HYBRID SIMULATION OF TUMOR GROWTH COMBINING CELLULAR AUTOMATA WITH CONTINUOUS STATE DYNAMICS

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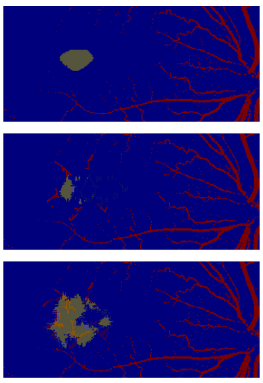
Abstract



Cellular Automaton theory has proved to be an innovative and reliable tool in describing complex processes such as tumor growth. The concept is extended with special interest on the extrusion of tissue with regard to angiogenesis. The model is divided into different components where the discrete states of the cellular automaton interact with the continuous states from the description of the nutrient supply. Computation of such models can be compared with clinical data from oncology and can provide a deeper understanding of tumor dynamics. The model under observation bases on an inhomogeneous nutrient supply and is able to simulate different supply scenarios. Therefore an arterial tree serves as input for the nutrient distribution. The supply is described by a diffusion process. The nutrient supply on the other hand serves as input for the cellular automaton which governs the growth of the simulated tumor. Angiogenesis is introduced by subsequent modification of the vascular network. The parameters are tuned to attain exponential growth with fixed growth factors in homogeneous environments. The model can be used to simulate tumor growth with a special focus on the effects of angiogenesis.

Keywords: Cellular Automaton, Alternative modeling, Tumor dynamics, Angiogenesis

Presenting Author's Biography

Daniel Leitner graduated in mathematics at the Technical University of Vienna. Currently he is working on his doctoral thesis about mesoscopic simulation of blood flow at the Austrian Research Centers. His research interests are numerical modeling, fluid dynamics in general, especially lattice Boltzmann methods and its application to biofluids.

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1 Introduction

Cellular Automata are used to describe the development of discrete entities. They are efficiently used in modeling of biological processes [1] [2] and were applied successfully to simulate tumor cell growth at microscopic level [3] [4]. In the description of tumor cell growth the nutrient supply plays a key role. The development of cells depends mainly on the nutrient concentration. Therefore the inhomogeneous nutrient supply of the tissue must be modeled accurately and reasonable haematocrit patterns have to be developed for the region of interest. Another emphasis must be placed on angiogenesis which changes the structure of the vascular tree and therefore the nutrient supply.

The model is calculated using three different lattices, which have the same spatial discretization and interact in various ways, see figure 1:

1. The first lattice represents the nutrient concentration. The nutrient distribution is described by a diffusion process. The diffusion is calculated with a Lattice Boltzmann model (LBM) which is a simple but for this application very stable explicit scheme.

2. In the second lattice the cells are simulated. This is the main component of the model. The cells are simulated with a cellular automaton which interacts with the other layers. In difference to models described in [4] or [5] the tumor growth is realized by displacement of other cells.

3. The third lattice describes the vascular arterial network. The network acts as a source for the nutrient distribution. With different arterial networks different supply scenarios can be simulated. The arterial network is influenced by angiogenesis. Angiogenesis is simulated with a Lattice Gas Cellular Automaton (LGCA) where the particles represent the Vascular endothelial growth factor (VEGF). Angiogenesis is strongly influenced by VEGF.

The first two lattices interact in both directions. The cells consume nutrients and on the other hand the nutrient concentration is a major input for the development of the cells. The cells interact with the arterial network because tumor cells create their own nutrient supply by angiogenesis. They do this by creating VEGF particles which lead to a vascular growth into the tumor. The arterial network acts as a source within calculation of the nutrient concentration in the first lattice.

All three components strongly interact. It is important that the lattices have the same spatial discretization but they are working on different time scales. In the following sections the three components of the model will be described in detail.

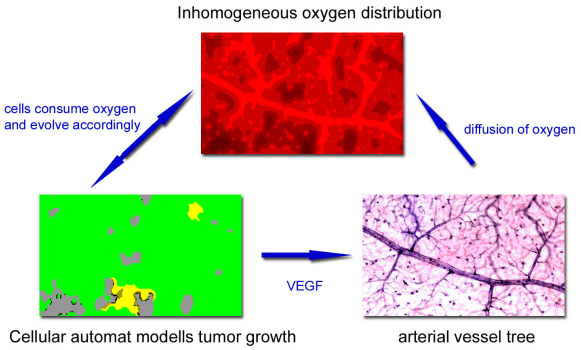

Fig. 1 Interaction of different layers

2 Modeling the nutrient distribution

The extracellular nutrient distribution is dependent on the arterial vascular tree. Nutrient diffuses from areas of high concentration to areas of low concentration, whereas the arterial vascular tree acts as supply system. Therefore the process is modeled by the diffusion equation where the vascular tree acts as a boundary condition:

$$\frac{\partial C(\mathbf{x},t)}{\partial t} = d\nabla^2 C(\mathbf{x},t) - k(\mathbf{x},t) \qquad (1)$$

where C is the concentration of extracellular nutrients, d is the diffusion coefficient and k the nutrient uptake rate at position $\mathbf{x}$.

This partial differential equation has complex and in consideration of angiogenesis alterable boundary conditions.It is solved with a lattice Boltzmann model (LBM) which was proposed in [6]. The main advantage of this method to normal explicit finite difference schemes is the higher stability and therefore bigger freedom in choosing the diffusion coefficient. The method will be shown for two spatial dimensions.

It is well known that 90 rotational invariance is enough to yield full isotropy for diffusive phenomena. Therefore the velocities are chosen in the following way:

$$\begin{aligned} \mathbf{c}_1 &= (1,0) \\ \mathbf{c}_2 &= (-1,0) \\ \mathbf{c}_3 &= (0,1) \\ \mathbf{c}_4 &= (0,-1) \end{aligned} \qquad (2)$$

The kinetic equation of lattice Boltzmann models is given by

$$C_i(\mathbf{x}+\mathbf{c}_i, t+1) = (1-\omega)C_i(\mathbf{x},t)\omega C_i^{(0)}(\mathbf{x},t) \qquad (3)$$

where $C_i(\mathbf{x},t) = C(\mathbf{c}_i,\mathbf{x},t)$ is the concentration in direction $\mathbf{c}_i$, $C_i^{(0)}$ is the equilibrium distribution and ω the collision frequency.

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Note that the concentration at position $\mathbf{x}$ can obtained by

$$C(\mathbf{x},t) = \sum C_i(\mathbf{x},t) \tag{4}$$

Conserved quantities and a linear ansatz shows that the equilibrium function can be chosen as

$$C_i^{(0)}(\mathbf{x},t) = \frac{C(\mathbf{x},t)}{4}, \qquad i = 1\ldots 4 \tag{5}$$

Multiscale expansion shows that the collision frequency ω is related to the diffusion coefficient in the following way:

$$k = \frac{1}{2}\left(\frac{1}{\omega} - \frac{1}{2}\right) \tag{6}$$

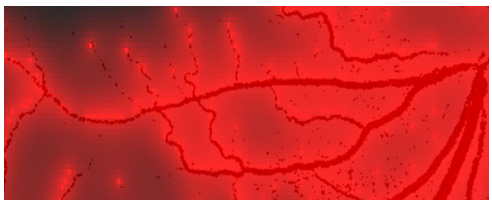

Fig. 2 The nutrient distribution is calculated as a diffusion process.

The resulting numerical scheme is used to calculate the nutrient distribution. Realistic geometries of vessel structures can be used as nutrient sources, see figure 2. The nodes that describe this sources are realized by setting their distribution function to a predetermined concentration c of the equilibrium distribution function 5 in every time step, thus

$$C_i^{source} = \frac{c}{4} \tag{7}$$

The nutrient uptake $k(\mathbf{x},t)$ is realized by simple subtraction of the concentration in every time step.

The vessel structure can be contained from tomographic images. A feasible lattice can be generated from binary segmentation of the image, see figure 5

The calculation the nutrient distribution depends not only on the chosen spatial and temporal discretization but although on parameters that shall be shortly summarized:

- Diffusion coefficient $D(\mathbf{x},t)$
- Uptake rates of different cell types $k(\mathbf{x},t)$.
- Concentration at the source nodes C^{source}

The right choice of the parameters will be discussed in section 5.

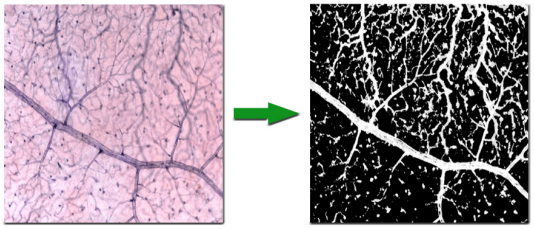

Fig. 3 A feasible lattice for LBM computation can be derived from tomographic images.

3 A cellular automaton for tumor growth

The cells are arranged on an equidistant quadratic grid. Since the lattice has the same spatial discretization as the nutrient distribution every cell has exactly one corresponding nutrient supply. The temporal discretization is done in a way that a time step is exactly the time the cells need for cell division.

Every cell has four different states:

1. Normal cells
2. Proliferative cancer cells
3. Quiescent cancer cells
4. Empty space or interstitium

The cellular automaton acts on a Moore neighborhood of 1. Basically cancer cells can grow in three different ways. They can be infiltrating, destructive or displace normal cells. The update rules of this work are based on ideas presented in [5] and [4] but in contrary to these works main focus lies on the displacement of cells. In the following the rules for every cell type is explained, the rules are dependent of the concentration $C(\mathbf{x},t)$.

3.1 Normal cells

If the nutrient supply sufficient is, thus the concentration $C(\mathbf{x},t)$ higher than a certain threshold T_n the cell stays a normal cell, otherwise the cell dies and is of the state 'empty cell' in the next time step.

3.2 Proliferative cancer cells

Proliferate cancer cells are unaltered if the nutrient supply is sufficient, thus the concentration $C(\mathbf{x},t)$ must be higher than a certain threshold T_c. Otherwise the cancer cell enters a quiescent state, thus changes its state to 'quiescent cancer cell'.

Proliferate cancer cells divide with a certain potability P_{div} per time step which is linearly related to the cells

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nutrient supply $C(\mathbf{x}, t)$ and a growth rate g, thus

$$P_{div} = C(\mathbf{x}, t)g \tag{8}$$

Note that in case of homogeneous nutrient supply, thus $C(\mathbf{x}, t) = const$, from an initial value c_0 of cancer cell the number of cells develop according to

$$cells(t) = c_0 \left(1 + P_{div}\right)^t, \tag{9}$$

thus arbitrary exponential growth can be achieved, see figure 4. As a result the growth factor g can be determined from in vitro experiments where the growth of a layer of tumor cells is under investigation.

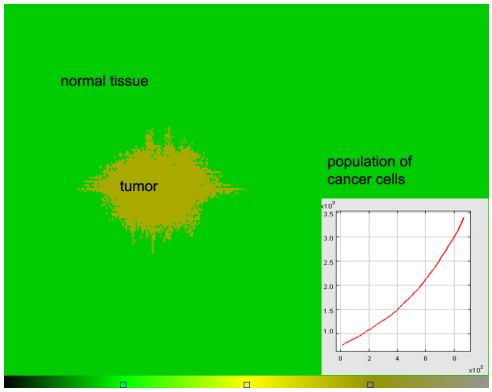

Fig. 4 Under an homogeneous nutrient supply the cancer cells grow exponentially

When a cancer cell divide there are two possible situations. One is that a neighboring cell is empty, then the empty cell will be a 'proliferative cancer cell' in the next time step. When no neighboring cell is empty the cellular automaton is stopped and all three lattices of the components of the model are altered. First randomly a direction of growth is chosen. From the position of the cancer cell depending on the this direction a column or row is shifted for one node. The new free neighbor of the cancer cell is set to to the state 'proliferative cancer cell'. In the nutrient lattice the free node is that to the average of the surrounding nodes and in the lattice containing the vessels the node is set to empty.

The displacement of all in all geometries is of major importance when angiogenesis is considered. In the simulation of tumor grow the tumor displaces its the existing supply system. When the tumor gets larger it starts to create its own supply system by angiogenesis.

3.3 Quiescent cancer cells

Quiescent cancer cells stay quiescent when the nutrient supply $C(\mathbf{x}, t)$ stays under the threshold value T_c. If the nutrient supply stays under this value for a certain time span T_q the quiescent cell dies, thus switches to the state 'empty'. If the nutrient supply is higher than the threshold value it gets active again and switches to the sate 'proliferate cancer cell'.

Note that quiescent cancer cells are not able to divide. They act as sources for the VEGF particles in the corresponding lattice used to simulate angiogenesis, see section 4. Thus the quiescent cancer cells alter the nutrient supply system by sending VEGF particle which enforce the vessel growth towards the quiescent cells.

3.4 Empty space or interstitium

An empty cell only changes its state when a neighboring cell wants to divide into it. In this work growth of normal cells is neglected, thus only proliferate cancer cells can divide into the empty cell.

The cellular automaton needs different parameters. The parameters shall be shortly summarized.

- Two threshold values expressing the dependency on the nutrient density $C(\mathbf{x}, t)$: T_n for normal cells, T_c for proliferate cancer cells
- The growth rate g of proliferate cells.
- The time span T_q that an quiescent cell survives.

4 Modeling angiogenesis

Angiogenesis is modeled with the help of a modified LGCA, see [6]. The particles represent the vascular endothelial growth factor (VEGF). They stream freely on a lattice with nine velocities, see figure 5, according to the operator

$$n_i(\mathbf{x}) = n_i(\mathbf{x} - \mathbf{e}_i), \qquad i = 0 \ldots 8 \tag{10}$$

where $\mathbf{x}$ is the lattice node, n_i is a boolean value (occupied or not) and $\mathbf{e}_i$ are the lattice velocities.

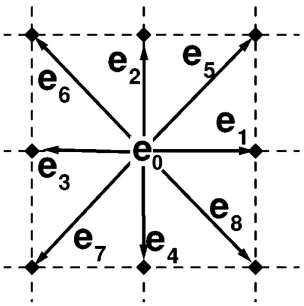

Fig. 5 The VEGF particles move on a cartesian grid with the velocities $\mathbf{e}_0 \ldots \mathbf{e}_8$

Instead of a collision the particles turn in the direction of highest nutrient concentration $C(\mathbf{x}, t)$ in every time step. In this way the particles will travel to the source of the nutrient distribution. When a particle hits a vessel node it is cleared and a counter in the corresponding direction is increased, see figure 6. When a certain amount of particles C_p have hit a vessel over a given time span a new vessel is created in the direction of the impact and the counters in the neighborhood are reset.

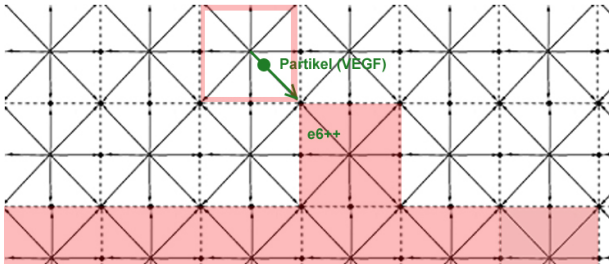

Fig. 6 The vessel grows in the direction of the impact of VEGF particles

The tumor quiescent cells act as a source for VEGF particles. They move towards the vessels. They act as source for the nutrient distribution and as a sink for VEGF particles.

The parameters that are needed in the angiogenesis simulation are

- Firing rate of the VEGF particles of quiescent cancer cells.
- Threshold C_p for the growth of the vessel.

5 Results

The tumor growth has been simulated for different supply scenarios and various haematocrit distributions. The results reflect the property that malignant cells are able to survive low nutrient concentrations and the effect of angiogenesis can be demonstrated.

In the following simulation a spatial domain of 0.5cm * 0.5cm is under investigation. The simulation uses a resolution of 200 * 200. As a result a cell in the simulation has 25 μ, thus approximately $10 - 30$ real cells are aggregated in a simulated cell.

5.1 Homogenous nutrient supply

The homogeneous situation is important for determining the growth factor q of the proliferate cells. When homogenous nutrient supply is under investigation a regular vessel structure is used that is not altered by the growth of the cells. The regular vessel structure leads to regular nutrient supply, see figure 7, that must be chosen to be sufficient for cancer and normal cells.

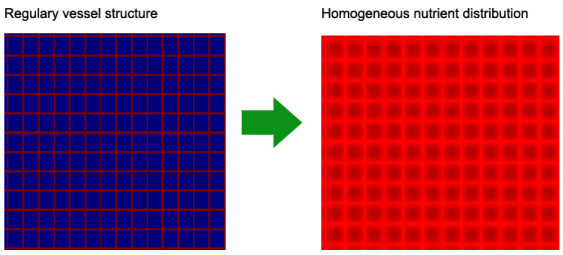

Fig. 7 A regular vessel structure leads to a sufficient nutrient distribution

The resulting simulation of tumor growth can be controlled by the growth factor g leading to exponential growth of the tumor cells and has representation given in figure 4.

5.2 Inhomogeneous nutrient supply

When inhomogeneous nutrient supply is under investigation the simplest approach is to start from an regular vessel structure as given in figure 7 but allow the displacement of the vessels.

As a result in the beginning the tumor grows like in the homogeneous case but pushes the vessels aside. As a result at a certain point there are too little vessels in the cancerous region to supply the cells sufficiently with nutrients.

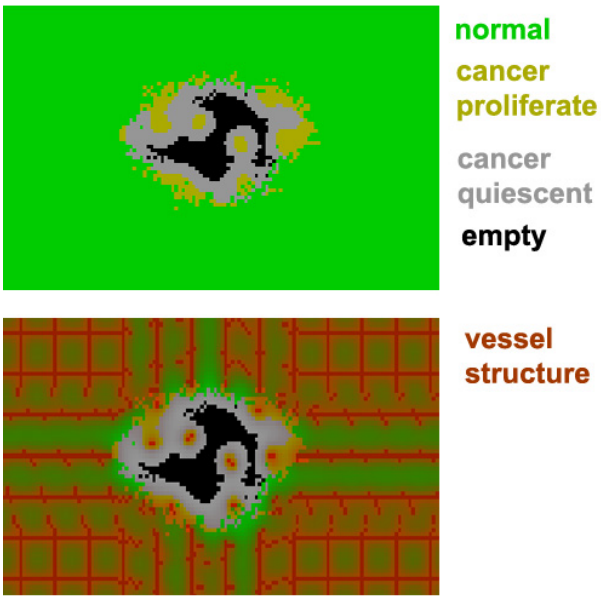

Fig. 8 With the growth of the tumor cells the nutrient supply becomes highly inhomogeneous

The proliferate cancer cells turn to quiescent which

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slows down the growth. When angiogenesis is neglected the cancer cells inside the tumor start to die, see figure 8.

5.3 Inhomogeneous nutrient supply with angiogenesis

A tumor develops its own supply by angiogenesis. As a result in a realistic simulation the tumor growth both factors have to be taken into account:

- Vessels are displaced by tumor growth
- Vessels grow into the tumor by angiogenesis

When the simulation from the previous section is considered the quiescent cancer cells start to send VEGF particles. These particles force a vessel growth in direction of the badly supplied areas. As a result there are no empty areas, see figure 9.

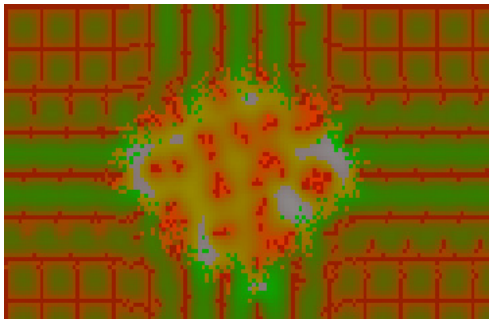

Fig. 9 New vessels are created ensuring a better nutrient supply.

The effect of angiogenesis can be recognized clearly when the simulation is started from an inhomogeneous nutrient distribution, see figure 10. First the tumor becomes smaller because of the bad supply situation. After a time span the vessels develop in direction of the quiescent cancer cells and the nutrient concentration gets higher, thus the tumor begins to grow rapidly.

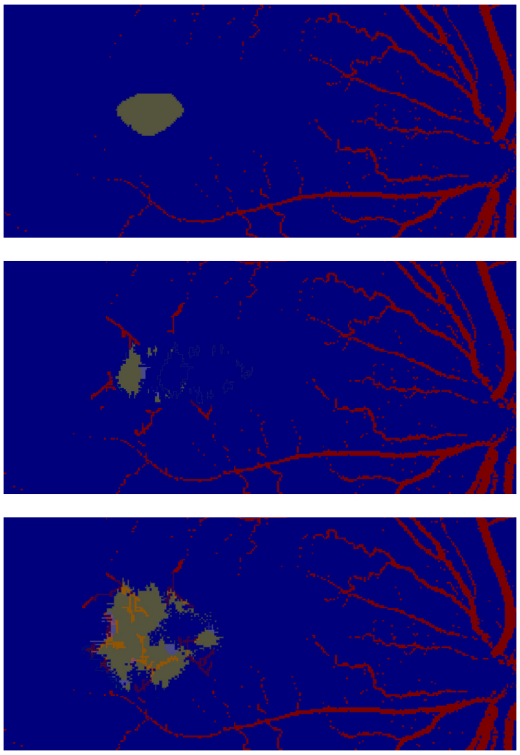

Fig. 10 The effect of angiogenesis

6 References

[1] M. Alber, M. Kiskowski, J. Glazier, and Y. Jiang. On cellular automaton approaches to modeling biological cells. *Technical Report*, (337), 2002.

[2] G. B. Ermentrout and L. Edelstein-Keshet. Cellular automata approaches to biological modeling. *Journal of Theoretical Biology*, 160, 1993.

[3] T. Alarcn, H.M. Byrne, and P.K. Maini. A cellular automaton model for tumour growth in inhomogeneous environment. *Journal of Theoretical Biology*, 225, 2003.

[4] Hötzendorfer H. Modeling of physiological processes by cellular automata - a model for tumorgrowth. *Master thesis - TU Vienna*, 2004.

[5] D. Leitner, M. Blaickner, H. Htzendorfer, and Wassertheurer S. Simulation of tumor growth with cellular automaton. *BMT Jahrestagung*, 2006.

[6] D.A. Wolf-Gladrow. *Lattice-Gas Cellular Automata and Lattice Boltzmann Models - An Introduction, Lecture Notes in Mathematics*. Springer, 2002.

