Well-posedness of a quasilinear hyperbolic-parabolic system arising in mathematical biology*

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Abstract

We study the existence of classical solutions of a taxis-diffusion-reaction model for tumour-induced blood vessel growth. The model in its basic form has been proposed by Chaplain and Stuart (IMA J. Appl. Med. Biol. (10), 1993) and consists of one equation for the endothelial cell-density and another one for the concentration of tumour angiogenesis factor (TAF). Here we consider the special and interesting case that endothelial cells are immobile in the absence of TAF, i.e. vanishing cell motility. In this case the mathematical structure of the model changes significantly (from parabolic type to a mixed hyperbolic-parabolic type) and existence of solutions is by no means clear. We present conditions on the initial and boundary data which guarantee local existence, uniqueness and positivity of classical solutions of the problem. Our approach is based on the method of characteristics and relies on known maximal L_p and Hölder regularity results for the diffusion equation.

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1 Introduction

A compact, solid tumour in the so-called *avascular state* resides in the tissue of the (human) body and has no direct connection to the blood circulation (vascular) system. This missing connection results in a limited availability of nutrients because the only means of transport from the vascular system to the tumour is by diffusion through the separating tissue. As a consequence, an avascular tumour cannot grow beyond a few millimetres in diameter. In order to grow further, it must initiate the outgrowth of new capillaries from the pre-existing vascular system in its direction.

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Once tumour and vascular system have established a connection, the tumour has reached the *vascular state*. This growth process, bringing the tumour from the avascular to the vascular state, is called *tumour-induced angiogenesis*. Due to the increased availability of nutrients, a vascularised tumour can grow further, can form metastasis and becomes potentially lethal. Understanding the mechanisms of tumour-induced angiogenesis is a key to successfully avoiding its completion, which can serve as a potential part of a cancer therapy.

The process of tumour-induced angiogenesis is initiated and controlled by a diffusive chemical compound, known as *tumour-angiogenesis factor* (TAF), which is released by the tumour cells into the surrounding tissue. Blood vessels and newly grown capillaries are lined by *endothelial cells* so that their density can be used as a measure of how well the vascular system is developed in the tissue around the tumour. A PDE system for the time- and space-dependent endothelial cell density $u(t, x)$ and the TAF concentration $c(t, x)$ as a model of tumour-induced angiogenesis has been proposed in 1993 by Chaplain and Stuart [12]. Despite its simplicity, this model captures many of the main events of the process and will serve as a motivation and starting point for our investigations presented here. Other models of tumour-induced angiogenesis, often taking into account more details of the process, are given in, for instance, [11, 6, 25].

If the process of tumour-induced angiogenesis is to be completed successfully, then this will happen in a finite time interval. For this reason we consider our model for times $t \in J_0 := [0, T_0]$. In space we consider a bounded domain $\Omega \subset \mathbb{R}^n$ of tissue surrounding the avascular tumour. An obvious choice is $n = 3$ whereas Chaplain and Stuart [12] use $n = 1$. The results of this paper will be valid for all $n \in \mathbb{N}$. We assume a smooth boundary Γ of Ω, which decomposes in two disjoint, closed and nonempty subsets Γ_1 and Γ_2. Here Γ_2 describes the shape of the tumour and Γ_1 is the “outer boundary” out of or through which new vasculature is growing under the influence of TAF. The situation is depicted in Fig. 1.

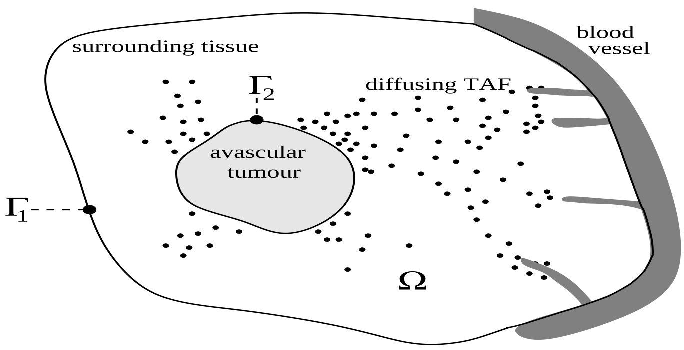

Figure 1: Schematic picture of the process of tumour-induced angiogenesis.

The model equations for u and c are derived using balance of mass and are given by

$$\partial_t u + \nabla \cdot (-\varepsilon \nabla u + \chi u \nabla c) = f(u, c)\,, \tag{1a}$$

$$\partial_t c + \nabla \cdot (-D \nabla c) = g(u, c)\,, \tag{1b}$$

see [12], where the reaction terms are

$$f(u, c) = \max\{0, c - c^*\} \cdot \mu u(1 - u) - \beta u\,, \tag{2a}$$

$$g(u, c) = -\frac{\alpha u c}{\gamma + c} - \lambda c\,. \tag{2b}$$

These model equations have to be supplemented with suitable initial and boundary conditions and non-negative real parameter values for $\varepsilon, \chi, c^*, \mu, \beta, D (> 0), \alpha, \gamma$, and λ. We assume $\varepsilon > 0$ for now and briefly outline the subprocesses of tumour-induced angiogenesis which are modelled by the various terms in the above set of equations; for more details we refer to [12]. TAF diffuses in Ω, is taken up by endothelial cells and decays linearly with rate λ. The TAF uptake by endothelial cells is modelled as a Michaelis-Menten kinetics term in $g(u, c)$. The release of TAF by the tumour cells is to be modelled by a Dirichlet or inflow boundary condition on Γ_2. On Γ_1, we assume that all TAF has been taken up, is decayed, or transported away in the blood system, and choose homogeneous Dirichlet boundary conditions there. With regard to the motile endothelial cells, the model assumes some random movement of them represented by linear diffusion with diffusion rate ε. More importantly, it is known that higher TAF concentrations have an attracting influence on endothelial cells and cause a directed migration of these towards areas of higher TAF concentration, i.e. ultimately towards the tumour. This latter process is termed *positive chemotaxis* and the flux of endothelial cells due to chemotaxis is modelled as $\chi u \nabla c$. Here, χ is the chemotactic constant and the gradient of c, pointing towards higher TAF concentrations, prescribes the direction of cell migration. The chemotaxis term leads to an additional coupling of the two PDEs and renders (1) quasilinear. In the reaction term $f(u, c)$, a linear loss of cells with rate β is assumed, and further logistic growth of them is modelled. Endothelial cells divide only if a sufficiently high TAF concentration is present in their surrounding and divide more often the higher the TAF concentration. This influence of TAF on cell division is modelled via the simple threshold function $\max\{0, c - c^*\}$ which multiplies the growth term. On the boundary Γ_1 we prescribe some spots of positive endothelial cell density representing some already grown capillaries which are trying to grow towards the tumour. On the boundary Γ_2 we prescribe homogenous Dirichlet boundary conditions having in mind that the model equations hold only up to the time when the vasculature connects with the tumour—thereafter other processes take over and other models must be used.

The PDE system (1) can be viewed as a generic case for many other models describing processes from developmental biology, e.g. tumour invasion [7], fracture [8] and wound [16] healing, and fungal growth [10]. Despite the more difficult nature of many of these other models, the unifying component is that they all contain a (chemo-)taxis-diffusion-reaction equation similar to (1a) with a positive random motility coefficient ε. Therefore these models are generically parabolic PDE systems. The PDE system (1) is a version of the well-known Keller-Segel model (cf. [23]) with an additional reaction term $f(u, c)$ in the first equation. As to literature, there is a wealth of results on several variants of the Keller-Segel model concerning existence and uniqueness as well as the qualitative behaviour of the solutions, see e.g. Yagi [30], Horstmann [21], Nagai *et al.* [27], and Alt [1] . We also refer the reader to the recent survey by Horstmann [22] and the references given therein. Classical results on quasilinear parabolic systems can be found in [24]. We further refer to Amann [3, 4]. It is well-known that local well-posedness of quasilinear parabolic problems in various function spaces can be established by means of maximal regularity results for related linear problems and the contraction mapping principle, see e.g. Clément and Li [13], Lunardi [26], and Amann [5].

In model (1, 2) it is assumed that the endothelial cells perform random motions because $\varepsilon > 0$. This assumption may not be correct as endothelial cells are relatively inert in the absence of TAF. Also, from a practical point of view, the cell random motility coefficient is often rather small and difficult to estimate experimentally. These considerations naturally lead to the questions:

1. Is there a loss of well-posedness if model (1, 2) is modified by setting $\varepsilon = 0$?

2. Is model (1, 2) with $\varepsilon = 0$ capable of describing the main events of tumour-induced angiogenesis?

The second question has been investigated numerically in some depth in [17] and a positive answer emerged. However, to the best of the authors knowledge, no analytic results on the local well-posedness of system (1, 2) with $\varepsilon = 0$ are known.[1] This new and challenging mathematical question is tackled in the present work and hence we contribute an answer to the first question. In particular, we give conditions on the problem data such that the local existence and uniqueness of classical solutions is guaranteed. These require that the threshold function $\max\{0, c - c^*\}$ in (2a) is replaced with a smooth approximation; this can be done without altering the essential features of the model. Due to $\varepsilon = 0$, and under the assumption that a solution $c(t, x)$ is known, equation (1a) is a first-order hyperbolic PDE for u. Therefore we consider system (1) with $\varepsilon = 0$ as a quasi-linear, mixed hyperbolic-parabolic PDE system. The gradient of c prescribes the flow direction of u and therefore we can prescribe boundary data for u only when the gradient of c points into Ω, i.e. on the inflow segment of Γ. From the modelling of tumour-induced angiogenesis it is clear that the inflow segment of Γ is Γ_1. These considerations will be reflected in the precise problem definition in the following section.

The remainder of the paper unfolds as follows. In Sec. 2 we present and describe our main result. This result is then proved in Sec. 3. Here we make use of the method of characteristics to derive, for a given function c, a solution operator for equation (1a) with $\varepsilon = 0$. Inserting this operator in equation (1b) results in a fully nonlinear equation and we prove local well-posedness by means of a fixed-point argument employing Hölder and L_p maximal regularity results for the diffusion equation. In the final section we discuss further questions and outline extensions of the presented results. Some comments on known results for related hyperbolic problems are included.

2 Main result

Let $J_0 = [0, T_0]$, $\Omega \subset \mathbb{R}^n$ be a bounded domain with smooth boundary Γ which decomposes according to $\Gamma = \Gamma_1 \cup \Gamma_2$, where Γ_1 and Γ_2 are disjoint, closed, and nonempty. The outer unit normal of Γ at position x is denoted by $\nu(x)$. For the unknowns $u : J_0 \times \bar{\Omega} \to \mathbb{R}$ and $c : J_0 \times \bar{\Omega} \to \mathbb{R}$ we consider the normalized ($\chi = D = 1$) taxis-diffusion-reaction system

$$\left\{ \begin{aligned} \partial_t u + \nabla c \cdot \nabla u + (\Delta c)u &= f(u, c), && t \in J_0,\ x \in \Omega \\ \partial_t c - \Delta c &= g(u, c), && t \in J_0,\ x \in \Omega \\ u(t, x) &= h_0(t, x), && t \in J_0,\ x \in \Gamma_1 \\ c(t, x) &= h(t, x), && t \in J_0,\ x \in \Gamma \\ u(0, x) &= u_0(x), && x \in \Omega \\ c(0, x) &= c_0(x), && x \in \Omega. \end{aligned} \right. \tag{3}$$

Our main result reads as follows.

Theorem 2.1. *Let $\alpha \in (0, 1)$, $J_0 = [0, T_0]$ and $\Omega \subset \mathbb{R}^n$ be a bounded domain with $C^{3+\alpha}$ boundary Γ which decomposes according to $\Gamma = \Gamma_1 \cup \Gamma_2$, where Γ_1 and Γ_2 are disjoint, closed, and nonempty. Suppose that the subsequent assumptions are satisfied.*

- (i) $h_0 \in C^{1+\alpha}(J_0 \times \Gamma_1),\ u_0 \in C^{1+\alpha}(\bar{\Omega})$;
- (ii) $h \in C^{(3+\alpha)/2, 3+\alpha}(J_0 \times \Gamma),\ c_0 \in C^{3+\alpha}(\bar{\Omega})$;
- (iii) $f,\ g \in C^{1+\alpha}(\bar{V})$, *where* $\{(u_0(x), c_0(x)) : x \in \bar{\Omega}\} \subset V,\ V \subset \mathbb{R}^2$ *open*;
- (iv) $u_0 = h_0|_{t=0}$ *and* $\partial_t h_0|_{t=0} + \nabla c_0 \cdot \nabla u_0 + (\Delta c_0)u_0 = f(u_0, c_0)$ *on* Γ_1;
- (v) $c_0 = h|_{t=0}$ *and* $\partial_t h|_{t=0} - \Delta c_0 = g(u_0, c_0)$ *on* Γ;
- (vi) $(-1)^i \nabla c_0 \cdot \nu > 0$ *on* $\Gamma_i,\ i = 1, 2$.

[1] We will comment on existing results for related hyperbolic chemotaxis models in Sec. 4.

Then there exists $T \in (0, T_0]$ such that (3) has a unique local solution

$$(u, c) \in C^{1+\alpha}([0, T] \times \bar{\Omega}) \times C^{(3+\alpha)/2, 3+\alpha}([0, T] \times \bar{\Omega}).$$

Moreover, if in addition to the above assumptions,

(vii) $\quad u_0 \geq 0,\ h_0 \geq 0,$ *and* $f(0, \eta) \geq 0$ *for all* $(0, \eta) \in V,\ \eta \geq 0;$

$(viii)$ $\quad c_0 \geq 0,\ h \geq 0,$ *and* $g(\xi, 0) \geq 0$ *for all* $(\xi, 0) \in V,\ \xi \geq 0;$

then u and c are non-negative on $[0, T] \times \bar{\Omega}$.

By $C^{\beta/2, \beta}([0, T] \times \bar{\Omega})$ we denote the classical parabolic Hölder space of order β, see e.g. [24, Chapter 1].

3 Proof of the main result

3.1 Basic ideas of the proof

The proof of the first part of Thm. 2.1 proceeds in two steps. In the first step, Section 3.2, we employ the method of characteristics to solve the hyperbolic subproblem for u for a given c (sufficiently smooth):

$$\begin{cases} \partial_t u + \nabla c \cdot \nabla u + (\Delta c) u = f(u, c), & t \in J,\ x \in \Omega \\ u(t, x) = h_0(t, x), & t \in J,\ x \in \Gamma_1 \\ u(0, x) = u_0(x), & x \in \Omega. \end{cases} \tag{4}$$

Here $J = [0, T]$, $T \in (0, T_0]$. Inserting the solution formula $u = \Phi(c)$ into the PDE for c, the quasilinear system (3) reduces to the single nonlocal, fully nonlinear equation for c:

$$\begin{cases} \partial_t c - \Delta c = g(\Phi(c), c), & t \in J,\ x \in \Omega \\ c(t, x) = h(t, x), & t \in J,\ x \in \Gamma \\ c(0, x) = c_0(x), & x \in \Omega. \end{cases} \tag{5}$$

In the second step, Section 3.3, problem (5) is then locally solved by means of a fixed point argument which makes use of maximal Hölder and L_p regularity of the diffusion equation.

To be more precise, let $Z_c^T = C^{(3+\alpha)/2,\, 3+\alpha}(J \times \bar{\Omega})$. We introduce the set

$$B_R^T = \{ w \in Z_c^T : w|_{t=0} = c_0 \text{ and } |w|_{Z_c^T} \leq R \},$$

where $R \geq R_0 := |c_0|_{C^{3+\alpha}(\bar{\Omega})}$. We fix further $p \in (2 + n, \infty)$ and consider the base space $Y^T = H_p^1(J; L_p(\Omega)) \cap L_p(J; H_p^2(\Omega))$. Here $L_p(J; X)$ resp. $H_p^1(J; X)$ mean the vector-valued Lebesgue resp. Sobolev space of functions on J taking values in the Banach space X ($X = L_p(\Omega),\ H_p^2(\Omega)$). It is well-known from parabolic L_p-theory that Y^T embeds into $C(J; C^1(\bar{\Omega}))$, in particular $Y^T \hookrightarrow C(J \times \bar{\Omega})$, see [9, Thm. 10.4] or [14, Thm. A3.14]. Employing Arsela-Ascoli's theorem it is not difficult to see that B_R^T is a closed subset in Y^T. The idea is then to apply the contraction mapping principle to the mapping $c \mapsto \tilde{c}$ defined on the set B_R^T by means of

$$\begin{cases} \partial_t \tilde{c} - \Delta \tilde{c} = g(\Phi(c), c), & t \in J,\ x \in \Omega \\ \tilde{c}(t, x) = h(t, x), & t \in J,\ x \in \Gamma \\ \tilde{c}(0, x) = c_0(x), & x \in \Omega. \end{cases} \tag{6}$$

In order to succeed, we will prove

Theorem 3.1. *Under the assumptions of Thm. 2.1 there is a pair $(T,R) \in (0,T_0] \times [R_0,\infty)$ such that the mapping $c \mapsto \tilde{c}$ defined by (6) (i) leaves B_R^T invariant; and (ii) is a strict Y^T contraction.*

We point out that due to the fact that equation (5) is fully nonlinear, one is really forced to employ optimal regularity estimates of the diffusion equation. Interestingly, it seems that the treatment of (5) requires maximal regularity results in both the L_p scale and a scale of Hölder spaces such as $C^{\beta/2,\beta}$. To prove invariance of B_R^T (property (i) in Thm. 3.1), we will use maximal Hölder regularity with $\beta = 1+\alpha$, while (ii) is shown by means of maximal L_p regularity with $p \in (2+n,\infty)$.

Finally, in Section 3.4, we prove the second part of Thm. 2.1. Here, the main tools are positivity theory for ODEs and a comparison principle for semilinear parabolic PDEs.

3.2 The hyperbolic equation for u

From now on we will assume that the data f, g, u_0, c_0, h_0, and h are subject to the conditions (i)-(vi) in Thm. 2.1. Suppose $c \in B_R^T$ is known. To solve the nonlinear hyperbolic problem (4) for u, we use the method of characteristics.

Let $\Pi_{in}^T = \{(0,x) : x \in \bar{\Omega}\} \cup \{(t,x) : t \in J, x \in \Gamma_1\}$ as well as $\Pi_{out}^T = \{(T,x) : x \in \bar{\Omega}\} \cup \{(t,x) : t \in J, x \in \Gamma_2\}$. Define the function $\psi : \Pi_{in}^T \to \mathbb{R}$ by means of

$$\psi(t,x) = \begin{cases} u_0(x) & : t = 0 \\ h_0(t,x) & : t > 0, \end{cases} \qquad (t,x) \in \Pi_{in}^T. \tag{7}$$

With $y = (t,x)$ and $z(s) = u(y(s))$, $s \in [0,s_0]$, the characteristic ODE system associated with (4) then reads

$$\dot{y}(s) = (1, \nabla c(y(s))), \quad s \in (0,s_0) \tag{8}$$

$$\dot{z}(s) = -\Delta c(y(s)) z(s) + f(z(s), c(y(s))), \quad s \in (0,s_0). \tag{9}$$

We have now the subsequent result.

Lemma 3.1. *Given $R \in [R_0,\infty)$, there exists $T_1(R) > 0$ such that for all $T \in (0,T_1(R)]$ and $c \in B_R^T$ the following statements hold true:*

(i) For every $y' = (t',x') \in J \times \bar{\Omega} \setminus (\Pi_{in}^T \cap \Pi_{out}^T)$ there are unique $s_0 = s_0(y',c) \geq 0$ and $y_0 = y_0(y',c) = (t_0,x_0) \in \Pi_{in}^T$ such that the (unique) solution $y(s) = y(s;y',c)$ of (8) with initial condition $y(0) = y_0$ fulfils $y(s_0) = y'$. (For $y' \in \Pi_{in}^T \cap \Pi_{out}^T$ we set $s_0(y',c) := 0$ and $y_0(y',c) := y'$.)

(ii) $t(s;y',c) = s + t' - s_0(y',c)$, $s \in [0,s_0(y',c)]$, in particular $t_0(y',c) = t' - s_0(y',c)$.

(iii) The solution u of (4) is given by

$$u(t',x') = z(s_0(y',c); y',c), \quad (t',x') \in J \times \bar{\Omega},$$

where $z(s;y',c)$, $s \in [0,s_0(y',c)]$, denotes the unique solution of

$$\begin{cases} \dot{z}(s) = -\Delta c(y(s;y',c)) z(s) + f(z(s), c(y(s;y',c))), & s \in (0,s_0(y',c)) \\ z(0) = \psi(y_0(y',c)). \end{cases} \tag{10}$$

(iv) *The solution of (4) is equivalently given by* $u(t', x') = \tilde{z}(t'; y', c)$, *where* $\tilde{z}(\rho; y', c)$ *for* $\rho \in [t_0(y', c), t']$ *solves*

$$\begin{cases} \dot{\tilde{z}}(\rho) = -\Delta c(\rho, \tilde{x}(\rho; y', c))\tilde{z}(\rho) + f(\tilde{z}(\rho), c(\rho, \tilde{x}(\rho; y', c))) \\ \tilde{z}(t_0(y', c)) = \psi(y_0(y', c)), \end{cases} \tag{11}$$

$\tilde{x}(\rho; y', c)$ *being the unique solution of*

$$\begin{cases} \dot{\tilde{x}}(\rho) = \nabla c(\rho, \tilde{x}(\rho)), \quad \rho \in (t_0(y', c), t') \\ \tilde{x}(t') = x'. \end{cases} \tag{12}$$

Moreover, $\tilde{x}(\rho; y', c) = x(\rho - t_0(y', c); y', c)$ *and* $\tilde{z}(\rho; y', c) = z(\rho - t_0(y', c); y', c)$, $\rho \in [t_0(y', c), t']$.

Proof. Suppose that $c \in B_R^T$. Clearly, $\nabla c \in C^1(J \times \bar{\Omega}; \mathbb{R}^n)$ and $|\nabla c(t, x) - \nabla c_0(x)| \leq C(R)T$ for all $(t, x) \in J \times \bar{\Omega}$, where $C(R)$ is a constant depending on R. This, together with (vi), implies that for sufficiently small $T_1(R)$ there exist positive δ_1, δ_2 independent of c such that for any $T \in (0, T_1(R)]$ we have

$$\delta_1 \leq (-1)^i \nabla c(t, x) \cdot \nu(x) \leq \delta_2, \quad t \in J, \, x \in \Gamma_i. \tag{13}$$

So we see that Π_{in}^T resp. Π_{out}^T are the inflow resp. outflow segment of the trajectories through the cylinder $J \times \bar{\Omega}$ corresponding to (8). This shows (i). Statement (ii) follows directly from $\dot{t}(s) \equiv 1$ and $t(s_0(y', c)) = t'$, while (iii) results from the method of characteristics, see e.g. Evans [15]. Here one has to possibly further decrease $T_1(R)$ in order to ensure that f in (10) is well-defined, see below. To obtain (iv), one uses (iii) and employs the change of variables $\rho = s + t_0(y', c)$.

It remains to show that $T_1(R)$ can be selected small enough such that the terms in (10) and (11) containing the function f are well-defined, which, in the tilde formulation, means that $(\tilde{z}(\rho; y', c), c(\rho, \tilde{x}(\rho; y', c))) \in V$ for all $\rho \in [t_0(y', c), t']$, $y' \in J \times \bar{\Omega}$, and $c \in B_R^T$. As to the second argument, it follows from (12) that

$$|\tilde{x}(\rho; y', c) - x'| \leq |\rho - t'| \, |\nabla c|_\infty \leq TC_1(R),$$

which, together with $c|_{t=0} = c_0$, entails

$$|c(\rho, \tilde{x}(\rho; y', c)) - c_0(x')| \leq C_2(R)(\rho + |\tilde{x}(\rho; y', c) - x'|) \leq \tilde{C}(R)T. \tag{14}$$

So the term on the left-hand side of (14) can be made arbitrarily small. Concerning the first argument, the ode (11) allows for the *a priori* estimate

$$|\tilde{z}(\rho; y', c)| \leq \frac{1}{1 - TC_3(R)}(T|f|_\infty + |\psi|_\infty) \leq C_d, \quad \rho \in [t_0(y', c), t'], \tag{15}$$

provided that e.g. $TC_3(R) \leq 1/2$; here C_d denotes a constant which depends only on the data. From (15) and (11) we deduce further that for $\rho \in [t_0(y', c), t']$,

$$|\tilde{z}(\rho; y', c) - \psi(y_0(y', c))| \leq T(|\Delta c|_\infty |\tilde{z}|_\infty + |f|_\infty) \leq T(C_3(R)C_d + \tilde{C}_d).$$

Finally, we have $\psi(y_0(y', c)) = u_0(x_0(y', c))$ in case $t_0(y', c) = 0$, and otherwise $\psi(y_0(y', c)) = h_0(y_0(y', c))$ as well as

$$|h_0(y_0(y', c)) - u_0(x_0(y', c))| = |h_0(y_0(y', c)) - h_0(0, x_0(y', c))| \leq C_d T,$$

where we used assumption (iv) of Thm. 2.1. □

We remark that in what follows we will work with both solution formulae for u provided by Lemma 3.1 (iii) and (iv). The advantage of the second formulation consists in the fact that the first argument of the ∇c and Δc terms in (11) and (12), which is ρ, does not depend (directly) on y' and c. This proves extremely useful in the estimates below, since one does not need so much time regularity of ∇c and Δc, respectively.

The next result concerns the regularity of the solution u of (4) and is crucial for the proof of the invariance property of the set B_R^T, (i) in Thm. 3.1.

Lemma 3.2. *Given $R \in [R_0, \infty)$, there exists a number $T_2(R) \in (0, T_1(R)]$ such that for any $T \in (0, T_2(R)]$ and $c \in B_R^T$, the solution $u = \Phi(c)$ of (4) belongs to the space $C^{1+\alpha}(J \times \bar{\Omega})$ and $|u|_{C^{1+\alpha}(J\times\bar{\Omega})} \leq C_{data}$, where the constant $C_{data} > 0$ depends on the data but* **not** *on T and R.*

Proof. **1. Geometric properties of the characteristics:** Given $c \in B_R^T$, it is appropriate to decompose the hyperbolic domain as $J \times \bar{\Omega} = \mathcal{H}_1 \cup \mathcal{H}_2 \cup \mathcal{H}_{crit}$, where

$$\begin{aligned} \mathcal{H}_{crit} &= \{y' \in J \times \bar{\Omega} : y_0(y', c) \in \{0\} \times \Gamma_1\}, \\ \mathcal{H}_1 &= \{y' \in (J \times \bar{\Omega}) \setminus \mathcal{H}_{crit} : t_0(y', c) = 0\}, \\ \mathcal{H}_2 &= \{y' \in (J \times \bar{\Omega}) \setminus \mathcal{H}_{crit} : x_0(y', c) \in \Gamma_1\}. \end{aligned}$$

Let $y' \in \mathcal{H}_2 \cup \mathcal{H}_{crit}$, that is $y_0(y', c) \in J \times \Gamma_1$. Putting

$$|y(s_*; y', c) - y_0(y', c)| := \max_{s\in[0, s_0(y',c)]} |y(s; y', c) - y_0(y', c)|$$

we have the uniform estimate

$$|y' - y_0(y', c)| \leq |y(s_*; y', c) - y_0(y', c)| \leq \int_0^{s_*} |(1, \nabla c(y(s; y', c)))|\, ds \leq T(1 + C(R)), \quad (16)$$

which means in particular that given $\varepsilon > 0$ the distance between the set Γ_1 and the orbit $\{x(s; y', c) : s \in [0, s_0(y', c)]\}$ is less than ε whenever T is sufficiently small.

Set $\varphi(x) := \text{dist}(x, \Gamma_1),\ x \in \bar{\Omega}$; clearly $\nabla\varphi(x) = -\nu(x),\ x \in \Gamma_1$. By (13), there exists $\varepsilon > 0$ and $\delta_0 > 0$ both not depending on $c \in B_R^T$ such that for sufficiently small T,

$$\nabla\varphi(x) \cdot \nabla c(y) \geq \delta_0, \quad y = (t, x) \in J \times \{\bar{x} \in \bar{\Omega} : \text{dist}(\bar{x}, \Gamma_1) < \varepsilon\} =: J \times \Lambda_\varepsilon. \quad (17)$$

Hereafter we will always assume that T is so small such that (17) is valid.

We show next that for sufficiently small T (and ε), the subsequent property (**A**) holds.

(**A**) For any $\hat{x} \in \Gamma_1$ and any $t' \in (0, T]$, there is exactly one $x' \in \Lambda_\varepsilon \cap \{\hat{x} + \lambda(-\nu(\hat{x})) :\ \lambda \geq 0\}$ such that $(t', x') \in \mathcal{H}_{crit}$.

To prove (**A**), note first that for continuity reasons it suffices to show uniqueness. To this end, fix two different points $x_0^1,\ x_0^2 \in \Gamma_1 \cap B(\hat{x}, \varepsilon_0)$, where $B(\hat{x}, \varepsilon_0)$ designates the ball with centre $\hat{x}$ and (small) radius ε_0; note that in view of (16) the assumption $x_0^1,\ x_0^2 \in B(\hat{x}, \varepsilon_0)$ is not a restriction of generality. Let $x_1(s)$ and $x_2(s)$ be the corresponding space components of the characteristics through $(0, x_0^1)$ resp. $(0, x_0^2)$, that is (cf. Lemma 3.1)

$$\left\{ \begin{array}{ll} \dot{x}_i(s) = \nabla c(s, x_i(s)), & s \in (0, t') \\ x_i(0) = x_0^i, & \end{array} \right. \quad (18)$$

for $i = 1, 2$. We are interested in the angle $\beta(s)$ between the vectors $(-\nu(\hat{x}))$ and $x_1(s) - x_2(s)$, for $s \in [0, t']$. Our goal is to show, that for sufficiently small T, the angle $\beta(t')$ is bounded away from zero, uniformly w.r.t. $\hat{x}$, t', x_0^1, and x_0^2, which clearly implies the uniqueness statement in (**A**).

Set $\delta = |x_0^1 - x_0^2|$ and $|x_1(s_*) - x_2(s_*)| = \max_{s\in[0,t']} |x_1(s) - x_2(s)|$. Then it follows from (18) that

$$\begin{aligned}|x_1(s_*) - x_2(s_*)| &\leq \int_0^{s_*} |\nabla c(s, x_1(s)) - \nabla c(s, x_2(s))|\, ds + |x_0^1 - x_0^2| \\ &\leq TC(R)|x_1(s_*) - x_2(s_*)| + \delta,\end{aligned}$$

and thus

$$|x_1(s_*) - x_2(s_*)| \leq \frac{\delta}{1 - TC(R)} \leq (1 + \varepsilon_1)\delta, \tag{19}$$

provided that $TC(R)$ is small enough. From (18) and (19) we further conclude that

$$\begin{aligned}|x_1(s) - x_2(s)| &\geq -TC(R)|x_1(s_*) - x_2(s_*)| + |x_0^1 - x_0^2| \\ &\geq -TC(R)(1 + \varepsilon_1)\delta + \delta \geq (1 - \varepsilon_1)\delta, \quad s \in [0, t'],\end{aligned} \tag{20}$$

as long as T is sufficiently small. Besides, (18), (19), and the triangle inequality imply

$$||x_1(s) - x_2(s)| - \delta| \leq |x_1(s) - x_2(s) - (x_0^1 - x_0^2)| \tag{21}$$

$$\leq TC(R)|x_1(s_*) - x_2(s_*)| \leq \varepsilon_1(1 + \varepsilon_1)\delta \tag{22}$$

for all $s \in [0, t']$, if T is sufficiently small. From (20), (21), (22) we then infer that

$$\begin{aligned}|\cos\beta(s) - \cos\beta(0)| &= \Big| \frac{[x_1(s) - x_2(s)] \cdot (-\nu(\hat{x}))}{|x_1(s) - x_2(s)|} - \frac{[x_0^1 - x_0^2] \cdot (-\nu(\hat{x}))}{|x_0^1 - x_0^2|} \Big| \\ &= \Big| \frac{[x_1(s) - x_2(s) - (x_0^1 - x_0^2)] \cdot (-\nu(\hat{x}))\delta - [x_0^1 - x_0^2] \cdot (-\nu(\hat{x}))[|x_1(s) - x_2(s)| - \delta]}{|x_1(s) - x_2(s)|\,\delta} \Big| \\ &\leq \frac{2\varepsilon_1(1 + \varepsilon_1)\delta^2}{(1 - \varepsilon_1)\delta^2} = \frac{2\varepsilon_1(1 + \varepsilon_1)}{1 - \varepsilon_1},\end{aligned}$$

thus $|\cos\beta(s) - \cos\beta(0)|$ can be bounded above by e.g. $1/2$ provided that T is small enough. Choosing ε_0 small enough, we certainly have $|\cos\beta(0)| \leq 1/4$, by the assumed smoothness of Γ_1, and hence $|\cos\beta(s)| \leq 3/4$ or $|\beta(s)| \geq \beta_0 > 0$ for all $s \in [0, t']$. This shows (**A**).

By means of a similar argument and a suitable variable transformation we describe below one can prove that for sufficiently small T (and ε), the following corresponding property (**B**) holds.

(**B**) For any $x' \in \Lambda_\varepsilon \setminus \Gamma_1$, there is at most one $t' \in [0, T]$ such that $(t', x') \in \mathcal{H}_{crit}$.

Given an arbitrary characteristic $y(\cdot; y', c)$ with $y_0(y', c) \in J \times \Gamma_1$ we may use the variable transformation $\zeta = \theta(s) = \varphi(x(s; y', c))$. Observe that (16) and (17) entail that

$$\frac{d\theta(s)}{ds} = \nabla\varphi(x(s; y', c)) \cdot \nabla c(y(s; y', c)) \geq \delta_0 > 0, \quad s \in [0, s_0(y', c)], \tag{23}$$

provided that T is small enough. So the inverse function θ^{-1} is well-defined, that is, we can recover s from ζ by means of $s = \theta^{-1}(\zeta)$. In view of $\theta(0) = \varphi(x(0; y', c)) = \varphi(x_0(y', c)) = 0$

and $\theta(s_0(y',c)) = \varphi(x(s_0(y',c);y',c)) = \varphi(x') =: \zeta_0(x')$, the s-interval $[0,s_0(y',c)]$ corresponds to the ζ-interval $[0,\zeta_0(x')]$. Letting then $\bar{y}(\zeta;y',c) = y(\theta^{-1}(\zeta);y',c),\ \zeta \in [0,\zeta_0(x')]$, the transformed ODE reads

$$\frac{d}{d\zeta}\bar{y}(\zeta;y',c) = \frac{d\theta^{-1}(\zeta)}{d\zeta}\,(1,\nabla c(\bar{y}(\zeta;y',c))),\ \zeta \in (0,\zeta_0(x')), \quad \bar{y}(\zeta_0(x');y',c) = y',$$

where

$$\frac{d\theta^{-1}(\zeta)}{d\zeta} = ((\nabla\varphi(\bar{x}(\zeta;y',c))\cdot\nabla c(\bar{y}(\zeta;y',c)))^{-1}, \quad \zeta \in [0,\zeta_0(x')].$$

Employing the notation

$$\gamma_c(y) = \frac{(1,\nabla c(y))}{\nabla\varphi(x)\cdot\nabla c(y)}, \quad y=(t,x)\in J\times\Lambda_\varepsilon,$$

we have

$$\dot{\bar{y}}(\zeta;y',c) = \gamma_c(\bar{y}(\zeta;y',c)),\ \zeta\in(0,\zeta_0(x')), \quad \bar{y}(\zeta_0(x');y',c)) = y'. \tag{24}$$

Observe that by (16),

$$|\zeta_0(x')| = |\varphi(x')| = |\varphi(x') - \varphi(x_0(y',c_1))| \le |\nabla\varphi|_\infty|x' - x_0(y',c_1)| \le T\tilde{C}(R). \tag{25}$$

Note also that (17) ensures that the denominator of γ_c in (24) is bounded away from zero.

In order to show (**B**), one can now proceed as in the proof of (**A**). In fact, given two different points $x_0^1,\ x_0^2 \in \Gamma_1$ one considers the corresponding (transformed) characteristics $\bar{y}_1(\zeta)$ and $\bar{y}_2(\zeta)$ ($\zeta \in [0,\zeta_0(x')]$) through $(0,x_0^1)$ resp. $(0,x_0^2)$ and verifies that the angle between the vectors $\bar{y}_1(\zeta)-\bar{y}_2(\zeta)$ and $(1,0,\ldots,0)\in\mathbb{R}^{n+1}$ can be bounded away from zero for all $\zeta\in[0,\zeta_0(x')]$, uniformly w.r.t. x', x_0^1, and x_0^2, provided that T has been selected small enough.

The properties (**A**) and (**B**) are needed below to extend the local to the desired global Hölder estimates. Observe that property (**A**) and compactness of $\bar{\Omega}$ ensure that there exists a number $N\in\mathbb{N}$ independent of R and $T\in(0,T_1(R)]$ such that any two different points $(t',x'),(t',\bar{x}')\in J\times\bar{\Omega}$ can be connected by a chain $\mathcal{C}$ of $k\le N$ line segments in the set $\{(t',x): x\in\bar{\Omega}\}$ of length $\le|x'-\bar{x}'|$ so that $\mathcal{C}$ satisfies the following property: if $(t',x'),(t',\bar{x}')\in\mathcal{H}_i\cup\mathcal{H}_{crit}$, then $\mathcal{C}\subset\mathcal{H}_i\cup\mathcal{H}_{crit}$, $i=1,\ 2$; otherwise $\mathcal{C}$ crosses $\mathcal{H}_{crit}$ precisely one time. In the case when t' varies and x' is fixed the situation is even simpler, thanks to (**B**).

2. A formula for ∇u: We will next derive a representation for ∇u. Suppose that $y'\in\mathcal{H}_1\cup\mathcal{H}_2$. From Lemma 3.1 (iv) we infer that

$$\frac{\partial u}{\partial x_i'}(t',x') = \frac{\partial\tilde{z}}{\partial x_i'}(t';t',x'),\ i=1,\ldots,n,$$

in the sense of differentiation w.r.t. a parameter, see e.g. Amann [2]. Here and in the following lines we suppress the dependence on c in the notation. One verifies that the function $(\partial\tilde{z}/\partial x_i')(\rho;t',x'),\ \rho\in[t_0(y'),t']$, solves the ODE

$$\dot{w}(\rho) = \kappa_i(\rho;y')w(\rho)+\eta_i(\rho;y'), \quad \rho\in(t_0(y'),t'), \tag{26}$$

with

$$\begin{aligned}\kappa_i(\rho;y') &= -\Delta c(\rho,\tilde{x}(\rho;y')) + f_u(\tilde{z}(\rho;y'),c(\rho,\tilde{x}(\rho;y'))),\\ \eta_i(\rho;y') &= \big(-\nabla\Delta c(\rho,\tilde{x}(\rho;y'))\tilde{z}(\rho;y') + f_c(\tilde{z}(\rho;y'),c(\rho,\tilde{x}(\rho;y')))\nabla c(\rho,\tilde{x}(\rho;y'))\big)\\ &\quad\cdot\frac{\partial\tilde{x}}{\partial x_i'}(\rho;y').\end{aligned}$$

Furthermore, $\partial\tilde z/\partial x_i'$ satisfies the initial condition

$$\frac{\partial \tilde z}{\partial x_i'}(t_0(y');y') = \xi_i(y'), \tag{27}$$

where

$$\xi_i(y') = \Big(\Delta c(y_0(y'))\psi(y_0(y')) - f(\psi(y_0(y')), c(y_0(y')))\Big)\frac{\partial t_0}{\partial x_i'}(y') + \frac{\partial}{\partial x_i'}(\psi(y_0(y'))); \tag{28}$$

in fact, differentiate $\tilde z(t_0(y');t',x') = \psi(y_0(y'))$ w.r.t. x_i' and employ (11) to see this.

From (26) and (27) we deduce that

$$\begin{aligned}\frac{\partial \tilde z}{\partial x_i'}(\rho;y',c) = &\exp\Big(\int_{t_0(y',c)}^{\rho}\kappa_i(\tau;y',c)\,d\tau\Big)\xi_i(y',c)\\ &+\int_{t_0(y',c)}^{\rho}\exp\Big(\int_{\sigma}^{\rho}\kappa_i(\tau;y',c)\,d\tau\Big)\,\eta_i(\sigma;y',c)\,d\sigma,\end{aligned} \tag{29}$$

thus with $\rho = t'$,

$$\begin{aligned}\frac{\partial u}{\partial x_i'}(t',x') = &\exp\Big(\int_{t_0(y',c)}^{t'}\kappa_i(\tau;y',c)\,d\tau\Big)\xi_i(y',c)\\ &+\int_{t_0(y',c)}^{t'}\exp\Big(\int_{\sigma}^{t'}\kappa_i(\tau;y',c)\,d\tau\Big)\,\eta_i(\sigma;y',c)\,d\sigma.\end{aligned} \tag{30}$$

Our next objective is to find more explicit expressions for ξ_i and η_i. Differentiating (12) with respect to the parameter x_i' shows that the function $(\partial\tilde x/\partial x_i')(\rho;y')$, $\rho \in [t_0(y'),t']$, solves the linear ODE problem

$$\dot w(\rho) = \nabla^2 c(\rho,\tilde x(\rho))w(\rho),\ \rho\in[t_0(y'),t'],\quad w(t') = e_i, \tag{31}$$

where $\nabla^2 c$ denotes the Hessian matrix of c w.r.t. the spatial variables and e_i designates the ith unit vector. From $x_0(y') = \tilde x(t_0(y');y')$ we obtain by differentiation w.r.t. x_i'

$$\begin{aligned}\frac{\partial x_0}{\partial x_i'}(y') &= \frac{\partial \tilde x}{\partial \rho}(t_0(y');y')\frac{\partial t_0}{\partial x_i'}(y') + \frac{\partial \tilde x}{\partial x_i'}(t_0(y');y')\\ &= \nabla c(y_0(y'))\frac{\partial t_0}{\partial x_i'}(y') + \frac{\partial \tilde x}{\partial x_i'}(t_0(y');y').\end{aligned} \tag{32}$$

Obviously $\partial t_0/\partial x_i' = 0$ in $\mathcal{H}_1$. If $y'\in\mathcal{H}_2$, we have $\varphi(x_0(y')) = 0$, which, by differentiation w.r.t. x_i', yields

$$\nabla\varphi(x_0(y'))\cdot\frac{\partial x_0}{\partial x_i'}(y') = 0.$$

In view of (32) and $\nabla\varphi(x) = -\nu(x)$, $x\in\Gamma_1$, we therefore get

$$\frac{\partial t_0}{\partial x_i'}(y') = -\frac{\nu(x_0(y'))\cdot\frac{\partial\tilde x}{\partial x_i'}(t_0(y');y')}{\nu(x_0(y'))\cdot\nabla c(y_0(y'))},\quad y'\in\mathcal{H}_2. \tag{33}$$

In analogous fashion one sees that the function $(\partial\tilde x/\partial t')(\rho;y')$ solves the linear ODE problem

$$\dot w(\rho) = \nabla^2 c(\rho,\tilde x(\rho))w(\rho),\ \rho\in[t_0(y'),t'],\quad w(t') = -\nabla c(y'), \tag{34}$$

and that

$$\frac{\partial x_0}{\partial t'}(y') = \nabla c(y_0(y'))\frac{\partial t_0}{\partial t'}(y') + \frac{\partial \tilde{x}}{\partial t'}(t_0(y');y'), \tag{35}$$

as well as

$$\frac{\partial t_0}{\partial t'}(y') = -\frac{\nu(x_0(y'))\cdot\frac{\partial \tilde{x}}{\partial t'}(t_0(y');y')}{\nu(x_0(y'))\cdot\nabla c(y_0(y'))}, \quad y'\in\mathcal{H}_2. \tag{36}$$

Observe that each of the derivatives computed above ($\partial t_0/\partial x_i'$, $\partial t_0/\partial t'$, ...) possesses a continuous extension from $\mathcal{H}_1$ to $\mathcal{H}_1\cup\mathcal{H}_{crit}$ and from $\mathcal{H}_2$ to $\mathcal{H}_2\cup\mathcal{H}_{crit}$.

3. Continuity of u and ∇u: Continuity of u in $J\times\bar{\Omega}$ follows from Lemma 3.1 and the compatibility condition $u_0 = h_0|_{t=0}$ on Γ_1.

We next show that ∇u is continuous in $J\times\bar{\Omega}$. To this end, let $y_*\in\mathcal{H}_{crit}$. In view of (28), (7), (32), and $\partial t_0/\partial x_i' = 0$ in $\mathcal{H}_1$, we see that

$$\lim_{\mathcal{H}_1\ni y'\to y_*}\xi_i(y') = \lim_{\mathcal{H}_1\ni y'\to y_*}\nabla u_0(x_0(y'))\cdot\frac{\partial x_0}{\partial x_i'}(y') = \nabla u_0(x_0(y_*))\cdot\frac{\partial\tilde{x}}{\partial x_i'}(t_0(y_*);y_*).$$

On the other hand, we may choose a function $v\in C^1(J\times\bar{\Omega})$ such that $v|_{t=0}=u_0$ and $v|_{\Gamma_1}=h_0$, thereby obtaining (with $\frac{\partial t_0}{\partial x_i'}(y_*) := \lim_{\mathcal{H}_2\ni y'\to y_*}\frac{\partial t_0}{\partial x_i'}(y')$)

$$\begin{aligned}
\lim_{\mathcal{H}_2\ni y'\to y_*}\xi_i(y') &= \Big(\Delta c_0(x_0(y_*))h_0(0,x_0(y_*)) - f(h_0(0,x_0(y_*)),c_0(x_0(y_*)))\Big)\frac{\partial t_0}{\partial x_i'}(y_*)\\
&\qquad + \partial_t v(0,x_0(y_*))\frac{\partial t_0}{\partial x_i'}(y_*) + \nabla v(0,x_0(y_*))\cdot\lim_{\mathcal{H}_2\ni y'\to y_*}\frac{\partial x_0}{\partial x_i'}(y')\\
&= \Big(\Delta c_0(x_0(y_*))u_0(x_0(y_*)) - f(u_0(x_0(y_*)),c_0(x_0(y_*))) + \partial_t h_0(0,x_0(y_*))\Big)\frac{\partial t_0}{\partial x_i'}(y_*)\\
&\qquad + \nabla u_0(x_0(y_*))\cdot\Big(\nabla c_0(x_0(y_*))\frac{\partial t_0}{\partial x_i'}(y_*) + \frac{\partial\tilde{x}}{\partial x_i'}(t_0(y_*);y_*)\Big)\\
&= \nabla u_0(x_0(y_*))\cdot\frac{\partial\tilde{x}}{\partial x_i'}(t_0(y_*);y_*);
\end{aligned}$$

here we used the compatibility conditions (iv) and (32). Therefore $\xi_i\in C(J\times\bar{\Omega})$, $i=1,\dots,n$. The continuity of ∇u in $J\times\bar{\Omega}$ follows now from (30).

4. Preparing the Hölder estimates: We next collect several basic inequalities, which will be needed for estimating u in the $C^{1+\alpha}(J\times\bar{\Omega})$ norm. In what is to follow, C, C_d, C_R, and $\mu(T)$ denote positive constants, which may differ from line to line, but which are such that C is independent of R, T, and the data; C_d depends only on the data; C_R depends on R but not on T and the data; $\mu(T)$ is independent of R and the data and satisfies $\mu(T)\to 0$ as $T\to 0$. By choosing T sufficiently small, we may assume that for each of the (**finitely** many) terms of the form $\mu(T)(C_R+C_d)$ appearing in the subsequent lines, the inequality

$$\mu(T)(C_R+C_d)\le\frac{1}{2}$$

is valid.

Observe first that under this convention $c\in B_R^T$ (i.e. $c|_{t=0}=c_0$) implies

$$|c|_\infty + |\nabla c|_\infty + |\nabla^2 c|_\infty + |\nabla^3 c|_\infty \le \mu(T)C_R + C_d \le \frac{1}{2} + C_d \le \tilde{C}_d. \tag{37}$$

Further, for $t_1,\, t_2 \in J,\, x \in \bar{\Omega}$,

$$|\Delta c(t_1, x) - \Delta c(t_2, x)| \le C_R |t_1 - t_2|^{(1+\alpha)/2} \le \mu(T) C_R |t_1 - t_2|^{\alpha} \le \frac{1}{2} |t_1 - t_2|^{\alpha}. \tag{38}$$

Since $\partial\tilde{x}/\partial x'_i$ solves (31), it follows that

$$|\frac{\partial \tilde{x}}{\partial x'_i}(\rho; y')| \le |e_i| + |\nabla^2 c|_\infty \int_\rho^{t'} |\frac{\partial \tilde{x}}{\partial x'_i}(\sigma; y')|\, d\sigma,\; \rho \in [t_0(y'), t'],$$

and thus, by Gronwall's lemma and (37),

$$|\frac{\partial \tilde{x}}{\partial x'_i}(\rho; y')| \le C_d, \quad \rho \in [t_0(y'), t'],\; i = 1, \dots, n. \tag{39}$$

Similarly, using (34) for $\partial\tilde{x}/\partial t'$, we find a bound

$$|\frac{\partial \tilde{x}}{\partial t'}(\rho; y')| \le C_d, \quad \rho \in [t_0(y'), t']. \tag{40}$$

From (17), (32), (33), (36), (39), and (40) we then infer that

$$|\frac{\partial t_0}{\partial t'}(y')| + |\frac{\partial t_0}{\partial x'_i}(y')| \le C_d, \quad y' \in \mathcal{H}_2 \cup \mathcal{H}_{crit}, \tag{41}$$

$$|\frac{\partial x_0}{\partial x'_i}(y')| \le C_d, \quad y' \in J \times \bar{\Omega}. \tag{42}$$

Differentiating further (31) and (34) with $w = \partial\tilde{x}/\partial x'_i$ and $w = \partial\tilde{x}/\partial t'$, respectively, with respect to t' and x', and employing (39), (40), and (37) ($|\nabla^3 c|_\infty \le C_d$!), we obtain, similarly as above, that

$$|\frac{\partial^2 \tilde{x}}{\partial x'_i \partial x'_j}(\rho; y')| + |\frac{\partial^2 \tilde{x}}{\partial x'_i \partial t'}(\rho; y')| \le C_d, \quad \rho \in [t_0(y'), t'],\; i,\, j = 1, \dots, n. \tag{43}$$

Recall further (15), which together with Lemma 3.1 (iv), gives $|u|_{C(J\times\bar{\Omega})} \le C_d$.

The following estimates involve the functions $\tilde{x}$ and $\tilde{z}$. Let $t' \in J,\, x',\, \bar{x}' \in \bar{\Omega}$, and assume that $t_0(t', x') \le t_0(t', \bar{x}')$. Setting

$$|\tilde{x}(\rho_*; t', x') - \tilde{x}(\rho_*; t', \bar{x}')| := \max_{\rho \in [t_0(t', \bar{x}'), t']} |\tilde{x}(\rho; t', x') - \tilde{x}(\rho; t', \bar{x}')|$$

and employing (12) we have

$$\begin{aligned} |\tilde{x}(\rho_*; t', x') - \tilde{x}(\rho_*; t', \bar{x}')| \le\; & \int_{\rho_*}^{t'} |\nabla c(\rho, \tilde{x}(\rho; t', x')) - \nabla c(\rho, \tilde{x}(\rho; t', \bar{x}'))|\, d\rho + |x' - \bar{x}'| \\ \le\; & \mu(T) C_R |\tilde{x}(\rho_*; t', x') - \tilde{x}(\rho_*; t', \bar{x}')| + |x' - \bar{x}'|, \end{aligned}$$

which yields

$$|\tilde{x}(\rho; t', x') - \tilde{x}(\rho; t', \bar{x}')| \le 2\, |x' - \bar{x}'|, \quad \rho \in [t_0(t', \bar{x}'), t']. \tag{44}$$

Similarly, using (11) and (44) we now show that

$$|\tilde{z}(\rho; t', x') - \tilde{z}(\rho; t', \bar{x}')| \le C_d |x' - \bar{x}'|, \quad \rho \in [t_0(t', \bar{x}'), t'], \tag{45}$$

whenever (t',x') and $(t',\bar{x}')$ are jointly from $\mathcal{H}_i\cup\mathcal{H}_{crit},\ i=1,2$. In fact, with

$$|\tilde{z}(\rho_{**};t',x')-\tilde{z}(\rho_{**};t',\bar{x}')|:=\max_{\rho\in[t_0(t',\bar{x}'),t']}|\tilde{z}(\rho;t',x')-\tilde{z}(\rho;t',\bar{x}')|$$

we may estimate

$$\begin{aligned}
|\tilde{z}(\rho_{**};t',x')-&\tilde{z}(\rho_{**};t',\bar{x}')|\\
\leq\ & C_d\,|t_0(t',x')-t_0(t',\bar{x}')|+|\psi(y_0(t',x',c))-\psi(y_0(t',\bar{x}',c))|\\
&+\int_{t_0(t',\bar{x}')}^{\rho_{**}}|\Delta c(\rho,\tilde{x}(\rho;t',x'))\tilde{z}(\rho;t',x')-\Delta c(\rho,\tilde{x}(\rho;t',\bar{x}'))\tilde{z}(\rho;t',\bar{x}')|\,d\rho\\
&+\int_{t_0(t',\bar{x}')}^{\rho_{**}}|f(\tilde{z}(\rho;t',x'),c(\rho,\tilde{x}(\rho;t',x')))-f(\tilde{z}(\rho;t',\bar{x}'),c(\rho,\tilde{x}(\rho;t',\bar{x}')))|\,d\rho\\
\leq\ & \Big(CC_d\,(|\frac{\partial t_0}{\partial x'}|_\infty+|\frac{\partial x_0}{\partial x'}|_\infty)+4TC_dC_R\Big)|x'-\bar{x}'|\\
&+T(C_R+C_d)|\tilde{z}(\rho_{**};t',x')-\tilde{z}(\rho_{**};t',\bar{x}')|,
\end{aligned}$$

which implies (45).

5. ∇u **belongs to** $C^{0,\alpha}(J\times\bar{\Omega};\mathbb{R}^n)$: From step 3 we already know that $\nabla u\in C(J\times\bar{\Omega})$. Employing (30) and the expressions for $\nabla[\psi(y_0)]$ derived in step 3 it is readily seen that $|\nabla u|_{C(J\times\bar{\Omega})}\leq C_d$.

Let now $y'=(t',x'),\bar{y}'=(t',\bar{x}')\in\mathcal{H}_2\cup\mathcal{H}_{crit}$. W.l.o.g. we may assume that $t_0(y')\leq t_0(\bar{y}')$. Then it follows from (44), (45), and assumption (iii) of Thm. 2.1 that

$$\begin{aligned}
|f_u(\tilde{z}(\rho;y'),c(\rho,\tilde{x}(\rho;y')))&-f_u(\tilde{z}(\rho;\bar{y}'),c(\rho,\tilde{x}(\rho;\bar{y}')))|\\
&\leq C_d(|\tilde{z}(\rho;y')-\tilde{z}(\rho;\bar{y}')|^\alpha+|c(\rho,\tilde{x}(\rho;y'))-c(\rho,\tilde{x}(\rho;\bar{y}'))|^\alpha)\\
&\leq C_d|x'-\bar{x}'|^\alpha,\qquad \rho\in[t_0(\bar{y}'),t'],
\end{aligned}\tag{46}$$

and the corresponding inequality being true for f_c. Therefore

$$\begin{aligned}
|\exp\,(&\int_{t_0(y')}^{t'}\kappa_i(\tau;y')\,d\tau)-\exp\,(\int_{t_0(\bar{y}')}^{t'}\kappa_i(\tau;\bar{y}')\,d\tau)|\\
&\leq e^{\mu(T)C_d}(\int_{t_0(y')}^{t_0(\bar{y}')}|\kappa_i(\tau;y')|\,d\tau+\int_{t_0(\bar{y}')}^{t'}|\kappa_i(\tau;y')-\kappa_i(\tau;\bar{y}')|\,d\tau)\\
&\leq\sqrt{e}(|t_0(y')-t_0(\bar{y}')|^{1-\alpha}C_d|x'-\bar{x}'|^\alpha+TC_d|x'-\bar{x}'|^\alpha)\ \leq\ C|x'-\bar{x}'|^\alpha.
\end{aligned}\tag{47}$$

We turn now to ξ_i. From (33) it is immediate that $\partial t_0/\partial x_i'\in C^1(\mathcal{H}_2\cup\mathcal{H}_{crit})$ and $\partial x_0/\partial x_i'\in C^1(\mathcal{H}_2\cup\mathcal{H}_{crit};\mathbb{R}^n)$ for all $i=1,\ldots,n$. From (17), (37), and (43) we further infer that

$$|\nabla^2 t_0(y')|+|\nabla^2 x_0(y')|\leq C_d,\quad y'\in\mathcal{H}_2.\tag{48}$$

Choosing an extension $v\in C^{1+\alpha}(J\times\bar{\Omega})$ of h_0 we have

$$\frac{\partial}{\partial x_i'}(\psi(y_0(y')))=\partial_t v(y_0(y'))\frac{\partial t_0}{\partial x_i'}(y')+\nabla v(y_0(y'))\cdot\frac{\partial x_0}{\partial x_i'}(y').$$

This, together with (38), (41), (42), (48), shows that for all $i=1,\ldots,n$,

$$|\xi_i(y')-\xi_i(\bar{y}')|\leq C_d|x'-\bar{x}'|^\alpha.\tag{49}$$

As to η_i, note first that (37), (31), and (44) yield

$$|\frac{\partial \tilde{x}}{\partial x_i'}(\rho; y') - \frac{\partial \tilde{x}}{\partial x_i'}(\rho; \bar{y}')| \leq C_d |x' - \bar{x}'|, \quad \rho \in [t_0(\bar{y}'), t']. \tag{50}$$

Since $c \in B_R^T$ and in view of (44), we further have

$$|\nabla \Delta c(\rho, \tilde{x}(\rho; y')) - \nabla \Delta c(\rho, \tilde{x}(\rho; \bar{y}'))| \leq C_R |x' - \bar{x}'|^\alpha, \quad \rho \in [t_0(\bar{y}'), t']. \tag{51}$$

Combining (51), (50), (44), (45), and (46) for f_c we obtain

$$|\eta_i(\rho; y') - \eta_i(\rho; \bar{y}')| \leq C_R C_d |x' - \bar{x}'|^\alpha, \quad \rho \in [t_0(\bar{y}'), t'], \tag{52}$$

and further

$$\begin{aligned}
&| \int_{t_0(y')}^{t'} \exp\,(\int_\sigma^{t'} \kappa_i(\tau; y')\, d\tau)\, \eta_i(\sigma; y')\, d\sigma - \int_{t_0(\bar{y}')}^{t'} \exp\,(\int_\sigma^{t'} \kappa_i(\tau; \bar{y}')\, d\tau)\, \eta_i(\sigma; \bar{y}')\, d\sigma| \\
&\leq \int_{t_0(y')}^{t_0(\bar{y}')} \exp\,(\int_\sigma^{t'} \kappa_i(\tau; y')\, d\tau)\, |\eta_i(\sigma; y')|\, d\sigma \\
&\quad + \int_{t_0(\bar{y}')}^{t'} |\exp\,(\int_\sigma^{t'} \kappa_i(\tau; y')\, d\tau)\, \eta_i(\sigma; y') - \exp\,(\int_\sigma^{t'} \kappa_i(\tau; \bar{y}')\, d\tau)\, \eta_i(\sigma; \bar{y}')|\, d\sigma \\
&\leq \sqrt{e} C_d |t_0(y') - t_0(\bar{y}')| + \mu(T)(C_d + C_R C_d)|x' - \bar{x}'|^\alpha \ \leq \ C|x' - \bar{x}'|^\alpha,
\end{aligned}$$

which, together with (47) and (49), implies $|\nabla u|_{C^{0,\alpha}(\mathcal{H}_2 \cup \mathcal{H}_{crit}; \mathbb{R}^n)} \leq C_d$. In the same fashion (it is even simpler) one can show that $|\nabla u|_{C^{0,\alpha}(\mathcal{H}_1 \cup \mathcal{H}_{crit}; \mathbb{R}^n)} \leq C_d$. Hence, by step 1, $|\nabla u|_{C^{0,\alpha}(J \times \bar{\Omega}; \mathbb{R}^n)} \leq C_d$.

6. ∇u **belongs to** $C^{\alpha,0}(J \times \bar{\Omega}; \mathbb{R}^n)$**:** Again we show only $|\nabla u|_{C^{\alpha,0}(\mathcal{H}_2 \cup \mathcal{H}_{crit}; \mathbb{R}^n)} \leq C_d$; the corresponding estimate $|\nabla u|_{C^{\alpha,0}(\mathcal{H}_1 \cup \mathcal{H}_{crit}; \mathbb{R}^n)} \leq C_d$ can be established much more easily. Combining both estimates and step 1 then yield $|\nabla u|_{C^{\alpha,0}(J \times \bar{\Omega}; \mathbb{R}^n)} \leq C_d$.

Let now $y_j' = (t_j', x') \in \mathcal{H}_2 \cup \mathcal{H}_{crit}$, $j = 1, 2$. W.l.o.g. we may assume that $t_0(y_1') \leq t_0(y_2')$. We distinguish three cases w.r.t. the numbers $t_0(y_1')$, t_1', $t_0(y_2')$, and t_2' as displayed in the following identity, which will be employed to estimate the integral terms in (30).

$$\int_{t_0(y_1')}^{t_1'} F_1 - \int_{t_0(y_2')}^{t_2'} F_2 = \begin{cases} \int_{t_0(y_1')}^{t_0(y_2')} \tilde{F}_1 - \int_{t_1'}^{t_2'} \tilde{F}_2 & : t_0(y_1') \leq t_1' \leq t_0(y_2') \leq t_2' \\ \int_{t_0(y_1')}^{t_0(y_2')} F_1 + \int_{t_0(y_2')}^{t_1'} (F_1 - F_2) - \int_{t_1'}^{t_2'} F_2 & : t_0(y_1') \leq t_0(y_2') \leq t_1' \leq t_2' \\ \int_{t_0(y_1')}^{t_0(y_2')} F_1 + \int_{t_0(y_2')}^{t_2'} (F_1 - F_2) + \int_{t_2'}^{t_1'} F_1 & : t_0(y_1') \leq t_0(y_2') \leq t_2' \leq t_1', \end{cases}$$

here $\tilde{F}_j(\rho) = F_j(\rho)$, $\rho \in [t_0(y_j'), t_j']$, and $\tilde{F}_j(\rho) = 0$, $\rho \notin [t_0(y_j'), t_j']$. The first case is the trivial one, as we do not have a term involving the difference $F_1 - F_2$. In the second and third case, one can use the estimation techniques from the preceding steps to get, one after another, the subsequent inequalities satisfied for any $\rho \in [t_0(y_2'), \min\{t_1', t_2'\}]$:

$$\begin{aligned}
|\tilde{x}(\rho; y_1') - \tilde{x}(\rho; y_2')| + |\tilde{z}(\rho; y_1') - \tilde{z}(\rho; y_2')| \ &\leq C_d |t_1' - t_2'|, \\
|f_u(\tilde{z}(\rho; y'), c(\rho, \tilde{x}(\rho; y'))) - f_u(\tilde{z}(\rho; \bar{y}'), c(\rho, \tilde{x}(\rho; \bar{y}')))| \ &\leq C_d |t_1' - t_2'|^\alpha, \\
|f_c(\tilde{z}(\rho; y'), c(\rho, \tilde{x}(\rho; y'))) - f_c(\tilde{z}(\rho; \bar{y}'), c(\rho, \tilde{x}(\rho; \bar{y}')))| \ &\leq C_d |t_1' - t_2'|^\alpha, \\
|\nabla \Delta c(\rho, \tilde{x}(\rho; y_1')) - \nabla \Delta c(\rho, \tilde{x}(\rho; y_2'))| \ &\leq C_R C_d |t_1' - t_2'|^\alpha,
\end{aligned}$$

$$\begin{aligned}
|\frac{\partial \tilde{x}}{\partial x_i'}(\rho;y_1') - \frac{\partial \tilde{x}}{\partial x_i'}(\rho;y_2')| &\leq C_d|t_1'-t_2'|,\\
|\kappa_i(\rho;y_1') - \kappa_i(\rho;y_2')| &\leq C_d|t_1'-t_2'|^\alpha,\\
|\eta_i(\rho;y_1') - \eta_i(\rho;y_2')| &\leq C_R C_d|t_1'-t_2'|^\alpha.
\end{aligned}$$

In the second case one can estimate the second summand in (30) as follows.

$$\begin{aligned}
&|\int_{t_0(y_1')}^{t_1'} \exp\big(\int_\sigma^{t_1'} \kappa_i(\tau;y_1')\,d\tau\big)\,\eta_i(\sigma;y_1')\,d\sigma - \int_{t_0(y_2')}^{t_2'} \exp\big(\int_\sigma^{t_2'} \kappa_i(\tau;y_2')\,d\tau\big)\,\eta_i(\sigma;y_2')\,d\sigma|\\
&\leq \int_{t_0(y_1')}^{t_0(y_2')} \exp\big(\int_\sigma^{t_1'} \kappa_i(\tau;y_1')\,d\tau\big)\,|\eta_i(\sigma;y_1')|\,d\sigma + \int_{t_1'}^{t_2'} \exp\big(\int_\sigma^{t_2'} \kappa_i(\tau;y_2')\,d\tau\big)\,|\eta_i(\sigma;y_2')|\,d\sigma\\
&\quad + \int_{t_0(y_2')}^{t_1'} |\exp\big(\int_\sigma^{t_1'} \kappa_i(\tau;y_1')\,d\tau\big)\,\eta_i(\sigma;y_1') - \exp\big(\int_\sigma^{t_2'} \kappa_i(\tau;y_2')\,d\tau\big)\,\eta_i(\sigma;y_2')|\,d\sigma\\
&\leq \sqrt{e}C_d(|t_0(y_1')-t_0(y_2')|+|t_1'-t_2'|)+\int_{t_0(y_2')}^{t_1'} \exp\big(\int_\sigma^{t_1'} \kappa_i(\tau;y_1')\,d\tau\big)\,|\eta_i(\sigma;y_1')-\eta_i(\sigma;y_2')|\,d\sigma\\
&\quad + \int_{t_0(y_2')}^{t_1'} |\exp\big(\int_\sigma^{t_1'} \kappa_i(\tau;y_1')\,d\tau\big) - \exp\big(\int_\sigma^{t_2'} \kappa_i(\tau;y_2')\,d\tau\big)|\,|\eta_i(\sigma;y_2')|\,d\sigma\\
&\leq C_d|t_1'-t_2'| + T\sqrt{e}C_R C_d|t_1'-t_2'|^\alpha + T\sqrt{e}(TC_d|t_1'-t_2'|^\alpha + C_d|t_1'-t_2'|)C_d\\
&\leq C|t_1'-t_2'|^\alpha\,.
\end{aligned}$$

The same Hölder estimate holds in the third case, by an analogous chain of estimates. It is then also clear how to treat the first integral term in (30) to get the desired Hölder estimate. Moreover, similarly as in step 5, one can show that

$$|\xi_i(y_1') - \xi_i(y_2{}')| \leq C_d|t_1'-t_2'|^\alpha,$$

and hence $|\nabla u|_{C^{\alpha,0}(\mathcal{H}_2\cup\mathcal{H}_{crit};\mathbb{R}^n)} \leq C_d$.

7. Regularity of $\partial_t u$: The remaining estimate $|\partial_t u|_{C^\alpha(J\times\bar{\Omega})} \leq C_d$ follows from

$$\partial_t u = -\nabla c\cdot\nabla u - (\Delta c)u + f(u,c)$$

and $c\in B_R^T$ as well as from the estimates obtained above for u and ∇u; recall here the crucial inequality (38). □

The subsequent lemma provides the basic estimates concerning the c-dependence of u.

Lemma 3.3. *Given $R\in[R_0,\infty)$, there exists a number $T_3(R)\in(0,T_2(R)]$ such that for any $T\in(0,T_3(R)]$, $y'\in J\times\bar{\Omega}$, and $c_1,\ c_2\in B_R^T$,*

$$|y_0(y',c_1)-y_0(y',c_2)| + |s_0(y',c_1)-s_0(y',c_2)| \leq \mu(T)|\nabla c_1 - \nabla c_2|_\infty \tag{53}$$

and

$$|u_1-u_2|_{L_p(J\times\Omega)} \leq \mu(T)(|c_1-c_2|_{C(J;C^1(\bar{\Omega}))} + |\Delta c_1 - \Delta c_2|_{L_p(J\times\Omega)}). \tag{54}$$

Proof. We will continue to employ the convention introduced in step 4 above concerning the usage of the constants C, C_d, C_R, and $\mu(T)$.

We begin with the estimate for $|y_0(y', c_1) - y_0(y', c_2)|$. Let $c_1, c_2 \in B_R^T$ and fix $y' \in J \times \bar{\Omega}$. We distinguish three cases.

Case 1: Suppose that $t_0(y', c_i) = 0$ for $i = 1, 2$. By Lemma 3.1 (ii), $s_0(y', c_i) = t'$ as well as $t(s; y', c_i) = s$ for $i = 1$, 2. With $x_i(s) := x(s; y', c_i)$ and

$$|x_1(s_*) - x_2(s_*)| = \max_{s \in [0,t']} |x_1(s) - x_2(s)|$$

we therefore have

$$\begin{aligned} |x_1(s_*) - x_2(s_*)| &\le \int_{s_*}^{t'} |\nabla c_1(\tau, x_1(\tau)) - \nabla c_2(\tau, x_2(\tau))| \, d\tau \\ &\le \int_{s_*}^{t'} (C_d |x_1(\tau) - x_2(\tau)| + |\nabla c_1(\tau, x_2(\tau)) - \nabla c_2(\tau, x_2(\tau))|) \, d\tau \\ &\le TC_d |x_1(s_*) - x_2(s_*)| + T |\nabla c_1 - \nabla c_2|_\infty. \end{aligned}$$

Thus

$$|x_0(y', c_1) - x_0(y', c_2)| \le |x_1(s_*) - x_2(s_*)| \le \mu(T) |\nabla c_1 - \nabla c_2|_\infty. \tag{55}$$

Case 2: Suppose that $y_0(y', c_i) \in J \times \Gamma_1$, $i = 1, 2$. We will use the transformed characteristics $\bar{y}_i(\zeta) := \bar{y}(\zeta; y', c_i)$, $i = 1, 2$, which were introduced in step 1 of the proof of Lemma 3.2 and which are solutions of (24). Analogously to the first case we consider

$$|\bar{y}_1(\zeta_*) - \bar{y}_2(\zeta_*)| := \max_{\zeta \in [0, \zeta_0(x')]} |\bar{y}_1(\zeta) - \bar{y}_2(\zeta)|.$$

Note that $c_i \in B_R^T$ and (17) yield

$$\begin{aligned} |\gamma_{c_1}(y_1) - \gamma_{c_1}(y_2)| &\le \delta_0^{-2} C_R |y_1 - y_2|, \quad y_1, \, y_2 \in J \times \Lambda_\varepsilon, \\ |\gamma_{c_1}(y) - \gamma_{c_2}(y)| &\le \delta_0^{-2} C_R |\nabla c_1 - \nabla c_2|_\infty, \quad y \in J \times \Lambda_\varepsilon; \end{aligned}$$

and thus

$$\begin{aligned} |\bar{y}_1(\zeta_*) - \bar{y}_2(\zeta_*)| &\le \int_{\zeta_*}^{\zeta_0(x')} |\gamma_{c_1}(\bar{y}_1(\zeta)) - \gamma_{c_2}(\bar{y}_2(\zeta))| \, d\zeta \\ &\le \int_{\zeta_*}^{\zeta_0(x')} (|\gamma_{c_1}(\bar{y}_1(\zeta)) - \gamma_{c_1}(\bar{y}_2(\zeta))| + |\gamma_{c_1}(\bar{y}_2(\zeta)) - \gamma_{c_2}(\bar{y}_2(\zeta))|) \, d\zeta \\ &\le TC_R (|\bar{y}_1(\zeta_*) - \bar{y}_2(\zeta_*)| + |\nabla c_1 - \nabla c_2|_\infty), \end{aligned}$$

where we used (25). Hence

$$|y_0(y', c_1) - y_0(y', c_2)| \le |\bar{y}_1(\zeta_*) - \bar{y}_2(\zeta_*)| \le \mu(T) |\nabla c_1 - \nabla c_2|_\infty. \tag{56}$$

Case 3: Suppose that $t_0(y', c_1) = 0$ and $y_0(y', c_2) \in J \times \Gamma_1$. For continuity reasons and by convexity of B_R^T, there exists $\lambda_* \in [0, 1]$ such that $c_* := \lambda_* c_1 + (1 - \lambda_*) c_2 \in B_R^T$ and $y_0(y', c_*) \in \{0\} \times \Gamma_1$. The desired estimate for $|y_0(y', c_1) - y_0(y', c_2)|$ follows then from the trivial inequality

$$|y_0(y', c_1) - y_0(y', c_2)| \le |y_0(y', c_1) - y_0(y', c_*)| + |y_0(y', c_*) - y_0(y', c_2)|,$$

estimates (55), (56), and the definition of c_*.

All in all we have proven an estimate of the form

$$|y_0(y',c_1)-y_0(y',c_2)|\le \mu(T)|\nabla c_1-\nabla c_2|_\infty,\quad y'\in J\times\bar\Omega,\ c_1,\,c_2\in B_R^T. \tag{57}$$

To see the corresponding inequality for $|s_0(y',c_1)-s_0(y',c_2)|$, we make use of the identity $s_0(y',c)=t'-t_0(y',c)$ (see Lemma 3.1 (ii)), which gives

$$|s_0(y',c_1)-s_0(y',c_2)|=|t_0(y',c_1)-t_0(y',c_2)|\le|y_0(y',c_1)-y_0(y',c_2)|;$$

(57) yields then the desired estimate. This completes the proof of (53).

We come now to (54). Let $c_1,c_2\in B_R^T$ and $y'\in J\times\bar\Omega$. W.l.o.g. we may assume that $t_0(y',c_1)\le t_0(y',c_2)$. Let

$$\begin{aligned}|\tilde z(\rho_*;y',c_1)-\tilde z(\rho_*;y',c_2)|&=\max_{\rho\in[t_0(y',c_2),t']}|\tilde z(\rho;y',c_1)-\tilde z(\rho;y',c_2)|,\\ |\tilde x(\rho_{**};y',c_1)-\tilde x(\rho_{**};y',c_2)|&=\max_{\rho\in[t_0(y',c_2),t']}|\tilde x(\rho;y',c_1)-\tilde x(\rho;y',c_2)|.\end{aligned}$$

Observe first that (12) entails

$$|\tilde x(\rho_{**};y',c_1)-\tilde x(\rho_{**};y',c_2)|\le\mu(T)|\nabla c_1-\nabla c_2|_\infty. \tag{58}$$

Using (11) we estimate now

$$\begin{aligned}&|\tilde z(\rho_*;y',c_1)-\tilde z(\rho_*;y',c_2)|\le\\ &\le\int_{t_0(y',c_1)}^{t_0(y',c_2)}(|\Delta c_1(\rho,\tilde x(\rho;y',c_1))\tilde z(\rho;y',c_1)|+|f(\tilde z(\rho;y',c_1),c_1(\rho,\tilde x(\rho;y',c_1)))|)\,d\rho\\ &\quad+\int_{t_0(y',c_2)}^{\rho_*}|\Delta c_1(\rho,\tilde x(\rho;y',c_1))\tilde z(\rho;y',c_1)-\Delta c_2(\rho,\tilde x(\rho;y',c_2))\tilde z(\rho;y',c_2)|\,d\rho\\ &\quad+\int_{t_0(y',c_2)}^{\rho_*}|f(\tilde z(\rho;y',c_1),c_1(\rho,\tilde x(\rho;y',c_1)))-f(\tilde z(\rho;y',c_2),c_2(\rho,\tilde x(\rho;y',c_2)))|\,d\rho\\ &\quad+|\psi(y_0(y',c_1))-\psi(y_0(y',c_2))|\ =:\ I_1+I_2+I_3+I_4.\end{aligned}$$

Thanks to (53), (15), and $c_1\in B_R^T$, we obtain for the first term

$$\begin{aligned}I_1\ &\le|t_0(y',c_1)-t_0(y',c_2)|\,(|\Delta c_1|_\infty|\tilde z(\cdot;y',c_1)|_\infty+|f|_\infty)\\ &\le\mu(T)C_d|\nabla c_1-\nabla c_2|_\infty\ \le\ \tilde\mu(T)|\nabla c_1-\nabla c_2|_\infty.\end{aligned}$$

As to I_2, we employ (58), (15), and $c_2\in B_R^T$ to estimate

$$\begin{aligned}I_2&\le\int_{t_0(y',c_2)}^{\rho_*}|\Delta c_1(\rho,\tilde x(\rho;y',c_1))-\Delta c_2(\rho,\tilde x(\rho;y',c_1))|\,|\tilde z(\cdot;y',c_1)|_\infty\,d\rho\\ &\quad+\int_{t_0(y',c_2)}^{\rho_*}|\Delta c_2(\rho,\tilde x(\rho;y',c_1))-\Delta c_2(\rho,\tilde x(\rho;y',c_2))|\,|\tilde z(\cdot;y',c_1)|_\infty\,d\rho\\ &\quad+\int_{t_0(y',c_2)}^{\rho_*}|\Delta c_2(\rho,\tilde x(\rho;y',c_2))|\,|\tilde z(\rho_*;y',c_1)-\tilde z(\rho_*;y',c_2)|\,d\rho\\ &\le C_d\int_{t_0(y',c_2)}^{t'}|\Delta c_1(\rho,\tilde x(\rho;y',c_1))-\Delta c_2(\rho,\tilde x(\rho;y',c_1))|\,d\rho\\ &\quad+\mu(T)C_d|\nabla c_1-\nabla c_2|_\infty+TC_d|\tilde z(\rho_*;y',c_1)-\tilde z(\rho_*;y',c_2)|.\end{aligned}$$

Concerning I_3, we use the Lipschitz continuity of f, (58), and $c_1 \in B_R^T$, thereby getting

$$\begin{aligned} I_3 &\le C_d \int_{t_0(y',c_2)}^{\rho_*} (|\tilde{z}(\rho;y',c_1) - \tilde{z}(\rho;y',c_2)| + |c_1(\rho,\tilde{x}(\rho;y',c_1)) - c_2(\rho,\tilde{x}(\rho;y',c_2))|)\, d\rho \\ &\le C_d T(|\tilde{z}(\rho_*;y',c_1) - \tilde{z}(\rho_*;y',c_2)| + |c_1 - c_2|_\infty + C_d \mu(T)|\nabla c_1 - \nabla c_2|_\infty). \end{aligned}$$

Finally, the Lipschitz continuity of ψ and (53) yield

$$I_4 \le C_d |y_0(y',c_1) - y_0(y',c_2)| \le C_d \mu(T) |\nabla c_1 - \nabla c_2|_\infty.$$

In sum,

$$\begin{aligned} |\tilde{z}(\rho_*;y',c_1) - \tilde{z}(\rho_*;y',c_2)| \le\ & \mu(T)(|c_1 - c_2|_\infty + |\nabla c_1 - \nabla c_2|_\infty) \\ &+ C_d \int_{t_0(y',c_2)}^{t'} |\Delta c_1(\rho,\tilde{x}(\rho;y',c_1)) - \Delta c_2(\rho,\tilde{x}(\rho;y',c_1))|\, d\rho. \end{aligned} \tag{59}$$

Setting

$$\tilde{\tilde{x}}(\rho;y',c_1) = \begin{cases} x' & : 0 \le \rho < t_0(y',c_1) \\ \tilde{x}(\rho;y',c_1) & : t_0(y',c_1) \le \rho \le t', \end{cases}$$

it follows from (59) and $|u_1(y') - u_2(y')| \le |\tilde{z}(\rho_*;y',c_1) - \tilde{z}(\rho_*;y',c_2)|$ that

$$\begin{aligned} |u_1(y') - u_2(y')| \le\ & \mu(T)|c_1 - c_2|_{C(J;C^1(\bar{\Omega}))} \\ &+ C_d \int_0^{t'} |\Delta c_1(\rho,\tilde{\tilde{x}}(\rho;y',c_1)) - \Delta c_2(\rho,\tilde{\tilde{x}}(\rho;y',c_1))|\, d\rho. \end{aligned} \tag{60}$$

We use now (60) to estimate $u_1 - u_2$ in the $L_p(J \times \Omega)$-norm. To begin with, observe that for any fixed $t' \in J$, the mapping $(\rho, x') \mapsto \tilde{\tilde{x}}(\rho;t',x',c_1)$ of $[0,t'] \times \bar{\Omega}$ into $\bar{\Omega}$ is product measurable (w.r.t. $\lambda_\rho \times \lambda_{x'}$, λ denoting the Lebesgue measure), and thus the integrand is as well, since $\Delta c_i \in C(J \times \bar{\Omega})$. In fact, we may write

$$\tilde{\tilde{x}}(\rho;t',x',c_1) = \chi_{\{\rho < t_0(t',x',c_1)\}} x' + \chi_{\{\rho \ge t_0(t',x',c_1)\}} \tilde{x}(\rho;t',x',c_1), \ \ \rho \in [0,t'],\ x' \in \bar{\Omega},$$

where both characteristic functions are product measurable, owing to the continuity of the function $(\rho, x') \mapsto \rho - t_0(t',x',c_1)$. Proceeding, the continuous version of Minkowski's inequality yields

$$\begin{aligned} I(t') &:= \Big(\int_\Omega \Big(\int_0^{t'} |\Delta c_1(\rho,\tilde{\tilde{x}}(\rho;y',c_1)) - \Delta c_2(\rho,\tilde{\tilde{x}}(\rho;y',c_1))|\, d\rho\Big)^p\, dx'\Big)^{1/p} \\ &\le \int_0^{t'} \Big(\int_\Omega |\Delta c_1(\rho,\tilde{\tilde{x}}(\rho;y',c_1)) - \Delta c_2(\rho,\tilde{\tilde{x}}(\rho;y',c_1))|^p\, dx'\Big)^{1/p} d\rho, \quad t' \in J. \end{aligned}$$

Next we use the decomposition $\Omega = \Omega_1(t',\rho) \cup \Omega_2(t',\rho)$ with $\Omega_1(t',\rho) = \{x' \in \Omega : \rho < t_0(t',x',c_1)\}$ and $\Omega_2(t',\rho) = \Omega \setminus \Omega_1(t',\rho)$ to conclude that for $t' \in J$,

$$\begin{aligned} I(t') \le I_I(t') + I_{II}(t') \ :=\ & \int_0^{t'} |\Delta c_1(\rho,\cdot) - \Delta c_2(\rho,\cdot)|_{L_p(\Omega)}\, d\rho \\ &+ \int_0^{t'} \Big(\int_{\Omega_2(t',\rho)} |\Delta c_1(\rho,\tilde{x}(\rho;y',c_1)) - \Delta c_2(\rho,\tilde{x}(\rho;y',c_1))|^p\, dx'\Big)^{1/p} d\rho. \end{aligned} \tag{61}$$

We then transform the variable of the inner integral of the second term according to $x' \mapsto \bar{x}' = \tilde{x}(\rho; t', x', c_1)$. To determine the Jacobian $D_{x'}\tilde{x}(\rho; t', x', c_1)$, we differentiate (12) with respect to x' to the result (cp. (31)) that for $x' \in \Omega_2(t', \rho)$,

$$\frac{\partial}{\partial \rho}\,[D_{x'}\tilde{x}(\rho; t', x', c_1)] = \nabla^2 c_1(\rho, \tilde{x}(\rho; t', x', c_1))D_{x'}\tilde{x}(\rho; t', x', c_1)$$

and

$$D_{x'}\tilde{x}(t'; t', x', c_1) = I_n,$$

where I_n denotes the identity matrix in $\mathbb{R}^{n\times n}$. Using Liouville's formula for the Wronskian, we then see that

$$\det((D_{x'}\tilde{x}(\rho; t', x', c_1))^{-1}) = \exp(\int_\rho^{t'} \mathrm{trace}(\nabla^2 c_1(\tau, \tilde{x}(\tau; t', x', c_1)))\, d\tau).$$

Since $c_1 \in B_R^T$, there is $C_1 > 0$ independent of ρ, t', x', c_1 such that

$$|\det((D_{x'}\bar{x}'(x'))^{-1})| \le \exp(\int_\rho^{t'} |\nabla^2 c_1(\tau, \tilde{x}(\sigma; t', x', c_1))|\, d\tau) \le e^{TC_d} \le C_1.$$

So, letting $\Omega_2'(t', \rho) := \{\tilde{x}(\rho; t', x', c_1) : x' \in \Omega_2(t', \rho)\} \subset \bar{\Omega}$, the change of variable formula allows us to estimate

$$\begin{aligned} &I_{II}(t')\\ &\le C_1^{1/p}\int_0^{t'}(\int_{\Omega_2(t',\rho)} |\Delta c_1(\rho, \tilde{x}(\rho; y', c_1)) - \Delta c_2(\rho, \tilde{x}(\rho; y', c_1))|^p\, |\det(D_{x'}\bar{x}'(x))|\, dx')^{1/p}\, d\rho\\ &= C_1^{1/p}\int_0^{t'}(\int_{\Omega_2'(t',\rho)} |\Delta c_1(\rho, \bar{x}') - \Delta c_2(\rho, \bar{x}')|^p\, d\bar{x}')^{1/p}\, d\rho \;\le C_1^{1/p} I_I(t'), \quad t' \in J. \end{aligned} \tag{62}$$

Finally, (60), (61), (62), and Young's inequality imply (54). □

3.3 The parabolic equation for c

We study now the fully nonlinear problem (5) for the unknown c. For the linear problem

$$\begin{cases} \partial_t v - \Delta v = \tilde{g}, & t \in J,\ x \in \Omega\\ v(t, x) = \tilde{h}(t, x), & t \in J,\ x \in \Gamma\\ v(0, x) = v_0(x), & x \in \Omega, \end{cases} \tag{63}$$

the subsequent maximal regularity results are well-known, see e.g. [24, Chap. IV, Thm. 5.2 and Thm. 9.1].

Theorem 3.2. *Let* $T \in (0, T_0]$.

(i) (maximal Hölder regularity) Let $\alpha \in (0, 1)$, *and assume that* $\Gamma \in C^{3+\alpha}$. *Then (63) has a unique solution* $v \in C^{(3+\alpha)/2,3+\alpha}(J \times \bar{\Omega})$ *if and only if* $\tilde{g} \in C^{(1+\alpha)/2,1+\alpha}(J \times \bar{\Omega})$, $\tilde{h} \in C^{(3+\alpha)/2,3+\alpha}(J \times \Gamma)$, $v_0 \in C^{3+\alpha}(\bar{\Omega})$, *and the compatibility conditions* $v_0 = \tilde{h}|_{t=0}$ *as well as* $\partial_t \tilde{h}|_{t=0} - \Delta v_0 = \tilde{g}|_{t=0}$ *are satisfied on* Γ*; in this case,*

$$|v|_{C^{(3+\alpha)/2,3+\alpha}(J\times\bar{\Omega})} \le M_\alpha(|\tilde{g}|_{C^{(1+\alpha)/2,1+\alpha}(J\times\bar{\Omega})} + |\tilde{h}|_{C^{(3+\alpha)/2,3+\alpha}(J\times\Gamma)} + |v_0|_{C^{3+\alpha}(\bar{\Omega})}),$$

where the constant $M_\alpha > 0$ does not depend on T.

(ii) (maximal L_p regularity) Let $1 < p < \infty$, and assume that $\Gamma \in C^2$. Suppose further that $\tilde{h} = 0$ and $v_0 = 0$. Then (63) possesses a unique solution $v \in H_p^1(J; L_p(\Omega)) \cap L_p(J; H_p^2(\Omega))$ if and only if $\tilde{g} \in L_p(J \times \Omega)$; in this case,

$$|v|_{H_p^1(J;L_p(\Omega))\cap L_p(J;H_p^2(\Omega))} \leq M_p|\tilde{g}|_{L_p(J\times\Omega)},$$

where the constant $M_p > 0$ is independent of T.

We are now in position to prove Thm. 3.1.

Proof. Suppose $c \in B_R^T$ and $T \in (0, T_3(R)]$. Setting $u = \Phi(c)$ we know from Lemma 3.2 that $|u|_{C^{1+\alpha}(J\times\bar{\Omega})} \leq C_d$. Evidently,

$$|u(t,x) - u_0(x)| + |c(t,x) - c_0(x)| \leq (C_d + C_R)T \leq \mu(T), \quad t \in J,\, x \in \bar{\Omega},$$

and so $(u(t,x), c(t,x)) \in V$, $t \in J$, $x \in \bar{\Omega}$, provided T is sufficiently small, say $T \leq T_4(R)$; we will assume this in what follows.

Put $G = g(u,c)$. Clearly, $|G|_\infty \leq C_d$ and

$$\begin{aligned}|g(u(t,x), c(t,x)) - g(u(\bar{t},x),c(\bar{t},x))| &\leq C_d(|u(t,x) - u(\bar{t},x)| + |c(t,x) - c(\bar{t},x)|)\\ &\leq C_d(C_d + C_R)|t - \bar{t}| \leq C|t - \bar{t}|^{(1+\alpha)/2}.\end{aligned}$$

Thus $|G|_{C^{(1+\alpha)/2,0}(J\times\bar{\Omega})} \leq C_d$. Since $\nabla G = g_u(u,c)\nabla u + g_c(u,c)\nabla c$, we conclude from

$$|g_u|_\infty + |g_c|_\infty + |\nabla u|_{C^{\alpha/2,\alpha}(J\times\bar{\Omega})} + |\nabla c|_{C^{\alpha/2,\alpha}(J\times\bar{\Omega})} \leq C_d$$

and

$$\begin{aligned}|g_u(u(t,x), c(t,x)) - g_u(u(\bar{t},\bar{x}), c(\bar{t},\bar{x}))| &+ |g_c(u(t,x), c(t,x)) - g_c(u(\bar{t},\bar{x}), c(\bar{t},\bar{x}))|\\ &\leq C_d(|u(t,x) - u(\bar{t},\bar{x})|^\alpha + |c(t,x) - c(\bar{t},\bar{x})|^\alpha)\\ &\leq C_d((C_d + C_R)|t - \bar{t}|^\alpha + C_d|x - \bar{x}|^\alpha)\\ &\leq C|t - \bar{t}|^{\alpha/2} + C_d|x - \bar{x}|^\alpha\end{aligned}$$

that $|\nabla G|_{C^{\alpha/2,\alpha}(J\times\bar{\Omega})} \leq C_d$. Hence $|G|_{C^{(1+\alpha)/2,1+\alpha}(J\times\bar{\Omega})} \leq C_d$, and so by Thm. 3.2(i),

$$|\tilde{c}|_{Z_c^T} \leq M_\alpha(|g(u,c)|_{C^{(1+\alpha)/2,1+\alpha}(J\times\bar{\Omega})} + |h|_{C^{(3+\alpha)/2,3+\alpha}(J\times\Gamma)} + |c_0|_{C^{3+\alpha}(\bar{\Omega})}) \leq C_{data},$$

for $T \leq T_4(R)$; the constant $C_{data} > 0$ depends on the data but not on T and R. Therefore, if we choose $R = C_{data}$ then $\tilde{c} \in B_R^T$, i.e. (i) is satisfied.

Let now $c_1, c_2 \in B_R^T$ and $u_i = \Phi(c_i)$. Thanks to $p > 2 + n$ the embedding $Y^T \hookrightarrow C(J; C^1(\bar{\Omega}))$ holds true. Besides $(c_1 - c_2)|_{t=0} = 0$, so we have the estimate

$$|c_1 - c_2|_{C(J;C^1(\bar{\Omega}))} \leq M_0|c_1 - c_2|_{Y^T}, \tag{64}$$

where the constant $M_0 > 0$ does not depend on $T \in (0, T_4(R)]$. By Lemma 3.3, Thm. 3.2 (ii), and (64), we may estimate

$$\begin{aligned}|\tilde{c}_1 - \tilde{c}_2|_{Y^T} \leq\ & M_p|g(u_1,c_1) - g(u_2,c_2)|_{L_p(J\times\Omega)}\\ &\leq M_pC_d(|u_1 - u_2|_{L_p(J\times\Omega)} + |c_1 - c_2|_{L_p(J\times\Omega)})\\ &\leq M_pC_d(\mu(T)(|c_1 - c_2|_{C(J;C^1(\bar{\Omega}))} + |\Delta c_1 - \Delta c_2|_{L_p(J\times\Omega)}) + T^{1/p}|c_1 - c_2|_{C(J\times\bar{\Omega})})\\ &\leq M_pC_d\mu(T)|c_1 - c_2|_{Y^T},\end{aligned}$$

i.e. (ii) is fulfilled, provided we choose T so small that the number $M_pC_d\mu(T)$ in the last line is strictly less than 1. □

3.4 Positivity of the solution

Suppose that the additional assumptions (vii) and (viii) are fulfilled. Let us assume for the moment that $f(0,\eta) \geq \varepsilon > 0$ for all $(0,\eta) \in V$ with $\eta \geq 0$ and that $g(\xi,0) \geq \varepsilon$ for all $(\xi,0) \in V$ with $\xi \geq 0$. Define the nonempty open sets $V_\eta^+ := \{(\xi,\eta) \in V \,:\, \eta > 0\}$ and $V_\xi^+ := \{(\xi,\eta) \in V \,:\, \xi > 0\}$. Choose $C^{1+\alpha}$ extensions f^*, g^* of $f|_{\overline{V_\eta^+}}$ and $g|_{\overline{V_\xi^+}}$, respectively, to all of $\mathbb{R}^2$ such that $f^*(0,\eta) \geq 0$ for all $\eta \in \mathbb{R}$ and $g^*(\xi,0) \geq 0$ for all $\xi \in \mathbb{R}$. In order to show that the unique local solution (u,c) of (3) is non-negative, i.e. $u \geq 0$ and $c \geq 0$ on $[0,T] \times \bar{\Omega}$, we consider the modified problem (3)* which differs from (3) only in that the reaction terms $f(u,c)$ and $g(u,c)$ are replaced by $f^*(u,c)$ and $g^*(u,c)$. By the first part of Thm. 2.1, problem (3)* possesses a unique local solution denoted by (u^*,c^*).

From Lemma 3.1, we see that $u^* = \Phi(c^*) \geq 0$ if $z(s_0(y',c^*);y',c^*) \geq 0$ for all $y' \in J \times \bar{\Omega}$. Observe that $z(\cdot;y',c^*)$ solves an ODE of the form

$$\dot{z}(s) = F(s,z(s)),\; s \in (0,s_0(y',c^*)), \quad z(0) = z_0,$$

where $z_0 \geq 0$, thanks to $u_0, h_0 \geq 0$, and $F(s,0) \geq 0,\; s \in [0,s_0(y',c^*)]$ since, by construction, $f^*(0,\eta) \geq 0$ for *all* $\eta \in \mathbb{R}$. Thus the positivity criterion for nonautonomous ODEs yields $z(s_0) \geq 0$, hence $u^* \geq 0$.

Consider next

$$\begin{cases} \partial_t \hat{c} - \Delta \hat{c} = g^*(u^*,\hat{c}), & t \in J,\, x \in \Omega \\ \hat{c} = 0, & t \in J,\, x \in \Gamma. \end{cases} \tag{65}$$

By construction of g^*, we have $g^*(u^*,0) \geq 0$ on $J \times \bar{\Omega}$. Thus $c_1 \equiv 0$ is a subsolution of (65), i.e.

$$\begin{cases} \partial_t c_1 - \Delta c_1 \leq g^*(u^*,c_1), & t \in J,\, x \in \Omega \\ c_1 \leq 0, & t \in J,\, x \in \Gamma. \end{cases} \tag{66}$$

On the other hand, due to $h \geq 0$, c^* is a supersolution of (65), i.e. the reverse inequalities hold in (66) for c^*. Furthermore $0 = c_1|_{t=0} \leq c^*|_{t=0} = c_0$. It follows then from the comparison principle for semilinear parabolic PDEs with homogeneous Dirichlet boundary conditions, see e.g. [14, Thm. 24.6], that $c_1 \leq c_*$, that is $c_* \geq 0$.

Since $\{(u_0(x),c_0(x)) : x \in \bar{\Omega}\} \subset V$, we know that $(u^*(t,x),c^*(t,x)) \in V$ for all $(t,x) \in J \times \bar{\Omega}$, provided T is sufficiently small. We deduce then from $u^*, c^* \geq 0$ that $(u^*(t,x),c^*(t,x)) \in \overline{V_\eta^+} \cap \overline{V_\xi^+}$ and hence $f^*(u^*,c^*) = f(u^*,c^*)$ as well as $g^*(u^*,c^*) = g(u^*,c^*)$. This shows that (u^*,c^*) also solves problem (3). Hence $u = u^* \geq 0$ and $c = c^* \geq 0$, by uniqueness.

In the general case, we approximate $f(u,c)$ and $g(u,c)$ by $f_\varepsilon(u,c) := f(u,c) + \varepsilon$ and $g_\varepsilon(u,c) := g(u,c) + \varepsilon$, respectively, where $\varepsilon > 0$. With $f_\varepsilon(u,c)$ and $g_\varepsilon(u,c)$ we are in the situation above and thus the problem (3) with f and g replaced by f_ε and g_ε has a unique non-negative solution $(u_\varepsilon,c_\varepsilon)$. As $\varepsilon \to 0$, these solutions converge to the unique solution (u,c) of (3), due to the continuous dependence of the solution on the data. This proves that (u,c) is non-negative and completes the proof of Thm. 2.1.

4 Discussion and concluding remarks

Theorem 2.1 yields local existence of a solution (u,c) of problem (3) in the regularity class $C^{1+\alpha}([0,T] \times \bar{\Omega}) \times C^{(3+\alpha)/2,3+\alpha}([0,T] \times \bar{\Omega})$. Taking T as initial time and $u(T,\cdot)$, $c(T,\cdot)$ as initial data, one can continue the solution to a larger interval. This procedure may be repeated indefinitely, thereby constructing a maximally defined solution $(u,c) : [0,T_{max}) \times \bar{\Omega} \to \mathbb{R}^2$

belonging to $C^{1+\alpha}([0,\tilde{T}]\times\bar{\Omega})\times C^{(3+\alpha)/2,3+\alpha}([0,\tilde{T}]\times\bar{\Omega})$ for each $\tilde{T}<T_{max}$. Provided that there is no restriction on T_{max} by the domain V of f and g, T_{max} - if it is finite - is characterized by

$$(\mathcal{T}_1)\quad \limsup_{T\uparrow T_{max}}(|u(T,\cdot)|_{C^{1+\alpha}(\bar{\Omega})}+|c(T,\cdot)|_{C^{3+\alpha}(\bar{\Omega})})=\infty$$

or $(\mathcal{T}_2)$ there exists $i\in\{1,2\}$ and $x_*\in\Gamma_i$ s.t. $\lim_{T\uparrow T_{max}}(-1)^i\nabla c(T,x_*)\cdot\nu(x_*)=0.$

There are biologically relevant situations, where T_{max} is solely characterized by $(\mathcal{T}_1)$. To give an example, assume that (vii) holds and $g(u,c)$ is of the form $g(u,c)=c\tilde{g}(u,c)$, where $\tilde{g}\le 0$ on $\mathbb{R}^2_+$; so g from the motivating model described in the introduction, see (2b), is admissible. Assume further that $0\le c_0\le 1$ and that $h=0$ on $\mathbb{R}_+\times\Gamma_1$ as well as $h=1$ on $\mathbb{R}_+\times\Gamma_2$. Thus (viii) is satisfied, and so the local solution (u,c) of (3) is non-negative. Let now $T_1>0$ and suppose that (u,c) solves (3) on $[0,T_1)\times\bar{\Omega}$. If $(\mathcal{T}_1)$ with T_{max} replaced by T_1 does not hold, then (u,c) solves (3) even on $[0,T_1]\times\bar{\Omega}$, in particular we have

$$\partial_t c-\Delta c-\tilde{g}(u,c)c\ge 0\quad\text{on } [0,T_1]\times\bar{\Omega}.$$

Since $(-\tilde{g})\ge 0$, we may apply the strong parabolic maximum principle, cf. Evans [15, Thm. 7.12], to conclude that $c>0$ in $(0,T_1]\times\Omega$, because c cannot be a constant function, by the chosen boundary conditions. By the parabolic Hopf lemma, cf. Protter *et al.* [28, Chapter 3, Sec. 3, Thm. 7], it follows then that $\partial_\nu c<0$ on $[0,T_1]\times\Gamma_1$. Moreover,

$$\partial_t c-\Delta c-\tilde{g}(u,c)c\le 0\quad\text{on } [0,T_1]\times\bar{\Omega}$$

together with the initial and boundary conditions for c, entails that $c\le 1$, by the weak parabolic maximum principle. Applying once more the strong maximum principle and Hopf's lemma, we see that $c<1$ in $(0,T_1]\times\Omega$ and $\partial_\nu c>0$ on $[0,T_1]\times\Gamma_2$. Hence $(\mathcal{T}_2)$ with T_{max} replaced by T_1 cannot occur.

In problem (3) we prescribe Dirichlet boundary conditions for c. In the above proof of the local well-posedness of (3), these play a role in Sec. 3.3, only, where the parabolic problem (5) is considered. So there are corresponding results concerning well-posedness in the case where c is subject to an inhomogeneous Neumann or Robin boundary condition; this also includes problems with different types of boundary conditions on Γ_1 and Γ_2. For example, if $c=h_1$ on $J\times\Gamma_1$ and $\partial_\nu c=h_2$ on $J\times\Gamma_2$, one needs that $h_1\in C^{(3+\alpha)/2,3+\alpha}(J_0\times\Gamma_1)$, $h_2\in C^{(2+\alpha)/2,2+\alpha}(J_0\times\Gamma_2)$, and

$(v)_1$ $\quad c_0=h_1|_{t=0}$ and $\partial_t h_1|_{t=0}-\Delta c_0=g(u_0,c_0)$ on Γ_1;

$(v)_2$ $\quad \partial_\nu c_0=h_2|_{t=0}$ and $\partial_t h_2|_{t=0}-\partial_\nu\Delta c_0=\partial_\nu[g(u_0,c_0)]$ on Γ_2.

Furthermore $h_2|_{t=0}$ must be strictly positive on Γ_2, so as not to contradict condition (vi) in Thm. 2.1. For this particular example one has also positivity of the solution, whenever (vii) and (viii) with $h=h_1,h_2$ (in Thm. 2.1) are additionally fulfilled.

We further remark that our method to prove the strong well-posedness of (3) extends to problems of the general form

$$\begin{cases}\partial_t u+a(t,x,c,\nabla c)\cdot\nabla u=f(t,x,u,c,\nabla c,\nabla^2 c,\partial_t c), & t\in J_0,\ x\in\Omega\\ \partial_t c=g(t,x,u,c,\nabla c,\nabla^2 c), & t\in J_0,\ x\in\Omega,\end{cases}\tag{67}$$

with sufficiently smooth nonlinearities $a,\ f,\ g$, where g satisfies an ellipticity condition, and with (vi) in Thm. 2.1 being replaced by $(-1)^i a(0,x,c_0(x),\nabla c_0(x))\cdot\nu(x)>0$ for all $x\in\Gamma_i,\ i=1,2.$

As to further generalizations, if e.g. a depends on $\partial_t c$ or $\nabla^2 c$, several of our arguments used in Sec. 3 break down, for instance step 1 (property (**B**)) in the proof of Lemma 3.2 as well as the Lipschitz estimate for the considered fixed point mapping (cf. Lemma 3.3).

It would be interesting to know whether one can allow a to depend on u; in this case the situation is much more involved, for the characteristic ODEs are fully coupled and one is confronted with the possible formation of shocks.

Concerning g, it is not possible to include derivatives of u as arguments, since in this case one does not have enough regularity on the right-hand side of the parabolic PDE to prove the desired invariance property of B_R^T.

The results obtained in this paper can be further generalized to models for chemotactic systems. In these models there are several populations interacting with each other and with several chemical agents. For a generalization of the Keller-Segel model in this direction, see e.g. Wolanski [29].

A recent series of papers [20, 19, 18] is concerned with variants of the hyperbolic model for chemotaxis in one space dimension of the form

$$\begin{aligned} u_t^+ + (\gamma(c, c_t, c_x)u^+)_x &= -\mu^+(c, c_t, c_x)u^+ + \mu^-(c, c_t, c_x)u^-, \\ u_t^- - (\gamma(c, c_t, c_x)u^-)_x &= \mu^+(c, c_t, c_x)u^+ - \mu^-(c, c_t, c_x)u^-, \\ \tau c_t - Dc_{xx} &= g(c, u^+ + u^-). \end{aligned} \tag{68}$$

Here the total particle (cell) density $u = u^+ + u^-$ has been split into densities for right and left moving particles u^+ and u^-, respectively. The turning rates μ^+ and μ^- as well as the speed γ depend on the density of the external signal c and its first order derivatives. The model is studied either on the real line or on a bounded interval (a, b) with suitable boundary conditions. For the special case of *constant* speed and for turning rates depending on c and c_x, only, Hillen and Stevens [20] prove local and global existence and uniqueness of weak solutions to (68) with both $\tau = 0$ and $\tau > 0$ using the method of characteristics and the contraction mapping principle together with certain regularity properties of the heat semigroup. Hillen *et al.* [19] investigate (68) with $\tau = 0$, $g(c, u^+ + u^-) = \kappa(u^+ + u^-) - \beta c$, turning rates depending on c and c_x, and they allow the speed to depend on c but not on derivatives of c. They are able to establish global existence, but not uniqueness, of weak solutions by means of the vanishing viscosity method. The authors of the present paper strongly believe that with the techniques employed in the proof of Thm. 2.1, in particular with maximal regularity of the diffusion equation in various function spaces, local existence and uniqueness of strong or even classical solutions to (68) with $\tau, D > 0$ can be established without restrictions on the dependencies of the speed and the turning rates; this is subject of ongoing investigations.

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