Mathematical Models and Methods in Applied Sciences

ENTROPY STRUCTURE OF A CROSS-DIFFUSION TUMOR-GROWTH MODEL

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The mechanical tumor-growth model of Jackson and Byrne is analyzed. The model consists of nonlinear parabolic cross-diffusion equations in one space dimension for the volume fractions of the tumor cells and the extracellular matrix (ECM). It describes tumor encapsulation influenced by a cell-induced pressure coefficient. The global-in-time existence of bounded weak solutions to the initial-boundary-value problem is proved when the cell-induced pressure coefficient is smaller than a certain explicit critical value. Moreover, when the production rates vanish, the volume fractions converge exponentially fast to the homogeneous steady state. The proofs are based on the existence of entropy variables, which allows for a proof of the nonnegativity and boundedness of the volume fractions, and of an entropy functional, which yields gradient estimates and provides a new thermodynamic structure. Numerical experiments using the entropy formulation of the model indicate that the solutions exist globally in time also for cell-induced pressure coefficients larger than the critical value. For such coefficients, a peak in the ECM volume fraction forms and the entropy production density can be locally negative.

Keywords: Tumor growth, encapsulation, cross diffusion, entropy variables, global existence of solutions, exponential decay of the solutions.

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1. Introduction

The modeling and simulation of tumor growth may provide biologists with complementary insight into the chemical and biological mechanisms which influence the development of solid tumors. Jackson and Byrne have developed in Ref. 19 a continuous mechanical model which gives some insight into tumor encapsulation and transcapsular spread. The model consists of strongly nonlinear cross-diffusion equations for the volume fractions of the tumor cells and the extracellular matrix (ECM). A particular feature of the model is tumor encapsulation which is triggered by the increase of the pressure of the ECM due to tumor growth. This increase is modeled by the cell-induced pressure coefficient $\theta \geq 0$. When $\theta > 0$, the ECM becomes more compressed as the tumor cell fraction increases. In this paper, we are interested in a mathematical analysis of this model.

From a mathematical point of view, the challenge is to deal with the cross-diffusion terms which prevent the use of standard tools such as maximum principles. Moreover, the diffusion matrix is neither symmetric nor positive definite such that even the local-in-time existence of solutions does not follow from standard results. In spite of these difficulties, we are able to prove the global-in-time existence of bounded weak solutions if $\theta \geq 0$ is smaller than an explicit critical value θ^* which depends on the cell and ECM pressure coefficients (see below). Numerical experiments show that for sufficiently large θ, a peak in the volume fraction of the ECM forms due to cross diffusion in the ECM equation.

From a more biological point of view, we show that the model, although its derivation is based on rather simplifying assumptions, possesses a surprising thermodynamic-type entropy structure: For sufficiently small $\theta \geq 0$ and vanishing tumor and ECM production rates, the logarithmic entropy is dissipated. Numerical experiments show that this holds true for $\theta > \theta^*$ but the entropy production density may become locally negative. The entropy structure is exploited in the mathematical analysis, since the entropy production provides a priori estimates for the gradients of the variables. Moreover, the entropy-variable formulation allows for a proof of the nonnegativity and boundedness of the solutions, thus circumventing the maximum principle.

Before explaining the entropy structure in detail, we review briefly the modeling of tumor growth (also see the monographs 1, 7). Tumor growth can be very roughly classified into three stages. The first stage is the avascular growth which is mostly governed by the proliferation of tumor cells. When the tumor grows, less and less nutrition is available for the cells in the tumor center, and the tumor starts developing its own blood supply (vascular stage). Later, the tumor cells are able to escape from the tumor via the circulatory system and lead to secondary tumors in the body (metastatic stage). The model considered in this paper describes the avascular stage only.

Most models for avascular tumor growth fall into two categories: discrete cell population models that track the individual cell behavior and continuum models that formulate the average behavior of tumor cells and their interactions with the tissue structure.[2] In the following, we concentrate on continuum models and in particular only on those which contain cross diffusion.

A possible continuum model ansatz is the use of reaction-diffusion equations. The system is then composed of mass balance equations for the cellular components, coupled to a system of reaction-diffusion equations for the concentrations of the extracellular substances. [2] The mass balance equations need to be closed by defining (or deriving) equations for the corresponding velocities. Roughly speaking, there are two classes of models: phenomenological and mechanical models (see Section 4 in Ref. 2).

In phenomenological models, it is assumed that the cells or the ECM do not move or that they move due to diffusion,[25] chemotaxis,[6] or other mechanisms. Mechanical models differ from phenomenological ones by the fact that the latter ones do not take into account mechanical causes of cell movement due to pressure produced by proliferating tumor cells to the surrounding tissue.[2] An example of such a model is given by Casciari et al.[5] When the cells are considered as an elastic fluid within a rigid ECM, the velocity may be closed according to the Darcy law, i.e., the velocity is proportional to the negative gradient of the pressure (see Formula (7) in Ref. 8 or Formula (4.4) in Ref. 2). Alternatively, the cell-matrix system may be supposed to behave as a viscous fluid, in which the stress depends on the viscosity,[3] as a viscoelastic fluid,[18] or as a cell mixture in a porous medium made of the ECM filled with extracellular liquid.[16] More details can be found in the review of Roose et al.[21]

The mechanical model of Jackson and Byrne[19] describes the growth and encapsulation of solid tumors. The mass balance equations for the volume fractions of the tumor cell, the ECM, and the water phases are supplemented by equations for the velocities, depending on the gradient of the corresponding pressure. It is assumed in Ref. 19 that the pressure of the tumor cells and the ECM increases with the respective volume fraction and that the presence of tumor cells induces an increase in the ECM pressure, which leads to a nonlinear term in the ECM pressure. The model is given by the following scaled equations in one space dimension for the volume fractions of the tumor cells c and the ECM m (see Section 2 for a sketch of its derivation),

$$\frac{\partial}{\partial t}\begin{pmatrix} c \\ m \end{pmatrix} - \left(D(c,m) \begin{pmatrix} c_x \\ m_x \end{pmatrix} \right)_x = R(c,m) \quad \text{in } \Omega,\ t > 0, \tag{1.1}$$

where $\Omega = (0,1)$, subject to the Neumann boundary and initial conditions

$$c_x = m_x = 0 \quad \text{on } \partial\Omega,\ t > 0, \quad c(\cdot,0) = c_0, \quad m(\cdot,0) = m_0 \quad \text{in } \Omega. \tag{1.2}$$

The mixture is supposed to be saturated, i.e., the volume fractions of the tumor cells c, the ECM m and water w sum up to one. Therefore, the volume fraction of water can be computed from $w = 1 - c - m$. Assuming that cell proliferation is proportional to the cell and water fractions (with rate γ), the tumor cells die with rate δ, and that the ECM production is proportional to all three fractions (with rate α), the net production rate is given by

$$R(c,m) = \begin{pmatrix} R_c(c,m) \\ R_m(c,m) \end{pmatrix} = \begin{pmatrix} \gamma c(1-c-m) - \delta c \\ \alpha c m (1-c-m) \end{pmatrix}. \tag{1.3}$$

The diffusion matrix

$$D(c,m) = \begin{pmatrix} 2c(1-c) - \beta\theta c m^2 & -2\beta c m (1+\theta c) \\ -2cm + \beta\theta(1-m)m^2 & 2\beta m(1-m)(1+\theta c) \end{pmatrix} \tag{1.4}$$

with the pressure coefficients $\beta > 0$ and $\theta \geq 0$ is generally neither symmetric nor positive definite, which makes the analysis of the above system quite challenging.

A key observation is that system (1.1)-(1.2) possesses an entropy functional if $\theta < \theta^* := 4/\sqrt{\beta}$. To explain this, we introduce the logarithmic entropy

$$
\begin{aligned}
H(c,m) &= \int_\Omega h(c,m)dx \qquad (1.5)\\
&= \int_\Omega \big(c(\log c - 1) + m(\log m - 1) + (1-c-m)(\log(1-c-m) - 1)\big)dx,
\end{aligned}
$$

where $h(c,m)$ is the entropy density, which is the sum of the logarithmic entropies of the three phases c, m, and $w = 1-c-m$. We call $-dH/dt$ the entropy production and its integrand the entropy production density. A computation, which is made rigorous in Section 3, shows that

$$
\begin{aligned}
&\frac{dH}{dt} + \int_\Omega \big(2c_x^2 + \beta\theta m c_x m_x + 2\beta(1+\theta c)m_x^2\big)dx \\
&\quad = \int_\Omega \Big(R_c(c,m)\log\frac{c}{1-c-m} + R_m(c,m)\log\frac{m}{1-c-m}\Big)dx.
\end{aligned}
$$

The right-hand side is bounded for all c, $m > 0$ satisfying $c+m < 1$. It turns out that the integrand of the second term on the left-hand side is a positive definite quadratic form in c_x and m_x if $\theta < \theta^*$, which provides gradient estimates for c and m.

Interestingly, system (1.1) features a formal gradient-flow structure. Indeed, introducing the entropy variables

$$
u = \frac{\partial h}{\partial c} = \log\frac{c}{1-c-m}, \quad v = \frac{\partial h}{\partial m} = \log\frac{m}{1-c-m}, \qquad (1.6)
$$

system (1.1) can be written as

$$
\frac{\partial}{\partial t}\begin{pmatrix} c \\ m \end{pmatrix} - \big(L(c,m)(\nabla h(c,m))_x\big)_x = R(c,m), \qquad (1.7)
$$

where the gradient $\nabla h(c,m) = (u,v)^\top$ is computed with respect to (c,m). The matrix $L = D(\nabla^2 h)^{-1}$ (with $\nabla^2 h$ being the Hessian of h with respect to (c,m)) becomes symmetric and positive definite if $\theta = 0$ and $c > 0$ and $m > 0$ satisfy $c+m < 1$. System (1.7) can be also written as $\rho_t = -\mathrm{grad}H|_\rho$, which is the more usual gradient-flow formulation, where $\rho = (c,m)^\top$ and grad is the gradient of the entropy functional H with respect to some metric involving the diffusion matrix L (see Ref. 24). Moreover, (1.7) can be interpreted as a parabolic system in the variables (u,v), where c and m are functions of (u,v). An important feature of the entropy-variable formulation (1.7) is that the inverse transformation

$$
c = \frac{e^u}{1+e^u+e^v}, \quad m = \frac{e^v}{1+e^u+e^v}
$$

leads automatically to positive volume fractions satisfying $c+m < 1$, which circumvents the maximum principle.

It has been shown in Ref. 12, 20 that the existence of an entropy is equivalent to the symmetry and positive definiteness of the transformed diffusion matrix. This has been exploited in several publications to provide a global-in-time existence analysis for models arising in physics and biology, see, e.g., Ref. 4, 9, 10, 11, 15, 17. The novelty in this paper is that system (1.1) does *not* possess this property for $\theta > 0$ which leads to additional difficulties.

We notice that a related cross-diffusion model has been analyzed in Ref. 4. This model describes a hopping system of two particles with size exclusion. It also features the entropy functional (1.5) and, consequently, the same entropy variables (1.6). The diffusion matrix of Ref. 4 in the entropy-variable formulation is diagonal which simplifies the analysis. However, this is not the case in our model (1.1).

In order to understand the solution behavior when $\theta > \theta^*$, we solve (1.1)-(1.2) using a (standard) finite-difference discretization. It turns out that the discretization of the entropy-variable formulation (1.7) is more stable than a direct discretization of (1.1). The numerical results show that for $\theta > \theta^*$, a peak forms in the volume fraction of the ECM, which may indicate a loss of regularity of the solution. The peak forming has been already observed in Ref. 19. In the absence of production rates, even for $\theta > \theta^*$, the entropy is numerically decreasing and, consequently, the entropy production $-dH/dt$ is positive. However, the entropy production density may be negative locally, which indicates that pointwise gradient estimates are not available. Thus, our analytical results, obtained from the entropy method, seem to be optimal. It is an open problem to prove the existence of global weak solutions for $\theta > \theta^*$.

Now, let us state our main results.

Theorem 1.1. *Let α, γ, $\delta \geq 0$, $\beta > 0$, $0 \leq \theta < 4/\sqrt{\beta}$, and let c_0, $m_0 \in L^1(\Omega)$ satisfy $c_0 \geq 0$, $m_0 \geq 0$, $c_0 + m_0 \leq 1$ in Ω, and $H(c_0, m_0) < \infty$. Then there exists a weak solution c, $m \in L^2_{\mathrm{loc}}(0,\infty; H^1(\Omega)) \cap H^1_{\mathrm{loc}}(0,\infty; (H^1(\Omega))')$ to (1.1)-(1.2) satisfying $c, m \geq 0$ and $c + m \leq 1$ in $\Omega \times (0,\infty)$.*

Although the method of our proof can be extended in principle to several space dimensions (as shown in, e.g., Ref. 9, 10), we consider the case of one space dimension only, since this is the situation of the original model in Ref. 19. To prove the theorem, we first discretize system (1.7) in time by the implicit Euler scheme with time parameter $\tau > 0$ and add the elliptic operator $-\varepsilon(u_{xx} - u, v_{xx} - v)^\top$ which guarantees the coercivity of the elliptic system in the entropy variables (u, v). Then we show the existence of semi-discrete weak solutions to the resulting nonlinear elliptic equations using the Leray-Schauder fixed-point theorem. A priori estimates are derived from the entropy inequality, as described above. These estimates are independent of τ and ε which allows us to pass to the limit $\tau \to 0$, $\varepsilon \to 0$ using weak compactness methods. The limit functions are weak solutions to the continuous problem (1.1)-(1.2).

When the net production terms vanish, we are able to prove the exponential decay of the weak solution (c, m) to the homogeneous steady state (c_0^*, m_0^*), where

$c_0^* = \int_\Omega c_0 dx$ and $m_0^* = \int_\Omega m_0 dx$ are assumed to satisfy c_0^*, $m_0^* > 0$ and $c_0^* + m_0^* < 1$. Although the long-time behavior of solutions is less important in the current tumor-growth model, it reveals a certain mathematical structure of the model equations. For the statement of the result, we define the relative entropy

$$\begin{aligned} H^*(c,m) &= \int_\Omega h^*(c,m)dx \\ &= \int_\Omega \Big(c \log \frac{c}{c_0^*} + m \log \frac{m}{m_0^*} + (1-c-m) \log \frac{1-c-m}{1-c_0^*-m_0^*} \Big) dx. \end{aligned} \tag{1.8}$$

Notice that for all (c,m) satisfying c, $m \geq 0$ and $c+m \leq 1$ such that $\int_\Omega c dx = c_0^*$ and $\int_\Omega m dx = m_0^*$, it holds that $H^*(c,m) \geq 0$.

Theorem 1.2. *Let the assumptions of Theorem 1.1 hold and let (c,m) be the bounded weak solution to (1.1)-(1.2) constructed in Theorem 1.1. Let $\alpha = \gamma = \delta = 0$ and let $c_0^* = \int_\Omega c_0 dx$, $m_0^* = \int_\Omega m_0 dx$ satisfy c_0^*, $m_0^* > 0$ and $c_0^* + m_0^* < 1$. Then there exist constants K, $\lambda > 0$ only depending on β, θ, c_0^*, and m_0^* such that*

$$\|c(\cdot,t) - c_0^*\|_{L^1(\Omega)} + \|m(\cdot,t) - m_0^*\|_{L^1(\Omega)} \leq K e^{-\lambda t} \sqrt{H^*(c_0,m_0)}.$$

The theorem is proved by estimating the discrete entropy production from below by the discrete relative entropy yielding an inequality which is solved by a discrete Gronwall-type argument. The main difficulty in the proof is that due to the regularizing ε-terms, the L^1-norms of the approximations of c and m are no longer conserved, and we need to control the dependence of these L^1-norms on ε. This is achieved by exploiting the Sobolev embedding $H^1(\Omega) \hookrightarrow L^\infty(\Omega)$ which is valid in one space dimension.

The paper is organized as follows. In Section 2 we sketch the derivation of the model (1.1). Theorems 1.1 and 1.2 are proved in Sections 3 and 4, respectively. Finally, numerical results using a finite-difference discretization are presented in Section 5.

2. Derivation of the model—scaling

For the convenience of the reader and to specify the biological assumptions, we sketch the derivation of the tumor-growth model following Jackson and Byrne.[19] They assume that the tumor-host environment, given by a fixed interval $(-\ell,\ell)$ with $\ell > 0$, consists of the tumor cells, the extracellular matrix (ECM), and interstitial fluid (water). Supposing that this mixture is saturated, the volume fractions of the tumor cells c, the ECM m, and water w sum up to one, $c+m+w = 1$. The tumor is assumed to expand symmetrically around $x = 0$ in one space direction such that it is sufficient to consider the interval $(0,\ell)$. Treating the tumor, the ECM, and the water phase as incompressible fluids with constant and equal densities, the mass balance equations for each phase are given by[14]

$$c_t + (cv_c)_x = R_c, \; m_t + (mv_m)_x = R_m, \; w_t + (wv_w)_x = R_w, \quad x \in (0,\ell), \; t > 0, \tag{2.1}$$

where v_c, v_m, and v_w are the velocities of the tumor, the ECM, and the water phase, respectively, and R_c, R_m, and R_w are the corresponding net production rates.

Supposing that the system is closed, the total net production vanishes, $R_c + R_m + R_w = 0$. Thus, together with the expression $c+m+w = 1$, the water volume fraction $w = 1 - c - m$ can be expressed in terms of c and m. In fact, adding all equations in (2.1) and recalling the tumor-growth symmetry, which implies that the velocities vanish at $x = 0$, we find that

$$wv_w = -cv_c - mv_m. \tag{2.2}$$

For the production terms, we make the following assumptions. The tumor cells proliferate at a rate being proportional to the cell and water fractions and they die at a rate being proportional to the cell fraction. The rate of the ECM production is proportional to all the volume fractions. This means that new ECM is produced only when all three phases are present. Hence, we obtain

$$R_c = \alpha_c cw - \delta_c c = \alpha_c c(1-c-m) - \delta_c c, \quad R_m = \alpha_m cmw = \alpha_m cm(1-c-m), \tag{2.3}$$

where α_c, α_m, $\delta_c \geq 0$, and the water production is computed from $R_w = -(R_c + R_m)$.

Next, we assume that inertial as well as external forces can be neglected. Then the momentum balance equations become the force balances

$$(c\sigma_c)_x + pc_x + F_{cm} + F_{cw} = 0, \tag{2.4}$$

$$(m\sigma_m)_x + pm_x - F_{cm} + F_{mw} = 0, \tag{2.5}$$

$$(w\sigma_w)_x + pw_x - F_{cw} - F_{mw} = 0, \tag{2.6}$$

where σ_j is the stress in phase $j = c, m, w$, p is a common pressure, and F_{ij} is the force which phase j exerts on phase $i \neq j$. We have to determine the stresses and forces.

The stresses are given by

$$\sigma_c = -(p + P_c), \quad \sigma_m = -(p + P_m), \quad \sigma_w = -p,$$

where the pressures P_c and P_m, respectively, distinguish the cell and the ECM phases from water. We assume that the pressures P_c and P_m are proportional to their respective volume fractions. Moreover, we expect that the tumor cells increase the ECM pressure but not inversely. Therefore, we write

$$P_c = s_c c, \quad P_m = s_m m(1 + \theta c), \tag{2.7}$$

where $s_c > 0$, $s_m > 0$ are constants, and $\theta \geq 0$ is a cell-induced pressure coefficient. When $\theta > 0$, the ECM becomes more compressed as the tumor cell fraction increases. By adding all three force balance equations (2.4)-(2.6), the force terms cancel and inserting the above expressions for P_c and P_m, since $(c + m + w)_x = 0$, we end up with

$$p_x = -(cP_c + mP_m)_x = -\big(s_c c^2 + s_m m^2(1 + \theta c)\big)_x. \tag{2.8}$$

Supposing that the forces are proportional to the difference of the fluid velocities and to their respective volume fractions, we have

$$F_{cm} = k_{cm}(v_m - v_c)cm, \quad F_{cw} = k_{cw}(v_w - v_c)cw, \quad F_{mw} = k_{mw}(v_w - v_m)mw.$$

The equations are significantly simplified when we take $k := k_{cm} = k_{cw} = k_{mw} > 0$. Indeed, using this simplification and replacing wv_w by (2.2) and w by $1 - c - m$, (2.4) becomes

$$(cP_c)_x + p_x c = F_{cm} + F_{cw} = k\big(-c(m+w)v_c + cmv_m + cwv_w\big) = -kcv_c.$$

Employing (2.8) to eliminate p_x and (2.7) to eliminate P_c and P_m, it follows that

$$cv_c = -k^{-1}\big((cP_c)_x + p_x c\big) = -k^{-1}\big((1-c)(s_c c^2)_x - c(s_m m^2(1+\theta c))_x\big).$$

In a similar way, we find that

$$mv_m = -k^{-1}\big((1-m)(s_m m^2(1+\theta c))_x - m(s_c c^2)_x\big).$$

These identities allow us to eliminate the velocities from the mass balance equations (2.1), leading to the system

$$\begin{aligned} c_t - k^{-1}\big((1-c)(s_c c^2)_x - c(s_m m^2(1+\theta c))_x\big)_x &= R_c, \\ m_t - k^{-1}\big((1-m)(s_m m^2(1+\theta c))_x - m(s_c c^2)_x\big)_x &= R_m, \end{aligned}$$

where $x \in (0,\ell)$, $t > 0$. Introducing the diffusion matrix

$$\widetilde{D}(c,m) = \frac{1}{k}\begin{pmatrix} 2s_c c(1-c) - s_m\theta cm^2 & -2s_m cm(1+\theta c) \\ -2s_c cm + s_m\theta(1-m)m^2 & 2s_m m(1-m)(1+\theta c) \end{pmatrix}$$

and inserting the production rates (2.3), the above system can be written as

$$\frac{\partial}{\partial t}\begin{pmatrix} c \\ m \end{pmatrix} - \left(\widetilde{D}(c,m)\begin{pmatrix} c_x \\ m_x \end{pmatrix}\right)_x = \begin{pmatrix} \alpha_c c(1-c-m) - \delta_c c \\ \alpha_m cm(1-c-m) \end{pmatrix}.$$

System (1.1) is obtained by rescaling time by $t_s = t/\tau$ and space by $x_s = x/\ell$, where $\tau = k\ell^2/s_c$. Then

$$\frac{\partial}{\partial t_s}\begin{pmatrix} c \\ m \end{pmatrix} - \left(D(c,m)\begin{pmatrix} c_{x_s} \\ m_{x_s} \end{pmatrix}\right)_{x_s} = \begin{pmatrix} \gamma c(1-c-m) - \delta c \\ \alpha cm(1-c-m) \end{pmatrix},$$

where $x_s \in (0,1)$, $t_s > 0$, $D(c,m)$ is defined in (1.4), $\alpha = \tau\alpha_m$, $\beta = s_m/s_c$, $\gamma = \tau\alpha_c$, and $\delta = \tau\delta_c$.

We remark that Jackson and Byrne[19] have employed a different scaling by setting $\tau = 1/\alpha_c$. Then, with $\beta_c = \tau s_c/(k\ell^2)$ and $\beta_m = \tau s_m/(k\ell^2)$, the scaled system writes as

$$\frac{\partial}{\partial t_s}\begin{pmatrix} c \\ m \end{pmatrix} - \left(D^{\mathrm{JB}}(c,m)\begin{pmatrix} c_{x_s} \\ m_{x_s} \end{pmatrix}\right)_{x_s} = \begin{pmatrix} c(1-c-m) - \delta c \\ \alpha cm(1-c-m) \end{pmatrix}, \tag{2.9}$$

where

$$D^{\mathrm{JB}}(c,m) = (D^{\mathrm{JB}}_{ij}) = \begin{pmatrix} 2\beta_c c(1-c) - \beta_m\theta cm^2 & -2\beta_m cm(1+\theta c) \\ -2\beta_c cm + \beta_m\theta(1-m)m^2 & 2\beta_m m(1-m)(1+\theta c) \end{pmatrix},$$

and α and δ are defined as above. This formulation is used in the numerical experiments, see Section 5.

3. Existence of weak solutions

The aim of this section is to prove Theorem 1.1. Let $\eta \in (0,1)$ and assume that the initial data satisfy $c_0 \geq \eta$, $m_0 \geq \eta$, and $c_0 + m_0 \leq 1 - \eta$ in Ω. By the change of variables (1.6), system (1.1) writes as

$$\frac{\partial}{\partial t}\begin{pmatrix} c(u,v) \\ m(u,v) \end{pmatrix} - \left(L(u,v)\begin{pmatrix} u_x \\ v_x \end{pmatrix}\right)_x = R(u,v),$$

where

$$c(u,v) = \frac{e^u}{1+e^u+e^v}, \quad m(u,v) = \frac{e^v}{1+e^u+e^v}$$

and

$$L(u,v) = D(c(u,v),m(u,v))\big(\nabla^2 h(c(u,v),m(u,v))\big)^{-1}, \tag{3.1}$$

$$R(u,v) = \begin{pmatrix} \gamma c(u,v)(1-c(u,v)-m(u,v)) - \delta c(u,v) \\ \alpha c(u,v)m(u,v)(1-c(u,v)-m(u,v)) \end{pmatrix}.$$

We notice that the inverse of the Hessian of h, $(\nabla^2 h(c,m))^{-1}$, which is computed with respect to (c,m), equals

$$(\nabla^2 h(c,m))^{-1} = \begin{pmatrix} c(1-c) & -cm \\ -cm & m(1-m) \end{pmatrix}$$

and that $c(u,v)$ and $m(u,v)$ are positive and satisfy $c(u,v)+m(u,v) < 1$ in Ω if u and v are bounded. The boundary and initial conditions are

$$u_x = v_x = 0 \quad \text{on } \partial\Omega,\ t>0, \quad u(\cdot,0) = u_0, \quad v(\cdot,0) = v_0 \quad \text{in } \Omega,$$

where

$$u_0 = \log\frac{c_0}{1-c_0-m_0}, \quad v_0 = \log\frac{m_0}{1-c_0-m_0} \in L^\infty(\Omega).$$

For later use, we remark that the matrix product $(\nabla^2 h)D$ simplifies:

$$(\nabla^2 h)D = \begin{pmatrix} 2 & 0 \\ \beta\theta m & 2\beta(1+\theta c) \end{pmatrix}. \tag{3.2}$$

An elementary computation shows that this matrix product is positive semidefinite,

$$x^\top(\nabla^2 h)Dx \geq 0 \quad \text{for all } x \in \mathbb{R}^2,\ c,m>0 \text{ satisfying } 1-c-m>0, \tag{3.3}$$

if the condition $0 \leq \theta \leq 4/\sqrt{\beta}$ holds. (In the scaling of Jackson and Byrne – see the end of Section 2 –, this condition becomes $\theta \leq 4\sqrt{\beta_c/\beta_m}$.)

Step 1: Existence of a time-discrete problem. Let $T>0$, $N \in \mathbb{N}$, $\tau = T/N$, and define the time steps $t_k = k\tau$, $k = 0,\ldots,N$. Let $1 \leq k \leq N$. For given functions $u_{k-1}, v_{k-1} \in L^\infty(\Omega)$, we wish to solve the sequence of approximate elliptic problems in Ω,

$$\frac{1}{\tau}\begin{pmatrix} c(u_k,v_k) - c_{k-1} \\ m(u_k,v_k) - m_{k-1} \end{pmatrix} - \left(\big(L(u_k,v_k) + \varepsilon\mathbb{I}\big)\begin{pmatrix} (u_k)_x \\ (v_k)_x \end{pmatrix}\right)_x + \varepsilon\begin{pmatrix} u_k \\ v_k \end{pmatrix} = R(u_k,v_k), \tag{3.4}$$

subject to the boundary conditions

$$(u_k)_x = (v_k)_x = 0 \quad \text{on } \partial\Omega. \tag{3.5}$$

Here, u_k and v_k are approximations of u and v at time t_k, respectively, $c_{k-1} = c(u_{k-1}, v_{k-1})$, $m_{k-1} = m(u_{k-1}, v_{k-1})$, $\mathbb{I}$ is the identity matrix in $\mathbb{R}^{2\times 2}$, and $\varepsilon > 0$ is a regularization parameter which ensures the uniform ellipticity of (3.4) with respect to (u_k, v_k).

Lemma 3.1. *Let $(u_{k-1}, v_{k-1}) \in L^\infty(\Omega)^2$ and $0 \le \theta < 4/\sqrt{\beta}$. Then there exists a constant $K_\theta > 0$ and a weak solution $(u_k, v_k) \in H^1(\Omega)^2$ to (3.4)-(3.5) satisfying*

$$\begin{aligned} H\big(c(u_k, v_k), m(u_k, v_k)\big) + \tau K_\theta \int_\Omega \big(c(u_k, v_k)_x^2 + m(u_k, v_k)_x^2\big)dx \\ + \tau\varepsilon \int_\Omega \big((u_k)_x^2 + (v_k)_x^2 + u_k^2 + v_k^2\big)dx \\ \le H\big(c(u_{k-1}, v_{k-1}), m(u_{k-1}, v_{k-1})\big) + \frac{\tau}{e}(\alpha + \gamma + \delta). \end{aligned} \tag{3.6}$$

Proof. The idea of the proof is to apply the Leray-Schauder fixed-point theorem (see Theorem B.5 in Ref. 22). To this end, we consider first a linear problem. Let $(\bar{u}, \bar{v}) \in L^\infty(\Omega)^2$. We show the existence of a unique solution $(u, v) \in H^1(\Omega)^2$ to the linear problem

$$a((u, v), (y, z)) = F(y, z) \quad \text{for all } (y, z) \in H^1(\Omega)^2, \tag{3.7}$$

where

$$a((u, v), (y, z)) = \int_\Omega \begin{pmatrix} y_x \\ z_x \end{pmatrix}^\top L(\bar{u}, \bar{v}) \begin{pmatrix} u_x \\ v_x \end{pmatrix} dx + \varepsilon \int_\Omega \big(u_x y_x + v_x z_x + uy + vz\big)dx,$$

$$F(y, z) = -\frac{1}{\tau} \int_\Omega \begin{pmatrix} c(\bar{u}, \bar{v}) - c_{k-1} \\ m(\bar{u}, \bar{v}) - m_{k-1} \end{pmatrix} \cdot \begin{pmatrix} y \\ z \end{pmatrix} dx + \int_\Omega R(\bar{u}, \bar{v}) \cdot \begin{pmatrix} y \\ z \end{pmatrix} dx.$$

The a.e. boundedness of $\bar{u}$ and $\bar{v}$ implies that the bilinear form $a : H^1(\Omega)^2 \times H^1(\Omega)^2 \to \mathbb{R}$ and the linear functional $F : H^1(\Omega)^2 \to \mathbb{R}$ are well-defined and continuous. Using the definition $L = D(\nabla^2 h)^{-1}$ and (3.3), we compute

$$\begin{aligned} \begin{pmatrix} u_x \\ v_x \end{pmatrix}^\top L(\bar{u}, \bar{v}) \begin{pmatrix} u_x \\ v_x \end{pmatrix} &= \left((\nabla^2 h)^{-1} \begin{pmatrix} u_x \\ v_x \end{pmatrix} \right)^\top (\nabla^2 h) L (\nabla^2 h)(\nabla^2 h)^{-1} \begin{pmatrix} u_x \\ v_x \end{pmatrix} \\ &= \left((\nabla^2 h)^{-1} \begin{pmatrix} u_x \\ v_x \end{pmatrix} \right)^\top (\nabla^2 h) D \left((\nabla^2 h)^{-1} \begin{pmatrix} u_x \\ v_x \end{pmatrix} \right) \ge 0 \end{aligned}$$

in Ω, since $0 \le \theta < 4/\sqrt{\beta}$. This shows that a is coercive:

$$\begin{aligned} a((u, v), (u, v)) &= \int_\Omega \begin{pmatrix} u_x \\ v_x \end{pmatrix}^\top L(\bar{u}, \bar{v}) \begin{pmatrix} u_x \\ v_x \end{pmatrix} dx + \varepsilon \int_\Omega \big(u_x^2 + v_x^2 + u^2 + v^2\big)dx \\ &\ge \varepsilon\big(\|u\|_{H^1(\Omega)}^2 + \|v\|_{H^1(\Omega)}^2\big) = \varepsilon \|(u, v)\|_{H^1(\Omega)^2}^2. \end{aligned}$$

By the Lax-Milgram lemma, there exists a unique solution $(u, v) \in H^1(\Omega)^2$ to (3.7).

Next, we define the fixed-point operator $S : L^\infty(\Omega)^2 \times [0,1] \to L^\infty(\Omega)^2$ by setting, for given $(\bar u, \bar v) \in L^\infty(\Omega)^2$ and $\sigma \in [0,1]$, $S(\bar u, \bar v, \sigma) = (u,v)$, where $(u,v) \in H^1(\Omega)^2$ is the solution to the linear problem

$$a((u,v),(y,z)) = \sigma F(y,z) \quad \text{for all } (y,z) \in H^1(\Omega)^2. \tag{3.8}$$

We notice that $S(\bar u, \bar v, 0) = 0$ for all $(\bar u, \bar v) \in L^\infty(\Omega)^2$. Standard arguments show that S is continuous and, because of the compact embedding $H^1(\Omega) \hookrightarrow L^\infty(\Omega)$ in one space dimension, also compact. It remains to prove that there exists a constant $K > 0$ such that for any $(u,v,\sigma) \in L^\infty(\Omega)^2 \times [0,1]$ satisfying $S(u,v,\sigma) = (u,v)$, the estimate $\|(u,v)\|_{L^\infty(\Omega)^2} \le K$ holds.

In order to prove this bound, we use the test function (u,v) in (3.8), yielding

$$\begin{aligned} \frac{\sigma}{\tau}\int_\Omega \begin{pmatrix} c(u,v) - c_{k-1} \\ m(u,v) - m_{k-1}\end{pmatrix} \cdot \begin{pmatrix} u \\ v \end{pmatrix} dx + \int_\Omega \begin{pmatrix} u_x \\ v_x \end{pmatrix}^\top L(u,v) \begin{pmatrix} u_x \\ v_x \end{pmatrix} dx \\ + \varepsilon \int_\Omega (u_x^2 + v_x^2 + u^2 + v^2) dx = \sigma \int_\Omega R(u,v) \cdot \begin{pmatrix} u \\ v \end{pmatrix} dx. \end{aligned} \tag{3.9}$$

We remark that $c_{k-1} = c(u_{k-1}, v_{k-1}) > 0$ and $m_{k-1} = m(u_{k-1}, v_{k-1}) > 0$ satisfy $c_{k-1} + m_{k-1} < 1$. Set $c = c(u,v)$ and $m = m(u,v)$. The convexity of the entropy density h with respect to (c,m) implies that

$$h(c,m) - h(\widetilde c, \widetilde m) \le \nabla h(c,m) \cdot \begin{pmatrix} c - \widetilde c \\ m - \widetilde m \end{pmatrix}$$

for all c, m, $\widetilde c$, $\widetilde m > 0$ satisfying $1 - c - m > 0$ and $1 - \widetilde c - \widetilde m > 0$. By (1.6), $\nabla h(c,m) = (u,v)$ and hence, the first term on the left-hand side of (3.9) can be estimated as

$$\frac{\sigma}{\tau}\int_\Omega \begin{pmatrix} c - c_{k-1} \\ m - m_{k-1}\end{pmatrix} \cdot \begin{pmatrix} u \\ v \end{pmatrix} dx \ge \frac{\sigma}{\tau}\big(H(c,m) - H(c_{k-1}, m_{k-1})\big).$$

We turn to the second integral on the left-hand side of (3.9). Because of (1.6), we have

$$\begin{pmatrix} u_x \\ v_x \end{pmatrix} = \nabla^2 h(c,m) \begin{pmatrix} c_x \\ m_x \end{pmatrix}.$$

Therefore, in view of $L = D(\nabla^2 h)^{-1}$ and (3.2), we find that the second integral on the left-hand side of (3.9) equals

$$\begin{aligned} \int_\Omega \begin{pmatrix} c_x \\ m_x \end{pmatrix}^\top (\nabla^2 h) L(u,v) (\nabla^2 h) \begin{pmatrix} c_x \\ m_x \end{pmatrix} dx &= \int_\Omega \begin{pmatrix} c_x \\ m_x \end{pmatrix}^\top (\nabla^2 h) D(c,m) \begin{pmatrix} c_x \\ m_x \end{pmatrix} dx \\ &= \int_\Omega \big(2c_x^2 + \beta\theta m c_x m_x + 2\beta(1+\theta c) m_x^2\big) dx. \end{aligned}$$

By (3.3), this integral is nonnegative if $\theta \le 4/\sqrt{\beta}$. This result can be strengthened: If $0 \le \theta < 4/\sqrt{\beta}$, there exists a constant $K_\theta > 0$ depending on θ (and β) such that

$$\int_\Omega \big(2c_x^2 + \beta\theta m c_x m_x + 2\beta(1+\theta c) m_x^2\big) dx \ge K_\theta \int_\Omega (c_x^2 + m_x^2) dx.$$

Here, we have used the properties c, $m > 0$, and $c+m < 1$, which are a consequence of the definitions of $c = c(u,v)$ and $m = m(u,v)$.

It remains to estimate the right-hand side of (3.9). Using $-1/e \le x\log x \le 0$ for all $0 \le x \le 1$ and c, m, $1-c-m > 0$ as well as $\log(1-c-m) < 0$, we find that

$$\begin{aligned}
R(u,v)\cdot\begin{pmatrix} u \\ v \end{pmatrix} &= \big(\gamma c(1-c-m) - \delta c\big)\log\frac{c}{1-c-m} \\
&\quad + \alpha cm(1-c-m)\log\frac{m}{1-c-m} \\
&= \gamma(c\log c)(1-c-m) - \gamma c(1-c-m)\log(1-c-m) \\
&\quad - \delta c\log c + \delta c\log(1-c-m) \\
&\quad + \alpha(m\log m)c(1-c-m) - \alpha cm(1-c-m)\log(1-c-m) \\
&\le (\alpha+\gamma+\delta)e^{-1}.
\end{aligned}$$

Summarizing, we estimate (3.9) as

$$\begin{aligned}
\sigma H(c,m) + \tau K_\theta \int_\Omega (c_x^2 + m_x^2)dx + \tau\varepsilon\int_\Omega (u_x^2 + v_x^2 + u^2 + v^2)dx \\
\le \sigma H(c_{k-1}, m_{k-1}) + \frac{\sigma\tau}{e}(\alpha+\gamma+\delta).
\end{aligned}$$

This shows that u and v are bounded in $H^1(\Omega)$, which provides the desired uniform estimate in $L^\infty(\Omega)^2$. The assumptions of the Leray-Schauder fixed-point theorem are verified, proving the existence of a fixed point of $S(\cdot,1)$, which solves (3.4)-(3.5). $\square$

Step 2: Uniform estimates. Let (u_k, v_k) be a weak solution to (3.4)-(3.5), whose existence is guaranteed by Lemma 3.1. We set $c_k = c(u_k, v_k)$, $m_k = m(u_k, v_k)$ and define the piecewise constant functions in time $u^{(\tau)}(x,t) = u_k(x)$, $v^{(\tau)}(x,t) = v_k(x)$, $c^{(\tau)}(x,t) = c_k(x)$, $m^{(\tau)}(x,t) = m_k(x)$ for $x \in \Omega$ and $t \in ((k-1)\tau, k\tau]$, $k = 1,\ldots,N$. At time $t = 0$, we set $c^{(\tau)}(\cdot,0) = c_0$ and $m^{(\tau)}(\cdot,0) = m_0$. Furthermore, we introduce the shift operator $(\sigma_\tau w^{(\tau)})(t) = w^{(\tau)}(\cdot, t-\tau)$ for $\tau < t \le T$ and the discrete time derivative $D_\tau w^{(\tau)} = (w^{(\tau)} - \sigma_\tau w^{(\tau)})/\tau$, where $w = c, m$. Then $(c^{(\tau)}, m^{(\tau)})$ solves

$$D_\tau\begin{pmatrix} c^{(\tau)} \\ m^{(\tau)} \end{pmatrix} - \left(D(c^{(\tau)}, m^{(\tau)})\begin{pmatrix} c_x^{(\tau)} \\ m_x^{(\tau)} \end{pmatrix}\right)_x - \varepsilon\begin{pmatrix} u_{xx}^{(\tau)} - u^{(\tau)} \\ v_{xx}^{(\tau)} - v^{(\tau)} \end{pmatrix} = R(c^{(\tau)}, m^{(\tau)}) \tag{3.10}$$

in Ω, $t > \tau$. The discrete entropy inequality (3.6) can be solved recursively to yield

$$\begin{aligned}
H(c_k, m_k) + \tau K_\theta \sum_{j=1}^k \int_\Omega \big((c_j)_x^2 + (m_j)_x^2\big)dx + \tau\varepsilon\sum_{j=1}^k \int_\Omega \big((u_j)_x^2 + (v_j)_x^2 + u_j^2 + v_j^2\big)dx \\
\le H(c_0, m_0) + \frac{T}{e}(\alpha+\gamma+\delta), \quad k = 1,\ldots,N,
\end{aligned}$$

where $T = \tau N$. This leads immediately to the following result.

Lemma 3.2. *The following uniform bounds hold:*

$$\begin{aligned}\|c^{(\tau)}\|_{L^2(0,T;H^1(\Omega))} + \|m^{(\tau)}\|_{L^2(0,T;H^1(\Omega))} &\le K,\\ \|c^{(\tau)}\|_{L^\infty(0,T;L^\infty(\Omega))} + \|m^{(\tau)}\|_{L^\infty(0,T;L^\infty(\Omega))} &\le K,\\ \sqrt{\varepsilon}\|u^{(\tau)}\|_{L^2(0,T;H^1(\Omega))} + \sqrt{\varepsilon}\|v^{(\tau)}\|_{L^2(0,T;H^1(\Omega))} &\le K,\end{aligned}$$

where $K > 0$ is here and in the following a generic constant independent of τ and ε.

We also need uniform estimates for the discrete time derivatives of $c^{(\tau)}$ and $m^{(\tau)}$.

Lemma 3.3. *The following uniform bounds hold:*

$$\|D_\tau c^{(\tau)}\|_{L^2(\tau,T;(H^1(\Omega))')} + \|D_\tau m^{(\tau)}\|_{L^2(\tau,T;(H^1(\Omega))')} \le K.$$

Proof. Let $\phi \in L^2(\tau, T; H^1(\Omega))$. Then, by (3.10) and the bounds on $c^{(\tau)}$, $m^{(\tau)}$, and $\sqrt{\varepsilon}u^{(\tau)}$,

$$\begin{aligned}\left|\int_\tau^T \langle D_\tau c^{(\tau)}, \phi\rangle dt\right| &= \bigg| -\int_\tau^T \int_\Omega \big(2c^{(\tau)}(1-c^{(\tau)})c_x^{(\tau)} - \beta\theta c^{(\tau)}(m^{(\tau)})^2 c_x^{(\tau)}\\ &\qquad - 2\beta c^{(\tau)} m^{(\tau)}(1+\theta c^{(\tau)})m_x^{(\tau)}\big)\phi_x dxdt\\ &\quad - \varepsilon\int_\tau^T\int_\Omega \big(u_x^{(\tau)}\phi_x + u^{(\tau)}\phi\big)dxdt\\ &\quad + \int_\tau^T\int_\Omega \big(\gamma c^{(\tau)}(1-c^{(\tau)}-m^{(\tau)}) - \delta c^{(\tau)}\big)\phi dxdt\bigg|\\ &\le K\big(\|c_x^{(\tau)}\|_{L^2(\tau,T;L^2(\Omega))} + \|m_x^{(\tau)}\|_{L^2(\tau,T;L^2(\Omega))}\big)\|\phi_x\|_{L^2(\tau,T;L^2(\Omega))}\\ &\quad + 2\varepsilon\|u^{(\tau)}\|_{L^2(\tau,T;H^1(\Omega))}\|\phi\|_{L^2(\tau,T;H^1(\Omega))}\\ &\quad + (\gamma+\delta)\|\phi\|_{L^1(\tau,T;L^1(\Omega))}\\ &\le K\|\phi\|_{L^2(\tau,T;H^1(\Omega))}.\end{aligned}$$

The estimate for $D_\tau m^{(\tau)}$ is shown analogously. □

Step 3: The limit $(\varepsilon,\tau) \to 0$. Lemmas 3.2 and 3.3 allow us to apply the Aubin lemma (see the version in Ref. 13) to conclude the strong convergence for subsequences (not relabeled) such that, as $\tau \to 0$ and $\varepsilon \to 0$,

$$c^{(\tau)} \to c, \quad m^{(\tau)} \to m \quad \text{strongly in } L^2(0,T;L^\infty(\Omega)),$$

observing that the embedding $H^1(\Omega) \hookrightarrow L^\infty(\Omega)$ is compact. In particular, up to subsequences, $(c^{(\tau)})$ and $(m^{(\tau)})$ converge a.e. in $\Omega \times (0,T)$. In view of the uniform bounds for $c^{(\tau)}$ and $m^{(\tau)}$ in $L^\infty(0,T;L^\infty(\Omega))$, this implies that

$$c^{(\tau)} \to c, \quad m^{(\tau)} \to m \quad \text{strongly in } L^p(0,T;L^p(\Omega)) \quad \text{for all } 1 \le p < \infty. \tag{3.11}$$

Moreover, up to subsequences,

$$
\begin{aligned}
c^{(\tau)} \rightharpoonup c, \quad m^{(\tau)} \rightharpoonup m \quad & \text{weakly in } L^2(0,T;H^1(\Omega)), \\
D_\tau c^{(\tau)} \rightharpoonup c_t, \quad D_\tau m^{(\tau)} \rightharpoonup m_t \quad & \text{weakly in } L^2(0,T;(H^1(\Omega))'), \\
\varepsilon u^{(\tau)} \to 0, \quad \varepsilon v^{(\tau)} \to 0 \quad & \text{strongly in } L^2(0,T;H^1(\Omega)).
\end{aligned}
$$

The above convergence results are sufficient to pass to the limit $\tau \to 0$ and $\varepsilon \to 0$ in the weak formulation of (3.10) and (3.5), showing that (c,m) is a weak solution to (1.1)-(1.2). Finally, in view of the uniform bounds and the finiteness of $H(c_0,m_0)$, we can perform the limit $\eta \to 0$ in the initial data (see the beginning of this section). This concludes the proof.

4. Long-time behavior of solutions

We assume that the initial data satisfy $c_0 \ge \eta$, $m_0 \ge \eta$, and $1 - c_0 - m_0 \ge \eta$ for some $\eta \in (0,1)$. Let $T > 0$ be arbitrary but fixed and let $\tau = T/N$ for $N \in \mathbb{N}$. Let $(u_k, v_k) \in H^1(\Omega)^2$ be a weak solution to (3.4)-(3.5) with vanishing right-hand side and with the properties stated in Lemma 3.1, where $1 \le k \le N$. We set $c_k = \exp(u_k)/(1+\exp(u_k)+\exp(v_k))$ and $m_k = \exp(v_k)/(1+\exp(u_k)+\exp(v_k))$. Furthermore, let $c_k^* = \int_\Omega c_k dx$, $m_k^* = \int_\Omega m_k dx$, $u_k^* = \int_\Omega u_k dx$, and $v_k^* = \int_\Omega v_k dx$. In the presence of the ε-terms, the L^1-norms of c_k and m_k are not conserved, but taking $(1,0)^\top$ and $(0,1)^\top$ as test functions in the weak formulation of (3.4)-(3.5), we find immediately that $c_k^* = c_{k-1}^* - \varepsilon\tau u_k^*$ and $m_k^* = m_{k-1}^* - \varepsilon\tau v_k^*$, from which we infer that

$$
c_k^* = c_0^* - \varepsilon\tau \sum_{j=1}^k u_j^*, \quad m_k^* = m_0^* - \varepsilon\tau \sum_{j=1}^k v_j^*.
$$

Step 1: Uniform bounds for the L^1-norms of c_k and m_k. We claim that c_k^*, m_k^*, and $1 - c_k^* - m_k^*$ are positive uniformly in $\varepsilon = \tau$ and k. To this end, let $K_S > 0$ be the constant of the Sobolev embedding $H^1(\Omega) \hookrightarrow L^\infty(\Omega)$. Furthermore, we choose $0 < \delta < \min\{1, (1-c_0^*-m_0^*)/(c_0^*+m_0^*)\}$, $\varepsilon = \tau$, and

$$
\tau_0 = \frac{(\delta \min\{c_0^*, m_0^*\})^2}{2TK_S^2(|H(c_0,m_0)| + 3/e + 3)}.
$$

In the following, let $0 < \tau < \tau_0$. Observing that $H(c_k,m_k) \ge -3/e - 3$, the discrete entropy inequality (3.6) shows that

$$
\begin{aligned}
\sum_{j=1}^k \big(\|u_j\|_{L^\infty(\Omega)}^2 + \|v_j\|_{L^\infty(\Omega)}^2\big) &\le K_S^2 \sum_{j=1}^k \big(\|u_j\|_{H^1(\Omega)}^2 + \|v_j\|_{H^1(\Omega)}^2\big) \\
&\le \frac{K_S^2}{\varepsilon\tau}\big(H(c_0,m_0) - H(c_k,m_k)\big) \le \frac{K_S^2}{\varepsilon\tau}\Big(|H(c_0,m_0)| + \frac{3}{e} + 3\Big).
\end{aligned}
$$

Hence, for all $0 < \tau < \tau_0$, since $\varepsilon = \tau$, $k\tau \le T$, and because of the definition of τ_0,

$$\begin{aligned}
\varepsilon\tau \sum_{j=1}^{k} \big(|u_j^*| + |v_j^*|\big) &\le \varepsilon\tau \sum_{j=1}^{k} \big(\|u_j\|_{L^\infty(\Omega)} + \|v_j\|_{L^\infty(\Omega)}\big) \\
&\le \varepsilon\tau\sqrt{2k} \left(\sum_{j=1}^{k} \big(\|u_j\|_{L^\infty(\Omega)}^2 + \|v_j\|_{L^\infty(\Omega)}^2\big) \right)^{1/2} \\
&\le \big(2\varepsilon\tau k K_S^2(|H(c_0,m_0)| + 3/e + 3)\big)^{1/2} \\
&\le \big(2\tau T K_S^2(|H(c_0,m_0)| + 3/e + 3)\big)^{1/2} \\
&\le \delta \min\{c_0^*, m_0^*\}.
\end{aligned}$$

This shows that

$$(1-\delta)c_0^* \le c_k^* \le (1+\delta)c_0^*, \quad (1-\delta)m_0^* \le m_k^* \le (1+\delta)m_0^*, \quad k = 1,\ldots,N, \quad (4.1)$$

and the claim is proved since $0 < 1-(1+\delta)(c_0^*+m_0^*) \le 1 - c_k^* - m_k^* \le 1-(1-\delta)(c_0^*+m_0^*)$, by definition of $\delta > 0$.

Step 2: Estimate for the relative entropy. Let $\hat{u}_k = \log(c_k^*/(1-c_k^*-m_k^*))$ and $\hat{v}_k = \log(m_k^*/(1-c_k^*-m_k^*))$. By (4.1), $\hat{u}_k$ and $\hat{v}_k$ are uniformly bounded. We employ $(u_k - \hat{u}_k, v_k - \hat{v}_k)^\top$ as a test function in the weak formulation of (3.4)-(3.5):

$$\begin{aligned}
0 &= \frac{1}{\tau}\int_\Omega \begin{pmatrix} c_k - c_{k-1} \\ m_k - m_{k-1} \end{pmatrix} \cdot \begin{pmatrix} u_k - \hat{u}_k \\ v_k - \hat{v}_k \end{pmatrix} dx + \int_\Omega \begin{pmatrix} (u_k)_x \\ (v_k)_x \end{pmatrix}^\top L(u_k,v_k) \begin{pmatrix} (u_k)_x \\ (v_k)_x \end{pmatrix} dx \\
&\quad + \varepsilon \int_\Omega \big((u_k)_x^2 + (v_k)_x^2 + u_k(u_k-\hat{u}_k) + v_k(v_k-\hat{v}_k)\big) dx. \qquad (4.2)
\end{aligned}$$

The modified relative entropy functional

$$\begin{aligned}
H_\varepsilon^*(c,m) &= \int_\Omega h_\varepsilon^*(c,m)dx \\
&= \int_\Omega \Big(c\log\frac{c}{c_k^*} + m\log\frac{m}{m_k^*} + (1-c-m)\log\frac{1-c-m}{1-c_k^*-m_k^*} \Big) dx
\end{aligned}$$

is well-defined for appropriate c and m, and it holds that $\nabla h_\varepsilon^*(c_k,m_k) = (u_k - \hat{u}_k, v_k - \hat{v}_k)^\top$. The convexity of the function $h_\varepsilon^*(c,m)$ implies that the first integral in (4.2) can be estimated as

$$\begin{aligned}
&\frac{1}{\tau}\int_\Omega \begin{pmatrix} c_k - c_{k-1} \\ m_k - m_{k-1} \end{pmatrix} \cdot \begin{pmatrix} u_k - \hat{u}_k \\ v_k - \hat{v}_k \end{pmatrix} dx = \frac{1}{\tau}\int_\Omega \begin{pmatrix} c_k - c_{k-1} \\ m_k - m_{k-1} \end{pmatrix} \cdot \nabla h_\varepsilon^*(c_k,m_k) dx \\
&\quad \ge \frac{1}{\tau}\int_\Omega \big(h_\varepsilon^*(c_k,m_k) - h_\varepsilon^*(c_{k-1},m_{k-1})\big) dx = \frac{1}{\tau}\big(H_\varepsilon^*(c_k,m_k) - H_\varepsilon^*(c_{k-1},m_{k-1})\big).
\end{aligned}$$

As in the proof of Lemma 3.1, for $\theta < \theta^*$, the second integral in (4.2) is bounded below:

$$\int_\Omega \begin{pmatrix} (u_k)_x \\ (v_k)_x \end{pmatrix}^\top L(u_k,v_k) \begin{pmatrix} (u_k)_x \\ (v_k)_x \end{pmatrix} dx \ge K_\theta \int_\Omega \big((c_k)_x^2 + (m_k)_x^2\big) dx.$$

By Young's inequality, the third integral in (4.2) can be estimated as

$$\begin{aligned}
&\varepsilon\int_\Omega \big((u_k)_x^2 + (v_k)_x^2 + u_k(u_k-\hat u_k) + v_k(v_k-\hat v_k)\big)dx \\
&\geq \frac{\varepsilon}{2}\int_\Omega \big(2(u_k)_x^2 + 2(v_k)_x^2 + u_k^2 + v_k^2 - \hat u_k^2 - \hat v_k^2\big)dx \geq -\frac{\varepsilon}{2}(\hat u_k^2 + \hat v_k^2).
\end{aligned}$$

Since $\hat u_k$ and $\hat v_k$ are uniformly bounded, there exists a constant $A > 0$ such that $(\hat u_k^2 + \hat v_k^2)/2 \leq A$ for all k. We conclude that, for $k = 1, \ldots, N$,

$$\frac{1}{\tau}\big(H_\varepsilon^*(c_k, m_k) - H_\varepsilon^*(c_{k-1}, m_{k-1})\big) + K_\theta\int_\Omega \big((c_k)_x^2 + (m_k)_x^2\big)dx \leq \varepsilon A. \tag{4.3}$$

Step 3: Estimate for the entropy production. We claim that the entropy production can be related to the modified relative entropy. To this end, we employ the elementary estimates

$$\begin{aligned}
(x-y)^2 = (\sqrt{x}+\sqrt{y})^2(\sqrt{x}-\sqrt{y})^2 &\geq y(\sqrt{x}-\sqrt{y})^2 \quad \text{for all } x, y \geq 0, \\
x^2\Big(\log\frac{x^2}{y^2} - 1\Big) + y^2 &\leq 2(1-\log y)(x-y)^2 \quad \text{for all } 0 < x, y < 1.
\end{aligned}$$

The second inequality is easily verified by Taylor expansion. Thus, by the Poincaré inequality with constant $K_p > 0$,

$$\begin{aligned}
K_p^2\int_\Omega (c_k)_x^2 dx &\geq \int_\Omega (c_k - c_k^*)^2 dx \geq c_k^*\int_\Omega \big(\sqrt{c_k} - \sqrt{c_k^*}\big)^2 dx \\
&\geq \frac{c_k^*}{2-\log c_k^*}\int_\Omega c_k \log\frac{c_k}{c_k^*}dx
\end{aligned}$$

and, equivalently,

$$\int_\Omega c_k\log\frac{c_k}{c_k^*}dx \leq \frac{K_p^2(2-\log c_k^*)}{c_k^*}\int_\Omega (c_k)_x^2 dx.$$

Analogously, we obtain

$$\begin{aligned}
\int_\Omega m_k\log\frac{m_k}{m_k^*}dx &\leq \frac{K_p^2(2-\log m_k^*)}{m_k^*}\int_\Omega (m_k)_x^2 dx, \\
\int_\Omega (1-c_k-m_k)\log\frac{1-c_k-m_k}{1-c_k^*-m_k^*}dx &\leq \frac{K_p^2(2-\log(1-c_k^*-m_k^*))}{1-c_k^*-m_k^*} \\
&\quad \times \int_\Omega (1-c_k-m_k)_x^2 dx \\
&\leq \frac{2K_p^2(2-\log(1-c_k^*-m_k^*))}{1-c_k^*-m_k^*} \\
&\quad \times \int_\Omega \big((c_k)_x^2 + (m_k)_x^2\big)dx.
\end{aligned}$$

Summing up the three expressions and employing (4.1), we infer that

$$\begin{aligned} H_\varepsilon^*(c_k, m_k) &\le K_p^2\left(\frac{2-\log c_k^*}{c_k^*} + \frac{2-\log m_k^*}{m_k^*} + 2\frac{2-\log(1-c_k^*-m_k^*)}{1-c_k^*-m_k^*}\right) \\ &\quad \times \int_\Omega \big((c_k)_x^2 + (m_k)_x^2\big)dx \\ &\le K_p^2 K_\delta \int_\Omega \big((c_k)_x^2 + (m_k)_x^2\big)dx, \end{aligned}$$

where

$$K_\delta = \frac{2-\log((1-\delta)c_0^*)}{(1-\delta)c_0^*} + \frac{2-\log((1-\delta)m_0^*)}{(1-\delta)m_0^*} + 2\frac{2-\log(1-c_0^*-m_0^*-\delta(c_0^*+m_0^*))}{1-c_0^*-m_0^*-\delta(c_0^*+m_0^*)}.$$

Setting $K^* = K_\theta K_p^{-2}K_\delta^{-1}$, we write this inequality as

$$K^* H_\varepsilon^*(c_k, m_k) \le K_\theta \int_\Omega \big((c_k)_x^2 + (m_k)_x^2\big)dx, \quad k = 1, \ldots, N. \tag{4.4}$$

Step 4: End of the proof. We come back to the entropy estimate (4.3). Employing (4.4), we obtain

$$(1+\tau K^*)H_\varepsilon^*(c_k, m_k) \le H_\varepsilon^*(c_{k-1}, m_{k-1}) + \varepsilon\tau A, \quad k = 1, \ldots, N.$$

Solving these recursive inequalities, it follows that

$$H_\varepsilon^*(c_k, m_k) \le (1+\tau K^*)^{-k} H_\varepsilon^*(c_0, m_0) + \varepsilon\tau A \sum_{j=1}^k (1+\tau K^*)^{-j}, \quad k = 1, \ldots, N.$$

Since $\sum_{j=1}^\infty x^j = x/(1-x)$ for $|x| < 1$, we find that

$$H_\varepsilon^*(c_k, m_k) \le (1+\tau K^*)^{-k} H_\varepsilon^*(c_0, m_0) + \varepsilon A (K^*)^{-1}.$$

This can be formulated as

$$H_\varepsilon^*(c^{(\tau)}, m^{(\tau)}) \le e^{-K^* t_k}|H_\varepsilon^*(c_0, m_0)| + \varepsilon A(K^*)^{-1} \le e^{-K^* t}|H_\varepsilon^*(c_0, m_0)| + \varepsilon A(K^*)^{-1}$$

for all $t \in ((k-1)\tau, k\tau]$, $k = 1, \ldots, N$. In the limit $\tau = \varepsilon \to 0$, (subsequences of) $(c^{(\tau)})$ and $(m^{(\tau)})$ converge strongly to c and m, respectively, in $L^p(0, T; L^p(\Omega))$ for all $1 \le p < \infty$ (see (3.11)). Moreover, we have $c_k^* \to c_0^*$ and $m_k^* \to m_0^*$ for $\varepsilon \to 0$ which follows from

$$|c_k^* - c_0^*| = \left|\varepsilon \sum_{j=1}^k \tau \int_\Omega u_j dx\right| \le \varepsilon \|u^{(\tau)}\|_{L^1(0,T;L^1(\Omega))} \to 0 \quad \text{as } \varepsilon \to 0$$

and similarly for m_k^* (see Lemma 3.2). Hence, by dominated convergence and the bounds (4.1),

$$H^*(c(\cdot, t), m(\cdot, t)) \le e^{-K^* t} H^*(c_0, m_0), \quad 0 < t < T.$$

However, $T > 0$ is chosen arbitrary and thus, this bound holds for $t > 0$. Moreover, we can pass to the limit $\eta \to 0$ in the initial data. Finally, by the Csiszár-Kullback inequality (see, e.g., Ref. 23) for some $K_{\rm CK} > 0$, since c and m conserve mass,

$$\begin{aligned}
&\|c(\cdot,t) - c_0^*\|_{L^1(\Omega)}^2 + \|m(\cdot,t) - m_0^*\|_{L^1(\Omega)}^2 \\
&\qquad\qquad \le K_{\rm CK} \int_\Omega \Big(c(\cdot,t) \log \frac{c(\cdot,t)}{c_0^*} + m(\cdot,t) \log \frac{m(\cdot,t)}{m_0^*} \Big) dx \\
&\qquad\qquad \le K_{\rm CK} H^*(c(\cdot,t), m(\cdot,t)) \le K_{\rm CK} e^{-K^* t} H^*(c_0, m_0)
\end{aligned}$$

for $t > 0$, which finishes the proof of Theorem 1.2.

5. Numerical results

In this section, the tumor-growth model (2.9), in the scaling of Jackson and Byrne, is discretized using finite differences in space and the implicit or explicit Euler method in time. In the experiments we concentrate on the behavior of the relative entropy and its entropy production since the dependence of the system on the model parameters has been extensively studied in Ref. 19.

The Neumann boundary conditions are discretized in such a way that, in the absence of production rates, the approximated total volume fractions $\int_\Omega c dx$ and $\int_\Omega m dx$ are exactly constant in time. It turns out that the discretization of the formulation (2.9) has stability problems due to the restrictions $0 \le c$, $m \le 1$ which may be violated numerically during the iteration procedure. The entropy-variable formulation (1.7) does not require any restriction on the variables and behaves numerically more stably than the direct formulation (2.9). We have compared our results from the explicit Euler discretization and from the implicit discretization (solved by Newton's method) with the output of the software Multiphysics from COMSOL, and all three algorithms lead to the same results.

Denoting by c_i^k and m_i^k the approximations of $c(x_i, t_k)$ and $m(x_i, t_k)$, respectively, where $x_i = ih$ ($i = 0, \ldots, N$, $hN = \ell$) and $t_k = k\tau$ ($k \in \mathbb{N}$, $\tau > 0$), the discretization (using an implicit time discretization) reads as follows:

$$\begin{aligned}
\frac{1}{\tau}(c_i^k - c_i^{k-1}) = \frac{1}{h^2}\big(& L_{11,i+1/2}^k (u_{i+1}^k - u_i^k) + L_{12,i+1/2}^k (v_{i+1}^k - v_i^k) \\
& - L_{11,i-1/2}^k (u_i^k - u_{i-1}^k) - L_{12,i-1/2}^k (v_i^k - v_{i-1}^k)\big) + R_c(c_i^k, m_i^k),
\end{aligned} \tag{5.1}$$

where $i = 1, \ldots, N-1$, $k \ge 1$,

$$\begin{aligned}
L_{j\ell,i\pm1/2}^k &= \frac{1}{2}\big(L_{j\ell}(c_{i\pm1}^k, m_{i\pm1}^k) + L_{j\ell}(c_i^k, m_i^k)\big), \\
u_i^k &= \log \frac{c_i^k}{1 - c_i^k - m_i^k}, \quad v_i^k = \log \frac{m_i^k}{1 - c_i^k - m_i^k},
\end{aligned}$$

and $L_{ij}(c, m)$ are the coefficients of the matrix defined in (3.1) with D replaced by $D^{\rm JB}$. The equation for m is discretized in a similar way. When an explicit time discretization is used, the index k on the right-hand side of (5.1) has to be replaced by $k - 1$.

The numerical parameters are chosen, if not stated otherwise, as follows. We take the interval length $\ell = 1$, $N = 200$ grid points, and the discretization parameters $h = 1/N$ and $\tau = 5 \cdot 10^{-5}$. The initial data are defined as in Ref. 19:

$$c_0(x) = \frac{C_1}{2}\Big(1 + \tanh\Big(\frac{x_0 - x}{\eta}\Big)\Big) + \varepsilon, \quad m_0(x) = \frac{M_1}{2}\Big(1 - \tanh\Big(\frac{x_0 - x}{\eta}\Big)\Big), \quad (5.2)$$

where $C_1 = M_1 = 0.25$, $x_0 = 0.1$, and $\eta = 0.05$. In order to avoid stability problems, we have added $\varepsilon = 2 \cdot 10^{-4}$ to the initial cell volume fraction. The diffusion coefficients are taken as in Ref. 19:

$$\beta_c = 0.2, \quad \beta_m = 0.0015.$$

First, we consider the case of vanishing production rates, $R_c = R_m = 0$. Figure 1 shows the volume fractions of the tumor cells and the ECM at various times, where we have used the cell-induced pressure coefficient $\theta = 1000$. The cross-diffusion term $D_{21}^{\mathrm{JB}} c_x$ causes a drift of the ECM to the right boundary, induced by variations of the tumor volume. The diffusion D_{22}^{JB} of the ECM outside of the tumor is very small, $D_{22}^{\mathrm{JB}} \approx 0.001$, such that the ECM cannot diffuse and forms a peak. The peak is not too singular since the discrete H^1-seminorm of m, $\|m_x\|_{1,h}$, and its maximal value, $\max_\Omega m$, stay bounded when $h \to 0$ numerically (see Table 1). However, the peak indicates a loss of regularity of m, and we conjecture that global *classical* solutions to the tumor-growth model do not exist. With increasing times, the tumor cell front moves to the right boundary, i.e., the tumor penetrates the surrounding ECM. The tumor cell fraction at the left boundary $x = 0$ is decreasing in time since the total volume fraction $\int_0^1 c\,dx$ is constant in time.

N	400	600	800	1000	1200
$\|m_x\|_{1,h}$	4.070	4.465	4.484	4.526	4.567
$\max_\Omega m$	0.630	0.646	0.637	0.645	0.649

Table 1. Discrete H^1-seminorm and maximum of m as a function of the number of grid points. Computed by using the explicit Euler scheme.

We expect that the relative entropy H^*, defined in (1.8), is converging to zero as $t \to \infty$ when the pressure coefficient θ is smaller than the critical value $\theta^* = 4\sqrt{\beta_c/\beta_m} \approx 46$. This behavior is illustrated in Figure 2 (left). In fact, the entropy is decreasing for larger values of θ, too. The semilogarithmic scale in Figure 2 (right) shows that the convergence for $\theta = 0$ and $\theta = 100$ is exponentially fast with a rate which is initially larger than for later times. For $\theta = 1000$, the convergence seems to be no longer exponential.

It is clear from Figure 2 that the entropy production

$$-\frac{dH^*}{dt} = \int_\Omega p\,dx = \int_\Omega \big(2\beta_c c_x^2 + \beta_m \theta m c_x m_x + 2\beta_m(1 + \theta c)m_x^2\big)dx$$

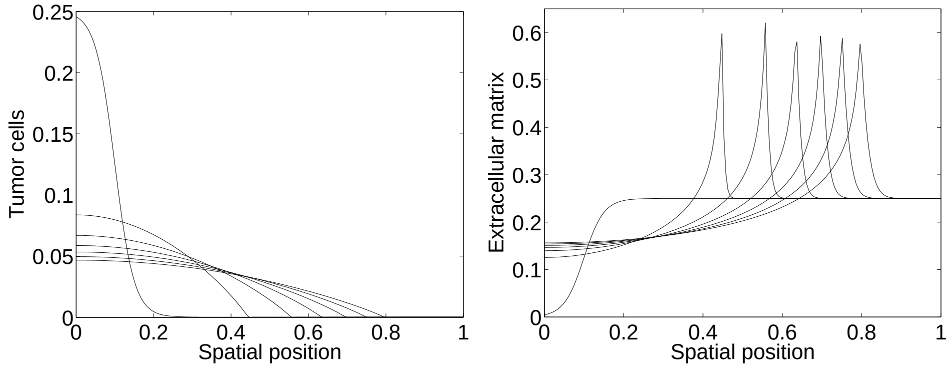

Fig. 1. Volume fractions of the tumor cells (left) and the ECM (right) versus position using $\theta = 1000$ at times $t = 0, 1, 2, 3, 4, 5, 6$. The production rates vanish, $R_c = R_m = 0$. The tumor cell front and the ECM peaks are moving from left to right as time increases.

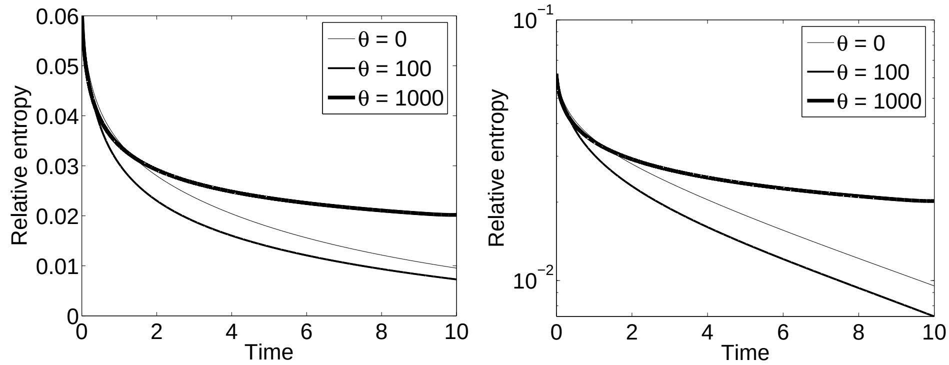

Fig. 2. Relative entropy H^* versus time. Left: Normal scale; right: Semilogarithmic scale. The production rates vanish, $R_c = R_m = 0$.

is positive. Interestingly, this is not true for the entropy production density $p = p(x,t)$, see Figure 3. The entropy production density $p(x,1)$ is nonnegative for all $x \in [0,1]$ if θ is sufficiently small but it may become negative at some points if θ is large enough. As a consequence, the entropy production does *not* lead to pointwise gradient estimates if θ is sufficiently large. This means that the presented existence analysis using entropy estimates is optimal. Clearly, the question remains if the existence of global solutions can be proved by another method.

Figure 3 shows that the entropy production density p is nonnegative in $[0,1]$ even for $\theta = 200$. However, the existence analysis works for much smaller values of θ only, namely $\theta < \theta^* \approx 46$. In the following, we explore this gap. We claim that there exist initial data such that $p(x,t) < 0$ at some (x,t) for θ close to the critial value θ^*. Indeed, let us take the initial data (5.2) with $C_1 = 0.02$ and

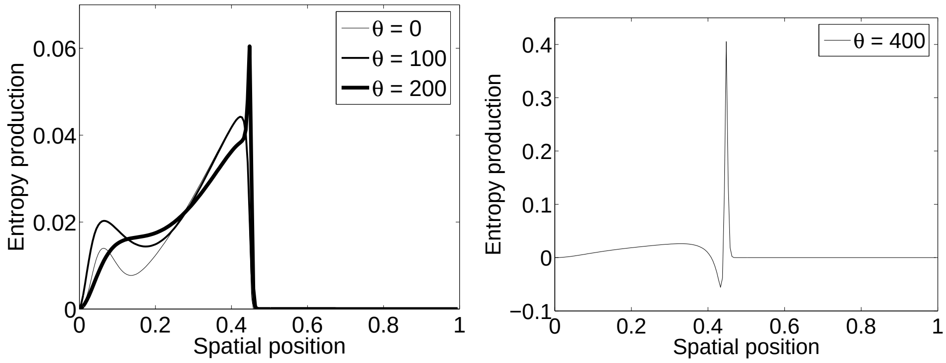

Fig. 3. Entropy production density p at time $t = 1$ versus position. The production rates vanish, $R_c = R_m = 0$.

$M_1 = 0.95$ (the other parameters are unchanged). Figure 4 (left) illustrates the volume fraction of the ECM at times $t = 0, 0.3, 0.6$ for $\theta = 70$. The right figure shows that the corresponding entropy production density p becomes negative in some region: $p_{\min} \approx -0.0051$ at $t = 0.6$. This holds true even for smaller values of θ: for $\theta = 55$, we have $p_{\min} \approx -0.0005$ at $t = 0.6$, and for $\theta = 50$ (choosing $C_1 = 0.03$), $p_{\min} \approx -1.6 \cdot 10^{-6}$ at $t = 0.4$. In the last two experiments, we have taken $N = 500$ grid points to improve the accuracy.

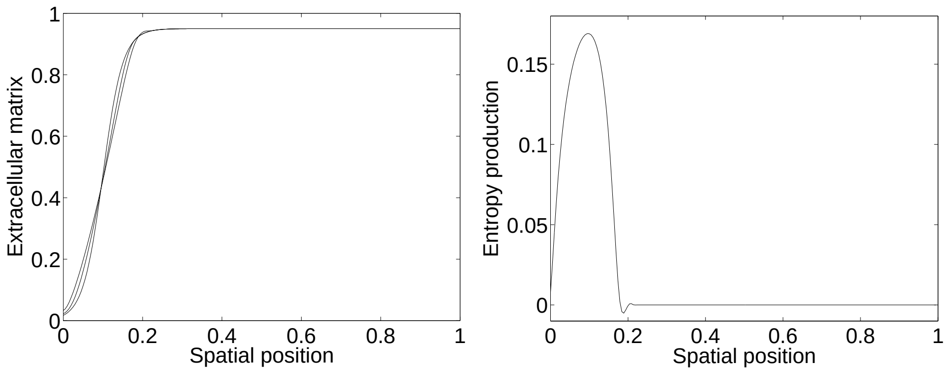

Fig. 4. Volume fraction of the ECM versus position at times $t = 0, 0.3, 0.6$ (left) and entropy production density p versus position at time $t = 0.6$ (right) using $\theta = 70$. The production rates vanish, $R_c = R_m = 0$. The minimal value of p is -0.0051.

Next, we include the production terms from (1.3) in the equations. In Figure 5, we see the time evolution of the volume fractions with $\theta = 1000$. In this experiment, we have taken $\varepsilon = 5 \cdot 10^{-4}$. Compared to Figure 1, the cell front and the ECM peaks are moving much faster. Furthermore, because of the production rates, the tumor cell volume is increasing. The height of the peak becomes smaller for smaller values of θ, see Figure 6. This behavior has been also observed by Jackson and Byrne[19] We remark that their scaling seems to be different such that we obtain different numerical results than those presented in Ref. 19.

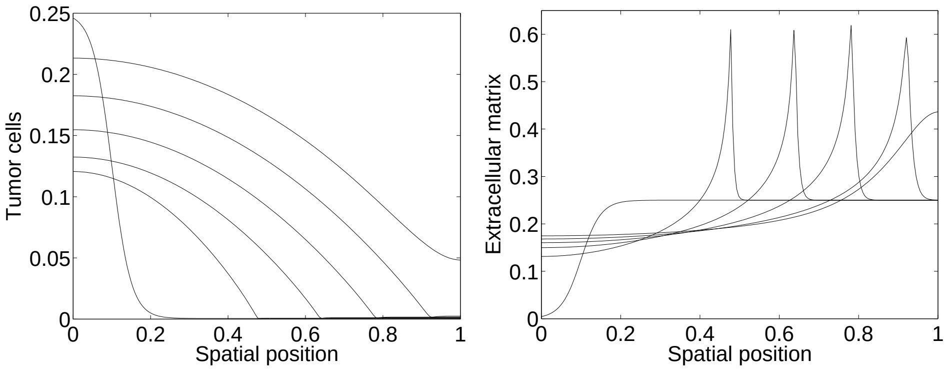

Fig. 5. Volume fractions of the tumor cells (left) and the ECM (right) versus position using $\theta = 1000$ at times $t = 0, 1, 2, 3, 4, 5$. The production rates are $\alpha = 0.1$, $\gamma = 1$, and $\delta = 0.35$.

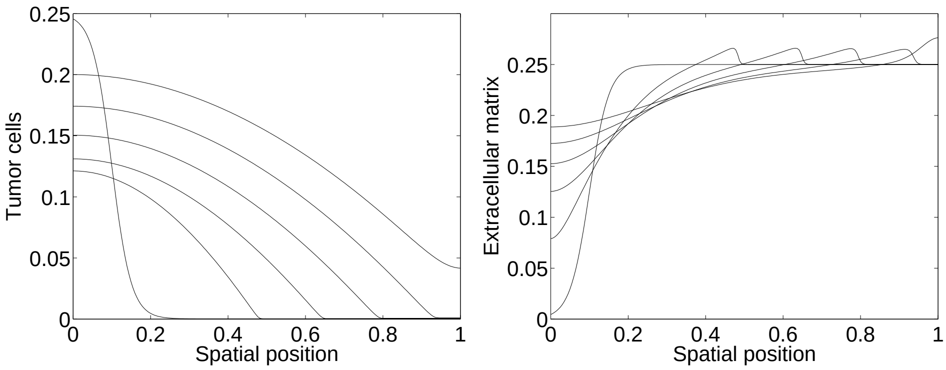

Fig. 6. Volume fractions of the tumor cells (left) and the ECM (right) versus position using $\theta = 100$ at times $t = 0, 1, 2, 3, 4, 5$. The production rates are $\alpha = 0.1$, $\gamma = 1$, and $\delta = 0.35$.

Due to the production terms, we cannot expect that the relative entropy H^* is decreasing in time but the analytical results show that H^* is uniformly bounded in time. This is confirmed in Figure 7 for various values of θ. Initially, the entropy is decreasing. Later, it is increasing up to $t \approx 15$, then decreasing and finally, it is very slowly increasing again.

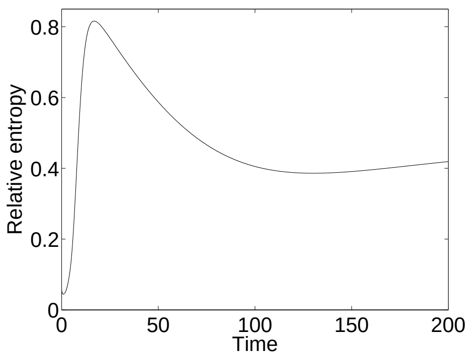

Fig. 7. Relative entropy H^* versus time using $\theta = 0$. The curves for $\theta = 100$ and $\theta = 1000$ are very similar. The production rates are $\alpha = 0.1$, $\gamma = 1$, and $\delta = 0.35$.

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