Mathematical Biosciences 276 (2016) 75–81

Contents lists available at ScienceDirect

Mathematical Biosciences

journal homepage: www.elsevier.com/locate/mbs

Travelling wave analysis of a mathematical model of glioblastoma growth

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ARTICLE INFO

Article history:
Received 8 September 2014
Revised 7 March 2016
Accepted 8 March 2016
Available online 25 March 2016

Keywords:
Cancer modelling
Cell-based model
Travelling waves
Glioblastoma

ABSTRACT

In this paper we analyse a previously proposed cell-based model of glioblastoma (brain tumour) growth, which is based on the assumption that the cancer cells switch phenotypes between a proliferative and motile state (Gerlee and Nelander, 2012). The dynamics of this model can be described by a system of partial differential equations, which exhibits travelling wave solutions whose wave speed depends crucially on the rates of phenotypic switching. We show that under certain conditions on the model parameters, a closed form expression of the wave speed can be obtained, and using singular perturbation methods we also derive an approximate expression of the wave front shape. These new analytical results agree with simulations of the cell-based model, and importantly show that the inverse relationship between wave front steepness and speed observed for the Fisher equation no longer holds when phenotypic switching is considered.

1. Introduction

The brain tumour glioblastoma kills approximately 80 000 people per year worldwide, and these patients have, despite decades of intense research, a dismal prognosis of approximately 12 months survival from diagnosis. The standard treatment is surgery, followed by radiotherapy and chemotherapy. However, one of the major hurdles in treating malignant glioblastomas surgically is their diffuse morphology and lack of distinct tumour margin. The high migration rate of glioblastoma cells is believed to be a main driver of progression [1], but precise knowledge of how glioblastoma growth is shaped by the underlying cellular processes, including cell migration, proliferation and adhesion, is still lacking, hampering the prospects of novel therapies and drugs.

One characteristic of glioblastoma cells which has gained considerable attention is the 'go or grow'—hypothesis, which states that proliferation and migration are mutually exclusive phenotypes of glioblastoma cells [1]. This observation was recently confirmed using single cell tracking [2], where individual cells were observed to switch between proliferative and migratory behaviour. In order to understand and control the growth of glioblastomas we hence need an appreciation of how the process of phenotypic switching influences glioblastoma growth and invasion. This paper presents a starting point for this understanding and reports on an analytical connection between cell-scale parameters and the properties of tumour invasion, which could be used for tailoring treatment based on single-cell measurements.

2. Previous work

The starting point of glioblastoma modelling was the seminal work of Murray and colleagues [3,4], which made use of the Fisher equation

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} + \rho u(1-u) \tag{1}$$

where $u(x, t)$ denotes the density or concentration of cancer cells, D is the diffusion coefficient of the cells, and ρ is the growth rate. The microscopic process that the above equation describes is that of cells moving according to a random walk, and simultaneously dividing at rate ρ. It can be shown that the Fisher equation exhibits travelling wave solutions, which medically corresponds to a tumour invading the healthy tissue. These solutions $U(z)$ remain stationary in a moving frame with coordinates $z = x - ct$, and it can be shown that velocity of the invading front is given by $c = 2\sqrt{D\rho}$.

Since then many different models of glioblastoma growth have been proposed, ranging from game theoretical models [5], and systems of partial differential equations [6], to individual-based models [7]. In particular there has been an interest among modellers

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http://dx.doi.org/10.1016/j.mbs.2016.03.004
0025-5564/

in the above mentioned 'go-or-grow' hypothesis, and several different approaches have been utilised. Hatzikirou et al. [8] used a lattice-gas cellular automaton in order to investigate the impact of the switching between proliferative and migratory behaviour, and went on to show that in the corresponding macroscopic (Fisher) equation, there is a tradeoff between diffusion and proliferation reflecting the inability of cells to migrate and proliferate simultaneously. Similar results were obtained by Fedotov and Iomin [9] but with a different type of model known as continuous time random walk model, where the movement of the cells is not constrained by a lattice. The effects of density-driven switching were investigated with a two-component reaction diffusion system in a study by Pham et al. [10], and they could show that this switching mechanism can produce complex dynamics growth patterns usually associated with tumour invasion.

In this paper we will be concerned with the analysis of an individual-based model put forward by Gerlee and Nelander [11]. In the initial study, it was shown that the average behaviour of the cell-based model can be described by a set of coupled PDEs, similar to the Fisher equation, which exhibit travelling wave solutions. A combination of analytical and numerical techniques made it possible to calculate the wave speed of the solutions, and it was shown to closely approximate the velocity of the tumour margin in the cell-based model.

In this paper we extend the analysis of the model, and show that if one assumes that cell migration occurs much faster than proliferation, then a closed form expression of the wave speed can be obtained, and also that an approximate solution for the front shape can be derived. The paper is organised as follows: in Section 3 we present the cell-based model and its continuum counter-part. Section 4 is concerned with obtaining a closed form expression for the wave speed, and in Section 5 we derive an asymptotic solution to the system. Finally we conclude and discuss the implications of the results in Section 6.

3. The model

The cells are assumed to occupy a d-dimensional square lattice containing N^d lattice sites, and each lattice site either is empty or holds a single glioma cell. For the sake of simplicity we do not consider any interactions between the cancer cells (adhesion or repulsion), although this could be included [12].

The behaviour of each cell is modelled as a time continuous Markov process where each transition or action occurs with a certain rate, which only depends on the current and not previous states. Each cell is assumed to be in either of two states: proliferating or migrating, and switching between the states occurs at rates q_p (into the P-state) and q_m (into the M-state). A proliferating cell is stationary, passes through the cell cycle, and thus divides at a rate α. The daughter cell is placed in one of the empty neighbouring lattice sites (using a von Neumann neighbourhood) with uniform probability across all empty neighbouring sites. If the cell has no empty neighbours cell division fails. A migrating cell performs a size exclusion random walk, where each jump occurs with rate ν (with dimension s^{-1}). When motion is initiated the cell moves into one of the empty neighbouring lattice sites with uniform probability across all empty neighbouring sites. If the cell has no empty neighbours cell migration fails.

Lastly, cells are assumed to die, through apoptosis, at a rate μ (with dimension s^{-1}) independent of the cell state. This model is naturally a gross simplification of the true process of glioblastoma growth, and for further discussion on this we refer the reader to [11].

The time scale is chosen such that $\alpha = 1$, which means that all other rates are given in the unit 'cell cycle^{-1}'. Experimental results suggest that the average time for the cell cycle is 16–24 h [1],

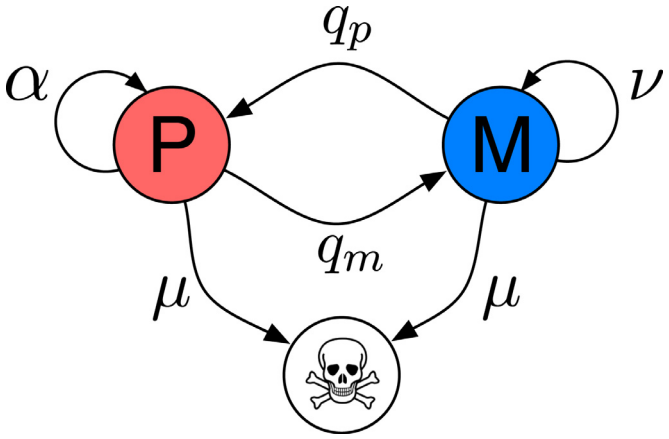

Fig. 1. A schematic of the continuous-time Markov chain which controls the behaviour of each cell in the individual-based model. The cells are either in a proliferative state (P) in which they divide at rate α or in a motile state where they jump between lattice points at rate ν. The switching between the two states occurs at rate q_p and q_m.

and that the phenotypic switching occurs on a faster time scale than cell division [2], roughly on the order of hours, implying that $q_{p,\,m} \in (10, 30)$. The death rate for an untreated tumour is on the other hand much smaller than the proliferation rate, approximately $\mu \sim 10^{-1} - 10^{-2}$. Tracking of single cells has shown that glioblastoma cells move with a velocity of up to 25 cell sizes/cell cycle [2], and consequently we set $\nu = 25$.

The stochastic process behind the phenotypic switching is depicted schematically in Fig. 1. When comparing the cell-based model with the analytical results we simulate the model in $d = 1$ dimensions. Each simulation is started with a single cell in the proliferative state at grid point $i = 0$. We record the cell density at $t = T_{\max}/2$ and $t = T_{\max}$, and by performing a large number of simulations we estimate the occupation probabilities $\mathcal{P}_i^t$ and $\mathcal{M}_i^t$ of having a proliferating/migratory cell at lattice site i at time t. By finding the lattice point where $\mathcal{P}_i^t + \mathcal{M}_i^t = 1/2$ for $t = T_{\max}/2$ and $T_{\max}$ we can calculate speed of the advancing front. If several such lattice points exist we pick the one with the smallest i. Typically the probabilities are estimated from 20 different simulations and $T_{\max} = 100$ cell cycles.

3.1. The continuum approximation

The system of PDEs that describes the average behaviour of the cell-based model in one dimension was derived in Gerlee and Nelander [11] and is given by:

$$\frac{\partial p}{\partial t} = D_\alpha (1-p-m)\frac{\partial^2 p}{\partial x^2} + \alpha p(1-p-m) - (q_m + \mu)p + q_p m \tag{2}$$

$$\frac{\partial m}{\partial t} = D_\nu \left((1-p)\frac{\partial^2 m}{\partial x^2} + m\frac{\partial^2 p}{\partial x^2} \right) - (q_p + \mu)m + q_m p \tag{3}$$

where $p(x, t)$ and $m(x, t)$ is the density of proliferating and motile cells respectively. The diffusion coefficient $D_\alpha = \alpha/2$ captures tumour expansion driven by proliferation, while $D_\nu = \nu/2$ comes from the random movement of migratory cells. The wave speed of this system can be determined by numerical investigation of the corresponding 4-dimensional autonomous system (for details see [11]). Here we show how the system can be simplified and the problem reduced to three dimensions, which allows for a closed form expression of the wave speed.