Hierarchies of Modeling Infections: Comparison of Reaction-Diffusion System and Cellular Automaton

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1. INTRODUCTION

Various mathematical models reproducing similar observations have different advantages and disadvantages. Consequently, the question evolves how to compare and relate models in a hierarchical order. We present two approaches for modeling viral liver infections such as hepatitis C, a world wide disease which chronifies in up to 75% of the cases, cf. Schwab (2011). The first model using reaction-diffusion equations allows analytical longterm behavior predictions. The second model, a cellular automaton, describes the interactions of virus and T cells in a smaller dimension and includes new mechanisms.

2. MODELING HEPATITIS

We list properties of the liver as well as of viral liver infections. Based on this, we present a reaction-diffusion system in Sec. 2.2 and a cellular automaton in Sec. 2.3.

2.1 Liver infections

The liver lobes consist of hepatic lobules connected to the veins. This results in a ramified small-scale system.

After the infection, the immune system reacts to the virus. First, dendritic cells report the presence of the virus. As a reaction, T cells are produced in the lymphocytes. Different kinds of T cells are involved in the primary immune reaction. T helper cells induce B lymphocytes to produce antigens. The killer T cells identify infected cells and trigger the programmed cell death. Killer T cells cause most of the damage caused by a liver infection, cf. Bowen et al. (2002). The incubation time between the infection and the attack of the killer T cells is several weeks.

The inflammation starts with an acute phase in which the killer T cells try to eliminate the virus. Then, either the virus is eliminated and the immune reaction fades, or in case of a chronic course, the virus remains in remote areas of the liver and a diminished immune reaction persists.

2.2 Reaction-diffusion model

In the model, first presented by Kerl (2012), the immune reaction is summarized in a term of T cells v. The interactions of the virus u and the T cells v are based on Lotka-Volterra equations with a logistic growth $w(u) = (1-u)\frac{u-\epsilon}{u+\kappa}$ of the virus, including the Allee effect, and an inflow term $j[u]$ which describes the inflow of T cells through the vein depending on the total virus population in the liver. For $\mathbf{x} \in \Omega$ and $t > 0$, the equations

$$\begin{aligned} \dot{u} &= uw(u) - \gamma uv + \alpha \Delta u\,, \\ \dot{v} &= j[u] - \eta(1-u)v + \beta \Delta v - \mu \Delta u \end{aligned} \tag{1}$$

describe the reactions between the virus and T cells, the diffusion spread of the populations (α, β) and the chemotactic effects (μ), which direct T cells to the virus. Initial values $u_0(\mathbf{x})$ and $v_0(\mathbf{x})$ and homogenous Neumann boundary conditions are used.

The occurrence of chronifications depends on the minimal eigenvalue λ of the negative Laplacian in Ω with Neumann boundary conditions, the maximal diffusion coefficient $d = \max\{\alpha, \beta\}$ and the maximal change rate of the reactions M. If these parameters fulfill $\sigma = \lambda d - M > 0$, chronic courses can be ruled out, see Smoller (1994).

2.3 Cellular automaton

We use a rectangular geometry with $n \times m$ cells and an additional cut with regard to the small-scale liver structure. The possible states of a cell are obstacle (-1), dead (0), healthy (1), infected (2) and attacked by T cells (3), see Fig. 1. We use these discrete states and a coupled map lattice for the amount of T cells in each cell. The automaton is inhomogeneous because we model an inflow area as described in Sec. 2.1. The update uses a Neumann neighborhood with radius 1. The chemotactic effects are gained from a Moore neighborhood with radius 3.

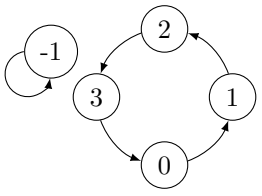

Fig. 1. Change of cell states: Obstacles (-1) remains, healthy cells (0) change over infected (1), and attacked by T cells (2) to dead (3). Dead cells may get healthy.

3. RESULTS

In this section, we compare the simulations of both models and highlight similarities and differences.

3.1 Reaction-diffusion model

The area Ω has a cut at $x_1 = 0.5$ with regard to the small-scale liver structure and an inflow area around $(x_1, x_2) = (1, 1)$. Depending on the parameters in Eq. (1), both main courses, healing and chronification, are reproducible. For parameters with $\sigma < 0$, we may observe spatial inhomogeneous, stationary solutions, which we interpret as chronic infections, see Fig. 2. The virus persists in an area remote from the inflow area. The immune reaction does not fade out.

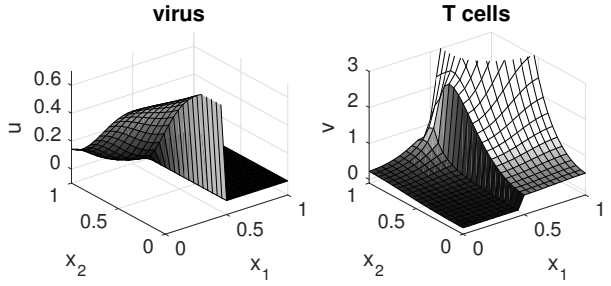

Fig. 2. Stationary virus and T cell distribution in a chronic infection course, modeled with Eq. (1).

3.2 Cellular automaton (CA)

The numerical simulation by hands of the cellular automaton reproduces both disease courses as well as the model in Eq. (1). For small chemotaxis parameters μ, it shows a behavior which is equivalent to the reaction-diffusion model. The system behavior of a chronic infection is comparable to the simulation in Fig. 2. For healing courses with strong chemotactic effects, we observe a new mechanism. A group of T cells follows the virus behind the cut. As an effect, there is a gap between the separated group and the inflow area without any virus and T cells. The group of T cells eliminates the virus and dies thereafter. The separated group of T cells in an active phase is shown in Fig. 3, in the lower right, behind the obstacle.

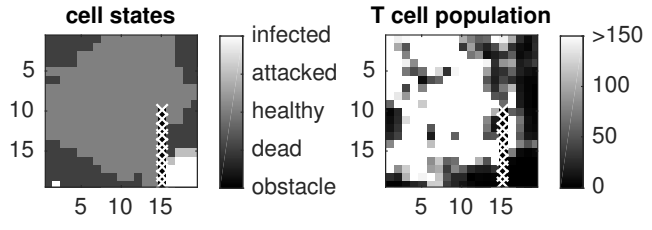

Fig. 3. Isolation of T cells in an active phase, simulation by hands of the cellular automaton. The barrier of obstacles is marked with white crosses.

3.3 Model family

Mathematical modeling starts with the observation of the object to be modeled. We presented the most relevant observations in Sec. 2.1. They form our constructed reality, the observed liver. From a philosophical point of view, the observations are already a first model of the real world or, in our case, of the real liver. In the next modeling step, we chose a way of modeling, e.g. partial differential equations, cellular automata or stochastic models. For each modeling approach, we select mechanisms for describing the constructed reality, i.e. the interaction of virus and T cells or chemotactic effects. Both presented models used an area with a cut as a model for the small-scale liver structure.

As a joint result, both models show healing and chronic courses, in dependency of the size of the area Ω, the chosen parameters and the initial conditions. The cellular automaton inherits the longterm behavior of system (1). This is reasonable because the average of the cellular automaton fits to the finite differences of the reaction diffusion system, cf. Weimar (1994). Besides this similarity, the numerical simulation of the cellular automaton shows a separation of some T cells, see Fig. 3. This effect is not included in the reaction diffusion model. Due to this, the question evolves, wether a reaction diffusion model including this additional effect exists, see Fig. 4.

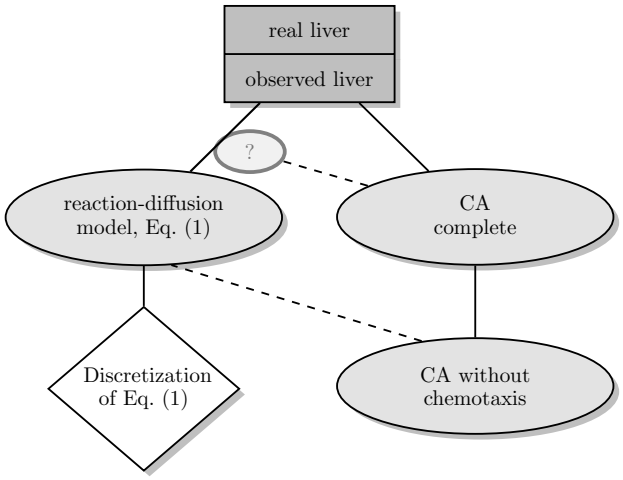

Fig. 4. Model hierarchy. Downwards: sub-models, upwards: model refinements. The discretization of Eq. (1) is equivalent to the CA without chemotaxis. This one is a discrete sub-model of the continuous Eq. (1) and a simplification of the CA described in Sec. 3.2. It is questionable whether there is a refined PDE model reproducing the separated T cell group.

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