Entropy functionals for finding requirements in hierarchical reaction-diffusion models for inflammations

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Based on an established model for liver infections, we open the discussion on the used reaction terms in the reaction-diffusion system. The mechanisms behind the chronification of liver infections are widely unknown, therefore we discuss a variety of reaction functions. By using theorems about existence, uniqueness, and nonnegativity, we identify properties of reaction functions which are indispensable to modelling liver infections. We introduce an entropy functional for reaction-diffusion models of this type, which allows predictions of the longtime behavior of the solutions. As a result, we find more conditions on the reaction functions to derive a model covering different inflammation courses. Finally, we discuss the models in the frame of a hierarchical model family.

KEYWORDS
entropy methods, inflammation, mathematical modeling, reaction-diffusion equations

MSC CLASSIFICATION
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1 | INTRODUCTION

In this paper, we present a two-population reaction-diffusion model for hepatitis C, which has different types of solutions depending on some parameters. The different solution types can be connected to the two main infection courses of hepatitis C, namely to acute and chronic courses of the disease. The presented model is one possible model out of a class of thinkable models. The underlying mechanisms of liver infections, especially of the development of chronic infections, are unknown. Due to the unavailability of qualitative and quantitative certainty about the reaction functions, we turn the point of view, and we consider a realistic class of reaction functions. We deduce requirements on reaction-diffusion equations for deducing a system, which is able to reproduce both solution types. In this sense, we are not directly in a modeling process of a particular application, but we ask, how much change in the reaction functions of the proposed model is allowed and when the qualitative solution behavior is conserved. Therefore, we find conditions for the nonnegativity, the existence, and the uniqueness of solutions.

The key issue of this paper is the use of entropy methods for showing whether a model can reproduce spatial inhomogeneous solutions or not, which are identified with chronic courses of the disease. The importance of considering such a named variety of reaction functions results from the inherent qualitative and quantitative uncertainty of the mechanisms leading to the chronification of liver infections, see Sections 1.2 and 1.3.

The paper is organized as follows. We first conclude biological and medical preliminaries in Section 1.1. Then, we present the model for describing liver infections and give a mathematical representation of the two main infection courses.
in Section 2.1. Afterwards, we reduce the model in two different ways to a one-population model. Based on the two reduced models, we open the discussion on the used reaction functions and find necessary conditions on the reaction functions for modeling liver infections.

In Section 3, we formulate conditions for the nonnegativity and the existence and uniqueness of solutions. We check the well-posedness of the conditions for our full model and the two reduced models.

The main subject of this paper is the definition of an entropy functional for the reaction-diffusion system. With an entropy functional, a prediction of the long-time behavior of the solutions and therefore a prediction of the infection course is possible. Entropy functionals are decaying along solutions of the reaction-diffusion system. They are Lyapunov functionals in a general setting of suitable function spaces, but they are based on Lyapunov functionals of the smaller position-independent system of ordinary differential equations, too.

We show that the Lyapunov functional of the classical Lotka-Volterra system does not provide a Lyapunov functional for the presented model for liver infections. Further, we show in Lemma 4 a necessary condition for the system to decay to zero. For the reduced model, we show in Theorem 1 that the reaction terms must have a certain shape for allowing solutions connected with chronic infections. For these reaction functions, we show the nonexistence of an entropy functional.

Finally, we resume the results, arrange the models in a hierarchical order, and discuss the inheritance of model properties in Section 4.

1.1 Biological background

Viral liver infections like hepatitis B (HBV) and C viruses (HCV) are diseases which affect people all over the world. In 2015, approximately 1.75 million new HBV infections occurred, and 71 million people were suffering from chronic HCV infections.2 In the same year, approximately 257 million people were suffering from chronic HBV infections.2

An acute liver infection can be divided into four phases. The first phase is an incubation phase, which lasts around 1 to 6 months and is free of symptoms. In the second phase, the first symptoms are present, but the immune reaction just starts in the third phase. This third phase is what we will call the active phase, because the immune reaction is active and therefore the inflammation is high. The active phase can take a few months. The last phase of the acute infection is the clearing of the infection and the decay of symptoms.

In contrast to this, a chronic infection passes over to an immune control phase after the active phase.3 During this time, which can take up to decades, the virus replicates few and the immune system reacts moderately.

On the length scale of a liver, we can observe differences between acute and chronic infections.4 During an acute infection, up to 95% of the hepatocytes are infected. In chronic infections, the virus persists in around 30% of the hepatocytes. There is more inflammation around portal triads, and the inflammation differs from one area of the liver to another.

1.2 Inflammation models in the literature

There are different approaches for modeling liver infections on different length scales. For example, there are compartment models describing the spread of hepatitis B and C in the world using epidemiological approaches.5 Liang et al5 compare different published models and vaccination strategies for hepatitis B.

Besides, there are models describing the populations in the whole liver by ordinary differential equations. Aston6 compares different models and presents a new model combining different mechanisms. Hattaf et al7 use delay differential equations for modeling the dynamics of liver infections.

Goyal and Murray8 model the interaction between the hepatocytes, the virus, and the immune cells more precisely in an agent-based model with stochastic effects. The focus of this work is the influence of cell-to-cell transmissions on the infection course.

To conclude, there are many different models on different length scales using different modeling approaches. All of them have in common that they describe the qualitative behavior of the infection process because there is an inherent lack of data, for example, it is impossible until today to measure the time- and position-dependent density of hepatitis virus in the liver of a living human organism.

1.3 Model assumptions

In this article, we model viral liver infections on a scale that lies between the size of a whole liver and the cell scale with all the microscopic, partly unknown, mechanisms. Therefore, we are not focussing on the interaction between all different cell types like CD 4 cells, cytotoxic T cells, and B cells, which play a role in the cell-mediated immune reaction.
On this medium scale, we observe the main mechanisms of the interaction between the virus and the immune reaction. One mechanism is the growth of the virus, which is limited by the supporting capacity of the liver, modeled by a saturated reaction known from logistic growth. In addition, the virus decay is depending on the strength of the immune reaction. This decay is, as oftentimes in life science applications, rarely quantified and is perhaps hardly quantifiable. That is why we regard the particular used mechanisms as representatives of a wide class of decay functions.

The immune reaction consists of an inflow of T cells into the liver depending on the virus load in the liver. As a second mechanism for the immune reaction, we find a decay of the immune reaction in absence of the virus. Besides, both the virus and the T cells as main actors spread out in a diffusive manner in the liver. This diffusive behavior is a representative of the migration of the virus and the immune reaction, too. A spatial resolution and a migration behavior are necessary to describe the inflammation differing in the different areas of the liver.

We begin the modeling of liver infections with the start of the active phase, see Section 1.1. Therefore, the virus is spread all over the liver, and there are no T cells in the beginning.

Finally, we want to compare the results of our model with qualitative observations. To start with, we find acute and chronic infections. A model for hepatitis should cover those both courses depending on model parameters and on the modeled liver domain. Until now, there is no medical explanation why the infection clears or becomes chronic. As well, there is a lack of dynamic measurements of the virus and T cell amount during an infection in the liver. Therefore, we compare the results with static pictures of a liver, showing the high virus load during an acute infection and the reduced virus loads with areas of different virus load in the case of chronic infections.

2 | REACTION-DIFFUSION EQUATIONS

We model the observed mechanisms as interactions based on predator-prey mechanisms with spatial diffusion. The two species of the predator-prey mechanism are the virus on the one hand and the immune reaction on the other hand. The virus $u = u(t,x)$ depending on the time $t$ and the space $x$ acts as a prey for the immune reaction, represented by the active T cells $v = v(t,x)$ in this setting. The observed part of the liver is described by a domain $\Omega \subset \mathbb{R}^v$ with $v \in \{1, 2, 3\}$. We write the two components as $q = (u, v)^T$ and get the reaction-diffusion equation

$$
\begin{align*}
\dot{q}(t, x) &= f(q, x) + D \Delta q, & x &\in \Omega, t > 0, \\
\nabla q \cdot n &= 0, & x &\in \partial \Omega, t > 0, \\
q(0, x) &= q_0(x), & x &\in \Omega,
\end{align*}
$$

(1)

where the positive diffusion constants are contained in the diagonal $D \in \mathbb{R}^{2 \times 2}$ and the function $f = (f_1(u, v, x), f_2(u, v, x))^T$ contains the reaction terms between the two species. We use homogeneous Neumann boundary conditions for describing no outflow from the observed part of the liver. This description reflects that fasciae are nearly impassable for both species. Furthermore, we are focussing on the interaction between the two species and their spatial behavior by diffusion. Therefore, the outflow of virus or T cells is less important.

We identify an acute infection course with a solution fulfilling

$$
\lim_{t \to \infty} u(t, x) = 0 \quad \text{and} \quad \lim_{t \to \infty} v(t, x) = 0.
$$

(2)

The definition in Equation (2) focusses on the longtime behavior. In the same way, we identify chronic infections with the longtime behavior of persisting infections. Therefore, in a mathematical description, we expect

$$
\lim_{t \to \infty} u(t, x) = u_{\text{chro}}(x),
$$

(3)

where $u_{\text{chro}}(x)$ is a stationary function which is not everywhere vanishing and which turns out to be nonconstant if existent. The mean of $u_{\text{chro}}(x)$ should be around 0.3 of the maximum virus load because this fits the observations, see Section 1.
2.1 Liver infection model

There are many different models for hepatitis C on different length scales of the observations, see Section 1.2. We want to model the interaction within the liver on a scale which covers a part of the liver. Therefore, we need a position depending model.

Kerl et al\textsuperscript{9} proposed the following reaction-diffusion model, using mechanisms on this length scale. Based on Equation (1), the reaction function $f_1$ for the change of the virus does not explicitly depend on the position $x$, hence the change of the virus is regarded as a local effect. It is given by

$$f_1(u, v) = w(u)u - \gamma uv,$$

where $w(u)$ is a growth factor and the second mechanism with the parameter $\gamma$ describes the decay of virus depending on the T cells. The growth term is

$$w(u) = w_A(u) = (1 - u) \frac{u - \epsilon}{u + \kappa},$$

which is a logistic growth including an Allee effect.\textsuperscript{10,11} The parameter $\epsilon$ describes the minimal population size for a survival of the species, and $\kappa$ is a parameter for adapting the growth function to a logistic growth. The reaction function for the T cells is

$$f_2(u, v, x) = \delta j[u](x) - \eta(1 - u)v,$$

where $j[u]$ is an inflow term depending on the virus load. The parameter $\delta$ describes the strength of the immune system. The decay of T cells $v$ in absence of virus $u$ is modeled as $\eta(1 - u)v$ with the parameter $\eta$. The second term in Equation (6) describes the decay of T cells in absence of virus. Kerl et al\textsuperscript{9} proposed the inflow term

$$j[u](x) = \frac{\chi_{\Theta}(x)}{|\Theta|} \int_{\Omega} u \, dx,$$

where $\Theta$ is an inflow area and $\chi_{\Theta}$ is its characteristic function. Let us mention that the inflow $j$ depends on the function $u$ and not on its particular values $u(x)$ at a position $x$. The immune response is a global effect. It depends on the sensed total virus load. That is why we note $j = j[u]$. We remark that the total inflow in Equation (7) is proportional to

$$\int_{\Omega} j[u](x) \, dx = \int_{\Omega} u \, dx,$$

and therefore proportional to the total virus population. The model concludes this, and Equation (1) specifies to

$$\dot{u}(t, x) = w_A(u)u - \gamma uv + \alpha \Delta u, \quad x \in \Omega, t > 0,$$

$$\dot{v}(t, x) = \delta j[u](x) - \eta(1 - u)v + \beta \Delta v, \quad x \in \Omega, t > 0,$$

$$\nabla u \cdot n = \nabla v \cdot n = 0, \quad x \in \partial \Omega, t > 0,$$

$$u(0, x) = u_0(x), \quad v(0, x) = v_0(x), \quad x \in \Omega.$$

As our model starts with the active phase, the preferred initial values are, according to Sections 1.1 and 1.3, and due to the maximal capacity $u_0(x) = 1$ and $v_0(x) = 0$.

**Lemma 1.** If the initial virus population $u_0(x)$ is given by the maximal capacity $u_0(x) = 1$, the virus population $u$ of system (9) is bounded by 1, in formula, $u(t, x) \leq 1$ for all $t > 0$ and for all $x \in \Omega$.

**Proof.** Due to $u_0(x) = 1$, we have $\dot{u}(0, x) = -\gamma v \leq 0$ for all $x \in \Omega$. Let $\bar{t}$ be a time instant for which $u$ touches 1 from below, so that $u(\bar{t}, \bar{x}) = 1$ for some $\bar{x} \in \Omega$ and $u(\bar{t}, x) \leq 1$ for all $x \in \Omega$. Then, $\dot{u}(\bar{t}, \bar{x}) = -\gamma v + \alpha \Delta u(\bar{t}, \bar{x}) \leq -\gamma v \leq 0$ because $\Delta u \leq 0$ in every maximum. Hence, $u$ stays bounded by 1. \hfill $\Box$

Kerl et al\textsuperscript{9} showed that this model has solutions associated with the two main infection courses. Consequently, the model in Equation (9) reproduces the observations collected in Section 1.1. Further, Kerl et al\textsuperscript{9} showed the existence and stability of stationary solutions in one space dimension.

Now, we change the point of view. In the further work, we use the model as an example out of a variety of models, and we identify conditions, that all models with solutions of the mentioned types have to fulfill. With this approach, we
take account of the uncertainty in modeling the qualitatively and quantitatively unknown mechanisms of the interaction during liver infections.

2.2 Reduced models

The system in Equation (9) describes the two components $u$ for the virus as prey and $v$ for the T cells as predators and considers only some main biological mechanisms out of a variety of known interactions. Nevertheless, the model in Equation (9) is already mathematically challenging. To identify mechanisms in the model, which are responsible for observations like the chronification behavior, we analyze one-population models of the form

$$\begin{align*}
\dot{u}(t, x) &= f(u, x) + a\Delta u, \quad x \in \Omega, t > 0, \\
\nabla u \cdot n &= 0, \quad x \in \partial\Omega, t > 0, \\
\n u(0, x) &= u_0(x), \quad x \in \Omega
\end{align*}$$

(10)

instead of the more general two-population model in Equation (1). For this reason, we present here two approaches to reduce the specific two-population model in Equation (9). The reduced models can be seen as submodels of the model in Equation (9). In this sense, they inherit some properties of the larger model and, under certain conditions, the larger model itself might inherit properties from the submodels. The reduced models use again examples out of the variety of possible reaction functions.

In the first reduction, we assume a constant immune reaction $\nu(t, x) = \text{const}$. This results in a one-population model for the virus

$$\begin{align*}
\dot{u}(t, x) &= w_A(u)u - \tilde{\gamma}u + a\Delta u, \quad x \in \Omega, t > 0, \\
\nabla u \cdot n &= 0, \quad x \in \partial\Omega, t > 0, \\
\n u(0, x) &= u_0(x), \quad x \in \Omega
\end{align*}$$

(11)

with $\tilde{\gamma} = \gamma v$. In this case, we get a one-population model of the form

$$\begin{align*}
\dot{u}(t, x) &= f(u) + a\Delta u, \quad x \in \Omega, t > 0, \\
\nabla u \cdot n &= 0, \quad x \in \partial\Omega, t > 0, \\
\n u(0, x) &= u_0(x), \quad x \in \Omega
\end{align*}$$

(12)

without an explicit space dependency of the reaction function $f(u) = w_A(u)u - \tilde{\gamma}u$.

In the second reduction, we assume a very fast immune reaction. We write the variable velocity of the immune reaction as an explicit parameter $k$, and we get

$$\dot{v} = k(\tilde{\delta}j[u] - \tilde{\eta}(1 - u)v + \tilde{\beta}\Delta v),$$

(13)

where we treat the parameters $\tilde{\eta}$, $\tilde{\beta}$, and $\tilde{\delta}$ as fixed values.

The Laplace transform $L$ with respect to the time $t$ of Equation (13) is

$$sL[v] - v(0, \cdot) = k(\tilde{\delta}L[j[u]] - \tilde{\eta}L[(1 - u)v] + \tilde{\beta}\Delta L[v]),$$

(14)

where

$$L[(1 - u)v](s, x) = \int_0^\infty e^{-st}(1 - u(t, x))v(t, x) \, dt.$$ 

Due to $u \in [0, 1]$, we have $1 - u(t, x) \in [0, 1]$, and therefore the estimate

$$L[(1 - u)v] \leq L[v]$$

yields for every $s \in \mathbb{R}$. The argumentation is analogous for imaginary $s$ by using the absolute values. Therefore, there is a factor $A = A(s, x) \in [0, 1]$ with $L[(1 - u)v] = AL[v]$. The factor $A$ depends on the function $u = u(t, x)$, which itself depends on $v$ again. Therefore, the Laplace transform of $(1 - u)v$ exists.

Equation (14) is consequently equivalent to

$$(s + k\tilde{\eta}A)L[v] - k\tilde{\beta}\Delta L[v] = k\tilde{\delta}L[j[u]],$$
and
\[
\left( \frac{\gamma}{k} + \bar{\eta} A \right) L[v] - \bar{\beta} \Delta L[v] = \bar{\delta} L[j[u]].
\]
As the limit for \( k \to \infty \), the Laplace transform \( L[v] \) of \( v \) tends to the solution of
\[
\bar{\eta} A L[v] - \bar{\beta} \Delta L[v] = \bar{\delta} L[j[u]].
\] (15)

So, for every fixed \( u \), there is a unique solution \( L[v] \) of the elliptic partial differential equation in Equation (15) with the transformed boundary conditions which are homogeneous Neumann conditions for \( L[v] \), too. The larger \( v \) is, the smaller \( u \) becomes. Therefore, the inflow \( j[u] \) decreases with decreasing \( u \), and finally the Laplace transform of the inflow \( L[j[u]] \) decreases. Consequently, we find that
\[
-\bar{\beta} \Delta L[v] = \bar{\delta} L[j[u]] - \bar{\eta} A L[v]
\]
is decreasing in \( v \). Together with the uniqueness of \( L[v] \) for every \( u \), a stationary solution of Equation (13) exists and it is unique. We call the unique stationary solution of Equation (15) with the named boundary conditions \( L[v_{\text{stat}}] = L[v_{\text{stat}}(x)] \).

Hence, as limit for \( k \to \infty \), we get the tendency \( v \to v_{\text{stat}}[u] \), and therefore \( v_{\text{stat}}[u] = v_{\text{stat}}[u](x) \) as a solution of the nonlinear stationary problem
\[
0 = \delta j[u](x) - \eta(1-u)v_{\text{stat}}[u] + \beta \Delta v_{\text{stat}}[u],
\]
consequently, \( v_{\text{stat}} \) makes the right-hand side of Equation (13) to be zero. As well as the reduced models, the nonlinear stationary problem is part of a model family for describing the interactions of liver infections. The solution of the reaction diffusion system inherits properties of the solution of the stationary problem.

We use the stationary solution \( v_{\text{stat}}(x) \) for gaining a single equation for \( u \). With Equation (9) and the position-depending parameter \( \gamma(x) = \gamma v_{\text{stat}}(x) \), we get the limit case of Equation (9) for a very fast immune reaction
\[
\begin{align*}
\dot{u}(t, x) &= w_A(u)u - \gamma(x)u + a \Delta u, & x \in \Omega, t > 0, \\
\nabla u \cdot n &= 0, & x \in \partial \Omega, t > 0, \\
u(0, x) &= u_0(x), & x \in \Omega 
\end{align*}
\] (16)
as a second reduced model for the virus population. In this case, we have a space-depending reaction function \( f = f(u,x) = w_A(u)u - \gamma(x)u \) like in the general model in Equation (10). The different models in Equations (11) and (16) underline the variability of possible models, even if these two particular models are submodels of the comparatively simple system in Equation (9).

3 | ANALYTICAL RESULTS

We presented a reaction-diffusion model describing both infection courses depending on the parameters in Equation (9) and reduced it to the one-population systems in Equations (11) and (16). Now, we think about the choice of the reaction functions. The presented reaction functions are compatible with our main observations, but there are many more thinkable reaction functions which would describe the observations as well. We ask which functions out of a variety of functions can be chosen as reaction functions and how much change in the functions is possible for still obtaining qualitatively comparable results as before.

We are looking for conditions on the reaction functions for the appearance of stationary spatially inhomogeneous solutions in the longtime behavior. Therefore, we return to our reaction-diffusion system in Equation (1) and try to specify what functions \( f \) are admissible. We expect to find classes for the functions but not one certain function, cf. Sections 1.2 and 1.3.

3.1 | Nonnegativity, existence, and uniqueness of solutions

A well-posed reaction-diffusion equation for describing infections should have a non-negative, unique solution. As \( q \) in Equation (1) describes the populations of virus and T cells, the nonnegativity of the solution is a necessary condition. A negative population is meaningless in this context. The necessary and sufficient conditions for the nonnegativity of the solutions are
\[
\begin{align*}
f_1(v, x) &= f_2(u, x) = 0 & \text{for all } v \geq 0, x \in \Omega & \text{and} \\
& & \text{for all } u \geq 0, x \in \Omega.
\end{align*}
\] (17)
These are the first two requirements on general reaction functions $f$ in Equation (1) for modeling liver infections.

There are conditions for existence and uniqueness for general reaction-diffusion systems$^{12,13}$ where the reaction functions depend on both populations and on the time. Adapted to our homogeneous Neumann boundary conditions and the dependency of $f_1$ and $f_2$ on the space variables $x$, we get some conditions on the reaction functions. We specify the conditions by Hollis et al.$^{12}$ for an autonomous system without explicitly time-depending reaction functions according to the general theorems in Friedman.$^{14}$

A local existence and uniqueness assertion requires that both reaction functions $f_1(u,v,x)$ and $f_2(u,v,x)$ are continuously differentiable with respect to $u$ and $v$, and have bounded initial data. In formula, we need

$$f_1, f_2 \in C^1([0, \infty)^2 \times \Omega),$$

the nonnegativity conditions in Equation (17) and the existence of a bound $M_0 \in \mathbb{R}$ so that

$$0 \leq u(0,x), v(0,x) \leq M_0 \quad \text{for } x \in \Omega.$$

Further, the reaction functions are bounded and measurable with respect to $x$.

For global existence and uniqueness, there are conditions$^{12,14}$ which seem to be asymmetric in both populations $u$ and $v$.

By changing the name of the two populations, we get the same conditions vice versa.

The first condition is a bounded growth of one of the populations, for example, $u$. The population should be bounded in every time interval by a continuous function in time, named $N_1(t)$, with $N_1 \in C([0, \infty))$.

In formula, we require

$$0 \leq u(t,x) \leq N_1(t) \quad \text{for all } t \geq 0.$$  

The condition in Equation (20) is fulfilled if, for example, the reaction function $f_1$ is bounded by a linearly growing function in $u$. We write this as

$$f_1(u,v,x) \leq \mu_1 u + \mu_2 \quad \text{for all } u, v > 0, x \in \Omega$$

for some $\mu_1, \mu_2 \in \mathbb{R}$, which are necessarily non-negative.

The second condition for global existence and uniqueness is the boundedness of the second reaction function by a polynomial function in $v$ and a continuous function in $u$. For a constant $\ell' \geq 1$ and a continuous function $L_0 \in C([0, \infty))$, the estimate

$$f_2(u,v,x) \leq L_0(\xi)(1 + v)^{\ell'} \quad \text{for all } u, v \geq 0, \ x \in \Omega \text{ and } u \leq \xi$$

is the necessary condition on $f_2$. We remark that Equation (22) remains true if $\ell'$ is replaced by a larger value so that $\ell' \geq 1$ does not contain a further restriction.

As a third condition, the sum of both population changes should be bounded by a continuous function $\mu_0 \in C([0, \infty))$ as

$$f_1(u,v,x) + f_2(u,v,x) \leq \mu_0(\xi) \quad \text{for all } u, v \geq 0, \ x \in \Omega \text{ and } u \leq \xi.$$  

With these three conditions in more general form, global existence and uniqueness of the solution of Equation (1) are shown by Hollis et al.$^{12}$ The space-dependency of $f_1$ and $f_2$ does not change the considerations too much, because one can handle the functions pointwise.$^{14}$

We test the conditions in Equations (17), (18), (21), (22), and (23) for the model by Kerl et al.$^9$ in Equation (9) and the two reduced models in Equation (11) and (16). Especially, model (9) should fulfill the conditions, otherwise those conditions would not be useful for our investigations in modelling liver infections.

We start with the condition for non-negative solutions in Equation (17). It is easy to see that the two conditions are fulfilled for the model in Equation (9), see

$$f_1(0,v) = 0 \quad \text{and} \quad f_2(u,0,x) = \delta_j[u](x) \geq 0.$$  

For the first reduced model Equation (11) and the second in Equation (16), we find $f(0) = 0$ and $f(0,x) = 0$ respectively. All three models fulfill the nonnegativity conditions (17) for the reaction functions.

As well, the initial data for all three models are bounded, see Section 1.3. Thus, Equation (19) is fulfilled. In addition, local existence and uniqueness require that the reaction functions are continuously differentiable. The reaction functions $f_1$ and $f_2$ are $C^1$ with respect to $u$, $v$, and Equation (18) is fulfilled. So, we have shown the local existence and uniqueness of the solutions of the models in Equations (9), (11), and (16).
For proving global existence, we need to show that the reaction functions yield different estimates. First, we show that our three models fulfill Equation (21). Since we can write
\[ f_1(u, v) = u \left( (1 - u) \frac{u - c}{u + \kappa} - \gamma v \right) < u (1 - u - \gamma v), \]
we see that \( f_1(u) \) is bounded, for example, by \( \mu_1 = 1 \) and \( \mu_2 = 0 \). Another possible choice would be \( \mu_1 = 0 \) and \( \mu_2 = 1 \).

The second condition in Equation (22) is a polynomial bound for \( f_2 \). In Equation (9), we find
\[ f_2(u, v, x) = \delta j[u](x) - \eta(1 - u)v, \]
where
\[ j[u](x) = \frac{\chi_0(x)}{\Theta} \int_\Omega u \, dx \leq \frac{\chi_0(x)}{\Theta} |\Omega| \leq \frac{|\Omega|}{|\Theta|} = W. \]

With this estimation, we have
\[ |f_2(u, v, x)| \leq \frac{\delta |\Omega|}{|\Theta|} + \eta(1 - u)v \leq \delta W + \eta v \leq (\delta W + \eta)(1 + v), \]
and therefore Equation (22) holds true for \( \ell' = 1 \) and \( L_0(\xi) = \delta W + \eta \). For the reduced models, we do not have a component \( f_2 \).

Therefore, the third condition in Equation (23) is fulfilled for the reduced models with \( \mu_0(\xi) = 1 \). For the model in Equation (9), we find an upper bound for both conditions by \( \mu_0(\xi) = 1 + \delta W + \eta \). Also, this bound is independent of \( \xi \) and thus of \( u \).

Altogether, all conditions for global existence and uniqueness are fulfilled for all three specified models. The conditions are therefore a first indicator whether the reaction functions are useful for modeling liver infections with reaction-diffusion equation. Our first conditions, which reduce the admissible function set, are Equations (17), (18), (21), (22), and (23).

### 3.2 Entropy for reaction-diffusion systems

The meaning of entropy evolved in physics over time. We give a short overview of different aspects of entropy, following Jüngel.\(^{15} \)

One of the first definitions was inspired by observations of Carnot\(^{16} \) concerning heat machines and the use of heat as source of mechanical energy. Based on this observations, Clausius\(^{17} \) defined “entropy” as a measure of the usefulness of energy with the view on physical work. Later, Boltzmann\(^{18} \) defined entropy in statistics and described with this term the connection between the microstates of particles and the macrostate of gas. Planck\(^{19} \) added to this definition the new idea of irreversibility of processes, which is a result of a nondecreasing manner of entropy in isolated systems. Shannon\(^{20} \) interpreted the concept of entropy in information theory. He described the loss in information during transportation with the term of entropy.

This overview is not complete, and there are aspects missing. Nevertheless, we find a few superior concepts in the different aspects of entropy. Based on a thermodynamic point of view, entropy characterizes the reversibility of processes and defines a direction of time in the case of irreversible processes. This concept is named as arrow of time.\(^{21} \) Besides, entropy can be seen as a measure of the disorder or the order of a system. In this meaning, entropy is nondecreasing in time. The definition of entropy as a nondecreasing quantity is in common with the second law of thermodynamics. Boltzmann proposed already in 1872 an entropy functional, which is nondecreasing in time and which is based on a local Lyapunov functional.\(^{22} \)

We return to these two aspects of entropy later when we interpret entropy in the field of reaction-diffusion equations and the interaction of species.

Before that, we have a look on the role of entropy in mathematics and especially in partial differential equations. In contrast to the definition in physics, in mathematics, the entropy is usually defined as a nonincreasing quantity. The entropy is, from the mathematical point of view, a functional, which is positive and decreasing—or at least nonincreasing—in time. Nevertheless, it still describes the irreversibility of time and a directed evolution of an order concept.

For hyperbolic equations, the existence of an entropy functional allows to choose a unique weak solution of the equation.\(^{23} \)
In the context of parabolic equations, entropy methods are often used to show the tendency towards spatially homogeneous solutions.\textsuperscript{24} Besides, there are entropy methods for reaction-diffusion equations, and they are used for showing the decay towards an equilibrium, for example, the solutions of systems with mass conservation.\textsuperscript{25}

We follow this theory and use an entropy functional for showing the tendency towards a homogeneous solution or for showing that, if there does not exist an entropy functional, the system needs not necessarily to decay towards such a homogeneous solution. As said in Equation (3) in Section 2, we interpret stationary spatially inhomogeneous solutions as chronic liver infections where the virus is unequally spread in the liver but persists. Solutions, which decay to a zero-solution, are interpreted as healing infections, see Equation (2). Remember, the model in Equation (1) is able to show both different infection courses depending on the used parameter values.

If there is an entropy functional for our model for hepatitis in Equation (9), which is independent of the parameter values, only healing courses can be reproduced. If there exists no entropy functional, solutions connected to chronic infections are possible.

For this reason, we first define the entropy concept of a reaction-diffusion system.

**Definition 1.** An entropy of a reaction-diffusion system like in Equation (1) with the solution $q(t, x)$ is a quantity $S(t) = S[q](t)$, which fulfills

\begin{equation}
\begin{aligned}
(a) & \quad S \in C^1([0, \infty)), \\
(b) & \quad S(t) \geq 0, \\
(c) & \quad \frac{d}{dt}S(t) \leq 0 .
\end{aligned}
\end{equation}

Mathematically, entropy is a Lyapunov functional depending on the time.\textsuperscript{15} We prove a lemma that gives us the relation between a Lyapunov functional $L = L(q)$ of the position-independent system $\dot{q} = f(q)$ and an entropy functional $S = S[q](t)$ in the way

\begin{equation}
S = S[q](t) = \int_{\Omega} L(q(t, x)) \, dx .
\end{equation}

A Lyapunov functional for a system $\dot{q} = f(q)$ with $q(0) = q_0$ is defined as functional $L = L(q)$ with

\begin{equation}
\begin{aligned}
(a) & \quad L(t) \geq 0, \\
(b) & \quad \frac{d}{dt}L(q(t)) \leq 0 \quad \text{for all solutions } q = q(t).
\end{aligned}
\end{equation}

**Lemma 2.** If $S = S[q](t) = \int_{\Omega} L(q(t, x)) \, dx$ is an entropy functional of Equation (1), the functional $L$ must be a Lyapunov functional of $\dot{q} = f(q)$.

**Proof.** The proof simply uses position-independent solutions $q(t, x) = q_c(t)$, so, these solutions are locally constant. Such solutions exist because locally constant solutions stay constant for increasing $t$ as long as the terms in Equation (1) do not depend on the position $x$ directly. Therefore,

\begin{equation}
S[q_c](t) = |\Omega| \cdot L(q_c(t))
\end{equation}

holds true.

Since an entropy functional must not increase for any $q = q(t, x)$, so, in particular, it must not increase for $q(t, x) = q_c(t)$. Consequently, $\frac{d}{dt}S[q_c](t) \leq 0$ is equivalent to $\frac{d}{dt}L(q_c(t)) \leq 0$, and $\frac{d}{dt}S[q](t) \leq 0$ for all $q = q(t, x)$ implies

\begin{equation}
\frac{d}{dt}L(q_c(t)) = \nabla_q L(q_c(t)) \cdot f(q_c) \leq 0
\end{equation}

for all $q \in \mathbb{R}^2$, which are identified with $q_c$. \hfill \Box

In the next step, we try to find an entropy functional for the model in Equation (9). Finding a Lyapunov functional for a system is quite difficult because there is no systematic approach. The model in Equation (9) is based on a Lotka-Volterra system. Therefore, we try to use the standard Lyapunov functional for a classical Lotka-Volterra system and formulate the following lemma, where the classical Lotka-Volterra system is adapted to the reaction terms in Equation (9) and therefore partly scaled.
**Lemma 3.** The classical Lotka-Volterra system $\dot{\mathbf{q}} = f_{LV}(\mathbf{q})$ with $\mathbf{q} = (u, v)^T$ and

$$
\dot{u} = f_{LV1}(u, v) = u - \gamma u v, \quad \dot{v} = f_{LV2}(u, v) = \eta(u v - v) = -\eta(1 - u)v
$$

has the Lyapunov functional

$$
L(u, v) = \eta(u - \ln u) + \gamma v - \ln v - (1 + \ln \gamma + \eta).
$$

**Proof.** First, the Lyapunov functional $L(\mathbf{q}) = L(u, v)$ is a convex functional with

$$
\min_{\mathbf{q} \in \mathbb{R}_+^2} L(\mathbf{q}) = \min_{u, v > 0} L(u, v) = L \left( 1, \frac{1}{\gamma} \right) = 0.
$$

From $\nabla L(\mathbf{q}) \cdot \mathbf{f}(\mathbf{q}) = L_{u}f_{LV1} + L_{v}f_{LV2} = 0$ follows $\frac{d}{dt} L(u(t), v(t)) = 0$ for all initial conditions $\mathbf{q}(0) = (u(0), v(0))$ in the first quadrant. □

Now, we take the functional $S(t) = S(\mathbf{q}(t))$ from Equation (25) as a candidate for an entropy functional of our system in Equation (9). As a next step, we check for the conditions for an entropy functional. The function $g_{1}(u) = u - \ln u$ is positive for $u > 0$ and has the global minimum $g_{1}(1) = 1$. Analogously, $g_{2}(v) = \gamma v - \ln v$ is positive for $v > 0$ and has its minimum at $v = \gamma^{-1}$ with $g_{2}(\gamma^{-1}) = 1 + \ln \gamma$. Therefore, $L(u, v) \geq 0$ yields for $u, v > 0$, and we find $\min_{u, v > 0} L(u, v) = 0$ like in Equation (28). For $u, v > 0$, we find $L \in C^1$. So, the most important condition on an entropy functional is still to check.

The time derivative of $S$ is handled by the chain rule, and we get

$$
\frac{d}{dt} S(t) = \int_{\Omega} \frac{d}{dt} L(\mathbf{q}(t, \mathbf{x})) \, d\mathbf{x} = \int_{\Omega} \frac{d}{dt} L(u(t, \mathbf{x}), v(t, \mathbf{x})) \, d\mathbf{x} = \int_{\Omega} \nabla_{u} L(u, v) \cdot \left( \frac{\dot{u}}{\dot{v}} \right) \, d\mathbf{x}.
$$

By using $\dot{\mathbf{q}} = \mathbf{f}(\mathbf{q}) + D\Delta \mathbf{q}$ from Equation (1), we get

$$
\frac{d}{dt} S(t) = \int_{\Omega} \nabla_{u} L(\mathbf{q}) \cdot \mathbf{f}(\mathbf{q}) + \nabla_{v} L(\mathbf{q}) \cdot D\Delta \mathbf{q} \, d\mathbf{x}.
$$

Now we consider $\mathbf{f}(\mathbf{q}, \mathbf{x}) = \mathbf{f}(u, v, \mathbf{x})$ in Equation (9) and the proposed Lyapunov functional of the classical Lotka-Volterra equations. We find

$$
\nabla_{u} L(\mathbf{q}) \cdot \mathbf{f}(\mathbf{q}) = \left( \frac{\eta \left( 1 - \frac{1}{u} \right)}{\gamma - \frac{1}{v}} \right) \cdot \left( f_{LV1} + w_{A}(u) u - u \right)
$$

$$
\quad = -\eta(1 - u)(w_{A}(u) - 1) + \delta f \left( u \right) \left( \gamma - \frac{1}{v} \right),
$$

where the first term is positive for all $u \in [0, 1]$ because of $w_{A}(u) < 1$. The second term is positive if $v > \frac{1}{\gamma}$. For homogeneous, that means position-independent, populations $u(t, \mathbf{x}) = u(t)$ and $v(t, \mathbf{x}) = v(t)$, the Laplacian is zero. Consequently, in this scenario,

$$
\frac{d}{dt} S(t) = \int_{\Omega} \nabla_{u} L(\mathbf{q}) \cdot \mathbf{f}(\mathbf{q}) + \nabla_{v} L(\mathbf{q}) \cdot D\Delta \mathbf{q} \, d\mathbf{x} = \int_{\Omega} \nabla_{u} L(\mathbf{q}) \cdot \mathbf{f}(\mathbf{q}) \, d\mathbf{x} > 0
$$

yields for populations with $v(t, \mathbf{x}) = v > \frac{1}{\gamma}$. The requirement $\frac{d}{dt} S(t) \leq 0$ in Definition 1 is therefore not fulfilled for all $u, v$. Therefore, the standard Lyapunov functional of the classical Lotka-Volterra system in Equation (27) is not suitable as a Lyapunov functional for the proposed model in Equation (9).

For gaining a first impression about possible entropy functionals, we analyze the reduced model in Equation (11) instead of model (9). As given in Equation (12), the reduced model is of the type $\dot{\mathbf{q}} = f(u) + \alpha \Delta u$ with homogeneous Neumann boundary conditions and the reaction function

$$
f(u) = (1 - u) \frac{u - \epsilon}{u + \kappa} u - \tilde{\gamma} u.
$$

This function has different zero sets depending on the parameters introduced in Section 2.1. We treat the two parameters $\kappa$ and $\epsilon$ of the Allee effect as constant. The third parameter $\tilde{\gamma}$ is a product of the T cell population $v$, which is assumed to be
constant in this reduced model in Equation (11), and the parameter $\gamma$ describing the decay of the virus caused by T cells.

Now, we regard the influence of this parameter on the properties of $f$.

Figure 1 shows examples of $f$ with $\epsilon = 0.1$ and $\kappa = 0.05$ for a weak immune reaction, $\tilde{\gamma} = 0.3$, and a stronger immune reaction $\tilde{\gamma} = 0.8$.

The reaction function in Figure 1A with a small $\tilde{\gamma}$ has three zeros, whereas the reaction function in Figure 1B, linked to a strong immune reaction, is negative for all positive population sizes $u$. This observation is generalizable because there is a threshold $\gamma_{th}$ where $u^*$ and $u_{max}$, comp. Figure 1a, coincide. Smaller $\tilde{\gamma}$ make $f$ to have three zeros $\{0, u^*, u_{max}\}$, and larger $\tilde{\gamma} > \gamma_{th}$ provoke negative $f(u)$ for all positive $u$. For the qualitative case in Figure 1B, we observe the following lemma about the mean population

$$\bar{u}(t) = \frac{1}{|\Omega|} \int_{\Omega} u(t, x) \, dx. \quad (31)$$

**Lemma 4.** If $f(u) < 0$ for all $u > 0$ holds true in Equation (11), then the mean population $\bar{u}$ decreases. If, furthermore, there exists a $\varphi > 0$ with $f(u) < -\varphi u$ for all $u \geq 0$, then the mean population $\bar{u}$ converges to zero.

**Proof.** We find the time derivative of the mean population

$$\dot{\bar{u}} = \frac{1}{|\Omega|} \int_{\Omega} f(u) \, dx + \alpha \Delta u \, dx = \frac{1}{|\Omega|} \int_{\Omega} f(u) \, dx$$

by use of Gauss's divergence theorem and due to the homogeneous Neumann boundary conditions. Consequently, if $f(u)$ is negative, the time derivative of the mean population $\dot{\bar{u}}$ decreases.

Next, we use $f(u) < -\varphi u$ and get

$$\dot{\bar{u}} = \frac{1}{|\Omega|} \int_{\Omega} f(u) \, dx < -\frac{\varphi}{|\Omega|} \int_{\Omega} u \, dx = -\varphi \bar{u}. \quad (32)$$

This is an ordinary differential equation with an exponential decay and thus $\lim_{t \to \infty} \bar{u}(t) = 0$ holds true.

**Remark 1.** Since $u \geq 0$ for all $x \in \Omega$, Equation (32) implies $\lim_{t \to \infty} u(t, x) = 0$ for all $x \in \Omega$.

So, if $f$ is negative for all positive $u$, which is connected to a strong immune reaction, the population size decreases. This suits the observation from the analysis of model (9) that a strong immune reaction is connected with the healing of the infection. A weaker immune reaction allows chronic infections. This fits to the positivity of $f$ for a medium population size of $u$.

We now take a closer look at a reaction function with a rather weak immune reaction like in Figure 1A. We discuss the tendency towards stationary inhomogeneous solutions for the case of an interval $\Omega \subset \mathbb{R}^1$.

**FIGURE 1** Reaction function $f$ of the reduced model in Equation (11) with different strengths of the immune reaction. (A) $f$ with small $\tilde{\gamma} = 0.3$ in a weak immune reaction and (B) $f$ with larger $\tilde{\gamma} = 0.8$ modeling a stronger immune reaction.
Now, we regard the three zeros of $f$ from Figure 1A. If we consider the ordinary differential equation $\dot{u}(t) = f(u)$, there are two stable equilibria, which are 0 and $u_{\text{max}}$, and one unstable equilibrium $u^*$. Every solution of the stationary partial differential equation is a candidate for a stationary spatially inhomogeneous solution of Equation (11). The stationary version of Equation (12) in the one-dimensional case is

$$-\alpha \Delta u(x) = -\alpha u''(x) = f(u) \quad \text{for} \quad x \in \Omega \subset \mathbb{R}^1$$

with homogeneous Neumann boundary conditions $u'(x) = 0$ for $x \in \partial \Omega$. The zeros of $f$ are as well zeros of $u''(x)$. Additionally, a positive value of $f(u)$ leads to a negative curvature of $u(x)$ and vice versa. Up to mirroring, the only possible qualitative behavior of $u$, respecting the boundary conditions and the sign of $f$, is therefore displayed in Figure 2. The reflection point of $u$ at the unstable zero $u^*$ of $f$ is denoted by $u^* = u(x^*)$.

Analogously to Lemma 4, it is clear that a solution $u = u(x,t)$ with $u(0,x) < u^*$ for all $x \in \Omega$ and thus $f(u(0,x)) < 0$ for all $x \in \Omega$ tends to the constant solution $u \equiv 0$. Similarly, a solution with $u(0,x) > u^*$ for all $x \in \Omega$ and thus $f(u(0,x)) > 0$ for all $x \in \Omega$ tends to $u \equiv u_{\text{max}}$.

Other possible stationary solutions $u_{\text{st}} = u_{\text{st}}(x)$ pass $u^*$, so that we have $f(u_{\text{st}}) > 0$ and $f(u_{\text{st}}) > 0$ simultaneously in certain areas of the interval $\Omega \subset \mathbb{R}$. We find the qualitative behavior of the stationary solution $u_{\text{st}}$ near $x^*$ shown in Figure 2. In every neighborhood of $x^*$, values $u$ smaller than $u^*$ and larger values than $u^*$ occur. Without loss of generality, we regard the case that $u'(x) > 0$ and thus $u(x) > u^*$ for $x > x^*$ in the neighborhood. Now, we ask whether the stationary solution $u_{\text{st}}$ exists and whether it might be the stable limit for $t \to \infty$ of Equation (11) with $f$ from Equation (30). Since $u_{\text{st}}(x) \equiv u^*$ is a stationary solution, too, first we regard small disturbances of this stationary solution and a linearized $f$. Later, we will discuss functions $f$ with curvature.

Now we study Equation (12) with a linearized version of $f$ from Equation (30). With the middle zero $u^*$, compare Figure 1A, we linearize $f$ by $f_{\text{lin}}(u) = \mu(u - u^*)$ in the neighborhood of $u^*$. Due to the shape of $f$, we get $\mu = f'(u^*) > 0$. We regard

$$u_t = \alpha u_{xx} + \mu(u - u^*) \quad \text{for} \quad x \in (0,\pi)$$

with homogeneous Neumann boundary conditions $u'(x) = 0$ for $x \in [0,\pi]$. Equation (34) has the stationary solution $u_{\text{st}} = u^*$ for all $t$ and $x$. Studying Equation (34) with $f_{\text{lin}}$ enables us to discuss the stability of the stationary solution and to investigate how small disturbances evolve.

We easily see that any constant disturbance $u(0,x) = u^* + \beta_0(x)$ with a value $\beta_0 \in \mathbb{R}$ independent of $x$ leads to $\dot{\beta}_0(t) = \mu \beta_0(t)$ with positive $\mu$. Thus, the mean $\bar{u}(t) = u^* + \beta_0(t)$ drifts off exponentially.

**Lemma 5.** The stationary solution $u_{\text{st}} = u^*$ of Equation (34) is stable against all disturbances with vanishing integral, if and only if $\alpha > \mu = f'_{\text{lin}}(u^*)$ yields.

**Proof.** We write the disturbance fulfilling the homogeneous Neumann boundary condition as Fourier series

$$u(0,x) - u^* = \sum_{k=1}^{\infty} \beta_k(t) \cos kx \quad \text{with} \quad \int_0^\pi u(0,x) - u^* \, dx = 0.$$  

**FIGURE 2** Qualitative shape of a solution $u_{\text{st}}$ of the one-dimensional stationary problem in Equation (33) near $x^*$, without loss of generality on $\Omega = (0,\pi)$, because scaling of the x-axis does not affect the qualitative shape.
The partial differential equation separates to ordinary differential equations for the Fourier coefficients \( b_k(t) \) as
\[
\dot{\beta}_k(t) = (-\alpha k^2 + \mu)\beta_k(t). \tag{36}
\]

If and only if \( \alpha > \mu \), we find \( \lim_{t \to \infty} \beta_k(t) = 0 \) for all \( k \in \mathbb{N} \).

Lemma 5 applies for Equation (12) for small disturbances and contains the known fact that strong diffusion effects damp weaker reaction terms.

**Remark 2.** Scaling in time \( \frac{d}{dt} = \frac{dr}{dt} \) with \( \frac{dr}{dt} = \alpha \) leads to \( u_r = u_{xx} + \frac{\nu}{\alpha}(u - u^*) \) and \( \alpha > \mu \) is conserved by \( 1 > \frac{\nu}{\alpha} \).

Scaling in space \( \frac{d^2}{dx^2} = \left( \frac{d}{dx} \right)^2 \frac{d^2}{dx^2} \) with \( \frac{d}{dx} = \frac{1}{\sqrt{\alpha}} \) leads to \( u_r = u_{xx} + \mu(u - u^*) \) and changes \( \alpha > \mu \) into \( 1 > \mu \). That means that a small diffusion coefficient \( \alpha \) corresponds to a large domain \( \Omega = \left( 0, \frac{\pi}{\sqrt{\alpha}} \right) \).

**Remark 3.** Lemma 5 and, in particular, Equation (36) show that high spatial oscillations quickly fade out and that a possible non-equilibrating solution behavior lies in the low-frequent solution parts for small \( k \).

In an abstract manner, this corollary reflects the biological observation that mice, which have relatively small livers, are seldom infected with chronic hepatitis.\(^2^6\)

**Corollary 1.** A small domain or a large \( \alpha \) correspond to a stable stationary solution \( u_{st} = u^* \). A tendency to an inhomogeneous solution is only possible for a large domain or a small \( \alpha < \mu \).

**Remark 4.** A disturbance from Equation (35) applied to Equation (12) with a more general function \( f \) with \( f''(u^*) \neq 0 \) leads to a drift of the mean population \( \bar{u} \) because, in general, we find
\[
\dot{\bar{u}}(t) = \int_0^\pi f \left( u^* + \sum_{k=1}^{\infty} \beta_k(t) \cos kx \right) \, dx \neq 0
\]
already for small coefficients \( \beta_k, k = 1, 2, \ldots \), that means, all disturbances will drift off.

Only in the case that \( f \) is odd with respect to \( u^* \), so \( f(u^* - v) = -f(u^* + v) \), we find
\[
\int_0^\pi f \left( u^* + \sum_{k \text{ odd}} \beta_k \cos kx \right) \, dx = 0
\]
and get a theoretically disturbance with odd frequencies \( k \) only, which conserves \( \bar{u} = u^* \). Of course, all realistic examples contain even frequencies at least in the range of the numerical rounding accuracy.

These investigations show that the one-component system in Equation (12) inherits the chronification tendency of Equation (9) in the case \( \alpha < \mu \), so, small disturbances are amplified, even if the drift off of \( \bar{u} \) dominates this separating chronification effect.

The separation of the drift off and the chronification tendency in Equation (12) gives us two equations:
\[
\dot{\bar{u}} = \frac{1}{|\Omega|} \int_{\Omega} f(u(t, x)) \, dx \tag{37}
\]
and
\[
\dot{z}(t, x) = \alpha \Delta z + f(z) - \frac{1}{|\Omega|} \int_{\Omega} f(z) \, dx. \tag{38}
\]

So, the variable \( z = z(t, x) \) can be seen as the development of the disturbance when the drift \( u - u^* \) is equalized by subtracting \( \dot{\bar{u}} \). The condition \( \alpha < \mu \) for the chronification turns into \( \alpha < f'(u^*) \).

Figure 3 compares a spatially inhomogeneous solution of Equation (9) with the chronification tendency in Equation (38) as a representative of Equation (16). If the reaction parameters, the diffusion constant, and the area \( \Omega \) fulfill certain conditions, the model in Equation (9) may have a spatially inhomogeneous solution.\(^9\) Figure 3A shows this tendency towards a solution of this type, which is interpreted as a chronic infection. For the one-population model in Equation (16),
we find two effects. On the one hand, we observe a drift of the population and, on the other hand, we find the tendency towards an inhomogeneous stationary solution. The solution of Equation (37) describes the drift, whereas the solution \( z \) of Equation (38) tends to a spatially inhomogeneous solution. Figure 3B shows the tendency of \( z \). This separated behavior is comparable with the tendency of the two-population model towards stationary, spatially inhomogeneous solutions. We chose a parameter set, where the tendency towards the spatially inhomogeneous solutions starts after some time. The initial conditions in Figure 3 are very small random variations around a small amount.

Now, we show that there exists no entropy functional based on a Lyapunov functional like in Equation (25) for reaction functions like in Figure 1A with three zeros and a sign change at each zero.

**Theorem 1.** Let \( u \) be a solution of the reaction-diffusion system (12) with a continuous reaction function \( f : [0, \infty) \to (-\infty, \infty) \). Let the reaction function be such that it has exactly three zeros \( 0 < u^* < u_{\text{max}} \) and fulfills \( f(u) < 0 \) for \( u \in (0, u^*) \) and for \( u > u_{\text{max}} \) and \( f(u) > 0 \) for \( u \in (u^*, u_{\text{max}}) \).

Then, there exists no entropy functional \( S[u](t) : C(\overline{\Omega}) \to \mathbb{R} \) with \( \frac{dS}{dt} \leq 0 \) and \( S[u](t) \geq 0 \) for all \( t > 0 \).

**Proof.** Let \( x \in \mathbb{R} \), so that, \( \Omega \subset \mathbb{R}^1 \). Due to Lemma 2, assume a functional \( S : C(\overline{\Omega}) \to \mathbb{R} \) with

\[
S[u](t) = \int_{\Omega} L(u(t,x)) \, dx
\]  

(39)

based on a Lyapunov functional \( L \), like in Equation (25). Then, if \( S \) is an entropy functional, it fulfills the one-dimensional version of Equation (29) which is

\[
\dot{S} = \frac{d}{dt} S[u](t) = \int_{\Omega} \frac{dL(u)}{du} \cdot \frac{du}{dt} \, dx = \int_{\Omega} \frac{dL(u)}{du} \left( f(u) + \alpha \frac{d^2 u}{dx^2} \right) \, dx < 0.
\]  

(40)

With partial integration and with respect to the homogeneous boundary conditions of \( u \), we get

\[
\dot{S} = \int_{\Omega} \frac{dL(u)}{du} f(u) - \alpha \left( \frac{d^3 L(u)}{du^3} \frac{du}{dx} \right) \, dx < 0.
\]  

(41)

In the next step, we take two different initial data and look whether the requirement \( \dot{S} < 0 \) for the entropy \( S \) might be fulfilled at least for the particular choice of these initial conditions. First, we take initial conditions \( u(0,x) = u_0(x) = \text{const} \). Then, the derivative of \( u \) with respect to \( x \) is zero, and we get the condition

\[
\int_{\Omega} \frac{dL(u)}{du} f(u) \, dx < 0.
\]  

(42)
This is fulfilled for every possible functions $u = u(\cdot, x)$ if and only if

\[
\text{sign}(L'(u)) = -\text{sign}(f(u)).
\] (43)

Second, we take initial conditions $u_0(x) = u^*$ for $x \in \Omega \setminus B_r(x_0)$ and $0 < u_0(x) < u^*$ for $x \in B_r(x_0)$, where $x_0$ and $r$ are such that $B_r(x_0) \subset \Omega$. Then, the first term in Equation (40) is negative due to Equation (42). In the second term, we find the squared term $\left( \frac{d}{dx} u \right)^2$ and the factor $-\frac{d^2}{dx^2} L(u)$. This factor is zero for $x \in \Omega \setminus B_r(x_0)$ and due to Equation (9) and the shape of $f$ non-positive for $x \in B_r(x_0)$. The squared term is potentially unbounded, therefore it is not true that the derivative of $S$ is negative for all possible initial conditions.

Therefore, an entropy functional of the form (39) does not exist for a reaction function with the shape of $f$ for small $\tilde{\gamma}$. Due to Lemma 2, this assertion holds true for any entropy functional.

For the shape of $f$ on the right-hand side in Figure 1B, we show the existence of an entropy functional $S$. The reaction function for a strong immune reaction is negative for all $u > 0$. The integral over $\frac{d}{du} L(u) \cdot f(u)$ in the derivative of $S$ in Equation (41) is negative if the derivative of $L$ is positive for all $u$. The second term in Equation (41) is the integral over the squared derivative of $u$ multiplied with the second derivative of $L$. If the second derivative of $L$ is a positive constant, the condition of a negative slope of $S$ is fulfilled.

For example, the Lyapunov functional $L(u) = u^2$ fulfills both conditions on the first and second derivatives. So, we found an entropy functional for reaction functions $f < 0$ for all $u > 0$. Therefore, the virus population $u$ decays to zero in time in the case of a negative reaction function associated with a strong immune reaction. This is in accordance with Lemma 4.

To summarize, we have studied the model in Equation (11), which is a submodel of Equation (9). For this submodel, we have shown that there does not exist an entropy functional for a reaction function with a weak immune reaction and therefore a small $\tilde{\gamma}$. For a strong immune reaction, we find an entropy functional. The population $u$ therefore tends to zero in time, which fits to the observation that strong immune reactions lead to a healing infection course.

In Section 4.2, we discuss the possibility of passing some of the submodel properties to the two-populations model.

4 | CONCLUSIONS

We summarize our results and interpret them in the context of the presented models and submodels.

4.1 | Resume of model properties

Our aim was to find conditions on the reaction function $f$ from Equation (1) in order to classify reaction functions which lead to solutions describing two different behaviors. We generalize the reaction function in Equation (9) for considering the uncertain mechanisms behind the reaction functions.

We found a requirement for non-negative solutions in Equation (17), which is a necessary condition for describing populations. The solutions of our reaction-diffusion system are continuously differentiable with respect to $u$ and $v$ if Equation (18) is fulfilled.

With the requirements in Equations (19), (21), (22), and (23), the solutions exist for all time, and they are unique. In more detail, we need bounded initial data, boundedness of $f_1$ by a function linear in $u$, a way of boundedness of $f_2$ and boundedness of $f_1$ and $f_2$ by a continuous function.

We further showed that the existence of an entropy functional of the submodel in Equation (11) is depending on the strength of the immune reaction but not on a certain function. The entropy describes in physics a measure of the order or disorder of a system. In this sense, we can interpret the entropy for our reaction-diffusion system. A spatially homogeneous state is in a high order, and it is connected to a low entropy, due to the term $\frac{d^2}{dx^2} L$ in Equation (40). For systems tending towards the zero state, there exists an entropy functional. The entropy functional is decaying in time and therefore describing the increase of the order in the system.

This interpretation is as well consistent with the interpretation of entropy following Shannon. There, the entropy is a measure for the average information of a message. A solution $q$ at a time $t$ has different quantities of information about how the system evolved until that time $t$ and how it will evolve afterwards. For example, solutions of the heat equations are decaying in the quantity of information they have. A concentrated heat quantity in the initial conditions spreads in space. After a while, it is impossible to reconstruct the exact initial condition because the same heat quantity might have evolved from a very concentrated heat or a lowly concentrated but wider spread heat. Therefore, the information in the
system decreases with time, just like a suitable entropy functional. Regarding this example, we easily find good reasons for the irreversibility of the time in the heat equation. If the time was reversible, the entropy and therewith the average information would increase with time. This is not consistent with our considerations. The same argument holds for the ill-posedness of the inverse heat equation.

We find a similar behavior in the reaction-diffusion equation describing liver infections. The average information of a solution describing a spatially homogeneous population is lower than the one of an inhomogeneous solution or a periodic solution. Regarding the two solutions linked to the typical infection courses, we find a decaying solution towards the zero state and a solution tending to a spatially inhomogeneous stationary state. The decay to zero occurs for a strong immune reaction, and in this case, we find an entropy functional for the submodel. In the other case, we have shown the nonexistence of an entropy functional, and we find a non-decay of information in the solution. This non-decay opens the possibility to find chronification effects.

4.2 Hierarchy of models

We looked at models with different sizes and properties. In Figure 4, the models are arranged in a hierarchical order. The two-population model in a general form is the highest model in the arrangement. The properties of this model are passed on to models in a lower order. Of course, not all properties are passed on to all lower order models. Every smaller model in this model family is a submodel of the more general model with respect to some selected properties. In Section 2.2, we have argued how the submodels evolved from the larger model. Now, we discuss which properties are inherited from a larger model or which properties are passed on to a larger model.

The requirements for the global existence and uniqueness of a solution are formulated for the general reaction-diffusion system in Equation (1). We tested them for the specific model for liver infections in Equation (9). Both lower-ordered models are fulfilling as well the requirements for global existence and uniqueness. That property of Equation (9) is therefore passed on to the submodels (11) and (16).

In Theorem 1, we formulated a requirement on the reaction function in Equation (12), respectively, Eq. (11). The property of a parameter-depending existence of an entropy would be transferable to the system in Equation (1) with the conditions on $f$ like in Theorem 1, if $f(q, x) = f(q)$ yields. Unfortunately, the system in Equation (9) modeling liver infection does not fulfill this condition of a space-independent reaction function. The space-depending effects of $f$ might override the tendency towards a certain solution type. For this reason, the transfer of properties from submodels with space-dependent reaction functions to those with a space-independent reaction function is not possible.

Moreover, we cannot argue with examples about properties of a class of systems. The dashed arrow between the two classes of submodels for one population in Figure 4 is showing a direction in which a transfer is not possible.

The highest possibility for a transferable property is the link between the space-dependent submodel and the whole model. However, our main observation of chronic infections are spatially inhomogeneous solutions. If we build up a model, which is using local effects, of course we easily gain solutions with local effects. Therefore, part of the future work is the development of a space-independent reaction function.

In the prospect, we want to find further requirements on the reaction functions for gaining spatially inhomogeneous stationary solutions. Besides, we want to generalize the concept of entropy functionals for showing the longtime behavior of reaction-diffusion equations.
CONFLICTS OF INTEREST

The authors declare no potential conflict of interests.

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REFERENCES

1. Thomas E, Liang TJ. Experimental models of hepatitis B and C—new insights and progress. Nat Rev Gastroenterol Hepatol. 2016;13(6):362-374.
2. WHO. Global hepatitis report, 2017. World Health Organization and Global Hepatitis Programme; 2017.
3. Schiff ER, Maddrey WC, Reddy KR. Schiff's diseases of the liver, 12 ed. Chichester, West Sussex: John Wiley and Sons Ltd; 2018.
4. Kanel GC. Pathology of liver diseases. Hoboken, NJ: John Wiley & Sons, Inc; 2017.
5. Liang P, Zu J, Zhuang G. A literature review of mathematical models of hepatitis B virus transmission applied to immunization strategies from 1994 to 2015. J Epidemiol. 2016;28(5):221-229.
6. Aston P. A new model for the dynamics of hepatitis C infection: derivation, analysis and implications. Viruses. 2018;10(4).
7. Hattaf K, Yousfi N, Tridane A. Stability analysis of a virus dynamics model with general incidence rate and two delays. Appl Math Comput. 2013;221:514-521.
8. Goyal A, Murray JM. Modelling the impact of cell-to-cell transmission in hepatitis B virus. PLoS ONE. 2016;11(8):e0161978.
9. Kerl HJ, Langemann D, Vollrath A. Reaction diffusion equations and the chronification of liver infections. Math Comput Simulat. 2012;82(11):2145-2156.
10. Allee WC. Principles of animal ecology. Philadelphia: Saunders Co.; 1949.
11. Stephens PA, Sutherland WJ. Consequences of the Allee effect for behaviour, ecology and conservation. Trends Ecol Evol. 1999;14(10):401-405.
12. Hollis SL, Martin RH, Pierre M. Global existence and boundedness in reaction-diffusion systems. SIAM J Math Anal. 1987;18(3):744-761.
13. Rothe F. Global solutions of reaction-diffusion systems, No. 1072 in Lecture Notes in Mathematics. Berlin: Springer; 1984.
14. Friedman A. Partial differential equations. Huntington, New York: R. E. Krieger Pub. Co; 1976.
15. Jüngel A. Entropy methods for diffusive partial differential equations. Cham: Springer; 2016.
16. Carnot NLS. Réflexions sur la puissance motrice du feu et sur les machines propres à développer cette puissance. Gauthier-Villars: Imprimeur-Libraire; 1878.
17. Clausius R. Ueber die Beziehung zwischen dem zweiten Hauptsatze des mechanischen Wärmetheorie und der Wahrscheinlichkeitsrechnung, respective den Sätzen über das Wärmegleichgewicht. Akademie der Wissenschaften in Wien, Mathematisch-naturwissenschaftliche Klasse Sitzungsberichte. 1877:373-435.
18. Boltzmann L. Weitere Studien über das Wärmegleichgewicht unter Gasmolekülen. Wiesbaden: Vieweg Teubner Verlag; 1970;115225.
19. Evans LC. Partial Differential Equations, Graduate Studies in Mathematics. Providence, R.I.: American Mathematical Society; 1998.
20. Reisch C, Langemann D. Entropy functionals for finding requirements in hierarchical reaction-diffusion models for inflammations. Math Meth Appl Sci. 2020;43:10098-10114.

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