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REGULAR ARTICLE

Lattice-Gas Cellular Automaton Models for Biology: From Fluids to Cells

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Abstract Lattice-gas cellular automaton (LGCA) and lattice Boltzmann (LB) models are promising models for studying emergent behaviour of transport and interaction processes in biological systems. In this chapter, we will emphasise the use of LGCA/LB models and the derivation and analysis of LGCA models ranging from the classical example dynamics of fluid flow to clotting phenomena in cerebral aneurysms and the invasion of tumour cells.

Keywords Lattice-gas cellular automaton · Lattice Boltzmann model · Discrete dynamical system · Tumour invasion · Blood clotting · Collective behaviour

1 Introduction

Cellular automata (CA) are discrete, local dynamical systems. They have been introduced by J. v. Neumann and S. Ulam in the 1950s as collective model of individual reproduction. During the last years it has become clear that CA have a much broader potential as models for physical, chemical and biological systems. In particular, CA models have now been proposed for a large number of biological applications in which one is interested in the emergence of collective macroscopic

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behaviours arising from the microscopic interaction of individual components—being it molecules, cells or organisms. However, there are drawbacks: currently, there exists a huge jungle of different rules for often the same or similar processes. Therefore, there is need for a specification and classification of CA rules. Wolfram made a promising start with the classification of 1D automata. Furthermore, analysis of CA models is still rather limited and often restricted to visual superficial inspection of simulation outcomes.

In the same spirit as CA, lattice-gas cellular automaton (LGCA) and lattice Boltzmann (LB) models are promising models for studying transport and interaction processes in biological systems (Chopard and Droz 1998; Deutsch and Dormann 2005; Wolf-Gladrow Dieter 2000). In these models the update rule is split into two parts which are called collision (interaction) and propagation, respectively. The collision rule of LGCA can be compared with the update rule for CA in that it assigns new states to each cell based on the states of the sites in a local neighborhood. After the collision step the state of each node is propagated to a neighboring node. This split of the update rule guarantees propagation of quantities while keeping the rules simple. The desired behaviour, e.g. spatio-temporal pattern formation of a LGCA shows up in the macroscopic limit which can be derived from a theory of statistical mechanics on a lattice. Instead of discrete particles, LB models deal with continuous distribution functions which interact locally and which propagate after "collision" to the next neighbour node.

In this chapter, we will emphasise the use of LGCA/LB models and the derivation and analysis of LGCA models ranging from the classical example dynamics of fluid flow to clotting phenomena in cerebra and the invasion of tumour cells.

2 LGCA for Fluid Flows

LGCA were introduced by Hardy et al. (1973; HPP) as simple systems of classical particles in order to study approach to equilibrium, time correlation functions, and transport phenomena in fluids. The term 'cellular automata' is never mentioned in HPP. LGCA allowing fluid flow simulations were introduced one decade later by Frisch et al. (1986, FHP) who used the term 'lattice-gas cellular automata' and by Wolfram (1986) who used the term "cellular automaton fluids" and considered cellular automata as discrete analogues to molecular dynamics. The Boolean dynamics of LGCA avoids amplification of round-off errors and thus is unconditional stable. Local interaction and propagation allows very efficient integrations on massively parallel computers.

The dynamics of fluids in the real world is based on the interaction of molecules. Despite the complicated paths of the molecules their interaction respects local conservation of mass and momentum. On the macroscopic level fluid flows obey partial differential equations, namely the continuity and Navier-Stokes equations. The form of these equations can actually be derived from conservation of mass and momentum alone via the Chapman-Enskog expansion. The viscosity depends, however, on details of the interaction. Scaling length and velocity by characteristic

scales of the flow leads to a dimensionless form of the Navier-Stokes equation that is characterized by the dimensionless Reynolds number $R_e = \frac{LU}{\nu}$, where L is the characteristic length scale, U is the characteristic velocity scale, and ν is the kinematic viscosity of the fluid. The law of dynamic similarity states that two flows behave similar when the scaling leads to the same geometry and Reynolds number. Thus, the transition from laminar to turbulent flow in similar geometry occurs at the same Reynolds number for fluids as different as air and water.

The basic idea of LGCA for simulation of fluid flow is to construct a simple artificial micro-world of particles which interact while conserving mass and momentum. The most simple dynamical systems are provided by cellular automata (CA) which are discrete in space, time, and state. CA develop in time by update rules identical and synchronous for each cell. The state s_i^{t+1} of cell i at time $t + 1$ is a function of the states of cell i and of n neighboring cells 1, 2, ..., n at time t, i.e. $s_i^{t+1} = f\left(s_i^t, s_1^t, s_2^t, \ldots, s_n^t\right)$.

In order to use CA to simulate flows one has to define mass and momentum in the artificial micro-world. For convenience let us consider identical cells that completely fill an unbounded checkerboard. Each cell is in one of two possible states: empty or occupied. The definition of mass of a single cell is quite obvious: empty cells possess mass zero, occupied cells possess unit mass. The definition of momentum requires the introduction of vectors. A possible choice are the links between the cell centre and the centres of its nearest neighbors. In this way each cell would possess several vectors and it it not obvious how to single out a momentum vector. HPP (Hardy et al. 1973) added an explicit lattice structure to the simple array of CA to solve this problem. They considered a square lattice and set one cell at each link of a lattice node to its nearest neighbor (Fig. 1). Thus each cell possesses a single vector that connects two lattice nodes. These vectors are called 'lattice velocities' , $\mathbf{c}_j$ (Fig. 1, upper right). Momentum can now be defined for each cell simply as mass times lattice velocity.

Update rules for LGCA have to conserve mass and thus cannot be defined for single cells because any change between empty and occupied violates mass conservation. One has to choose a small bunch of cells and update them together (which is different from synchronous updating) $\left(s_1^{t+1}, s_2^{t+1}, \ldots, s_n^{t+1}\right) = F\left(s_1^t, s_2^t, \ldots, s_n^t\right)$. The joint update of all cells at a node is an obvious choice. For the sake of simplicity the uptake rules depend on this bunch of cells only.

An obvious question is: Do nontrivial update rules exist, i.e. can one find transitions between different joint states that conserve mass and momentum? For the HPP model there exists just one nontrivial transition which can be interpreted as the collision (or scattering) of two particles that leads to a rotation by 90° (head-on collision, Fig. 1, middle right).

The collision step changes the states of cells at a single node but has no impact on the state of cells at other nodes. The propagation of mass and momentum to neighboring nodes has to be implemented explicitly: after the collision step each particle (=occupied cell) is transfered along the links to the nearest neighbor node (Fig. 1), i.e. mass and momentum propagates like in a gas between collisions. The complete update rule consists of a collision step followed by propagation.

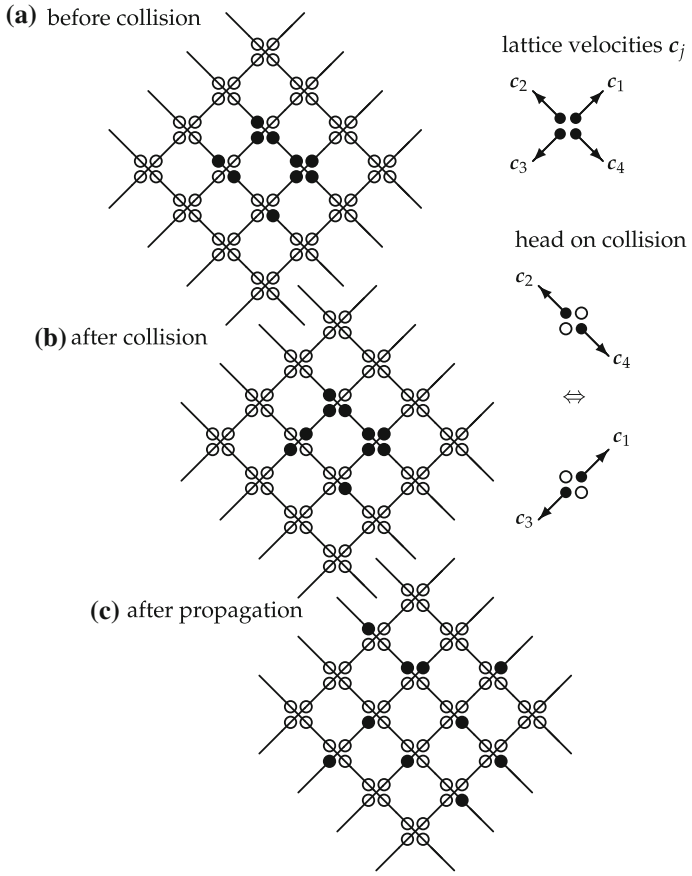

Fig. 1 HPP: collision and propagation. *Filled circles* denote occupied cells and *open circles* empty cells. The lattice velocities $\mathbf{c}_j$ are shown in the *upper right*. Head-on collision leads to rotation of particles by 90° (*middle right*). **a** Part of the lattice before collision (e.g. after propagation); there is only one collision configuration (two particles in opposite cells at the same node; on the left). **b** After collision (e.g. before propagation): the configuration of the cells at one node has changed. **c** After propagation: all particles have moved along the links to their nearest neighbors (the lattice outside the part shown was assumed to be empty, e.g. no propagation of particles from 'outside')

Macroscopic mass and momentum density are calculated by coarse-graining (averaging over larger domains including order of 1000 lattice sites). It came at a surprise that the HPP recipe does not lead to Navier-Stokes in the macroscopic limit: the non-linear advection term is non-isotropic. It took one decade to identify the cause of this problem: insufficient lattice symmetry. Frisch, Haslacher, and Pomeau (Frisch et al. 1986) could show that a sixfold symmetry in two dimensions is large enough to yield an isotropic advection term.

There is no single-speed lattice with sufficient symmetry in three dimensions. Frisch et al. (1986) and Wolfram (1986) proposed to use the face-centered hypercube in 4D and to project onto 3D. The collision rules for this LGCA with 24 lattice velocities per node and thus $2^{24} = 16777216$ possible states per node are quite

complicated (Hénon 1987; Rem and Somers 1989; Somers and Rem 1989). An alternative for 3D simulations is the pair interaction model by Nasilowski (1991) that uses a simple cubic lattice for the prize of separate cells for mass and momentum components.

LGCA for the simulation of fluid flows have been applied very successfully. In order to avoid the noise in LGCA simulations that stems from the Boolean dynamics, lattice Boltzmann (LB) models have been developed first as an extension of LGCA. Further developments of LB methods have led to models that are much more flexible than LGCA and that allow, for example, to simulate turbulent (high Reynolds number) flows (Succi 2001; Wolf-Gladrow Dieter 2000), and literature cited therein). Although in fluid dynamics LGCA have been largely replaced by LB methods, the splitting of CA update rules in interaction and propagation is very useful in other fields, for example if one is interested in the dynamics of interacting cells (Sect. 4).

3 The Lattice Boltzmann Approach to Simulate Clotting in Cerebral Aneurysms

Aneurysms are abnormal bubble-like local deformations of a blood vessel (see Fig. 2). Under some circumstances which are still not well understood, they may rupture and cause patient death. Among the causes that impact the growth and evolution of aneurysms, it is well accepted that haemodynamics plays a central role (Humphrey 2001).

A natural mechanism of self-repair is the occurrence of thrombosis inside the aneurysm which eventually leads to the cavity occlusion. Since recently, stent (see Fig. 2) endovascular procedures are considered as a promising non-invasive technique to canalize the blood flow in the parent vessel, thus reducing flow in the aneurysm and promoting thrombosis (Hirabayashi et al. 2003) therein.

A lattice Boltzmann based numerical model for blood flow and blood clotting in a vessel on which an aneurysm has grown has been proposed first in (Ruefenacht et al. 2007; Ouared and Chopard 2005) while more mathematical insight has been given recently in (Chopard et al. 2005). In this approach, we are interested in capturing the large time and space scales hence ignoring a molecular level description. We will consider a mesoscopic model only including the features that

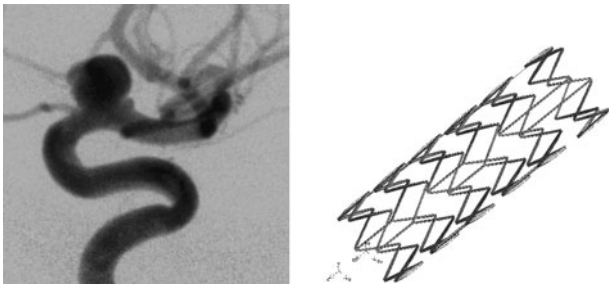

Fig. 2 *Left* an aneurysm from an angiogram. *Right* illustration of a stent

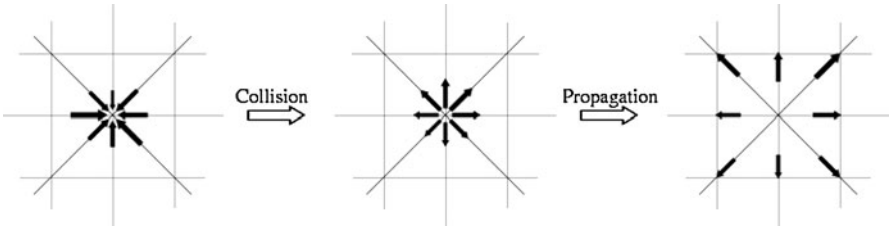

Fig. 3 Illustration of the collision and propagation phases in a LB model defined on a 2D square lattice (the so-called D2Q9 model). The size of the *arrows* is proportional to the density of particles entering the lattice site along the corresponding direction. As suggested by the figure, mass and momentum are conserved in the collision process

are relevant to the aneurysm occlusion. Such a simulation tool will be of central importance to predict the evolution of thrombogenesis within an aneurysm, be it driven by anatomy or/and by stents.

Here, blood flow is described by a lattice Boltzmann (LB) fluid model. The LB method is an extension of the lattice-gas cellular automata discussed previously (see Sect. 2), where the state of the cells is described by real-valued variables instead of Boolean ones. Figure 3 illustrates one time iteration δ_t of a 2D LB-fluid model, at a given spatial location r. It can be shown that running the process described in Fig. 3 is equivalent to model a fluid flow provided that the collision step is properly chosen. More information on the LB method can be found in text books and reviews (Chen and Doolen 1998; Chopard and Droz 1998; Succi 2001; Wolf-Gladrow Dieter 2000).

On top of a LB-fluid model, the advection-diffusion of passive scalars can be added to include the transport of platelets and red blood cells. From the modeling point of view we describe these particles with a multiparticle cellular automaton (CA) (see Chopard and Droz 1998). At our description scale, clotting is simply the result of the aggregation of "blood particles", under suitable conditions.

Our central hypothesis is that clotting is initiated in low shear rate regions (Ruefenacht et al. 2007). There is clear evidence for endothelium dysfunction when the bloodflow does not produce a high enough shear rate at a vessel wall (Davis 1995). As a result, platelets can adhere on the sub-endothelium. Some biological studies (Bell et al. 1989; Moroi and Jung 1998; Williams and Nollert 2004) clearly show that platelets adhere and aggregate when the shear rate decreases. Platelet aggregation is then followed by the formation of a thrombus. The growth of this thrombus is maintained as long as the blood shear rate at the interface region remains low enough.

The above mechanisms can be translated rather easily in a LB-CA modeling framework (Ruefenacht et al. 2007; Chopard et al. 2005; Ouared and Chopard 2005). The clotting model is based on two shear rate thresholds: S_{start} below which clotting can starts at a wall and $S_{stop} \geq S_{start}$ above which the thrombus stops growing). These cutoff values are model parameters that eventually have to be obtained from biological studies.

Figure 4 shows the typical scenarios that can be expected from this model (assuming $S_{start} = S_{stop}$). When the threshold is low, clotting is almost nonexistent.

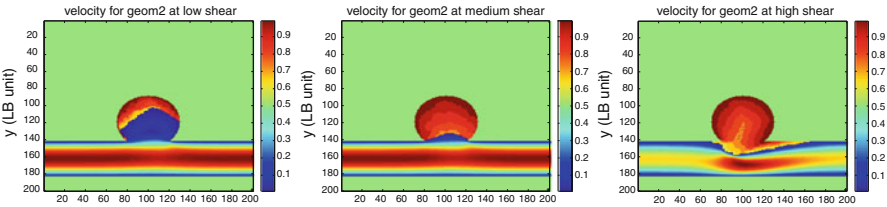

Fig. 4 Simulations of low-shear rate induced clotting in aneurysms, for various valued of the threshold $S_{start} = S_{stop}$

Such an aneurysm will not clot spontaneously and inserting a stent as a flow diverter is a solution to decrease the shear rate in the aneurysm below the clotting threshold. For higher values of the threshold, we observe partial or full clotting. If the threshold is too large, the clot can even invade the parent vessel. All the scenarios proposed in Fig. 4 are also observed in clinical investigations (Teng 2003; Whittle et al. 1982). In addition, the simulation shows that the clot forms in successive layers, a feature well observed in giant aneurysms that clot spontaneously.

Our LB simulations also indicate that the value of the shear rate at the aneurysm wall (be it endothelium or forming clot membrane) is related to the geometry of the cavity. A key parameter is the aspect ratio (ratio of the aneurysm diameter to its neck size). For small aspect ratios, the wall shear rate is higher than for large aspect ratios. That explains why giant aneurysms are likely to clot spontaneously (Teng 2003; Whittle et al. 1982) unlikewise for smaller aneurysms.

Figure 5 compares clinical observations with simulations and clearly suggests a critical value of the aspect ratio around 1.8. Aneurysms with aspect ratio below this value do not clot and are characterized by high shear rate value. On the other hand, aneurysms with high aspect ratios are subject to low wall shear rate and exhibit

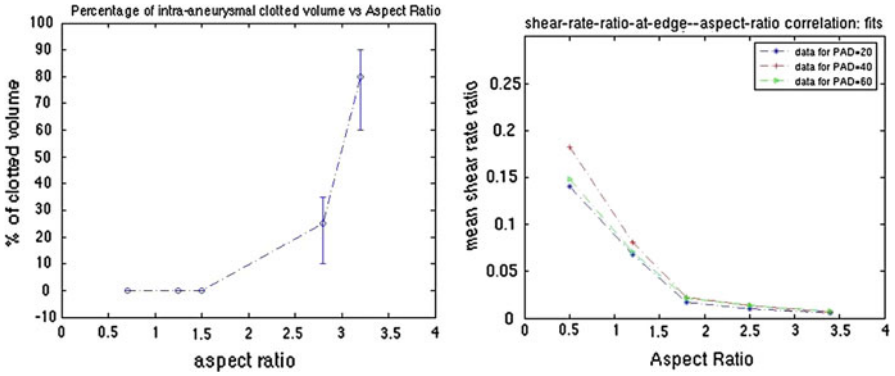

Fig. 5 *Left* clotting fraction as a function of the aneurysm aspect ratio (clinical observations by O. Brina, Hospital of Geneva). *Right* shear rate at the aneurysm wall as a function of the aspect ratio (LB simulations)

partial to full clotting. This observation provides a promising qualitative validation of our LB-CA model of clotting.

4 Lattice-Gas Cellular Automata Models for the Analysis of Tumor Invasion

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 (Nowell 1976). In particular, 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. Thereby, a phenotype refers to any kind of observed morphology, function or behavior of a living cell. Hanahan and Weinberg (2000) have identified six cancer phenotypes: unlimited proliferative potential, environmental independence for growth, evasion of apoptosis, angiogenesis, invasion and metastasis.

Here, we concentrate on 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. Biomedically, invasion involves the following tumor cell *processes*:

- tumor cell proliferation,
- tumor cell migration, which is a result of down-regulation of cadherins and corresponding loss of cell-cell adhesion, and
- tumor cell-extracellular matrix (ECM) 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 (Friedl 2004).

Our aim is to formulate a mathematical model that allows the prediction of tumor invasion behavior under controlled conditions. Our approach relies on a suitable abstraction of the tumor invasion problem. In particular, we restrict the tumor invasion problem to the *interplay* of the two main tumor cell processes, i.e. proliferation and migration. Our strategy is to describe the relevant phenomena that influence tumor cell migration and proliferation (e.g. ECM cues) at the cellular scale and to predict the emergent invasive tumor behavior at the macroscopic scale. Motivated by the success of the lattice-gas cellular automaton method to model interacting particles in a fluid in a very abstract form, which however facilitates prediction of macroscopic flow properties (see Sect. (2). We have extended the approach to a model of interacting cells in a heterogeneous environment (Hatzikirou and Deutsch 2008). In the following, we summarize our results with respect to the tumor invasion problem.

Firstly, we investigate the influence of tumor cell proliferation and migration on the invasive behavior in a homogeneous environment (i.e. we neglect effects of the ECM). The main question is how fast the tumor expands or, in other words, what is

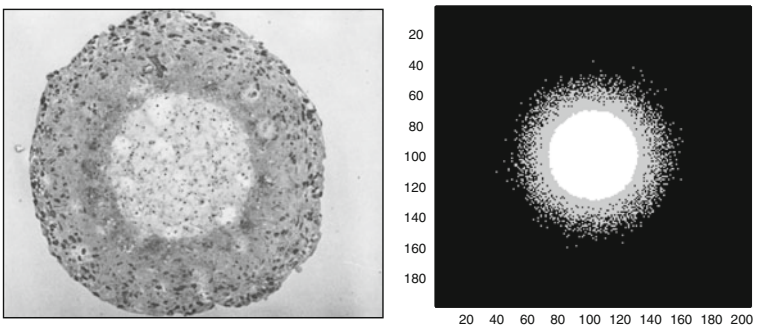

Fig. 6 *Left* Typical spatio-temporal pattern formation of in vitro tumors (reprinted with permission from Folkman and Hochberg (1973). One observes the presence of a necrotic core and an outer rim of proliferative tumor cells. *Right* LGCA simulations exhibit a similar structure. In the simulation, tumor cells are depicted in *grey*, necrotic entities in *white*, and empty nodes in *black*

the invasion speed of a tumor. Therefore, we develop a LGCA model of tumor cell proliferation, necrosis and tumor cell migration (see Fig. 6, (Hatzikirou et al. 2010) for details). Our analysis aims at predicting the velocity of the traveling invasion front, which strongly depends upon fluctuations that arise from the motion of the discrete cells at the front. We find an excellent quantitative 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 (LB) 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.

In a further model we have analyzed the influence of a heterogeneous microenvironment. The tumor microenvironment is a highly heterogeneous medium including the extracellular matrix composed of fibrillar structures, collagen matrices, diffusible chemical signals as well as other mobile and immobile cells (Friedl 2004). A LGCA model of cell migration together with a mathematical characterization of different biological environments can contribute to understand the interplay of moving cells with their heterogeneous environment (Hatzikirou and Deutsch 2008). In particular, we have shown how the mathematical analysis of the LGCA model can yield an estimate for the cell dispersion speed within a given environment.

The ultimate goal is to use mathematical models and corresponding simulations to predict invasion behavior in real patients. We have moved initial steps into this direction by focusing our attention to a very malignant and invasive brain tumor, namely glioblastoma multiforme tumor (or just gliomas). Glioma cells tend to spread faster along fiber tracks. Diffusion Tensor Imaging (DTI) is a Magnetic Resonance Imaging (MRI)-based method that provides the local anisotropy information in terms of diffusion tensors. High anisotropy points indicate the brain's white matter consisting of fiber tracks. A preprocessing of the diffusion tensor field can lead to the principle eigenvectors' extraction of the diffusion tensors, that provides us with the local principle axis of motion. By considering a

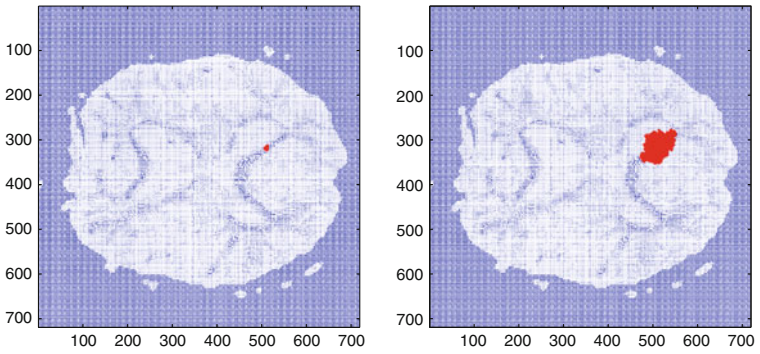

Fig. 7 Brain's fiber track effect on glioma growth. We use a LGCA of a proliferating cancer cell population moving in a tensor field provided by clinical DTI data, representing the brain's fiber tracks. *Left* Initial tumor mapped (*red*) on the DTI data of a real brain. *Right* Final state of tumor growth along the fiber tracks

proliferative cell population, like in (Hatzikirou et al. 2010), and using the resulting eigenvector field we can model and simulate glioma cell invasion. In Fig. 7, we simulate an example of glioma growth and show the effect of the fiber tracks in tumor growth using the DTI information.

Finally, in order to predict the spatio-temporal in vivo tumor invasion also quantitatively, we need to design parameter optimzation algorithms. Therefore, we developed an evolutionary algorithm (Tektonidis 2008) that estimates the parameters of a tumor growth LGCA model based on time-series of patient medical data (in particular MR and DT Imaging data). In the future, these parameters may allow to reproduce clinically relevant tumor growth scenarios for a specific patient, providing a prediction of the tumor growth at a later time stage.

5 Discussion

In this article, we have shown how lattice-gas cellular automaton and lattice Boltzmann (LB) models that originated in fluid dynamical applications can be extended to analyze important medical problems. In fluid dynamics LGCA has been replaced to a large extent by LB methods. However, mean-field methods such as LB methods do not provide a good description when spontaneous fluctuations and many-particle correlations play an essential role (compare (Deutsch and Dormann 2005), p.51). Spontaneous fluctuations and many-particle correlations might be important in various biological systems (e.g. in "small cellular systems" the number of cells is much smaller than the number of molecules in fluid flow) and thus LGCA models are advantageous compared to LB methods. Corresponding approximation methods are especially interesting if one is interested in predicting macroscopic behavior from a well-known mesoscopic behavior.

The need for discrete models, especially cellular automata, goes beyond the examples presented here. A discrete cell-oriented approach is required if the

dynamic system behaviour depends on fluctuations at the individual cell level. This is, for example, the case at the front of invading tumours and crucial for the formation of metastases. Lately, experimental findings of Bru et al. (2003) indicate that many tumors share the same surface dynamics. This finding motivated the analysis of the tumor interface by means of a fractal scaling analysis. Obviously, corresponding cancer models have also to be of a discrete nature and CA models are promising candidates to identify growth mechanisms that lead to a particular scaling.

Based on the variability in the local dynamics, we demonstrated that the "interaction-module oriented" cellular automaton modeling provides an intuitive and powerful approach to capture essential aspects of complex phenomena on various scales. In conclusion, there are both challenging future perspectives with regards to interesting biological applications of the lattice-gas cellular automaton idea and possible refinements of analytical tools for the investigation of lattice-gas cellular automata. Surely, the potential of cellular automata for modeling essential aspects of biological systems will be further exploited in the future.

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