

Existence and uniqueness of global classical solutions to a two dimensional two species cancer invasion haptotaxis model

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Abstract

We consider a haptotaxis cancer invasion model that includes two families of cancer cells. Both families, migrate on the extracellular matrix and proliferate. Moreover the model describes an epithelial-to-mesenchymal-like transition between the two families, as well as a degradation and a self-reconstruction process of the extracellular matrix.

We prove in two dimensional space positivity and conditional global existence and uniqueness of the classical solutions of the problem for large initial data.

1 Introduction

Cancer research is a multidisciplinary effort to understand the causes of cancer and to develop strategies for its diagnosis and treatment. The involved disciplines include the medical science, biology, chemistry, physics, informatics, and mathematics. From a mathematical point of view, the study of cancer has been an active research field since the 1950s and addresses different biochemical processes relevant to the development of the disease, see e.g. [34, 4, 47, 28, 37].

In particular, a large amount of the research focuses on the modelling of the *invasion* of the *Extracellular Matrix* (ECM); the first step in *cancer metastasis* and one of the *hallmarks of cancer*, [13, 33, 7, 32]. The invasion of the ECM involves also a secondary family of cancer cells that is more resilient to cancer therapies. These cells are believed to possess *stem cell-like* properties, such as self-renewal and differentiation, as well as the ability to metastasize, i.e. detach from the primary tumour, afflict secondary sites within the organism and engender new tumours [6, 19]. These cells are termed *Cancer Stem Cells* (CSCs) and originate partly from the more usual *Differentiated Cancer Cells* (DCCs) via a cellular differentiation program that is related to another cellular differentiation program found also in normal tissue, the *Epithelial-Mesenchymal Transition* (EMT) [26, 12]; see also [36] for a discussion on the relation between “Stem cells, cancer, and cancer stem cells”.

Both types of cancer cells invade the ECM and while doing so, affect its architecture, composition, and functionality. One of the methods they use, is to secrete *matrix metalloproteinases* (MMPs), i.e. enzymes that degrade the ECM and allow for the cancer cells to move through it more freely, [11, 10].

During the EMT and the subsequent invasion of the ECM, *chemotaxis*¹, and *haptotaxis*², play funda-

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¹cellular movement under the influence of one or more chemical stimuli

²cellular movement along gradients of cellular adhesion sites or ECM bound chemoattractants

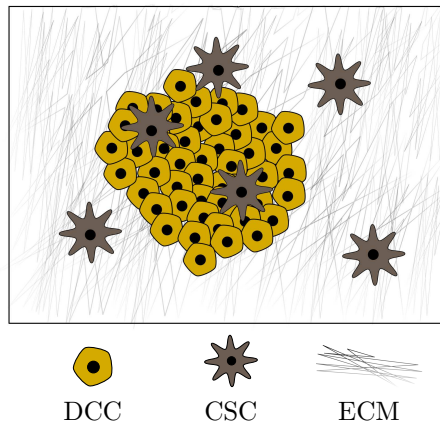


Figure 1: *Graphical description on the model (1.1). The more aggressive CSCs escape the main body of the tumour and invade the ECM faster than the DCCs. At the same time, cancer secreted MMPs degrade the ECM.*

mental roles [38, 35]. These processes are typically described using macroscopic deterministic models with the densities of the participating components as their primal variables. These models follow the path laid in [31, 20] (and later (re-)derived using a many particle system approach in [40]) to describe the chemotactic movement and aggregation of *Dictyostelium discoideum* bacteria. When accounting for chemotaxis, these models are called Keller-Segel (KS) or KS-type systems. They are known to potentially lead to blow-up of solutions (depending on the spatial dimension and the initial mass) in finite time and their analysis has been a field of intensive research, e.g. [5, 9].

In a similar spirit, KS-like models have been used to model cancer invasion while taking into account chemotaxis, haptotaxis, and other processes important in development of cancer, see e.g. [3, 43]. Although these models are simplifications of the biochemical reality of the tumour, their solutions display complex dynamics and their mathematical analysis is challenging. We refer indicatively to some relevant results on the analysis of these models. It is by far not an exhaustive list of the topic, rather an insight to analytical approaches for similar models.

In [27] a single family of cancer cells is considered. The model is haptotaxis with cell proliferation, matrix degradation by the MMPs, without matrix remodelling. In this work global existence of weak solutions is proven. In addition, the solutions are shown to be uniformly bounded using the method of “bounded invariant rectangles”, which can be applied once the model is reformulated in divergence form using a particular change of variables.

In [45] the author considers a haptotaxis model with one type of cancer cells, which accounts for self-remodelling of the ECM, and ECM degradation by MMPs. With respect to the MMPs, the model is parabolic. The decoupling between the PDE governing the cancer cells, and the ODE describing the ECM, is facilitated by a particular non-linear change of variables. The global existence of classical solutions follows by a series of delicate a-priori estimates and corresponding limiting processes.

In [46] a single family of cancer cells is considered that responds in chemotactic-haptotactic way to its environment. The ECM is degraded by the MMPs and is self-remodelled. The diffusion of the MMPs is assumed to be very fast and the resulting equation is elliptic. Global existence of classical solutions follows after a-priori estimates, that are established using energy-type arguments.

In [42] a single family of cancer cells was considered in a chemotaxis-haptotaxis model where the subcellular binding of integrins was taken into account, and where the focus was on the coupling of the motility of the cells with the subcellular dynamics. Conveniently chosen regularized (neighbouring) problems are used to construct the generalized solution of the model while exploiting the “quasi-dissipative property” that the coupling of the cancer cells with the ECM exhibits.

In [41] two species of cancer cells are considered using a motility-proliferation dichotomy hypothesis on

the cancer cells. Further assumptions include the matrix degradation and (self-)remodelling, as well as a type of radiation therapy. The authors prove global existence of weak solutions via an appropriately chosen “approximate” problem and entropy-type estimates.

For further results on the analysis of similar models we refer to the works [8, 17, 50, 44, 16, 42]. Overall, many techniques have been developed in the literature to tackle the particularities that these models exhibit, i.e. one or more cancer cell species, chemotaxis or haptotaxis systems, constant or not constant diffusion coefficients, and constant or non-constant EMT rates.

In our paper the cancer invasion model features DCCs and CSCs, with their densities denoted by c^D and c^S respectively, and the EMT transition between them. We consider the model in two space dimensions and assume that both families of cancer cells perform a haptotaxis biased random motion modelled by the combination of diffusion and advection terms. We assume moreover that they proliferate with a rate that is influenced by the local density of the total biomass. The ECM (with density denoted by v) is assumed to be *self-remodelled* and to compete for free space and resources with the DCCs and the CSCs in a typical logistic way. Its is moreover assumed to be degraded by the MMPs (of density m) which in turn are produced by the cancer cells. The MMPs are assumed to diffuse freely in the environment and to decay with a constant rate.

The model proposed in [39, 14] reads as follows:

$$\begin{cases} c_t^D = \Delta c^D - \chi_D \nabla \cdot (c^D \nabla v) - \mu_{\text{EMT}} c^D + \mu_D c^D (1 - c^S - c^D - v) , \\ c_t^S = \Delta c^S - \chi_S \nabla \cdot (c^S \nabla v) + \mu_{\text{EMT}} c^D + \mu_S c^S (1 - c^S - c^D - v) , \\ v_t = -mv + \mu_v v (1 - c^S - c^D - v), \\ m_t = \Delta m + c^S + c^D - m, \end{cases} \quad (1.1)$$

with (fixed) coefficients $\chi_D, \chi_S, \mu_S, \mu_D, \mu_v > 0$ and an EMT rate function μ_{EMT} whose properties will be specified below.

The system (1.1) is complemented with the no-flux boundary conditions

$$\partial_\nu c^D - \chi_D c^D \partial_\nu v = \partial_\nu c^S - \chi_S c^S \partial_\nu v = \partial_\nu m = 0 \quad \text{in } \partial\Omega \times (0, T) \quad (1.2)$$

and the initial data

$$c^D(\cdot, 0) = c_0^D, \quad c^S(\cdot, 0) = c_0^S, \quad v(\cdot, 0) = v_0, \quad m(\cdot, 0) = m_0 \quad \text{on } \Omega, \quad (1.3)$$

for which we assume that

$$c_0^D, c_0^S, m_0 \geq 0, \quad 0 \leq v_0 \leq 1, \quad c_0^D, c_0^S, m_0, v_0 \in C^{2+l}(\bar{\Omega}), \quad (1.4)$$

for a given $0 < l < 1$. The domain $\Omega \subset \mathbb{R}^2$ is bounded with smooth boundary $\partial\Omega$ that satisfies

$$\partial\Omega \in C^{2+l}. \quad (1.5)$$

The model (1.1) has been scaled with respect to reference values of the primary variables. Moreover, the coefficients of the diffusion terms and of the reaction diffusion equation for the MMPs have been reduced to 1 since they do not participate in the final (conditional) global existence result. For the complete coefficient/parameter set we refer to [39].

We moreover assume that the parameters of the problem satisfy

$$\mu_D \geq \chi_D \mu_v, \quad \mu_S \geq \chi_S \mu_v. \quad (1.6)$$

This condition is crucial for the analysis presented in this paper. Similarly to the open problem posed at the end of [45] it is not clear whether solutions to (1.1) may blow up in case (1.6) does not hold.

We assume that the EMT rate μ_{EMT} is a function $\mu_{\text{EMT}} : \mathbb{R}^4 \rightarrow \mathbb{R}$, that is Lipschitz continuous, has Lipschitz continuous first derivatives, and satisfies moreover for $\mu_M > 0$,

$$0 \leq \mu_{\text{EMT}} \leq \mu_M. \quad (1.7a)$$

Due to the continuity, we get for μ_{EMT} that,

$$\begin{aligned} \|\mu_{\text{EMT}}(c_1^{\text{D}}, c_1^{\text{S}}, v_1, m_1) - \mu_{\text{EMT}}(c_2^{\text{D}}, c_2^{\text{S}}, v_2, m_2)\|_{C^{1,0}(\bar{Q}_T)} &\leq L(\|c_1^{\text{D}} - c_2^{\text{D}}\|_{C^{1,0}(\bar{Q}_T)} + \|c_1^{\text{S}} - c_2^{\text{S}}\|_{C^{1,0}(\bar{Q}_T)} \\ &\quad + \|v_1 - v_2\|_{C^{1,0}(\bar{Q}_T)} + \|m_1 - m_2\|_{C^{1,0}(\bar{Q}_T)}), \end{aligned} \quad (1.7b)$$

for an L with

$$L = C_1 \|(c_1^{\text{D}}, c_1^{\text{S}}, v_1, m_1)\|_{C^{1,0}(\bar{Q}_T)}. \quad (1.7c)$$

Here \bar{Q}_T is the closure of the cylinder

$$Q_T := \Omega \times (0, T). \quad (1.8)$$

Let us note that throughout this work we will call solutions of (1.1) *strong solutions* provided they are regular enough that all derivatives appearing in (1.1) are weak and the solution belongs to the corresponding Sobolev space, e.g. $W_p^{2,1}(Q_T)$. We refer to solutions of (1.1) as *classical solutions* provided their regularity is such that all terms in (1.1) are pointwise well-defined. The main result in this work is the proof of existence and uniqueness of global classical solutions to the problem (1.1).

Theorem 1.1 (Global existence). *Let (1.6) hold, then for any $T > 0$ and $0 < l < 1$ there exists a unique classical solution*

$$(c^{\text{D}}, c^{\text{S}}, v, m) \in (C^{2+l, 1+l/2}(\bar{Q}_T))^4,$$

of the system (1.1)–(1.5) with $c^{\text{D}}, c^{\text{S}}, m \geq 0$ and $0 \leq v \leq 1$.

The proof of Theorem 1.1 is mainly based on Theorem 2.1, which is a local existence result for strong solutions, on Theorem 2.2 proving that the strong solutions are classical solutions, and on a series of a-priori estimates, inspired by [45], that enable us to extend the local solutions for large times. We note that the raise of the regularity, which takes place in Lemma 5.1, could not be achieved by means of energy-type techniques as in [45]. We instead base our argumentation on parabolic L^p theory and Sobolev embeddings, using an approach that resembles the strategy employed in [46].

Comparing this work with [27, 45, 46] we note that the model (1.1) features two types of cancer cells. We treat their corresponding equations separately due to the different motility parameters of the two families, but their non-linear coupling by the EMT necessitates particular treatment. In comparison to [41] the model we consider in this work assumes that both families of cancer cells migrate and proliferate and that the EMT takes place only in one direction. Thus, we do not consider *mesenchymal-epithelial transition*. Moreover, we allow for a wide variety of EMT coefficient (functions) that are bounded and Lipschitz continuous (1.7a). The study of (1.1) is mostly motivated by its properties; in particular, by its prediction that CSCs invade the ECM while remaining “below detection levels” [39] and by the very dynamic solutions that develop “sharp” concentrations and “thin” interaction waves, see also Section 6. Moreover, the analysis is neither trivial nor a straight forward application of existing theories.

The rest of this paper is structured as follows: in Section 2 we perform a change of variables and prove local existence of strong solutions by a fixed point argument. In addition, we show that these strong solutions are classical solutions. Section 3 is devoted to a series in of a-priori estimates which continues in Section 4. These estimates allow us to extend the local solutions to global solutions in Section 5. We conclude with two appendices. Appendix A gathers some facts from parabolic theory and Appendix B contains the proof of a technical lemma.

2 Local existence of classical solutions regularity

In this section we show local in time existence of classical solutions. To this end we reformulate (1.1) using a change of variables.

2.1 Change of variables

Following [45, 46] we perform the change of variables

$$\begin{cases} a^D &= c^D e^{-\chi_D v} \\ a^S &= c^S e^{-\chi_S v} \end{cases}.$$

Consequently, the system (1.1) recasts as

$$\begin{cases} a_t^D = e^{-\chi_D v} \nabla \cdot (e^{\chi_D v} \nabla a^D) + \chi_D a^D v m - \mu_{\text{EMT}} a^D + (\mu_D - \chi_D \mu_v v) a^D \rho_{\text{dev}} \\ a_t^S = e^{-\chi_S v} \nabla \cdot (e^{\chi_S v} \nabla a^S) + \chi_S a^S v m + \mu_{\text{EMT}} a^D e^{\chi_D v - \chi_S v} + (\mu_S - \chi_S \mu_v v) a^S \rho_{\text{dev}}, \\ m_t = \Delta m + e^{\chi_S v} a^S + e^{\chi_D v} a^D - m, \\ v_t = -m v + \mu_v v \rho_{\text{dev}} \end{cases}, \quad (2.1)$$

where

$$\rho_{\text{dev}} = 1 - e^{\chi_S v} a^S - e^{\chi_D v} a^D - v \quad (2.2)$$

describes the deviation of the *total density* from the equilibrium value 1.

The system is closed with initial and boundary conditions resulting from (1.2) and (1.3)

$$\begin{cases} \partial_\nu a^D = \partial_\nu a^S = \partial_\nu m = 0 & \text{in } \partial\Omega \times (0, T) \\ a^D(\cdot, 0) = a_0^D, \quad a^S(\cdot, 0) = a_0^S, \quad v(\cdot, 0) = v_0, \quad m(\cdot, 0) = m_0 & \text{on } \Omega, \end{cases} \quad (2.3)$$

Analogously, (1.4) implies

$$a_0^D, a_0^S, m_0 \geq 0, \quad 0 \leq v_0 \leq 1, \quad a_0^D, a_0^S, m_0, v_0 \in C^{2+l}(\bar{\Omega}). \quad (2.4)$$

For the rest of this work we will use the notations

$$\begin{aligned} W_p^{2,1}(Q_T) &= \{u : Q_T \rightarrow \mathbb{R} \mid u, \nabla u, \nabla^2 u, \partial_t u \in L^p(Q_T)\}, \\ W_p^2(\Omega) &= \{u : Q_T \rightarrow \mathbb{R} \mid u, \nabla u, \nabla^2 u \in L^p(Q_T)\}, \\ C^{1,1}(\bar{Q}_T) &= \{u : Q_T \rightarrow \mathbb{R} \mid u, \nabla u, \partial_t u \in C^0(\bar{Q}_T)\}, \\ C^{1,0}(\bar{Q}_T) &= \{u : Q_T \rightarrow \mathbb{R} \mid u, \nabla u \in C^0(\bar{Q}_T)\}. \end{aligned}$$

2.2 Local existence

In this section we establish existence and uniqueness of local (in time) classical solutions of (2.1). We begin by showing existence and uniqueness of local (in time) strong solutions.

Theorem 2.1 (Local existence and uniqueness). *Let (2.4) and (1.5) be satisfied. Then there exists a unique strong solution $(a^D, a^S, v, m) \in W_p^{2,1}(Q_{T_0}) \times W_p^{2,1}(Q_{T_0}) \times C^{1,1}(\bar{Q}_{T_0}) \times W_p^{2,1}(Q_{T_0})$ (for any $p > 5$) of system (2.1), (2.3) for a final time $T_0 > 0$ depending on*

$$M = 3\|a_0^D\|_{C^2} + 3\|a_0^S\|_{C^2} + 9\|v_0\|_{C^1} + \|m_0\|_{C^2} + 3.$$

Moreover,

$$a^D, a^S, m \geq 0, \quad 0 \leq v \leq 1.$$

Proof. We will prove the local existence by Banach's fixed point theorem

Spaces. Let X be the Banach space of functions (a^D, a^S, v) with finite norm

$$\|(a^D, a^S, v)\|_X = \|a^D\|_{C^{1,0}(\bar{Q}_T)} + \|a^S\|_{C^{1,0}(\bar{Q}_T)} + \|v\|_{C^{1,0}(\bar{Q}_T)}, \quad 0 < T < 1 \quad (2.5)$$

and

$$X_M := \{(a^D, a^S, v) \in (C^{1,0}(\bar{Q}_T))^3 : a^D, a^S, v \text{ are nonnegative, satisfy (2.3), and } \|(a^D, a^S, v)\|_X \leq M\}.$$

Fixed point. For any $(a^D, a^S, v) \in X_M$ we define $(a_*^D, a_*^S, v_*) = F(a^D, a^S, v)$ given such that

$$m_t - \Delta m + m = a^D e^{\chi_D v} + a^S e^{\chi_S v} \quad \text{in } Q_T, \quad (2.6a)$$

$$\partial_\nu m = 0 \text{ in } \partial\Omega \times (0, T), \quad m(\cdot, 0) = m_0 \text{ in } \Omega, \quad (2.6b)$$

$$v_{*t} = -mv_* + \mu_\nu v_* \rho_{\text{dev}} \quad \text{in } Q_T, \quad (2.6c)$$

$$v_*(\cdot, 0) = v_0, \quad (2.6d)$$

$$a_{*t}^D - \Delta a_*^D - \chi_D \nabla v_* \cdot \nabla a_*^D + [\mu_{\text{EMT}} - (\mu_D - \chi_D \mu_\nu v) \rho_{\text{dev}}] a_*^D = \chi_D a^D v m, \quad (2.6e)$$

$$\partial_\nu a_*^D = 0 \text{ in } \partial\Omega \times (0, T), \quad a_*^D(\cdot, 0) = a_0^D \text{ in } \Omega, \quad (2.6f)$$

$$a_{*t}^S - \Delta a_*^S - \chi_S \nabla v_* \cdot \nabla a_*^S - (\mu_S - \chi_S \mu_\nu v) \rho_{\text{dev}} a_*^S = \chi_S a^S v m + \mu_{\text{EMT}} a_*^D e^{\chi_D v - \chi_S v}, \quad (2.6g)$$

$$\partial_\nu a_*^S = 0 \text{ in } \partial\Omega \times (0, T), \quad a_*^S(\cdot, 0) = a_0^S \text{ in } \Omega, \quad (2.6h)$$

where $\rho_{\text{dev}} = 1 - e^{\chi_S v} a^S - e^{\chi_D v} a^D - v$. For the proof we fix some (arbitrary) $p > 5$ and set $\lambda = 1 - \frac{5}{p}$.

F is well defined and $F(X_M) \subset X_M$. We start with the component m and consider the equations (2.6a)-(2.6b). Since $0 < T < 1$ and $(a^D, a^S, v) \in X_M$ this linear parabolic problem has a unique solution by Theorem A.1:

$$\|m\|_{W_p^{2,1}(Q_T)} \leq C_2(M). \quad (2.7)$$

Here we can apply the Sobolev embedding Theorem A.3 and get

$$\|m\|_{C^{1,0}(\bar{Q}_T)} \leq C_3(M). \quad (2.8)$$

Moreover, the parabolic comparison principle yields

$$m \geq 0. \quad (2.9)$$

The initial value problem (2.6c), (2.6d) can be written as

$$v_{*t} = h_1 v_*, \quad v_*(\cdot, 0) = v_0, \quad (2.10)$$

where

$$\|h_1\|_{C^{1,0}(\bar{Q}_T)} = \|-m + \mu_\nu \rho_{\text{dev}}\|_{C^{1,0}(\bar{Q}_T)} \leq C_4(M) \quad (2.11)$$

due to (2.8) and $(a^S, a^D, v) \in X_M$. The ODE system has the solution

$$v_* = v_0(x) \exp\left(\int_0^t h_1(x, s) ds\right) \geq 0 \quad (2.12)$$

with gradient

$$\nabla v_* = \nabla v_0(x) \exp\left(\int_0^t h_1(x, s) ds\right) + v_0(x) \exp\left(\int_0^t h_1(x, s) ds\right) \int_0^t \nabla h_1(x, s) ds. \quad (2.13)$$

For $T \leq \frac{1}{2C_4(M)} < \log(2)/C_4(M)$ we get

$$\|v_*\|_{C(\bar{Q}_T)} \leq \|v_0\|_{C(\bar{\Omega})} e^{C_4(M)T} \leq 2\|v_0\|_{C(\bar{\Omega})} \quad (2.14)$$

$$\begin{aligned} \|\nabla v_*\|_{C(\bar{Q}_T)} &\leq \|\nabla v_0(x)\|_{C(\bar{\Omega})} \exp(C_4(M)T) + \|v_0(x)\|_{C(\bar{\Omega})} \exp(C_4(M)T) T C_4(M) \\ &\leq 2\|\nabla v_0\|_{C(\bar{\Omega})} + \|v_0\|_{C(\bar{\Omega})} \end{aligned} \quad (2.15)$$

and thus

$$\|v_*\|_{C^{1,0}(\bar{Q}_T)} = \|v_*\|_{C(\bar{Q}_T)} + \|\nabla v_*\|_{C(\bar{Q}_T)} \leq 3\|v_0\|_{C(\bar{\Omega})} + 2\|\nabla v_0\|_{C(\bar{\Omega})} \leq 3\|v_0\|_{C^1(\bar{\Omega})} \leq M/3. \quad (2.16)$$

Next, we deal with the parabolic problem (2.6e), (2.6f) that can be written as

$$a_{*t} - \Delta a_* - \chi \nabla v_* \cdot \nabla a_* - h_2 a_* = h_3 \quad (2.17)$$

with boundary and initial conditions given by (2.6f) where $a_* = a_*^D$, $\chi = \chi_D$. We have

$$\|\nabla v_*\|_{L^\infty(Q_T)} \leq M, \quad \|h_2\|_{L^\infty(Q_T)} \leq C_5(M), \quad \|h_3\|_{L^\infty(Q_T)} \leq C_6(M), \quad (2.18)$$

because of $(a^D, a^S, v) \in X_M$, (2.8), (1.7a). Applying the maximal parabolic regularity result (Theorem A.1), there is a unique solution a_* that satisfies

$$\|a_*\|_{W_p^{2,1}(\bar{Q}_T)} \leq C_7(M) \quad \text{for all } p > 1. \quad (2.19)$$

Further the Sobolev embedding A.3: $W_p^{2,1}(\bar{Q}_T) \hookrightarrow C^{1+\lambda, (1+\lambda)/2}(\bar{Q}_T)$ gives us

$$\|a_*\|_{C^{1+\lambda, (1+\lambda)/2}(\bar{Q}_T)} \leq C_8(M). \quad (2.20)$$

If $T \leq C_8(M)^{\frac{-2}{1+\lambda}}$ we get

$$\begin{aligned} \|a_*\|_{C^{1,0}} &= \|a_*\|_{C^{0,0}(\bar{Q}_T)} + \|\nabla a_*\|_{C^{0,0}(\bar{Q}_T)} \\ &\leq \|a_* - a_0\|_{C^{0,0}(\bar{Q}_T)} + \|a_0\|_{C^0(\bar{\Omega})} + \|\nabla a_* - \nabla a_0\|_{C^{0,0}(\bar{Q}_T)} + \|\nabla a_0\|_{C^0(\bar{\Omega})} \\ &\leq \sup_{t_1, t_2 \in [0, T]} \|a_*(t_1) - a_*(t_2)\|_{C^1(\bar{\Omega})} + \|a_0\|_{C^1(\bar{\Omega})} \\ &\leq T^{(1+\lambda)/2} \|a_*\|_{C^{1, (1+\lambda)/2}(\bar{Q}_T)} + \|a_0\|_{C^1(\bar{\Omega})} \\ &\leq T^{(1+\lambda)/2} C_8(M) + \|a_0\|_{C^1(\bar{\Omega})} \\ &\leq 1 + \|a_0\|_{C^1(\bar{\Omega})} \\ &\leq M/3, \end{aligned} \quad (2.21)$$

where we have used the definition of the Hölder norm in the third inequality. Moreover,

$$a_* \geq 0 \quad (2.22)$$

by the parabolic comparison principle since the right hand side of (2.6e) is non negative. Since we have shown that $a_*^D \in X_M$, the assertion (2.18) is true also for $a = a^S$ in the problem (2.17). Hence (2.21), (2.22) for $a_* = a_*^S$ follow by the same arguments.

F is a contraction. We take $(a_1^D, a_1^S, v_1), (a_2^D, a_2^S, v_2) \in X_M$ and consider $(a_{1*}^D, a_{1*}^S, v_{1*}) = F(a_1^D, a_1^S, v_1)$, $(a_{2*}^D, a_{2*}^S, v_{2*}) = F(a_2^D, a_2^S, v_2)$. As shown before one can find

$$m_1, m_2, \quad \|m_1\|_{C^{1,0}(\bar{Q}_T)}, \|m_2\|_{C^{1,0}(\bar{Q}_T)} \leq C_9(M)$$

that satisfy (2.6a), (2.6b) for $(a^D, a^S, m, v) = (a_1^D, a_1^S, m_1, v_1), (a_2^D, a_2^S, m_2, v_2)$. Further we have

$$(m_1 - m_2)_t - \Delta(m_1 - m_2) + (m_1 - m_2) = a_1^D e^{\chi_D v_1} + a_1^S e^{\chi_S v_1} - a_2^D e^{\chi_D v_2} - a_2^S e^{\chi_S v_2} \quad \text{in } Q_T, \quad (2.23)$$

$$\partial_\nu(m_1 - m_2) = 0 \quad \text{in } \partial\Omega \times (0, T), \quad (m_1 - m_2)(\cdot, 0) = 0 \quad \text{in } \Omega, \quad (2.24)$$

where

$$\begin{aligned} &\|a_1^D e^{\chi_D v_1} + a_1^S e^{\chi_S v_1} - a_2^D e^{\chi_D v_2} - a_2^S e^{\chi_S v_2}\|_{L^\infty(Q_T)} \\ &\leq \|e^{\chi_D v_1} (a_1^D - a_2^D)\|_{L^\infty(Q_T)} + \|e^{\chi_S v_1} (a_1^S - a_2^S)\|_{L^\infty(Q_T)} \\ &\quad + \|(e^{\chi_D v_1} - e^{\chi_D v_2})(a_2^D)\|_{L^\infty(Q_T)} + \|(e^{\chi_S v_1} - e^{\chi_S v_2})(a_2^S)\|_{L^\infty(Q_T)} \\ &\leq C_{10}(M) (\|a_1^D - a_2^D\|_{L^\infty(Q_T)} + \|a_1^S - a_2^S\|_{L^\infty(Q_T)} + \|v_1 - v_2\|_{L^\infty(Q_T)}). \end{aligned} \quad (2.25)$$

Hence by Theorem A.1 there is a solution to (2.23), (2.24) satisfying

$$\|m_1 - m_2\|_{W_p^{2,1}(Q_T)} \leq C_{11}(M) (\|a_1^D - a_2^D\|_{L^\infty(Q_T)} + \|a_1^S - a_2^S\|_{L^\infty(Q_T)} + \|v_1 - v_2\|_{L^\infty(Q_T)})$$

for all $p > 1$. The Sobolev embedding A.3 once again yields

$$\|m_1 - m_2\|_{C^{1,0}(\bar{Q}_T)} \leq C_{12}(M) (\|a_1^D - a_2^D\|_{L^\infty(Q_T)} + \|a_1^S - a_2^S\|_{L^\infty(Q_T)} + \|v_1 - v_2\|_{L^\infty(Q_T)}). \quad (2.26)$$

We get from (2.6c), (2.6d) that

$$(v_{1*} - v_{2*})_t = h_4(v_{1*} - v_{2*}) + h_5, \quad (v_{1*} - v_{2*})(\cdot, 0) = 0, \quad (2.27)$$

where

$$h_4 = -m_1 + \mu_v \rho_{\text{dev},1}, \quad h_5 = (m_2 - m_1)v_{2*} - \mu_v v_{2*}(\rho_{\text{dev},2} - \rho_{\text{dev},1}).$$

There we have used the notation

$$\rho_{\text{dev},1} = 1 - e^{\chi_S v_1} a_1^S - e^{\chi_D v_1} a_1^D - v_1, \quad \rho_{\text{dev},2} = 1 - e^{\chi_S v_2} a_2^S - e^{\chi_D v_2} a_2^D - v_2.$$

Since $(a_i^D, a_i^S, v_i) \in X_M$, $i = 1, 2$ and due to (2.26), we get

$$\|h_4\|_{C^{1,0}(\bar{Q}_T)} \leq C_{13}(M), \quad (2.28)$$

$$\|h_5\|_{C^{1,0}(\bar{Q}_T)} \leq C_{14}(M)(\|a_1^D - a_2^D\|_{C^{1,0}(\bar{Q}_T)} + \|a_1^S - a_2^S\|_{C^{1,0}(\bar{Q}_T)} + \|v_1 - v_2\|_{C^{1,0}(\bar{Q}_T)}). \quad (2.29)$$

The solution of the ODE (2.27) is given by

$$v_{1*} - v_{2*} = \int_0^t \exp\left(\int_\tau^t h_4(x, s) ds\right) h_5(x, \tau) d\tau, \quad (2.30)$$

and thus

$$\nabla(v_{1*} - v_{2*}) = \int_0^t \exp\left(\int_\tau^t h_4(x, s) ds\right) \nabla_x h_5(x, \tau) d\tau + \int_0^t \exp\left(\int_\tau^t h_4(x, s) ds\right) h_5(x, \tau) \int_\tau^t \nabla_x h_4(x, s) ds d\tau. \quad (2.31)$$

Finally we obtain by using $0 < T < 1$ and the bounds (2.28), (2.29) that

$$\begin{aligned} \|v_{1*} - v_{2*}\|_{C^{1,0}(\bar{Q}_T)} &\leq TC_{15}(M) \|h_5\|_{C^{1,0}(\bar{Q}_T)} \\ &\leq TC_{16}(M)(\|a_1^D - a_2^D\|_{C^{1,0}(\bar{Q}_T)} + \|a_1^S - a_2^S\|_{C^{1,0}(\bar{Q}_T)} + \|v_1 - v_2\|_{C^{1,0}(\bar{Q}_T)}). \end{aligned} \quad (2.32)$$

Next, we derive the parabolic problem for $a \in \{a^D, a^S\}$ with the variables $(\chi, h_6, h_7) \in \{(\chi_D, h_6^D, h_7^D), (\chi_S, h_6^S, h_7^S)\}$ by (2.6e)–(2.6h)

$$(a_{1*} - a_{2*})_t - \Delta(a_{1*} - a_{2*}) - \chi \nabla v_{1*} \cdot \nabla(a_{1*} - a_{2*}) + h_6(a_{1*} - a_{2*}) = h_7 \text{ in } Q_T, \quad (2.33)$$

$$\partial_\nu(a_{1*} - a_{2*}) = 0 \text{ in } \partial\Omega, \quad (a_{1*} - a_{2*})(\cdot, 0) = 0 \text{ on } \Omega, \quad (2.34)$$

where

$$\begin{aligned} h_6^D &= \mu_{\text{EMT},1} - (\mu_D - \chi_D \mu_v v_1) \rho_{\text{dev},1}, \quad h_6^S = -(\mu_S - \chi_S \mu_v v_1) \rho_{\text{dev},1}, \\ h_7^D &= \chi_D (a_1^D m_1 v_1 - a_2^D m_2 v_2) + \chi_D \nabla(v_{1*} - v_{2*}) \cdot \nabla a_{2*}^D \\ &\quad + a_{2*}^D [(\mu_D - \chi_D \mu_v v_1) \rho_{\text{dev},1} - (\mu_D - \chi_D \mu_v v_2) \rho_{\text{dev},2} - (\mu_{\text{EMT},1} - \mu_{\text{EMT},2})], \\ h_7^S &= \chi_S (a_1^S m_1 v_1 - a_2^S m_2 v_2) + \chi_S \nabla(v_{1*} - v_{2*}) \cdot \nabla a_{2*}^S + a_{2*}^S [(\mu_S - \chi_S \mu_v v_1) \rho_{\text{dev},1} \\ &\quad - (\mu_S - \chi_S \mu_v v_2) \rho_{\text{dev},2}] - (\mu_{\text{EMT},1} a_{1*}^D e^{\chi_D v_1 - \chi_S v_1} - \mu_{\text{EMT},2} a_{2*}^D e^{\chi_D v_2 - \chi_S v_2}). \end{aligned}$$

We have used the notation

$$\mu_{\text{EMT},1} = \mu_{\text{EMT}}(c_1^D, c_1^S, v_1, m_1), \quad \mu_{\text{EMT},2} = \mu_{\text{EMT}}(c_2^D, c_2^S, v_2, m_2).$$

Due to $(a_i^D, a_i^S, v_i) \in X_M$, (2.16), (2.21), (2.26), (2.32), (1.7b), (1.7c) we can estimate

$$\|\chi_D \nabla v_{1*}\|_{L^\infty(Q_T)}, \|\chi_S \nabla v_{1*}\|_{L^\infty(Q_T)} \leq C_{17}(M) \quad (2.35)$$

$$\|h_6^D\|_{L^\infty(Q_T)}, \|h_6^S\|_{L^\infty(Q_T)} \leq C_{18}(M), \quad (2.36)$$

$$\begin{aligned} \|h_7^D\|_{L^\infty(Q_T)}, \|h_7^S\|_{L^\infty(Q_T)} &\leq C_{19}(M)(\|a_1^D - a_2^D\|_{C^{1,0}(\bar{Q}_T)} + \|a_1^S - a_2^S\|_{C^{1,0}(\bar{Q}_T)} \\ &\quad + \|v_1 - v_2\|_{C^{1,0}(\bar{Q}_T)}). \end{aligned} \quad (2.37)$$

Since $0 < T < 1$ a solution of (2.33), (2.34) exists by Theorem A.1 with

$$\begin{aligned} \|a_{1*} - a_{2*}\|_{W_p^{2,1}(Q_T)} &\leq C_{20}(M)\|h_7\|_{L^p(Q_T)} \\ &\leq C_{21}(M)(\|a_1^D - a_2^D\|_{C^{1,0}(\bar{Q}_T)} + \|a_1^S - a_2^S\|_{C^{1,0}(\bar{Q}_T)} \\ &\quad + \|v_1 - v_2\|_{C^{1,0}(\bar{Q}_T)}), \end{aligned}$$

hence the bound can be extended using the Sobolev embedding A.3 and we get

$$\|a_{1*} - a_{2*}\|_{C^{1+\lambda, (1+\lambda)/2}(\bar{Q}_T)} \leq C_{22}(M)(\|a_1^D - a_2^D\|_{C^{1,0}(\bar{Q}_T)} + \|a_1^S - a_2^S\|_{C^{1,0}(\bar{Q}_T)} + \|v_1 - v_2\|_{C^{1,0}(\bar{Q}_T)}). \quad (2.38)$$

Then follows

$$\begin{aligned} \|a_{1*} - a_{2*}\|_{C^{1,0}(\bar{Q}_T)} &= \|(a_{1*} - a_{2*})(x, t) - (a_{1*} - a_{2*})(x, 0)\|_{C^{1,0}(\bar{Q}_T)} \\ &\leq T^{(1+\lambda)/2} \|a_{1*} - a_{2*}\|_{C^{1, (1+\lambda)/2}(\bar{Q}_T)} \\ &\leq T^{(1+\lambda)/2} C_{22}(M) (\|a_1^D - a_2^D\|_{C^{1,0}(\bar{Q}_T)} + \|a_1^S - a_2^S\|_{C^{1,0}(\bar{Q}_T)} + \|v_1 - v_2\|_{C^{1,0}(\bar{Q}_T)}). \end{aligned} \quad (2.39)$$

If we take $T_0 = T$ such that

$$\max\{TC_{16}(M), T^{(1+\lambda)/2}C_{22}(M)\} < \frac{1}{3}$$

we see by (2.32) and (2.39) that F is a contraction in X_M .

Conclusion and regularity. According to the Banach fixed-point theorem F has a unique fixed point (a^D, a^S, v) , which together with m from (2.7) is the unique solution of (2.1), (2.3). By (2.7) and (2.19) we have that

$$m, a^D, a^S \in W_p^{2,1}(Q_T).$$

Due to (2.10), (2.11), and (2.16) we get

$$v \in C^{1,1}(\bar{Q}_T).$$

By (2.22), (2.12), and (2.9) we get the non-negativity

$$a^D, a^S, v, m \geq 0.$$

Moreover we note that due to the non negativity of v , $0 \leq v_0 \leq 1$, and

$$(1 - v)_t \geq -\mu_v v(1 - v), \quad (1 - v)(\cdot, 0) \geq 0$$

$(1 - v)$ can not become negative and hence $v \leq 1$. □

Our next result shows that the strong solutions which we constructed in Theorem (2.1) are indeed classical solutions.

Theorem 2.2 (Regularity). *Under the initial and boundary conditions (2.3) and (2.4) the solution in Theorem 2.1 satisfies*

$$(a^S, a^D, v, m) \in (C^{2+l, 1+l/2}(\bar{Q}_{T_0}))^4, \quad (2.40)$$

for $0 < l < 1$.

Proof. We use Theorem 2.1 and the Sobolev embedding A.3. Then we obtain for a sufficiently large $p > 5$, that

$$a^D, a^S, m \in C^{1+l, (1+l)/2}(\bar{Q}_{T_0}). \quad (2.41)$$

We further derive from (2.1) that

$$(\partial_{x_i} v)_t = h_8 \partial_{x_i} v - h_9, \quad (2.42)$$

where

$$h_8 = -m + \mu_v \rho_{\text{dev}} - \mu_v v(1 + \chi_S e^{\chi_S v} a^S + \chi_D e^{\chi_D v} a^D), \quad (2.43)$$

$$h_9 = v \partial_{x_i} m + \mu_v v(e^{\chi_S v} \partial_{x_i} a^S + e^{\chi_D v} \partial_{x_i} a^D). \quad (2.44)$$

Because of (2.41) and $v \in C^{1,1}(\bar{Q}_T)$ we get

$$h_8, h_9 \in C^{l,l/2}(\bar{Q}_{T_0}). \quad (2.45)$$

The solution of (2.42) is given by

$$\partial_{x_i} v = \partial_{x_i} v_0(x) e^{\int_0^t h_8(x,s) ds} - \int_0^t h_9(x,\tau) e^{\int_\tau^t h_8(x,s) ds} d\tau, \quad (2.46)$$

and hence by (2.45)

$$\partial_{x_i} v \in C^{l,l/2}(\bar{Q}_{T_0}). \quad (2.47)$$

The equation for a^D in (2.1) can be written as

$$a_t^D - \Delta a^D - \chi_D \nabla v \cdot \nabla a^D - h_{10} a^D = h_{11}, \quad (2.48)$$

where

$$h_{10} = (\mu_D - \chi_D \mu_v v) \rho_{\text{dev}} \in C^{l,l/2}(\bar{Q}_{T_0}) \quad (2.49)$$

$$h_{11} = \chi_D a^D v m - \mu_{\text{EMT}} a^D \in C^{l,l/2}(\bar{Q}_{T_0}) \quad (2.50)$$

by (2.41), (2.47), and (1.7b). Thus, we can apply Theorem A.2 and get together with (2.47) that the solution of (2.48) satisfies

$$a^D \in C^{2+l,1+l/2}(\bar{Q}_{T_0}). \quad (2.51)$$

Similarly, the equation for a^S in (2.1) can be rewritten as

$$a_t^S - \Delta a^S - \chi_S \nabla v \cdot \nabla a^S - h_{12} a^S = h_{13}, \quad (2.52)$$

$$h_{12} = (\mu_S - \chi_S \mu_v v) \rho_{\text{dev}} \in C^{l,l/2}(\bar{Q}_{T_0}), \quad (2.53)$$

$$h_{13} = \chi_S a^S v m + \mu_{\text{EMT}} a^D e^{\chi_D v - \chi_S v} \in C^{l,l/2}(\bar{Q}_{T_0}). \quad (2.54)$$

Applying Theorem A.2 we obtain

$$a^S \in C^{2+l,1+l/2}(\bar{Q}_{T_0}). \quad (2.55)$$

Furthermore, (2.41), $v \in C^{1,1}(\bar{Q}_T)$, (2.6a), and (2.6b) yield

$$m \in C^{2+l,1+l/2}(\bar{Q}_{T_0}). \quad (2.56)$$

By using (2.47) together with (2.51), (2.55), and (2.56) and repeating the proof of (2.47) for $\partial_{x_i, x_j}^2 v$, we get

$$\partial_{x_i, x_j}^2 v \in C^{l,l/2}(\bar{Q}_{T_0}). \quad (2.57)$$

The equation for v in (2.1) provides further that

$$v_t = -mv + \mu_v v \rho_{\text{dev}} \in C^{2+l,l/2}(\bar{Q}_{T_0}),$$

which yields together with $v \in C^{1,1}(\bar{Q}_{T_0})$ and (2.57) that

$$v \in C^{2+l,1+l/2}(\bar{Q}_{T_0}).$$

□

Remark 2.3. *Let us note that the local existence of classical solutions that follow from the Theorems 2.1 and 2.2 is valid also for more than two space dimensions.*

3 A-priori estimates for $\|a^D(t)\|_{L^\infty(\Omega)}$, $\|a^S(t)\|_{L^\infty(\Omega)}$

To extend the local (in time) solutions whose existence we have established in the last section to global (in time) solutions we need some *a priori* estimates. Establishing those estimates is the purpose of this section. Let $(a^D, a^S, v, m) \in (C^{2,1}(Q_T))^4$ be a classical solution of (2.1) in $[0, T]$ for any $T > 0$. In what follows we will show the corresponding a priori estimates. We begin by proving $\|\cdot\|_{L^1(\Omega)}$ bounds for a^D , a^S and m uniformly in time.

Lemma 3.1. *Let $(a^D, a^S, v, m) \in (C^{2,1}(Q_T))^4$ be a solution of (2.1), then we have for all $t \in (0, T)$,*

$$\|a^D(t)\|_{L^1(\Omega)} \leq \|c^D(t)\|_{L^1(\Omega)} \leq \max\{\|c_0^D\|_{L^1(\Omega)}, |\Omega|\} \quad (3.1a)$$

$$\|a^S(t)\|_{L^1(\Omega)} \leq \|c^S(t)\|_{L^1(\Omega)} \leq \max\{\|c_0^S\|_{L^1(\Omega)}, c_{\max}^S\} \quad (3.1b)$$

$$\|m(t)\|_{L^1(\Omega)} \leq \max\{\|m_0\|_{L^1(\Omega)}, \max\{\|c_0^D\|_{L^1(\Omega)}, |\Omega|\} + \max\{\|c_0^S\|_{L^1(\Omega)}, c_{\max}^S\}\} \quad (3.1c)$$

with

$$c_{\max}^S := \frac{|\Omega|}{2} \left(1 + \sqrt{1 + 4 \frac{\mu_M}{\mu_S |\Omega|} \max\{\|c_0^D\|_{L^1(\Omega)}, |\Omega|\}} \right).$$

Proof. We integrate the c^D equation in (1.1) over Ω and employ the boundary conditions (2.3) and $c^D \geq 0$:

$$\begin{aligned} \frac{d}{dt} \|c^D(t)\|_{L^1(\Omega)} &= -\|\mu_{\text{EMT}} c^D(t)\|_{L^1(\Omega)} + \mu_D \|c^D(t)\|_{L^1(\Omega)} - \mu_D \int_{\Omega} c^D(x, t) c^S(x, t) dx \\ &\quad - \mu_D \int_{\Omega} (c^D(x, t))^2 dx - \mu_D \int_{\Omega} c^D(x, t) v(x, t) dx. \end{aligned}$$

Due to the positivity of c^D, c^S and v we obtain

$$\frac{d}{dt} \|c^D(t)\|_{L^1(\Omega)} \leq \mu_D \|c^D(t)\|_{L^1(\Omega)} - \mu_D \int_{\Omega} (c^D(x, t))^2 dx.$$

or, after the boundedness of Ω and the corresponding embeddings, as

$$\frac{d}{dt} \|c^D(t)\|_{L^1(\Omega)} \leq \mu_D \|c^D(t)\|_{L^1(\Omega)} - \frac{\mu_D}{|\Omega|} \|c^D(t)\|_{L^1(\Omega)}^2.$$

Since the right hand side is a quadratic polynomial with roots 0 and $|\Omega|$, we deduce by comparison

$$\|c^D(t)\|_{L^1(\Omega)} \leq \max\{\|c_0^D\|_{L^1(\Omega)}, |\Omega|\}.$$

Similarly, we see that due to the positivity of c^S, v , the c^S equation (1.1) implies

$$\begin{aligned} \frac{d}{dt} \|c^S(t)\|_{L^1(\Omega)} &= \|\mu_{\text{EMT}}\|_{L^\infty(\Omega)} \|c^D(t)\|_{L^1(\Omega)} + \mu_S \|c^S(t)\|_{L^1(\Omega)} - \mu_S \int_{\Omega} c^S(x, t) c^D(x, t) dx \\ &\quad - \mu_S \int_{\Omega} (c^S(x, t))^2 dx - \mu_S \int_{\Omega} c^S(x, t) v(x, t) dx \\ &\leq \mu_M \|c^D(t)\|_{L^1(\Omega)} + \mu_S \|c^S(t)\|_{L^1(\Omega)} - \mu_S \int_{\Omega} (c^S(x, t))^2 dx \\ &\leq \mu_M \|c^D(t)\|_{L^1(\Omega)} + \mu_S \|c^S(t)\|_{L^1(\Omega)} - \frac{\mu_S}{|\Omega|} \|c^S(t)\|_{L^1(\Omega)}^2 \\ &\leq \mu_M \max\{\|c_0^D\|_{L^1(\Omega)}, |\Omega|\} + \mu_S \|c^S(t)\|_{L^1(\Omega)} - \frac{\mu_S}{|\Omega|} \|c^S(t)\|_{L^1(\Omega)}^2. \end{aligned}$$

The right-hand side has two roots, one negative and one positive that is larger than $|\Omega|$:

$$\frac{|\Omega|}{2} \left(1 + \sqrt{1 + 4 \frac{\mu_M}{\mu_S |\Omega|} \max\{\|c_0^D\|_{L^1(\Omega)}, |\Omega|\}} \right) = c_{\max}^S.$$

We deduce by comparison

$$\|c^S(t)\|_{L^1(\Omega)} \leq \max \{ \|c_0^S\|_{L^1(\Omega)}, c_{\max}^S \}.$$

For m we get from (1.1), after integration over Ω , due to the positivity of c^D , c^S , m , and the boundary conditions (2.3), that:

$$\frac{d}{dt} \|m(t)\|_{L^1(\Omega)} \leq \|c^D(t)\|_{L^1(\Omega)} + \|c^S(t)\|_{L^1(\Omega)} - \|m(t)\|_{L^1(\Omega)}.$$

Using (3.1a) and (3.1b) we obtain

$$\frac{d}{dt} \|m(t)\|_{L^1(\Omega)} \leq \max \{ \|c_0^D\|_{L^1(\Omega)}, |\Omega| \} + \max \{ \|c_0^S\|_{L^1(\Omega)}, c_{\max}^S \} - \|m(t)\|_{L^1(\Omega)}.$$

Finally we deduce that

$$\|m(t)\|_{L^1(\Omega)} \leq \max \{ \|m_0\|_{L^1(\Omega)}, \max \{ \|c_0^D\|_{L^1(\Omega)}, |\Omega| \} + \max \{ \|c_0^S\|_{L^1(\Omega)}, c_{\max}^S \} \}.$$

□

We have shown uniform in time L^1 bounds of a^D , a^S , m . In order to prove a uniform in time L^∞ estimate for a we need the following Lemma which can be found (for an arbitrary number of dimensions) in [23, Lemma 1] and is an extension of [17, Lemma 4.1]

Lemma 3.2. *Let $m_0 \in W_\infty^1(\Omega)$ and let c^D, c^S, m satisfy the equation m in (1.1) together with $\frac{\partial m}{\partial \nu}|_{\Gamma_T} = 0$. Moreover, we assume that $\|c^D(t) + c^S(t)\|_{L^\rho(\Omega)} \leq C_{23}$ for $1 \leq \rho$ and all $t \in (0, T)$. Then for $\rho < 2$*

$$\|m(t)\|_{W_q^1(\Omega)} \leq C_{24}(q), \quad t \in (0, T), \quad (3.2)$$

where

$$q < \frac{2\rho}{2-\rho}. \quad (3.3)$$

Moreover, if $\rho = 2$ then (3.2) is valid for $q < +\infty$, if $\rho > 2$ then (3.2) is valid for $q = +\infty$.

Proof. See Appendix B. □

We now combine Lemma 3.2 with a suitable Sobolev embedding to obtain a uniform bound for m in higher Lebesgue spaces:

Lemma 3.3. *Let $m_0 \in W_\infty^1(\Omega)$, and c^D, c^S, m satisfy the equation for m in (1.1) together with $\frac{\partial m}{\partial \nu}|_{\Gamma_T} = 0$. Moreover, we assume that $\|c^D(t) + c^S(t)\|_{L^\rho(\Omega)} \leq C_{25}$ for $1 \leq \rho$, and all $t \in (0, T)$. Then,*

$$\|m(t)\|_{L_r(\Omega)} \leq C_{26}(q) \quad t \in (0, T), \quad (3.4)$$

for any $r > \rho$ that satisfies

$$\frac{1}{r} + 1 > \frac{1}{\rho}. \quad (3.5)$$

Proof. The proof is based on the Sobolev embedding $W_q^1(\Omega) \hookrightarrow L^{r'}(\Omega)$ for $r' < \frac{2q}{2-q}$, and Lemma 3.2.

Since $q < \frac{2\rho}{2-\rho}$, it holds that $2r' < (2+r')q < (2+r')\frac{2\rho}{2-\rho}$. That is, $\left(2 - \frac{2\rho}{2-\rho}\right)r' < \frac{4\rho}{2-\rho}$ or

$$\frac{1}{\rho} - 1 < \frac{1}{r'}. \quad (3.6)$$

Then it holds

$$\|m(t)\|_{L^{r'}(\Omega)} \leq C_{27}, \quad t \in (0, T), \quad (3.7)$$

where $r' > \rho$ such that

$$\frac{1}{r'} + 1 > \frac{1}{\rho}. \quad (3.8)$$

□

The main result of this section is the following theorem which asserts uniform in time a priori bounds for a^D and a^S in $\|\cdot\|_{L^\infty(\Omega)}$.

Theorem 3.4. *Let $(a^D, a^S, v, m) \in (\mathcal{C}^{2,1}(Q_T))^4$ be a solution of (2.1), and let (1.6) hold. Then for all $t \in (0, T)$:*

$$\|a^D(t)\|_{L^\infty(\Omega)}, \|a^S(t)\|_{L^\infty(\Omega)} \leq C_{28}. \quad (3.9)$$

Proof. The proof is divided into 4 steps. We first derive a basic estimate, prove L^p bounds for all p in step two and three and finally prove the $L^\infty(\Omega)$ estimate.

Step 1: First $L^p(\Omega)$ estimates. We set $\gamma = 0$ if $p \leq 2$ and $\gamma \in (0, 1)$ otherwise, and $a_\gamma = a + \gamma \geq \gamma \geq 0$ so that

$$\nabla \left((a_\gamma^D)^{p/2} \right) = \frac{p}{2} (a_\gamma^D)^{p/2-1} \nabla a_\gamma^D, \quad \nabla \left((a_\gamma^S)^{p/2} \right) = \frac{p}{2} (a_\gamma^S)^{p/2-1} \nabla a_\gamma^S, \quad \text{for any } p > 1. \quad (3.10)$$

Since $0 \leq v \leq 1$ we can consider the integrals $\int_\Omega e^{\chi_D v} (a_\gamma^D)^p dx$, $\int_\Omega e^{\chi_S v} (a_\gamma^S)^p dx$ instead of $\int_\Omega (a_\gamma^D)^p dx$, $\int_\Omega (a_\gamma^S)^p dx$, and get moreover

$$0 \leq \mu_D - \chi_D \mu_v \leq \mu_D, \quad 0 \leq \mu_S - \chi_S \mu_v \leq \mu_S, \quad (3.11)$$

using the above assumption. Using (2.1), (3.11), partial integration, (3.10), (1.7a), and the fact that $0 \leq v \leq 1$, we obtain

$$\begin{aligned} \frac{d}{dt} \int_\Omega e^{\chi_D v} (a_\gamma^D)^p dx &= \int_\Omega \chi_D e^{\chi_D v} \partial_t v (a_\gamma^D)^p dx + \int_\Omega e^{\chi_D v} p (a_\gamma^D)^{p-1} \partial_t a^D dx \\ &= -\chi_D \int_\Omega e^{\chi_D v} m v (a_\gamma^D)^p dx + \chi_D \mu_v \int_\Omega e^{\chi_D v} (a_\gamma^D)^p v \rho_{\text{dev}} dx \\ &\quad + \int_\Omega p (a_\gamma^D)^{p-1} \nabla \cdot (e^{\chi_D v} \nabla a^D) dx + \chi_D \int_\Omega e^{\chi_D v} p (a_\gamma^D)^{p-1} a^D v m dx \\ &\quad - \int_\Omega \mu_{\text{EMT}} a^D e^{\chi_D v} p (a_\gamma^D)^{p-1} dx + \int_\Omega e^{\chi_D v} p (a_\gamma^D)^{p-1} (\mu_D - \chi_D \mu_v v) a^D \rho_{\text{dev}} dx \\ &\leq (\mu_D p + \chi_D \mu_v) \int_\Omega e^{\chi_D v} (a_\gamma^D)^p dx + \chi_D p \int_\Omega e^{\chi_D v} (a_\gamma^D)^p m dx \\ &\quad - \int_\Omega p(p-1) (a_\gamma^D)^{p-2} |\nabla a_\gamma^D|^2 e^{\chi_D v} dx \\ &\leq -\frac{4(p-1)}{p} \int_\Omega |\nabla (a_\gamma^D)^{p/2}|^2 dx + (\mu_D p + \chi_D \mu_v) e^{\chi_D} \int_\Omega (a_\gamma^D)^p dx \\ &\quad + \chi_D p e^{\chi_D} \int_\Omega m (a_\gamma^D)^p dx. \end{aligned} \quad (3.12)$$

Similarly, we get

$$\begin{aligned} \frac{d}{dt} \int_\Omega e^{\chi_S v} (a_\gamma^S)^p dx &= \int_\Omega \chi_S e^{\chi_S v} \partial_t v (a_\gamma^S)^p dx + \int_\Omega e^{\chi_S v} p (a_\gamma^S)^{p-1} \partial_t a^S dx \\ &= -\chi_S \int_\Omega e^{\chi_S v} m v (a_\gamma^S)^p dx + \chi_S \mu_v \int_\Omega e^{\chi_S v} (a_\gamma^S)^p v \rho_{\text{dev}} dx \\ &\quad + \int_\Omega p (a_\gamma^S)^{p-1} \nabla \cdot (e^{\chi_S v} \nabla a^S) dx + \chi_S \int_\Omega e^{\chi_S v} p (a_\gamma^S)^{p-1} a^S v m dx \\ &\quad + \int_\Omega \mu_{\text{EMT}} a^D e^{\chi_D v} p (a_\gamma^S)^{p-1} dx \\ &\quad + \int_\Omega e^{\chi_S v} p (a_\gamma^S)^{p-1} (\mu_S - \chi_S \mu_v v) a^S \rho_{\text{dev}} dx \\ &\leq -\frac{4(p-1)}{p} \int_\Omega |\nabla (a_\gamma^S)^{p/2}|^2 dx + (\mu_S p + \chi_S \mu_v) e^{\chi_S} \int_\Omega (a_\gamma^S)^p dx \\ &\quad + \chi_S p e^{\chi_S} \int_\Omega m (a_\gamma^S)^p dx + \mu_M p e^{\chi_D} \int_\Omega a^D (a_\gamma^S)^{p-1} dx. \end{aligned} \quad (3.13)$$

Step 2: Raise of p . We assume that both $\|a_\gamma^D(t)\|_{L^q(\Omega)}, \|a_\gamma^S(t)\|_{L^q(\Omega)} \leq C_{29}$ for some $q \geq 1$ and show that

$$\|a_\gamma^D(t)\|_{L^p(\Omega)}, \|a_\gamma^S(t)\|_{L^p(\Omega)} \leq C_{30},$$

where $p = \frac{4q}{3}$.

Since we are in $d = 2$ space dimensions the inequality

$$\frac{dp}{dp + 2q} < 1 + \frac{2}{d} - \frac{1}{q}, \quad (3.14)$$

is true and allows us to find $r > 1$, such that

$$\frac{dp}{dp + 2q} < \frac{1}{r} < 1 + \frac{2}{d} - \frac{1}{q}. \quad (3.15)$$

The first inequality justifies the Gagliardo-Nirenberg inequality

$$\|\cdot\|_{L^{2r}}^{2r} \leq C_{31} \|\cdot\|_{L^{2q/p}}^{2(r-1)} \|\cdot\|_{W_2^1}^2, \quad (3.16)$$

and due to the second inequality there is a dual exponent r' of r that satisfies the conditions of Lemma 3.3. We take $a \in \{a_\gamma^D, a_\gamma^S\}$. Applying Young's inequality, (3.16), Lemma 3.3, and assumption $\|a(t)\|_{L^q(\Omega)} \leq C_{29}$, we get for any $\varepsilon > 0$

$$\begin{aligned} \int_\Omega ma^p dx &\leq C_{32}(\varepsilon) \int_\Omega m^{r'} dx + \varepsilon \int_\Omega a^{pr} dx \\ &\leq C_{33}(\varepsilon) + \varepsilon \|a^{p/2}\|_{L^{2r}}^{2r} \\ &\leq C_{33}(\varepsilon) + \varepsilon C_{34} \|a\|_{L^q}^{p(r-1)} \|a^{p/2}\|_{W_2^1}^2 \\ &\leq C_{33}(\varepsilon) + \varepsilon C_{35} \int_\Omega a^p dx + \varepsilon C_{35} \int_\Omega |\nabla a^{p/2}|^2 dx. \end{aligned} \quad (3.17)$$

Since we are in two space dimensions we have the Gagliardo-Nirenberg interpolation inequality

$$\|\cdot\|_{L^2} \leq C_{36} \|\cdot\|_{W_2^1}^{1/4} \|\cdot\|_{L^{3/2}}^{3/4}, \quad (3.18)$$

and we can moreover estimate $\int_\Omega a^p dx$ by employing (3.18), Young's inequality and $\|a(t)\|_{L^q(\Omega)} \leq C_{29}$

$$\begin{aligned} (C_{37} + \beta) \int_\Omega a^p dx &= (C_{37} + \beta) \int_\Omega (a^{p/2})^2 dx \\ &= (C_{37} + \beta) \|a^{p/2}\|_{L^2}^2 \\ &\leq C_{38} (C_{37} + \beta) \|a^{p/2}\|_{W_2^1(\Omega)}^{1/2} \|a^{p/2}\|_{L^{3/2}(\Omega)}^{3/2} \\ &\leq \frac{\beta}{2} \|a^{p/2}\|_{W_2^1(\Omega)}^2 + C_{39} \|a^{p/2}\|_{L^{3/2}(\Omega)}^2 \\ &= \frac{\beta}{2} \|a^{p/2}\|_{W_2^1(\Omega)}^2 + C_{39} \|a\|_{L^{3p/4}(\Omega)}^p \\ &\leq \frac{\beta}{2} \|a^{p/2}\|_{W_2^1(\Omega)}^2 + C_{40}, \end{aligned} \quad (3.19)$$

where C_{37} and β are arbitrary positive numbers.

In order to prove the L^p bound for a^D we insert (3.17) where $a = a^D$ into (3.12) and fix ε such that $\varepsilon \chi_D p e^{\chi_D} C_{35} < 2(p-1)/p$ to obtain

$$\frac{d}{dt} \int_\Omega e^{\chi_D v} (a_\gamma^D)^p dx \leq -\frac{2(p-1)}{p} \int_\Omega |\nabla (a_\gamma^D)^{p/2}|^2 dx + C_{41} \int_\Omega (a_\gamma^D)^p dx + C_{42}. \quad (3.20)$$

By adding $\beta \int_\Omega (a_\gamma^D)^p dx$ to both sides of (3.20) we get

$$\frac{d}{dt} \int_\Omega e^{\chi_D v} (a_\gamma^D)^p dx + \beta \int_\Omega (a_\gamma^D)^p dx \leq -\frac{2(p-1)}{p} \int_\Omega |\nabla (a_\gamma^D)^{p/2}|^2 dx + (C_{41} + \beta) \int_\Omega (a_\gamma^D)^p dx + C_{42}. \quad (3.21)$$

We can now insert (3.19), where $a = a^D$ and $\beta = 2(p-1)/p$ into (3.21) and get

$$\frac{d}{dt} \int_{\Omega} e^{\chi_{D^v}} (a_{\gamma}^D)^p dx + \frac{p-1}{p} \int_{\Omega} (a_{\gamma}^D)^p dx \leq C_{43}, \quad (3.22)$$

which implies

$$\frac{d}{dt} \int_{\Omega} e^{\chi_{D^v}} (a_{\gamma}^D)^p dx + \frac{p-1}{p e^{\chi_D}} \int_{\Omega} e^{\chi_{D^v}} (a_{\gamma}^D)^p dx \leq C_{43}, \quad (3.23)$$

and thus

$$\int_{\Omega} e^{\chi_{D^v}} (a_{\gamma}^D)^p dx \leq C_{44}. \quad (3.24)$$

Hence we have shown that

$$\|a^D(t)\|_{L^p(\Omega)} \leq C_{45}. \quad (3.25)$$

An application of Young's inequality and (3.25) lead to

$$\begin{aligned} \int_{\Omega} a^D (a_{\gamma}^S)^{p-1} dx &\leq \frac{p-1}{p} \int_{\Omega} (a_{\gamma}^S)^p dx + \frac{1}{p} \int_{\Omega} (a^D)^p dx \\ &\leq C_{46} \int_{\Omega} (a_{\gamma}^S)^p dx + C_{47}. \end{aligned} \quad (3.26)$$

Inserting (3.26) into (3.13) yields

$$\frac{d}{dt} \int_{\Omega} e^{\chi_{S^v}} (a_{\gamma}^S)^p dx \leq -\frac{4(p-1)}{p} \int_{\Omega} |\nabla (a_{\gamma}^S)^{p/2}|^2 dx + C_{48} \int_{\Omega} (a_{\gamma}^S)^p dx + C_{49} \int_{\Omega} m (a_{\gamma}^S)^p dx + C_{50}. \quad (3.27)$$

Since (3.17) and (3.19) are also valid for $a = a^S$ we can repeat the steps in (3.20)–(3.24) for (3.27) to get

$$\|a^S(t)\|_{L^p(\Omega)} \leq C_{51}. \quad (3.28)$$

Step 3: L^p bounds for all $p \geq 1$. From Lemma 3.1 and the previous step,

$$\|a^D(t)\|_{L^{(4/3)^n}(\Omega)}, \|a^S(t)\|_{L^{(4/3)^n}(\Omega)} \leq C_{52}(n) < \infty \quad \text{for all } n \in \mathbb{N}, \quad (3.29)$$

follows from induction. Hence, we have that

$$\|a^D(t)\|_{L^p(\Omega)}, \|a^S(t)\|_{L^p(\Omega)} \leq C_{53}(p) < \infty \quad \text{for all } p \geq 1. \quad (3.30)$$

Step 4: L^∞ bounds. For the step we employ this technique used in [1] and applied in the case of KS system in [8]. We are in $d = 2$ space dimensions and we know from step 3 that there is $\rho > d = 2$ such that $\|c^D + c^S\|_{L^\rho(\Omega)} \leq C_{20}$. Therefore we get by Lemma 3.2

$$\|m\|_{L^\infty(Q_T)} \leq C_{54}. \quad (3.31)$$

Inserting (3.31) back into (3.12) we get that

$$\frac{d}{dt} \int_{\Omega} e^{\chi_{D^v}} (a^D)^p dx + \frac{4(p-1)}{p} \int_{\Omega} |\nabla (a^D)^{p/2}|^2 dx \leq C_{55} p \int_{\Omega} (a^D)^p dx \quad \text{for all } p \geq \rho. \quad (3.32)$$

We define the sequence $p_k = 2^k$, $k \in \mathbb{N}$ and moreover, we apply the Gagliardo-Nirenberg inequality

$$\|\cdot\|_{L^2} \leq C_{56} \|\cdot\|_{W_2^1}^{1/2} \|\cdot\|_{L^1}^{1/2}. \quad (3.33)$$

Thus, we get for $a \in \{a^D, a^S\}$ by (3.33) and Young's inequality that

$$\int_{\Omega} a^{p_k} dx = \|a^{p_k-1}\|_{L^2(\Omega)}^2 \leq C_{57} \|a^{p_k-1}\|_{W_2^1(\Omega)} \|a^{p_k-1}\|_{L^1(\Omega)} \leq C_{57} \left(\frac{1}{\varepsilon_k} \|a^{p_k-1}\|_{L^1(\Omega)}^2 + \varepsilon_k \|a^{p_k-1}\|_{W_2^1(\Omega)}^2 \right) \quad (3.34)$$

which implies for sufficiently small ε_k

$$\int_{\Omega} a^{p_k} dx \leq C_{57} \left(\frac{1}{\varepsilon_k} \|a^{p_{k-1}}\|_{L^1(\Omega)}^2 + \varepsilon_k \|\nabla a^{p_{k-1}}\|_{L^2(\Omega)}^2 \right). \quad (3.35)$$

Adding $\varepsilon_k e^{\chi_D} \int_{\Omega} (a^D)^{p_k} dx$ to both sides of (3.32), choosing ε_k such that

$$(C_{55} p_k + \varepsilon_k e^{\chi_D}) C_{57} \varepsilon_k \leq 4(p_k - 1)/p_k < 4 \quad (3.36)$$

in (3.35) for $a = a^D$ and inserting in (3.32) yield for $k \geq 2$

$$\frac{d}{dt} \int_{\Omega} e^{\chi_D v} (a^D)^{p_k} dx + \varepsilon_k e^{\chi_D} \int_{\Omega} (a^D)^{p_k} dx \leq \frac{(C_{55} p_k + \varepsilon_k e^{\chi_D}) C_{57}}{\varepsilon_k} \left(\int_{\Omega} (a^D)^{p_{k-1}} dx \right)^2. \quad (3.37)$$

The later implies that

$$\frac{d}{dt} \int_{\Omega} e^{\chi_D v} (a^D)^{p_k} dx \leq -\varepsilon_k \int_{\Omega} e^{\chi_D v} (a^D)^{p_k} dx + \frac{(C_{55} p_k + \varepsilon_k e^{\chi_D}) C_{57}}{\varepsilon_k} M_{k-1}^2, \quad (3.38)$$

where

$$M_k = \max \left\{ 1, \sup_{0 < t < T} \int_{\Omega} e^{\chi_D v} (a^D)^{p_k} dx \right\}. \quad (3.39)$$

By Gronwall's lemma we get from (3.38), that

$$\int_{\Omega} e^{\chi_D v} (a^D)^{p_k} dx \leq \max \left\{ \int_{\Omega} e^{\chi_D v_0} (a_0^D)^{p_k} dx, \frac{(C_{55} p_k + \varepsilon_k e^{\chi_D}) C_{57}}{\varepsilon_k^2} M_{k-1}^2 \right\} \quad \text{for } k \geq 2. \quad (3.40)$$

Hence

$$M_k \leq \max \left\{ 1, |\Omega| e^{\chi_D} \|(a_0^D)\|_{L^\infty(\Omega)}^{p_k}, \delta_k M_{k-1}^2 \right\} \quad \text{for } k \geq 2, \quad (3.41)$$

where $\delta_k = \max\{1, (C_{55} p_k + \varepsilon_k e^{\chi_D}) C_{57} / \varepsilon_k^2\}$. Note that by (2.4) and (3.30) we can find a constant C_{58} such that

$$M_1 + 1 \leq C_{58}, \quad |\Omega| e^{\chi_D} \|(a_0^D)\|_{L^\infty(\Omega)}^{p_k} \leq C_{58}^{p_k} \quad \text{for } k \geq 1. \quad (3.42)$$

From (3.41), (3.42) and $\delta_k \geq 1$ we get that

$$M_k \leq \delta_k \delta_{k-1}^{p_1} \delta_{k-2}^{p_2} \cdots \delta_2^{p_{k-2}} \delta_1^{p_{k-1}} C_{58}^{p_k}. \quad (3.43)$$

Furthermore, we get from (3.36) that ε_k can be chosen as $\varepsilon_k = C_{59}/p_k$, where the constant C_{59} is independent of k . This yields

$$\delta_k \leq C_{60} p_k^3$$

and hence

$$M_k^{1/p_k} \leq C_{60}^{\sum_{i=0}^{k-1} 2^{i-k}} 2^{3 \sum_{i=0}^{k-1} 2^{i-k} (k-i)} C_{58} \leq C_{60}^{1-\frac{1}{p_k}} 2^{3 \sum_{i=1}^k \frac{i}{2^i}} C_{58}. \quad (3.44)$$

For $0 < t < T$ we note that $\max\{1, \|a^D(\cdot, t)\|_{L^{p_k}(\Omega)}\} \leq M_k^{1/p_k}$ by $0 \leq v \leq 1$ and when taking $k \rightarrow \infty$ in (3.44) we eventually get

$$\|a^D(\cdot, t)\|_{L^\infty(\Omega)} \leq C_{61}. \quad (3.45)$$

Using the bounds (3.31), (3.45) as well as the sequence $p_k = 2^k$, $k \in \mathbb{N}$ in (3.13) yields for $k \geq 2$

$$\frac{d}{dt} \int_{\Omega} e^{\chi_S v} (a^S)^{p_k} dx + \frac{4(p_k - 1)}{p_k} \int_{\Omega} |\nabla (a^S)^{p_{k-1}}|^2 dx \leq C_{62} p_k \int_{\Omega} (a^S)^{p_k} dx + C_{63} p_k \int_{\Omega} (a^S)^{p_{k-1}} dx. \quad (3.46)$$

By Hölder's inequality we estimate

$$\int_{\Omega} (a^S)^{p_{k-1}} dx \leq |\Omega|^{1/p_k} \left(\int_{\Omega} (a^S)^{p_k} dx \right)^{(p_k-1)/p_k} \leq C_{64} \left(\int_{\Omega} (a^S)^{p_k} dx + 1 \right) \quad (3.47)$$

and get

$$\frac{d}{dt} \int_{\Omega} e^{\chi_S v} (a^S)^{p_k} dx + \frac{4(p_k - 1)}{p_k} \int_{\Omega} |\nabla (a^S)^{p_k - 1}|^2 dx \leq C_{65} p_k \left(\int_{\Omega} (a^S)^{p_k} dx + 1 \right). \quad (3.48)$$

We add again $\varepsilon_k e^{\chi_S} \int_{\Omega} (a^S)^{p_k} dx$ on both sides of (3.48) and choose ε_k such that

$$(C_{65} p_k + \varepsilon_k e^{\chi_S}) C_{57} \varepsilon_k \leq 4(p_k - 1)/p_k < 4, \quad (3.49)$$

where C_{57} , and ε_k are chosen such that (3.35) is true for $a = a^S$. By setting $\varepsilon_k = C_{66}/p_k$ we find a constant $C_{67} > C_{57}$ such that

$$\frac{(C_{65} p_k + \varepsilon_k e^{\chi_S}) C_{67}}{\varepsilon_k} \geq C_{65} p_k. \quad (3.50)$$

Inserting (3.50) into (3.48) yields

$$\frac{d}{dt} \int_{\Omega} e^{\chi_S v} (a^S)^{p_k} dx \leq -\varepsilon_k \int_{\Omega} e^{\chi_S v} (a^S)^{p_k} dx + \frac{2(C_{65} p_k + \varepsilon_k e^{\chi_S}) C_{67}}{\varepsilon_k} M_{k-1}^2, \quad (3.51)$$

where

$$M_k = \max \left\{ 1, \sup_{0 < t < T} \int_{\Omega} e^{\chi_S v} (a^S)^{p_k} \right\}. \quad (3.52)$$

Using the same argumentation as in (3.40)–(3.45) it follows for $0 < t < T$ that also

$$\|a^S(t)\|_{L^\infty(\Omega)} \leq C_{68}, \quad (3.53)$$

which completes the proof. \square

4 A priori estimate for $\|\nabla v(t)\|_{L^4(\Omega)}$

We begin by deriving estimates for ∇a^D , a_t^D , ∇a^S and a_t^S . Let us recall (1.6) and, hence, by (3.9) and Lemma 3.2 we have

$$\|a^D(t)\|_{L^\infty(\Omega)}, \|a^S(t)\|_{L^\infty(\Omega)} \text{ and } \|m(t)\|_{W_\infty^1(\Omega)} \leq C. \quad (4.1)$$

Lemma 4.1. *Assume that $(a^D, a^S, v, m) \in (C^{2,1}(\bar{Q}_T))^4$ is a solution of (2.1). Then for all $t \in (0, T)$ the following inequalities are fulfilled*

$$\|\nabla a^D(t)\|_{L^2(\Omega)} \leq C_{69} e^{\chi_D \mu_v t}, \quad \|a_t^D\|_{L^2(Q_t)} \leq C_{70} t + C_{71} e^{\chi_D \mu_v t} \quad (4.2)$$

$$\|\nabla a^S(t)\|_{L^2(\Omega)} \leq C_{72} e^{\chi_S \mu_v t}, \quad \|a_t^S\|_{L^2(Q_t)} \leq C_{73} t + C_{74} e^{\chi_S \mu_v t}. \quad (4.3)$$

Proof. We begin by multiplying equation for a^D in (2.1) by $e^{\chi_D v} a_t^D$ and integrating over Ω . We obtain

$$\begin{aligned} \int_{\Omega} e^{\chi_D v} (a_t^D)^2 dx &= \int_{\Omega} a_t^D \nabla \cdot (e^{\chi_D v} \nabla a^D) dx + \int_{\Omega} e^{\chi_D v} a_t^D \chi_D a^D v m dx \\ &\quad - \int_{\Omega} \mu_{\text{EMT}} a^D e^{\chi_D v} a_t^D dx + \int_{\Omega} e^{\chi_D v} a_t^D (\mu_D - \chi_D \mu_v v) a^D \rho_{\text{dev}} dx =: I_1^D + I_2^D + I_3^D + I_4^D. \end{aligned} \quad (4.4)$$

Due to (2.1), the bounds from Theorem 2.1 and the no-flux boundary condition for a^D we have

$$\begin{aligned} I_1^D &= \int_{\Omega} a_t^D \nabla \cdot (e^{\chi_D v} \nabla a^D) dx \\ &= -\frac{1}{2} \int_{\Omega} (e^{\chi_D v} \frac{\partial}{\partial t} (|\nabla a^D|^2)) dx \\ &= -\frac{1}{2} \frac{d}{dt} \int_{\Omega} e^{\chi_D v} (|\nabla a^D|^2) dx + \frac{\chi_D}{2} \int_{\Omega} e^{\chi_D v} |\nabla a^D|^2 v_t dx \\ &= -\frac{1}{2} \frac{d}{dt} \int_{\Omega} e^{\chi_D v} (|\nabla a^D|^2) dx + \frac{\chi_D}{2} \int_{\Omega} e^{\chi_D v} |\nabla a^D|^2 (-mv + \mu_v v \rho_{\text{dev}}) dx \\ &\leq -\frac{1}{2} \frac{d}{dt} \int_{\Omega} e^{\chi_D v} (|\nabla a^D|^2) dx + \frac{\chi_D \mu_v}{2} \int_{\Omega} e^{\chi_D v} |\nabla a^D|^2 dx. \end{aligned} \quad (4.5)$$

By Cauchy's inequality, the bounds from Theorem 2.1 and (4.1) we have

$$I_2^D = \int_{\Omega} e^{\chi_{Dv}} a_t^D \chi_D a^D v m dx \quad (4.6)$$

$$\begin{aligned} &= \frac{1}{4} \int_{\Omega} e^{\chi_{Dv}} (a_t^D)^2 dx + \chi_D^2 \int_{\Omega} e^{\chi_{Dv}} (a^D)^2 m^2 v^2 dx \\ &= \frac{1}{4} \int_{\Omega} e^{\chi_{Dv}} (a_t^D)^2 dx + C_{75}. \end{aligned} \quad (4.7)$$

Analogously we obtain using (1.7a)

$$I_3^D = - \int_{\Omega} \mu_{\text{EMT}} a^D e^{\chi_{Dv}} a_t^D dx \leq \frac{1}{4} \int_{\Omega} e^{\chi_{Dv}} (a_t^D)^2 dx + C_{76}. \quad (4.8)$$

By Cauchy's inequality, the bounds from Theorem 2.1 and (4.1) we have

$$\begin{aligned} I_4^D &= \int_{\Omega} e^{\chi_{Dv}} a_t^D (\mu_D - \chi_D \mu_v) a^D \rho_{\text{dev}} dx \\ &\leq C_{77} \int_{\Omega} e^{\chi_{Dv}} |a_t^D| dx \\ &\leq \frac{1}{4} \int_{\Omega} e^{\chi_{Dv}} |a_t^D|^2 dx + C_{78}. \end{aligned} \quad (4.9)$$

Inserting (4.5)- (4.9) into (4.4) we obtain

$$\frac{1}{4} \int_{\Omega} e^{\chi_{Dv}} (a_t^D)^2 dx + \frac{1}{2} \frac{d}{dt} \int_{\Omega} e^{\chi_{Dv}} (|\nabla a^D|^2) dx \leq \frac{\chi_D \mu_v}{2} \int_{\Omega} e^{\chi_{Dv}} |\nabla a^D|^2 dx + C_{79}, \quad (4.10)$$

which implies

$$\frac{d}{dt} \int_{\Omega} e^{\chi_{Dv}} (|\nabla a^D|^2) dx \leq \chi_D \mu_v \int_{\Omega} e^{\chi_{Dv}} |\nabla a^D|^2 dx + 2C_{79}. \quad (4.11)$$

Applying Gronwall's lemma to (4.11) implies

$$\int_{\Omega} e^{\chi_{Dv}} (|\nabla a^D|^2) dx \leq C_{80} e^{\chi_D \mu_v t}. \quad (4.12)$$

Integrating both sides of (4.10) in time and using (4.12) gives

$$\int_0^t \int_{\Omega} e^{\chi_{Dv}} (a_t^D)^2 dx ds \leq 4C_{79}t + C_{81} e^{\chi_D \mu_v t}. \quad (4.13)$$

This completes the proof of the first line of (4.2). The proof of the second line is obtained analogously by multiplying the equation for a^S in (2.1) by $e^{\chi_{Sv}} a_t^S$ and integrating over Ω .

□

The following lemma relates $\|\nabla v(t)\|_{L^p(\Omega)}$ with $\|\nabla a^D(t)\|_{L^p(\Omega)}$ and $\|\nabla a^S(t)\|_{L^p(\Omega)}$.

Lemma 4.2. *Assume that $(a^D, a^S, v, m) \in (C^{2,1}(\bar{Q}_T))^4$ is a solution of (2.1). Then the following inequality holds*

$$\|\nabla v(t)\|_{L^p(\Omega)}^p \leq C_{82}(T, p) \left(\|\nabla a^D\|_{L^p(Q_T)}^p + \|\nabla a^S\|_{L^p(Q_T)}^p + 1 \right) \quad \text{for any } p > 1. \quad (4.14)$$

Proof. We use the chain rule in (2.1) to obtain

$$\nabla v_t = h_{14} \nabla v - (v \nabla m + \mu_v v e^{\chi_{Sv}} \nabla a^S + \mu_v v e^{\chi_{Dv}} \nabla a^D) \quad (4.15)$$

with

$$h_{14} = -m + \mu_v \rho_{\text{dev}} - \mu_v v e^{\chi_{Sv}} \chi_S a^S - \mu_v v e^{\chi_{Dv}} \chi_D a^D - 1. \quad (4.16)$$

Further we use equation (4.15) and multiply it by $p\nabla v|\nabla v|^{p-2}$. Employing (4.1), the bounds from Theorem 2.1 and Young's inequality we obtain

$$\begin{aligned} (|\nabla v|^p)_t &= h_{14}p|\nabla v|^p - \left(pv\nabla v \cdot \nabla m|\nabla v|^{p-2} + p\mu_v v e^{\chi_S v} \nabla a^S \cdot \nabla v|\nabla v|^{p-2} + p\mu_v v e^{\chi_D v} \nabla a^D \cdot \nabla v|\nabla v|^{p-2} \right) \\ &\leq \mu_v p|\nabla v|^p + p\|\nabla m\|_{L^\infty(\Omega)}|\nabla v|^{p-1} + p\mu_v e^{\chi_D} |\nabla a^D||\nabla v|^{p-1} + p\mu_v e^{\chi_S} |\nabla a^S||\nabla v|^{p-1} \\ &\leq C_{83}|\nabla v|^p + C_{84}|\nabla a^D|^p + C_{85}|\nabla a^S|^p + C_{86}. \end{aligned} \quad (4.17)$$

By integration over Ω we get

$$\frac{d}{dt} \int_{\Omega} |\nabla v|^p dx \leq C_{87} \left(\int_{\Omega} |\nabla v|^p dx + \int_{\Omega} |\nabla a^D|^p dx + \int_{\Omega} |\nabla a^S|^p dx + 1 \right), \quad (4.18)$$

which yields also

$$\frac{d}{dt} \left(\int_{\Omega} |\nabla v|^p dx + 1 \right) \leq C_{88} \left(\int_{\Omega} |\nabla a^D|^p dx + \int_{\Omega} |\nabla a^S|^p dx + 1 \right) \left(\int_{\Omega} |\nabla v|^p dx + 1 \right). \quad (4.19)$$

The estimate (4.14) follows by the Gronwall Lemma applied to (4.19). \square

Our next lemma provides $L^4(Q_T)$ -bounds for ∇a^D , ∇a^S which only depend on T , thereby ruling out finite time blowup of these norms.

Lemma 4.3. *Assume that $(a^D, a^S, v, m) \in (C^{2,1}(\bar{Q}_T))^4$ is a solution of (2.1). Then the following inequalities are satisfied*

$$\int_0^T \|\Delta a^D(t)\|_{L^2(\Omega)}^2 dt \leq C_{89}(T) \quad \text{and} \quad \int_0^T \|\Delta a^S(t)\|_{L^2(\Omega)}^2 dt \leq C_{90}(T) \quad (4.20)$$

as well as

$$\int_0^T \|\nabla a^D(t)\|_{L^4(\Omega)}^4 dt \leq C_{91}(T) \quad \text{and} \quad \int_0^T \|\nabla a^S(t)\|_{L^4(\Omega)}^4 dt \leq C_{92}(T) \quad (4.21)$$

Proof. Due to the bounds in Theorem 2.1 and (4.1) we may rewrite the equations for a^D , a^S of (2.1) as

$$a_t^D = \Delta a^D + \chi_D \nabla v \cdot \nabla a^D + h_{15}, \quad (4.22)$$

$$a_t^S = \Delta a^S + \chi_S \nabla v \cdot \nabla a^S + h_{16}, \quad (4.23)$$

with

$$\|h_{15}\|_{L^\infty(\Omega)} = \|\chi_D a^D v m - \mu_{\text{EMT}} a^D + (\mu_D - \chi_D \mu_v v) a^D \rho_{\text{dev}}\|_{L^\infty(\Omega)} \leq C_{93}, \quad (4.24)$$

$$\|h_{16}\|_{L^\infty(\Omega)} = \|\chi_S a^S v m + \mu_{\text{EMT}} a^D e^{\chi_D v - \chi_S v} + (\mu_S - \chi_S \mu_v v) a^S \rho_{\text{dev}}\|_{L^\infty(\Omega)} \leq C_{94}. \quad (4.25)$$

From equations (4.22), (4.24) and the estimate (4.2) we get for any $0 \leq t \leq T$

$$\int_0^t \|\Delta a^D(s)\|_{L^2(\Omega)}^2 ds \leq C_{95}T^2 + C_{96}e^{2\chi_D T} + 2\chi_D^2 \int_0^t \|\nabla v \cdot \nabla a^D\|_{L^2(\Omega)}^2 ds, \quad (4.26)$$

$$\int_0^t \|\Delta a^S(s)\|_{L^2(\Omega)}^2 ds \leq C_{97}T^2 + C_{98}e^{2\chi_S T} + 2\chi_S^2 \int_0^t \|\nabla v \cdot \nabla a^S\|_{L^2(\Omega)}^2 ds. \quad (4.27)$$

The last term on the right hand side needs to be estimated further. Using Hölder's inequality, equation (4.14) for $p = 4$ and

$$\sqrt{y+z} \leq \sqrt{y} + \sqrt{z} \quad \text{for all } y, z \geq 0$$

we obtain the following estimate for $I \in \{S, D\}$ and $J \in \{S, D\} \setminus \{I\}$ for all $0 \leq t \leq T$

$$\begin{aligned}
\int_0^t \|\nabla v \cdot \nabla a^I\|_{L^2(\Omega)}^2 ds &\leq \int_0^t \|\nabla v\|_{L^4(\Omega)}^2 \|\nabla a^I\|_{L^4(\Omega)}^2 ds \\
&= \int_0^t \left(\|\nabla v\|_{L^4(\Omega)}^4 \|\nabla a^I\|_{L^4(\Omega)}^4 \right)^{1/2} ds \\
&\leq \left(\int_0^t 1 ds \right)^{1/2} \left(\int_0^t \|\nabla v\|_{L^4(\Omega)}^4 \|\nabla a^I\|_{L^4(\Omega)}^4 ds \right)^{1/2} \\
&= \sqrt{t} \left(\int_0^t \|\nabla v\|_{L^4(\Omega)}^4 \|\nabla a^I\|_{L^4(\Omega)}^4 ds \right)^{1/2} \\
&\leq \sqrt{t} \left(\int_0^t e^{C_{99}t} \left[C_{100} + C_{101} \int_0^s \|\nabla a^I\|_{L^4(\Omega)}^4 + \|\nabla a^J\|_{L^4(\Omega)}^4 d\tau \right] \|\nabla a^I\|_{L^4(\Omega)}^4 ds \right)^{1/2} \\
&= \sqrt{t} \left\{ \int_0^t \left[C_{100} e^{C_{99}T} \|\nabla a^I\|_{L^4(\Omega)}^4 + \frac{C_{101}}{2} e^{C_{99}T} \frac{d}{ds} \left(\int_0^s \|\nabla a^I\|_{L^4(\Omega)}^4 d\tau \right)^2 \right] ds \right. \\
&\quad \left. + C_{101} e^{C_{99}T} \int_0^t \|\nabla a^I\|_{L^4(\Omega)}^4 ds \int_0^t \|\nabla a^J\|_{L^4(\Omega)}^4 ds \right\}^{1/2} \\
&\leq \sqrt{t} \left\{ C_{100} e^{C_{99}T} \int_0^t \|\nabla a^I\|_{L^4(\Omega)}^4 ds + C_{101} e^{C_{99}T} \left(\int_0^t \|\nabla a^I\|_{L^4(\Omega)}^4 ds \right)^2 \right. \\
&\quad \left. + C_{101} e^{C_{99}T} \left(\int_0^t \|\nabla a^J\|_{L^4(\Omega)}^4 ds \right)^2 \right\}^{1/2} \\
&\leq \sqrt{t} \sqrt{C_{100}} e^{\frac{C_{99}}{2}T} \left(\int_0^t \|\nabla a^I\|_{L^4(\Omega)}^4 ds \right)^{1/2} + \sqrt{t} \sqrt{C_{101}} e^{\frac{C_{99}}{2}T} \int_0^t \|\nabla a^I\|_{L^4(\Omega)}^4 ds \\
&\quad + \sqrt{t} \sqrt{C_{101}} e^{\frac{C_{99}}{2}T} \int_0^t \|\nabla a^J\|_{L^4(\Omega)}^4 ds \\
&\leq \sqrt{t} (\sqrt{C_{100}} + \sqrt{C_{101}}) e^{\frac{C_{99}}{2}T} \int_0^t \|\nabla a^I\|_{L^4(\Omega)}^4 ds + \sqrt{T} \sqrt{C_{100}} e^{\frac{C_{99}}{2}T} \\
&\quad + \sqrt{t} \sqrt{C_{101}} e^{\frac{C_{99}}{2}T} \int_0^t \|\nabla a^J\|_{L^4(\Omega)}^4 ds. \tag{4.28}
\end{aligned}$$

Since we consider the case of two space dimensions, the Gagliardo-Nirenberg inequality, and the estimate $\|D^2 w\|_{L^2(\Omega)} \leq C \|\Delta w\|_{L^2(\Omega)}$ for any $w \in H^2(\Omega)$ with $\frac{\partial w}{\partial \nu} = 0$ on $\partial\Omega$ imply the following inequalities for any $0 \leq t \leq T$:

$$\int_0^t \|\nabla a^D\|_{L^4(\Omega)}^4 ds \leq C_{102} e^{2\chi_D \mu_v T} \int_0^t \|\Delta a^D\|_{L^2(\Omega)}^2 ds + C_{103} T e^{4\chi_D \mu_v T}, \tag{4.29}$$

$$\int_0^t \|\nabla a^S\|_{L^4(\Omega)}^4 ds \leq C_{104} e^{2\chi_S \mu_v T} \int_0^t \|\Delta a^S\|_{L^2(\Omega)}^2 ds + C_{105} T e^{4\chi_S \mu_v T}. \tag{4.30}$$

Inserting (4.29) and (4.30) into (4.28) we obtain

$$\begin{aligned}
&\int_0^t \|\nabla v \cdot \nabla a^I\|_{L^2(\Omega)}^2 ds \\
&\leq \sqrt{t} C_{106} e^{C_{107}T} \left(\int_0^t \|\Delta a^D\|_{L^2(\Omega)}^2 ds + \int_0^t \|\Delta a^S\|_{L^2(\Omega)}^2 ds \right) + C_{108} \sqrt{T} (1+T) e^{C_{109}T}. \tag{4.31}
\end{aligned}$$

By taking the maximum of the constants in the individual estimates of a^D and a^S , we obtain the same constants in (4.31). Inserting (4.31) into (4.26) implies

$$\int_0^t \|\Delta a^D\|_{L^2(\Omega)}^2 ds \leq 2\sqrt{t} \chi_D^2 C_{106} e^{C_{107}T} \left(\int_0^t \|\Delta a^D\|_{L^2(\Omega)}^2 ds + \int_0^t \|\Delta a^S\|_{L^2(\Omega)}^2 ds \right) + C_{110}(T) \tag{4.32}$$

$$\int_0^t \|\Delta a^S\|_{L^2(\Omega)}^2 ds \leq 2\sqrt{t} \chi_S^2 C_{106} e^{C_{107}T} \left(\int_0^t \|\Delta a^D\|_{L^2(\Omega)}^2 ds + \int_0^t \|\Delta a^S\|_{L^2(\Omega)}^2 ds \right) + C_{111}(T). \tag{4.33}$$

Adding the two estimates above yields

$$\begin{aligned} & \int_0^t \|\Delta a^D\|_{L^2(\Omega)}^2 ds + \int_0^t \|\Delta a^S\|_{L^2(\Omega)}^2 ds \\ & \leq 2\sqrt{t}(\chi_D^2 + \chi_S^2)C_{106}e^{C_{107}T} \left(\int_0^t \|\Delta a^D\|_{L^2(\Omega)}^2 ds + \int_0^t \|\Delta a^S\|_{L^2(\Omega)}^2 ds \right) + C_{112}(T), \end{aligned} \quad (4.34)$$

so that

$$\left(1 - 2\sqrt{t}(\chi_D^2 + \chi_S^2)C_{106}e^{C_{107}T}\right) \left(\int_0^t \|\Delta a^D\|_{L^2(\Omega)}^2 ds + \int_0^t \|\Delta a^S\|_{L^2(\Omega)}^2 ds \right) \leq C_{113}(T). \quad (4.35)$$

Choosing

$$t_1 = t_1(T) = \frac{1}{\left(4(\chi_D^2 + \chi_S^2)C_{106}e^{C_{107}T}\right)^2}$$

we obtain

$$\int_0^t \|\Delta a^D\|_{L^2(\Omega)}^2 ds + \int_0^t \|\Delta a^S\|_{L^2(\Omega)}^2 ds \leq 2C_{114}(T) \quad \text{for all } 0 \leq t \leq t_1. \quad (4.36)$$

If $t_1(T) \geq T$ we have completed the proof of the lemma. If $t_1(T) < T$ we may repeat the procedure described above by taking $t_0 = t_1(T)$ as new initial datum. Since $t_1(T)$ only depends on T we can extend the estimate (4.34) to the whole time interval $[0, T]$ after finitely many steps. This completes the proof of (4.20). The bounds now (4.21) follow by combining (4.20) and (4.29),(4.30). \square

We are now in position to state the main result of this section, i.e., $\|\nabla v(\cdot)\|_{L^4(\Omega)}$ does not blow up in finite time.

Lemma 4.4. *Assume that $(a^D, a^S, v, m) \in (C^{2,1}(\bar{Q}_T))^4$ is a solution of (2.1). Then the following inequality is fulfilled*

$$\|\nabla v(t)\|_{L^4(\Omega)} \leq C_{115}(T). \quad (4.37)$$

Proof. Follows directly by combining (4.21) with (4.14). \square

5 Proof of the global existence Theorem 1.1

In this section we show existence and uniqueness of classical solutions of (2.1) based on the local well-posedness results and a priori estimates from the previous sections. We begin by establishing uniform in time bounds for $\|a^D(\cdot)\|_{C^2(\Omega)}$, $\|a^S(\cdot)\|_{C^2(\Omega)}$, $\|v(\cdot)\|_{C^1(\Omega)}$, $\|m(\cdot)\|_{C^2(\Omega)}$.

Lemma 5.1. *Let $(a^D, a^S, v, m) \in (C^{2,1}(Q_T))^4$ be a solution of (2.1), and let (1.6) hold. Then for all $t \in (0, T)$*

$$\|a^D(t)\|_{C^2(\Omega)}, \|a^S(t)\|_{C^2(\Omega)}, \|v(t)\|_{C^1(\Omega)}, \|m(t)\|_{C^2(\Omega)} \leq C_{116}(T). \quad (5.1)$$

Proof. Using (2.1) we can rewrite the equations for a^D and a^S as

$$a_t^D = \Delta a^D + \chi_D \nabla v \cdot \nabla a^D + h_{17} a^D \quad \text{in } \Omega \times (0, T), \quad (5.2)$$

$$a_t^S = \Delta a^S + \chi_S \nabla v \cdot \nabla a^S + h_{18} a^S + \mu_{\text{EMT}} a^D e^{\chi_D v - \chi_S v} \quad \text{in } \Omega \times (0, T), \quad (5.3)$$

where

$$h_{17} = -\mu_{\text{EMT}} + (\mu_D - \chi_D \mu_v v) \rho_{\text{dev}} + \chi_D v m, \quad (5.4)$$

$$h_{18} = (\mu_S - \chi_S \mu_v v) \rho_{\text{dev}} + \chi_S v m. \quad (5.5)$$

By employing (4.14) for $p = 4$, $0 \leq v \leq 1$, (4.1), and (1.7a) we have

$$\|\nabla v(t)\|_{L^4(\Omega)}, \|h_{17}(t)\|_{L^\infty(\Omega)}, \|h_{18}(t)\|_{L^\infty(\Omega)}, \|\mu_{\text{EMT}} a^D(t) e^{\chi_D v - \chi_S v}\|_{L^\infty(\Omega)} \leq C_{117}(T). \quad (5.6)$$

This allows us to use the maximal parabolic regularity result in L^p , see Theorem A.1, for both equations (5.2), (5.3) to obtain

$$\|a^D\|_{W_4^{2,1}(Q_T)}, \|a^S\|_{W_4^{2,1}(Q_T)} \leq C_{118}(T). \quad (5.7)$$

Thanks to the Sobolev embedding A.4 there is a constant $C_{119}(p)$ such that for all $p > 1$ it holds

$$\|\nabla a^D\|_{L^p(Q_T)}, \|\nabla a^S\|_{L^p(Q_T)} \leq C_{119}(p)C_{118}(T), \quad (5.8)$$

which yields together with (4.14) that

$$\|\nabla v(t)\|_{L^p(\Omega)} \leq C_{120}(p, T) \quad \text{for all } p > 1. \quad (5.9)$$

Using Theorem A.2 again for (5.2), (5.3) together with (5.6) and (5.9), we get

$$\|a^D\|_{W_p^{2,1}(Q_T)}, \|a^S\|_{W_p^{2,1}(Q_T)} \leq C_{121}(p, T) \quad \text{for all } p > 1. \quad (5.10)$$

Moreover, applying A.1 again in equation for m in (2.1) we obtain

$$\|m\|_{W_p^{2,1}(Q_T)} \leq C_{122}(p) \quad \text{for all } p > 1. \quad (5.11)$$

Applying the Sobolev embedding A.3 to (5.10), (5.11) for a fixed $p > 5$ yields for $\lambda = 1 - 5/p$

$$\|a^D\|_{C^{1+\lambda, (1+\lambda)/2}(\bar{Q}_T)}, \|a^S\|_{C^{1+\lambda, (1+\lambda)/2}(\bar{Q}_T)}, \|m\|_{C^{1+\lambda, (1+\lambda)/2}(\bar{Q}_T)} \leq C_{123}(T). \quad (5.12)$$

By considering $0 \leq v \leq 1$, the equation for a^S in (2.1) together with (5.12) as well as (2.46), (2.43), and (2.44) with (5.12) we get

$$\|v\|_{C^{1,1}(\bar{Q}_T)} \leq C_{124}(T). \quad (5.13)$$

Using now the same arguments as in the proof of Theorem 2.2 we obtain

$$\|a^D\|_{C^{2+\lambda, 1+\lambda/2}(\bar{Q}_T)}, \|a^S\|_{C^{2+\lambda, 1+\lambda/2}(\bar{Q}_T)}, \|m\|_{C^{2+\lambda, 1+\lambda/2}(\bar{Q}_T)} \leq C_{125}(T). \quad (5.14)$$

Estimate (5.1) follows from (5.14) and (5.13). \square

Finally we can prove the existence and uniqueness of the global classical solutions, as stated in the main Theorem 1.1.

Proof of the main Theorem 1.1. Due to the equivalence of (1.1) and (2.1) the proof is a consequence of Theorem 2.1, Theorem 2.2 and Lemma 5.1. Indeed we know that there exist (regular) local-in-time solutions due to Theorem 2.1 and Theorem 2.2. If they only existed until some maximal final time $T_{max} < \infty$, then the a priori bounds in Lemma 5.1 would enable us to use Theorem 2.1 in order to extend the solution beyond T_{max} and Theorem 2.2 would ensure the regularity of this extension. This shows that there cannot be a finite maximal time of existence. \square

6 Numerical simulations

We perform in this section a series of numerical experiments to demonstrate the dynamics of the system (1.1) and the effect that the constraints placed on its parameters have. As the primary aim of the paper is the mathematical analysis of the model we refrain from a detailed numerical investigation and refer to [39, 14] for more details.

In the first numerical experiment, the parameters we consider satisfy the constraints (1.6), and the solutions exhibit a smooth profile that smears-out even more with time. In the second experiment we consider similar initial conditions and a parameter set that violates (1.6); this time the solutions exhibit steeper gradients and more complex and dynamic structures.

The numerical results presented here should be understood as indications of the influence that the parameters have on the dynamics of the solutions, not as evidence that the analysis results of this work are no longer valid when the constraints (1.6) are violated.

To numerically solve the system (1.1) we first rewrite it in the more convenient form

$$\mathbf{w}_t(\mathbf{x}, t) = A(\mathbf{w}(\mathbf{x}, t)) + D(\mathbf{w}(\mathbf{x}, t)) + R(\mathbf{w}(\mathbf{x}, t)), \quad \mathbf{x} \in \Omega, \quad (6.1)$$

with $\mathbf{w}(\mathbf{x}, t) := (c^D(\mathbf{x}, t), c^S(\mathbf{x}, t), v(\mathbf{x}, t), m(\mathbf{x}, t))^T$, and where

$$A(\mathbf{w}) = \begin{pmatrix} -\chi_D \nabla \cdot (c^D \nabla v) \\ -\chi_S \nabla \cdot (c^S \nabla v) \\ 0 \\ 0 \end{pmatrix}, \quad R(\mathbf{w}) = \begin{pmatrix} -\mu_{\text{EMT}} c^D + \mu_D c^D (1 - c^S - c^D - v) \\ \mu_{\text{EMT}} c^D + \mu_S c^S (1 - c^S - c^D - v) \\ -mv + \mu_v v (1 - c^S - c^D - v) \\ c^S + c^D - m \end{pmatrix}, \quad D(\mathbf{w}) = \begin{pmatrix} \Delta c^D \\ \Delta c^S \\ 0 \\ \Delta m \end{pmatrix},$$

denote the *advection*, *reaction*, and *diffusion* operators respectively.

We consider a uniform spatial discretization grid with diameter h , and denote by $\mathbf{w}_h(t)$ the piecewise constant *Finite Volume* (FV) approximation of the exact solution \mathbf{w} , that satisfies the semi-discrete numerical scheme

$$\partial_t \mathbf{w}_h = \mathcal{A}(\mathbf{w}_h) + \mathcal{R}(\mathbf{w}_h) + \mathcal{D}(\mathbf{w}_h). \quad (6.2)$$

The operators \mathcal{A} , \mathcal{R} , and \mathcal{D} are *discrete approximations* of the advection, reaction, and diffusion operators A , R , and D in (6.1) respectively. For the diffusion terms we use central differences, and we employ *central upwind* numerical fluxes for the advection terms. At the interfaces of the computational cells we use values of \mathbf{w}_h reconstructed by the *minimized-central* (MC) limiter, [49].

We solve (6.2) with an *Implicit-Explicit Runge-Kutta* (IMEX-RK) numerical method, [30], that is based on the *time splitting* of (6.2), in *explicit* and *implicit* terms, in the form

$$\partial_t \mathbf{w}_h = \mathcal{I}(\mathbf{w}_h) + \mathcal{E}(\mathbf{w}_h). \quad (6.3)$$

In the typical case, and also in the current paper, the advection terms are treated explicitly, the diffusion terms implicitly, and the reaction terms partly explicitly and partly implicitly. The particular choice depends primarily on the stiffness of the reaction terms but also on the nature of their (possible) non-linearity.

For the implicit part of the scheme we employ a diagonally implicit RK method and an explicit RK for the explicit part

$$\left\{ \begin{array}{l} \mathbf{W}_i^* = \mathbf{w}_h^n + \tau_n \sum_{j=1}^{i-2} \bar{a}_{i,j} \mathbf{E}_j + \tau_n \bar{a}_{i,i-1} \mathbf{E}_{i-1}, \quad i = 1, \dots, s \\ \mathbf{W}_i = \mathbf{W}_i^* + \tau_n \sum_{j=1}^{i-1} a_{i,j} \mathbf{I}_j + \tau_n a_{i,i} \mathbf{I}_i, \quad i = 1, \dots, s \\ \mathbf{w}_h^{n+1} = \mathbf{w}_h^n + \tau_n \sum_{i=1}^s \bar{b}_i \mathbf{E}_i + \tau_n \sum_{i=1}^s b_i \mathbf{I}_i \end{array} \right. , \quad (6.4)$$

where $s = 4$ are the stages of the IMEX method, $\mathbf{E}_i = \mathcal{E}(\mathbf{W}_i)$, $\mathbf{I}_i = \mathcal{I}(\mathbf{W}_i)$, $i = 1 \dots s$, $\{\bar{b}, \bar{A}\}$, $\{b, A\}$ are respectively the coefficients for the explicit and the implicit part of the scheme, given in the Butcher Tableau in Table 1, see also [21].

We solve the linear systems in (6.4) using the *iterative biconjugate gradient stabilized Krylov subspace* method [24, 48].

Experiment 1. In this first experiment the parameter constraints (1.6) are satisfied. We consider the domain $\Omega = [-7, 7] \times [-12, 5]$ and the initial conditions

$$(c^D(\mathbf{x}, 0), c^S(\mathbf{x}, 0), v(\mathbf{x}, 0), m(\mathbf{x}, 0)) = (0.7 e^{-5\chi_y < g(x)} (\mathbf{x})(y-g(x))^2, 0, 0.2, 0), \quad (6.5)$$

with $g(x) = 0.7 \sin(1.4x) + 0.004x^3 + 2$ and $\mathbf{x} = (x, y) \in \Omega$. The parameters are chosen as

$$(\chi_D, \chi_S, \mu_D, \mu_S, \mu_v) = (8 \cdot 10^{-3}, 400, 0.2, 0.1, 2.5 \cdot 10^{-4}), \quad (6.6)$$

Table 1: *Butcher tableaux for the explicit (upper) and the implicit (lower) parts of the third order IMEX scheme (6.4), see also [21].*

0				
$\frac{1767732205903}{2027836641118}$	$\frac{1767732205903}{2027836641118}$			
$\frac{3}{5}$	$\frac{5535828885825}{10492691773637}$	$\frac{788022342437}{10882634858940}$		
1	$\frac{6485989280629}{16251701735622}$	$-\frac{4246266847089}{9704473918619}$	$\frac{10755448449292}{10357097424841}$	
	$\frac{1471266399579}{7840856788654}$	$-\frac{4482444167858}{7529755066697}$	$\frac{11266239266428}{11593286722821}$	$\frac{1767732205903}{4055673282236}$
0	0			
$\frac{1767732205903}{2027836641118}$	$\frac{1767732205903}{4055673282236}$	$\frac{1767732205903}{4055673282236}$		
$\frac{3}{5}$	$\frac{2746238789719}{10658868560708}$	$-\frac{640167445237}{6845629431997}$	$\frac{1767732205903}{4055673282236}$	
1	$\frac{1471266399579}{7840856788654}$	$-\frac{4482444167858}{7529755066697}$	$\frac{11266239266428}{11593286722821}$	$\frac{1767732205903}{4055673282236}$
	$\frac{1471266399579}{7840856788654}$	$-\frac{4482444167858}{7529755066697}$	$\frac{11266239266428}{11593286722821}$	$\frac{1767732205903}{4055673282236}$

and the EMT coefficient μ_{EMT} is set to the constant value $\mu_{\text{EMT}} = 0.55$. In this experiment we have considered and compared the cases with explicit and implicit discretization of the EMT terms and the results were indistinguishable. The discretization of the cell proliferation, the ECM remodelling, and the rest of the reaction terms is explicit. Note moreover that the parameters satisfy the restrictions (1.6).

We present the simulation results for this experiment in Figure 2, and mostly focus on the dynamics of the CSCs. We can clearly see that the CSCs escape the main body of the tumour and invade the ECM in a more dynamic way than the DCCs. We also see the formation of smooth CSC “invasion islands” that merge with each other and smear-out further. At the same time, the DCCs evolve mostly under the influence of diffusion.

Experiment 2. In this second experiment, the parameters considered violate the constraints (1.6). In some more detail, we consider the domain $\Omega = [-5 \cdot 10^3, 5 \cdot 10^3] \times [-5 \cdot 10^3, 5 \cdot 10^3]$ and endow (1.1) with the initial conditions

$$(c^D(\mathbf{x}, 0), c^S(\mathbf{x}, 0), v(\mathbf{x}, t), m(\mathbf{x}, 0)) = \left(0.7 e^{-5\mathcal{X}_{y < g(x)}(\mathbf{x})(y-g(x))^2}, 0, 0.2, 0\right), \quad (6.7)$$

where $g(x) = 1.5 \cdot 10^3 \sin(9 \cdot 10^{-4}x) + 2.4 \cdot 10^{-5}x^3 + 2 \cdot 10^3$ and $\mathbf{x} = (x, y) \in \Omega$. These initial conditions are similar to the ones in Experiment 1, in the sense that they also represent (a two-dimensional transverse section of) an *organotypic assay* with sinusoidal profile, see e.g. [29, 18].

The parameters employed here are inspired by [39], where particular assumptions of biological nature were made, and they read

$$(\chi_D, \chi_S, \mu_D, \mu_S, \mu_v) = (1.2 \cdot 10^4, 10^6, 0.2, 0.1, 0.01). \quad (6.8)$$

It can be easily seen that these parameters violate the constraints (1.6).

Following [39] again, we set the EMT coefficient μ_{EMT} to depend on the DCC density in the following way

$$\mu_{\text{EMT}} = \mu_M \frac{c_{\mu_{\text{EMT}},1} c^D}{c_{\mu_{\text{EMT}},2} + c_{\mu_{\text{EMT}},1} c^D}. \quad (6.9)$$

The coefficients $\mu_M, c_{\mu_{\text{EMT}},1}, c_{\mu_{\text{EMT}},2} > 0$ are constants that reflect, through the above relation, the particular EMT triggering mechanism that is considered in [39]. It can be easily seen that μ_{EMT} is Lipschitz continuous as a function of c^D (and also has a Lipschitz continuous first derivative) and satisfies the required boundedness condition (1.7a). To ease the computations, we have discretized in this experiment the EMT terms, as well as the proliferation, remodelling, and degradation terms, explicitly.

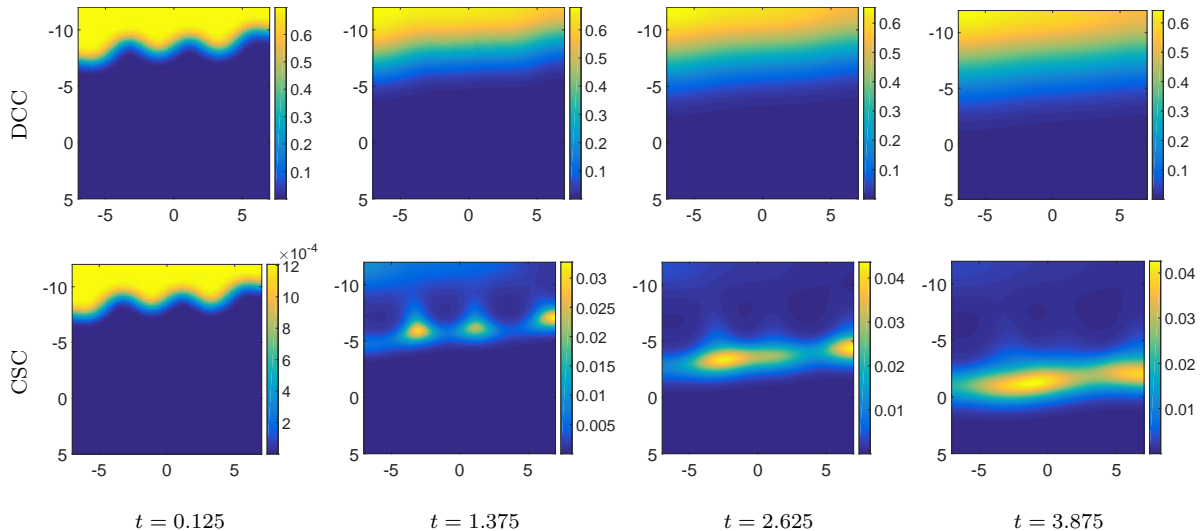


Figure 2: *Simulation results of the Experiment 1. Showing here the spatial distribution of the DCC and CSC densities at several time instances. The CSCs invade the ECM by forming smooth “islands” that merge and smear-out further with time. On the other hand, the evolution of the DCCs is mostly diffusion dominated.*

The simulation results for this experiment are presented in Figure 3 where, again, we focus on the dynamics of the CSCs. We clearly see that the CSCs escape the main body of the tumour and invade the ECM in a more dynamic way than the DCCs. We also see that the dynamics that the CSCs exhibit are much richer than in Experiment 1, namely they invade the ECM with a number of small waves and invasion “islands” which, as they interact with each other, they create a complex landscape.

Such invasion-patterns are typical in organotypic assays of several types of cancer, see e.g. [29, 18], and constitute a *sought-for property* in the field of cancer growth and invasion modelling and simulation, we refer indicatively to [7, 2, 41, 22].

Furthermore, it was seen in [39] that the choice of a non-constant EMT coefficient μ_{EMT} as in (6.9), leads potentially to a CSC profile that is substantially lower than the density of the DCC tumour, and so it remains below “detection levels”. On the contrary, constant EMT coefficients μ_{EMT} lead to CSC densities that quickly rise to the levels of the DCC density and can be easily detected.

This particular property of the non-constant μ_{EMT} (6.9) serves as a potential mathematical explanation of the difficulty to detect CSCs, and justifies to a large extent, the numerical (in [14, 39]) and analytical (in the current paper) study of the model (1.1).

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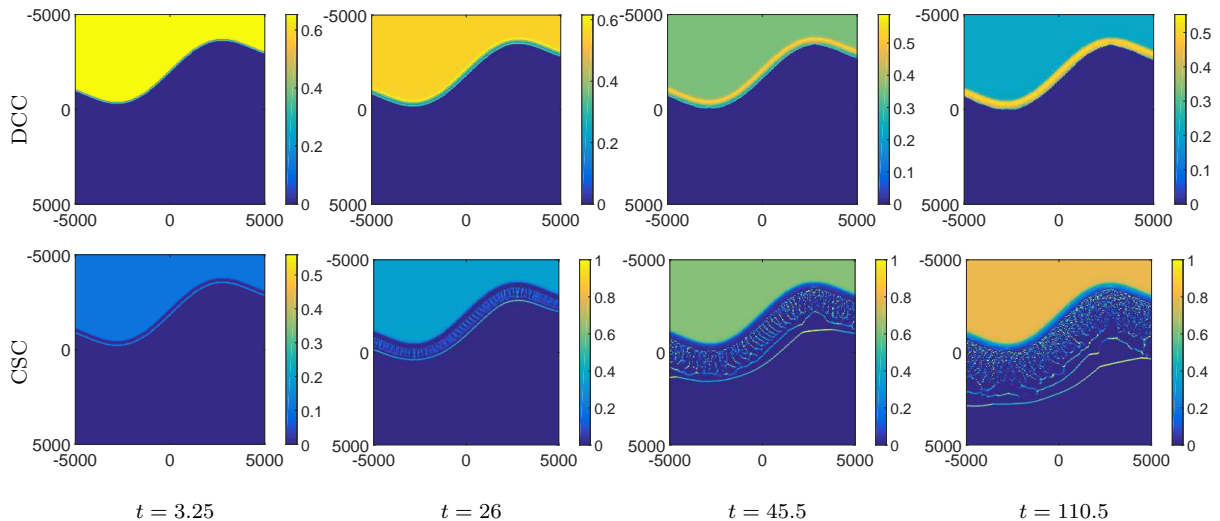


Figure 3: Numerical simulation of the Experiment 2. Showing here the spatial distribution of the densities of the DCCs, CSCs components at several time instances. As opposed to Experiment 1, the particular choice of parameters leads to a highly dynamic invasion of the ECM by the CSCs. Thin waves interact and lead to complex invasion landscape.

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A Parabolic theory

We consider the problem

$$u_t - D\Delta u + \sum_{i=1}^d a_i \frac{\partial u}{\partial x_i} + au = f \text{ in } Q_T, \quad (\text{A.1})$$

$$\partial_\nu u = 0 \text{ on } \partial\Omega \times (0, T), \quad (\text{A.2})$$

$$u(\cdot, 0) = u_0 \text{ in } \Omega, \quad (\text{A.3})$$

where $D \in \mathbb{R}^+$, and a, a_i are real valued functions in Q_T . For the initial condition we assume for a fixed $\lambda \in (0, 1)$ that

$$u_0(x) \geq 0, \quad u_0 \in C^{2+\lambda}(\Omega), \quad (\text{A.4})$$

and the compatibility condition

$$\partial_\nu u_0 = 0. \quad (\text{A.5})$$

Furthermore, we assume a bounded domain Ω with

$$\partial\Omega \in C^{2+\lambda}, \quad (\text{A.6})$$

and $Q_T = \Omega \times (0, T)$.

Theorem A.1. *Let the conditions (A.4) and (A.5) hold, and let the coefficients in (A.1) satisfy*

$$a, a_i \in L^{d+2}(Q_T), \quad f \in L^p(Q_T) \quad 1 \leq i \leq d, \quad \partial\Omega \in C^2,$$

for $d+2 < p$ and assume that

$$\lim_{\tau \rightarrow 0} \|a\|_{L^p(\Omega \times (t, t+\tau))} = \lim_{\tau \rightarrow 0} \|a_i\|_{L^p(\Omega \times (t, t+\tau))} = 0.$$

Then the problem (A.1)–(A.3) has a unique solution

$$u \in W_p^{2,1}(Q_T),$$

which can be bounded by

$$\|u\|_{W_p^{2,1}(Q_T)} \leq C \left(\|f\|_{L^p(\Omega)} + \|u_0\|_{L^p(\Omega)}^{2-2/p} \right).$$

Proof. Follows from [25, Theorem 9.1 p. 342]. □

Theorem A.2. *Assume that,*

$$a, a_i, f \in C^{\lambda, \lambda/2}(\bar{Q}_T) \quad 1 \leq i \leq d, \quad 0 < T < 1, \quad \partial\Omega \in C^{2+\lambda}$$

and that (A.4), (A.5) are satisfied. Then the problem (A.1)–(A.3) has a unique solution

$$u \in C^{\lambda+2, \lambda/2+1}(\bar{Q}_T).$$

Proof. Follows from [25, Theorem 5.3 p. 320]. □

Theorem A.3. Assume that Ω satisfies a weak cone condition and $d \in \{1, 2, 3\}$. If $p > 5$, then

$$\|u\|_{C^{1+\lambda, (1+\lambda)/2}(\bar{Q}_T)} \leq C \|u\|_{W_p^{2,1}(Q_T)}, \quad \lambda = 1 - \frac{5}{p},$$

for all $u \in W_p^{2,1}(Q_T)$.

Proof. Follows from [25, Lemma 3.3 p. 80]. \square

Theorem A.4. Assume that Ω satisfies a weak cone condition and $d = 2$. If $q \geq 4$ and $u \in W_p^{2,1}(Q_T)$ then

$$\|\nabla u\|_{L^p(\bar{Q}_T)} \leq C(p) \|u\|_{W_q^{2,1}(Q_T)}, \quad \text{for all } p > 4.$$

Proof. Follows from [25, Lemma 3.3 p. 80]. \square

B Proof of Lemma 3.2

Proof. Let A_ρ be the sectorial operator defined by $A_\rho u = -\Delta u$ over the domain

$$D(A_\rho) = \left\{ u \in W^{2,\rho}(\Omega) \text{ with } \frac{\partial u}{\partial \nu} \Big|_{\Gamma_T} = 0 \right\}.$$

We will be needing the following embedding properties of the domains of fractional powers of the operators $A_p + 1$:

$$D((A_p + 1)^\beta) \hookrightarrow W_p^1(\Omega), \quad \text{for } \beta > \frac{1}{2}, \quad (\text{B.1a})$$

$$D((A_p + 1)^\beta) \hookrightarrow C^\delta(\Omega), \quad \text{for } \beta - \frac{d}{2p} > \frac{\delta}{2} \geq 0, \quad (\text{B.1b})$$

and refer to [17, 15] and the references therein for further details.

We consider the representation formula for the solution of the equation for m in (1.1)

$$m(t) = \underbrace{e^{-t(A_\rho+1)} m_0}_{B_1(t)} + \underbrace{\int_0^t e^{-(t-r)(A_\rho+1)} (c^D(r) + c^S(r)) dr}_{B_2(t)}, \quad t \in (0, T).$$

To deduce a control over m we consider the two components separately.

For $B_1(t)$.

- If $2 \leq q \leq \infty$, then B_1 and m_0 have the same regularity, see [17], and hence

$$\|B_1(t)\|_{W_q^1(\Omega)} \leq C \|m_0\|_{W_q^1(\Omega)}. \quad (\text{B.2a})$$

- If $q < 2$, then

$$\|B_1(t)\|_{W_q^1(\Omega)} \leq \|B_1(t)\|_{W_2^1(\Omega)} \leq C \|m_0\|_{W_2^1(\Omega)}. \quad (\text{B.2b})$$

For $B_2(t)$.

We consider the analytic semigroup $(e^{-tA_\rho})_{t \geq 0}$, which has the properties

$$\|(A_\rho + 1)^\beta e^{-t(A_\rho+1)} u\|_{L^p(\Omega)} \leq ct^{-\beta} e^{-v_1 t} \|u\|_{L^p}$$

for all $u \in L^p(\Omega)$, $t \geq 0$, and for some $v_1 > 0$, and

$$\|e^{-tA_\rho} u\|_{L^q(\Omega)} \leq ct^{-\frac{d}{2}(\frac{1}{p} - \frac{1}{q})} \|u\|_{L^p(\Omega)}$$

, for all $t \in (0, 1)$ and $1 \leq p < q < \infty$, see also [17].

Accordingly we can write the following L^ρ - L^q estimate, for $\tau > 0$

$$\begin{aligned} \|(A_\rho + 1)^\beta e^{-2\tau A_\rho} u\|_{L^q(\Omega)} &= \|(A_\rho + 1)^\beta e^{-\tau(A_\rho+1)} e^{-\tau A_\rho} e^\tau u\|_{L^q(\Omega)} \\ &\leq C \tau^{-\beta} e^{-v_1 \tau} \|e^{-\tau A_\rho} e^\tau u\|_{L^q(\Omega)} \\ &\leq \tilde{c} \tau^{-\beta} e^{-v_1 \tau} \tau^{-\frac{d}{2}(\frac{1}{\rho} - \frac{1}{q})} \|e^\tau u\|_{L^p(\Omega)} \\ &\leq \tilde{c} \tau^{-\beta - \frac{d}{2}(\frac{1}{\rho} - \frac{1}{q})} e^{(1-v_1)\tau} \|u\|_{L^p(\Omega)}, \end{aligned}$$

or by setting $t = 2\tau$,

$$\begin{aligned} \|(A_\rho + 1)^\beta e^{-t A_\rho} u\|_{L^q(\Omega)} &\leq \tilde{c} \left(\frac{t}{2}\right)^{-\beta - \frac{d}{2}(\frac{1}{\rho} - \frac{1}{q})} e^{(1-v_1)\frac{t}{2}} \|u\|_{L^p(\Omega)} \\ &\leq C t^{-\beta - \frac{d}{2}(\frac{1}{\rho} - \frac{1}{q})} e^{(1-\mu)t} e^{-\frac{t}{2}} \|u\|_{L^p(\Omega)} \\ &\leq C t^{-\beta - \frac{d}{2}(\frac{1}{\rho} - \frac{1}{q})} e^{(1-\mu)t} \|u\|_{L^p(\Omega)} \end{aligned} \tag{B.3}$$

for some $\mu > 0$.

Applying now (B.3) to B_2 , it reads

$$\begin{aligned} \|(A_\rho + 1)^\beta B_2\|_{L^q(\Omega)} &\leq C \int_0^t (t-r)^{-\beta - \frac{d}{2}(\frac{1}{\rho} - \frac{1}{q})} e^{-\mu(t-r)} \|u(r)\|_{L^\rho(\Omega)} dr \\ &\leq C \sup_t \|u(t)\|_{L^\rho(\Omega)} \int_0^t (t-r)^{-\beta - \frac{d}{2}(\frac{1}{\rho} - \frac{1}{q})} e^{-\mu(t-r)} dr, \end{aligned}$$

where the integral is finite, and in effect $B_2(t) \in D((A_\rho + 1)^\beta)$, as long as

$$-\beta - \frac{d}{2} \left(\frac{1}{\rho} - \frac{1}{q} \right) > -1. \tag{B.4}$$

In order to obtain bounds for suitable norms of B_2 (and m) we distinguish the following sub-cases:

- If $\rho < d$ then there exist $\frac{1}{2} < \beta < 1$ such that (B.4) reads

$$q < \frac{1}{\frac{1}{\rho} - \frac{1}{d} + \frac{2}{d}(\beta - \frac{1}{2})}.$$

By the embedding now (B.1a) of the domain of the operator $(A_q + 1)^\beta$ we deduce that

$$\|B_2(t)\|_{W_q^1(\Omega)} \leq C, \tag{B.5}$$

which along with the bounds (B.2a) and (B.2b) of $\|B_1\|$ leads to (3.2).

- If $\rho = d$, the condition (B.4) recasts into

$$\beta < \frac{1}{2} + \frac{d}{2q},$$

which is satisfied by some $\frac{1}{2} < \beta < 1$ for every $q > \rho = d$, and thus (3.2) follows for $q < \infty$.

- If $\rho > d$ there by (B.4) $\beta < 1 - \frac{d}{2\rho} + \frac{d}{2q}$ and since $\frac{1}{2} + \frac{d}{2q} < 1 - \frac{d}{2\rho} + \frac{d}{2q}$ there exist β such that

$$\frac{1}{2} + \frac{d}{2q} < \beta < 1 - \frac{d}{2\rho} + \frac{d}{2q},$$

such that the embedding (B.1b) is valid for $\delta = 1$, and reads

$$D((A_q + 1)^\beta) \hookrightarrow C^1(\bar{\Omega}),$$

from which (3.2) yields for $q = \infty$.

□