simulation of tumour growth,
cellular automata

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MATHEMATICAL MODELLING AND SIMULATION OF INTERACTING CELL SYSTEMS WITH CELLULAR AUTOMATA

EXTENDED ABSTRAKT

1. INTRODUCTION

Examples of interacting cell systems are life cycles of bacteria or social amoebae, embryonic tissue formation, wound healing or tumour growth and metastasis. What are the principles underlying the dynamics of interacting cell systems? Mathematical models of spatio-temporal pattern formation can offer insight into the principles of cooperative phenomena which can not be explained at the single cell level but are emergent properties of interacting cell systems. Typical modelling attempts focus on a macroscopic perspective (formulated for example as partial differential eqution system), i.e. such models describe the spatio-temporal dynamics of cell concentrations (see for example [8]. A modelling alternative are cell-based models, e.g. cellular automata, in which the fate of each individual cell can be tracked which is not possible in continuous models. Here, we briefly describe cellular automaton model applications for bacterial pattern formation and avascular tumour growth.

2. CELLULAR AUTOMATA

Cellular automata are dynamical systems – discrete in space, time and state. The automaton concept was originally introduced by John v. Neumann and S. Ulam as a model of self-reproducing systems but has been applied extensively to many other biological and also physical, chemical and even sociological problems [2,5,9]. Configurations are updated simultaneously or asynchronously and only depend on the local neighborhood configuration. The essential question is always how macroscopic (global) behaviour can arise from individual (local) rules. Cellular automata have become paradigms of self-organizing complex systems in which collective behavior arises from simple interaction rules of even more simple components. An important insight of complex system research is that macroscopic behavior is rather independent of the precise choice of the microscopic

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interaction. An introduction to the cellular automaton modelling concept and biological applications of automaton models can be found in [3].

3. MODELLING BACTERIAL PATTERN FORMATION

Single cell organisms as bacteria, yeast and amoebae normally divide and proliferate individually. Under starvation conditions or at large cell densities an increasing degree of coordination among previously autonomous cells can be observed. Here we focus on pattern formation of myxobacteria which are striking examples for coordinated behaviour of communities consisting of single cell organisms.

Myxobacteria exhibit a complex developmental cycle with individual and social phases and a variety of emerging patterns such as alignment, aggregation and standing wave oscillations of the cell density (rippling) (Fig. 1). These patterns require communication between bacterial cells in order to coordinate their movements. We have developed a simple discrete model for ripple formation based on the interplay between cell migration and collisions of cells which may cause cell reversal [1]. The spatial and temporal synchronization is due to a refractory phase during which cell reversal is prohibited. It could be demonstrated that the duration of this phase determines wavelength and period of the ripple patterns (Fig. 2).

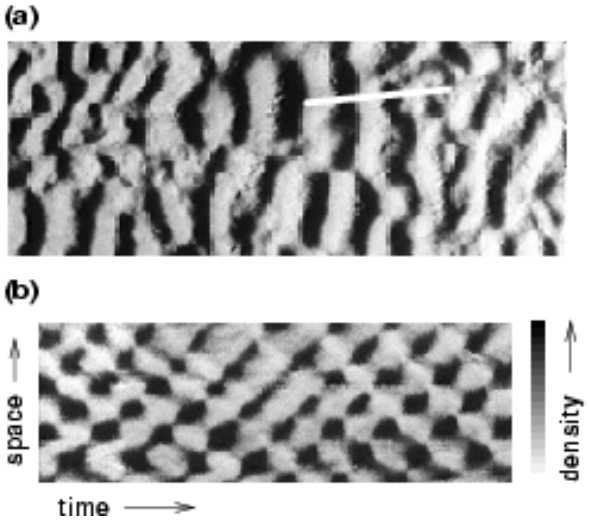

Fig.1. (a) Snapshot from a rippling sequence in myxobacteria taken from a time-lapse movie (H. Reichenbach, Braunschweig)). Ridges of cells (dark regions) are separated by regions with lower density (white). White bar: 300 μ*m*. (b) Space-time plot of the density profile along the white line in (a). Wavelength is 105 μ*m*, temporal period is 10 *min*.

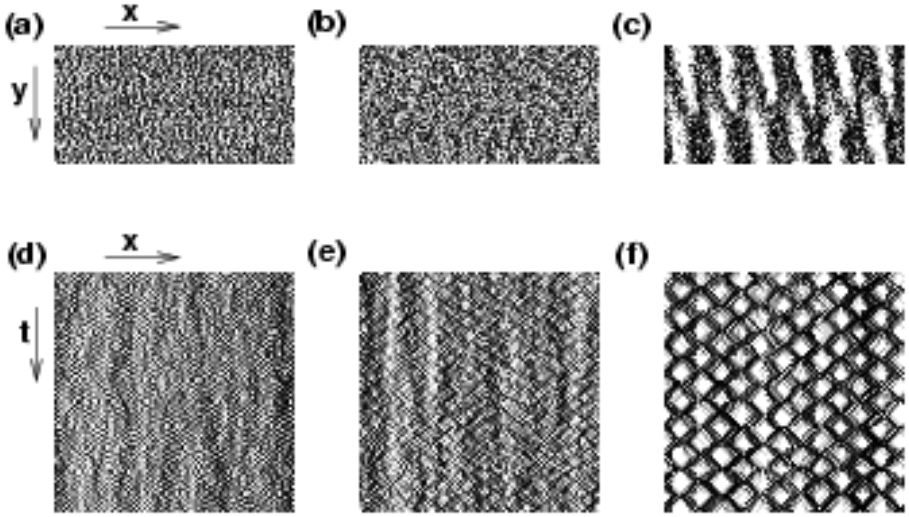

Fig.2. (a) Simulation snapshot in a system of size 100×50 containing 15000 cells with a refractory phase τ=1 time step after ca 5000 time steps (black corresponds to high cells columns). (b),(c) Same as (a) with τ=3 *resp.* τ=5. In (d),(e),(f) we show the corresponding space-time plots along 100 substrate sites in *x*-direction over 100 time steps (courtesy of Uwe Börner, Dresden).

4. A MODEL OF AVASCULAR TUMOUR GROWTH

Cancer development can be viewed as an example of spatio-temporal pattern formation. Several attempts have been made to model and predict malignant tumour behaviour and also to account for immune system response and the impact of possible clinical treatments. Modelling started from macroscopic approaches and developed towards cell-based approaches, from which cellular automaton models are an example (see [7] for a critical review of automaton models).

Here, we briefly report on a hybrid lattice gas-cellular automaton model for pattern formation in multicellular spheroids [4]. Multicellular spheroids serve as experimental model system for the study of avascular tumour growth. Typically, multicellular spheroids consist of a necrotic core surrounded by rings of quiescent and proliferating tumour cells, respectively [6]. Furthermore, after an initial exponential growth phase further spheroid growth is significantly slowed down even if further nutrient is supplied. The cellular automaton model explicitly takes into account mitosis, apoptosis and necrosis as well as nutrient consumption and a diffusible signal that is emitted by cells becoming necrotic. All cells follow identical interaction rules. The necrotic signal induces a chemotactic migration of tumour cells towards maximal signal concentrations. Starting from a small number of tumour cells automaton simulations exhibit the self-organized formation of a layered structure consisting of a necrotic core, a ring of quiescent tumour cells and a thin outer ring of proliferating tumour cells.

5. OUTLOOK

The general advantage to use individual-based approaches (particularly cellular automaton models) over models based on locally averaged cell densities is that local properties of cells on small length scales, as the detachment of a single cell from the primary tumour that may precede metastasis formation, or (de-)differentiation and apoptosis (if only a small number of cells at special positions are concerned) cannot be described appropriately by a continuum approach. Furthermore, stochastic effects as intrinsic noise due to the discreteness of the system and molecular processes within and outside the cell that appear as stochastic elements in the cell migration and division can naturally be included in an cell-based approach. Finally, we stress that the models introduced here for the case of bacterial and tumour pattern formation can easily be adapted to gain theoretical insight into the behavior of a wide range of other biological systems (e.g. immune system). It turns out that in many important cases the coarse-grained perspective of the cellular automaton model covers the essential aspects of the cell interaction behavior.

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