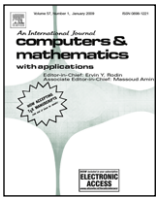
Computers and Mathematics with Applications 59 (2010) 2326–2339

Contents lists available at ScienceDirect

Computers and Mathematics with Applications

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



Prediction of traveling front behavior in a lattice-gas cellular automaton model for tumor invasion

H. Hatzikirou [a,*], L. Brusch [a], C. Schaller [c], M. Simon [b], A. Deutsch [a]

[a] Center for Information Services and High Performance Computing, Technische Universität Dresden, Nöthnitzerstr. 46, 01069 Dresden, Germany

[b] Department of Neurosurgery, University of Bonn Medical Center, Sigmund-Freud-Str. 25, 53105 Bonn, Germany

[c] Department of Neurosurgery, University Hospital of Geneva, 24 Rue Micheli-du-Crest, 1211 Geneva, Switzerland

ARTICLE INFO

Keywords:
Tumor invasion
Lattice-gas cellular automata
Lattice Boltzmann equation
Traveling fronts
Cut-off mean-field approximation

ABSTRACT

Cancer invasion is the process of cells detaching from a primary tumor and infiltrating the healthy tissue. Cancer invasion has been recognized as a complex system, since a tumor's invasive behavior emerges from the combined effect of tumor cell proliferation, tumor cell migration and cell–microenvironment interactions. Cellular automata (CA) provide simple models of self-organizing complex systems in which collective behavior can emerge out of an ensemble of many interacting "simple" components. Here, we introduce a lattice-gas cellular automaton (LGCA) model of tumor cell proliferation, necrosis and tumor cell migration. The impact of the tumor environment on tumor cells has been investigated in a previous study. Our analysis aims at predicting the velocity of the traveling invasion front, which depends upon fluctuations that arise from the motion of the discrete cells at the front. We find an excellent agreement between the velocities measured in simulations of the LGCA and an analytical estimate derived in the cut-off mean-field approximation via the discrete Lattice Boltzmann equation and its linearization. In particular, we predict the front velocity to scale with the square root of the product of probabilities for mitosis and the migration coefficient. Finally, we calculate the width of the traveling front which is found to be proportional to the front velocity.

1. Introduction

Cancer describes a group of genetic and epigenetic diseases, characterized by uncontrolled growth of cells, leading to a variety of pathological consequences and frequently death. Cancer has long been recognized as an evolutionary disease [1]. Cancer progression can be depicted as a sequence of traits or phenotypes that cells have to acquire if a neoplasm (benign tumor) is to become an invasive and malignant cancer. A phenotype refers to any kind of observed morphology, function or behavior of a living cell. Hanahan and Weinberg [2] have identified six cancer cell phenotypes: unlimited proliferative potential, environmental independence for growth, evasion of apoptosis, angiogenesis, invasion and metastasis.

In this article, we concentrate on the behavior of the invasive phenotype. The progression of a benign tumor with limited growth to a tumor that is invasive and potentially metastatic is the major cause of poor clinical outcome in cancer patients, in terms of therapy and prognosis. Understanding tumor invasion could potentially lead to the design of novel therapeutical strategies. However, despite the immense amounts of funds invested in cancer research, the dynamics that govern tumor invasiveness *in vivo* remain poorly understood.

* Corresponding author.
E-mail address: haralambos.hatzikirou@tu-dresden.de (H. Hatzikirou).

0898-1221/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.camwa.2009.08.041

Biomedically, invasion involves the following tumor cell *processes*:

- tumor cell migration, which is a result of down-regulation of cadherins[1] and corresponding loss of cell–cell adhesion,
- tumor cell–extracellular matrix (ECM)[2] interactions, such as cell-ECM adhesion, and ECM degradation/remodeling, by means of proteolysis. These processes allow for the penetration of the migrating tumor cells into host tissue barriers, such as basement and interstitial stroma [3], and
- tumor cell proliferation.

Tumor invasion facilitates the emergence of metastases, i.e. the spread of cancer cells to another part of the body and the formation of secondary tumors. It is obvious that tumor invasion comprises a central aspect in cancer progression. However, invasive phenomena occur not only in pathological cases of malignant tumors but also during normal morphogenesis and wound healing. In this study, we focus on the impact of tumor cell migration and proliferation on invasive behavior. The effect of the tumor environment on tumor cells, and in particular on the migration of tumor cells, has been discussed in a previous study by the authors [4].

Several mathematical models have been proposed to describe the temporal or spatio-temporal dynamics of tumor proliferation and invasion. Much of the experimental data that exists has been modeled using purely time-dependent growth laws based on the assumption of either exponential or Gompertzian growth [5]. Additionally, the spatio-temporal evolution of a proliferative tumor cell population has been modeled as a behavior that emerges from local micro-interactions [6]. Deterministic reaction–diffusion models have been used to model the spatio-temporal growth of tumors, usually assuming that tumor growth is a wave propagation phenomenon [7–11] and is driven by random movement of malignant cells [12]. Swanson et al. [13] modeled proliferation and migration of brain tumors based on actual clinical data. Recently, innovative methods have been developed by employing a mathematical and computational model that describes tumor growth and invasion [14].

Whilst these models are able to capture the tumor structure at the tissue level they fail to describe the tumor at the cellular and the sub-cellular levels. Cellular automata (CA) models can provide such a micro-scale description and allow a more realistic stochastic approach at the cellular level. In particular, Hatzikirou et al. [15] present a detailed review of cellular automata of tumor invasion. We introduce a particular class of CA with a structure that allows for a feasible mathematical analysis, the so-called lattice-gas cellular automata (LGCA) [16,17]. In contrast to traditional cellular automata, LGCA allow for a straightforward and intuitive implementation of cell migration and interactions. LGCA have been recently used to study tumor growth [18], cell motion under the influence of a heterogeneous environment [4] and the investigation of brain tumor invasion [19].

In this paper we combine a detailed micro-scale model with an analysis of the corresponding macro-scale approximation. We describe a simple LCGA model of interacting tumor cells and "necrotic entities". LGCA provide a concrete framework to conduct analytical and numerical analysis [16,20,21]. By means of a mean-field approximation, we are able to derive a macroscopic partial differential equation (PDE) describing our system. This equation characterizes the spatio-temporal tumor expansion at the tissue level. Introducing a cut-off in the mean-field macroscopic description allows for a quantitative characterization of the traveling wavefront. We calculate analytically the front speed and we compare it with the values derived from simulations. This analysis enables us to estimate tumor spreading by known tumor cell features, such as cell motility and proliferation rate. Finally, we provide an analytical estimate of the front width and we demonstrate that it is proportional to the front speed.

2. Model definition

2.1. Prerequisites

We consider a lattice-gas cellular automaton defined on a two-dimensional regular lattice $\mathcal{L} = L_1 \times L_2 \in \mathbb{Z}^2$, where L_1, L_2 are the lattice dimensions. Let b denote the coordination number of the lattice, that is $b = 4$ for a square lattice. Cells move on the discrete lattice with discrete velocities, i.e. they hop at discrete time steps from a given node to a neighboring one, as determined by the cell velocity. The set of velocities for the square lattice as considered here, is represented by the two-dimensional channel velocity vectors

$$\mathbf{c}_1 = \begin{pmatrix} 1 \\ 0 \end{pmatrix}, \qquad \mathbf{c}_2 = \begin{pmatrix} 0 \\ 1 \end{pmatrix}, \qquad \mathbf{c}_3 = \begin{pmatrix} -1 \\ 0 \end{pmatrix}, \qquad \mathbf{c}_4 = \begin{pmatrix} 0 \\ -1 \end{pmatrix}, \qquad \mathbf{c}_5 = \begin{pmatrix} 0 \\ 0 \end{pmatrix}.$$

In each of these channels, we consider an exclusion principle, i.e. we allow at most one cell per channel. We denote by $\tilde{b} = b + b_0$ the total number of channels per node which can be occupied simultaneously, where b_0 is the number of channels with zero velocity (rest channels), here $b_0 = 4$.[3] In our LGCA, we represent healthy tissue by the empty channels and we

[1] Cadherins: Important class of transmembrane proteins. They play a significant role in cell–cell adhesion, ensuring that cells within tissues are bound together.

[2] Extracellular matrix: Components that are surrounding cells and composed of secreted fibrous proteins (e.g. collagen) and gel-like polysaccharides (e.g. glycosaminoglycans) binding cells and tissues together.

[3] The value of the number of rest channels b_0 is defined upon scaling of the model to a corresponding experiment or *in vivo* situation. Since the model is not representing any specific experiment, the choice of b_0 remains arbitrary here and qualitatively identical results were obtained for tests with different choices.