On the Growth of Brain Tumours: enhancing imaging techniques, highlighting limitations of current imaging, quantifying therapy efficacy and estimating patient life expectancy

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Abstract

The prognosis for patients with high grade brain tumours (gliomas) is grim and the various treatment protocols such as surgery, radiation and chemotherapy cannot effect a cure. I describe, without any technical details, a simple but very practical model which uses patient data and brain scans to quantify the spatio-temporal growth of such brain tumours. Analysis of the model shows how difficult it is to decide on the tumour volume to be treated and shows why such treatments have so little success. The model simulations can estimate life expectancy for individual patients and show how it is possible to use the patient's past record to predict the efficacy of possible treatments. Recent patient data indicates that calculating such an index of treatment efficacy is indeed a realistic aim. With the increasing discussion about cell phone use and a possible increase in brain tumours, I describe how to obtain an estimate for when a brain tumour started given its size at detection.

Introduction

High grade brain tumours, gliomablastoma multiforme (GBM), are the most aggressive brain tumours and make up more than 50% of all brain tumours. There is 100% mortality rate for patients with such tumours with an approximate median life expectancy of 9-12 months. The various treatment protocols such as surgery (resection), radiation and chemotherapy cannot effect a cure but can sometimes extend survival time. Treatment efficacy depends on various factors such as where the tumour is located in the brain and the size of the key parameters, namely the growth rate and the diffusion rate. Diffusion in white matter is larger than in grey matter. It is the aggressive infiltration of cancer cells which make treatment protocols so difficult to localize. In spite of increasing accuracy of imaging techniques they still cannot detect cancer cell densities sufficiently accurately. The inadequacy of medical imaging is substantiated by the fact that irrespective of the extent of surgical resection or focused irradiation of the tumour it is always followed by multifocal tumour recurrence at or near the edge of the resected volume (Silbergeld *et al*. 1991).

A basic practical model which encompasses the two key elements in the growth of such tumours, namely the invasive diffusive properties of the cancer cells and their growth rate is qualitatively given by the equation:

Rate of change of tumour cell density
= diffusion (invasion) of tumour cells
+ net proliferation of tumour cells (1)

The mathematical form which quantifies the various terms in (1) is

$$\frac{\partial c}{\partial t} = \nabla . D(x) \nabla \mathrm{c} + \rho \mathrm{c} \qquad (2)$$

where the various terms in this equation are defined as:

- $c(\boldsymbol{x},t)$ = glioma cell density, cells/mm^3, which is a function of the position, $\mathbf{x}$, in the brain at time.
- t = time, measured in months.
- $D(\boldsymbol{x})$ = diffusion (invasion), mm^2/month, which quantifies the invasiveness of the cancer cells at position $\mathbf{x}$ in the brain.
- ρ = proliferation rate (/month) of the cancer cells which gives the turnover time as log2/ρ (months).

The solutions of (2) are unbounded as time increases because of the form of the growth term which implies exponential growth. A more accurate model has in place of ρc the expression $\rho c(1\text{-}c/k)$ where k is a constant associated with the maximum concentration possible in the brain tissue. This equation, with a constant diffusion coefficient, is a classical population equation known as the Fisher-Kolmogoroff equation (Murray 2002). Solutions of it are bounded and exhibit traveling waves. However, in the time scales relevant to glioma growth and patient survival time it does not contribute significantly to the solutions relevant to cancer patients.

With two individual patient brain scans, such as CT, MRI and others, the key model parameters, namely diffusion and cell growth can be calculated. With these we can then predict the subsequent growth of such brain tumours. As illustrated below, analysis of the model shows how difficult it is to decide on the tumour volume to be treated and shows why such treatments can have little success. The model simulations can estimate life expectancy for individual patients and how to

predict the efficacy of different treatments. Patient data indicates that calculating such an index of treatment efficacy is a realistic aim. With the increasing debate on the possible increase in brain tumours as a result of cell phone radiation, realistic and scientific clinical trials will require information such as when a tumour started, how fast it grows and where it is in the brain outside of what can be detected with current brain imaging techniques. Here we show how the model provides a means of estimating the time from tumour initiation and life expectancy from tumour detection for individual patients.

The original model was first proposed and analised in various situations. The brain was considered to be homogeneous matter bounded by the ventricles and skull (Cruywagen *et al*. 1995). Even with such a simple anatomical model the predictions of the analysis were broadly in line with patient observation of both low and high grade brain tumours. The limitations of current imaging techniques were clear. The model was then used to mimic various accepted medical treatments, specifically radiation, surgical resection (Woodward *et al*. 1996) and chemotherapy (Tracqui *et al*. 1995), Swanson *et al*. (2002), Rockne *et al*. (2010). A three dimensional model was proposed and studied by Burgess *et al*. (1997) who were the first to demonstrate that cancer cell diffusion, mainly ignored up to that time, is a major component of glioma growth. They showed that only those tumours with a low diffusion rate could benefit from wide surgical resection although eventually there will be multifocal recurrence. See Murray (2003) for a full discussion and review which encompasses anatomically correct brains.

Virtual gliomas: enhanced imaging and current limitations

A major advance in the practical application of the model (1) was the availability of the brain web atlas (Collins *et al*. 1998). This allowed the model to be applied to anatomically correct brains (Swanson *et al*. 2002, 2004, Murray 2003). Among other things it made it possible to refine the gross anatomic boundaries and to vary the degree of motility of glioma cells in grey or white matter: these are biologically significant.

With the BrainWeb it was possible to solve equation (2) in a three dimensional anatomically correct brain in which the grey and white matter is clearly delineated.

The procedure is to evaluate the tumour size from brain scans and, crucially, estimate the parameter values for each patient to obtain the average diffusion coefficient and the average growth rate. There is a lower threshold of detection of cancer cells with all imaging techniques, whether CT or MRI, such as T1Gd and T2 imaging, or microscopic studies. To use the predictive potential of the mathematical model (2), serial imaging of the tumour was used to calculate its volume which was then taken as the volume of an equivalent sphere with radius r, namely $4\pi r^3/3$. We then consider the model to be radially symmetric with a constant diffusion coefficient, based on averaging the values from imaging. Equation (2) then becomes

$$\frac{\partial c}{\partial t} = D\left[\frac{\partial^2 c}{\partial r^2} + \frac{2}{r}\frac{\partial c}{\partial r}\right] + \rho \mathrm{c} \qquad (3)$$

We consider that at time t=0 there is a concentrated number of cancer cells, N cells/mm^3, at r=0 in which case the solution of (3) is given by

$$\mathrm{c}(r,t) = \frac{\mathrm{N}\exp(\rho \mathrm{t} - \frac{r^2}{4Dt})}{8(\pi Dt)^{3/2}} \qquad (4)$$

If the smallest level of image detection is denoted by c_1 cells/mm^3, then the radius, r, of the tumour for this cell density is, from (4) on solving for r,

$$r = 2t\sqrt{D\rho}\sqrt{1 - \frac{1}{\rho t}\log\left(\frac{c_1}{N}(4\pi Dt)^{3/2}\right)} \qquad (5)$$

For large time, t, the solution (5) gives the radius of detectable tumour and the velocity of growth, v, as approximately

$$r = 2t\sqrt{D\rho} \quad \Rightarrow \quad \mathrm{v} = r/t = 2\sqrt{D\rho} \qquad (6)$$

That is, the equivalent radial growth is linear in time.

Approximate *in vivo* patient survival time

If we consider detection is when the spherical equivalent tumour volume is of radius 15mm and that death occurs when the radius is 30mm the approximate survival time from detection, in the absence of any treatments, is given, from (6), by

Survival time (months)

$$= t_{\mathrm{survival}} = t_{r=30} - t_{r=15} = \frac{7.5}{\sqrt{D\rho}} \qquad (7)$$

Typical growth rates vary quite widely, approximately from 1-5 /month and diffusion rates from 1-8 mm^2/month. The medians for 9 patients in the study by Rockne *et al*. (2010) are D=0.9 mm^2/month and ρ=1.16/month which gives a median survival time of 7.34 months.

Survival time, however, depends on where the tumour is mainly situated. If it is primarily in the grey area of the thalamus, for example, the diffusion is smaller and so the survival time is longer, as is clear from (7).

The diffusion in grey matter, D_g, is smaller than that in white matter, D_w: they can vary by as much as 100-fold. Swanson *et al*. (2002) defined by γ the ratio of the diffusion coefficient in white to that in grey matter, that is $\gamma = D_w/D_g$. An average diffusion coefficient for the entire brain can be defined as the diffusion coefficient in white matter times the volume fraction of brain that is white matter plus the diffusion coefficient in grey matter times the volume fraction of brain that is grey matter. The figures from the brain web database give the fraction of grey matter as 0.5723 and of white matter

as 0.4277 (Collins *et al*. 1998). So an average diffusion is given by

$$D_{average} = 0.5723D_g + 0.4277D_w = D_g(0.5723 + 0.4277\gamma)$$
$$\Rightarrow D_g = D_{average}/(0.5723+0.4277\gamma)$$

Swanson *et al*. (2002a) took as a typical average diffusion, $D_{average}$ = 3.9 mm^2/month so the diffusion in grey matter from the last equation gives D_g = 3.9/(0.5723 + 0.4277γ) mm^2/month. They evaluated survival time as a function of γ for a frontal tumour where it is mainly white matter and in the thalamic region where it is mainly grey matter.

Simulations of an anatomically correct brain highlights the problems with current imaging techniques. Figure 1 is a computed solution of equation (2) which shows the detectable tumour at death and the spread of the tumour cells beyond what can be detected by the most accurate current CT or MRI imaging techniques. Simulations of the model thus greatly enhance current imaging techniques to whatever level of cancer cell density is required.

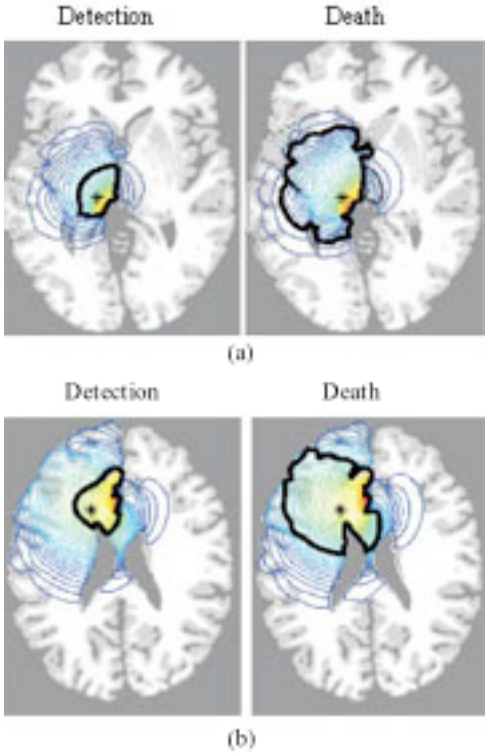

Figure 1 Computed solutions of equation (1) in a three dimensional anatomically accurate brain. These show the horizontal section of the virtual human brain through the site of the original tumour (+ in (a), * in (b)). The left image in each is the tumour at diagnosis while the right image is the same tumour at time of death. The thick black contour defines the edge of the tumour that can be detected by enhanced CT. The blue contours outside this black line represent cancer cell densities peripheral to the imaging limits. (a) Tumour in grey matter: the time from diagnosis to death is approximately 256 days. (b) Tumour in white matter: the time from diagnosis to death is approximately 158 days. (Figures extracted from Swanson *et al*. 2002a).

The model described here has been used to quantify the effect of different treatment efficacies prior to their use. Incorporating periodic chemotherapy was studied by Tracqui *et al.* (1995) and Swanson *et al*. (2002b). The model used was equation (1) with a further (negative) term on the right hand side which quantifies the periodic reduction in growth as a consequence of the chemotherapy. Incorporating subtotal and total tumour resection in patient survival was considered by Woodward *et al*. (1996). This involves visually excising a given volume of the tumour in the model simulations. The predictions compared well with the data of Kreth *et al*. (1993). The modeling study (Woodward *et al*. 1996) predicted patient survival rates which, considering the basic aspect of their model, compared surprisingly accurately with the extant data at the time and recently published by Ramakrishna *et al*. (2010). Incorporating radiation treatment was also considered in the model and it has been used by Rockne *et al*. (2010) in the clinical study of 9 patients. A full review and how such treatments are incorporated are given by Murray (2003).

Estimating the time from tumour initiation

An unsolved problem with all cancers is how to determine when a tumour started. In the case of glioma brain tumours detection is when the tumour volume is approximately equal to an equivalent sphere of radius 3cm in diameter but this also depends on the imaging technique used and where the tumour is in the brain. With the increasing discussion and justifiable concern of the possible increase in brain tumours as a consequence of the ever expanding use of cell phones it is inevitable that serious clinical studies will be carried out in the relatively near future. The paper by Tafforeau *et al*. (2004) clearly demonstrates the serious effect cell phone radiation has on plant growth. They showed that a single 2 hour exposure to radiation emitted at 105 GHz from a (GSM) cell phone resulted in considerable growth deformity. The *Journal of the American Medical Association* article by Volkow *et al*. (2011) reports on an increase in brain glucose in the region closest to the antenna. To date no study has definitively stated that brain tumours can arise from prolonged use of cell phones (I personally believe that there will be an increase in tumour incidence.)

Irrespective of the possible cell phone use connection, knowing when a tumour actually started is useful information which could possibly provide clues and pose relevant questions in any major clinical study.

With the increasing use and the quantitative clinical confirmation of many of the predictions of the model discussed here and in numerous publications since it was first introduced, it is reasonable to use it to obtain estimates of brain tumour initiation times. As a first approximation expression (6) gives the radius of the tumour and its velocity as a function of the diffusion coefficient and growth rate but for large times, mainly from when the tumour is first detectable, that is when it has an equivalent spherical volume of at least diameter 3cm. This however is only valid for sufficiently large times and although useful for calculating approximate life expectancy it is insufficiently accurate to back extrapolate to when the tumour started: it significantly underestimates the time.

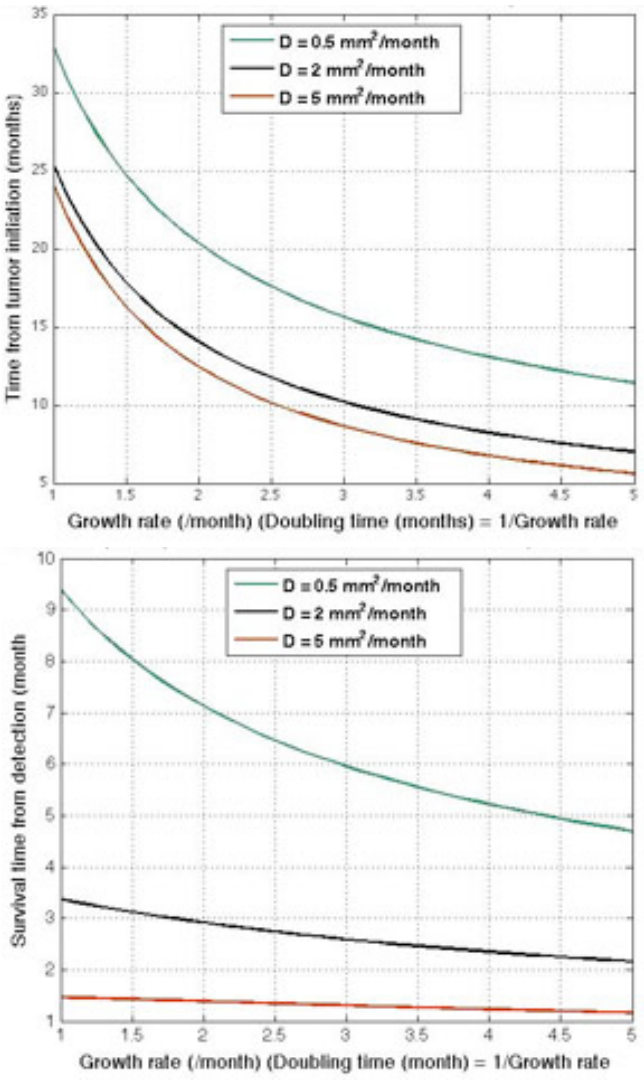

Figure 2 (top) This shows the survival time from initiation for a typical range of diffusion coefficients while (bottom) shows the survival time from detection at an equivalent tumour diameter of 3cm to death at a tumour diameter of 6cm.

We can obtain a considerably more accurate estimate using the exact solution (4) for the cell concentration as a function of time. If $c_1(r,t)$ is the outermost cancer cell density level of detection when the tumour has an equivalent sphere radius of r then the time it takes for a density of N cells to grow and diffuse is given by the solution of (5) for given r, c_1, N, D and ρ, namely the value of t such that

$$2t\sqrt{D\rho}\sqrt{1-\frac{1}{\rho t}\log\left(\frac{c_1}{N}(4\pi Dt)^{3/2}\right)}-r=0 \qquad (9)$$

There is no analytical solution of this equation but it is possible to use MATLAB to obtain the value for t for given r, c_1, N, D and ρ. This gives the time to initiation for all radii r, not only the radius at the smallest detection but whenever the tumour is first observed. It also gives a more accurate estimate for the survival time by assigning the radius to be 3cm. We do not know how many cancer cells are required before they start to diffuse nor an accurate value for the detection level c_1. By way of example we chose c_1/N in (9) to be 80,000. Figure 2 illustrates the times from initiation for a typical range of growth rates and diffusion coefficients.

From Figure 2 the effect of higher growth rates play a smaller role than diffusion variability while at low growth rates the interplay between growth and diffusion is more complex.

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