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'Go or Grow': the key to the emergence of invasion in tumour progression?

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Uncontrolled proliferation and abnormal cell migration are two of the main characteristics of tumour growth. Of ultimate importance is the question what are the mechanisms that trigger the progression from benign neoplasms (uncontrolled/autonomous proliferation) to malignant invasive tumours (high migration). In the following, we challenge the currently prevailing view that the emergence of invasiveness is mainly the consequence of acquired cancer cell mutations. To study this, we mainly focus on the 'glioblastoma multiforme' (GBM) tumour which is a particularly aggressive and invasive tumour. In particular, with the help of a simple growth model, we demonstrate that the short time required for the recurrence of a GBM tumour after a gross total resection cannot be deduced solely from a mutation-based theory. We propose that the transition to invasive tumour phenotypes can be explained on the basis of the microscopic 'Go or Grow' mechanism (migration/proliferation dichotomy) and the oxygen shortage, i.e. hypoxia, in the environment of a growing tumour. We test this hypothesis with the help of a lattice-gas cellular automaton. Finally, we suggest possible therapies that could help prevent the progression towards malignancy and invasiveness of benign tumours.

Keywords: migration/proliferation dichotomy; glioblastoma multiforme; tumour progression; invasion; hypoxia; lattice-gas cellular automata; mean-field approximation.

1. Introduction

Cancer progression can be described as a sequence of traits or phenotypes that cells have to acquire if a neoplasm (benign tumour) is to become an invasive and malignant cancer. A phenotype characterizes

any kind of observed morphology, function or behaviour of a living cell. Hanahan & Weinberg (2000) have identified six cancer cell phenotypes, which are characterized by unlimited proliferative potential, environmental independence of growth, evasion of apoptosis, angiogenesis, high motility rates (invasion) and metastasis. Recently, Fang *et al.* (2008) have proposed further possible cancer cell phenotypes such as the hypoxic one.

It is widely believed that tumour cells change their phenotype due to mutations that are acquired during cancer progression. Initially, mutations alter the proliferation control of the cells which leads to uncontrolled cell division (Hanahan & Weinberg, 2000). Then, the transformed cells form a neoplastic lesion and the tumour can grow up to a size at which the diffusion-driven oxygen supply becomes insufficient (hypoxia) to support further growth. Furthermore, the hypoxic environment and the high mutational rates of tumour cells, due to their damaged genetic material, may lead to the emergence of phenotypes characterized by anaerobic metabolism (Gatenby & Gillies, 2004), high motility or/and angiogenesis. These new attributes allow the tumour to grow further and at this stage metastases are often observed. The important difference between cells in benign (composed mainly of tumour cells with a proliferative phenotype) and malignant tumours is the presence of cells with increased motility in the latter (Giese *et al.*, 2003). Since the emergence of a motile tumour cell population is so important for tumour progression towards malignancy, we are interested in the conditions that drive the transition from the proliferative to the motile phenotype.

The principle question that we attempt to answer is which are the cellular mechanisms that promote the emergence of an invasive tumour phenotype at the expense of a proliferative one. The prevailing view concerning the emergence of invasive, or any other, phenotype is mutation based. Random mutations of the appropriate combination of genes can switch the phenotype from a proliferative to an invasive one (or can trigger any other phenotypic change). In Section 2, we show that only mutation-driven phenotypic changes are not sufficient to explain the typically fast evolution and the rapid adaptation of tumours, such as ‘glioblastoma multiforme’ (GBM or simply glioma tumours). Therefore, there is a need for an alternative hypothesis.

Experiments with cultures of glioma cells (Giese *et al.*, 2003) have shown a relationship between migratory and proliferative behaviour. Especially, cell motion and proliferation are mutually exclusive processes since highly motile glioma cells tend to have lower proliferation rates, i.e. cells proliferate only when they do not move (resting phase). This phenomenon is known as migration/proliferation dichotomy (or ‘Go or Grow’ mechanism) (Giese *et al.*, 1996a,b). Biological evidence indicates that migratory and proliferative processes share common signalling pathways, suggesting a unique intracellular mechanism that regulates both behaviours (Giese *et al.*, 2003). Recently, in Godlewski *et al.* (2010), the authors have identified a protein that is responsible for the regulation of migration and proliferation pathways according to the metabolic stress. This publication provides strong evidences for the existence and the details of ‘Go or Grow’ mechanism in glioma cells.

In the light of the aforementioned biological observations, we propose an alternative explanation, based on phenotypic plasticity that challenges the dominant hypothesis that mutations primarily trigger the switch from a proliferative phenotype to an invasive one. In particular, the response of a microscopic intracellular mechanism, such as ‘Go or Grow’, to oxygen shortage (hypoxia) may be responsible for the transition from a highly proliferative to an invasive phenotype in a growing tumour (Fig. 1).

Recently, several studies have investigated the influence of the migration/proliferation dichotomy for tumour invasion. Athale *et al.* (2006) have proposed an agent-based model to test the effect of a potential regulatory network related to the ‘Go or Grow’ mechanism in the emergence of invasive phenotypes. A lattice-based game theoretical approach (Mansury *et al.*, 2006), involving motile and proliferative populations, has been used to investigate the dynamics of tumour growth. Fedotov & Iomin (2007) have

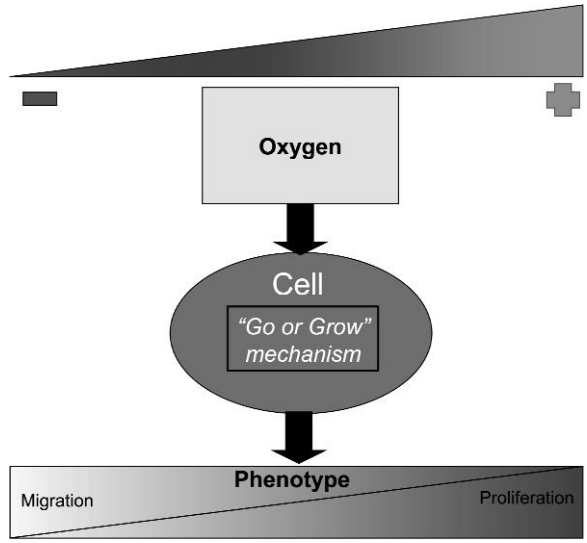

FIG. 1. This sketch shows how the oxygen concentration influences the phenotype of a tumour cell. Cells respond to low oxygen supply with a non-proliferative phenotype, which is highly motile due to the ‘Go or Grow’ mechanism. On the contrary, high oxygen level favours the occurrence of the proliferative phenotype which is non-motile due to the migration/proliferation dichotomy.

been interested in the effect of the ‘Go or Grow’ mechanism on glioma cell diffusion, analysed by means of a continuous random walk model. Finally, in a recent work (Tektonidis *et al.*, 2011), the ‘Go or Grow’ mechanism has been identified as a central mechanism for the reproduction of *in vitro* glioma tumour invasion data. However, none of the existing studies have tested our hypothesis: the response of the ‘Go or Grow’ mechanism to hypoxia may trigger the switch from a highly proliferative to an invasive phenotype.

To test and analyse our hypothesis, we use a lattice-gas cellular automaton (LGCA). Our LGCA models a phenotypically homogeneous, avascular tumour growing in a homogeneous oxygen concentration field. In our model, the cells accomplish two key processes: (i) cells execute an unbiased random walk and (ii) cell proliferation is influenced by the local oxygen concentration. The phenotype of the cells is controlled by a single-model parameter, which represents the ratio between motility and proliferation rates. Varying the oxygen concentration allows us to identify the fittest tumour phenotype. In this paper, fitness is characterized by the total number of tumour cells, i.e. offsprings, after a certain time interval. The simplicity of the model allows numerical and analytical investigations. In the following, we collect the most important biological implications of our study:

- We challenge the widely accepted theory that mutations are responsible for any phenotypic change involved in tumour progression. Our analysis suggests that the response of the microscopic ‘Go or Grow’ mechanism to hypoxia, i.e. oxygen shortage, can trigger the switch from a proliferative to a motile phenotype and *vice versa* (Fig. 1).
- For each oxygen level, there exists a dominant (fittest) tumour cell phenotype that corresponds to a certain ratio of proliferation/migration rates.

- Finally, our model exhibits the non-intuitive behaviour that invasive phenotypes, which show microscopically low proliferation and high motility, can produce more offsprings than phenotypes with much higher proliferation rates under certain microenvironmental circumstances.

In Section 2, we answer the question why mutation-based explanations fail in the case of glioma tumour recurrence and why we need an alternative hypothesis. Then, we test this hypothesis with an LGCA model that describes a growing tumour cell population. In particular, we introduce the assumptions of our model and we discuss the biological relevance of the model parameters. Then, we present the numerical results of the model simulations. Moreover, we determine the model's macroscopic behaviour, which corresponds to the collective behaviour of the tumour cell colony, through a multiscale Chapman–Enskog approach. Finally, in the last section, we critically discuss the results and we elaborate clinical implications of our theoretical analysis.

2. Why not mutations?

In the introduction of this study, we challenge the prevailing view that 'primarily' mutations drive the cancer evolution. We evidence theoretically that a mutation-based hypothesis alone cannot explain the progression of all tumours by identifying an appropriate counterexample. A particularly interesting counter-paradigm is the recurrence of GBM tumours after extensive resection (Hatzikirou *et al.*, 2005), where a mutation-based hypothesis fails to explain the short time span until the tumour's recurrence.

It is known that glioma tumours even after extensive resections, of almost 99% of the tumour mass, fully recur in less than six months (Fig. 2). Typically, a full-grown GBM tumour containing 10^9 cells (corresponds to a tumour diameter larger than 1cm) after surgery can be reduced down to $\propto 10^6$–10^7 cells. These remnant glioma cells are not resected because they have escaped far away from the bulk of the tumour (Fig. 3). These cells typically belong to the invasive phenotype. According to the migration/proliferation dichotomy, highly motile cells should exhibit low proliferation rates. The question that arises is how these invasive tumour cells are able to regenerate the initial tumour in a very short time. In the following, we test if a mutation-driven phenotypic change is sufficient to support the recurrence of the initial tumour within a time span less than that of six months.

Firstly, we develop a simple tumour model with two phenotypes—populations, a proliferative $\rho_p(t)$ and an invasive $\rho_i(t)$ one, respectively. The cells that belong to the invasive phenotype proliferate

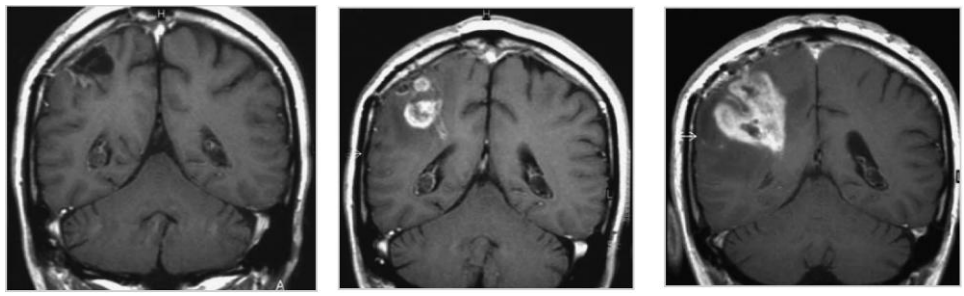

FIG. 2. T1-weighted contrast-enhanced coronal magnetic resonance imaging (MRI) of recurrent glioblastoma. Left: T1-weighted contrast-enhanced coronal MRI section showing the resection cavity in the right parietal lobe, 3 months postoperatively. There is no evidence of tumour recurrence. Middle: corresponding MRI of the same patient, 6 months postoperatively, clearly showing tumour recurrence (=hyperintense or white mass). Right: control MRI, 9 months postoperatively, showing tumour extension beyond the previous resection cavity along the cerebral white matter. Images are courtesy of Bonn university hospital.

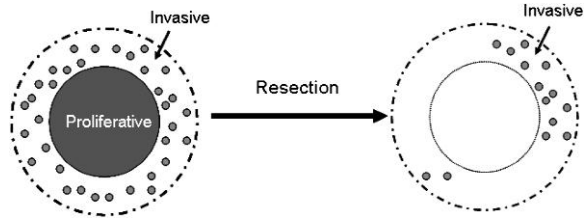

FIG. 3. Sketch of pre- and postoperative scenario of a glioblastoma tumour. In the preoperative state, a GBM tumour consists of an inner core of proliferative cells and an outer ring of invasive tumour cells (for simplification the necrotic core is neglected). After a gross total resection, the core part of the tumour has disappeared but some cells of the invasive zone stay intact. These cells are assumed to be responsible for tumour recurrence.

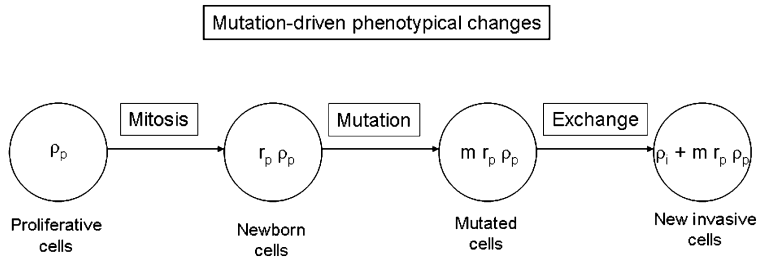

FIG. 4. Schematic representation of mutation-driven phenotypic changes (from the proliferative to the invasive phenotype). Cells that belong to the proliferative population (ρ_p) undergo mitosis and the newborn cells ($r_p\rho_p$) are subject to mutation events. The mutation of the appropriate combination of genes leads to the change of phenotype in $mr_p\rho_p$ cells.

much less than the proliferative ones, i.e. the invasive proliferation rate is less than the proliferative one, $r_i < r_p$. We assume that mutations are responsible for the change of phenotypes, and the rate of change of phenotypes depends solely on the mutation rate. The mechanism of mutation-driven phenotypic changes is depicted in Fig. 4. In particular, let cells that belong to jth population undergo mitosis with a constant rate r_j. Mutations occur in the newborn cells of population j and the proportion of cells that change to phenotype k is $m_j r_j p_j$, where $j \neq k$ and $j, k \in \{p, i\}$. It is plausible to consider that $m_i = m_p = m$ since there is no reason to assume that mutations favour just one direction. The following system of equations describes the time evolution of the two phenotypes:

$$\frac{d\rho_p}{dt} = \overbrace{r_p\rho_p}^{\text{proliferation}} + \overbrace{mr_i\rho_i}^{\text{gain i}\to\text{p}} - \overbrace{mr_p\rho_p}^{\text{loss p}\to\text{i}} - \overbrace{d_p\rho_i}^{\text{death}}, \tag{2.1}$$

$$\frac{d\rho_i}{dt} = \overbrace{r_i\rho_i}^{\text{proliferation}} + \overbrace{mr_p\rho_p}^{\text{gain p}\to\text{i}} - \overbrace{mr_i\rho_i}^{\text{loss i}\to\text{p}} - \overbrace{d_i\rho_i}^{\text{death}}. \tag{2.2}$$

The total tumour population at time t is given by the sum of the two phenotypes, i.e. $\rho(t) = \rho_p(t) + \rho_i(t)$. Please note that the above model 'overestimates' the total tumour growth for long times. However, this simple model suffices to demonstrate our hypothesis. In the following, we investigate some resection scenarios.

Let us assume that a GBM tumour of 10^9 cells is resected up to 99.9%, i.e. the postoperative glioma population counts up to 10^6 invasive tumour cells, i.e. the initial conditions after the resection are

TABLE 1 *Parameters for the mutation model. The proliferative rates of the invasive phenotype found in Stein et al. (2007) refer to an in vitro culture of glioma cells. In Giese et al. (2003), the invasive phenotype exhibits lower apoptotic rates than the proliferative one. Here, we assume one order of magnitude difference between the two apoptotic rates*

Parameter	Notation	Value	Reference
Mitotic rate of proliferative phenotype	r_p	10^{-1} days^{-1}	Spencer *et al.* (2004)
Mitotic rate of invasive phenotype	r_i	10^{-2} days^{-1}	Stein *et al.* (2007)
Apoptotic rate of proliferative phenotype	d_p	10^{-2} days^{-1}	Spencer *et al.* (2004)
Apoptotic rate of invasive phenotype	d_i	10^{-3} days^{-1}	Giese *et al.* (2003)

$(r_p(0), r_i(0)) = (0, 10^6)$, where $t = 0$ is the resection time. From the literature, we can determine, approximately, the values of the mitotic and apoptotic rates for both phenotypes (Table 1).

Firstly, we assume that no phenotypic changes are required to achieve full recurrence, i.e. $m = 0$. In this limit case, we investigate if the invasive cells alone are able to reproduce the resected tumour. After 180 days, the total population accounts for $\rho(t = 180) \propto 10^7$ cells, i.e. the recurrent tumour is two orders of magnitude smaller than the initial one. Therefore, we conclude that for the full tumour recurrence, in a time interval of 180 days, the contribution of proliferative cells is required, i.e. the occurrence of phenotypic changes of tumour cells from the invasive to the proliferative phenotype ($m > 0$).

Now, our aim is to determine the minimal value of the phenotypic change rate m, based on mutations, that implies a fully recurrent tumour within six months $t = 180$ days. From the model, we calculate the minimal rate that allows for a full recurrence as $m_{\min} = 10^{-3}$ changes/cell division. However, such a phenotypic change rate based on mutations is completely unrealistic. The probability of randomly mutating a specific combination of genes, that is related to a specific phenotypic change, is very low. For example, if we assume that changing a phenotype requires the mutation of N genes out of 30000 (approximate total number of genes in humans), then the probability of this phenotypic change is $p = 1 \Big/ \binom{3 \times 10^4}{N} < 10^{-4}$. In particular, let us assume that the 'minimal' requirement that a tumour cell switches phenotype is a point mutation ($N = 1$), i.e. $p = 1/30000 \propto 10^{-4}$. In the literature, it is assumed that the 'maximum mutation rate' is 0.01 mutation/gene/cell division (Spencer *et al.*, 2004). Therefore, the maximum phenotypic change rate is estimated as $m_{\text{lit}} = \{\text{rate of finding the right gene}\} \times \{\text{rate of mutations per gene}\} \propto 10^{-4} \times 10^{-2} = 10^{-6}$, i.e. three orders of magnitude larger than $m_{\min}$. Thus, this fact leads us to the conclusion that the switch between proliferative and invasive phenotype cannot be 'only' mutation driven. Consequently, we can assume that a further mechanism should be responsible for this phenotypic change. At this point, we would like to remind that we have used a model that overestimated the growth and the upper bounds of the related parameters. Even under these assumptions, the overestimated tumour growth of our model cannot explain the clinically observed recurrence solely on the basis of mutations. In the following, we develop an LGCA to test our hypothesis that the response of the 'Go or Grow' mechanism to hypoxia, i.e. oxygen shortage, can trigger the switch from a proliferative to a motile phenotype and *vice versa*.

3. The LGCA model

3.1 *The LGCA concept*

In this study, we use a special type of cellular automaton, called LGCA. The strength of the LGCA method lies in unravelling the potential effects of movement and interaction of individuals (e.g. cells).

In traditional cellular automaton models, the implementation of individual movement is not straightforward, as one node in the lattice can typically contain only one individual. Consequently, movement of individuals can cause, e.g. collisions when two individuals want to move into the same empty node. However, classical cellular automata tackle the same problem in different ways, where several of them are described in Boccara (2004). In a lattice-gas model, this problem is avoided by having separate channels for each direction of movement. The channels specify the direction and magnitude of movement, which may include zero velocity (resting) states. For example, a square lattice has four non-zero velocity channels and an arbitrary number of rest channels. Additionally, LGCA impose an 'exclusion principle' on channel occupation, i.e. each channel may at most host one individual.

Typically, the transition rule of an LGCA, that defines the automaton dynamics, can be decomposed into two steps (operators). An 'interaction' step updates the state of each channel at each lattice site. For instance, individuals may change their velocity state (reorientation) and appear or disappear (kinetics) as long as they do not violate the exclusion principle. In the 'propagation' step, individuals move synchronously into the direction and by the distance specified by their velocity state. The propagation step is deterministic and conserves mass and momentum. Synchronous transport prevents individual collisions which would violate the exclusion principle (other models have to define a collision resolution algorithm). LGCA models allow parallel synchronous movement and fast updating of a large number of individuals.

3.2 *Nomenclature and definitions*

We consider an LGCA defined on a 2D regular lattice $\mathcal{L} = L_1 \times L_2 \subset \mathbb{Z}^2$, where L_1 and L_2 are the lattice dimensions. Tumour cells move on the discrete lattice with discrete velocities, i.e. they hop at discrete time steps $k \in \mathbb{N}$ from a given node to a neighbouring one, as determined by the 'single cell speed'. A set of velocity channels $(\mathbf{r}, \mathbf{c}_i)$, $i = 1, \ldots, b$, is associated with each node $\mathbf{r} \in \mathcal{L} \subset \mathbb{Z}^2$ of the lattice. The parameter b is the 'coordination number', i.e. the number of velocity channels on a node which coincides with the number of nearest neighbours on a given lattice. The set of velocities for the square lattice as considered here is represented by the 2D channel velocity vectors $\mathbf{c_1} = \begin{pmatrix}1\\0\end{pmatrix}$, $\mathbf{c_2} = \begin{pmatrix}0\\1\end{pmatrix}$, $\mathbf{c_3} = \begin{pmatrix}-1\\0\end{pmatrix}$, $\mathbf{c_4} = \begin{pmatrix}0\\-1\end{pmatrix}$. In each of these channels, we consider an exclusion principle, i.e. we allow at most one cell per channel. We denote by $\tilde{b} = b + \beta$ the total number of channels per node which can be occupied simultaneously, where β is the number of channels with zero velocity, the rest channels $\mathbf{c_i} = \begin{pmatrix}0\\0\end{pmatrix}$, $i = b + 1, \ldots, \tilde{b}$. We represent the channel occupancy by a Boolean random variable called 'occupation number' $\eta_i(\mathbf{r}, k) \in \{0, 1\}$, where $i = 1, \ldots, \tilde{b}$ for cancer particles, $\mathbf{r} = (r_x, r_y) \in \mathcal{L} \subset \mathbb{Z}^2$ the spatial variable and $k \in \mathbb{N}$ the time variable. The $\tilde{b}$-dimensional vector

$$\boldsymbol{\eta}(\mathbf{r}, k) := (\eta_1(\mathbf{r}, k), \ldots, \eta_{\tilde{b}}(\mathbf{r}, k)) \in S$$

is called 'node configuration' and $S = \{0, 1\}^{\tilde{b}}$ the automaton 'state space'. 'Node density' is the total number of cells present at a node $\mathbf{r} \in \mathcal{L}$ and denoted by

$$n(\mathbf{r}, k) := \sum_{i=1}^{\tilde{b}} \eta_i(\mathbf{r}, k).$$

3.3 *The microenvironment: oxygen concentration*

We assume that the number of tumor cells supported in a node is proportional to the available oxygen on that node. In this study, oxygen is assumed to be homogeneously distributed on the lattice and replenished to a given constant value at each time step. We define the parameter $C \in [0, \tilde{b}]$ that represents the 'maximum node occupancy' which depends on the oxygen availability. We would like to stress that the parameter C plays a crucial role.

3.4 *Tumour cell dynamics*

In our model, cell dynamics are modelled by a set of automaton rules (operators): propagation (P), reorientation (O) and kinetics (R). In particular, the reorientation and the propagation operators dictate the cell transport and the cell kinetics operator controls the change of the local number of cells on a node through a birth/death process. The composition $\mathrm{R} \circ \mathrm{O} \circ \mathrm{P}$ of the three operators is applied independently at every node of the lattice at each time step. The cell dynamics are subjected to the following assumptions:

- A1 Tumour cells move randomly.
- A2 Mitotic and apoptotic rates depend on the local cell density.
- A3 The 'Go or Grow' mechanism influences the birth/death process (mitosis/apoptosis) of the tumour cells (for details see below).

3.4.1 *Propagation* (P) Cell translocation on the substrate is modelled by the propagation step. The propagation step is deterministic and is governed by an operator P. By the application of P, all cells are transported simultaneously to nodes in the direction of their velocity, i.e. a cell residing in channel $(\mathbf{r}, \boldsymbol{c}_\mathrm{i})$ at time $k \in \mathbb{N}_0$ is moved to a neighbouring channel $(\mathbf{r} + m\boldsymbol{c}_\mathrm{i}, \boldsymbol{c}_\mathrm{i})$ during one time step. Here, $m \in \mathbb{N}$ determines the speed and $m\mathbf{c}_\mathrm{i}$ is the translocation of the cell. The cells residing on the rest channel do not move as they have zero velocity. In terms of occupation numbers, the state of a channel $(\mathbf{r} + m\boldsymbol{c}_\mathrm{i}, \boldsymbol{c}_\mathrm{i})$ after propagation becomes

$$\eta_\mathrm{i}^\mathrm{P}(\mathbf{r} + m\boldsymbol{c}_\mathrm{i}, k + \tau) = \eta_\mathrm{i}(\mathbf{r}, k),$$

where τ is the time step of the LGCA. We note that the propagation operator is mass and momentum conserving.

3.4.2 *Reorientation* (O) The reorientation operator is responsible for the redistribution of cells within the velocity channels of a node, providing a new node velocity distribution. In this paper, we assume that individual cells perform random walks. This implies a random redistribution of the cells among the node's channels. The stationary[1] transition probabilities are

$$\mathbb{P}(\boldsymbol{\eta} \to \boldsymbol{\eta}^\mathrm{O})(\mathbf{r}, \cdot) = \frac{1}{Z}\delta\left(n(\mathbf{r}, \cdot), n^\mathrm{O}(\mathbf{r}, \cdot)\right), \tag{3.1}$$

where the normalization factor $Z = \sum_{\boldsymbol{\eta}^{\mathrm{O}}(r,\cdot)} \delta(n(\mathbf{r}, \cdot), n^\mathrm{O}(\mathbf{r}, \cdot))$ corresponds to the equivalence class defined by the value of the preinteraction node density $n(\mathbf{r}, \cdot)$. The Kronecker δ assumes the mass conservation of this operator. Our choice for the reorientation operator is one out of various possible

[1] The transition probabilities are independent of the time variable (indicated by a dot in the respective formulae).

ways to describe random motion by means of LGCA (Chopard & Droz, 1998; Deutsch & Dormann, 2005). The particular choice of the rule greatly simplifies the subsequent analytical derivation of the equations describing the meso- and macroscopic evolution of the automaton.

3.4.3 *Cell kinetics* (R) In our model, tumour cells are allowed to proliferate and to undergo apoptosis. The migration/proliferation dichotomy plays a crucial role in the definition of these processes. Moreover, the oxygen supply influences the individual cell's apoptotic rate. In detail, we define a stochastic birth–death process for the tumour cells as follows:

- Mitosis: Abnormal proliferation is a principle characteristic of cancer cells. Cells proliferate according to a 'carrying capacity-limited' proliferation mechanism (alternatively called 'space-inhibited proliferation'). The carrying capacity density reflects cell crowding effects, i.e. cells proliferate when the cell density is below carrying capacity but proliferation ceases when the cell density reaches the capacity density. For the creation of a new cell on a node, the existence of at least one cell and at least one free channel are required (A2), i.e.:

$$\mathcal{R}_i(\mathbf{r},\cdot) = \xi_i(\mathbf{r},\cdot)(1-\eta_i(\mathbf{r},\cdot)), \tag{3.2}$$

  where $\xi_i(\mathbf{r},\cdot)$'s are random Boolean variables, with $\sum_{i=1}^{\tilde{b}} \xi_i(\mathbf{r},\cdot) = 1$, and the corresponding probabilities are

$$\mathbb{P}(\xi_i(\mathbf{r},\cdot)=1) = r_{\mathrm{m}} \frac{\sum_{i=1}^{\tilde{b}} \eta_i(\mathbf{r},\cdot)}{\tilde{b}}. \tag{3.3}$$

  Here, r_{m} is the probability of occupying a channel, if at least one cell exists on the node. The proliferation rate r_{m} cannot be deliberately chosen. Growth of tumour cells is dictated by the 'Go or Grow' mechanism (A3), which means that cells are allowed to proliferate only when they rest, i.e. when they are positioned on a rest channel. Therefore, we can conclude that the proliferation rate is proportional to the number of rest channels β, i.e.

$$r_{\mathrm{m}} = \beta \bar{r}_{\mathrm{m}}, \tag{3.4}$$

  where $\bar{r}_{\mathrm{m}}$ is a base cell proliferation rate.

- Apoptosis: We assume that oxygen availability implies a maximum node occupancy C, i.e. the node oxygen supply cannot support more than C living tumour cells. Thus, we define an apoptotic rate for each tumour cell that ensures the existence of at most C cells per node:

$$r_d = \frac{\tilde{b}-C}{\tilde{b}} \beta \bar{r}_{\mathrm{m}}, \tag{3.5}$$

  where the factor $\frac{\tilde{b}-C}{\tilde{b}}$ is a dimensionless quantity. Note that the apoptotic rate is monotonically increasing with respect to β, i.e. the number of rest channels.

Both mitotic and apoptotic cell rates depend on the number of rest channels β. We will later demonstrate that the parameter β (number of rest channels) can be interpreted as the ratio of motility versus proliferation 'strength' which characterizes the tumour cell phenotype. Moreover, cells with proliferative phenotypes, i.e. large β, possess larger apoptotic rates and cells with invasive phenotypes lower apoptotic rates (see (3.5)), respectively. This interpretation is consistent with experimental observations

which indicate that, due to the migration/proliferation dichotomy (A3), invasive cells with 'low propensity to proliferate also may be resistant to apoptosis' (Giese *et al.*, 2003).

4. Simulations

In this study, the principle question concerns the regulation mechanisms that trigger the switch from proliferative to invasive phenotypes. The 'Go or Grow' mechanism imposes a relation between cell motility and proliferation. The crucial quantity is the total number of cells after a given period of time since this quantifies the success of a phenotype for a given oxygen level, i.e. defines the 'fitness' of the tumour in a given 'environment'. The control parameters are β as a phenotype parameter and C as an environmental parameter. The systematic variation of β allows us to identify the most successful phenotype in an environment characterized by C. In the following, we provide the simulation results.

Firstly, we have simulated our LGCA model on a 2D 500×500 lattice for 1000 time steps. In Fig. 5, we show simulations for variations of the number of rest channels $\beta = \{2, \ldots, 8\}$ (and $\tilde{b} = \{6, \ldots, 12\}$, respectively), for fixed maximum occupancy $C = \tilde{b}$ and for fixed base proliferation rate $\bar{r}_{\mathrm{m}} = 0.05$. The initial condition comprises just a small disc in the center. From the simulations, we conclude the following:

- The pattern evolving from a localized initial occupation is an isotropically growing disc.
- Simulations indicate a moving front along which the occupancy of the initially empty nodes is increasing from zero cells to the maximum occupancy C.
- Increasing the number of rest channels, we observe that the emerging disc decreases in size since the cells become less motile. Moreover, the infiltration zone, i.e. the region between the periphery of the

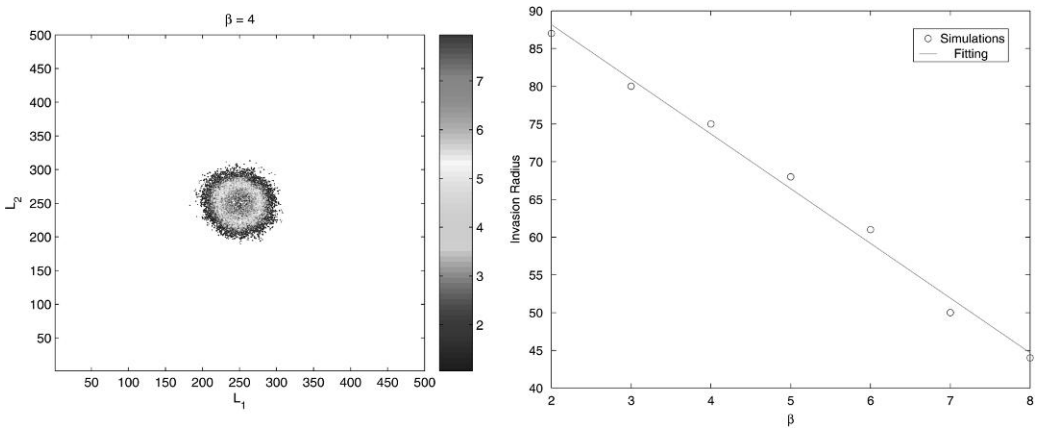

FIG. 5. Left: Typical tumour pattern after 1000 time steps. For maximum occupancy $C = \tilde{b}$ and for a fixed proliferation rate $r_{\mathrm{m}} = 0.05$ and with $\beta = 4$ rest channels (and $\tilde{b} = 8$). The initial tumour mass was located in the center of the lattice. The colours encode the node density. Right: Infiltration radius against phenotype. For maximum occupancy $C = \tilde{b}$ and for a fixed base proliferation rate $r_{\mathrm{m}} = 0.05$, we show how the invasive radius varies by increasing the number of rest channels β, i.e. by making the tumour cells more proliferative. We observe a linear decrease of the infiltration radius as β increases.

disc and the beginning of the core (maximum occupancy region) shrinks as β increases (right panel of Fig. 5).

In order to get a deeper insight into the effects of the 'Go or Grow' mechanism on tumour progression, we use a different simulation set-up. We consider a 'tube', especially a 2000×100 lattice with periodic boundary condition on the L_2-axis and a thin stripe of tumour cells as initial condition. A typical simulation time lasts for 2000 time steps. The result of our simulations is a propagating 2D front along the L_1-axis, mimicking a 'growing tube'. This setting has the following advantages:

- We project our system to 1D by averaging the concentration profile along the L_2-axis, i.e. $n(r_x, k) = \frac{1}{|L_2|} \sum_{r_y \in |L_2|} n(\mathbf{r}, k)$.
- The front is well defined as the mean position of the foremost cells.
- The interface diffusion, i.e. the front width variation, relaxes faster to an equilibrium than in the case of discoidal 2D evolution.
- The front profile relaxes to an almost time-invariant shape, which translates almost uniformly along the L_1-axis.

We simulate our system for different combinations of the parameters $\beta = \{1, \ldots, 6\}$ and $C = 6, 7, 8$ (we fix the base proliferation rate to $\bar{r}_{\mathrm{m}} = 0.05$). For these parameter combinations, we measure the total number of cells after the above-mentioned typical simulation time. The most interesting results are the following:

1. The total number of cells evolves linearly in time.
2. For each C isocline, i.e. 'isonutrient curve', we obtain a maximum value of the total number of cells for a unique β (Fig. 6). This implies that the fittest phenotype for a given oxygen supply C is unique.
3. Figure 6 shows that under hypoxic conditions, i.e. after lowering the oxygen supply C, the fittest phenotype corresponds to the invasive one, i.e. higher motility and lower proliferation (low β).
4. Moreover, in Fig. 6, we observe that a proliferative population (high β) can give rise to a lower number of offspring cells than populations of motile populations, i.e. low β, with lower proliferative rates. This result shows that the best strategy of cells in scarce environments is the faster exploration of new territories and the lowering of the proliferation rates.

Observations (2) and (3) confirm our main hypothesis that the response of the 'Go or Grow' mechanism to a hypoxic environment favours the emergence of invasion.

At this point, we return to the case of glioma tumour recurrence. We have demonstrated that mutation-based phenotypic changes alone are insufficient to explain the speed of glioma recurrence. Therefore, an alternative hypothesis for the mechanisms that control the tumour phenotypic transitions is required. We claim that the switch from a proliferative to a motile phenotype is controlled by the interplay of the 'Go or Grow' mechanism and the local oxygen supply. In particular, we claim that an increase in the oxygen supply can accelerate the transition rates from an invasive to a proliferative phenotype (Fig. 6). Especially in the case of the tumour bulk resection, the oxygen availability rises abruptly back to normoxic levels. This can trigger our proposed mechanism and consequently increase the transition rates towards a proliferative phenotype. Finally, this leads to an increase of the proportion of proliferative cells and the acceleration of the recurrent tumour's growth rates.

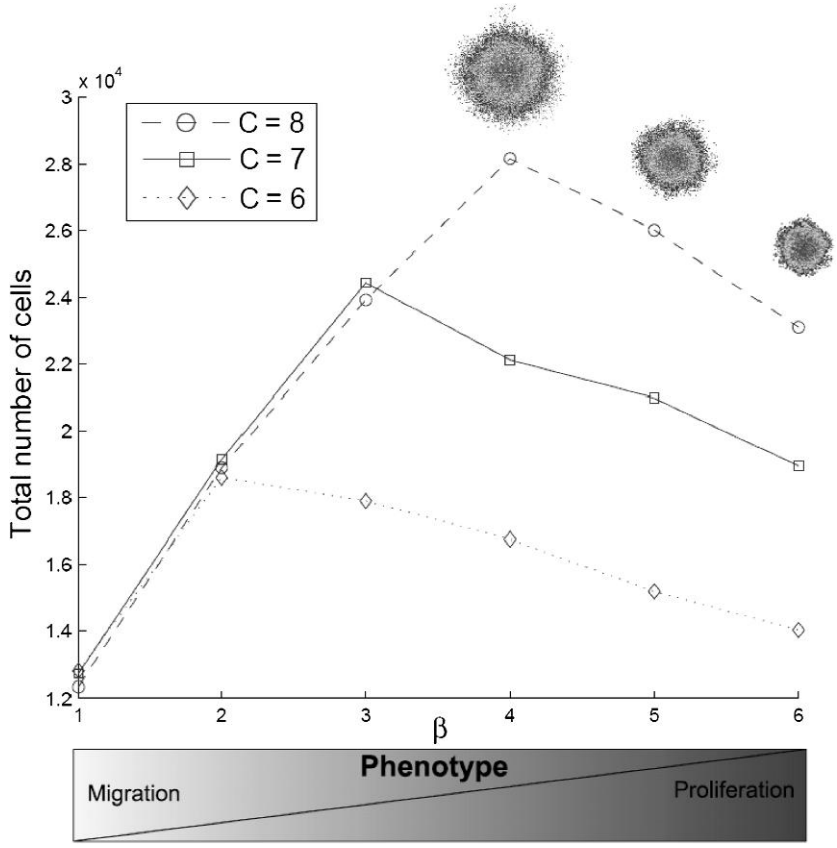

FIG. 6. Optimal tumour strategy depending on microenvironmental conditions. On the x-axis, we vary the parameter β, which characterizes the tumour cell phenotype, ranging from motile populations (β small) to proliferative ones (β large). Each of the curves represents an isonutrient, i.e. the behaviour of the population under the same oxygen availability. We observe that each isonutrient curve has a maximum, which corresponds to the best fitted phenotype (β) in this specific environmental setting.

5. Analysis

In this section, we provide the results of the mean-field analysis of our model which leads to partial differential equation that describes the collective behaviour of our LGCA. The goal is to derive an average cell diffusion coefficient and proliferative rate, which together define the average phenotype of the population. This mathematical analysis allows for the generalization of our numerical results. Note that the mathematical details of our analysis can be found in the "Supplementary material" of our paper.

In order to derive a macroscopic description, corresponding to the collective behaviour of the whole tumour cell population, we use the Chapman–Enskog methodology (Chopard & Droz, 1998). Here, we define the 'mean node density' as

$$\rho(\mathbf{r}, k) = \langle n(\mathbf{r}, k) \rangle.$$

Note that the average $\langle \cdots \rangle$ is defined over an arbitrary node distribution at a given time k. The main assumption of our method is the diffusive scaling of space and time, i.e.

$$\mathbf{x} = \epsilon \mathbf{r} \quad \text{and} \quad t = \epsilon^2 k, \tag{5.1}$$

where $(\mathbf{x}, t)$ are the continuous variables as $\epsilon \to 0$. Working out the mathematical details, we derive a macroscopic description of our system which belongs to the class of Fisher–Kolmogorov equations:

$$\partial_t \rho = \frac{m^2}{\tilde{b}\tau} \nabla^2 \rho + \frac{\beta \bar{r}_{\mathrm{m}} C}{\tau \tilde{b}} \rho (1 - \rho). \tag{5.2}$$

Note that (5.2) is valid only for very small mitotic rates, i.e. $\bar{r}_{\mathrm{m}} \ll 1$[2]. The macroscopic proliferation and motility rates are identified by $\tilde{r}_{\mathrm{m}}$ and D, respectively,

$$\tilde{r}_{\mathrm{m}} = \frac{\beta \bar{r}_{\mathrm{m}} C}{\tau \tilde{b}}, \tag{5.3}$$

$$D = \frac{m^2}{(b + \beta)\tau}. \tag{5.4}$$

We observe that the 'Go or Grow' mechanism is manifested in the above macroscopic coefficients since the proliferation rate (5.3) is monotonically increasing with respect to the number of rest channels (the more resting cells, the greater the proliferation rate) and the diffusive coefficient (5.4) is monotonically decreasing (more resting cells induce reduced motility). Finally, using (5.3) and (5.4), we confirm that the parameter β characterizes the population phenotype since it is proportional to the ratio of proliferation and diffusion rate, i.e.

$$\beta \propto \frac{\tilde{r}_{\mathrm{m}}}{D}. \tag{5.5}$$

6. Discussion

Here, we have investigated potential mechanisms that may promote the progression from benign neoplasms to malignant invasive tumours characterized by high migration rates. Traditionally, the tumour progression is assumed to be mutation driven. Here, we propose that the "Go or Grow" mechanism and oxygen shortage in a growing tumour are sufficient to trigger the switch from a proliferative to an invasive phenotype in some cells. Our hypothesis can be considered as a consequence of phenotypic plasticity and microenvironmental effects on the emergence of tumour phenotypes (Anderson *et al.*, 2006; Merlo *et al.*, 2002; Quaranta *et al.*, 2008). In particular, a correlation of a hypoxic environment with the emergence of invasive phenotypes has only been observed so far in game theoretical studies based on mutation-driven evolution, such as Basanta *et al.* (2008a,b). Recently, in the biomathematical literature, several studies discuss the variations of migration and proliferation with respect to tumour progression (Chauviere *et al.*, 2009; Enderling *et al.*, 2009; Thalhauser *et al.*, 2009; Wang *et al.*, 2009). The need for an alternative hypothesis is prominent in the case of GBM recurrence after surgery. Our investigation showed that the sole assumption of mutation-driven tumour progression is insufficient to explain the fast GBM recurrence after resection. To test our new hypothesis, we set up an LGCA model. We represent the tumour phenotype by a single parameter β corresponding to the ratio between proliferative and motility rates. The tumour's microenvironment is represented by the oxygen concentration C, which is a crucial model parameter that influences the proliferative ability and the apoptotic rate

[2]This is a result of the scaling of the growth term, i.e. $r_{\mathrm{m}} = \epsilon^2 \tilde{r}_{\mathrm{m}} \ll 1$, where $\tilde{r}_{\mathrm{m}} \propto \mathrm{O}(1)$.

of tumour cells. The parameter β plays a key role in the modelling of the 'Go or Grow' mechanism since its value is related to the proliferation rate of the cells. Interestingly, the apoptotic rate (3.5) is monotonically increasing with respect to the parameter β, implying that invasive cells (low β) with low propensity to proliferate also may be resistant to apoptosis (Giese *et al.*, 2003). Finally, our model exhibits the intriguing behaviour that invasive phenotypes, which show microscopically low proliferation and high motility, may produce more offspring than phenotypes with much higher proliferation rates. This may explain, in part, the rapid expansion rates of some invasive tumours.

6.1 *Biological evidence*

Hypoxia is a common feature of most cancers. Recently, several biological studies have linked hypoxia to the invasive behaviour of tumours. In particular, it has been observed that hypoxia is responsible for down-regulation of cadherins, resulting is the disruption of cell–cell adhesive interactions, the promotion of invasive and metastatic behaviour (Sullivan & Graham, 2007) and the reduction of the proliferative activity (Daruwalla & Christophi, 2006). These biological observations support our hypothesis that hypoxia triggers the switch from a proliferative to an invasive phenotype.

The dependence of the invasion/proliferation switch on the oxygen level suggests that the regulatory network responsible for the control of mitosis and migration may share common signalling pathways with the oxygen uptake network. Candidate molecular mechanisms that link hypoxia to invasive behaviour have already been suggested. In particular, it has been found that in glioma cell lines, hypoxia induces the expression of the c-Met protein which enhances glioma cell migration and invasiveness (Eckerich *et al.*, 2007). The hypoxia induced factor protein has been recognized as a key molecule responsible for the hypoxia-induced tumour invasiveness (Fujiwara *et al.*, 2007).

Finally, a recent publication Godlewski *et al.* (2010) qualitatively confirms our main result, i.e. that migration/proliferation dichotomy is regulated by the levels of the metabolic stress. In particular, they claim that abundance of nutrients allows for the high expression of miR-451 which promotes high proliferation. On the other hand, in scarce environments miR-451 levels are decreased slowing the proliferation and enhancing the migration of the glioma cells.

6.2 *'Go or Grow' strategies in nature*

Interestingly, in ecology, we can identify a correlation of increased motility and species extinctions (Viswanathan *et al.*, 2008). In particular, high motility strategies seem to confer a vital advantage in the limit of low densities—at the edge of extinction. Actually, empirical data indicate that some insects (Sisterson & Averill, 2002) and fish (Lamine *et al.*, 2005) near starvation increase their movement intensity and diffusiveness in the search for food when compared to their foraging activity under normal conditions. Under scarce environmental conditions, species presenting such behaviour can have an adaptive advantage.

Finally, also in the field of social psychology, the evolutionary benefits of a motile strategy have been observed. In particular, Aktipis (2004, 2008) have analysed a so-called 'walk away' strategy that promotes the evolution of cooperation and confers significant advantages to the fitness of the whole population. It is based on the notion that individuals can leave regions, partners or groups that are insufficiently productive, which can be done by simply coopting foraging adaptations. In general, we can claim that the 'Go or Grow' strategy is a cognitively simple, evolutionary ancient, phylogentically widespread and well known in nature.

6.3 *Therapy*

Clinically, hypoxia correlates with an adverse prognosis and renders tumour cells more resistant to radiation and chemotherapy (Daruwalla & Christophi, 2006; Kizaka *et al.*, 2003). Hence, improving tumour oxygenation may result in better treatment outcomes. This paradigm has been investigated in numerous clinical studies (Daruwalla & Christophi, 2006). Our results point to a different therapeutic paradigm that could potentially be applied to many cancers. Certain brain tumours (gliomas) are a typical example for invasive and diffusive tumours. Gliomas not only proliferate but also actively invade the surrounding brain parenchyma. The surgical resection of these diffusive tumours will not result in a cure since the cancer cells have already invaded the surrounding healthy and functional brain tissue. This leads to recurrence of the tumour in all but a few cases. The prognosis for patients suffering from malignant gliomas is very poor. It has been suggested (Giese *et al.*, 2003) that invasive glioma cells are able to revert to a proliferative cellular program and *vice versa*, depending on the environmental stimuli. Our model suggests that reactivation of the proliferative program of invasive tumour cells by increasing oxygen tension (medical term for oxygenation) in the tumour will enhance the dominance of proliferative over the motile phenotypes. The result will be a tumour characterized by a more confined growth pattern and lower expansion speed. The analysis of our model shows that the switch from a motile to a proliferative phenotype will not lead to a faster growing neoplasm. Quite to the contrary, overall tumour growth will slow down. Hence, this therapeutical strategy may directly improve the patient's prognosis. It may also allow for more radical and therefore successful tumour resection. Finally, Gatenby proposed a similar perspective in designing new therapeutic strategies for controlling tumour growth instead of trying to eradicate the tumour cells (Gatenby, 2009).

Supplementary material

Supplementary material is available at http://www.imammb.oxfordjournals.org/.

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References

AKTIPIS, A. (2004) Know when to walk away: contingent movement and the evolution of cooperation. *J. Theor. Biol.*, **231**, 249–260.

AKTIPIS, A. (2008) When to walk away and when to stay: cooperation evolves when agents can leave unproductive partners and groups. *Ph.D. Thesis*, University of Pennsylvania, Philadelphia, PA.

ANDERSON, A. R., WEAVER, A. M., CUMMINGS, P. T. & QUARANTA, V. (2006) Tumor morphology and phenotypic evolution driven by selective pressure from the microenvironment. *Cell*, **127**, 905–915.

ATHALE, C., MANSURY, Y. & DEISBOECK, T. (2006) Simulating the impact of a molecular decision-process on cellular phenotype and multicellular patterns in brain tumors. *J. Theor. Biol.*, **239**, 516–527.

BASANTA, D., HATZIKIROU, H. & DEUTSCH, A. (2008a) Studying the emergence of invasiveness in tumours using a game theory. *Eur. Phys. J. B*, **63**, 393–397.

BASANTA, D., SIMON, M., HATZIKIROU, H. & DEUTSCH, A. (2008b) An evolutionary game theory perspective elucidates the role of glycolysis in tumour invasion. *Cell Prolif.*, **41**, 980–987.

BOCCARA, N. (2004) *Modeling Complex Systems*. New York: Springer.

CHAUVIERE, A., PREZIOSI, L. & BYRNE, H. (2009) A model of cell migration within the extracellular matrix based on a phenotypic switching mechanism. *Math. Med. Biol.*, **27**, 255–281.

CHOPARD, B. & DROZ., M. (1998) *Cellular Automata Modeling of Physical Systems*. Cambridge: Cambridge University Press.

DARUWALLA, J. & CHRISTOPHI, C. (2006) Hyperbaric oxygen therapy for malignancy: a review. *World J. Surg.*, **30**, 2112–2131.

DEUTSCH, A. & DORMANN, S. (2005) *Cellular Automaton Modeling of Biological Pattern Formation*. Boston, MA: Birkhäuser.

ECKERICH, C., ZAPF, S., FILLBRANDT, R., LOGES, S., WESTPHAL, M. & LAMSZUS, K. (2007) Hypoxia can induce c-met expression in glioma cells and enhance sf/hgf-induced cell migration. *Int. J. Cancer.*, **15**, 276–283.

ENDERLING, H., HLATKY, L. & HAHNFELDT, P. (2009) Migration rules: tumours are conglomerates of self-metastases. *Br. J. Cancer*, **100**, 1917–1925.

FANG, J., GILLIES, R. & GATENBY, R. (2008) Adaptation to hypoxia and acidosis in carcinogenesis and tumor progression. *Semin. Cancer Biol.*, **18**, 330–337.

FEDOTOV, S. & IOMIN, A. (2007). Migration and proliferation dichotomy in tumor-cell invasion. *Phys. Rev. Lett.*, **98**, 118101–118104.

FUJIWARA, S., NAKAGAWA, K., HARADA, H., NAGATO, S., FURUKAWA, K., TERAOKA, M., SENO, T., OKA, K., IWATA, S. & OHNISHI, T. (2007) Silencing hypoxia-inducible factor-1α inhibits cell migration and invasion under hypoxic environment in malignant gliomas. *Int. J. Oncol.*, **30**, 793–802.

GATENBY, R. A. (2009) A change of strategy in the war on cancer. *Nature*, **459**, 508–509.

GATENBY, R. A. & GILLIES, R. J. (2004) Why do cancers have high aerobic glycolysis? *Nat. Rev. Cancer.*, **4**, 891–899.

GIESE, A., BJERKVIG, R., BERENS, M. & WESTPHAL, M. (2003) Cost of migration: invasion of malignant gliomas and implications for treatment. *J. Clin. Oncol.*, **21**, 1624–1636.

GIESE, A., KLUWE, L., LAUBE, B. & BERENS, M. E. (1996a) Migration of human glioma cells on myelin. *Neurosurgery*, **38**, 755–764.

GIESE, A., LOO, M. A., TRAN, D., HASKETT, S. W. & COONS, B. M. E. (1996b) Dichotomy of astrocytoma migration and proliferation. *Int. J. Cancer*, **67**, 275–282.

GODLEWSKI, J., NOWICKI, M. O., BRONISZ, A., NUOVO, G., PALATINI, J., LAY, M. D., BROCKLYN, J. V., OSTROWSKI, M. C. & CHIOCCA, E. A. (2010) Microrna-451 regulates lkb1/ampk signaling and allows adaptation to metabolic stress in glioma cells. *Mol. Cell*, **37**, 620–632.

HANAHAN, D. & WEINBERG, R. (2000) The hallmarks of cancer. *Cell*, **100**, 57–70.

HATZIKIROU, H., DEUTSCH, A., SCALLER, C., SIMON, M. & SWANSON, K. (2005) Mathematical modelling of glioblastoma tumour development: a review. *Math. Models Methods Appl. Sci.*, **15**, 1779–1794.

KIZAKA, S., INOUE, M., HARADA, H. & HIROKA, M. (2003) Tumor hypoxia: a target for selective cancer therapy. *Cancer Sci.*, **94**, 1021–1028.

LAMINE, K., LAMBIN, M. & ALAUZET, C. (2005) Effect of starvation on the searching path of the predatory bug deraeocoris lutescens. *BioControl*, **50**, 717–727.

MANSURY, Y., DIGGORY, M. & DEISBOECK, T. (2006) Evolutionary game theory in an agent-based brain tumor model: exploring the genotype-phenotype link. *J. Theor. Biol.*, **238**, 146–156.

MERLO, L., PEPPER, J., REID, B. & MALEY, C. (2002) Cancer as an evolutionary and ecological process. *Nat. Rev. Cancer*, **2**, 924–935.

QUARANTA, V., REJNIAK, K. A., GERLEE, P. & ANDERSON, A. R. A. (2008) Invasion emerges from cancer cell adaptation to competitive microenvironments: quantitative predictions from multiscale mathematical models. *Semin. Cancer Biol.*, **250**, 705–722.

SISTERSON, M. S. & AVERILL, A. L. (2002) Costs and benefits of food foraging for a braconid parasitoid. *J. Insect Behav.*, **15**, 571–588.

SPENCER, S. L., BERRYMAN, M. J., GARCIA, J. A. & ABBOTT, D. (2004) An ordinary differential equation model for the multistep transformation to cancer. *J. Theor. Biol.*, **231**, 515–524.

STEIN, A. M., DEMUTH, T., MOBLEY, D., BERENS, M. & SANDER, L. K. (2007) A mathematical model of glioblastoma tumor spheroid invasion in a three-dimensional in vitro experiment. *Biophys. J.*, **92**, 356–365.

SULLIVAN, R. & GRAHAM, C. H. (2007) Hypoxia-driven selection of the metastatic phenotype. *Cancer Metastasis Rev.*, **26**, 319–331.

TEKTONIDIS, M., HATZIKIROU, H., CHAUVIERE, A., SIMMON, M., SCHALLER, C. & DEUTSCH, A. (2011) Identifications of the intrinsic mechanisms for glioma tumor invasion. *J. Theor. Biol.*, **287**, 131–147.

THALHAUSER, C. J., SANKAR, T., PREUL, M. C. & KUANG1, Y. (2009) Explicit separation of growth and motility in a new tumor cord model. *Bull. Math. Biol.*, **71**, 585–601.

VISWANATHAN, G. M., RAPOSO, E. P. & DA LUZ, M. G. E. (2008) Levy flights and superdiffusion in the context of biological encounters and random searches. *Phys. Life Rev.*, **5**, 133–150.

WANG., S. E., HINOW, P., BRYCE, N., WEAVER, A. M., ESTRADA, L., ARTEAGA, C. L. & WEBB, G. F. (2009) A mathematical model quantifies proliferation and motility effects of TGF-β on cancer cells. *Comput. Math. Methods Med.*, **10**, 71–83.