Hybrid mathematical model of glioma progression

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Abstract

Objectives: Gliomas are an important form of brain cancer, with high mortality rate. Mathematical models are often used to understand and predict their behaviour. However, using current modeling techniques one must choose between simulating individual cell behaviour and modeling tumours of clinically significant size.

Materials and Methods: We propose a hybrid compartment-continuum-discrete model to simulate glioma growth and malignant cell invasion. The discrete portion of the model is capable of capturing intercellular interactions, including cell migration, intercellular communication, spatial cell population heterogeneity, phenotype differentiation, epigenetic events, proliferation, and apoptosis. Combining this with a compartment and continuum model allows clinically significant tumour sizes to be evaluated.

Results and Conclusions: This model is used to perform multiple simulations to determine sensitivity to changes in important model parameters, specifically, the fundamental length parameter, necrotic cell degradation rate, rate of cell migration, and rate of phenotype transformation. Using these values, the model is able to simulate tumour growth and invasion behaviour, observed clinically. This mathematical model provides a means to simulate various tumour development scenarios, which may lead to a better understanding of how altering fundamental parameters can influence neoplastic progression.

Introduction

Primary brain tumours are among the most aggressive and lethal forms of cancer (1), and gliomas are the most

prevalent form of these. Gliomas are derived from transformed glial cells and account for 30–40% of all primary intracranial neoplasms (2). The most common and lethal are glioblastoma multiforme (GBM), a World Health Organization grade IV astrocytoma (3). Patients diagnosed with GBM have a median survival time of approximately 1 year despite use of a variety of medical interventions (3–6). One reason for this poor prognosis is that GBMs are highly invasive and generate hair-like projections of migratory cells that invade healthy brain tissue. The projections cannot be completely removed surgically or through radiation therapy, where treatment is localized to a specific area also, they may be more resistant to therapies than other tumour cells. As a result, these migratory cells continue to invade the brain despite medical treatment, and constitute a substrate for regrowth.

GBM cells can exhibit a variety of different characteristics, one of which is magnitude of migratory capability. This characteristic may be used to differentiate two phenotypes (7), that is, a phenotype of stationary cells that forms the main tumour body and a migratory phenotype that forms the hair-like projections. Different expression of migratory characteristics between the two phenotypes may result from a series of genetic events or from different gene expressions such as those induced by the local environment.

Research on the origin and possible sustenance of brain cancer has implicated a subpopulation of self-renewing brain cancer stem cells (8,9); genes that regulate self-renewal of normal stem cells are also found in cancer stem cells (10). Mutations in healthy stem cells may result in abnormal stem cells capable of producing abnormal progeny according to the cancer stem cell hypothesis (11–15). These abnormal progeny may lack the ability to detect feedback signals that limit proliferation of normal stem cells and thus, cause uncontrolled cell proliferation. Such an event may lead to rapid tissue growth and to tumour initiation. As the tumour becomes larger, rate of tumour growth decreases due to relative deficiency of vital nutrients at the inner core (16).

Mathematical models can be used to develop a better understanding of how different parameters contribute to

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glioma growth. In addition to predicting disease progression, simulation can sometimes lead to useful non-intuitive insight into the disease, which may ultimately improve clinical outcomes. Several mathematical models have been developed to understand glioma growth and predict the effects of therapeutic interventions; some of the most common approaches are discussed below.

Discrete models are able to incorporate parameters and biological rules discovered from cellular research. Such models have been used to simulate effects of chemotaxis, hepatotaxis, intercellular communication through gap junctions (17) and other factors that may affect cell migration. However, discrete models are computationally intensive. For a 10- μm glioma cell diameter, cell populations can reach 200 billion by the time the body of a tumour reaches 3 cm, the diameter at which GBMs are often first detected (18). Discrete modelling of 200 billion individual units is beyond the capability of most computers even using only simple algorithms of intercellular interactions. Thus, such models are limited to analyses of small developing tumours that are well below the level of clinical detection.

An alternative approach is to use a continuum model. Rather than treating each cell as a discrete individual, continuum models regard tumours as spatial distributions of cell densities. As a result, computational requirements are substantially reduced allowing tumours of clinically significant size to be modelled (7,18–20). Continuum models can also more readily account for changing chemical gradients (such as glucose, oxygen, fibronectin, and chemotherapeutic drugs) within the brain tissue (19). However, since continuum models do not consider cells individually, they lack the capability to simulate cell-to-cell interactions.

A third approach is to use a compartment model to simulate tumour growth (11,12,21). Here, cells are grouped based on phenotype and level of differentiation. Such models are effective at describing how subpopulations of various types of cells grow. Mutations, differentiation, proliferation, and apoptosis are readily accommodated as additions or subtractions from the cell populations within each compartment. These models are computationally efficient and can handle many different types of cell, but they lack the ability to account for spatial distributions.

Recently, hybrid or multiscaled models have been developed to overcome some of the limitations of the distinct approaches discussed above. Hybrid models that use a continuum approach to microenvironment while tracking discrete cell interactions have been developed to investigate microscopic tumours (22–26). Some of these models are also multiscaled, integrating at the molecular and cellular level, but not at the tissue level.

In this paper, we propose a hybrid compartment-continuum-discrete (CCD) model that uses advantageous properties of each of the above approaches. It is also multiscaled, integrating at the cellular level and tissue/tumour level. As a result, it is able to simulate tumours of clinically significant sizes, while also having the ability to account for phenotypic differences affecting individual cells. The key to this approach is to model the tumour body, which accounts of the vast majority of the cells, using continuum and compartment modelling techniques and to model migratory cells that are discretely on the invading front of the tumour.

Mathematical model

Mathematical simulations were performed using MATLAB® software (MathWorks, Natick, MA, UK). Our hybrid CCD model has two components. First, a coupled deterministic compartmental-continuum model of the tumour body was developed, which enables simulation of tumours to a clinically significant size (18). The compartment approach was used to track glioma cell subpopulations based on viability and phenotype. The coupled continuum component was used to account for differences in local environment that cells may experience within each compartment. Second, a discrete stochastic model was used to track movement and location of each migratory cell within the migratory compartment. This discrete stochastic model also accounted for apoptosis and progeny of migratory cells.

Deterministic tumour body model

Individual gliomas differ in their rates of proliferation, diffusion, and degree of vascularization. Although GBMs are often highly vascular, their neovascularization is disorganized and usually inefficient in nutrient transport, resulting in tumour cell hypoxia and necrosis. This condition was accounted for in the model using a diffusion constant for nutrient transport which considered tumour vascularization to be homogeneous (that is, higher degrees of vascularization were accounted for using larger diffusion constants). The tumour body was modeled using the spherically symmetric assumption which simulates tumours with an aspect ratio close to one. It may also be used to approximate tumours with multiple nodules, since each nodule can be considered as a separate, spherically symmetrical tumour.

The tumour is assumed to consist of three compartments: one representing viable tumour body cells, another associated with dysfunctional/dead cells in the tumour body, and a third containing cells migratory from the tumour body surface (Fig. 1). However, a compartment

Figure 1. A compartmental model is used to determine how group populations change during the growth of the tumour.

Figure 2. The tumour is modelled using three distinct categories based on the tumour size. (a) Small tumours contain only proliferating cells. (b) Developing tumours are somewhat larger and contain a hypoxic core. (c) Fully developed tumours contain a necrotic core surrounded by a hypoxic ring and a proliferating cell ring.

model alone cannot account for spatial distribution of the cells. Due to poorly organized vascularity of GBMs, cells that are below the surface of the tumour have limited access to nutrients. This problem is overcome by determining the local environment of each cell using a continuum model for nutrient transport and absorption. The nutrient concentration $c(r, t)$ is based on Fickian diffusion; that is:

$$\frac{\partial c(r, t)}{\partial t} = \frac{D}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial c(r, t)}{\partial r} \right) - S, \quad (1)$$

where D , S , r , and t are the diffusion rate, metabolic rate, radial distance, and time, respectively.

Tumour body growth is simulated using one of three methods based on tumour size. First, when a tumour is small, there are sufficient nutrients available and waste is easily removed through diffusion. During this stage, the tumour grows exponentially with a proliferation rate ω_p associated with pathway P_B in Fig. 1 (11,16). At this stage of growth, all cells are contained within the proliferating region as shown in Fig. 2a. Second, when the tumour reaches a critical size, diffusion of nutrients into the tumour core is insufficient to fully satisfy the needs of interior cells. This results in formation of a hypoxic

central core that is a quiescent region incapable of proliferation (16), and a surrounding proliferating shell, as depicted in Fig. 2b. Third, with further tumour growth, nutrient concentration in the tumour core decreases to a level that induces necrosis (16). Here, nutrient levels are insufficient to support cell life and cells begin to die faster than the normal rate of apoptosis. A fully developed tumour containing these three regions is illustrated in Fig. 2c.

Since nutrient diffusion timescale through a cell is much smaller than characteristic proliferation time, implying quasi steady-state conditions, we assume that $c = c(r)$. This reduces the time-dependent term on the left-hand side of equation (1) to zero. Equation (1) may be solved for concentration, yielding an equation with two arbitrary constants. The first constant is found by applying the boundary condition of a constant nutrient concentration C_0 outside the tumour body. This reduces the concentration equation to:

$$c(r) = C_0 - (S/6D)(R_T^2 - r^2) - K_1(1/r - 1/R_T), \quad (2)$$

where R_T is the radius of the tumour body and K_1 is an arbitrary constant. The second boundary condition is dependent on size of the tumour. If the tumour is small and nutrient concentration at the core is greater than zero, rate of change of nutrient concentration is zero at the core due to conservation of mass. In this case:

$$c(r) = C_0 - (S/6D)(R_T^2 - r^2). \quad (3)$$

If the tumour is larger, the second boundary condition occurs when nutrient concentration reduces to necrotic concentration C_N . Using this boundary condition, the unknown constant in equation (2) can be found in terms of another unknown value, the necrotic radius R_N , where:

$$K_1 = \frac{C_0 - C_N - (S/6D)(R_T^2 - R_N^2)}{(1/R_N - 1/R_T)}. \quad (4)$$

The value of R_N cannot be solved explicitly, but may be determined numerically by searching for values of R_N that satisfy $c(R_N) = C_N$ in equation (2). With R_N determined, hypoxic radius R_H may be evaluated directly.

$R_{H*} = [(C_0 - C_H)/(S/6D)]^{1/2}$ denotes the critical tumour body radius at which a hypoxic core begins to develop. If $r < R_{H*}$, the tumour can be modelled as a small proliferating tumour in the manner described above. Critical radius for a developing tumour with only a necrotic core, R_{N*} , can be calculated by replacing C_H with C_N in the equation above.

Assuming that the individual glioma cell has a volume equal to that of a sphere of 5×10^{-3} mm radius (18,27), the relationship between tumour radius and cell number is:

Table 1. Nomenclature and model parameters

Nomenclature	Symbols	Values	
Nutrient concentration	c	M/mm ³	
Radial distance from centre of tumour body	r	mm	
Radius of the tumour body	R_T	mm	
Radius of the hypoxic core	R_H	mm	
Radius of the necrotic core	R_N	mm	
Time parameter	t	days	
Parameter	Symbol	Values	Source
Nutrient concentration outside the tumour	C_0	1.0 nmol/mm ³	28
Nutrient concentration necessary for proliferation	C_H	$0.75 \times C_0$	Selected
Nutrient concentration required to avoid necrosis	C_N	$0.5 \times C_0$	19
Diffusion rate (1.5×10^{-6} cm ² /s)	D	12.96 mm ² /day	29
Metabolic consumption rate	S	1786 nmol/mm ³ ·day	30
Radius of glioma cell	R_c	5×10^{-3} mm	18
Proliferation rate – tumour body phenotype	ω_p	1/day	7,19
Apoptosis rate – tumour body phenotype	ω_d	0.32/day	19
Necrosis rate	ω_n	5/day	Selected
Proliferation rate – migratory phenotype	μ_p	1/45day	Selected
Apoptosis rate – migratory phenotype	μ_d	0.01/day	Selected
Migration velocity	v_m	0.25/day	Selected
Migration distance	μ_c	0.624 mm	32
Transformation rate to migratory phenotype	P_M	1×10^{-10}	Selected

$$R_T = R_C(N_B + N_D)^{1/3}, \quad (5)$$

where R_C denotes radius of the glioma cell, and N_B and N_D number of live and dead cells, respectively (Table 1).

Using R_T , R_N , and R_H , the volume of each region (that is proliferating, hypoxic, or necrotic) of the tumour can be calculated. Assuming that cells in the ‘dead’ compartment lie only within the necrotic region, the number of live cells in each region, i , can be calculated based on the volume fraction of that region; that is:

$$N_i = V_i/V_T(N_B + N_D), \text{ and } N_N = V_Q/V_T(N_B + N_D) - N_D \quad (6)$$

Indices $i = P$ and Q , respectively denote proliferating and quiescent regions. V_i/V_T is the volume fraction and N_i is the number of cells in region i . N_B and N_D are, respectively, number of viable and dead cells in the tumour body. The necrotic region consists of a mixture of both dead and dying cells. A conservation relation for population of viable cells is:

$$dN_B/dt = \omega_P N_P - \omega_A N_B - \omega_N N_N - \omega_T N_P, \quad (7)$$

where ω_P , ω_A , ω_N , and ω_T denote proliferation, apoptosis, necrosis, and transformation (from the stationary

to migratory phenotype) rates, respectively. While ω_P , ω_N , and ω_T apply to subpopulations of the total number of live cells, ω_A applies to the entire live cell population.

In our model, dead cells within the tumour body occupy space until they are degraded. Thus, the rate of change of the dead cell population is:

$$dN_D/dt = \omega_N N_N - \omega_{Deg} N_D, \quad (8)$$

where ω_{Deg} denotes degradation rate of dead cells. (Since apoptosis is controlled cell death, these cells are treated differently in the model. They are removed immediately and do not occupy space after death.)

Migratory cells arise from the deterministic model describing growth of the tumour body. The number of new migrating cells added during each time step is equal to the product of N_P and ω_M rounded down to an integer value. Number of new migrating cells added during each time step is saved for later use in the migratory simulation.

Stochastic migration model

The migratory phenotype is characteristic of glioma cells that have undergone an additional mutation (5), epigenetic

events, or environmentally induced gene expression, that provide these cells with enhanced migratory ability. Unlike cells in the tumour interior that exhibit low mobility, migratory cells at the surface move away from the main tumour body (31). As a result, cell bodies collectively form long hair-like strands that invade healthy brain tissue. Lengths of these projections and their densities vary over the surface of the tumour body.

Glioma cell migration is characterized by short bursts of movement (32,33). We have used a stochastic model to characterize the inherently discontinuous nature of this movement. The migratory cell portion of the model is decoupled from the tumour body portion so that a simulation of tumour body growth can be completed prior to simulating the movement of migratory cells.

In the model, migratory cells are stored in a matrix where rows of the matrix represent individual cells and columns contain parameters related to that cell. These parameters include number of days since the last proliferation event T_P , number of days since the last migration event T_M , and cell location in spherical coordinates. New migratory cells are added to the matrix with proliferation and migration counters set to zero and the radius equal to current tumour radius with angles θ and ϕ randomly prescribed.

Next, each migratory glioma cell is evaluated for proliferation, migration, or apoptosis. A Gaussian normal test function P_P is generated to determine probability of proliferation; that is:

$$P_P = N(\mu_P, \sigma_P). \quad (9)$$

Here, $N(\mu_P, \sigma_P)$ denotes the Gaussian normal function, μ_P mean value, and $\sigma_P = \mu_P/3$ standard deviation of the proliferation test function (Fig. 3). The curve represents probability of the randomly generated test function having a certain value with the most likely value being μ_P . Probability of generating a different value decreases the further the value deviates from μ_P . The test is performed by determining if the random value generated by the test function is smaller than the number of days since the last proliferation event. A positive test indicates that cell division has occurred; namely:

$$P_P \leq T_P \rightarrow \text{proliferation}. \quad (10)$$

This test applies as well to stochastic models since proliferation occurs as discrete time steps (as opposed to fractions of a time step); however, average time between proliferations is not simply μ_P . Since a test is performed at each time step, higher values of μ_P result in lower average proliferation rates, due to the cumulative effect. Evaluating $\mu_P = 45$ days, results in an average time between

Figure 3. The probability test function for proliferation P_P indicates probability that the specific cell will divide during a particular time step. If proliferation does not occur, proliferation time counter T_P is incremented by one and thus, increases the probability of proliferation during the next time step.

proliferation of 25.8 days. This value is much lower than the rate used for stationary cells in the tumour body, consistent with previous findings (22,34).

When cell division occurs, a new cell is added to the matrix, and its proliferation counter reset to zero. It is located at the same angle θ and ϕ as the dividing cell, but it is radially one cell diameter closer to the tumour body. If no proliferation occurs during this time step, then the counter for the cell is incremented by one. Testing for cell migration is performed in a similar manner.

Probability of migration continues to increase over time until the migration criterion is met. Thereafter, a cell moves a specified distance radially outward, as indicated by a characteristic migration distance, L_C , based on Gaussian normal distribution.

$$L_C = N(\mu_C, \sigma_C). \quad (11)$$

This method is consistent with previous observations that migration velocity of glioma cells fits a normal distribution (35). A constraint is placed on the model so that migrating cells are always beyond the surface of the tumour body. In order to maintain this constraint, radial distance of each migrating cell is set to the maximum of its current radial distance and outside diameter of the tumour body. During simulation, migratory cells are mapped to a one-dimensional vector space for ease of computation; however, it is helpful to remap these solutions into a three-dimensional space as shown in Fig. 4 to improve visualization of the results.

Results and discussion

Simulations begin with a single glioma cell that divides into two daughter cells. Subsequent divisions over time involving these cells and their progeny develop a tumour body (Fig. 4). As cell population enlarges, some cells

Figure 4. Three-dimensional visualization of glioma simulation is generated by remapping the tumour body growth results and cell migration results.

acquire the ability to migrate. These cells and their progeny migrate away from the tumour body forming the hair-like projections characteristic of gliomas.

Fundamental length parameter

Analysis was performed to determine sensitivity of the results to changes in model parameters. Through examination of equations (3) and (4), a fundamental length parameter

$$\tilde{\chi} = ((DC_0/S)^{1/2}) \quad (12)$$

was revealed, which is related to distance that nutrients are capable of penetrating by diffusion into the tumour body (recall that diffusion rate is a function of degree of vascu-

larization of the tumour body). It combines nutrient diffusion, nutrient concentration at the surface of the tumour body, and metabolic consumption, into a single model parameter. Thus, modifying values of D , C_0 , and S does not alter the results if $\tilde{\chi}$ remains unaltered.

A value of ≈ 1.0 mm results in a tumour growing from 3 to 6 cm in 7.5 months (Fig. 5a), which is consistent with clinical data (18,36,37). Larger values represent high nutrient diffusivities or lower metabolic consumption rates when the proliferating outer shell thickness is thicker and cell population growth rates are larger. Conversely, smaller values arise due to either small diffusivities or high consumption rates, resulting in a thinner proliferating outer layer and slower tumour growth rates.

Value of $\tilde{\chi}$ influences thickness of the proliferating shell that forms the outer surface of the tumour body (Fig. 5b); initially, the proliferating region grows rapidly. However, upon development of hypoxic and necrotic regions, shell thickness quickly stabilizes as a result of tumour geometry. By 100 days, proliferating shell thickness is smaller than 1 : 15 of tumour body radius. This thin shell can be approximated as a planar sheet with diffusion from one side and consumption within the volume (that is, the curvature is negligible). Planar sheet thickness is dependent on diffusion rate, consumption rate, and outside nutrient concentration, only, as shown in equation (12). Since this sheet thickness is independent of tumour radius, thickness of the proliferating shell stabilizes. Minor decreases are observed as time progresses, accounting for further decreases in shell curvature. The spike in the curve at approximately 35 days occurs due to overshoot in the dynamic system, since it takes time for necrotic cells to die.

Figure 5. Sensitivity analysis of fundamental length parameter $\tilde{\chi}$, an indicator of nutrient penetration depth. (a) A typical clinical tumour body growth rate is achieved with a value of $\tilde{\chi} = 1$ mm. (b) Proliferating cell shell thickness stabilizes full development of the tumour and is dependent on the value of $\tilde{\chi}$.

Figure 6. Sensitivity analysis of ω_{Deg} , the cell degradation rate in which cells die through necrosis and the space is reoccupied. A value of 0.005 or less results in tumour growth rate within the range of clinical results.

Cell degradation rate

A sensitivity analysis was used to determine cell degradation rate, ω_{Deg} (Fig. 6). ω_{Deg} is defined as the rate at which dead cells are removed from the tumour and the space reoccupied. Degradation rate of 0.005/day was assumed based on clinical tumour growth rates discussed previously (18,36,37). At this degradation rate, most dead cells in the necrotic core continue to occupy space, resulting in almost linear growth. This result is consistent with previous reports that tumours grow at a nearly constant rate (7). The degradation rate may seem low, but previously it was defined as the rate at which dead cells are removed so that they no longer occupy space. Thus, a necrotic cell may degrade physiologically and be replaced by an equal volume of fluid without having an effect on the model. A cell is not considered to have degraded in the model until the fluid is also removed and the tumour body collapses inward to occupy the volume.

When degradation rate in the model is increased (0.1, ..., 10/day), a steady-state tumour diameter is obtained in less than 1 year. This occurs because rate of increase in cell population due to proliferation equals the combined degradation and apoptotic rates. These steady-state diameters are smaller than those observed clinically implying that degradation rates cannot be inordinately large. From simulation results, the value of ω_{Deg} is determined to be in the order of 0.005/day or smaller.

Cell migration rate

Cell migration velocity $\mu_0 \approx 6.5 \mu\text{m/h}$ was used in the model based on *in vitro* studies (35). Tumour expansion rate was determined to be $2.9 \mu\text{m/h}$ by evaluating growth

rate required to increase tumour diameter from 3 to 6 cm, over a period of 7 months (5100 h). Periodic migration test function, μ_p , of 0.25 was selected for the model. This resulted in an average time between movement cycles of 5.05 days. Although faster migration frequencies are typically observed *in vitro*, the timescale of this movement was fast when compared to total analysis time of 365 days. If a more accurate evaluation of periodic movement is required in future work, the step time and migration rate can easily be modified. Migration frequency of 5.05 days and characteristic migration distance of 0.624 mm results in a migration rate of $5.15 \mu\text{m/h}$. Although this value is lower than $\mu_0 \approx 6.5 \mu\text{m/h}$, it exceeds the rate of $4.5 \mu\text{m/h}$ reported by others (22,38). Glioma growth was simulated using these parameters (Fig. 7).

Reducing migration rate to $(1/2) \mu_0$ results in migratory cells that are 'pushed' by the expanding tumour body. As a result, lengths of the hair-like projections are reduced. Physiologically, this represents a tumour that grows at approximately the same rate as the invading glioma cells. Since migratory cells in GBMs are normally characterized by invading beyond the surface of the tumour body, this lower migratory velocity may be associated with lower grades of glioma. For a larger migration rate, $2\mu_0$, these cells extend further away from the tumour body. Comparing these values leads to our contention that cell migration rate is in the order of twice tumour body expansion rate. We are unaware of any published clinical data that may be used to more closely approximate the value of this parameter and, therefore, provide our model guidance.

Our simulation distributes new migratory cells randomly on the tumour surface. The resulting distribution histogram is irregular because randomly located cells with migratory phenotypes proliferate locally. Thus, cell populations in specific regions increase, resulting in the formation of hair-like projections.

Transformation rate to migratory phenotype

In order to evaluate the rate at which transformation to the migratory phenotype occurs, proliferation of cells with a migratory phenotype is suppressed (Fig. 8). This has the effect of eliminating progeny of the migratory phenotype, so that all migratory cells in this simulation would originate directly from the stationary cell phenotype. Transformation rate of 1×10^{-10} oncogenic events per proliferation (oe/p) generates approximately 340 new cells with the migratory phenotype. Reducing this rate to 1×10^{-11} oe/p, the simulation does not generate migratory cells since the number of new migratory cells added each time step is rounded down to zero. Only 16 cells would be generated at a mutation rate of 3×10^{-11} oe/p. When transformation rate is increased to 1×10^{-9} and 1×10^{-8}

Figure 7. Sensitivity analysis of μ_c , which is the cell migration rate. Values of approximately $6 \mu\text{m/h}$, $\mu_c = \mu_0$, are large enough to generate the hair like projections observed clinically.

oe/p, number of new mutation sites also increases to 3400 and 34 000, respectively.

As the tumour grows larger, number of migrating cells and each time step increase. Since these new migrating cells are added at the surface of the tumour, this results in radial distribution of cells with higher population density close to the tumour body. Cells that lie furthest from the tumour surface transformed earlier, migrated further, and were generated when the tumour body was smaller. Since clinical observations of gliomas show decreasing density of tumour cells with increasing

distance from the tumour body, this model suggests that transformation of glioma cells to migratory cells dominates over proliferation of migratory cells. This conclusion is consistent with *in vitro* tests showing that cells with migratory phenotype have reduced proliferation rates (34).

Summary and conclusions

A hybrid model has been developed that uses a coupled compartment-continuum model to simulate growth of

Figure 8. Sensitivity analysis of P_M , the transformation rate associated with conversion from the stationary to migratory phenotype. Values in the order of 10^{-9} or greater result in radial distribution of migratory cells that decreases with distance from the tumour body, matching clinical observations.

tumour body, and a discrete model to simulate behaviour of migratory cells. This hybrid CCD model was used to simulate tumour growth from a single cell to a fully developed tumour of over 6 cm in diameter. Sensitivity of the results to changes in model parameters was evaluated. These parameters included effects of the fundamental length parameter associated with nutrient penetration depth, degradation rate of cells in the necrotic region, cell migration rate, and rate of transformation from stationary phenotype to migratory phenotype. Since every tumour is different, it is inappropriate to use a mathematical model to determine exact values for each of these parameters. However, orders of magnitude for these parameters may be estimated so that simulated behaviour of the tumour matches that observed clinically.

Of particular interest is the fundamental length parameter. In addition to quantifying penetration depth of vital nutrients, this parameter can be used to quantify penetration depth and potential effectiveness of new chemotherapeutic agents. Guided by equation (12), increases in diffusion rates of chemotherapeutics into the tumour or increases in local chemical concentrations around the tumour body will increase depth of penetration. Furthermore, decreasing the rate of degradation or metabolic consumption of chemotherapeutic agent would also be beneficial.

The hybrid CCD model was shown to be capable of simulating a tumour of clinically significant size while simultaneously being able to track individual cells; the matrix method used to track each cell may be easily adapted

to include other parameters. As a result, multiple cellular interactions may be included in future models with only slight modifications to the current one.

Although the model is able to simulate migration of individual cells, actual migratory cell populations may also exceed the enhanced computational capability provided by this method. One approach to combat this dilemma is to remap migratory cells on to a smaller area of tumour body. This can be used to represent higher cell population densities, but limits the results to a small solid angular region. Another approach is to consider cell groups rather than individual cells. A number of cells could be modelled to move together as a group. This approach would reduce the computational power necessary to model behaviour while still retaining the capability of having distinctly different behaviour of each cell group.

In summary, we have shown how a hybrid mathematical model can be used to gain better understanding of parameters that effect brain tumour growth and invasion. The results may lead to insights that can be used to sharpen the focus of future experiments (19) and ultimately improve prognosis of patients who are diagnosed with gliomas.

Such a model is capable of relatively rapid simulations while modelling cell migration, intercellular communication, spatial cell population heterogeneity, phenotype differentiation, epigenetic events, proliferation, and apoptosis (39). Restricted by medical ethics, human experiments cannot be conducted on GBM patients that would allow a tumour to grow without intervention, with the

knowledge that better clinical treatments are recommended. As such, a mathematical model offers recourse to understanding various tumour development scenarios. Second, although experiments can be conducted to determine the effects of changing parameters, some of these might be difficult if not impossible to control. Thus, fundamentally sound models can allow for better analysis and visualization of neoplastic progression.

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