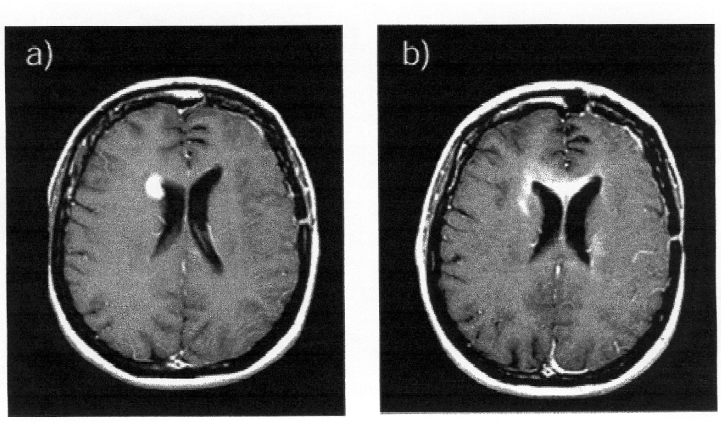

Figure 5. Patient example for which chemotherapy resulted in the disappearance of the contrast enhancing portion of the lesion lying in grey matter, shown in a), while the tumor continued to invade peripherally through the white matter corpus callosum, shown in b). The gadolinium-enhanced T1-weighted MRI's, shown here for this patient: a) before treatment and b) following three weeks of treatment.

This is similar to the theoretical case described in Figure 4 for which the bulk lesion, shown on enhanced-T1 imaging, resolves while there continues to be diffuse invasion of the lesion throughout the white matter. This suggests the possibility that differential delivery of the chemotherapeutic agent to the grey and white matter of the brain could describe the long-standing confounding clinical problem of shrinkage of the lesion in certain areas of the brain with continued growth in other areas.

5. DISCUSSION

Despite the lack of success of essentially all current treatments for high-grade gliomas, chemotherapy remains a common component of many treatment regimes. There is an array of mechanisms by which these chemotherapies are thought to act, ranging from cell-cycle specific and non-specific cytotoxicity to antiangiogenic and antimotility functions. In this article, we speak of a chemotherapy in general terms as resulting in a cellular loss proportional to the dose delivered locally. This assumes a drug that is permeable enough to bypasss the blood-brain-barrier to reach the tumor laden tissue but does so in proportion to the vascular density of the tissue. We highlight the possible effects of vascular heterogeneity amongst the two primary tissue types of the brain: grey and white matter. So, drug delivery is limited by the vascular density within each region of tissue of the brain.

For the simulations of this model we assume drug delivery is sufficient to result in a net decay of cells in grey matter while allowing for a net proliferation of the tumor cells in white matter. The results show that although the total number of tumor cells within the brain may be decreasing, the extent of invasion of the tumor remains practically unaffected due to the increased motility of those cells within the white matter regions. Therefore, despite a potential observation of regression of disease on MRI, extensively invaded tumor cells remain occult, below the detection abilities of the MRI, primarily throughout the white matter of the brain. Once treatment is stopped, diffuse recurrences seem inevitable. This suggests a potential difficulty with the design of clinical trials relying solely on MRI data as a measure of success of treatment. If present studies of PET, MRSI or other imaging modalities continue to show success in differentiating malignant tissue from minimally invased tissue, this analysis suggests that these additional images may be necessary to reflect more accurately the efficacy of the specific treatment that is being studied. This may include considering PET or MRSI-positive regions that may appear normal on MRI following treatment as remaining viable and requiring further treatment if clinically feasible for the patient.

Despite their inherent heterogeneity, such as hypoxia (hypoxic or oxygen-deprived tissue is known to be resistant to standard photon beam irradiation) and other mechanisms of resistance to treatment, it seems that the diffuse nature of gliomas remains the most effective and pervasive hindrance to successful treatment. Even in the idealized case described here in which the chemotherapy is effective in bypassing the BBB as well as destroying malignant cells when sufficient drug is delivered locally, it remains that the diffusely invased cells peripheral to the abnormality on standard medical imaging are most likely to produce the clinically evident recurrence. Even a nonlocalized diffusely deliverable treatment like chemotherapy may not be

effective in containing this disease, at least not without special targeting of individual malignant cells found in otherwise normal tissue.

APPENDIX

Homogeneous Drug Delivery

Nondimensional Variables

We introduce the nondimensional variables:

$$\mathbf{x} = \sqrt{\frac{\rho}{D_W}}\,\bar{\mathbf{x}}, \quad t = \rho(\bar{t} - \bar{t}_C), \quad c(\mathbf{x}, t) = \frac{1}{N_0}\frac{D_W}{\rho}\,\bar{c}\left(\sqrt{\frac{\rho}{D_W}}\bar{\mathbf{x}}, \rho(\bar{t} - \bar{t}_C)\right) \tag{9}$$

where $N_0 = \int \bar{f}(\bar{\mathbf{x}})\, d\bar{\mathbf{x}}$ represents the initial number of cells present in the brain at model time $\bar{t} = \bar{t}_C$. The resulting nondimensionalized model (3) is given in (4) with initial condition

$$c(\mathbf{x}, 0) = f(x) = \frac{1}{N_0}\frac{D_W}{\rho}\bar{f}\left(\sqrt{\frac{\rho}{D_W}}\,\bar{\mathbf{x}}\right).$$

Solution on 2-D Infinite Domain

Neglecting boundaries, the model equation (4) on the infinite two-dimensional domain is written

$$\frac{\partial c}{\partial t} = \frac{\partial^2 c}{\partial x^2} + \frac{\partial^2 c}{\partial y^2} + (1 - G(t))c, \quad \text{for } t > 0 \text{ and all } x \text{ and } y. \tag{10}$$

For simplicity, we consider a point source of cells at the origin as the initial conditions $c(x, y) = \delta(r)$ where $r^2 = x^2 + y^2$. Seek a solution of (10) of the form $c(x, y, t) = v(t)\, w(x, y, t)$ where we choose $v(t)$ such that

$$\frac{\partial v}{\partial t} = (1 - G(t))v, \quad \text{with } v(0) = 1$$

then $w(x, y, t)$ satisfies

$$\frac{\partial w}{\partial t} = \frac{\partial^2 w}{\partial x^2} + \frac{\partial^2 w}{\partial y^2}, \quad \text{with } w(x, y, 0) = \delta(r).$$

Solving we find

$$v(t) = \exp\left(t - \int_0^t G(\tau)\, d\tau\right)$$

$$w(t) = \frac{1}{4\pi t}\exp\left(-\frac{r^2}{4t}\right)$$

The solution of (10) is given by

$$c(x,y,t)=\frac{1}{4\pi t}\exp\left[t\left(1-\left\langle G(t)\right\rangle\right)-\frac{r^2}{4t}\right] \tag{11}$$

where we define the average value of *G(t)*: $\left\langle G(t)\right\rangle=\frac{1}{t}\int_0^t G(\tau)\,d\tau$.

Heterogeneous Drug Delivery

Solution on 1-D Infinite Domain

If chemotherapy is being administered, the solution of (5) is continuous across the interface $x_n = nl$,

$$\lim_{x\to x_n^+} c(x,t)=\lim_{x\to x_n^-} c(x,t) \tag{12}$$

and flux is conserved across the interface

$$\lim_{x\to x_n^+} D(x)\frac{\partial c}{\partial x}=\lim_{x\to x_n^-} D(x)\frac{\partial c}{\partial x}. \tag{13}$$

Substitution of $c(x,t)=\phi(x)\exp(\lambda t)$ into (5) gives the characteristic equation

$$\frac{d}{dx}\left(D(x)\frac{d\phi}{dx}\right)+(P(x,t)-\lambda)\phi(x)=0 \tag{14}$$

where λ is the eigenvalue; this is Hill's equation. From the theory of Hill's equation with periodic coefficient, associated with the nontrivial solutions of (14) there exists a monotonically increasing infinite sequence of real eigenvalues λ. For extensive theory on Hill's equation with periodic coefficient see, for example, Coddington and Levinson (1972) and Magnus and Winkler (1966).

Since we expect periodic solutions of (14), it is useful to represent the solutions as Fourier series expansions. While chemotherapy is being administered, in the white matter patches $nl < x < nl + l_W$,

$$c(x,t)=c_W(x,t)=\sum_{j=0}^{\infty} A_j\exp(\lambda_j t)\ \cos\left(\sqrt{1-\beta-\lambda_j}\left(x-\frac{l_W}{2}-nl\right)\right)$$

and in the grey matter patches $nl - l_G < x < nl$,

$$c(x,t)=c_G(x,t)=\sum_{j=0}^{\infty} B_j\exp(\lambda_j t)\ \cos\left(\sqrt{\frac{1-\alpha\beta-\lambda_j}{\gamma}}\left(x+\frac{l_G}{2}-(n+1)l\right)\right).$$

Imposing the matching conditions (12) and (13) at the interface between grey and white matter patches the following condition results:

$$\sqrt{1-\beta-\lambda}\ \tan\left(-\frac{l_W}{2}\sqrt{1-\beta-\lambda}\right)=\sqrt{\frac{1-\alpha\beta-\lambda}{\gamma}}\ \tan\left(\frac{l_G}{2}\sqrt{\frac{1-\alpha\beta-\lambda}{\gamma}}\right). \tag{15}$$

This equation provides the eigenvalues of (14). We are interested in the sign of the largest eigenvalue λ^*. When $\lambda^* < 0$, the trivial solution $c = 0$ is stable and treatment is considered effective. The bifurcation value for stability occurs at $\lambda = \lambda^* = 0$ in (15). This leads to the minimum requirement for the chemotherapy treatment to be successful given in (6).

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