A Mathematical Model to Simulate Glioma Growth and Radiotherapy at the Microscopic Level

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Abstract

In the present work, a new mathematical approach for modelling the influence of radiotherapy on the progression of malignant primary brain tumours is proposed. A hybrid approach is used to model the cellular tumour progression, the development of the local nutrient concentration and the density of the extracellular matrix (ECM). The description of radiotherapy is based on the linear-quadratic model. The effects of irradiation are influenced by the administrated dose and two parameters, which represent the radiosensitivity of the tissue. Due to the discrete approach, the impact of the therapy can be described for every single tumour cell. The implementation of the cell cycle allows, alongside the more precise description of the biological processes, for mapping the variability of the radiosensitivity of cells in the different cell phases. Furthermore, the choice of different fractionation schemes allows a variable adaption of the radiotherapy to the tumour. The main contribution is the novel combination of the microscopic tumour growth model including the microenvironment with the influences of the radiotherapy model. Furthermore we can provide a comparison of the growth model results to histological data of glioblastoma.

1 Introduction

Glioblastoma (GB) is the most aggressive and most common primary brain tumour in adults. The classification of the tumour according to WHO is based on conventional histologic criteria such as cellular anaplasia and proliferative activity, microvascular proliferation and necrosis (Image 1). Typically, malignant gliomas infiltrate the surrounding brain tissue diffusely. By surgical resection usually only the bulk of the tumour can be removed. Therefore, only a median survival of slightly more than one year is achieved [1]. One of the standard therapies after surgical resection is radiotherapy. The goal is to destroy cancer tissue by using high energy rays.

A powerful tool to test hypotheses on tumour evolution for individual patients and thus, to improve the understanding of the disease, is mathematical modelling. The present work deals with modelling the progression of gliomas of the central nervous system and the effects of radiotherapy on a microscopic scale. Mathematical approaches for simulating tumour growth on the cellular level typically consist of reaction–diffusion equations that describe the movement of cancer cells under the influence of the microenvironment. In this work, the extracellular matrix (ECM) and nutrients, such as glucose and oxygen, are considered. The effects of those on the migration of tumour cells are referred to as haptotaxis and chemotaxis, respectively. For simulating the impact of radiotherapy, the standard linear-quadratic model is used. Furthermore, we con-

Image 1 Glioblastoma (microscopic image): A Cell rich tumour tissue with characteristic microvascular glomeru-
loid proliferations (arrows). Bottom, necrotic tumour tissue (arrow heads) (dyeing method: Elastica van Gieson, x100).
B (Tumour detail) Higly cellular and pleomorphic tumour, note variations in nuclear size. Several mitotic figures (ar-
rows), dense delicate capillary network (arrow heads) (dyeing method: H & E, x400).

consider the variability of the radiation sensitivity of individual cells as a function of the cell cycle phases. Modelling the progression of brain tumours is an active area of research. Mathematical models can be divided into discrete and continuous models. In [2], a three-dimensional model of tumour progression is proposed. In addition to a
macroscopic description of tumour growth using the cell cycle the influence of radiation therapy is also considered. However, a description of the diffusive nature of malignant tumours is missing. The model proposed in [3] describes the progression of the tumour based on a reaction-diffusion equation. The difference in motility of cancer cells within gray and white matter is hereby incorporated by an anisotropic diffusion coefficient. This approach can also be extended to include the effect of radiation therapy [4]. However, these models simplify the complex processes at the microscopic and molecular level. The model in [5] is based on partial differential equations to simulate the tumour growth at the cellular level. The effects of radiotherapy, as described in [6] are neglected. The main contribution of this work is a hybrid model of avascular tumour growth including the microenvironment by means of the extracellular matrix as well as nutrients and the effect of radiation therapy based on the linear-quadratic approach [2,4,6]. Radiosensitivity parameters are varied according to the cell cycle phases.

2 Methods

A two-dimensional domain $\Omega = [0,1] \times [0,1]$ with Dirichlet and Neumann boundary $\Gamma_D \cup \Gamma_N = \Gamma = \partial \Omega$ is considered and discretised with a $400 \times 400$ grid. This domain represents a region of 4 mm x 4 mm. At this, each square of the grid corresponds approximately to the area of one biological tumour cell with a diameter of approximately 10 μm [5].

2.1 Growth Model

The spatio-temporal tumour growth model consists of reaction-diffusion equations that describe the movement of cancer cells $c$ in interaction with nutrients as well as the extracellular matrix. The distribution of the nutrients $n$ and the density of the ECM $f$ are covered by partial differential equations:

$$\frac{\partial c}{\partial t} = \nabla \cdot (D_c \nabla c) - \chi V \cdot (c \nabla u) - \rho V \cdot (c \nabla f),$$

$$\frac{\partial u}{\partial t} = \nabla \cdot (D_u \nabla u) - \alpha_u u c,$$

$$\frac{\partial f}{\partial t} = -\alpha_f f c + \beta_f f \left(1 - f\right),$$

with boundary conditions

$$\frac{\partial c}{\partial n} = 0, \frac{\partial f}{\partial n} = 0 \quad \text{on } \Gamma \times [0,T],$$

$$\frac{\partial u}{\partial n} = 0 \quad \text{on } \Gamma_N \times [0,T],$$

$$u = 1 \quad \text{on } \Gamma_D \times [0,T],$$

and initial conditions

$$c = c_0, u = u_0, f = f_0, \forall x \in \Omega,$$

where $D_c$ and $D_u$ are the diffusion coefficients, $\chi$ is the chemotactic parameter and $\rho$ the haptotactic parameter, respectively. The uptake rates are $\alpha_u$ and $\alpha_f$ and the remodelling parameter for the ECM is $\beta_f$.

At each time step and for each tumour cell, we consider the local nutrient concentration, and then decide on how the cell responds. In case the nutrient level is below a critical threshold $a_{crit}$, we assume that the cell will die due to the lack of oxygen with a probability of 80%. Consequently, the cell is marked as necrotic tissue and not considered for the next step. After checking the necrosis criterion, each tumour cell moves according to the scheme described below. In case the nutrient concentration is high enough, the cell is selected to divide, with a total cell cycle time of 8 h (cf. [5]) for the inner proliferative zone and of 13 h for the outer invasive rim [7,8]. The duration for the phases of the cell cycle are $T_p = 6/11$ h and $T_g = 2$ h, where $P$ contains the postmitotic (G1), premitotic (G2) and the mitotic phase (M). $S$ refers to the synthesis phase. The values are taken in reference to [9], where the duration of the different phases of the cell cycle is described.

In case there is no free space in the neighbourhood for migration or division, the tumour cell becomes quiescent until free space is available or the cell becomes necrotic due to insufficient nutrients. The quiescent state is equivalent to the $G_0$ phase of the cell cycle. The simulation stops, when a cell reaches the boundary of the area.

To obtain a similar magnitude in the range $[0,1]$ for all computed quantities, we rescale and non-dimensionalise the variables and parameters [10].

For the computation of the nutrients (2) we use the method of finite elements. Because of the discrete-continuum interaction in every time step, we have to solve the equations for each simulation time step $t_n = m\Delta t = mk; m = 1,2,\ldots$ in the steady state (i.e., $\partial u / \partial t = 0$). The boundary and initial conditions for the nutrients depend on their position relative to the nutrient delivering blood vessels or capillaries. This can be modelled by placing them at all four surrounding boundaries, at three of them, at two of them or only at a single side. For the sites occupied by blood vessels we apply a Dirichlet boundary condition with a constant function $u = 1$ since the concentration of glucose and oxygen (nutrients) is highest in the capillaries. For the remaining boundaries we use zero flux Neumann boundary conditions. For the tumour cell equation (1) we use the resulting coefficients of the five- and nine-point finite-difference stencil to generate the probabilities of the movement of an individual cell in response to its local milieu. The 5-point stencil is equivalent to the von Neumann neighbourhood and the 9-point stencil to the Moore neighbourhood. We implement both and use a random switching mechanism to select one of them for each iteration and each cell. For the extracellular matrix a constant value $f(x,t) = 0.8$ is taken to allow for the assumption that the density of the ECM is high at the beginning, but smaller than 1, which would be equivalent to the maximal density. This choice of value is taken with reference to [10], where the extracellular space of gliomas is described. To discretise the continuous equation (3) we use the Euler finite difference approximation.

Initially, a group of 100 tumour cells is placed in the centre of the domain $\Omega$. The initial cell cycle phases are randomly chosen for each individual cell.
2.2 Radiotherapy Model

The description of the influence of irradiation on tumour growth is based on the linear-quadratic model [2,4,6]. The fraction of surviving cells is given by

\[ S(D) = e^{-(\alpha D + \beta D^2)} \]

where \( D \) is the dose, \( \alpha \) is the cell kill parameter of the initial linear component and \( \beta \) the cell kill parameter of the quadratic component of the survival curve. Both parameters describe the radiosensitivity of tissue and vary according to the cell cycle. Based on eq. (4) probabilities for lethal and sublethal damage can be calculated as:

\[ P_{lh} = 1 - e^{-(\alpha D + \beta D^2)} \]
\[ P_{slh} = 1 - e^{-\beta D} \]

Depending on a random value \( z \in [0, 1] \) and on the probabilities \( P_{lh} \) and \( P_{slh} \), three cases can be differentiated:

1. For \( 0 \leq z < P_{lh} \), the tumour cell has lethal damages. The cell dies.
2. For \( P_{lh} \leq z < P_{lh} + P_{slh} \), the tumour cell has sublethal damages. The cell can be repaired.
3. For \( P_{lh} + P_{slh} \leq z \), the tumour cell is not affected. The cell survives.

A cell with sublethal damages needs 6 hours to be repaired, until then the cell is not considered for the active cell cycle.

The majority of the cells with lethal damages dies during the next mitosis phase. Damages are detected within this period and the programmed cell death (apoptosis) is initiated. Some of these cells can still divide a few times. Similar to [6] for this process, a probability of postmitotic survival of 30 % is adopted. Newly formed daughter cells inherit the damage from the mother cell and are also marked as a cell with lethal damages.

3 Results

In this section first results of our model are shown. As a standard treatment plan is a conventional fractionation (irradiation over 5 days per week with one fraction per day) beginning at day 6 with a dose of 2 Gray per fraction is employed. The radiation sensitivities vary depending on the cell cycle phase (P/S/G0): \( \alpha = 0.3/0.2/0.1 \) and \( \alpha/\beta = 10 \), for a radio-resistant tumour [2].

Image 2 shows the tumour after 35, 140, 350 and 590 hours, wherein the nutrient supply is secured through blood vessels located at all boundaries of the area (Image 3, bottom). As for the cells (Image 2) red and light red are active or quiescent tumour cells. Yellow correspond to dead cells due to the lack of nutrients. The lethally damaged cells are shown in green and the sublethally damaged cells are represented in light blue. The extracellular matrix is shown for the time points \( t = 35 \) h and \( t = 590 \) h in Image 3, top.

The evolution of the different states of the cell population (necrotic, quiescent, active tumour cell) together with the total number of tumour cells is shown in Image 4. During therapy, the population decreases, while in the treatment breaks the cell number increases again. Image 5 shows the increase of the number of tumour cells with radiotherapy and without any treatment.

4 Conclusion

In the present study, the development of a model for the description of avascular tumour growth and the integration of a model for radiation therapy was introduced at the cellular level. The invasive behaviour of the tumour can clearly be observed (Image 2). Furthermore, at a later time point the typical necrotic regions (Image 1) due to the lack of nutrients in the centre of the tumour can be seen in Image 2 (bottom, right) and in Image 3 (bottom), where the consumed concentration of the nutrients is visible. Also the degradation of the extracellular matrix by the tumour cells can clearly be observed (Image 3, top).

The effect of radiotherapy is shown by the plot in Image 4. After each day and hence after a treatment fractionation the number of tumour cells (quiescent, active and total) is decreased. Usually, the weekend allows the healthy tissues to recover a little and is left out of treatment. In this stage, the cancer is growing even faster than in the first growth stage.

In summary, the simulation results of the presented model display the biologically expected cell distributions and are similar to that described in the literature.
Prospectively, it will also be essential to extend the devised model by e.g. interactions with the host tissue. Further, as stated above, we aim at devising multi-scale tumour growth models that not only account for cell-cell interaction but also for molecular events as well as for information available from the macro-environment.

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5 Literature