Global solvability and explicit bounds for a non-local adhesion model

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Adhesion between cells and other cells (cell-cell adhesion) or other tissue components (cell-matrix adhesion) components is an intrinsically non-local phenomenon. Consequently, a number of recently developed mathematical models for cell adhesion have taken the form of non-local partial differential equations, where the non-local term arises inside a spatial derivative. The mathematical properties of such a non-local gradient term are not yet well understood. Here we use sophisticated estimation techniques to show local and global existence of classical solutions for such examples of adhesion-type models, and we provide a uniform upper bound for the solutions. Further, we discuss the significance of these results to applications in cell-sorting and in cancer invasion and support the theoretical results through numerical simulations.

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1 Introduction

Cell-cell adhesion is fundamental for the development, homoeostasis and repair of the tissues and organs that form our bodies. Regulatory change during tumour progression, for example, can lead to modified adhesion, allowing cells to break away from a solid mass and infiltrate surrounding tissue [6]. For realistic models to be developed it is desirable that cell-cell adhesion can be accounted for within standard modelling frameworks. A characteristic feature of adhesive populations lies in their capacity to self-organise and exhibit pattern formation: a loosely connected population of self-adhering cells can collect into tightly clustered aggregates; tissues composed from multiple cell types organise into characteristic arrangements according to their relative adhesions strengths, as revealed by classic cell sorting experiments (e.g. see [38]). Consequently it is desirable that models for cell adhesion account for such phenomena.

Incorporating cell-cell adhesion within individual-based models is relatively straightforward, yet accounting for it in continuous models has proven somewhat awkward. Näive approaches, based on underlying discrete random walks, can lead to backward diffusion equations in the continuous limit (e.g. see (5.1) and also [33, 22, 3]): such equations are not well-defined in a mathematical sense and their continuous forms have little practical use. Alternative approaches using similar principles can be more successful, in that they generate well-behaved continuous models that capture certain characteristics of adhesive populations, yet may not show more complicated patterning dynamics such as cell sorting (e.g. [23, 24]).

A phenomenological approach has been to formulate an integro-partial differential equation based on cell movement in response to the forces generated by adhering to other cells in some non-local region: the net movement occurs in the direction of the net force generated, which in turn depends on the neighbouring cell distribution. A non-local PDE model formulated according to these principles was developed phenomenologically in Armstrong, Painter and Sherratt [4] (see also [17]), and more recently derived from an underlying stochastic random walk model in Buttenschoen et al. [8]. Crucially, this model recapitulates clustering and sorting and has proven somewhat popular in applications, in particular to cancer invasion: there, the capacity to invade is believed to depend (amongst numerous other factors) on the critical balance between cell-cell (adhesive binding between two cells) and cell-matrix adhesion (binding of a cell to the surrounding extracellular matrix, ECM). Consequently, a number of studies have included the non-local cell-cell adhesion form into models incorporating additional factors such as the ECM and regulatory molecules [16, 37, 17, 31, 25, 2, 9, 10, 14].

Beyond the model of [4], a number of related non-local models have been derived by others. In fact, Sekimura *et al.* [36] developed an earlier non-local PDE to describe adhesion-driven cell movements during wing patterning of moths and butterflies, although the subsequent analysis focussed on the (local) fourth-order PDE derived via Taylor expansion. Non-local models to describe animal flocking have been developed by Mogilner and Edelstein-Keshet, and extended in various directions by others (e.g. [28, 27, 11, 39, 13, 12]). Here, the population movement flux was proposed according to the attracting (i.e. akin to adhesion) and/or repelling interactions between individual members over some potentially unbounded region. Further, a non-local *gradient* model has been introduced in [30, 20] to describe chemotaxis. The adhesion model of Armstrong et al. has also been criticised for an oversimplification of the diffusion part of the model, with a porous-medium form suggested by Murakawa and Togashi [29] as a proposed modification. In that case, cell sorting dynamics become more distinct compared to the original adhesion model.

1.1 The three adhesion models

We focus on non-local models for cell adhesion and their application to cancer invasion. In particular, we consider a rough grouping of models into three classes of increasing sophistication: a basic non-local adhesion model (ADH); a cell-cell and cell-ECM adhesion model (ECM-ADH); and the cell-cell and cell-ECM adhesion model with secretion of diffusible metalloproteinases (MMP-ADH). We formulate and describe these models in detail below.

The goal is to develop a rigorous existence and uniqueness framework for the non-local adhesion model (ADH), along with its extension to include matrix interactions (ECM-ADH). We use rather mild assumptions on parameter functions and initial data to establish the existence of solutions which are smooth and classical, and which moreover enjoy some decay properties at spatial infinity. Appropriate knowledge of such regularity properties enables us to rigorously derive explicit and pointwise upper bounds for the cell density. Finally, numerical simulations are used to support the theoretical findings and investigate whether similar results are obtained for forms outside the current theory.

We note that biologically-motivated upper bounds for (ADH) and (ECM-ADH) have been derived in one dimension in [37], although arguments there necessitated some strong assumptions (see below): we use our paper to *a posteriori* justify these assumptions and extend to higher dimensions and more general functional forms of the parameter functions. Existence, uniqueness and boundedness of a form of model including metalloproteinases, see (MMP-ADH), has also been studied by Chaplain et al.[9]: their results, however, do not apply to either (ADH) or (ECM-ADH) due to their dependence on the regularising properties of the heat solution semigroup for the metalloproteinase class.

1.1.1 *The cell-cell adhesion model (ADH)*

The n-dimensional model for cell-cell adhesion from Armstrong, et al. [4] is given by

$$u_t = D\Delta u - \nabla(I(u)u) + f(u) \tag{ADH}$$

with

$$I(u) = \int_V h(u(x+\xi,t))\frac{\xi}{|\xi|}\Omega(\xi)\, d\xi\,. \tag{1.1}$$

The solution $u(x,t)$ denotes the cell density as function of space x and time $t \geqslant 0$. The non-local term $I(u)$ is an advective velocity stemming from the sum impact of adhesive interactions with neighbouring cells. The integration is over a region $V \subset \mathbb{R}^n$ defining an n-dimensional ball of radius R, where the parameter R is the *sensing radius* and denotes a cell's maximum reach; this could be several times the mean cell radius. The vector $\xi \in V$ determines the position at which an adhesion bond is formed relative to the cell at x, and hence $\xi/|\xi|$ gives the directional impact of this local bond on movement. $\Omega(\xi)$ defines how the strength of a bond depends on the position relative to the cell at x: typically this function will depend on the distance $|\xi|$ between them. For example a decreasing function of $|\xi|$ would reflect a diminished likelihood of two cells interacting as their separation increases. We note that an alternative formulation would be to take $R = \infty$, such that $V = \mathbb{R}^n$ and the integration is over an unbounded region: any limitations in the interactions at large distances can be directly included via the weight function Ω. In fact this is taken in various other non-local formulations, such as those in [28, 36, 32]. The function $h(u(x+\xi,t))$ measures the adhesion strength between a cell at x and the cell population at $x+\xi$. Together, $I(u)$ measures the effective velocity resulting from the direction of the adhesion force that acts on a given cell. A detailed, cell-based derivation of (ADH) is given in [8].

1.1.2 *The cell-matrix and cell-cell adhesion model (ECM-ADH)*

As mentioned above, non-local adhesion terms of the above type have been adopted in broader models for cancer invasion, where one must also account for other important factors such as cell-matrix adhesion. In a relatively simple formulation of Sherratt, Painter and co-workers [37, 31], the model (ADH) was extended to include cell-matrix adhesion as follows:

$$\begin{aligned} u_t &= D\Delta u - \nabla\cdot(I(u,v)u) + f(u)\,, \\ v_t &= \rho(u,v)\,. \end{aligned} \tag{ECM-ADH}$$

In the above, $I(u,v)$ now defines an adhesive force generated through the combined actions of cell-cell and cell-matrix adhesion:

$$I(u,v)(x,t) := \int_V h\Big(u(x+\xi,t), v(x+\xi,t)\Big)\frac{\xi}{|\xi|}\Omega(\xi)d\xi\,. \tag{1.2}$$

The new variable $v(x,t)$ describes ECM density as a function of space and time, while $\rho(u,v)$ models its degradation (and possible reconstruction): in [37] its destruction by invading cancer cells was assumed to dominate and the specific form $\rho(u,v) = -\gamma uv^2$ was used.

1.1.3 *The MMP-regulated cell-matrix and cell-cell adhesion model (MMP-ADH)*

The model given in (ECM-ADH) greatly simplifies the biochemical signalling complexities that regulate cell and matrix interactions. A range of more sophisticated models that explicitly account for some of these signalling pathways, along with the adhesion processes, have been developed – e.g. [16, 2, 9, 10] – and have proven adept at recapitulating certain features observed in cancer invasion. For example, in a recent model of Domschke *et al.* [10], cancer patterns in heterogeneous environments were explored, with cell-cell adhesion allowing cancer cells to organise themselves not as a solid mass, but in a spongy form that resemble typical patterns of breast carcinomas in situ.

As a simplified representation of some of these more sophisticated models, we consider an extended version of (ECM-ADH) that explicitly incorporates the release of proteolytic enzymes, such as metalloproteinases, that diffuse freely and actively degrade the ECM

[31]. This model reads:

$$\begin{aligned} u_t &= D\Delta u - \nabla \cdot (I(u,v)u) + f(u)\,, \\ v_t &= \rho(m,v)\,, \\ m_t &= D_m \Delta m - \lambda m + g(v)u\,, \end{aligned} \qquad \text{(MMP-ADH)}$$

where $m(x,t)$ denotes the concentration of metalloproteinase, which diffuses with rate $D_m > 0$, is produced by the cells with a rate $g(v) > 0$ and decays exponentially with rate $\lambda > 0$.

1.2 Bounds, existence and uniqueness results

Estimates for bounds are desirable in models: for example, to determine whether cell densities remain within biologically realistic ranges. The analysis of the mathematical properties of models (ADH) and (ECM-ADH) was started by Sherratt et al. [37], by finding a very specific and biologically motivated bound. Consider (ECM-ADH) with h and ρ given by

$$h(u,v) = (\alpha u + \beta v)\max\{K - u - v, 0\}, \qquad \text{and} \qquad \rho(u,v) = -\gamma u v^2,$$

or some conveniently chosen smooth approximations thereof, where $\gamma \geqslant 0$ and, in non-dimensional form, $K = 2$. A biological interpretation of this $h(u,v)$ is that cells only feel an attractive pull towards some particular point if the total (cell plus ECM) density is below some maximum permissible tissue density (in this case, 2).

Sherratt et al. [37] showed that solutions would stay bounded, but could still locally exceed the supposed crowding threshold of 2 for particular forms of Ω. However, these results were predicated on a number of implicit assumptions concerning the analytical properties of models (ADH) and (ECM-ADH). Within this paper we significantly extend the results in [37] via:

- removing the (implicit) assumption of smooth solutions – we prove classical solutions exist;
- allowing a wider class of general adhesion functions h and ECM dynamics ρ;
- proving existence and uniqueness in multiple dimensions;
- giving explicit upper bounds for the solutions (although not a specific upper bound, as sought in [37]).

It is noted that we derive a general upper bound for a general class of adhesion models in any space dimension, based on some rough estimates. The specific value of the upper bound for a given situation might be vast compared to the actual maximum in particular solutions. In [37] a special case of (ECM-ADH) is considered in one dimension which, under certain assumptions, generates solutions that remain bounded below some carrying capacity K. This is a much stronger estimate than the global bound derived here.

We also note that the pure adhesion model (ADH) has not yet been specifically analysed for its mathematical properties: while we develop our results for (ECM-ADH), they apply directly to (ADH) and we gain local, global existence, uniqueness and global bounds there as a bonus[1].

Chaplain et al [9] analysed an adhesion model that includes both ECM and metalloproteinases, as in (MMP-ADH), on a bounded smooth domain with homogeneous von Neumann boundary conditions. Via fractional diffusion calculus they showed (under mild assumptions on the parameter functions) classical solutions exist globally in Hölder spaces. As mentioned above, their arguments are based on the regularising properties of the third equation of (MMP-ADH) for $D_m > 0$, which therefore do not permit extension to the other two cases (ADH) and (ECM-ADH) under consideration here.

2 Model assumptions and main results

We consider the adhesion model (ADH) and the cell-ECM adhesion model (ECM-ADH) for $x \in \mathbb{R}^n$. The set of sampling directions V is an open set in $\mathbb{R}^n$ which need not be bounded, and may even coincide with all of $\mathbb{R}^n$. The cell kinetics are described by a function $f(u)$, where we assume that

$$f \in W^{1,\infty}_{loc}(\mathbb{R}) \quad \text{is such that } f(0) = 0. \tag{2.1}$$

Our standard example is logistic growth $f(u) = ru(a - u)$ with $r, a > 0$.

The ECM kinetics are described by a decay rate ρ which satisfies

$$\rho \in W^{1,\infty}_{loc}(\mathbb{R}^2) \quad \text{and } \rho(u, 0) = 0 \quad \text{for all } u \in \mathbb{R}. \tag{2.2}$$

Notice that this condition includes the choice of $\rho \equiv 0$, which relates (ECM-ADH) to (ADH).

The local adhesion force is measured by the function h which satisfies

$$h \in C^2(\mathbb{R}^j), \tag{2.3}$$

where $j = 1$ for (ADH) and $j = 2$ for (ECM-ADH). Our standard choice for h is the function used by Sherratt *et al.* [37]:

$$h(u) = \alpha u g(u), \quad \text{or} \quad h(u, v) = (\alpha u + \beta v) g(u + v), \tag{2.4}$$

respectively, where

$$g : \mathbb{R} \to \mathbb{R} \text{ is such that } g \equiv 0 \text{ on } [b, \infty),$$

with positive constants r, a, b, α and β fulfilling $b > a$.

The distance weighting function $\Omega(\xi)$ is combined with the directional unit vector and we introduce

$$\omega(\xi) = \frac{\xi}{|\xi|}\Omega(\xi), \qquad \xi \in V\,, \tag{2.5}$$

[1] For the specific case $v(x, 0) = 0$, model (ECM-ADH) reduces to (ADH) and the results apply there as well.

where we assume

$$\Omega \in L^1(V).$$

This condition is equivalent with

$$\omega \in (L^1(V))^n. \tag{2.6}$$

As for the initial data, we shall suppose that with some $p \in [1, \infty]$,

$$u_0 \in X_p := C^0(\mathbb{R}^n) \cap L^\infty(\mathbb{R}^n) \cap L^p(\mathbb{R}^n) \quad \text{is nonnegative,} \tag{2.7}$$

and that

$$v_0 \in C^0(\mathbb{R}^n) \cap L^\infty(\mathbb{R}^n) \quad \text{is nonnegative.} \tag{2.8}$$

Here and below, X_p is to be understood as the Banach space with norm $\|\cdot\|_{X_p} := \|\cdot\|_{L^\infty(\mathbb{R}^n)} + \|\cdot\|_{L^p(\mathbb{R}^n)}$.

2.1 Main results for the cell-cell and cell-ECM adhesion model

The first of our results for (ECM-ADH) asserts that, under the above assumptions, a solution always exists at least locally in time, where its first component u is continuous as an X_p-valued function of t. Moreover, this solution can cease to exist in finite time only when the norm of $(u(\cdot,t), v(\cdot,t))$ in $X_p \times L^\infty(\mathbb{R}^n)$ blows up:

Proposition 2.1 *Suppose that (2.1), (2.2), (2.3) and (2.6) hold, and that for some $p \in [1, \infty]$, the initial data u_0 and v_0 satisfy (2.7) and (2.8). Then there exist $T_{max} \in (0, \infty]$ and at least one pair (u, v) of nonnegative functions*

$$u \in C^0([0, T_{max}); X_p) \cap C^{2,1}(\mathbb{R}^n \times (0, T_{max}))$$

and

$$v \in C^0(\mathbb{R}^n \times [0, T_{max})) \cap C^1((0, T_{max}); C^0(\mathbb{R}^n))$$

which solve (ECM-ADH) in the classical sense in $\mathbb{R}^n \times (0, T_{max})$, and which are such that

$$\text{either } T_{max} = \infty, \text{ or } \limsup_{t \nearrow T_{max}} \Big(\|u(\cdot,t)\|_{L^\infty(\mathbb{R}^n)} + \|u(\cdot,t)\|_{L^p(\mathbb{R}^n)} + \|v(\cdot,t)\|_{L^\infty(\mathbb{R}^n)} \Big) = \infty. \tag{2.9}$$

The above conditions, especially those on f and ρ, are clearly insufficient to enforce global solvability in (ECM-ADH). Indeed, we can define special choices of h, f and ρ which lead to well known equations that blow-up in finite time. One such choice would be $h \equiv 0$, $f(u) = u^2$ and $\rho \equiv 0$, while another example arises for $h \equiv 0, f \equiv 0$ and $-\rho(u, v) = v^2$. Both are consistent with assumptions (2.1)-(2.3) and yet they produce solutions that become unbounded. To rule out such phenomena we evidently need to impose appropriate restrictions on growth, especially on f for large u and on $-\rho$ for large values of v. Indeed, it turns out that besides (2.1)-(2.6) we require the condition that

$$\text{there exists } r \geqslant 0 \text{ such that} \quad f(u) \leqslant ru \quad \text{for all } u \geqslant 0 \tag{2.10}$$

with some $r \geqslant 0$. Furthermore we assume that

$$h \in L^\infty(\mathbb{R}^2), \tag{2.11}$$

and that

$$\text{for each } R > 0 \text{ there exists } A(R) > 0 \text{ such that } \quad -\rho(u,v) \leqslant A(R)v \tag{2.12}$$

for all $u \in [0,R]$ and $v \geqslant 0$. Then, in the case $p < \infty$, our solutions are all global in time:

Theorem 2.2 *Assume the conditions of Proposition 2.1 hold and that in addition (2.10)-(2.12) are valid. Then $T_{max} = \infty$.*

Finally, we can derive global bounds on the solutions with the following additional assumptions. We assume that the set of possible sensing directions

$$V \text{ is a bounded domain in } \mathbb{R}^n \text{ with Lipschitz boundary,} \tag{2.13}$$

that the directed weighting function

$$\omega \in W^{1,1}(V) \quad \text{with} \quad \omega \cdot \nu \begin{cases} \geqslant 0 \text{ a.e. on } \partial V & \text{if } h \geqslant 0 \text{ in } \mathbb{R}^2, \\ = 0 \text{ a.e. on } \partial V & \text{otherwise.} \end{cases} \tag{2.14}$$

Note that in $\mathbb{R}^2$ we assume that there are no inward pointing forces on the boundary of the sensing region, while in dimensions $n \neq 2$ we assume all adhesive forces are generated inside the domain and not on the boundary of the sensing region. Furthermore, we assume that the kinetics are given by a logistic law in the sense that

$$\text{there exist } r > 0 \text{ and } a \geqslant 0 \text{ such that } \quad f(u) = ru(a-u) \quad \text{for all } u \geqslant 0. \tag{2.15}$$

In dimensions 2 and higher condition (2.14) can be translated into a condition for the original weighting function Ω by observing that

$$\nabla \cdot \omega = \nabla \cdot \left(\frac{\xi}{|\xi|} \Omega(\xi) \right) = \frac{n-1}{|\xi|} \Omega(\xi) + \frac{\xi}{|\xi|} \cdot \nabla \Omega(\xi). \tag{2.16}$$

Hence, requiring $\omega \in W^{1,1}(V)$ is equivalent to

$$\left(\xi \mapsto \frac{1}{|\xi|} \Omega(\xi) \right) \in L^1(V), \quad \text{and} \quad \Omega \in W^{1,1}(V). \tag{2.17}$$

Under these stronger conditions we can derive the following explicit upper bound for our solution.

Theorem 2.3 *Assume that (2.1)-(2.6), (2.11) and (2.12) are satisfied. Moreover let (2.13), (2.14) and (2.15) hold. Then for each $p \in [1, \infty)$ and any couple of nonnegative functions $u_0 \in X_p$ and $v_0 \in C^0(\mathbb{R}^n) \cap L^\infty(\mathbb{R}^n)$, the solution (u,v) of (ECM-ADH) from Theorem 2.2 is bounded in its first component in $\mathbb{R}^n \times (0,\infty)$; more precisely, we have*

$$u(x,t) \leqslant \max \left\{ \|u_0\|_{L^\infty(\mathbb{R}^n)} \,,\ a + \frac{1}{r} \|h\|_{L^\infty(\mathbb{R}^2)} \cdot \|\nabla \cdot \omega\|_{L^1(V)} \right\} \qquad \text{for all } x \in \mathbb{R}^n \text{ and } t > 0. \tag{2.18}$$

The latter generalises the main analytical result in [37] in two directions. First, it provides an explicit bound for solutions in the multidimensional case. Second, even for the specific one spatial dimension setting, assumptions in Theorem 2.3 are weak enough so as to include large classes of parameter functions not covered by [37, Prop. 2].

2.2 Main results for the cell-cell adhesion model

The original cell-cell adhesion model of Armstrong *et al.* [4] arises as a special case of the cell-cell and cell-ECM adhesion model: the choices $v_0 \equiv 0$ and $\rho \equiv 0$ lead directly from (ECM-ADH) to (ADH). Since this special case is of great importance in many applications, we summarise the corresponding result in the following Corollary:

Corollary 2.4 (1) *Suppose that (2.1), (2.3) and (2.6) hold, and that for some* $p \in [1, \infty]$*, the initial datum* u_0 *satisfies (2.7). Then there exist* $T_{max} \in (0, \infty]$ *and a nonnegative solution* u *of (ADH) such that*

$$u \in C^0([0, T_{max}); X_p) \cap C^{2,1}(\mathbb{R}^n \times (0, T_{max})),$$

and such that

$$\text{either } T_{max} = \infty, \text{ or } \limsup_{t \nearrow T_{max}} \Big(\|u(\cdot, t)\|_{L^\infty(\mathbb{R}^n)} + \|u(\cdot, t)\|_{L^p(\mathbb{R}^n)} \Big) = \infty. \qquad (2.19)$$

(2) *Assume that in addition (2.10) and (2.11) are valid then* $T_{max} = \infty$.

(3) *In addition assume that (2.13), (2.14) and (2.15) are satisfied. Then for each* $p \in [1, \infty)$ *and any nonnegative function* $u_0 \in X_p$*, the above solution* u *of (ADH) is bounded in* $\mathbb{R}^n \times (0, \infty)$ *in the sense that (2.18) holds.*

2.3 Examples

Many common examples, often used in applications, arise under compactly supported and smooth weighting functions $\Omega(\xi)$. In many cases, furthermore, Ω is constant. Hence, as example we assume

$$\omega(\xi) = \frac{\xi}{|\xi|} \Omega(\xi),$$

with

$$\Omega(\xi) \geqslant 0, \quad \text{supp}\{\Omega\} \subset B_R(0), \quad \Omega \in C^1(B_R(0)). \qquad (2.20)$$

This choice of Ω certainly satisfies condition (2.6), hence, given that the other assumptions of Theorem 2.3 and those of Corollary 2.4 are satisfied, solutions to (ADH) and (ECM-ADH) are classical and global. It is interesting to consider the global bound from Theorem 2.3 in this case.

In two dimensions and higher we have the relation (2.16). Since $\Omega \in C^1(B_R)$ then $\frac{1}{|\xi|} \Omega(\xi) \in L^1(B_R)$ and $\Omega \in W^{1,1}(B_R)$, hence conditions (2.14) and (2.17) are satisfied.

In one dimension we have

$$\omega(\xi) = \text{sign}(\xi) \Omega(\xi).$$

In this case

$$\int_{-R}^{R} |\omega'(\xi)| d\xi = \int_{-R}^{R} |\Omega'(\xi)| d\xi + (\Omega(\xi^+) + \Omega(\xi^-))$$
$$= \int_{-R}^{R} |\Omega'(\xi)| d\xi + 2\Omega(0),$$

which is bounded for $\Omega \in C^1(B_R)$. In fact, the above integral coincides with the BV norm of ω (bounded variation).

Hence in each dimension $n = 1, 2, 3, \ldots$ condition (2.14) is satisfied and the global bounds of Theorem 2.3 apply.

In the special case of constant $\Omega(\xi) = \chi_{[-R,R]}\Omega_0$ we find, in $1 - D$:

$$\|\nabla \cdot \omega\|_{L^1(B_R)} = \int_{-R}^{R} |\omega'(\xi)| d\xi = 2R\Omega_0 + 2\Omega_0 = 2\Omega_0(R + 1). \tag{2.21}$$

For dimensions $n \geqslant 2$ we find

$$\begin{aligned}
\|\nabla \cdot \omega\||_{L^1(B_R)} &= \left| \frac{\xi}{|\xi|} \Omega_0 \right|_{L^1(B_R)} \\
&= (n-1)\Omega_0 \int_{B_R} \frac{1}{|\xi|} d\xi \\
&= (n-1)\Omega_0 \int_0^R \int_{\mathbb{S}^{n-1}} \frac{1}{r} r^{n-1} dr d\sigma \\
&= \Omega_0 R^{n-1} |\mathbb{S}^{n-1}|,
\end{aligned} \tag{2.22}$$

where $\mathbb{S}^{n-1}$ denotes the unit sphere in $\mathbb{R}^n$.

2.4 Outline of proofs

To facilitate navigation of the remaining paper for readers with less direct interest in the technical details we employ this subsection to briefly outline the proof construction. Those readers are subsequently directed to Section 4 for a numerical exploration, while those interested in the analytical details are invited to proceed directly to Section 3.

The proof to Proposition 2.1 – local existence of classical solutions – is founded on two preliminary lemmas: Lemma 3.2 employs a Banach fixed point argument to demonstrate existence and uniqueness of mild solutions, while Lemma 3.3 shows that these mild solutions are, indeed, classical solutions. Combined, these prove 2.1.

The extension to prove Theorem 2.2 – global existence – follows through augmenting the results of Proposition 2.1 with the additional assumptions (2.10), (2.11) and (2.12) and taking $p < \infty$. In light of the extensibility criterion (2.9), verifying this theorem reduces to excluding blow-up of $u(\cdot, t)$ with respect to the norm in X_p, achieved via a standard testing procedure, and then ruling out blow-up of $v(\cdot, t)$ in the space $L^\infty(\mathbb{R}^n)$. The proof is constructed through a sequence of lemmas: Lemma 3.4 establishes a central L^q formulation for test functions; this leads to L^q bounds for u in Lemma 3.5 and for $\dot{u}$ in Lemma 3.6; Lemmas 3.7 and 3.8 respectively prepare arguments from recursive sequences and ordinary differential equations; these are subsequently used in lemmas for L^∞ bounds for each of u (Lemma 3.9) and v (Lemma 3.10). Collectively these prove Theorem 2.2.

Finally we prove the explicit upper bound for the cell density u postulated in Theorem 2.3. Building on the knowledge gained on the regularity of solutions and postulating (biologically reasonable) assumptions on the form of the weighting function and the choice of cell kinetics, a comparison-type technique is employed to prove Theorem 2.3.

3 Proofs

For our construction of solutions to (ECM-ADH) we recall that the heat semigroup $(e^{t\Delta})_{t\geqslant 0}$ on $C^0(\mathbb{R}^n) \cap L^\infty(\mathbb{R}^n)$ is explicitly determined by

$$(e^{t\Delta}w)(x) := \int_{\mathbb{R}^n} G(x-y,t)w(y)dy, \qquad x \in \mathbb{R}^n,\ t>0, \tag{3.1}$$

for $w \in C^0(\mathbb{R}^n) \cap L^\infty(\mathbb{R}^n)$, with the Gaussian heat kernel given by

$$G(z,t) := (4\pi t)^{-\frac{n}{2}} e^{-\frac{|z|^2}{4t}}, \qquad z \in \mathbb{R}^n,\ t>0. \tag{3.2}$$

In several places we use standard estimates for $(e^{t\Delta})_{t\geqslant 0}$, which are well-known consequences of this representation (see [35], for instance). Moreover, according to (3.1) and (3.2) it is evident that when applied to sufficiently regular functions, $e^{t\Delta}$ commutes with all spatial differential operators $D^\alpha, \alpha \in \mathbb{N}_0^n$, in the sense that e.g.

$$D^\alpha e^{t\Delta} w = e^{t\Delta} D^\alpha w \qquad \text{for all } t>0 \text{ and } w \in C^{|\alpha|}(\mathbb{R}^n) \cap W^{|\alpha|,\infty}(\mathbb{R}^n). \tag{3.3}$$

In particular, we obtain a formal representation of the first component of solutions to (ECM-ADH) according to the associated variation-of-constants formula,

$$u(\cdot,t) = e^{t\Delta}u_0 - \int_0^t e^{(t-s)\Delta}\nabla\cdot\Big(u(\cdot,s)I(u(\cdot,s),v(\cdot,s))\Big)ds + \int_0^t e^{(t-s)\Delta} f(u(\cdot,s))ds,$$

for $t>0$. This suggests rewriting $e^{(t-s)\Delta}\nabla\cdot = \nabla\cdot e^{(t-s)\Delta}$ in the first integral, so as to obtain a relation which may hold even without a priori requiring u or v to possess any derivative:

Definition 3.1 *Let $T>0$ and $p\in[1,\infty]$. Then a pair (u,v) of nonnegative functions*

$$u \in C^0([0,T];X_p) \quad \textit{and} \quad v \in C^0(\mathbb{R}^n\times[0,T]) \cap C^1((0,T];C^0(\mathbb{R}^n))$$

will be called a mild L^p-solution *of (ECM-ADH) if*

$$\begin{aligned} u(\cdot,t) \quad &= \quad e^{t\Delta}u_0 - \textstyle\int_0^t \nabla\cdot e^{(t-s)\Delta}\Big(u(\cdot,s)I(u(\cdot,s),v(\cdot,s))\Big)ds \\ &\qquad + \textstyle\int_0^t e^{(t-s)\Delta} f(u(\cdot,s))ds, \end{aligned} \tag{3.4}$$

for all $t\in[0,T]$, and if $v_t = \rho(u,v)$ is satisfied in the classical sense in $\mathbb{R}^n\times(0,T)$ with $v(\cdot,0)=v_0$.

3.1 Existence and uniqueness of mild solutions

In order to prepare an appropriate control of certain expressions stemming from the adhesive interaction in (ECM-ADH) in several parts of our analysis, let us state the following pointwise bound for $I(u,v)$ which immediately results from our assumption (2.11).

Lemma 3.1 *Suppose that (2.11) holds, and let $u \in C^0([0,T];X_p)$ and $v \in C^0(\mathbb{R}^n \times [0,T]) \cap C^1((0,T];C^0(\mathbb{R}^n))$ for some $p \in [1,\infty]$ and $T > 0$. Then*

$$|I(u,v)(x,t)| \leqslant K_I := \|h\|_{L^\infty(\mathbb{R}^2)} \cdot \|\omega\|_{L^1(V)} \qquad \text{for all } x \in \mathbb{R}^n \text{ and } t \in (0,T).$$

Proof This is evident from the trivial estimate

$$\begin{aligned} |I(u,v)(x,t)| &= \Big| \int_V h\Big(u(x+\xi,t), v(x+\xi,t)\Big)\omega(\xi)d\xi \Big| \\ &\leqslant \int_V \|h\|_{L^\infty(\mathbb{R}^2)} \cdot |\omega(\xi)| d\xi, \end{aligned}$$

valid for all $(x,t) \in \mathbb{R}^n \times (0,T)$. □

A first application thereof will arise in the derivation of the following result on local existence of mild solutions.

Lemma 3.2 *Suppose that (2.1), (2.2), (2.3) and (2.6) hold, and that with some $p \in [1,\infty]$, u_0 and v_0 satisfy (2.7) and (2.8). Then there exist $T_{max} \in (0,\infty]$ and a uniquely determined mild L^p-solution (u,v) of (ECM-ADH) in $\mathbb{R}^n \times (0,T_{max})$ such that*

$$\text{if } T_{max} < \infty \text{ then } \limsup_{t \nearrow T_{max}} \Big(\|u(\cdot,t)\|_{L^\infty(\mathbb{R}^n)} + \|u(\cdot,t)\|_{L^p(\mathbb{R}^n)} + \|v(\cdot,t)\|_{L^\infty(\mathbb{R}^n)} \Big) = \infty. \tag{3.5}$$

Proof By known smoothing estimates for the heat semigroup [35], we can find $c_1 > 0$ such that for all $t > 0$ we have

$$\|\nabla \cdot e^{t\Delta}\varphi\|_{L^p(\mathbb{R}^n)} \leqslant c_1 t^{-\frac{1}{2}} \|\varphi\|_{L^p(\mathbb{R}^n)} \qquad \text{for all } \varphi \in L^p(\mathbb{R}^n, \mathbb{R}^n) \tag{3.6}$$

and

$$\|\nabla \cdot e^{t\Delta}\varphi\|_{L^\infty(\mathbb{R}^n)} \leqslant c_1 t^{-\frac{1}{2}} \|\varphi\|_{L^p(\mathbb{R}^n)} \qquad \text{for all } \varphi \in L^\infty(\mathbb{R}^n, \mathbb{R}^n). \tag{3.7}$$

We next define $R := \|u_0\|_{X_p} + 1$ and $M := \|v_0\|_{L^\infty(\mathbb{R}^n)} + 1$, set

$$K_\rho := \|\rho(\cdot,0)\|_{L^\infty((-R,R))} \qquad \text{and} \qquad K_h := \|h\|_{L^\infty((-R,R)\times(-M,M))}$$

and let L_ρ, L_h and L_f denote positive Lipschitz constants of ρ, h and f over $[-R,R] \times [-M,M]$, $[-R,R] \times [-M,M]$ and $[-R,R]$, respectively. It is then possible to fix $T \in (0,1)$ small enough fulfilling

$$2c_1 K_I R T^{\frac{1}{2}} + L_f R T \leqslant 1 \tag{3.8}$$

and

$$(M-1)e^{L_\rho T} \leqslant M - \frac{3}{4} \qquad \text{and} \qquad e^{L_\rho T} \leqslant 1 + \frac{L_\rho}{4K_\rho} \tag{3.9}$$

as well as

$$2c_1K_IT^{\frac{1}{2}} + L_fT + c_1c_2RT \leqslant \frac{1}{2}, \tag{3.10}$$

where

$$c_2 := L_h \cdot \Big(1 + L_\rho T e^{L_\rho T}\Big) \cdot \|\omega\|_{L^1(V)}. \tag{3.11}$$

We thereupon consider the Banach space

$$X_{p,T} := C^0([0,T]; X^p),$$

equipped with its natural norm $\|\cdot\|_{X_{p,T}}$, along with the closed subset thereof defined by

$$S := \Big\{\varphi \in X_{p,T} \;\Big|\; \|\varphi\|_{X_{p,T}} \leqslant R\Big\}.$$

On S, we consider the mapping Φ given by

$$\Phi u(\cdot,t) := e^{t\Delta}u_0 - \int_0^t \nabla\cdot e^{(t-s)\Delta}\Big(u(\cdot,s)I(u(\cdot,s),v(\cdot,s))\Big)ds + \int_0^1 e^{(t-s)\Delta}f(u(\cdot,s))ds$$

for $t \in [0,T]$ and $u \in S$, where v denotes the u-dependent solution of the initial-value problem

$$\begin{cases} v_t = \rho(u,v), & x \in \mathbb{R}^n,\ t \in [0,T], \\ v(x,0) = v_0(x), & x \in \mathbb{R}^n. \end{cases} \tag{3.12}$$

To see that Φ maps S into itself, we first make sure that

$$|v(x,t)| \leqslant M \qquad \text{for all } x \in \mathbb{R}^n \text{ and } t \in (0,T). \tag{3.13}$$

Indeed, since $|v_0| \leqslant M-1$, the number $T_0 := \sup\{\tilde{T} \in (0,T) \mid |v| \leqslant M \text{ in } \mathbb{R}^n \times (0,\tilde{T})\}$ is well-defined, and by definition of L_ρ and K_ρ and the inequality $|u| \leqslant R$, valid since $u \in S$, we know that

$$v_t = \rho(u,v) = \rho(u,0) + \Big(\rho(u,v) - \rho(u,0)\Big) \leqslant K_\rho + L_\rho|v| \qquad \text{in } \mathbb{R}^n \times (0,T_0),$$

which entails that

$$v(x,t) \leqslant K_\rho t + L_\rho \int_0^t |v(x,s)|ds \qquad \text{for all } x \in \mathbb{R}^n \text{ and } t \in (0,T_0).$$

Likewise, we derive the inequality

$$v_t \geqslant -K_\rho - L_\rho|v| \qquad \text{in } \mathbb{R}^n \times (0,T_0)$$

and thereby obtain

$$-v(x,t) \leqslant K_\rho t + L_\rho \int_0^t |v(x,s)|ds \qquad \text{for all } x \in \mathbb{R}^n \text{ and } t \in (0,T_0),$$

so that altogether

$$|v(x,t)| \leqslant K_\rho t + L_\rho \int_0^t |v(x,s)|ds \qquad \text{for all } x \in \mathbb{R}^n \text{ and } t \in (0,T_0).$$

Thus, the Grønwall lemma and (3.9) assert that

$$\begin{aligned}|v(x,t)| &\leqslant |v_0(x)|\cdot e^{L_\rho t} + K_\rho \int_0^t e^{L_\rho (t-s)} ds \\ &= |v_0(x)|\cdot e^{L_\rho t} + \frac{K_\rho}{L_\rho}(e^{L_\rho t}-1) \\ &\leqslant (M-1)e^{L_\rho t} + \frac{K_\rho}{L_\rho}(e^{L_\rho t}-1) \\ &\leqslant M - \frac{3}{4} + \frac{1}{4} \\ &= M - \frac{1}{2} \qquad \text{for all } x\in\mathbb{R}^n \text{ and } t\in(0,T_0),\end{aligned}$$

which in particular shows that in fact $T_0 = T$ and hence (3.13) holds.
Next aiming at a control of $\Phi(u)$ in $X_{p,T}$, we use that for each $q\in[p,\infty]$ we have

$$\|e^{t\Delta}\varphi\|_{L^q(\mathbb{R}^n)} \leqslant \|\varphi\|_{L^q(\mathbb{R}^n)} \qquad \text{for all } t>0 \text{ and each } \varphi\in L^q(\mathbb{R}^n) \tag{3.14}$$

to estimate

$$\|e^{t\Delta}u_0\|_{X_p} \leqslant \|u_0\|_{X_p} \qquad \text{for all } t>0. \tag{3.15}$$

Moreover, according to Lemma 3.1, (3.6) and (3.7), for $q\in\{p,\infty\}$ we obtain

$$\begin{aligned}\left\|\int_0^t \nabla\cdot e^{(t-s)\Delta} uI(u,v)ds\right\|_{L^q(\mathbb{R}^n)} &\leqslant c_1\int_0^t (t-s)^{-\frac{1}{2}}\|uI(u,v)(\cdot,s)\|_{L^q(\mathbb{R}^n)}ds \\ &\leqslant c_1K_I\int_0^t (t-s)^{-\frac{1}{2}}\|u(\cdot,s)\|_{L^q(\mathbb{R}^n)}ds \qquad \text{for all } t\in(0,T),\end{aligned}$$

so that

$$\begin{aligned}\left\|\int_0^t \nabla\cdot e^{(t-s)\Delta} uI(u,v)ds\right\|_{X_p} &\leqslant c_1K_I\int_0^t (t-s)^{-\frac{1}{2}}\|u(\cdot,s)\|_{X_p}ds \\ &\leqslant c_1K_I\|u\|_{L^\infty((0,T);X_p)}\cdot\int_0^t (t-s)^{-\frac{1}{2}}ds \\ &\leqslant c_1K_IR\cdot 2T^{\frac{1}{2}} \qquad \text{for all } t\in(0,T).\end{aligned} \tag{3.16}$$

As in the pointwise sense we have

$$|f(u)| \leqslant L_f|u| \qquad \text{in } \mathbb{R}^n\times(0,T)$$

thanks to our assumption $f(0)=0$ and the fact that $|u|\leqslant R$, again by (3.14) we find that for all $q\in[p,\infty]$,

$$\left\|\int_0^t e^{(t-s)\Delta}f(u(\cdot,s))ds\right\|_{L^q(\mathbb{R}^n)} \leqslant \int_0^t \|f(u(\cdot,s))\|_{L^q(\mathbb{R}^n)}ds \leqslant L_f\int_0^t \|u(\cdot,s)\|_{L^q(\mathbb{R}^n)}ds$$

and hence

$$\left\|\int_0^t e^{(t-s)\Delta}f(u(\cdot,s))ds\right\|_{X_p} \leqslant L_f\int_0^t \|u(\cdot,s)\|_{X_p}ds \leqslant L_fRT \qquad \text{for all } t\in(0,T).$$

Combined with (3.15) and (3.16), according to the smallness condition (3.8) on T this ensures that

$$\begin{aligned} \Big\|\Phi u(\cdot,t)\Big\|_{X_p} &\leqslant \|u_0\|_{X_p} + c_1 K_I R\cdot 2T^{\frac{1}{2}} + L_f RT \\ &\leqslant \|u_0\|_{X_p} + 1 \\ &\leqslant R \qquad \text{for all } t\in(0,T) \end{aligned}$$

and thus proves the desired inclusion $\Phi S \subset S$.

Next, in order to show that Φ actually is a contraction of S, we let u and $\overline{u}$ belong to S and split

$$\begin{aligned} \Big\|\Phi u(\cdot,t) - \Phi\overline{u}(\cdot,t)\Big\|_{X_p} &\leqslant \Big\|\int_0^t \nabla\cdot e^{(t-s)\Delta}(u-\overline{u})(\cdot,s)I(u,v)(\cdot,s)ds\Big\|_{X_p} \\ &\quad + \Big\|\int_0^t \nabla\cdot e^{(t-s)\Delta}\overline{u}(\cdot,s)\Big[I(u,v)-I(\overline{u},\overline{v})\Big](\cdot,s)ds\Big\|_{X_p} \\ &\quad + \Big\{\int_0^t e^{T-s)\Delta}\Big\{f(u)-f(\overline{u})\Big\}(\cdot,s)ds\Big\|_{X_p} \\ &=: J_1(t)+J_2(t)+J_3(t) \qquad \text{for } t\in(0,T), \end{aligned} \tag{3.17}$$

where $\overline{v}$ denotes the corresponding solution of (3.12) with u replaced by $\overline{u}$. Here, again by (3.6), (3.7) and Lemma 3.1 we can estimate

$$\begin{aligned} J_1(t) &\leqslant c_1 K_I \int_0^t (t-s)^{-\frac{1}{2}}\|u(\cdot,s)-\overline{u}(\cdot,s)\|_{X_p}ds \\ &\leqslant C_1 K_I\cdot 2T^{\frac{1}{2}}\cdot\|u-\overline{u}\|_{X_{p,T}} \qquad \text{for all } t\in(0,T). \end{aligned} \tag{3.18}$$

Moreover, since

$$|f(u)-f(\overline{u})| \leqslant L_f|u-\overline{u}| \qquad \text{in } \mathbb{R}^n\times(0,T)$$

by definition of L_f and the fact that $|u|\leqslant R$ and $|\overline{u}|\leqslant R$, recalling (3.14) we find that

$$\begin{aligned} J_3(T) &\leqslant \int_0^t \Big\|f(u(\cdot,s))-f(\overline{u}(\cdot,s))\Big\|_{X_p}ds \\ &\leqslant L_f\int_0^t \|u(\cdot,s)-\overline{u}(\cdot,s)\|_{X_p}ds \\ &\leqslant L_f T\cdot\|u-\overline{u}\|_{X_{p,T}} \qquad \text{for all } t\in(0,T). \end{aligned} \tag{3.19}$$

To control $J_2(t)$ appropriately, we first note that since clearly both $|v|\leqslant M$ and $|\overline{v}|\leqslant M$ hold in $\mathbb{R}^n\times(0,T)$ (cf. (3.13)), we have

$$|\rho(u,v)-\rho(\overline{u},\overline{v})| \leqslant L_\rho\Big(|u-\overline{u}|+|v-\overline{v}|\Big) \qquad \text{in } \mathbb{R}^n\times(0,T).$$

Therefore,

$$|(v-\overline{v})_t| = |-\rho(u,v)+\rho(\overline{u},\overline{v})| \leqslant L_\rho\Big(|u-\overline{u}|+|v-\overline{v}|\Big) \qquad \text{in } \mathbb{R}^n\times(0,T),$$

which readily implies that

$$|v(x,t)-\overline{v}(x,t)| \leqslant L_\rho \int_0^t |u(x,s)-\overline{u}(x,s)|ds + L_\rho \int_0^t |v(x,s)-\overline{v}(x,s)|ds$$

for all $x \in \mathbb{R}^n$ and $t \in (0,T)$. Once again invoking the Grønwall lemma, from this we infer that

$$\begin{aligned}|v(x,t)-\overline{v}(x,t)| &\leqslant \int_0^t e^{L_\rho(t-s)} \cdot L_\rho|u(x,s)-\overline{u}(x,s)|ds\\ &\leqslant L_\rho e^{L_\rho T} \int_0^T \|u(\cdot,s)-\overline{u}(\cdot,s)\|_{L^\infty(\mathbb{R}^n)} ds\\ &\leqslant L_\rho e^{L_\rho T} \cdot T \cdot \|u-\overline{u}\|_{X_{p,T}} \qquad \text{for all } x \in \mathbb{R}^n \text{ and } t \in (0,T).\end{aligned}$$

We thereby gain the poinwise estimate

$$\begin{aligned}\Big|\Big[I(u,v)-I(\overline{u},\overline{v})\Big](x,t)\Big| &\leqslant \int_V \Big|\Big[h(u,v)-h(\overline{u},\overline{v})\Big](x+\xi,t)\Big| \cdot |\omega(\xi)|d\xi\\ &\leqslant L_h \int_V \Big(|u-\overline{u}|(x+\xi,t)+|v-\overline{v}|(x+\xi,t)\Big) \cdot |\omega(\xi)|d\xi\\ &\leqslant L_h\Big(|u(\cdot,t)-\overline{u}(\cdot,t)\|_{L^\infty(\mathbb{R}^n)} + \|v(\cdot,t)-\overline{v}(\cdot,t)\|_{L^\infty(\mathbb{R}^n)}\Big) \cdot \|\omega\|_{L^1(V)}\\ &\leqslant L_h\Big(1+L_\rho e^{L_\rho T}T\Big) \cdot \|\omega\|_{L^1(V)} \cdot \|u-\overline{u}\|_{X_{p,T}}\\ &= c_2\|u-\overline{u}\|_{X_{p,T}} \qquad \text{for all } x \in \mathbb{R}^n \text{ and } t \in (0,T)\end{aligned}$$

with c_2 as given by (3.11).

Consequently, once more by (3.6) and (3.7) we see that

$$\begin{aligned}J_2(t) &\leqslant c_1 \int_0^t \|\overline{u}(\cdot,s)\|_{X_p} \cdot \Big\|\Big[I(u,v)-I(\overline{u},\overline{v})\Big](\cdot,s)\Big\|_{L^\infty(\mathbb{R}^n)} ds\\ &\leqslant c_1c_2\|u-\overline{u}\|_{X_{p,T}} \cdot \int_0^t \|\overline{u}\|_{X_{p,T}} ds\\ &\leqslant c_1c_2RT \cdot \|u-\overline{u}\|_{X_{p,T}} \qquad \text{for all } t \in (0,T).\end{aligned} \tag{3.20}$$

According to our limitation (3.10) of T, we thus obtain from (3.17), (3.18), (3.19) and (3.20) that

$$\begin{aligned}\Big\|\Phi u(\cdot,t)-\Phi\overline{u}(\cdot,t)\Big\|_{X_p} &\leqslant \Big(c_1K_I \cdot 2T^{\frac{1}{2}} + L_fT + c_1c_2RT\Big) \cdot \|u-\overline{u}\|_{X_{p,T}}\\ &\leqslant \frac{1}{2}\|u-\overline{u}\|_{X_{p,T}} \qquad \text{for all } t \in (0,T),\end{aligned}$$

and hence conclude that Φ indeed acts as a contraction on S. Therefore, the Banach fixed point theorem warrants the existence of a uniquely determined mild L^p-solution (u,v) of (ECM-ADH) in $\mathbb{R}^n \times (0,T)$. That this solution in fact can be continued up to a maximal existence time $T_{max} \leqslant \infty$ satisfying (3.5) is now a consequence of a standard extensibility argument based on the fact that our above choice of T only depends on the initial data u_0 and v_0 through their norms in X_p and in $L^\infty(\mathbb{R}^n)$, respectively. □

3.2 Mild solutions are classical

Let us next make sure that the above mild solutions are actually classical; indeed, by carefully adapting essentially well-established arguments to the present framework we shall see the following.

Lemma 3.3 *Let $T > 0$, and suppose that (u, v) is a mild L^p-solution of (ECM-ADH) in $\mathbb{R}^n \times (0, T)$. Then u belongs to $C^{2,1}(\mathbb{R}^n \times (0, T))$, and (u, v) is a classical solution of (ECM-ADH) in $\mathbb{R}^n \times (0, T)$.*

Proof Abbreviating $F_1(x, t) := (uI(u, v))(x, t)$ and $F_2(x, t) := f(u(x, t))$ for $(x, t) \in \mathbb{R}^n \times (0, T)$, from the regularity properties of the mild L^p-solution (u, v) we obtain that both F_1 and F_2 are continuous and bounded in $\mathbb{R}^n \times [0, T]$.

Step 1. We first claim that

$$w(\cdot, t) := \int_0^t \nabla \cdot e^{(t-s)\Delta} F_1(\cdot, s) ds, \qquad t \in [0, T], \tag{3.21}$$

defines a very weak solution of the problem $w_t = \Delta w + \nabla \cdot F_1$ in $\mathbb{R}^n \times (0, T)$, $w(\cdot, 0) \equiv 0$, in the sense that

$$-\int_0^T \int_{\mathbb{R}^n} w\varphi_t = \int_0^T \int_{\mathbb{R}^n} w\Delta\varphi - \int_0^T \int_{\mathbb{R}^n} F_1 \cdot \nabla\varphi \qquad \text{for all } \varphi \in C_0^\infty(\mathbb{R}^n \times [0, T)). \tag{3.22}$$

To see this, for $\varepsilon \in (0, T)$ we introduce

$$w_\varepsilon(\cdot, t) := \int_0^{(t-\varepsilon)_+} \nabla \cdot e^{(t-s)\Delta} F_1(\cdot, s) ds, \qquad t \in [0, T],$$

and then obtain from standard smoothing estimates for the heat semigroup that w_ε is smooth and bounded in $\mathbb{R}^n \times [0, T]$ with

$$w_\varepsilon \to w \quad \text{in } C^0(\mathbb{R}^n \times [0, T]) \qquad \text{as } \varepsilon \searrow 0. \tag{3.23}$$

Moreover, for fixed $\varphi \in C_0^\infty(\mathbb{R}^n \times [0, T))$ we may invoke Fubini's theorem in computing

$$\begin{aligned} \int_0^T \int_{\mathbb{R}^n} w_\varepsilon \varphi_t &= \int_{\mathbb{R}^n} \int_\varepsilon^T \int_0^{t-\varepsilon} \nabla \cdot e^{(t-s)\Delta} F_1(\cdot, s) ds \cdot \varphi_t(\cdot, t) ds dt dx \\ &= \int_{\mathbb{R}^n} \int_0^{T-\varepsilon} \int_{s+\varepsilon}^T \nabla \cdot \Big(e^{(t-s)\Delta} F_1(\cdot, s)\Big) \varphi_t(\cdot, t) dt ds dx. \end{aligned} \tag{3.24}$$

Here, integrating by parts and using the symmetry of the heat semigroup we obtain

$$\begin{aligned} &\int_{\mathbb{R}^n} \int_0^{T-\varepsilon} \int_{s+\varepsilon}^T \nabla \cdot \Big(e^{(t-s)\Delta} F_1(\cdot, s)\Big) \varphi_t(\cdot, t) dt ds dx \\ &\quad = \int_{\mathbb{R}^n} \int_0^{T-\varepsilon} F_1(\cdot, s) \cdot \bigg(\int_{s+\varepsilon}^T e^{(t-s)\Delta} \nabla\varphi_t(\cdot, t) dt \bigg) ds dx \\ &\quad = \int_{\mathbb{R}^n} \int_0^{T-\varepsilon} F_1(\cdot, s) \cdot \bigg\{ -\int_{s+\varepsilon}^T \Delta e^{(t-s)\Delta} \nabla\varphi(\cdot, t) dt - e^{\varepsilon\Delta} \nabla\varphi(\cdot, s+\varepsilon) \bigg\} ds dx. \end{aligned} \tag{3.25}$$

By (3.3) and, again, by symmetry of $e^{(t-s)\Delta}$, once more integrating by parts and using the Fubini theorem we infer that

$$\begin{aligned}
&-\int_{\mathbb{R}^n}\int_0^{T-\varepsilon}\int_{s+\varepsilon}^T F_1(\cdot,s)\Delta e^{(t-s)\Delta}\nabla\varphi(\cdot,t)dtdsdx\\
&=\int_{\mathbb{R}^n}\int_0^{T-\varepsilon}\int_{s+\varepsilon}^T e^{(t-s)\Delta}F_1(\cdot,s)\cdot\nabla\Delta\varphi(\cdot,t)dtdsdx\\
&=-\int_{\mathbb{R}^n}\int_0^{T-\varepsilon}\int_{s+\varepsilon}^T \nabla\cdot e^{(t-s)\Delta}F_1(\cdot,s)\Delta\varphi(\cdot,t)dtdsdx\\
&=-\int_{\mathbb{R}^n}\int_0^T w_\varepsilon\Delta\varphi.
\end{aligned}$$

Therefore, (3.24) and (3.25) yield

$$-\int_0^T\int_{\mathbb{R}^n} w_\varepsilon\varphi_t=\int_0^T\int_{\mathbb{R}^n} w_\varepsilon\Delta\varphi+\int_0^{T_\varepsilon}\int_{\mathbb{R}^n} F_1(\cdot,s)\cdot e^{\varepsilon\Delta}\nabla\varphi(\cdot,s+\varepsilon)dsdx.$$

Since clearly

$$\mathbb{R}^n\times(0,T)\ni(x,s)\mapsto\Big(e^{\varepsilon\Delta}\nabla\varphi(\cdot,s+\varepsilon)\Big)(x)\rightharpoonup\nabla\varphi\quad\text{in } L^1(\mathbb{R}^n\times(0,T))\qquad\text{as }\varepsilon\searrow 0,$$

along with (3.23) this readily implies (3.22).

Step 2. We next assert that u is a very weak solution to its respective sub-problem of (ECM-ADH) in the sense that

$$-\int_0^T\int_{\mathbb{R}^n} u\varphi_t-\int_{\mathbb{R}^n} u_0\varphi(\cdot,0)=\int_0^T\int_{\mathbb{R}^n} u\Delta\varphi-\int_0^T\int_{\mathbb{R}^n} F_1\cdot\nabla\varphi+\int_0^T\int_{\mathbb{R}^n} F_2\varphi$$
$$\text{for all }\varphi\in C_0^\infty(\mathbb{R}^n\times[0,T)).\tag{3.26}$$

Indeed, this follows from Step 1 and a simplified variant of the reasoning therein applied to $z(\cdot,t):=\int_0^t e^{(t-s)\Delta}F_2(\cdot,s)ds$, $t\in[0,T]$, combined with the fact that $e^{t\Delta}u_0$ is a classical solution of the heat equation with initial data u_0.

Step 3. Let us now make sure that for all $\tau\in(0,T)$ we actually have $\nabla u\in L^2_{loc}(\mathbb{R}^n\times(\tau,T))$ and

$$-\int_\tau^T\int_{\mathbb{R}^n} u\varphi_t-\int_{\mathbb{R}^n} u(\cdot,\tau)\varphi(\cdot,\tau)=-\int_\tau^T\int_{\mathbb{R}^n}\nabla u\cdot\nabla\varphi-\int_\tau^T\int_{\mathbb{R}^n} F_1\cdot\nabla\varphi+\int_\tau^T\int_{\mathbb{R}^n} F_2\varphi$$
$$\text{for all }\varphi\in C_0^\infty(\mathbb{R}^n\times[\tau,T)).\tag{3.27}$$

To verify this, we restrict the initial value problem formally associated with (3.27) to balls $B_R:=B_R(0)$ for arbitrary $R>0$ and aim at showing that for any such R, u coincides in $B_R\times(0,T)$ with a certain alternative solution $\overline{u}$, smooth enough so as to comply with the above regularity requirement, of the corresponding problem with artificially prescribed boundary values u on $\partial B_R\times(0,T)$.

For this purpose, we first note that by a standard argument, (3.26) implies that whenever

$0 < \tau < t_0 < T$ and $R > 0$,

$$
\begin{aligned}
&-\int_\tau^{t_0}\int_{B_R} u\varphi_t + \int_{B_R} u(\cdot,t_0)\varphi(\cdot,t_0) - \int_{B_R} u(\cdot,\tau)\varphi(\cdot,\tau) \\
&= \int_\tau^{t_0}\int_{B_R} u\Delta\varphi - \int_\tau^{t_0}\int_{B_R} F_1\cdot\nabla\varphi + \int_\tau^{t_0}\int_{B_R} F_2\varphi \qquad (3.28)\\
&\quad \text{for all } \varphi \in C_0^\infty(B_R\times[\tau,t_0]).
\end{aligned}
$$

We now let $\overline{u}$ denote the generalized solution of

$$
\begin{cases}
\overline{u}_t = \Delta\overline{u} + \nabla\cdot F_1 + F_2, & x\in B_R,\ t\in(\tau,T),\\
\overline{u} = u, & x\in\partial B_R,\ t\in(\tau,T),\\
\overline{u}(x,\tau) = u(x,\tau), & x\in B_R.
\end{cases}
\qquad (3.29)
$$

Then since u, being a mild L^p-solution of (ECM-ADH), actually satisfies $u \in C^{\alpha,\frac{\alpha}{2}}_{loc}(\mathbb{R}^n \times (0,T])$ for all $\alpha \in (0,1)$ by standard estimates for the Gaussian heat kernel, it follows ([26], [34]) that (3.29) indeed possesses a solution $\overline{u}$ fulfilling

$$
\overline{u} \in L^2(\tau,T);W^{1,2}(B_R)) \cap C^{\beta,\frac{\beta}{2}}(\bar{B}_R\times[\tau,T]) \qquad (3.30)
$$

for some $\beta \in (0,1)$, as well as

$$
\begin{aligned}
&-\int_\tau^{t_0}\int_{B_R} \overline{u}\varphi_t + \int_{B_R} \overline{u}(\cdot,t_0)\varphi(\cdot,t_0) - \int_{B_R} u(\cdot,\tau)\varphi(\cdot,\tau) \\
&= \int_\tau^{t_0}\int_{B_R} \overline{u}\Delta\varphi - \int_\tau^{t_0}\int_{B_R} F_1\cdot\nabla\varphi + \int_\tau^{t_0}\int_{B_R} F_2\varphi \qquad (3.31)\\
&\quad \text{for all } \varphi \in C_0^\infty(B_R\times[\tau,t_0])
\end{aligned}
$$

for any $t_0 \in (\tau,T)$. Therefore, subtracting (3.31) from (3.28) shows that $U := u - \overline{u}$ satisfies

$$
\int_{B_R} U(\cdot,t_0)\varphi(\cdot,t_0) = \int_\tau^{t_0} U\cdot(\varphi_t + \Delta\varphi) \qquad \text{for all } \varphi\in C_0^\infty(B_R\times[\tau,t_0]) \qquad (3.32)
$$

and each $t_0 \in (\tau,T)$. Here we take any sequence $(U_j)_{j\in\mathbb{N}} \subset C_0^\infty(B_R)$ such that $U_j \to U(\cdot,t_0)$ in $L^2(B_R)$ as $j\to\infty$, and let ψ_j denote the solution of

$$
\begin{cases}
\psi_{jt} + \Delta\psi_j = 0, & x\in B_R,\ t\in(\tau,t_0),\\
\psi_j = 0, & x\in\partial B_R,\ t\in(\tau,t_0),\\
\psi_j(x,t_0) = U_j(x), & x\in B_R,
\end{cases}
\qquad (3.33)
$$

which by a time reflection can easily be transformed into a proper parabolic problem and hence possesses a unique classical solution $\psi \in C^\infty(\bar{B}_R\times[\tau,t_0])$. For $\delta\in(0,\frac{R}{2})$, we now let

$$
\varphi(x,t) := \chi_\delta(x)\cdot\psi_j(x,t), \qquad x\in B_R,\ t\in(\tau,t_0),
$$

where $\chi_\delta \in C_0^\infty(B_R)$ is such that $0 \leqslant \chi_\delta \leqslant 1$ in B_R, $\chi_\delta \equiv 1$ in $B_{R-\delta}$, $|\nabla\chi_\delta| \leqslant \frac{c_1}{\delta}$ in B_R and $|\Delta\chi_\delta| \leqslant \frac{c_2}{\delta^2}$ in B_R with some $c_1 > 0$ and $c_2 > 0$ independent of δ. Then φ may be inserted into (3.32), which thereupon yields

$$\int_{B_R} \chi_\delta(x) U(x,t_0) U_j(x) dx = \int_\tau^{t_0} \int_{B_R} U \cdot \Big(2\nabla\chi_\delta \cdot \nabla\psi_j + \Delta\chi_\delta \cdot \psi_j \Big) \tag{3.34}$$

for all $j \in \mathbb{N}$ and $\delta \in (0, \frac{R}{2})$. Now according to (3.29) and (3.30) we can find $c_3 > 0$ such that

$$|U(x,t)| \leqslant c_3 \delta^\alpha \qquad \text{for all } x \in B_R \setminus B_{R-\delta} \text{ and } t \in (\tau, T), \tag{3.35}$$

and hence we can estimate

$$\left| \int_\tau^{t_0} \int_{B_R} U \cdot 2\nabla\chi_\delta \cdot \nabla\psi_j \right| \leqslant c_3 \delta^\alpha \cdot \frac{2c_1}{\delta} \cdot \|\nabla\psi_j\|_{L^\infty(B_R \times (\tau,t_0))} \cdot t_0 \cdot |B_R \setminus B_{R-\delta}| \ \to 0$$

as $\delta \searrow 0$, because $|B_R \setminus B_{R-\delta}| \leqslant c_4 \delta$ with some $c_4 > 0$. Similarly, since moreover the boundary condition in (3.33) ensures that

$$|\psi_j(x,t)| \leqslant c_5(j) \cdot \delta \qquad \text{for all } x \in B_R \setminus B_{R-\delta} \text{ and } t \in (\tau, t_0),$$

we obtain

$$\left| \int_\tau^{t_0} \int_{B_R} U \cdot \Delta\chi_\delta \cdot \psi_j \right| \leqslant c_3 \delta^\alpha \cdot \frac{c_2}{\delta^2} \cdot c_5(j) \delta \cdot t_0 \cdot |B_R \setminus B_{R-\delta}| \to 0 \qquad \text{as } \delta \searrow 0.$$

Therefore, by the dominated convergence theorem we infer from (3.34) that $\int_{B_R} U(x,t_0) \cdot U_j(x) dx = 0$ for all $j \in \mathbb{N}$, which by construction of U_j entails that $\int_{B_R} U^2(x,t_0) = 0$. We thus infer that actually $u \equiv \overline{u}$ in $B_R \times (\tau, T)$, so that the claim of Step 3 becomes a consequence of (3.30) and the weak formulation of (3.29).

Step 4. We finally claim that the conclusion of the lemma is valid.
Indeed, this results from a straightforward bootstrap procedure: By Step 3, we know that for each $\tau \in (0,T)$, $\nabla \cdot F_1$ belongs to $L^2_{loc}(\mathbb{R}^n \times [\tau, T])$. Therefore, (3.27) in conjunction with parabolic regularity theory ([26]) asserts that u actually lies in $L^2((\tau,T); W^{2,2}_{loc}(\mathbb{R}^n))$. By the Galiardo-Nirenberg inequality, for each fixed ball $B \subset \mathbb{R}^n$, any $p > 2$ such that $(n-2)p < 2n$ and each $q \in [1, \frac{np}{(n-p)_+})$ we can find $c_6 > 0$ such that

$$\int_\tau^T \|u(\cdot,t)\|^p_{W^{1,p}(B)} dt \leqslant c_6 \int_\tau^T \|u(\cdot,t)\|^{pa}_{W^{2,2}(B)} \cdot \|u(\cdot,t)\|^{p(1-a)}_{L^q(B)} dt$$

with $a = \frac{1-\frac{n}{p}+\frac{n}{q}}{2-\frac{n}{2}+\frac{n}{q}} \in (0,1)$. Since $a(q) \to 0$ as $q \nearrow \frac{np}{(n-p)_+}$, we thus conclude from the above and the boundedness of u that $u \in L^p((\tau,T); W^{1,p}_{loc}(\mathbb{R}^n))$ for any such p. Repeating this argument, we eventually obtain that $u \in L^p((\tau,T); W^{2,p}_{loc}(\mathbb{R}^n))$ for all $p \in (1,\infty)$), whereupon parabolic Schauder estimates ([26]) warrant that $u \in C^{1+\gamma, \frac{1+\gamma}{2}}_{loc}(\mathbb{R}^n \times [\tau,T])$ for some $\gamma \in (0,1)$ and hence $\nabla \cdot F_1 + F_2 \in C^{\gamma, \frac{1+\gamma}{2}}_{loc}(\mathbb{R}^n \times [\tau,T])$. Again by parabolic Schauder theory, this finally shows that in fact $u \in C^{2+\gamma', 1+\frac{\gamma'}{2}}_{loc}(\mathbb{R}^n \times [\tau,T])$ for some $\gamma' \in (0,1)$, and that (u,v) solves the first equation in (ECM-ADH) classically in $\mathbb{R}^n \times (\tau,T)$. Since $\tau \in (0,T)$ was arbitrary, the proof is complete. □

Combining Lemma 3.2 with Lemma 3.3, we can now verify our main result on local existence of classical solutions.

Proof of Proposition 2.1. We let T_{max} and (u,v) be as provided by Lemma 3.2, so that (2.9) coincides with (3.5). Moreover, since the mild L^p-solution (u,v) actually is a classical solution of (ECM-ADH) in $\mathbb{R}^n \times (0,T_{max})$ by Lemma 3.3, we may apply the parabolic maximum principle to see that our overall assumptions $f(0)=0$ and $u_0 \geqslant 0$ imply nonnegativity of u. Moreover, as $\rho(u,0)=0$ and $v_0 \geqslant 0$ in $\mathbb{R}^n$, a simple ODE comparison argument yields that also $v \geqslant 0$ in $\mathbb{R}^n \times (0,T_{max})$. □

3.3 Global existence

We proceed to show that if in addition to the above we assume that (2.10), (2.11) and (2.12) hold and that $p<\infty$, then the solution from Proposition 2.1 can in fact be extended for all times. In light of the extensibility criterion (2.9), verifying this reduces to excluding blow-up of $u(\cdot,t)$ with respect to the norm in X_p, and to ruling out blow-up of $v(\cdot,t)$ in the space $L^\infty(\mathbb{R}^n)$. Our method to achieve the former will be based on the following result of a straightforward testing procedure. Here and below, without further mentioning this explicitly we shall always assume (u,v) to be the solution of (ECM-ADH) in $\mathbb{R}^n \times (0,T_{max})$, as constructed in Proposition 2.1.

Lemma 3.4 *Let $q \in (1,\infty)$. Then for each $\zeta \in C_0^\infty(\mathbb{R}^n)$, the solution (u,v) from Proposition 2.1 satisfies*

$$\frac{1}{q}\int_{\mathbb{R}^n}\zeta^2 u^q(\cdot,t) - \frac{1}{r}\int_{\mathbb{R}^n}\zeta^2 u^q(t_0) \tag{3.36}$$

$$\begin{aligned}
&= -(q-1)\int_{t_0}^t\int_{\mathbb{R}^n}\zeta^2 u^{q-2}|\nabla u|^2 - 2\int_{t_0}^t\int_{\mathbb{R}^n}\zeta u^{q-1}\nabla u\cdot\nabla\zeta \\
&\quad +(q-1)\int_{t_0}^t\int_{\mathbb{R}^n}\zeta^2 u^{q-1} I(u,v)\cdot\nabla u + 2\int_{t_0}^t\int_{\mathbb{R}^n}\zeta u^q I(u,v)\cdot\nabla\zeta \\
&\quad +\int_{t_0}^t\int_{\mathbb{R}^n}\zeta^2 u^{q-1} f(u)
\end{aligned} \tag{3.37}$$

for all $t_0 \in [0,T_{max})$ and each $t \in (t_0,T_{max})$.

Proof Since (u,v) is a classical solution of (ECM-ADH) in $\mathbb{R}^n \times (0,T_{max})$ and ζ has compact support, $(0,T_{max}) \ni t \mapsto \int_{\mathbb{R}^n}\zeta^2 u^q(\cdot,t)$ is continuously differentiable with its derivative being computable using integration by parts according to

$$\begin{aligned}
\frac{1}{q}\frac{d}{dt}\int_{\mathbb{R}^n}\zeta^2 u^q &= \int_{\mathbb{R}^n}\zeta^2 u^{q-1}u_t \\
&= -\int_{\mathbb{R}^n}\nabla(\zeta^2 u^{q-1})\cdot\nabla u + \int_{\mathbb{R}^n}\nabla(\zeta^2 u^{q-1})u\cdot I(u,v) + \int_{\mathbb{R}^n}\zeta^2 u^{q-1}f(u)
\end{aligned}$$

for all $t \in (0,T_{max})$. As $\nabla(\zeta^2 u^{q-1}) = (q-1)\zeta^2 u^{q-2}\nabla u + 2\zeta u^{q-1}\nabla\zeta$, a time integration thus yields (3.36). □

In order to appropriately control the integrals in (3.36) stemming from the adhesive interaction in (ECM-ADH), we will again make use of (3.1). Now to specify our choice of ζ in (3.36), let us fix a nonincreasing $\Theta \in C^\infty(\mathbb{R})$ such that $\Theta \equiv 1$ in $(-\infty,0]$, $\Theta \equiv 0$

in $[1,\infty)$ and $|\Theta'| \leqslant 2$ on $\mathbb{R}$, and let

$$\zeta_R(x) := \Theta^2(|x|-R) \qquad \text{for } x \in \mathbb{R}^n \text{ and } R>0, \tag{3.38}$$

so that in particular

$$|\nabla\zeta_R(x)| = \left|2\Theta(|x|-R)\Theta'(|x|-R)\frac{x}{|x|}\right| \leqslant 4\chi_{B_{R+1}\setminus B_R} \qquad \text{for all } x \in \mathbb{R}^n \text{ and } R>0, \tag{3.39}$$

where $B_R := B_R(0)$ for $R > 0$.

Then employing these functions in (3.36) and again making use of Lemma 3.1, in the limit $R \to \infty$ we obtain the following.

Lemma 3.5 *Suppose that (2.10) and (2.11) hold, and that $p < \infty$. Then for each $q \in [p,\infty)$ and any $T > 0$, both $u^{q-2}|\nabla u|^2$ and $u^{q-1}|f(u)|$ belong to $L^1(\mathbb{R}^n \times (0,\widehat{T}))$, and there exists $C(q,T) > 0$ such that*

$$\int_{\mathbb{R}^n} u^q(\cdot,t) \leqslant C(q,T) \qquad \text{for all } t \in (0,\widehat{T}) \tag{3.40}$$

and

$$\int_0^{\widehat{T}}\int_{\mathbb{R}^n} u^{q-2}|\nabla u|^2 \leqslant C(q,T) \tag{3.41}$$

as well as

$$\int_0^{\widehat{T}}\int_{\mathbb{R}^n} u^{q-1}|f(u)| \leqslant C(q,T), \tag{3.42}$$

where $\widehat{T} := \min\{T, T_{max}\}$.

Proof For $R > 0$ we use the function ζ_R from (3.38) in (3.36) with $t_0 := 0$. Then using Young's inequality, on the resulting right-hand side we can estimate

$$-2\int_0^t\int_{\mathbb{R}^n} \zeta_R u^{q-1}\nabla u\cdot\nabla\zeta_R \leqslant \frac{q-1}{2}\int_0^t\int_{\mathbb{R}^n}\zeta_R^2 u^{q-2}|\nabla u|^2 + \frac{2}{q-1}\int_0^t\int_{\mathbb{R}^n} u^q|\nabla\zeta_R|^2, \tag{3.43}$$

whereas by (3.1),

$$2\int_0^t\int_{\mathbb{R}^n}\zeta_R u^q I(u,v)\cdot\nabla\zeta_R \leqslant 2K_I\int_0^t\int_{\mathbb{R}^n} u^q|\nabla\zeta_R| \tag{3.44}$$

for all $t \in (0, T_{max})$. Next, the third integral on the right of (3.36) can be estimated by Young's inequality and (3.1) according to

$$(q-1)\int_0^t\int_{\mathbb{R}^n}\zeta_R^2 u^{q-1} I(u,v)\cdot\nabla u \leqslant \frac{q-1}{4}\int_0^t\int_{\mathbb{R}^n}\zeta_R^2 u^{q-2}|\nabla u|^2 + (q-1)K_I\int_0^t\int_{\mathbb{R}^n}\zeta_R^2 u^q, \tag{3.45}$$

and in the fifth we use (2.10) to find that in

$$\int_0^t\int_{\mathbb{R}^n}\zeta_R^2 u^{q-1} f(u) = \int_0^t\int_{\mathbb{R}^n}\zeta_R^2 u^{q-1} f_+(u) - \int_0^t\int_{\mathbb{R}^n}\zeta_R^2 u^{q-1} f_-(u) \tag{3.46}$$

we have

$$\int_0^t \int_{\mathbb{R}^n} \zeta_R^2 u^{q-1} f_+(u) \leqslant r \int_0^t \int_{\mathbb{R}^n} \zeta_R^2 u^q \tag{3.47}$$

for all $t \in (0, T_{max})$, where we write $f(u) = f_+(u) - f_-(u) = \max(f(u), 0) - \min(f(u), 0)$. Collecting (3.43), (3.44) and (3.45)-(3.47), from (3.36) we altogether obtain

$$\begin{aligned} \frac{1}{q} \int_{\mathbb{R}^n} \zeta_R^2 u^q(\cdot, t) + \frac{q-1}{4} \int_0^t \int_{\mathbb{R}^n} \zeta_R^2 u^{q-2} |\nabla u|^2 + \int_0^t \int_{\mathbb{R}^n} \zeta_R^2 u^{q-1} f_-(u) \\ \leqslant \frac{1}{q} \int_{\mathbb{R}^n} \zeta_R^2 u_0^q + [(q-1)K_I + r] \int_0^t \int_{\mathbb{R}^n} \zeta_R^2 u^q \\ + \frac{2}{q-1} \int_0^t \int_{\mathbb{R}^n} u^q |\nabla \zeta_R|^2 + 2K_I \int_0^t \int_{\mathbb{R}^n} u^q |\nabla \zeta_R| \end{aligned} \tag{3.48}$$

for all $t \in (0, T_{max})$. Here, according to (3.39) and the dominated convergence theorem we have

$$\frac{2}{q-1} \int_0^t \int_{\mathbb{R}^n} u^q |\nabla \zeta_R|^2 \leqslant \frac{8}{q-1} \int_0^t \int_{B_{R+1} \setminus B_R} u^q \to 0 \qquad \text{as } R \to \infty \tag{3.49}$$

and similarly

$$2K_I \int_0^t \int_{\mathbb{R}^n} u^q |\nabla \zeta_R| \leqslant 4K_I \int_0^t \int_{B_{R+1} \setminus B_R} u^q \to 0 \qquad \text{as } R \to \infty, \tag{3.50}$$

for our hypothesis $q \in [p, \infty)$ warrants that $u \in C^0([0, T_{max}); L^q(\mathbb{R}^n))$ and hence $u^q \in L^1(\mathbb{R}^n \times (0, t))$. Since $\int_{\mathbb{R}^n} \zeta_R^2 u^q(\cdot, t) \nearrow \int_\Omega u^q(\cdot, t)$ for $R \to \infty$ by Beppo Levi's theorem, (3.48) therefore in particular implies that

$$\int_\Omega u^q(\cdot, t) \leqslant \int_\Omega u_0^q + q[(q-1)K_I + r] \int_0^t \int_{\mathbb{R}^n} u^q \qquad \text{for all } t \in (0, T_{max}).$$

Again since $[0, T_{max}) \ni t \mapsto \int_\Omega u^q(\cdot, t)$ is continuous, Grønwall's lemma applies to yield

$$\int_{\mathbb{R}^n} u^q(\cdot, t) \leqslant \Big(\int_{\mathbb{R}^n} u_0^q \Big) \cdot e^{q[(q-1)K_I + r] \cdot t} \qquad \text{for all } t \in [0, T_{max}). \tag{3.51}$$

This entails (3.40), whereupon (3.41) and (3.42) result from (3.48) and (3.47) in view of (3.49), (3.50) and Fatou's lemma. □

As a particular consequence of the latter, under the above assumptions we can exclude the possibility that $\|u(\cdot, t)\|_{L^p(\mathbb{R}^n)}$ become unbounded within finite time. For the derivation of a corresponding bound for $\|u(\cdot, t)\|$ with respect to the norm in $L^\infty(\mathbb{R}^n)$, and hence in X_p, a further argument appears to be necessary. To achieve this, we shall first use the integrability properties of Lemma 3.5 to show that for $q \in [p, \infty)$, the functionals $\int_\Omega u^q(\cdot, t)$, known to be continuous by Proposition 2.1, actually are *absolutely* continuous and have the expected derivative a.e. in $(0, T_{max})$. This will afterwards allow us to apply ODE comparison methods in Lemma 3.9 to establish bounds on $\int_{\mathbb{R}^n} u^q(\cdot, t)$ for arbitrarily large $q < \infty$, and eventually for $q \to \infty$ upon a limit procedure.

Lemma 3.6 *Assume that (2.10) and (2.11) hold, and that $p < \infty$. Then for all $q \in$*

$[p,\infty)$, the function $[0,T_{max}) \ni t \mapsto \int_{\mathbb{R}^n} u^q(\cdot,t)$ is absolutely continuous and satisfies

$$\frac{1}{q}\frac{d}{dt}\int_{\mathbb{R}^n} u^q = -(q-1)\int_{\mathbb{R}^n} u^{q-2}|\nabla u|^2 + (q-1)\int_{\mathbb{R}^n} u^{q-1} I\cdot\nabla u + \int_{\mathbb{R}^n} u^{q-1} f(u) \tag{3.52}$$

for a.e. $t \in (0,T_{max})$.

Proof We again take ζ_R as given by (3.38) and may now make use of our knowledge gained in Lemma 3.5: Indeed, whenever $0 \leqslant t_0 < t < T_{max}$, on the right-hand side of (3.36) by the Cauchy-Schwarz inequality we then have

$$\begin{aligned}\Big| -2\int_{t_0}^t\int_{\mathbb{R}^n} \zeta_R u^{q-1}\nabla u\cdot\nabla\zeta_R\Big| &\leqslant 2\Big(\int_0^t\int_{\mathbb{R}^n} u^{q-2}|\nabla u|^2\Big)^{\frac{1}{2}}\cdot\Big(\int_0^t\int_{\mathbb{R}^n} u^q|\nabla\zeta_R|^2\Big)^{\frac{1}{2}}\\ &\leqslant 4\Big(\int_0^t\int_{\mathbb{R}^n} u^{q-2}|\nabla u|^2\Big)^{\frac{1}{2}}\cdot\Big(\int_0^t\int_{B_{R+1}\setminus B_R} u^q\Big)^{\frac{1}{2}}\\ &\to 0 \qquad \text{as } R\to\infty,\end{aligned}$$

because $u^{q-2}|\nabla u|^2 \in L^1(\mathbb{R}^n\times(0,t))$ thanks to Lemma 3.5, and because $u\in C^0([0,t];L^q(\mathbb{R}^n))$. Likewise, once more invoking (3.1) we obtain

$$\Big|2\int_{t_0}^t\int_{\mathbb{R}^n}\zeta_R u^q I(u,v)\cdot\nabla\zeta_R\Big| \leqslant 2K_I\int_0^t\int_{\mathbb{R}^n} u^q|\nabla\zeta_R| \leqslant 4K_I\int_0^t\int_{B_{R+1}\setminus B_R} u^q \to 0$$

as $R\to\infty$. Now by the monotone convergence theorem we have

$$\frac{1}{q}\int_{\mathbb{R}^n}\zeta_R^2 u^q(\cdot,t) - \frac{1}{q}\int_{\mathbb{R}^n}\zeta_R^2 u^q(\cdot,t_0) \to \frac{1}{q}\int_{\mathbb{R}^n} u^q(\cdot,t) - \frac{1}{q}\int_{\mathbb{R}^n} u^q(\cdot,t_0)$$

and

$$-(q-1)\int_{t_0}^t\int_{\mathbb{R}^n}\zeta_R^2 u^{q-2}|\nabla u|^2 \to -(q-1)\int_{t_0}^t\int_{\mathbb{R}^n} u^{q-2}|\nabla u|^2$$

as $R\to\infty$. Furthermore, again using (3.1) we obtain the pointwise majorizations

$$\Big|(q-1)\zeta_R^2 u^{q-1} I(u,v)\cdot\nabla u\Big| \leqslant (q-1)K_I\cdot u^{q-1}|\nabla u| \qquad \text{in } \mathbb{R}^n\times(0,T_{max})$$

and

$$\Big|\zeta_R^2 u^{q-1} f(u)\Big| \leqslant u^{q-1}|f(u)| \qquad \text{in } \mathbb{R}^n\times(0,T_{max})$$

which along with (3.41), (3.42) and the fact that

$$\int_0^t\int_{\mathbb{R}^n} u^{q-1}|\nabla u| \leqslant \Big(\int_0^t\int_{\mathbb{R}^n} u^{q-2}|\nabla u|^2\Big)^{\frac{1}{2}}\cdot\Big(\int_0^t\int_{\mathbb{R}^n} u^q\Big)^{\frac{1}{2}} < \infty$$

yield

$$(q-1)\int_{t_0}^t\int_{\mathbb{R}^n}\zeta_R^2 u^{q-1} I(u,v)\cdot\nabla u \to (q-1)\int_{t_0}^t\int_{\mathbb{R}^n} u^{q-1} I(u,v)\cdot\nabla u$$

and

$$\int_{t_0}^t\int_{\mathbb{R}^n}\zeta_R^2 u^{q-1} f(u) \to \int_{t_0}^t\int_{\mathbb{R}^n} u^{q-1} f(u)$$

as $R \to \infty$ by the dominated convergence theorem. Therefore, (3.36) entails that

$$\frac{1}{q}\int_{\mathbb{R}^n} u^q(\cdot,t) - \frac{1}{q}\int_{\mathbb{R}^n} u^q(\cdot,t_0) = -(q-1)\int_{t_0}^t\int_{\mathbb{R}^n} u^{q-2}|\nabla u|^2$$
$$+(q-1)\int_{t_0}^t\int_{\mathbb{R}^n} u^{q-1} I\cdot\nabla u + \int_{t_0}^t u^{q-1} f(u)$$

for all $t_0 \in [0, T_{max})$ and any $t \in (t_0, T_{max})$, which readily yields the claim. □

For later reference, let us state an elementary lemma on recursively given real sequences which shall be used in Lemma 3.9.

Lemma 3.7 *Let $a_0, a_1, a_2, \ldots$ be nonnegative real numbers satisfying*

$$a_k \leqslant b^k a_{k-1} \qquad \textit{for all } k \geqslant 1$$

with some $b > 0$. Then

$$a_k \leqslant b^{2^{k+1}-k-2} \cdot a_0^{2^k} \qquad \textit{for all } k \geqslant 0.$$

Proof The claimed inequality can be verified by a straightforward induction and we omit the details. □

The next lemma generalizes an elementary ODE comparison result to functions which are merely assumed to be absolutely continuous.

Lemma 3.8 *Let $\psi \in C^0([0,\infty))$ be such that $\psi(s) < 0$ for all $s > s_0$ with some $s_0 > 0$. Then if for some $T > 0$, $y: [0,T] \to \mathbb{R}$ is a nonnegative absolutely continuous function such that*

$$y'(t) \leqslant \psi(y(t)) \qquad \textit{for a.e. } t \in (0,T), \tag{3.53}$$

we necessarily have

$$y(t) \leqslant \max\{y(0), s_0\} \qquad \textit{for all } t \in (0,T), \tag{3.54}$$

Proof We write $c_1 := \max\{y(0), s_0\}$ and let $S_\varepsilon := \{\tilde{T} \in (0,T) \mid y < c_1 + \varepsilon \text{ in } (0,\tilde{T})\}$ for $\varepsilon > 0$. Then clearly S_ε is not empty and hence $t_\varepsilon := \sup S_\varepsilon$ well-defined, and if we had $t_\varepsilon < T$ for some $\varepsilon > 0$, then we could easily check that $y(t_\varepsilon) = c_1 + \varepsilon$, and that there exists $t_0 \in [0, t_\varepsilon)$ such that $y(t) > s_0$ for all $t \in [t_0, t_\varepsilon]$. Therefore, (3.53) would yield

$$y(t_\varepsilon) \leqslant y(t_0) + \int_{t_0}^{t_\varepsilon} \psi(y(t))dt < y(t_0)$$

and thereby contradict the definition of t_ε. This shows that actually $y < c_1 + \varepsilon$ throughout $(0,T)$ for any $\varepsilon > 0$, and thereby proves (3.54). □

We are now in the position to establish a bound for $\|u(\cdot,t)\|_{L^\infty(\mathbb{R}^n)}$ along the lines of the well-known iterative method developed by Moser and Alikakos (cf. [1], for instance).

Lemma 3.9 *Suppose that (2.10) and (2.11) are in force, and that $p < \infty$. Then for all*

$T>0$ one can find $C(T)>0$ such that

$$\|u(\cdot,t)\|_{L^\infty(\mathbb{R}^n)} \leqslant C(T) \qquad \textit{for all } t\in(0,\widehat{T}), \tag{3.55}$$

where $\widehat{T}:=\min\{T,T_{max}\}$.

Proof We fix any $q_0 \geqslant p$ and then apply Lemma 3.5 to find $c_1=c_1(T)>0$ such that

$$\int_{\mathbb{R}^n} u^{q_0}(\cdot,t) \leqslant c_1 \qquad \text{for all } t\in(0,\widehat{T}). \tag{3.56}$$

For nonnegative integers k, we now let $q_k:=2^k q_0$ and

$$M_k := \sup_{t\in(0,\widehat{T})} \int_{\mathbb{R}^n} u^{q_k}(\cdot,t),$$

and observe that all M_k are finite thanks to Lemma 3.5. To derive an upper bound for M_k, we apply Lemma 3.6 to $q:=q_k$ for $k\geqslant 1$ to see that $y(t):=\int_{\mathbb{R}^n} u^q(\cdot,t)$, $t\in[0,\widehat{T}]$, defines an absolutely continuous function which according to (3.52), Lemma 3.1, (2.10) and Young's inequality satisfies

$$\begin{aligned}
\frac{1}{q}y'(t) &= -(q-1)\int_{\mathbb{R}^n} u^{q-2}|\nabla u|^2 + (q-1)\int_{\mathbb{R}^n} u^{q-1} I\cdot\nabla u + \int_{\mathbb{R}^n} u^{q-1} f(u) \\
&\leqslant -\frac{q-1}{2}\int_{\mathbb{R}^n} u^{q-2}|\nabla u|^2 + \frac{q-1}{2}K_I\int_\Omega u^q + r\int_\Omega u^q \\
&= -\frac{2(q-1)}{q^2}\int_\Omega |\nabla u^{\frac{q}{2}}|^2 + \Big(\frac{q-1}{2}K_I + r\Big)\int_\Omega u^q \\
&\leqslant -\frac{1}{q}\int_{\mathbb{R}^n} |\nabla u^{\frac{q}{2}}|^2 + c_1 q\int_\Omega u^q \qquad \text{for a.e. } t\in(0,\widehat{T})
\end{aligned} \tag{3.57}$$

with $c_1 := \frac{K_I+r}{2}$, because $r\leqslant \frac{r}{2}q$ and $\frac{2(q-1)}{q}\geqslant 1$ due to the fact that $q\geqslant q_1\geqslant 2$. Here the Gagliardo-Niremberg inequality provides $c_2>0$ fulfilling

$$\begin{aligned}
\int_\Omega u^q &= \|u^{\frac{q}{2}}\|^2_{L^2(\mathbb{R}^n)} \\
&\leqslant c_2 \|\nabla u^{\frac{q}{2}}\|^{\frac{2n}{n+2}}_{L^2(\mathbb{R}^n)} \cdot \|u^{\frac{q}{2}}\|^{\frac{4}{n+2}}_{L^2(\mathbb{R}^n)} \\
&\leqslant c_2 \Big(\int_{\mathbb{R}^n} |\nabla u^{\frac{q}{2}}|^2\Big)^{\frac{n}{n+2}} \cdot M_{k-1}^{\frac{4}{n+2}} \qquad \text{for a.e. } t\in(0,\widehat{T}),
\end{aligned}$$

which means that

$$\int_{\mathbb{R}^n} |\nabla u^{\frac{q}{2}}|^2 \geqslant c_3 M_{k-1}^{-\frac{4}{n}} \cdot \Big(\int_{\mathbb{R}^n} u^q\Big)^{\frac{n+2}{n}} \qquad \text{for a.e. } t\in(0,\widehat{T})$$

with $c_3 := c_2^{-\frac{n+2}{n}}$. Inserted into (3.57), this shows that

$$y'(t) \leqslant -c_3 M_{k-1}^{-\frac{4}{n}} \cdot y^{\frac{n+2}{n}}(t) + c_1 q^2 y(t) \qquad \text{for a.e. } t\in(0,\widehat{T}),$$

whence Lemma 3.8 applies to yield

$$y(t) \leqslant \max\Big\{y(0)\ ,\ c_4 q^n M_{k-1}^2\Big\} \qquad \text{for all} t\in(0,\widehat{T}),$$

where we have set $c_4 := (\frac{c_1}{c_3})^{\frac{n}{2}}$. Consequently, we obtain the recursive inequality

$$M_k \leqslant \max\Big\{ \int_{\mathbb{R}^n} u_0^{q_k} \ , \ c_4 q_k^n M_{k-1}^2 \Big\} \qquad \text{for all } k \geqslant 1. \tag{3.58}$$

Now in the case when there exists a sequence $(k_j)_{j\in\mathbb{N}} \subset \mathbb{N}$ such that $k_j \to \infty$ as $j \to \infty$ and $M_{k_j} \leqslant \int_{\mathbb{R}^n} u_0^{q_{k_j}}$ for all $j \in \mathbb{N}$, it immediately follows that

$$\|u(\cdot,t)\|_{L^\infty(\mathbb{R}^n)} \leqslant \lim_{j\to\infty} \Big(\int_{\mathbb{R}^n} u_0^{q_{k_j}} \Big)^{\frac{1}{q_{k_j}}} = \|u_0\|_{L^\infty(\mathbb{R}^n)} \qquad \text{for all } t \in (0,\widehat{T}).$$

Otherwise, we can find $k_0 \in \mathbb{N}$ such that $M_k > \int_{\mathbb{R}^n} u_0^{q_k}$ for all $k \geqslant k_0$, whence (3.58) implied that

$$M_k \leqslant c_4 q_k^n M_{k-1}^2 \qquad \text{for all } k \geqslant k_0.$$

By definition of q_k, it is therefore clear that if we pick $b > 1$ sufficiently large, than we obtain

$$M_k \leqslant b^k M_{k-1}^2 \qquad \text{for all } k \geqslant 1.$$

Thus, Lemma 3.7 becomes applicable to guarantee that

$$M_k \leqslant b^{(2^{k+1}-k-2} \cdot M_0^{2^k} \leqslant \Big(b^2 M_0\Big)^{2^k} \qquad \text{for all } k \geqslant 1,$$

which entails that

$$\|u(\cdot,t)\|_{L^\infty(\mathbb{R}^n)} \leqslant \liminf_{k\to\infty} M_k^{\frac{1}{2^k q_0}} \leqslant b^{\frac{2}{q_0}} M_0^{\frac{1}{q_0}} = b^{\frac{2}{q_0}} c_1$$

according to (3.56). □

With the above bound for u at hand, without any further difficulty we can now show that under the growth assumption (2.12), also $\|v(\cdot,t)\|_{L^\infty(\mathbb{R}^n)}$ cannot explode after finite time.

Lemma 3.10 *Assume that (2.10), (2.11) and (2.12) hold, and suppose that $p < \infty$. Then for all $T > 0$ there exists $C(T) > 0$ with the property that*

$$\|v(\cdot,t)\|_{L^\infty(\mathbb{R}^n)} \leqslant C(T) \qquad \textit{for all } t \in (0,\widehat{T}), \tag{3.59}$$

where $\widehat{T} = \min\{T, T_{max}\}$.

Proof Since (2.10) and (2.11) are valid, we can invoke Lemma 3.9 to find $R(T) > 0$ fulfilling

$$|u(x,t)| \leqslant R(T) \qquad \text{for all } x \in \mathbb{R}^n \text{ and } t \in (0,\widehat{T}).$$

Therefore, (2.12) asserts that

$$v_t = \rho(u,v) \leqslant A(R(T))v \qquad \text{for all } x \in \mathbb{R}^n \text{ and } t \in (0,\widehat{T}),$$

which upon integration yields

$$v(x,t) \leqslant v_0(x) \cdot e^{A(R(T))\cdot t} \qquad \text{for all } x \in \mathbb{R}^n \text{ and } t \in (0,\widehat{T}).$$

Since v is nonnegative by Proposition 2.1, this implies (3.59). $\square$

Our main result on global solvability of (ECM-ADH) now follows immediately:

PROOF of Theorem 2.2. We only need to combine Lemma 3.5, Lemma 3.9 and Lemma 3.10 and apply the extensibility criterion (2.9) in Proposition 2.1. $\square$

3.4 An explicit upper bound

Now the previously gained knowledge about regularity and decay of solutions can be used in a straightforward manner to develop a comparison-type technique for the proof of our main result on boundedness of solutions.

PROOF of Theorem 2.3. For $R > 0$, we let ζ_R be as introduced in (3.38). Moreover, we fix a nondecreasing $\widetilde{\Theta} \in C^\infty(\mathbb{R})$ such that $\widetilde{\Theta} \equiv 0$ in $(-\infty, 0]$ and $\widetilde{\Theta} \equiv 1$ in $[1, \infty)$, and let

$$\psi_\delta(s) := \int_0^s \widetilde{\Theta}\Big(\frac{\sigma}{\delta}\Big) d\sigma, \qquad s \geqslant 0,$$

for $\delta \in (0,1)$. Then assuming without loss of generality that $p > 1$, we multiply the first equation in (ECM-ADH) by $\zeta_R^2(x) \cdot {\psi_\delta}^{p-1}(u-b)\psi_\delta'(u-b)$ for

$$b := \max\Big\{ \|u_0\|_{L^\infty(\mathbb{R}^n)} \ , \ a + \frac{A}{r} \Big\}, \qquad A := \|h\|_{L^\infty(\mathbb{R}^n)} \cdot \|\nabla \cdot \omega\|_{L^1(V)}, \tag{3.60}$$

and integrate by parts to obtain

$$\begin{aligned}
\frac{1}{p}\frac{d}{dt}\int_{\mathbb{R}^n} \zeta_R^2 \psi_\delta^p(u-b) &= \int_{\mathbb{R}^n} \zeta_R^2 \psi_\delta^{p-1}(u-b)\psi_\delta'(u-b) u_t \\
&= -\int_{\mathbb{R}^n} \nabla u \cdot \nabla\Big(\zeta_R^2 \psi_\delta^{p-1}(u-b)\psi_\delta'(u-b)\Big) \\
&\quad - \int_{\mathbb{R}^n} \nabla \cdot \Big(uI(u,v)\Big) \zeta_R^2 \psi_\delta^{p-1}(u-b)\psi_\delta'(u-b) \\
&\quad - \int_{\mathbb{R}^n} f(u) \zeta_R^2 \psi_\delta^{p-1}(u-b)\psi_\delta'(u-b) \\
&= -(p-1)\int_{\mathbb{R}^n} \zeta_R^2 \psi_\delta^{p-2}(u-b)\psi_\delta'^2(u-b)|\nabla u|^2 \\
&\quad - \int_{\mathbb{R}^n} \zeta_R^2 \psi_\delta^{p-1}(u-b)\psi_\delta''(u-b)|\nabla u|^2 \\
&\quad -2\int_{\mathbb{R}^n} \zeta_R \psi_\delta^{p-1}(u-b)\psi_\delta'(u-b)\nabla u \cdot \nabla \zeta_R \\
&\quad - \int_{\mathbb{R}^n} \zeta_R^2 \psi_\delta^{p-1}(u-b)\psi_\delta'(u-b) I(u,v) \cdot \nabla u \\
&\quad - \int_{\mathbb{R}^n} \zeta_R^2 \psi_\delta^{p-1}(u-b)\psi_\delta'(u-b) u \nabla \cdot I(u,v) \\
&\quad - \int_{\mathbb{R}^n} \zeta_R^2 \psi_\delta^{p-1}(u-b)\psi_\delta'(u-b) f(u) \qquad \text{for all } t > 0.
\end{aligned} \tag{3.61}$$

Here since $\widetilde{\Theta}$ is nondecreasing, we have $\psi_\delta''(u-b) \geqslant 0$ and hence

$$-\int_{\mathbb{R}^n} \zeta_R^2 \psi_\delta^{p-1}(u-b)\psi_\delta''(u-b)|\nabla u|^2 \leqslant 0 \qquad \text{for all } t>0, \tag{3.62}$$

whereas by Young's inequality we obtain

$$-2\int_{\mathbb{R}^n} \zeta_R \psi_\delta^{p-1}(u-b)\psi_\delta'(u-b)\nabla u\cdot\nabla\zeta_R \leqslant \frac{p-1}{2}\int_{\mathbb{R}^n} \zeta_R^2\psi_\delta^{p-2}(u-b)\psi_\delta'^2(u-b)|\nabla u|^2 + \frac{2}{p-1}\int_{\mathbb{R}^n}|\nabla\zeta_R|^2\psi_\delta^p(u-b) \tag{3.63}$$

for all $t>0$. Furthermore, according to (2.11) we can use Lemma 3.1, which combined with Young's inequality shows that for all $t>0$,

$$\begin{aligned}-\int_{\mathbb{R}^n} \zeta_R^2\psi_\delta^{p-1}(u-b)\psi_\delta'(u-b)I(u,v)\cdot\nabla u &\leqslant \frac{p-1}{2}\int_{\mathbb{R}^n}\zeta_R^2\psi_\delta^{p-2}(u-b)\psi_\delta'^2(u-b)|\nabla u|^2\\ &\quad+\frac{1}{2(p-1)}\int_{\mathbb{R}^n}\zeta_R^2\psi_\delta^p(u-b)|I(u,v)|^2\\ &\leqslant \frac{p-1}{2}\int_{\mathbb{R}^n}\zeta_R^2\psi_\delta^{p-2}(u-b)\psi_\delta'^2(u-b)|\nabla u|^2\\ &\quad+\frac{K_I^2}{2(p-1)}\int_{\mathbb{R}^n}\zeta_R^2\psi_\delta^p(u-b).\end{aligned} \tag{3.64}$$

Now in order to cope with the second last integral in (3.61), we first use the specific structure if I along with (2.14): Indeed, in the case $h \geqslant 0$, in which (2.14) requires $\omega\cdot\nu \geqslant 0$ on ∂V, we can integrate by parts to infer that

$$\begin{aligned}\nabla\cdot I(u,v)(x,t) &= \int_V \nabla_x h\Big(u(x+\xi,t),v(x+\xi,t)\Big)\cdot\omega(\xi)d\xi\\ &= \int_V \nabla_\xi h\Big(u(x+\xi,t),v(x+\xi,t)\Big)\cdot\omega(\xi)d\xi\\ &= \int_V h\Big(u(x+\xi,t),v(x+\xi,t)\Big)\nabla\cdot\omega(\xi)d\xi\\ &\quad+\int_{\partial V} h\Big(u(x+\xi,t),v(x+\xi,t)\Big)\omega(\xi)\cdot\nu(\xi)ds(\xi)\\ &\geqslant \int_V h\Big(u(x+\xi,t),v(x+\xi,t)\Big)\nabla\cdot\omega(\xi)d\xi \qquad \text{for all } x\in\mathbb{R}^n \text{ and } t>0.\end{aligned}$$

Since this conclusion remains valid if h is not necessarily nonnegative but instead $\omega\cdot\nu = 0$ a.e. on ∂V, (2.11) and the first hypothesis in (2.14) allow us to estimate

$$\nabla\cdot I(u,v) \geqslant -\|h\|_{L^\infty(\mathbb{R}^2)}\cdot\|\nabla\cdot\omega\|_{L^1(V)} = -A \qquad \text{in } \mathbb{R}^n\times(0,\infty),$$

so that

$$-\int_{\mathbb{R}^n}\zeta_R^2\psi_\delta^{p-1}(u-b)\psi_\delta'(u-b)u\nabla\cdot I(u,v) \leqslant A\int_{\mathbb{R}^n}\zeta_R^2\psi_\delta^{p-1}(u-b)\psi_\delta'(u-b)\cdot u \qquad \text{for all } t>0, \tag{3.65}$$

because $\psi_\delta' \geqslant 0$. The latter term can be compensated by means of (2.15), which namely ensures that

$$-\int_{\mathbb{R}^n} \zeta_R^2 \psi_\delta^{p-1}(u-b)\psi_\delta'(u-b)f(u) = -r\int_{\mathbb{R}^n} \zeta_R^2 \psi_\delta^{p-1}(u-b)\psi_\delta'(u-b)u(u-a)$$
$$\leqslant -r(b-a)\int_{\mathbb{R}^n} \zeta_R^2 \psi_\delta^{p-1}(u-b)\psi_\delta'(u-b)\cdot u \quad (3.66)$$

for all $t > 0$, for at each point where $\psi_\delta(u-b) \neq 0$ we have $u > b$ and hence $u-a > b-a$. When inserted into (3.61), upon a time integration (3.62)-(3.66) yield

$$\begin{aligned}\frac{1}{p}\int_{\mathbb{R}^n} \zeta_R^2 \psi_\delta^p(u(\cdot,t)-b) &\leqslant \frac{2}{p-1}\int_0^t\int_{\mathbb{R}^n} |\nabla\zeta_R|^2\psi_\delta^p(u-b)\\ &\quad + \frac{K_I^2}{2(p-1)}\int_0^t\int_{\mathbb{R}^n}\zeta_R^2\psi_\delta^p(u-b)\\ &\quad + \Big[A - r(b-a)\Big]\cdot\int_0^t\int_{\mathbb{R}^n}\zeta_R^2\psi_\delta^{p-1}(u-b)\psi_\delta'(u-b)\cdot u\\ &\leqslant \frac{2}{p-1}\int_0^t\int_{\mathbb{R}^n} |\nabla\zeta_R|^2\psi_\delta^p(u-b)\\ &\quad + \frac{K_I^2}{2(p-1)}\int_0^t\int_{\mathbb{R}^n}\zeta_R^2\psi_\delta^p(u-b) \qquad \text{for all } t>0, \qquad (3.67)\end{aligned}$$

where we have used that $\psi_\delta(u_0 - b) \equiv 0$ in $\mathbb{R}^n$ thanks to the fact that $u_0 \leqslant b$ in $\mathbb{R}^n$ and, again, that $\psi_\delta \equiv 0$ in $[0, b]$. Here since $|\nabla\zeta_R| \leqslant 2$, and since $\widetilde{\Theta} \leqslant 1$ on $\mathbb{R}$ and thus $\psi_\delta(s-b) \leqslant (s-b)_+ \leqslant s$ for all $s \geqslant 0$, we can estimate

$$\frac{2}{p-1}\int_0^t\int_{\mathbb{R}^n} |\nabla\zeta_R|^2\psi_\delta^p(u-b) \leqslant \frac{8}{p-1}\int_0^t\int_{B_{R+1}\setminus B_R} u^p \to 0 \qquad \text{as } R\to\infty$$

by the dominated convergence theorem, because $u \in C^0([0,\infty); L^p(\mathbb{R}^n))$. Using that for all $x \in \mathbb{R}^n$ we have $\zeta_R(x) \nearrow 1$ as $R \to \infty$, by Beppo Levi's theorem from (3.67) we hence obtain the inequality

$$\frac{1}{p}\int_{\mathbb{R}^n}\psi_\delta^p(u(\cdot,t)-b) \leqslant \frac{K_I^2}{2(p-1)}\int_0^t\int_{\mathbb{R}^n}\psi_\delta^p(u-b) \qquad \text{for all } t>0,$$

so that the Grönwall lemma guarantees that $\psi_\delta(u-b) \equiv 0$ in $\mathbb{R}^n \times (0,\infty)$. Since for all $s > 0$ we have $\psi_\delta(s) \nearrow (s-b)_+$ as $\delta \searrow 0$, this ensures that $(u-b)_+ \equiv 0$ and thus $u \leqslant b$ in $\mathbb{R}^n \times (0,\infty)$, as claimed. □

4 Numerical examples

In this section we perform a sequence of numerical experiments of models (ADH), (ECM-ADH) and (MMP-ADH). Our principal objective is to test the validity of our boundedness and existence results, yet we also explore scenarios outside the present theory to determine whether similar results may hold. For numerical convenience we primarily concentrate on the one-dimensional interval $[0, L]$, however a set of investigations are also presented for the two-dimensional square domain $[0, L] \times [0, L]$. The numerical simulations follow the methodology described in [15, 17]. Note that, to limit the impact from boundaries, throughout this section we impose periodic boundary conditions: we wrap the domain onto a circle (for 1D) or torus (for 2D).

4.1 The basic adhesion model

We begin with the basic adhesion model (ADH). Initially we consider either (I1) a Gaussian centred in the domain (representing a "loose" cell cluster), or (I2) a small perturbation from a spatially uniform cell distribution. We consider the following *standard set* of functional forms, chosen as they both satisfy our theory's requirements and have been employed in previous modelling studies:

$$f(u) = ru(1 - u/U)\,; \quad h(u) = \alpha u \max\{1 - u/K, 0\}\,; \quad \Omega(|\xi|) = H(R - |\xi|)/R\,. \quad (4.1)$$

In this example $h(u)$ is not C^2, and hence we consider the mollification of h on a small scale. The global estimates in Theorem 2.3 depend on the L^∞-norm of h only, which is unchanged by mollification. The cell kinetics $f(u)$ are of logistic type, for growth parameter $r > 0$ and "carrying capacity" U. As we recall, $h(u)$ describes the adhesive pull from neighbouring cells: the choice above describes an increase at lower cell densities, since more cells will lead to a greater degree of adhesive binding, and subsequent decrease to zero, for example due to an impact from volume exclusion; α and K respectively describe the adhesive strength and "crowding capacity" parameters. The function $\Omega(|\xi|)$ defines how the adhesive pull varies with the distance between cells: this is defined in terms of the Heaviside function $H(\cdot)$ and (for simplicity) is constant (and normalised) within the sensing region, and zero outside.

4.1.1 *Standard set simulations*

Figure 1 plots the evolving cell density profiles in one-dimension for simulations of (ADH) under (4.1), as three key parameters are altered: the adhesive strength α, the growth rate r and the crowding capacity K. Note that the simulations here employ initial conditions of form (I1) and set $L = 20$, although simulations under (I2) display similar behaviour. Note further that for simulations we employ a convenient, but arbitrary, parameter set rather than formally estimating values according to biochemical data: the primary objective here is to numerically illustrate the theory rather than perform a detailed study relevant to a specific cellular context.

In all simulations we observe the formation of smooth and bounded solutions. Further, when compared with Theorem 2.3, we find that solutions globally lie below the explicit bounds of (2.18). Note that simulations cover scenarios where spiked cell aggregates develop and where solutions evolve to a uniform steady state; in the latter, adhesion is insufficient to overcome stabilising processes, such as diffusion. We further note that final plots do not necessarily represent long-term steady state solutions, yet simulations performed over longer time intervals continue to generate smooth and bounded solutions.

We extend our numerical analysis to two-dimensions. Simulations in two dimensions become significantly more demanding, particularly given the fine discretisation necessary for accurate computations, and we therefore restrict to a few illustrative cases. Figure

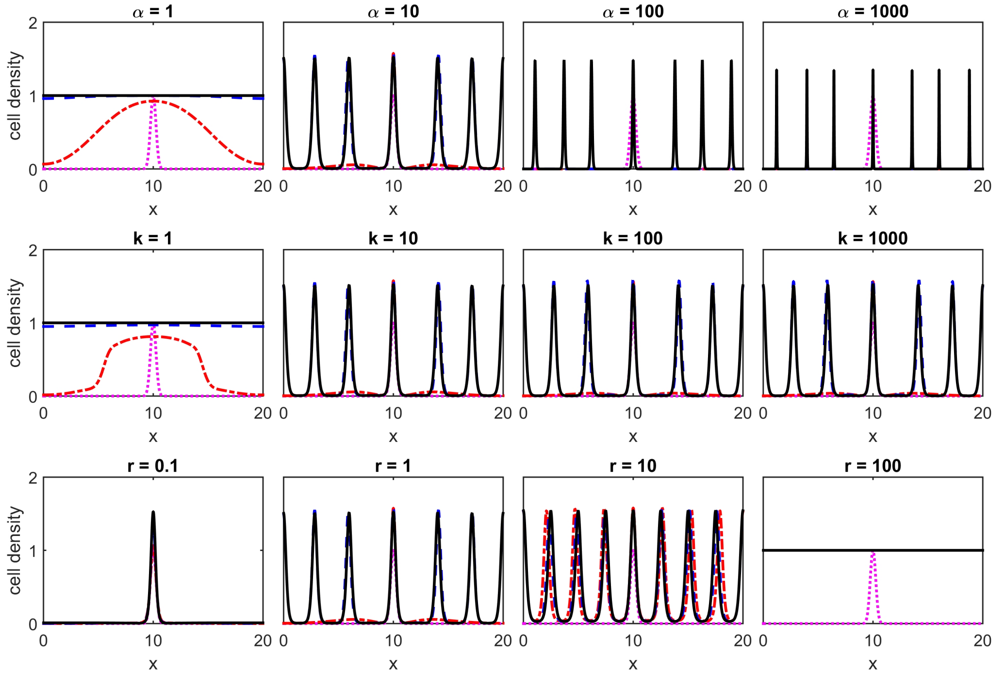

Figure 1. Simulations of the basic adhesion model (ADH) under function set (4.1). In each plot we show the cell density profile at times: $t = 0$, (magenta dotted); $t = 5$, (red dot-dashed); $t = 10$ (blue dashed); $t = 20$ (black solid). For each sequence of simulations we fix $D = R = U = 1$, $L = 20$ and: (Top row) set $K = 10$, $r = 1$ and vary α as stated; (Middle row) set $\alpha = 10$, $r = 1$ and vary K; (Bottom row) set $\alpha = 10$, $K = 10$ and vary r. Simulations performed on a uniform mesh of lattice spacing $\Delta x = 0.01$.

2 shows numerical solutions of (ADH) under (4.1) for the two-dimensional domain of dimensions 20×20. Clearly, the dimensionless nature of the theory holds: we observe smooth and bounded solutions, here forming separated cell aggregates.

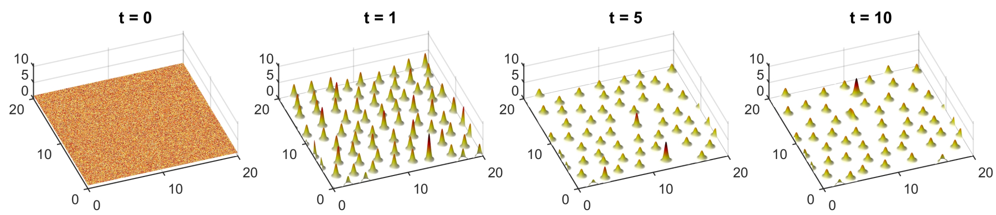

Figure 2. Simulations of the basic adhesion model (ADH) under function set (4.1) in two dimensions. Plots from left to right show two-dimensional cell density profile at times $t = 0, 1, 5, 10$. For these simulations we fix $D = R = r = U = 1$, $K = \alpha = 10$. Simulations performed on a uniform mesh of lattice spacing $\Delta x = \Delta y = 0.04$.

4.1.2 *Alternative functional forms*

Founding a rigorous theory inevitably requires some underlying set of assumptions: the set (4.1), which falls under our more general requirements, is relevant with regards to certain previous applications, yet other applications and/or theoretical studies may demand choices not covered by the current theory. We therefore consider some expository studies for functional choices lying outside the present theory: specifically, we explore whether existence and boundedness properties can be expected to hold as certain limiting effects are relaxed.

In particular, we remark on two "aggregation-limiting" effects included through our functional choices: (i) the boundedness to adhesive pull as the cell density increases; (ii) the dominating cell death at high cell densities due to logistic growth. We first revisit $h(u)$. It is natural to expect boundedness for this function: adhesive pull will inevitably be limited by, amongst other factors, the number of potential adhesive binding sites or mechanical considerations. Yet, unbounded forms can sometimes offer an ideal choice in theoretical studies. We therefore consider solutions for non-bounded forms of $h(u)$: the convenient linear form $h(u) = \alpha u$ and a theoretically-motivated, superlinear "über-adhesion" form $h(u) = \alpha u^2$; the latter is chosen to test boundedness under extreme functional forms.

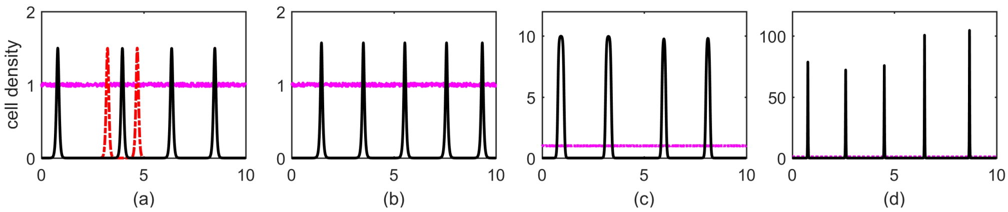

Figure 3. Simulations of the basic adhesion model (ADH) under alternative function sets. We consider the function set (4.1) with one or more functions altered as follows: (a) $h(u) = \alpha u$, (b) $h(u) = \alpha u^2$, (c) $f(u) = 0$, (d) $h(u) = \alpha u$, $f(u) = 0$. In each plot we show the cell density profile at times $t = 0$ (magenta dotted), $t = 5$ (red dot-dashed), $t = 10$ (blue dashed) and $t = 20$ (black solid). For each simulation we fix $D = R = 1$, $L = 10$, $\alpha = 100$ and, where relevant, $r = U = 1$ and $K = 10$. Simulations performed on a uniform mesh of lattice spacing $\Delta x = 0.01$. Note that simulations of (d) remain essentially the same under a finer mesh discretisation ($\Delta x = 0.0025$), suggesting the sharp peaks are not a numerical artifact.

Figure 3 (a–b) shows solutions of (ADH) for $f(u)$ and $\Omega(|\xi|)$ as given by (4.1) and (a) $h(u) = \alpha u$, (b) $h(u) = \alpha u^2$. Clearly, for either case we continue to observe smooth and bounded solutions: note that initial conditions here are of the form (I2), although solutions under (I1) show similar properties.

We next consider the cell growth function $f(u)$. While logistic growth presents a classic choice, utilised in applications ranging from microbiology to cancer growth, it may be less relevant for other instances: particularly, those where cell growth/death is assumed to be negligible. In Figure 3 (c) we show solutions to (ADH) under functions (4.1), but with $r = 0$ to cater for a negligible cell growth/death scenario. Once again, we continue to observe smooth and bounded solutions.

Finally we investigate both unbounded adhesive pull and negligible growth: i.e. we relax both aggregation-limiting processes simultaneously. Figure 2 (d) shows solutions for $h(u) = \alpha u$, $f(u) = 0$ and Ω as before. Aggregates are notably "spikier" in nature, yet continue to appear smooth and bounded. Overall our results hint that the theory can potentially be extended to encompass a wider class of base functional forms. Note that the displayed simulations have not altered the choice of Ω: our general theory already permits a wide class for Ω and simulations under different forms (e.g. exponentially decaying) confirm this (data not shown).

4.2 Cancer invasion models

Our theory applies to the cancer invasion model (ECM-ADH), while earlier results of Chaplain and others [9] cover the extended cancer invasion model that explicitly accounts for protease dynamics, (MMP-ADH). We perform some simulations to illustrate the boundedness properties of these models. For both models we set $f(u)$ and $\Omega(|\xi|)$ as in (4.1), along with

$$h(u,v) = (\alpha u + \beta v)\max\{1 - (u+v)/K, 0\}\ , \quad \rho(u,v) = -\gamma u v^2\,,$$

for (ECM-ADH), or

$$h(u,v) = (\alpha u + \beta v)\max\{1 - (u+v)/K, 0\}\ , \quad \rho(v,m) = -\gamma v m\,, \quad g(v) = \phi v\,,$$

for model (MMP-ADH). In the above, α and β are the cell-cell and cell-matrix adhesion strength parameters while K is the crowding capacity, γ is a matrix degradation rate parameter and ϕ is a MMP production rate parameter. For the simulations we set $D = R = \rho = \gamma = U = 1, K = 10$ and, for model (MMP-ADH), $D_m = \lambda = \phi = 1$. We consider two parameter sets $(\alpha, \beta) = (1, 10)$ and $(10, 1)$, representing (weak-strong) and (strong-weak) cell-cell/cell-matrix couplings. Simulations are performed on a one-dimensional domain of length $L = 100$ with periodic boundary conditions. Initially we deposit a population of tumour cells centrally according to a Gaussian, set $v(x, 0) = 1$ and $m(x, 0) = 0$.

Figure 4 illustrates typical simulations. For both parameter sets and both models we observe well-behaved and bounded solutions. Weak/strong cell-cell/cell-matrix adhesion profiles generates a faster-moving invasion front which degrades the ECM and leaves a uniform cell density profile in its wake, while strong/weak profiles generate spiked cell aggregates behind the wave due to the strong cell-cell adhesion.

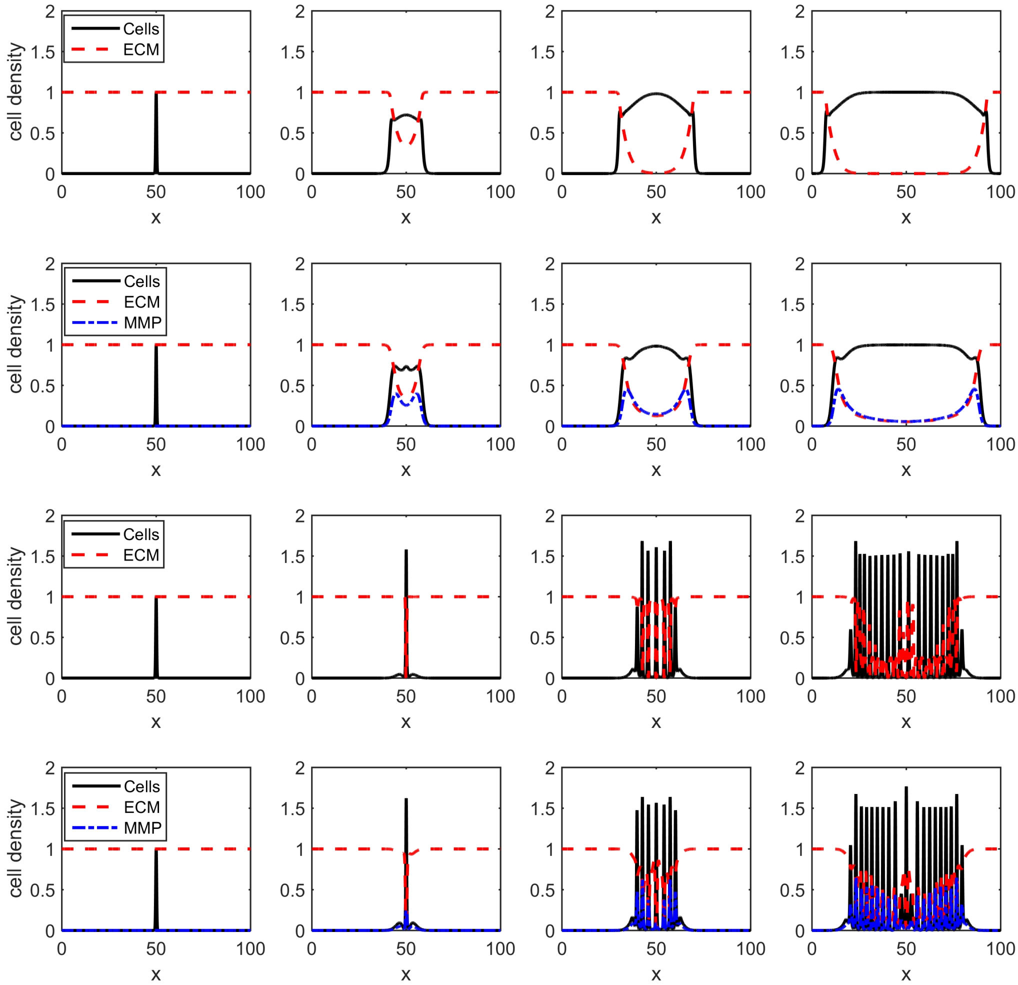

Figure 4. Simulations of the cancer invasion models (ECM-ADH) and (MMP-ADH). In each row, subplots from left to right represent profiles at $t = 0, 5, 10$ and 20. (Top row) ECM model (ECM-ADH) for $\alpha = 1$ and $\beta = 10$. (Second row) MMP-ECM model (ECM-ADH) for $\alpha = 1$ and $\beta = 10$. (Third row) ECM model (ECM-ADH) for $\alpha = 10$ and $\beta = 10$. (Fourth row) MMP-ECM model (ECM-ADH) for $\alpha = 10$ and $\beta = 10$. Other parameters are $D = R = 1$. Simulations performed on a uniform mesh of lattice spacing $\Delta x = 0.02$.

5 Conclusions

Viewed from the perspective of applications, it is always questioned whether pages of existence proofs on a model that has appeared to be successful in applications represents a fruitful endeavour. What can be gained by a uniform bound in terms of $|\nabla \cdot \omega|$, when model (ADH) (and its extensions) has already been successfully applied to describe cell clustering and sorting, or models (ECM-ADH) and (MMP-ADH) have been shown to recapitulate certain cancer invasion profiles?

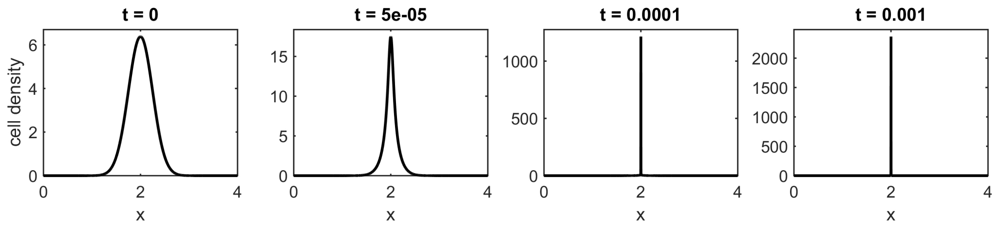

Figure 5. Ambiguous blow-up/boundedness in the adhesion model. We simulate (ECM-ADH) subject to (4.1) with parameters $D = R = 1$, $\alpha = 1000$, $r = 0.001$ and $U = 100$, $K = 10000$. In this case, the uniform upper bound in (2.18) is 2,500,000. Solutions shown at times indicated, with an initial Gaussian distribution centred in the domain of length 4.

Such questions are important to raise, and for a response consider the simulation shown in Figure 5: this simulation is based on functions that satisfy our theory, yet the exact parameters have been chosen in a (purposefully) naive manner. How confident of boundedness would we be based on this simulation, where the mass appears to rapidly accumulate at a single point? Numerical simulations on their own can be ambiguous, but when accompanied by a rigorous theory that ensures solutions remain well-behaved a more confident set of conclusions can be drawn.

Moreover, while the adhesion model represents a relatively new and successful framework for modelling cell interactions, it also initiates new mathematics. Non-local models with integral terms appearing inside the derivative have yet to be studied systematically, and novel methods will be required to deal with the corresponding integral terms and their derivatives. Non-local adhesion models generate a wide variety of interesting phenomena, ranging from spatio-temporal pattern formation to travelling wave dynamics. Our theory, combined with the work of Chaplain et al. [9] ensures that the models discussed here are well defined and give biologically relevant solutions, opening the door for more application oriented analysis. We remark that while the upper estimate provided in Theorem 2.3 may be large compared to those observed numerically, it covers an infinitely broad spectrum of specific scenarios that would be impossible to cover numerically. Further, it provides an important starting point for future analyses.

The adhesion model studied here shares similarities with other well-known PDE models for biological pattern formation: namely, chemotaxis models [21, 19, 5]). Simple chemotaxis models are well-known for their subtle blow-up/global existence properties: while simple models can exhibit blow-up, a fairly subtle modification can lead to regular solutions [19]. Hillen *et al,* [20] considered a non-local chemotaxis model, assuming a cell measures the chemical concentration around its perimeter and hence replacing the local chemical gradient with the *non-local gradient*:

$$\overset{\circ}{\nabla}_R\, h(u) = \frac{n}{|\mathbb{S}^{n-1}|R} \int_{\mathbb{S}^{n-1}} \xi h(u(x + R\xi)) d\xi.$$

It was shown in [20] that including the finite sampling radius immediately regularises the chemotaxis equation: where the local gradient model exhibits finite-time blow up, the non-local gradient model allows global classical solutions (see also [19]). Further steady states of the non-local chemotaxis model were recently analysed by Xiang in [40], who show non-constant positive steady states existing for small cell diffusion, large chemotactic sensitivity and small sampling radius.

The ambiguity surrounding well-defined or undefined solutions in non-local models can be illustrated as follows. In Hillen [18] it was shown that for small R the non-local gradient has the following expansion

$$\overset{\circ}{\nabla}_R\, h(u) = \nabla h(u) + \frac{R^2}{2(2+n)} \nabla\Delta h(u) + O(R^4)\,.$$

If we use $h(u) = \alpha u$, such that the attraction of cells to a point increases linearly with the density of cells at that position (where α is an adhesive strength parameter), then to leading order we have a local gradient of u and we obtain

$$u_t = D\Delta u - \nabla(\alpha u \nabla u) = (D - \alpha u)\Delta u - |\nabla u|^2. \tag{5.1}$$

Clearly, if $\alpha u > D$ then this model shows backward diffusion, which is undefined, and hence does not form a useful model: we expect instantaneous blow-up. However, if the next order terms in the expansion are considered, then we observe fourth-order countering effect, and the question arises as to whether these can act to provide a regularising element. In fact, as we have shown, the non-local adhesion model for $R > 0$ is well defined but our global bound can diverge to $+\infty$ as the sampling radius R converges to 0, which corresponds to (5.1).

Here we considered adhesion models in the full space $\mathbb{R}^n$. Modelling adhesion in bounded domains will require further considerations, since the non-local term $I(u, v)$ will extend outside the domain sufficiently close to the boundary. That is, particles will interact with the boundary and a detailed modelling of the adhesive binding of cells to the physical domain boundary is required (see Buttenschoen [7]). The case of periodic boundary conditions is easier, since integrals can simply be extended periodically. In that case our general existence and uniqueness results in Proposition 2.1 and Corollary 2.4 remain valid for the choice of $p = \infty$. However, global bounds in Theorem 2.3 and Corollary 2.4 do not directly apply for $p = \infty$ and new L^∞-estimates need to be derived. Other boundary conditions would require treatment on a case by case basis according to the relevant boundary conditions for a particular biological application.

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