

# Mathematical modeling and analysis of a tumor invasion problem with angiogenesis and taxis cascade

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## Abstract

We propose a mathematical model for tumor invasion supported by angiogenesis and interactions with the surrounding tissue. For the model deduction we employ a multiscale approach starting from lower scales and obtaining by an informal parabolic upscaling a system of reaction-diffusion-taxis equations with a so-called ‘taxis cascade’, where one species is performing taxis towards a signal whose production/decay is controlled by the other, for which it also serves as a tactic cue. We prove global existence and uniqueness of solutions to the obtained PDE-ODE system and perform numerical simulations to illustrate the behavior of solutions.

**Key words:** multiscale modeling; chemotaxis; haptotaxis; taxis cascade; global existence, uniqueness

**MSC:** 35Q92, 35B44, 35K55, 92C17, 35A01

## 1 Introduction and model set up

### 1.1 Biological motivation and previous continuous models

Cancer metastasis is crucially influenced by tumor cell migration and interactions with the peritumoral environment. Angiogenesis is one of the cancer hallmarks [24]. It involves the growth and development of new blood capillaries by chemotactically attracting endothelial cells (ECs) from neighboring vessels. The environment of a growing tumor becomes increasingly hypoxic, due to sustained glycolytic activity of the cancer cells [1, 20]. To further develop and metastasize, tumors require blood supply: they release pro-angiogenic factors (e.g., vascular endothelial growth factor = VEGF) that serve as chemoattractants for ECs [45]. Hence, they stimulate the formation of new blood vessels, eventually forming a network of capillaries that infiltrate the neoplasm, thus providing it with nutrients [25, 54]. Tumor angiogenesis is often targeted in cancer therapy, in order to inhibit tumor expansion.

Migrating cancer cells are also guided by gradients of surrounding tissue, see e.g., [36]. For instance, this is particularly prominent in glioma cells, which are known to follow white matter tracts and blood vessels to infiltrate the brain at distant sites from the original tumor [15, 21, 32]. Such behavior is typically described by haptotaxis in the framework of continuous reaction-diffusion-drift models.

Previous continuous models describing tumor angiogenesis and haptotaxis typically consider PDE-ODE systems set up in a more or less heuristic manner and coupling the dynamics of endothelial cells and extracellular matrix (ECM) or its components [53], possibly with a further PDE for some chemotactic signal [4, 9, 34, 37]. Some of these hence belong to the class of models with multiple taxis reviewed in [28]. For a recent review of mathematical models for tumor angiogenesis we refer to [27]. In this note we propose a model for tumor invasion guided by angiogenesis (here described by endothelial cell dynamics) and by ECM. Our multiscale approach connects meso- and macroscopic dynamics of tumor and endothelial cells, ECM, and VEGF and leads to a PDE-ODE system of reaction-diffusion-taxis equations where the ECs perform taxis towards VEGF gradients, thus following a signal produced by the tumor cells. The latter, in turn, follow gradients of EC density. Such tactic scenario is sometimes called a ‘taxis cascade’, see e.g. [43, 44, 50] for its use in another context.

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## 1.2 Model set up

We aim to deduce a macroscopic description for the dynamics of a population of tumor cells migrating in a tissue (mainly ECM) and interacting with endothelial cells. The cancer cells preferentially bias their motion towards gradients of tissue and EC densities, while the ECs follow the gradient of VEGF expressed by the tumor cells, which also degrade the ECM. Hence, the obtained mathematical model should involve partial differential equations with diffusion and taxis terms describing the mentioned biases. We follow the informal derivation performed e.g., in [10, 11, 29] within the kinetic theory of active particles (KTAP) framework [7] and adapt it here to the biological problem sketched above.

### 1.2.1 Micro-meso description

Cells perceive signals from their surroundings by way of their receptors binding to the respective ligands and of subsequent processing the therewith transmitted biochemical and/or biophysical information. Thus, we start by describing simple mass action kinetics for receptor binding (subcellular level) of the involved cell types (cancer cells, ECs) to their respective environmental cues (ECs and tissue for tumor cells, VEGF for ECs).

Let  $y_1$  and  $y_2$  denote the amounts of cancer cell receptors bound to tissue and ECs, respectively. We will also use  $u(t, x)$ ,  $w(t, x)$ , and  $v(t, x)$  to denote the macroscopic densities (volume fractions) of tumor cells, tissue, and ECs, respectively, as well as  $z(t, x)$  for the concentration of VEGF. Further, the mesoscopic quantities  $p(t, x, \vartheta_c, y)$  and  $\omega(t, x, \vartheta_e)$  represent the distribution functions of tumor cells and of ECs, respectively, each of them depending on a kinetic variable  $\vartheta$  representing cell velocity. We take  $t \geq 0$ ,  $x \in \mathbb{R}^N$ ,  $\vartheta_c \in s\mathbb{S}^{N-1} =: \Theta_c$ ,  $\vartheta_e \in \sigma\mathbb{S}^{N-1} =: \Theta_e$ , where  $\mathbb{S}^{N-1}$  is the unit sphere in  $\mathbb{R}^N$  and we assume constant speeds for the tumor cells and for the ECs:  $s = \frac{\vartheta_c}{|\vartheta_c|} > 0$ ,  $\sigma = \frac{\vartheta_e}{|\vartheta_e|} > 0$ ; hence, only the directions of the velocity vectors change.

$$\begin{aligned} \frac{v}{v_M} + (R_0 - y_1 - y_2) \xrightarrow[k_1^-]{k_1^+} y_1, \\ \frac{w}{w_M} + (R_0 - y_1 - y_2) \xrightarrow[k_2^-]{k_2^+} y_2, \end{aligned}$$

where  $v_M$  and  $w_M$  denote reference quantities for  $v$  and  $w$ , respectively; they are used for purposes of nondimensionalization occurring later on. Here  $R_0$  denotes the total amount of receptors on a cell membrane, which for simplicity we assume to be constant. If we rescale  $y_1$  and  $y_2$  by  $R_0$ , while keeping the same notation, and consider  $y := y_1 + y_2$  to be the total amount of bound receptors, then we can describe the receptor binding dynamics on a cancer cell by

$$\dot{y} = k_1^+ \frac{v}{v_M} + k_2^+ \frac{w}{w_M} - (k_1^+ \frac{v}{v_M} + k_2^+ \frac{w}{w_M} + k^-)y, \quad (1.1)$$

where we also assumed that the cell detachment rates from tissue and ECs are equal:  $k_1^- = k_2^- =: k^-$ . The so-called activity variable  $y$  is supposed to belong to the open interval  $(0, 1)$ ; for more details on this we refer to [33]. As in [11–13, 15–17, 29], we consider deviations  $\zeta := y_* - y$  from the steady-state

$$y_* = \frac{k_1^+ \frac{v}{v_M} + k_2^+ \frac{w}{w_M}}{B(v, w)}, \quad (1.2)$$

where we denoted  $B(v, w) := k_1^+ \frac{v}{v_M} + k_2^+ \frac{w}{w_M} + k^-$ . They satisfy the ODE

$$\dot{\zeta} = -B(v, w)\zeta + \frac{k^-}{(B(v, w))^2} \left( \frac{k_1^+}{v_M} D_t v + \frac{k_2^+}{w_M} D_t w \right) =: G(\zeta, v, w), \quad (1.3)$$

with  $D_t v = v_t + \vartheta_c \cdot \nabla v$  denoting the pathwise gradient of  $v$  (analogously  $D_t w$ ). Since the receptor binding dynamics is very fast when compared to the other biological processes described here, we will assume in the following that the deviations  $\zeta$  are very small. We denote by  $Z \subseteq [y_* - 1, y_*]$  the set to which the shifted activity variable  $\zeta$  belongs.

On the mesoscopic level the following kinetic transport equations (KTEs) hold for the cell distribution functions  $p(t, x, \vartheta_c, y)$  and  $\omega(t, x, \vartheta_e)$ :

$$p_t + \nabla_x \cdot (\vartheta_c p) + \partial_\zeta(G(\zeta, v, w)p) = \mathcal{L}[\lambda(\zeta)]p \quad (1.4)$$

$$\omega_t + \nabla_x \cdot (\vartheta_e \omega) = \mathcal{L}[\eta(\vartheta_e, z)]\omega, \quad (1.5)$$

where the turning operators on the right hand sides characterize cell reorientations in response to extracellular influences:

$$L[\lambda(\zeta)]p(t, x, \vartheta_c, \zeta) := -\lambda(\zeta)p(t, x, \vartheta_c, \zeta) + \lambda(\zeta) \int_{\Theta_c} K(\vartheta_c, \vartheta'_c) p(t, x, \vartheta'_c, \zeta) d\vartheta'_c = \lambda(\zeta) \left( \frac{\bar{p}}{|\Theta_c|} - p \right) \quad (1.6)$$

for the cancer cells, where we chose a uniform turning kernel  $K(\vartheta_c, \vartheta'_c) = \frac{1}{|\Theta_c|}$  and denoted  $\bar{p}(t, x, \zeta) = \int_{\Theta_c} p(t, x, \vartheta_c, \zeta) d\vartheta_c$ . In (1.6) the coefficient  $\lambda(\zeta)$  denotes the turning rate and, following [11, 15–17, 29], to which we also refer for more details about calculations in this Subsection, we take it in the affine form  $\lambda(\zeta) = \lambda_0 - \lambda_1 \zeta$ , with  $\lambda_0, \lambda_1 > 0$  constants.

On the other hand, we let the VEGF concentration act upon reorientations of ECs by way of selecting the turning rate in (1.5) of the form

$$\eta(\vartheta_e, z) := \eta_0 e^{-D_t z/z_M}, \quad D_t(z/z_M) = z_t/z_M + \vartheta_e \cdot \nabla_x z/z_M, \quad \eta_0 > 0 \text{ constant.} \quad (1.7)$$

We therewith have the turning operator for ECs (still with a uniform turning kernel)

$$L[\eta(\vartheta_e, z)]\omega(t, x, \vartheta_e) = -\eta(\vartheta_e, z)\omega(t, x, \vartheta_e) + \frac{1}{|\Theta_e|} \int_{\Theta_e} \eta(\vartheta'_e, z)\omega(t, x, \vartheta'_e) d\vartheta'_e. \quad (1.8)$$

This approach to including effects of environmental signals into KTE descriptions of mesoscopic cell density dynamics was proposed in [35] for bacteria swimming and adapted in [11, 29] to the case of cancer cell migration. It provides an alternative way<sup>1</sup> to the previous receptor binding dynamics for obtaining chemotaxis terms on the macrolevel. An informal relationship between these approaches was studied in [29], a rigorous one (in the case of bacteria) in [39].

### 1.2.2 Parabolic scaling

We perform a parabolic scaling of the mesoscopic system (1.4), (1.5), i.e. we rescale  $t \rightsquigarrow \varepsilon^2 t$ ,  $x \rightsquigarrow \varepsilon x$ . At this stage we also want to include some proliferation terms for the two types of cells. Since cells need a much longer time to proliferate than perform other functions (in particular migration), such terms will be correspondingly scaled (by  $\varepsilon^2$ ), as done e.g. in [11, 12, 16, 29]. Thus, (1.4), (1.5) become

$$\begin{aligned} \varepsilon^2 p_t + \varepsilon \nabla_x \cdot (\vartheta_c p) - \partial_\zeta \left( \left( \zeta B(v, w) - \frac{k^-}{(B(v, w))^2} \left( \frac{k_1^+}{v_M} (\varepsilon^2 \frac{v_t}{v_M} + \varepsilon \vartheta_c \cdot \nabla_x v) + \frac{k_2^+}{w_M} (\varepsilon^2 \frac{w_t}{w_M} + \varepsilon \vartheta_c \cdot \nabla_x w) \right) \right) p \right) \\ = L[\lambda(\zeta)]p + \varepsilon^2 \mu_c(u, v, w) \int_Z \Gamma(x, \zeta, \zeta') p(t, x, \vartheta_c, \zeta') d\zeta', \end{aligned} \quad (1.9)$$

$$\varepsilon^2 \omega_t + \varepsilon \nabla_x \cdot (\vartheta_e \omega) = L[\eta^\varepsilon(\vartheta_e, z)]\omega + \varepsilon^2 \mu_e(u, v, z)\omega, \quad (1.10)$$

where  $u(t, x) = \int_{\Theta_c} \int_Z p(t, x, \vartheta_c, \zeta) d\zeta d\vartheta_c$ ,  $v(t, x) = \int_{\Theta_e} \omega(t, x, \vartheta_e) d\vartheta_e$ , and  $\Gamma(x, \zeta, \zeta')$  is a kernel satisfying  $\int_Z \Gamma(x, \zeta, \zeta') d\zeta = 1$  and characterizing the transition from the (deviation of) cell receptor binding state  $\zeta'$  to  $\zeta$  during interaction with signals (tissue, inter- and intrapopulation exchange); thereby only the volume fractions (and not local directionality) are relevant, hence only macroscopic quantities are considered. In (1.10) we denoted

$$\eta^\varepsilon(\vartheta_e, z) = \eta_0 \exp(-(\varepsilon^2 z_t/z_M + \varepsilon \vartheta_e \cdot \nabla_x z/z_M)).$$

Using the moments w.r.t.  $\zeta$ :

$$m(t, x, \vartheta_c) = \int_Z p(t, x, \vartheta_c, \zeta) d\zeta, \quad m^\zeta(t, x, \vartheta_c) = \int_Z \zeta p(t, x, \vartheta_c, \zeta) d\zeta, \quad u^\zeta(t, x) = \int_{\Theta_c} \int_Z \zeta p(t, x, \vartheta_c, \zeta) d\zeta d\vartheta_c,$$

along with their Hilbert expansions  $m = \sum_{i=0}^{\infty} \varepsilon^i m_i$ ,  $m^\zeta = \sum_{i=0}^{\infty} \varepsilon^i m_i^\zeta$ , and  $u^\zeta = \sum_{i=0}^{\infty} \varepsilon^i u_i^\zeta$ , a linearization of  $\eta^\varepsilon$ , neglecting the higher order moments w.r.t.  $\zeta$  in virtue of the smallness assumption about these deviations, and equating the powers of  $\varepsilon$  in (1.9), (1.10) we obtain in the usual way (for details see e.g. [11, 12, 29]) the following macroscopic equations for  $u$  and  $v$ :

$$u_t = \nabla \cdot (\mathbb{D}_T \nabla u) - \nabla \cdot \left( \left( g(v, w) \frac{k_1^+}{v_M} \mathbb{D}_T \nabla v + g(v, w) \frac{k_2^+}{w_M} \mathbb{D}_T \nabla w \right) u \right) + \mu_c(u, v, w)u \quad (1.11)$$

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<sup>1</sup>yet another one can be found in [12, 14] or -more rigorously- in [56]

$$v_t = \nabla \cdot (\mathbb{D}_E \nabla v) - \nabla \cdot (\eta_0 v \mathbb{D}_E \nabla z / z_M) + \mu_e(u, v, z)v, \quad (1.12)$$

where:

$$\mathbb{D}_T = \frac{1}{\lambda_0} \int_{\Theta_c} \vartheta_c \otimes \vartheta_c \frac{1}{|\Theta_c|} d\vartheta_c = \frac{s^2}{N\lambda_0} \mathbb{I}_N \quad (\text{tumor diffusion tensor}) \quad (1.13)$$

$$\mathbb{D}_E = \frac{1}{\eta_0} \int_{\Theta_e} \vartheta_e \otimes \vartheta_e \frac{1}{|\Theta_e|} d\vartheta_e = \frac{\sigma^2}{N\eta_0} \mathbb{I}_N \quad (\text{EC diffusion tensor}) \quad (1.14)$$

$$g(v, w) = \frac{\lambda_1 k^-}{(B(v, w))^2(\lambda_0 + B(v, w))} \quad (\text{tactic sensitivity of tumor cells}). \quad (1.15)$$

The concrete forms of coefficient functions  $\mu_c, \mu_e$  will be provided in *Section 3*.

Performing an appropriate nondimensionalization leads to the system<sup>2</sup>

$$\begin{cases} u_t = \Delta u - \nabla \cdot (u\chi(v, w)\nabla v) - \nabla \cdot (u\xi(v, w)\nabla w) + \mu_c(u, v, w)u, \\ v_t = \Delta v - \nabla \cdot (v\nabla z) + \mu_e(u, v, z)v, \end{cases} \quad (1.16)$$

with

$$\chi(v, w) = \frac{\kappa_1}{(B(v, w))^2(1 + B(v, w))}, \quad \xi(v, w) = \frac{\kappa_2}{(B(v, w))^2(1 + B(v, w))}, \quad (1.17)$$

$\kappa_1, \kappa_2 > 0$  constants.

Proceeding e.g., as in [12], no-flux boundary conditions can be obtained (still in a formal way) for the formulation on a bounded space domain  $\Omega \subset \mathbb{R}^N$ . This system is to be supplemented with equations for the evolution of the macroscopic quantities  $w$  and  $z$ , for which no deduction from lower scales is needed. We assume that the tissue (of density  $w$ ) is degraded by the tumor cells<sup>3</sup> and that VEGF (of concentration  $z$ ) is uptaken by ECs and produced by cancer cells. This leads to the (nondimensional) equations

$$\begin{cases} w_t = -\psi(uw) \\ z_t = D_z \Delta z - \mu_z vz + \phi(u), \end{cases} \quad (1.18)$$

where  $D_z, \mu_z > 0$  are constants, and with functions  $\psi, \phi$  yet to be specified.

## 2 Global existence and uniqueness of solutions

### 2.1 Main results

In the sequel we consider a version of system (1.16) together with the equations for  $w$  and  $z$ , and with more general tactic sensitivity functions  $\chi, \xi$ . However, since we are mainly interested in the dynamics due to taxis and self-diffusion, we will not take into account any source terms for the two types of cells (tumor and ECs). For simplicity of writing we will omit the constants in (1.18), but reconsider them when performing numerical simulations in *Section 3*.

Concretely, we study here the following system:

$$\begin{cases} u_t = \Delta u - \nabla \cdot (u\chi(v, w)\nabla v) - \nabla \cdot (u\xi(v, w)\nabla w), & x \in \Omega, t > 0, \\ v_t = \Delta v - \nabla \cdot (v\nabla z), & x \in \Omega, t > 0, \\ w_t = -\psi(uw), & x \in \Omega, t > 0, \\ z_t = \Delta z - vz + \phi(u), & x \in \Omega, t > 0, \\ \frac{\partial u}{\partial \nu} - u\chi(v, w)\frac{\partial v}{\partial \nu} - u\xi(v, w)\frac{\partial w}{\partial \nu} = \frac{\partial v}{\partial \nu} = \frac{\partial z}{\partial \nu} = 0, & x \in \partial\Omega, t > 0, \\ u(x, 0) = u_0(x), \quad v(x, 0) = v_0(x), \quad w(x, 0) = w_0(x), \quad z(x, 0) = z_0(x), & x \in \Omega, \end{cases} \quad (2.19)$$

in a bounded convex domain  $\Omega \subset \mathbb{R}^2$  with smooth boundary. Our assumptions on the initial data are that

$$\begin{cases} u_0 \in C^{2+\vartheta}(\bar{\Omega}) & \text{is nonnegative with } \frac{\partial u_0}{\partial \nu} = 0 \text{ on } \partial\Omega \text{ and } u_0 \not\equiv 0, \\ v_0 \in C^{2+\vartheta}(\bar{\Omega}) & \text{is nonnegative with } \frac{\partial v_0}{\partial \nu} = 0 \text{ on } \partial\Omega \text{ and } v_0 \not\equiv 0, \\ w_0 \in C^{2+\vartheta}(\bar{\Omega}) & \text{is nonnegative with } \frac{\partial w_0}{\partial \nu} = 0 \text{ on } \partial\Omega, \text{ and that} \\ z_0 \in C^{2+\vartheta}(\bar{\Omega}) & \text{is nonnegative with } \frac{\partial z_0}{\partial \nu} = 0 \text{ on } \partial\Omega \text{ and } z_0 \not\equiv 0, \end{cases} \quad (2.20)$$

<sup>2</sup>we kept the previous notations for the scaled  $\mu_c, \mu_e$ , and  $B$  functions

<sup>3</sup>Unlike other works with stronger modeling focus (e.g., [12, 33]) here we do not take into account the fine, possibly anisotropic structure of tissue fibers and their degradation by tumor cells which depends on directionality and orientation of tissue and cells, but consider a depletion due to the mere cell-fibers interaction.

with some  $\vartheta \in (0, 1)$ , and concerning the coefficient functions in (2.19) we shall suppose that

$$\phi \in C^1([0, \infty)), \quad \psi \in C^3([0, \infty)), \quad \chi \in C^2([0, \infty)^2) \quad \text{and} \quad \xi \in C^3([0, \infty)^2), \quad (2.21)$$

that

$$|\chi(v, w)| \leq \frac{C_\chi}{v+1} \quad \text{for all } (v, w) \in [0, \infty)^2 \quad (2.22)$$

and

$$|\xi(v, w)| \leq C_\xi \quad \text{and} \quad |\xi_v(v, w)| \leq C_\xi \quad \text{for all } (v, w) \in [0, \infty)^2, \quad (2.23)$$

and that

$$0 \leq s\psi'(s) \leq C_\psi \quad \text{for all } s \geq 0 \quad (2.24)$$

as well as

$$\phi(u) \geq 0 \quad \text{and} \quad u|\phi'(u)| \leq C_\phi \quad \text{for all } u \geq 0 \quad (2.25)$$

with some positive constants  $C_\chi, C_\xi, C_\psi$  and  $C_\phi$ .<sup>4</sup>

Here we note that according to (2.24),

$$\psi(s) \leq \psi(1) + \int_1^s \frac{C_\psi}{\sigma} d\sigma = \psi(1) + C_\psi \ln s \quad \text{for all } s \geq 1,$$

whence abbreviating  $\tilde{C}_\psi := C_\psi + \max_{s \in [0, 1]} \psi(s)$  and  $\ln_+(s) := \max\{0, \ln s\}$  for  $s > 0$ , we obtain the pointwise inequality

$$\psi(s) \leq \tilde{C}_\psi \cdot (1 + \ln_+ s) \quad \text{for all } s > 0 \quad (2.26)$$

for  $\psi$  itself, and from (2.25) it similarly follows that

$$\phi(u) \leq \tilde{C}_\phi \cdot (1 + \ln_+ u) \quad \text{for all } u > 0 \quad (2.27)$$

with  $\tilde{C}_\phi := C_\phi + \max_{s \in [0, 1]} \phi(s)$ .

## Main results.

**Theorem 2.1.** *Let  $\Omega \subset \mathbb{R}^2$  be a bounded convex domain with smooth boundary, assume that  $\chi, \xi, \psi$  and  $\phi$  satisfy (2.21), (2.22), (2.23), (2.24) and (2.25). Then given any  $(u_0, v_0, w_0, z_0)$  satisfying (2.20) with some  $\vartheta \in (0, 1)$ , one can find a uniquely determined globally defined classical solution  $(u, v, w, z) \in (C^{2,1}(\overline{\Omega} \times [0, \infty))^4$  of (2.19) such that  $u, v, w$  and  $z$  are nonnegative.*

**Challenges and ideas.** A major challenge arising in the analysis of (2.19) is linked to the circumstance that the haptotactic sensitivity coefficient function  $\xi$  therein depends, besides on the haptotaxis mechanism ([18], [19], [38]), this gives rise to substantial additional complexity: Namely, the ambition to accordingly join the fluxes  $\nabla u - u\xi(v, w)\nabla w$  suggests to introduce the new dependent variable

$$a := ue^{-\Xi(v, w)}, \quad (2.28)$$

where in contrast to the case when  $\xi = \xi(w)$ , the function

$$\Xi(v, w) := \int_0^w \xi(v, s) ds, \quad (v, w) \in [0, \infty)^2, \quad (2.29)$$

now depends on  $v$  as well. As a consequence, the evolution of  $a$  is explicitly influenced by the time derivative  $v_t$ , which unlike  $w_t$  can apparently not be replaced with zero-order quantities, and which in view of the identity  $v_t = \Delta v - \nabla \cdot (v\nabla z)$  can hence rather be considered as an additional contribution of cross-diffusive and hence particularly delicate character (cf. also (2.32) below).

Thus led to investigating regularity properties of  $v_t$ , we shall lay a first focus on the chemotaxis-consumption subsystem of (2.19) made up by its second and fourth equation. Here we intend to make use of an essentially well-known structural property associated with the taxis-absorption interplay therein, and hence build this part on an analysis of the functional

$$\mathcal{F} := \int_{\Omega} v \ln v + \frac{1}{2} \int_{\Omega} \frac{|\nabla z|^2}{z}. \quad (2.30)$$

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<sup>4</sup>Observe that the coefficient functions  $\chi$  and  $\xi$  obtained in (1.17) satisfy these assumptions.

Due to the presence of the production term  $\phi(u)$  in the fourth equation from (2.19), however, the evolution of this functional along trajectories (cf. (2.48)) is, inter alia, determined by a summand of the form

$$\int_{\Omega} \phi'(u) \frac{\nabla z}{z} \cdot \nabla u, \quad (2.31)$$

an adequate estimation of which on the basis of (2.25) will be preceded by two arguments controlling the singular behavior of  $z$  and  $u$  by providing spatio-temporal  $L^2$  bounds for  $\nabla \ln z$  and  $\nabla \ln u$  (*Lemma 2.4* and *Lemma 2.7*). This will pave the way for our derivation of an estimate for  $v$  in  $L \log L(\Omega)$  through an examination of  $\mathcal{F}$  (*Lemma 2.8*), and in the considered two-dimensional setting this can thereafter be seen to actually entail estimates for  $v_t$  and  $D^2v$  in space-time  $L^p$  norms for arbitrarily large  $p > 1$  (*Lemma 2.12*). In *Lemma 2.14*, this will be found to be sufficient to imply  $L^\infty$  bounds for the crucial quantity  $a$ , whereupon an adequately arranged bootstrap procedure will provide estimates for all solution components with respect to the norm in  $C^{2+\theta}(\bar{\Omega})$  for some  $\theta \in (0, 1)$ , and thereby allow for global extensibility of a local-in-time solution which exists according to a standard argument (*Lemma 2.22*, *Lemma 2.23* and *Lemma 2.2*).

## 2.2 An equivalent problem reformulation. Local existence

Following the strategy outlined above, we note that the substitution (2.28)-(2.29)) transforms (2.19) to the problem

$$\begin{cases} a_t = e^{-\Xi(v,w)} \nabla \cdot \left\{ e^{\Xi(v,w)} \nabla a \right\} - e^{-\Xi(v,w)} \nabla \cdot \left\{ a e^{\Xi(v,w)} (\chi(v,w) - \Xi_v(v,w)) \nabla v \right\} \\ \quad - a \Xi_v(v,w) v_t + a \xi(v,w) \psi(a w e^{\Xi(v,w)}), & x \in \Omega, t > 0, \\ v_t = \Delta v - \nabla \cdot (v \nabla z), & x \in \Omega, t > 0, \\ w_t = -\psi(a w e^{\Xi(v,w)}), & x \in \Omega, t > 0, \\ z_t = \Delta z - v z + \phi(a e^{\Xi(v,w)}), & x \in \Omega, t > 0, \\ \frac{\partial a}{\partial \nu} = \frac{\partial v}{\partial \nu} = \frac{\partial z}{\partial \nu} = 0, & x \in \partial \Omega, t > 0, \\ a(x, 0) = u_0(x) e^{-\Xi(v_0(x), w_0(x))}, \quad v(x, 0) = v_0(x), \quad w(x, 0) = w_0(x), \quad z(x, 0) = z_0(x), & x \in \Omega, \end{cases} \quad (2.32)$$

which in the considered framework of classical solvability can indeed be seen to be equivalent to (2.19), because the boundary condition  $\frac{\partial w_0}{\partial \nu} = 0$  on  $\partial \Omega$  imposed in (2.20) ensures that classical solutions  $(u, v, w, z)$  to (2.19) satisfy  $\frac{\partial w}{\partial \nu} = 0$  throughout evolution.

Based on the observation that due to the second equation in (2.32) the expression  $v_t$  appearing in the first equation can actually be replaced with the additional cross-diffusion term  $\Delta v - \nabla \cdot (v \nabla z)$ , we may resort to a standard reasoning in order to assert local existence of classical solutions, along with an appropriate extensibility criterion and some essentially evident basic positivity, conservation and dissipation properties, in the following flavor.

**Lemma 2.2.** *Assume (2.21), (2.22), (2.23), (2.24) and (2.25), and suppose that  $u_0, v_0, w_0$  and  $z_0$  are such that (2.20) holds with some  $\vartheta \in (0, 1)$ . Then there exist  $T_{max} \in (0, \infty]$  and a uniquely determined quadruple of nonnegative functions  $a, v, w$  and  $z$  which belong to  $C^{2,1}(\bar{\Omega} \times [0, T_{max}))$ , and which are such that  $(a, v, w, z)$  solves (2.32) in the classical sense in  $\Omega \times (0, T_{max})$ , and that*

$$\text{if } T_{max} = \infty, \quad \text{then} \quad \limsup_{t \nearrow T_{max}} \left\{ \|a(\cdot, t)\|_{C^{2+\theta}(\bar{\Omega})} + \|v(\cdot, t)\|_{C^{2+\theta}(\bar{\Omega})} + \|w(\cdot, t)\|_{C^{2+\theta}(\bar{\Omega})} + \|z(\cdot, t)\|_{C^{2+\theta}(\bar{\Omega})} \right\} = \infty \quad (2.33)$$

for all  $\theta \in (0, 1)$ . Moreover, this solution has the properties that  $a > 0, v > 0$  and  $z > 0$  in  $\bar{\Omega} \times (0, T_{max})$ , that with  $u := e^{\Xi(v,w)} a$  we have

$$\int_{\Omega} u(\cdot, t) = \int_{\Omega} u_0 \quad \text{for all } t \in (0, T_{max}) \quad (2.34)$$

and

$$\int_{\Omega} v(\cdot, t) = \int_{\Omega} v_0 \quad \text{for all } t \in (0, T_{max}), \quad (2.35)$$

and that

$$w(x, t) \leq \|w_0\|_{L^\infty(\Omega)} \quad \text{for all } x \in \Omega \text{ and } t \in (0, T_{max}). \quad (2.36)$$

*Proof.* The statements concerning local existence and (2.33) can be verified by means of a quite well-established argument based on Banach's fixed point theorem, so that we may content ourselves with a

reference to the reasoning detailed in [41, Lemma 2.1] for a closely related situation.

The claimed positivity properties of  $a$ ,  $v$  and  $z$  thereafter result from (2.20) and the strong maximum principle, whereas (2.34), (2.35) and (2.36) are obvious consequences of (2.32) and the nonnegativity of  $\psi$  entailed by (2.24).  $\square$

Throughout the sequel, without further explicit mentioning we shall suppose that (2.21), (2.22), (2.23), (2.24), (2.25) and (2.20) hold, and let  $(a, v, w, z)$ ,  $u$  and  $T_{max}$  be as provided by *Lemma 2.2*, noting that then  $(u, v, w, z)$  forms a classical solution of (2.19) in  $\Omega \times (0, T_{max})$ .

## 2.3 A bound for $v$ in $L \log L(\Omega)$

### 2.3.1 $L^2$ estimates for $\nabla \ln z$ and $\nabla \ln u$

In this section concerned with the time evolution of the functional in (2.30), with a view to (2.31) we shall first focus on the derivation of some estimates for  $z$  and  $u$  which, in some contrast to those explicitly appearing in (2.33), mainly concentrate on a control of the behavior near *small* values of the respective quantities.

As a preparation, let us first draw a consequence of a basic bound for  $\phi(u)$ , as implied by (2.27) and (2.34), when combined with nonpositivity of the summand  $-vz$  in the forth equation from (2.19). This, namely, already asserts an  $L^\infty$  estimate for  $z$  through a straightforward argument based on well-known parabolic regularity theory:

**Lemma 2.3.** *If  $T_{max} < \infty$ , then there exists  $C > 0$  such that*

$$z(x, t) \leq C \quad \text{for all } x \in \Omega \text{ and } t \in (0, T_{max}). \quad (2.37)$$

*Proof.* We first observe that due to the validity of the elementary inequality  $\ln s \leq \frac{2\sqrt{s}}{e}$  for all  $s > 0$ , from (2.27) it follows that

$$\phi(u) \leq \tilde{C}_\phi \cdot \left(1 + \frac{2}{e}\sqrt{u}\right) \quad \text{in } \Omega \times (0, T_{max}),$$

and that thus, by Young's inequality and (2.34),

$$\int_\Omega \phi^2(u) \leq 2\tilde{C}_\phi^2 \int_\Omega \left(1 + \frac{4}{e^2}u\right) = c_1 := 2\tilde{C}_\phi^2 \cdot \left\{|\Omega| + \frac{4}{e^2} \int_\Omega u_0\right\} \quad \text{for all } t \in (0, T_{max}). \quad (2.38)$$

Now by nonnegativity of  $v$  and  $z$ , from (2.19) we obtain the one-sided inequality  $z_t \leq \Delta z + \phi(u)$  in  $\Omega \times (0, T_{max})$ , which thanks to the comparison principle implies that

$$z(\cdot, t) \leq e^{t\Delta} z_0 + \int_0^t e^{(t-s)\Delta} \phi(u(\cdot, s)) ds \quad \text{in } \Omega \quad \text{for all } t \in (0, T_{max}), \quad (2.39)$$

where  $(e^{\sigma\Delta})_{\sigma \geq 0}$  denotes the Neumann heat semigroup over  $\Omega$ . Here we employ a well-known smoothing estimate for  $(e^{\sigma\Delta})_{\sigma \geq 0}$  ([47, Lemma 1.4]) to find  $c_2 > 0$  such that

$$\|e^{\sigma\Delta} \varphi\|_{L^\infty(\Omega)} \leq c_2(1 + \sigma^{-\frac{1}{2}}) \|\varphi\|_{L^2(\Omega)} \quad \text{for all } \sigma > 0 \text{ and any } \varphi \in C^0(\bar{\Omega}),$$

so that again thanks to the comparison principle, (2.39) together with (2.38) entails that

$$\begin{aligned} z(\cdot, t) &\leq \|e^{t\Delta} z_0\|_{L^\infty(\Omega)} + c_2 \int_0^t \left(1 + (t-s)^{-\frac{1}{2}}\right) \|\phi(u(\cdot, s))\|_{L^2(\Omega)} ds \\ &\leq \|z_0\|_{L^\infty(\Omega)} + \sqrt{c_1} c_2 \int_0^t \left(1 + (t-s)^{-\frac{1}{2}}\right) ds \quad \text{in } \Omega \quad \text{for all } t \in (0, T_{max}). \end{aligned}$$

Since

$$\int_0^t \left(1 + (t-s)^{-\frac{1}{2}}\right) ds = t + 2\sqrt{t} \leq T_{max} + 2\sqrt{T_{max}} \quad \text{for all } t \in (0, T_{max}),$$

in view of the presupposed finiteness of  $T_{max}$  this establishes (2.37).  $\square$

As a first consequence, through a fairly simple testing procedure the latter already entails an  $L^2$  bound for  $\nabla \ln z$  in the intended flavor:

**Lemma 2.4.** *If  $T_{max} < \infty$ , then*

$$\int_{\tau}^{T_{max}} \frac{|\nabla z|^2}{z^2} < \infty \quad \text{for all } \tau \in (0, T_{max}). \quad (2.40)$$

*Proof.* Recalling that  $z$  is positive in  $\bar{\Omega} \times (0, T_{max})$ , we may multiply the fourth equation in (2.19) by  $-\frac{1}{z}$  and integrate by parts to see that

$$-\frac{d}{dt} \int_{\Omega} \ln z + \int_{\Omega} \frac{|\nabla z|^2}{z^2} = \int_{\Omega} v - \int_{\Omega} \frac{\phi(u)}{z} \leq \int_{\Omega} v_0 \quad \text{for all } t \in (0, T_{max})$$

according to (2.35) and the nonnegativity of  $\phi$  required in (2.25). Therefore,

$$\begin{aligned} \int_{\tau}^t \int_{\Omega} \frac{|\nabla z|^2}{z^2} &\leq \int_{\Omega} \ln z(\cdot, t) - \int_{\Omega} \ln z(\cdot, \tau) + (t - \tau) \int_{\Omega} v_0 \\ &\leq |\Omega| \cdot \ln \|z(\cdot, t)\|_{L^\infty(\Omega)} - \int_{\Omega} \ln z(\cdot, \tau) + T_{max} \int_{\Omega} v_0 \quad \text{for all } \tau \in (0, T_{max}) \text{ and } t \in [\tau, T_{max}), \end{aligned}$$

which implies (2.40) since  $\sup_{t \in (0, T_{max})} \|z(\cdot, t)\|_{L^\infty(\Omega)}$  is finite by Lemma 2.3, and since, again by positivity of  $z$  in  $\bar{\Omega} \times (0, T_{max})$ , also  $-\int_{\Omega} \ln z(\cdot, \tau) < \infty$  for all  $\tau \in (0, T_{max})$ .  $\square$

Once again relying on Lemma 2.3, from the latter we immediately obtain an  $L^2$  bound for  $\nabla z$  also without any weight.

**Corollary 2.5.** *If  $T_{max} < \infty$ , then*

$$\int_{\tau}^{T_{max}} |\nabla z|^2 < \infty \quad \text{for all } \tau \in (0, T_{max}).$$

*Proof.* This can immediately be seen by combining Lemma 2.4 with Lemma 2.3.  $\square$

This information now provides sufficient regularity of the taxis gradient in the second equation from (2.19) to ensure a singular estimate for  $\nabla v$  quite similar to that from Lemma 2.4.

**Lemma 2.6.** *If  $T_{max} < \infty$ , then*

$$\int_{\tau}^{T_{max}} \frac{|\nabla v|^2}{v^2} < \infty \quad \text{for all } \tau \in (0, T_{max}). \quad (2.41)$$

*Proof.* Thanks to the positivity of  $v$  in  $\bar{\Omega} \times (0, T_{max})$ , from the second equation in (2.19) and Young's inequality we obtain that

$$-\frac{d}{dt} \int_{\Omega} \ln v + \int_{\Omega} \frac{|\nabla v|^2}{v^2} = \int_{\Omega} \frac{\nabla v}{v} \cdot \nabla z \leq \frac{1}{2} \int_{\Omega} \frac{|\nabla v|^2}{v^2} + \frac{1}{2} \int_{\Omega} |\nabla z|^2 \quad \text{for all } t \in (0, T_{max}),$$

and that thus, given  $\tau \in (0, T_{max})$  we have

$$\int_{\tau}^t \int_{\Omega} \frac{|\nabla v|^2}{v^2} \leq 2 \int_{\Omega} \ln v(\cdot, t) - 2 \int_{\Omega} \ln v(\cdot, \tau) + \int_{\tau}^t \int_{\Omega} |\nabla z|^2 \quad \text{for all } t \in [\tau, T_{max}).$$

Since here  $\sup_{t \in (\tau, T_{max})} \int_{\tau}^t \int_{\Omega} |\nabla z|^2 < \infty$  by Corollary 2.5 and  $\int_{\Omega} \ln v(\cdot, \tau) > -\infty$  by positivity of  $v(\cdot, \tau)$  in  $\bar{\Omega}$ , (2.41) results upon observing that

$$\int_{\Omega} \ln v(\cdot, t) \leq \int_{\Omega} v(\cdot, t) = \int_{\Omega} v_0 \quad \text{for all } t \in (0, T_{max})$$

due to (2.35) and the fact that  $\ln s \leq s$  for all  $s > 0$ .  $\square$

Now making essential use of our overall assumption (2.24), by analyzing the time evolution of  $-\int_{\Omega} \ln u + \int_{\Omega} |\nabla w|^2$  we can turn the information from Lemma 2.6 into the following second main result of this subsection:

**Lemma 2.7.** *If  $T_{max} < \infty$ , then*

$$\int_{\tau}^{T_{max}} \frac{|\nabla u|^2}{u^2} < \infty \quad \text{for all } \tau \in (0, T_{max}). \quad (2.42)$$

*Proof.* Since  $u$  is positive in  $\bar{\Omega} \times (0, T_{max})$ , on the basis of the first equation in (2.19) we may integrate by parts and use Young's inequality along with (2.22) and (2.23) to see that

$$\begin{aligned} -\frac{d}{dt} \int_{\Omega} \ln u + \int_{\Omega} \frac{|\nabla u|^2}{u^2} &= \int_{\Omega} \chi(v, w) \frac{\nabla u}{u} \cdot \nabla v + \int_{\Omega} \xi(v, w) \frac{\nabla u}{u} \cdot \nabla w \\ &\leq \frac{1}{2} \int_{\Omega} \frac{|\nabla u|^2}{u^2} + \int_{\Omega} \chi^2(v, w) |\nabla v|^2 + \int_{\Omega} \xi^2(v, w) |\nabla w|^2 \\ &\leq \frac{1}{2} \int_{\Omega} \frac{|\nabla u|^2}{u^2} + C_{\chi}^2 \int_{\Omega} \frac{|\nabla v|^2}{v^2} + C_{\xi}^2 \int_{\Omega} |\nabla w|^2 \quad \text{for all } t \in (0, T_{max}). \end{aligned} \quad (2.43)$$

To appropriately compensate the rightmost summand herein, we furthermore utilize the third equation from (2.19) to compute

$$\begin{aligned} \frac{d}{dt} \int_{\Omega} |\nabla w|^2 &= -2 \int_{\Omega} \nabla w \cdot \nabla \psi(uw) \\ &= -2 \int_{\Omega} uw\psi'(uw) |\nabla w|^2 - 2 \int_{\Omega} w\psi'(uw) \nabla u \cdot \nabla w \quad \text{for all } t \in (0, T_{max}), \end{aligned}$$

so that since (2.24) asserts that  $uw\psi'(uw) \geq 0$  and  $0 \leq uw\psi'(uw) \leq C_{\psi}$  in  $\Omega \times (0, T_{max})$ , by means of Young's inequality we obtain that

$$\begin{aligned} \frac{d}{dt} \int_{\Omega} |\nabla w|^2 &\leq -2 \int_{\Omega} uw\psi'(uw) \frac{\nabla u}{u} \cdot \nabla w \\ &\leq \frac{1}{4} \int_{\Omega} \frac{|\nabla u|^2}{u^2} + 4 \int_{\Omega} \left\{ uw\psi'(uw) \right\}^2 |\nabla w|^2 \\ &\leq \frac{1}{4} \int_{\Omega} \frac{|\nabla u|^2}{u^2} + 4C_{\psi}^2 \int_{\Omega} |\nabla w|^2 \quad \text{for all } t \in (0, T_{max}). \end{aligned}$$

In conjunction with Paragraph 2.3.1, this shows that writing  $c_1 := C_{\xi}^2 + 4C_{\psi}^2$  we have

$$\frac{d}{dt} \left\{ -\int_{\Omega} \ln u + \int_{\Omega} |\nabla w|^2 \right\} + \frac{1}{4} \int_{\Omega} \frac{|\nabla u|^2}{u^2} \leq c_1 \int_{\Omega} |\nabla w|^2 + C_{\chi}^2 \int_{\Omega} \frac{|\nabla v|^2}{v^2} \quad \text{for all } t \in (0, T_{max}),$$

so that since  $\int_{\Omega} \ln u \leq \int_{\Omega} u = c_2 := \int_{\Omega} u_0$  for all  $t \in (0, T_{max})$  by (2.34), it follows that  $y(t) := -\int_{\Omega} \ln u(\cdot, t) + \int_{\Omega} |\nabla w(\cdot, t)|^2$ ,  $g(t) := \frac{1}{4} \int_{\Omega} \frac{|\nabla u(\cdot, t)|^2}{u^2(\cdot, t)}$  and  $h(t) := C_{\chi}^2 \int_{\Omega} \frac{|\nabla v(\cdot, t)|^2}{v^2(\cdot, t)} + c_1 c_2$ ,  $t \in (0, T_{max})$ , satisfy

$$\int_{\Omega} |\nabla w|^2 = y(t) + \int_{\Omega} \ln u \leq y(t) + c_2 \quad \text{for all } t \in (0, T_{max}) \quad (2.44)$$

and hence

$$y'(t) + g(t) \leq c_1 \cdot (y(t) + c_2) + C_{\chi}^2 \int_{\Omega} \frac{|\nabla v|^2}{v^2} \leq c_1 y(t) + h(t) \quad \text{for all } t \in (0, T_{max}). \quad (2.45)$$

For fixed  $\tau \in (0, T_{max})$ , upon simply estimating  $g \geq 0$  and noting that

$$c_3 := y(\tau) \quad \text{and} \quad c_4 := \int_{\tau}^{T_{max}} h(s) ds$$

are both finite by positivity of  $u(\cdot, \tau)$  and  $\bar{\Omega}$  and Lemma 2.6, from this we firstly infer through an ODE comparison argument that

$$\begin{aligned} y(t) &\leq y(\tau) e^{c_1 \cdot (t-\tau)} + \int_{\tau}^t e^{c_1 \cdot (t-s)} h(s) ds \\ &\leq c_5 := c_3 e^{c_1 T_{max}} + c_4 e^{c_1 T_{max}} \quad \text{for all } t \in [\tau, T_{max}). \end{aligned}$$

Thereupon, once more going back to (2.45) we infer that, again by (2.44),

$$\begin{aligned} \int_{\tau}^t g(s) ds &\leq y(\tau) - y(t) + c_1 \int_{\tau}^t y(s) ds + \int_{\tau}^t h(s) ds \\ &\leq c_5 + \left\{ c_2 - \int_{\Omega} |\nabla w|^2 \right\} + c_1 c_5 \cdot (t - \tau) + c_4 \\ &\leq c_5 + c_2 + c_1 c_5 T_{max} + c_4 \quad \text{for all } t \in [\tau, T_{max}), \end{aligned}$$

which by definition of  $g$  implies (2.42).  $\square$

### 2.3.2 The chemotaxis-consumption interaction in (2.19). A bound for $v$ in $L \log L$

We are now prepared for our analysis of the chemotaxis-consumption subsystem of (2.19) at the fundamental level of the functional  $\mathcal{F}$  in (2.30), well-known to play the role of a genuine energy in the accordingly unperturbed case when  $\phi \equiv 0$  in convex domains ([42]). In particular, *Lemma 2.4* and *Lemma 2.7* will enable us to appropriately control the respective additional contribution due to the coupling to the crucial quantity  $u$ , as foreshadowed in (2.31), and to thereby derive the following key estimate for  $v$ .

**Lemma 2.8.** *If  $T_{max} < \infty$ , then there exists  $C > 0$  such that*

$$\int_{\Omega} v(\cdot, t) |\ln v(\cdot, t)| \leq C \quad \text{for all } t \in (0, T_{max}). \quad (2.46)$$

*Proof.* Again relying on the positivity of  $v$  and  $z$  in  $\overline{\Omega} \times (0, T_{max})$ , by means of several integrations by parts in the second and fourth equation from (2.19) we compute

$$\frac{d}{dt} \int_{\Omega} v \ln v + \int_{\Omega} \frac{|\nabla v|^2}{v} = \int_{\Omega} \nabla v \cdot \nabla z \quad \text{for all } t \in (0, T_{max}) \quad (2.47)$$

and

$$\begin{aligned} \frac{1}{2} \frac{d}{dt} \int_{\Omega} \frac{|\nabla z|^2}{z} &= \int_{\Omega} \frac{\nabla z}{z} \cdot \nabla \left\{ \Delta z - vz + \phi(u) \right\} - \frac{1}{2} \int_{\Omega} \frac{|\nabla z|^2}{z^2} \cdot \left\{ \Delta z - vz + \phi(u) \right\} \\ &= - \int_{\Omega} z |D^2 \ln z|^2 + \frac{1}{2} \int_{\partial\Omega} \frac{1}{z} \cdot \frac{\partial |\nabla z|^2}{\partial \nu} \\ &\quad - \int_{\Omega} \nabla v \cdot \nabla z - \frac{1}{2} \int_{\Omega} \frac{v}{z} |\nabla z|^2 \\ &\quad + \int_{\Omega} \phi'(u) \frac{\nabla z}{z} \cdot \nabla u - \frac{1}{2} \int_{\Omega} \frac{|\nabla z|^2}{z^2} \phi(u) \quad \text{for all } t \in (0, T_{max}), \end{aligned} \quad (2.48)$$

where we have used that  $\nabla z \cdot \nabla \Delta z = \frac{1}{2} \Delta |\nabla z|^2 - |D^2 z|^2$  in  $\Omega \times (0, T_{max})$ , and that

$$\frac{1}{2} \int_{\Omega} \frac{1}{z^2} \nabla z \cdot \nabla |\nabla z|^2 - \frac{1}{z} |D^2 z|^2 - \frac{1}{2} \int_{\Omega} \frac{1}{z^2} |\nabla z|^2 \Delta z = - \int_{\Omega} z |D^2 \ln z|^2 \quad \text{for all } t \in (0, T_{max})$$

(cf. [48, Lemma 3.2] for a detailed derivation of the latter identity). Here since  $\frac{\partial |\nabla z|^2}{\partial \nu} \leq 0$  on  $\partial\Omega \times (0, T_{max})$  by convexity of  $\Omega$  ([31]), in view of the nonnegativity of  $\phi$  postulated in (2.25) it follows that the second, fourth and sixth summands on the right of (2.48) are all nonpositive, whereas in the crucial second last integral therein we make use of the upper bound for  $\phi'$  in (2.25) to see that thanks to Young's inequality,

$$\begin{aligned} \int_{\Omega} \phi'(u) \frac{\nabla z}{z} \cdot \nabla u &\leq \int_{\Omega} \frac{|\nabla z|^2}{z^2} + \frac{1}{4} \int_{\Omega} (\phi'(u))^2 |\nabla u|^2 \\ &\leq \int_{\Omega} \frac{|\nabla z|^2}{z^2} + \frac{C_{\phi}^2}{4} \int_{\Omega} \frac{|\nabla u|^2}{u^2} \quad \text{for all } t \in (0, T_{max}). \end{aligned}$$

When adding (2.48) to (2.47) and taking benefit from a favorable cancellation thereby induced on the right-hand side of (2.47), we thus obtain that

$$\begin{aligned} \frac{d}{dt} \left\{ \int_{\Omega} v \ln v + \frac{1}{2} \int_{\Omega} \frac{|\nabla z|^2}{z} \right\} + \int_{\Omega} \frac{|\nabla v|^2}{v} + \int_{\Omega} z |D^2 \ln z|^2 \\ \leq \int_{\Omega} \frac{|\nabla z|^2}{z^2} + \frac{C_{\phi}^2}{4} \int_{\Omega} \frac{|\nabla u|^2}{u^2} \quad \text{for all } t \in (0, T_{max}), \end{aligned}$$

which upon an integration in time implies that, writing  $\tau := \frac{1}{2} T_{max}$ , for all  $t \in [\tau, T_{max}]$ , we have

$$\begin{aligned} \int_{\Omega} v(\cdot, t) \ln v(\cdot, t) + \frac{1}{2} \int_{\Omega} \frac{|\nabla z(\cdot, t)|^2}{z(\cdot, t)} &\leq c_1 := \int_{\Omega} v(\cdot, \tau) |\ln v(\cdot, \tau)| + \frac{1}{2} \int_{\Omega} \frac{|\nabla z(\cdot, \tau)|^2}{z(\cdot, \tau)} \\ &\quad + \int_{\tau}^{T_{max}} \int_{\Omega} \frac{|\nabla z|^2}{z^2} + \frac{C_{\phi}^2}{4} \int_{\tau}^{T_{max}} \int_{\Omega} \frac{|\nabla u|^2}{u^2}, \end{aligned}$$

with  $c_1$  being finite and positive due to *Lemma 2.4* and *Lemma 2.7*. Since  $\int_{\Omega} v |\ln v| = \int_{\Omega} v \ln v - 2 \int_{\{v < 1\}} v \ln v \leq \int_{\Omega} v \ln v + \frac{2|\Omega|}{e}$  for all  $t \in (0, T_{max})$  due to the fact that  $s \ln s \geq -\frac{1}{e}$  for all  $s > 0$ , this entails that

$$\int_{\Omega} v(\cdot, t) |\ln v(\cdot, t)| \leq c_1 + \frac{2|\Omega|}{e} \quad \text{for all } t \in [\tau, T_{max}),$$

and that thus (2.46) holds if we let  $C := \max \left\{ \sup_{t \in (0, \tau)} \int_{\Omega} v(\cdot, t) |\ln v(\cdot, t)|, c_1 + \frac{2|\Omega|}{e} \right\}$ .  $\square$

## 2.4 Maximal Sobolev regularity results for $z$ and $v$ . $L^p$ bounds for $v_t$

In this section we shall use the outcome of *Lemma 2.8*, and again that of *Lemma 2.3*, as a starting point for a bootstrap procedure applied to the second and fourth equations in (2.19). Thanks to the availability of suitable embedding properties, in the considered two-dimensional framework this initial regularity information will actually be seen to imply estimates for both  $(z, \nabla z, D^2 z, z_t)$  and  $(v, \nabla v, D^2 v, v_t)$  in arbitrary space-time  $L^p$  spaces.

Our first step in this direction establishes the following by analyzing the evolution of  $\int_{\Omega} v^2 + \frac{1}{2} \int_{\Omega} |\nabla z|^4$ .

**Lemma 2.9.** *If  $T_{max} < \infty$ , then there exists  $C > 0$  such that*

$$\int_{\Omega} |\nabla z(\cdot, t)|^4 \leq C \quad \text{for all } t \in (0, T_{max}). \quad (2.49)$$

*Proof.* Following the strategy from [6, Lemma 3.3], we use the second and fourth equations in (2.19) to see that again since  $\nabla z \cdot \nabla \Delta z = \frac{1}{2} \Delta |\nabla z|^2 - |D^2 z|^2$  in  $\Omega \times (0, T_{max})$  and  $\frac{\partial |\nabla z|^2}{\partial \nu} \leq 0$  on  $\partial\Omega \times (0, T_{max})$ , according to Young's inequality we have

$$\frac{1}{2} \frac{d}{dt} \int_{\Omega} v^2 + \int_{\Omega} |\nabla v|^2 = \int_{\Omega} v \nabla v \cdot \nabla z \leq \frac{1}{2} \int_{\Omega} |\nabla v|^2 + \frac{1}{2} \int_{\Omega} v^2 |\nabla z|^2 \quad \text{for all } t \in (0, T_{max}) \quad (2.50)$$

and

$$\begin{aligned} \frac{1}{4} \frac{d}{dt} \int_{\Omega} |\nabla z|^4 &= \int_{\Omega} |\nabla z|^2 \nabla z \cdot \nabla \{ \Delta z - vz + \phi(u) \} \\ &= -\frac{1}{2} \int_{\Omega} |\nabla |\nabla z|^2|^2 + \frac{1}{2} \int_{\partial\Omega} |\nabla z|^2 \frac{\partial |\nabla z|^2}{\partial \nu} - \int_{\Omega} |\nabla z|^2 |D^2 z|^2 \\ &\quad + \int_{\Omega} \phi'(u) |\nabla z|^2 \nabla u \cdot \nabla z + \int_{\Omega} vz \nabla \cdot (|\nabla z|^2 \nabla z) \\ &\leq -\int_{\Omega} |\nabla z|^2 |D^2 z|^2 + (2 + \sqrt{2})c_1 \int_{\Omega} v |\nabla z|^2 |D^2 z| \\ &\quad + \int_{\Omega} \phi'(u) |\nabla z|^2 \nabla u \cdot \nabla z \\ &\leq -\frac{1}{2} \int_{\Omega} |\nabla z|^2 |D^2 z|^2 + \frac{(2 + \sqrt{2})^2 c_1^2}{2} \int_{\Omega} v^2 |\nabla z|^2 \\ &\quad + \int_{\Omega} \phi'(u) |\nabla z|^2 \nabla u \cdot \nabla z \quad \text{for all } t \in (0, T_{max}), \end{aligned} \quad (2.51)$$

where  $c_1 := \|z\|_{L^\infty(\Omega \times (0, T_{max}))}$  is finite by (2.37), and where we have used that for each  $\gamma \geq 1$ ,

$$\begin{aligned} |\nabla \cdot (|\nabla \varphi|^{2\gamma} \nabla \varphi)| &= |2\gamma |\nabla \varphi|^{2\gamma-2} \nabla \varphi \cdot (D^2 \varphi \cdot \nabla \varphi) + |\nabla \varphi|^{2\gamma} \Delta \varphi| \\ &\leq (2\gamma + \sqrt{2}) |\nabla \varphi|^{2\gamma} |D^2 \varphi| \quad \text{in } \Omega \quad \text{for all } \varphi \in C^2(\bar{\Omega}). \end{aligned} \quad (2.52)$$

A combination of (2.50) with (2.51) thus shows that

$$\begin{aligned} \frac{d}{dt} \left\{ \int_{\Omega} v^2 + \frac{1}{2} \int_{\Omega} |\nabla z|^4 \right\} + \int_{\Omega} |\nabla v|^2 + \int_{\Omega} |\nabla z|^2 |D^2 z|^2 \\ \leq c_2 \int_{\Omega} v^2 |\nabla z|^2 + 2 \int_{\Omega} \phi'(u) |\nabla z|^2 \nabla u \cdot \nabla z \quad \text{for all } t \in (0, T_{max}) \end{aligned} \quad (2.53)$$

with  $c_2 := 1 + (2 + \sqrt{2})^2 c_1^2$ , and to proceed from this we note that again thanks to (2.52), for arbitrary  $\varphi \in C^2(\bar{\Omega})$  satisfying  $\frac{\partial \varphi}{\partial \nu} = 0$  on  $\partial\Omega$  we have

$$\begin{aligned}\int_{\Omega} |\nabla \varphi|^6 &= \int_{\Omega} |\nabla \varphi|^4 \nabla \varphi \cdot \nabla \varphi \\ &= - \int_{\Omega} \varphi \nabla \cdot (|\nabla \varphi|^4 \nabla \varphi) \\ &\leq (4 + \sqrt{2}) \int_{\Omega} |\varphi| \cdot |\nabla \varphi|^4 \cdot |D^2 \varphi| \\ &\leq (4 + \sqrt{2}) \|\varphi\|_{L^\infty(\Omega)} \cdot \left\{ \int_{\Omega} |\nabla \varphi|^6 \right\}^{\frac{1}{2}} \cdot \left\{ \int_{\Omega} |\nabla \varphi|^2 |D^2 \varphi|^2 \right\}^{\frac{1}{2}}\end{aligned}$$

as a consequence of the Cauchy-Schwarz inequality, and that thus

$$\int_{\Omega} |\nabla \varphi|^6 \leq c_3 \|\varphi\|_{L^\infty(\Omega)}^2 \int_{\Omega} |\nabla \varphi|^2 |D^2 \varphi|^2$$

holds for any such  $\varphi$  if we let  $c_3 := (4 + \sqrt{2})^2$ . Therefore, namely, by definition of  $c_1$  we obtain that with  $c_4 := c_1^2 c_3$ ,

$$\int_{\Omega} |\nabla z|^6 \leq c_4 \int_{\Omega} |\nabla z|^2 |D^2 z|^2 \quad \text{for all } t \in (0, T_{max}), \quad (2.54)$$

and in line with this we apply Young's inequality on the right-hand side of (2.53) in such a way that

$$c_2 \int_{\Omega} v^2 |\nabla z|^2 \leq \frac{1}{2c_4} \int_{\Omega} |\nabla z|^6 + \frac{c_2^2 c_4}{2} \int_{\Omega} v^3 \quad \text{for all } t \in (0, T_{max})$$

and

$$2 \int_{\Omega} \phi'(u) |\nabla z|^2 \nabla u \cdot \nabla z \leq \frac{1}{2c_4} \int_{\Omega} |\nabla z|^6 + 2c_4 \int_{\Omega} (\phi'(u))^2 |\nabla u|^2 \quad \text{for all } t \in (0, T_{max}),$$

so that recalling (2.25) we infer that due to (2.54),

$$\begin{aligned}c_2 \int_{\Omega} v^2 |\nabla z|^2 + 2 \int_{\Omega} \phi'(u) |\nabla z|^2 \nabla u \cdot \nabla z &\leq \frac{1}{c_4} \int_{\Omega} |\nabla z|^6 + \frac{c_2^2 c_4}{2} \int_{\Omega} v^3 + 2c_4 C_\phi^2 \int_{\Omega} \frac{|\nabla u|^2}{u^2} \\ &\leq \int_{\Omega} |\nabla z|^2 |D^2 z|^2 + \frac{c_2^2 c_4}{2} \int_{\Omega} v^3 + 2c_4 C_\phi^2 \int_{\Omega} \frac{|\nabla u|^2}{u^2} \quad (2.55)\end{aligned}$$

for all  $t \in (0, T_{max})$ . Here the second last summand can be controlled by relying on the  $L \log L$  estimate provided by Lemma 2.8, which in conjunction with a well-known variant of the Gagliardo-Nirenberg inequality ([8]), namely, entails the existence of  $c_5 > 0$  such that

$$\frac{c_2^2 c_4}{2} \int_{\Omega} v^3 \leq \int_{\Omega} |\nabla v|^2 + c_5 \quad \text{for all } t \in (0, T_{max}).$$

Inserted into (2.55), this shows that (2.53) implies the inequality

$$\frac{d}{dt} \left\{ \int_{\Omega} v^2 + \frac{1}{2} \int_{\Omega} |\nabla z|^4 \right\} \leq c_5 + 2c_4 C_\phi^2 \int_{\Omega} \frac{|\nabla u|^2}{u^2} \quad \text{for all } t \in (0, T_{max}),$$

from which by integration over  $[\tau, t]$  with  $\tau := \frac{1}{2}T_{max}$  and  $t \in [\tau, T_{max}]$  it particularly follows that for any such  $t$ ,

$$\frac{1}{2} \int_{\Omega} |\nabla z(\cdot, t)|^4 \leq c_6 := \int_{\Omega} v^2(\cdot, \tau) + \frac{1}{2} \int_{\Omega} |\nabla z(\cdot, \tau)|^2 + c_5 \cdot (T_{max} - \tau) + 2c_4 C_\phi^2 \int_{\tau}^{T_{max}} \int_{\Omega} \frac{|\nabla u|^2}{u^2},$$

with finiteness of  $c_6$  asserted by Lemma 2.7. Since also  $c_7 := \sup_{t \in (0, \tau)} \int_{\Omega} |\nabla z(\cdot, t)|^4$  is finite by Lemma 2.2, this entails (2.49) with  $C := \max\{c_7, 2c_6\}$ .  $\square$

Using that the integrability exponent in (2.49) exceeds the considered spatial dimension, by means of an essentially well-established argument based on semigroup estimates we can turn this into an  $L^\infty$  bound for  $v$ .

**Lemma 2.10.** *If  $T_{max} < \infty$ , then there exists  $C > 0$  such that*

$$v(x, t) \leq C \quad \text{for all } x \in \Omega \text{ and } t \in (0, T_{max}). \quad (2.56)$$

*Proof.* We abbreviate  $c_1 := \int_{\Omega} v_0$  and take  $c_2 > 0$  such that in accordance with Lemma 2.9 we have  $\|\nabla z(\cdot, t)\|_{L^4(\Omega)} \leq c_2$  for all  $t \in (0, T_{max})$ , and to estimate the numbers

$$M(T) := \sup_{t \in (0, T_{max})} \|v(\cdot, t)\|_{L^\infty(\Omega)}, \quad T \in (0, T_{max}),$$

we recall a well-known smoothing property of the Neumann heat semigroup ([55]) to fix  $c_3 > 0$  such that for all  $\sigma > 0$ ,

$$\|e^{\sigma\Delta} \nabla \cdot \varphi\|_{L^\infty(\Omega)} \leq c_3 \cdot (1 - \sigma^{-\frac{5}{6}}) \|\varphi\|_{L^3(\Omega)} \quad \text{for all } \varphi \in C^1(\Omega; \mathbb{R}^2) \text{ such that } \varphi \cdot \nu = 0 \text{ on } \partial\Omega.$$

On the basis of a Duhamel representation, we then see that for each  $T \in (0, T_{max})$ , due to the maximum principle we have

$$\begin{aligned} \|v(\cdot, t)\|_{L^\infty(\Omega)} &= \left\| e^{t\Delta} v_0 - \int_0^t e^{(t-s)\Delta} \nabla \cdot (v(\cdot, s) \nabla z(\cdot, s)) ds \right\|_{L^\infty(\Omega)} \\ &\leq \|v_0\|_{L^\infty(\Omega)} + c_3 \int_0^t \left(1 + (t-s)^{-\frac{5}{6}}\right) \|v(\cdot, s) \nabla z(\cdot, s)\|_{L^3(\Omega)} ds \\ &\leq \|v_0\|_{L^\infty(\Omega)} + c_3 \int_0^t \left(1 + (t-s)^{-\frac{5}{6}}\right) \|v(\cdot, s)\|_{L^\infty(\Omega)}^{\frac{11}{12}} \|v(\cdot, s)\|_{L^1(\Omega)}^{\frac{1}{12}} \|\nabla z(\cdot, s)\|_{L^4(\Omega)} ds \\ &\leq c_4 + c_4 M^{\frac{11}{12}}(T) \quad \text{for all } t \in (0, T) \end{aligned}$$

with  $c_4 := \max \left\{ \|v_0\|_{L^\infty(\Omega)}, c_1^{\frac{1}{12}} c_2 c_3 \int_0^{T_{max}} (1 + \sigma^{-\frac{5}{6}}) d\sigma \right\}$ . Consequently,  $M(T) \leq c_4 + c_4 M^{\frac{11}{12}}(T)$  and hence  $M(T) \leq \max\{1, (2c_4)^{12}\}$  for all  $T \in (0, T_{max})$ , as intended.  $\square$

The latter now provides sufficient regularity information on the expression  $z_t - \Delta z$  to warrant accessibility to maximal Sobolev regularity theory:

**Lemma 2.11.** *If  $T_{max} < \infty$ , then for all  $p > 1$ ,*

$$\int_0^{T_{max}} \left\{ \|z(\cdot, t)\|_{W^{2,p}(\Omega)}^p + \|z_t(\cdot, t)\|_{L^p(\Omega)}^p \right\} dt < \infty. \quad (2.57)$$

*Proof.* In view of the logarithmic bound in (2.27) and of (2.34) it readily follows from (2.37) and (2.10) that  $h := -vz + \phi(u)$  belongs to  $L^p(\Omega \times (0, T_{max}))$  for each finite  $p > 1$ . The claim is an immediate consequence of a standard result on maximal Sobolev regularity in the Neumann problem for the inhomogeneous linear heat equation  $z_t = \Delta z + h(x, t)$  with initial data satisfying the regularity and compatibility conditions stated in (2.20) ([22]).  $\square$

Along with (2.56), this in turn facilitates an application of the same token to the more delicate second equation in (2.19):

**Lemma 2.12.** *If  $T_{max} < \infty$ , then for all  $p > 1$ ,*

$$\int_0^{T_{max}} \left\{ \|v(\cdot, t)\|_{W^{2,p}(\Omega)}^p + \|v_t(\cdot, t)\|_{L^p(\Omega)}^p \right\} dt < \infty. \quad (2.58)$$

*Proof.* We fix  $p > 1$  and then infer from Lemma 2.11 and Lemma 2.10 that there exist  $c_1(p) > 0$ ,  $c_2(p) > 0$  and  $c_3 > 0$  such that

$$\int_0^T \int_{\Omega} |\nabla z|^{2p} \leq c_1(p) \quad \text{for all } T \in (0, T_{max}) \quad (2.59)$$

and

$$\int_0^T \int_{\Omega} |\Delta z|^p \leq c_2(p) \quad \text{for all } T \in (0, T_{max}) \quad (2.60)$$

as well as

$$v(x, t) \leq c_3 \quad \text{for all } x \in \Omega \text{ and } t \in (0, T_{max}), \quad (2.61)$$

while maximal Sobolev regularity theory ([22]) provides  $c_4(p) > 0$  with the property that whenever  $h \in C^0(\bar{\Omega} \times [0, T_{max}))$  and  $\varphi \in C^{2,1}(\bar{\Omega} \times [0, T_{max}))$  are such that

$$\begin{cases} \varphi_t = \Delta\varphi + h(x, t), & x \in \Omega, t \in (0, T_{max}), \\ \frac{\partial \varphi}{\partial \nu} = 0, & x \in \partial\Omega, t \in (0, T_{max}), \\ \varphi(x, 0) = v_0(x), & x \in \Omega, \end{cases}$$

we have

$$\int_0^T \left\{ \|\varphi(\cdot, t)\|_{W^{2,p}(\Omega)}^p + \|\varphi_t(\cdot, t)\|_{L^p(\Omega)}^p \right\} dt \leq c_4(p) + c_4(p) \int_0^T \int_\Omega |h|^p \quad \text{for all } T \in (0, T_{max}). \quad (2.62)$$

Furthermore, using the Gagliardo-Nirenberg inequality to choose  $c_5(p) > 0$  such that

$$\int_\Omega |\nabla \varphi|^{2p} \leq c_5(p) \|\varphi\|_{W^{2,p}(\Omega)}^p \|\varphi\|_{L^\infty(\Omega)}^p \quad \text{for all } \varphi \in W^{2,p}(\Omega), \quad (2.63)$$

we infer from (2.62) that, using the second equation in (2.19), along with (2.60), (2.61), the Cauchy-Schwarz inequality, (2.59) and (2.63),

$$\begin{aligned} & \int_0^T \left\{ \|v(\cdot, t)\|_{W^{2,p}(\Omega)}^p + \|v_t(\cdot, t)\|_{L^p(\Omega)}^p \right\} dt \\ & \leq c_4(p) + c_4(p) \int_0^T \int_\Omega \left| -\nabla \cdot (v \nabla z) \right|^p \\ & \leq c_4(p) + 2^{p-1} c_4(p) \int_0^T \int_\Omega |v \Delta z|^p + 2^{p-1} c_4(p) \int_0^T \int_\Omega |\nabla v \cdot \nabla z|^p \\ & \leq c_4(p) + 2^{p-1} c_4(p) \|v\|_{L^\infty(\Omega \times (0, T))} \int_0^T \int_\Omega |\Delta z|^p \\ & \quad + 2^{p-1} c_4(p) \cdot \left\{ \int_0^T \int_\Omega |\nabla v|^{2p} \right\}^{\frac{1}{2}} \cdot \left\{ \int_\Omega |\nabla z|^{2p} \right\}^{\frac{1}{2}} \\ & \leq c_4(p) + 2^{p-1} c_4(p) \|v\|_{L^\infty(\Omega \times (0, T))} \int_0^T \int_\Omega |\Delta z|^p \\ & \quad + 2^{p-1} c_4(p) c_5^{\frac{1}{2}}(p) \|v\|_{L^\infty(\Omega \times (0, T))}^{\frac{p}{2}} \cdot \left\{ \int_0^T \|v(\cdot, t)\|_{W^{2,p}(\Omega)}^p dt \right\}^{\frac{1}{2}} \cdot \left\{ \int_0^T \int_\Omega |\nabla z|^{2p} \right\}^{\frac{1}{2}} \\ & \leq c_6(p) + c_6(p) \cdot \left\{ \int_0^T \|v(\cdot, t)\|_{W^{2,p}(\Omega)}^p dt \right\}^{\frac{1}{2}} \quad \text{for all } T \in (0, T_{max}) \end{aligned}$$

with  $c_6(p) := \max \left\{ c_4(p) + 2^{p-1} c_2(p) c_3 c_4(p), 2^{p-1} c_1^{\frac{1}{2}}(p) c_3^{\frac{p}{2}} c_4(p) c_5^{\frac{1}{2}}(p) \right\}$ . Since

$$c_6(p) \cdot \left\{ \int_0^T \|v(\cdot, t)\|_{W^{2,p}(\Omega)}^p dt \right\}^{\frac{1}{2}} \leq \frac{1}{2} \int_0^T \|v(\cdot, t)\|_{W^{2,p}(\Omega)}^p dt + \frac{c_6^2(p)}{2} \quad \text{for all } T \in (0, T_{max})$$

by Young's inequality, this implies (2.58).  $\square$

For later reference, let us also explicitly state here the following immediate consequence concerning Hölder regularity of  $v$  and  $\nabla v$ .

**Lemma 2.13.** *If  $T_{max} < \infty$ , then there exists  $\theta \in (0, 1)$  such that*

$$v \in C^{1+\theta, \theta}(\bar{\Omega} \times [0, T_{max}]). \quad (2.64)$$

*Proof.* Due to a well-known embedding property ([3]), this directly results from an application of Lemma 2.12 to some suitably large  $p > 1$ .  $\square$

## 2.5 Pointwise boundedness of $a$

Next, approaching the core of our analysis, we shall use the regularity information gained so far, and especially the  $L^p$  bounds for  $v_t$  included in Lemma 2.12, to derive an  $L^\infty$  estimate for the apparently most crucial solution component  $a$ . This will be achieved by means of an appropriately designed  $L^p$  iteration of Moser type on the basis of the first equation in (2.32), noting that, inter alia, due to the explicit presence of  $v_t$  therein, classical results in this regard ([2], [40]) apparently do not apply directly to the current situation.

**Lemma 2.14.** If  $T_{max} < \infty$ , then there exists  $C > 0$  such that

$$a(x, t) \leq C \quad \text{for all } x \in \Omega \text{ and } t \in (0, T_{max}). \quad (2.65)$$

*Proof.* For integers  $k \geq 0$ , we let  $p_k := 2^k$  and

$$M_k(T) := \max \left\{ 1, \sup_{t \in (0, T)} \int_{\Omega} a^{p_k}(\cdot, t) \right\}, \quad T \in (0, T_{max}). \quad (2.66)$$

To appropriately control the latter quantities we note that according to (2.36), (2.23), (2.29), (2.22) and (2.26) we can find positive constants  $c_i, i \in \{1, \dots, 6\}$ , such that

$$0 \leq w \leq c_1, \quad |\xi(v, w)| \leq c_2, \quad |\Xi(v, w)| \leq c_3, \quad |\Xi_v(v, w)| \leq c_4 \quad \text{and} \quad |\chi(v, w)| \leq c_5 \quad \text{in } \Omega \times (0, T_{max}) \quad (2.67)$$

as well as

$$\psi(s) \leq c_6 s^{\frac{1}{3}} + c_6 \quad \text{for all } s \geq 0. \quad (2.68)$$

Moreover, Lemma 2.13 and Lemma 2.12 allow us to fix  $c_7 > 0$  and  $c_8 > 0$  fulfilling

$$|\nabla v| \leq c_7 \quad \text{in } \Omega \times (0, T_{max}) \quad (2.69)$$

and

$$\int_0^T \int_{\Omega} v_t^4 \leq c_8 \quad \text{for all } T \in (0, T_{max}). \quad (2.70)$$

Therefore, namely, we particularly know that due to (2.28) and (2.34),

$$\int_{\Omega} a = \int_{\Omega} u e^{-\Xi(v, w)} \leq e^{c_3} \int_{\Omega} u = e^{c_3} \int_{\Omega} u_0 \quad \text{for all } t \in (0, T_{max}),$$

and that thus

$$M_0(T) \leq \max \left\{ 1, e^{c_3} \int_{\Omega} u_0 \right\} \quad \text{for all } T \in (0, T_{max}). \quad (2.71)$$

Moreover, (2.67)-(2.70) enable us to estimate  $M_k(T)$  for  $k \geq 1$  and  $T \in (0, T_{max})$  by means of a refined testing procedure on the basis of (2.32): Indeed, for any such  $k$  we see that abbreviating  $p := p_k$  we have

$$\begin{aligned} \frac{d}{dt} \int_{\Omega} e^{\Xi(v, w)} a^p &= p \int_{\Omega} e^{\Xi(v, w)} a^{p-1} \cdot \left\{ e^{-\Xi(v, w)} \nabla \cdot \left\{ e^{\Xi(v, w)} \nabla a \right\} \right. \\ &\quad \left. - e^{-\Xi(v, w)} \nabla \cdot \left\{ a e^{\Xi(v, w)} (\chi(v, w) - \Xi_v(v, w)) \nabla v \right\} \right. \\ &\quad \left. - a \Xi_v(v, w) v_t + a \xi(v, w) \psi(a w e^{\Xi(v, w)}) \right\} \\ &\quad + \int_{\Omega} e^{\Xi(v, w)} a^p \cdot \left\{ \Xi_v(v, w) v_t - \xi(v, w) \psi(a w e^{\Xi(v, w)}) \right\} \\ &= p \int_{\Omega} a^{p-1} \nabla \cdot \left\{ e^{\Xi(v, w)} \nabla a \right\} - p \int_{\Omega} a^{p-1} \nabla \cdot \left\{ a e^{\Xi(v, w)} (\chi(v, w) - \Xi_v(v, w)) \nabla v \right\} \\ &\quad - p \int_{\Omega} e^{\Xi(v, w)} \Xi_v(v, w) a^p v_t + p \int_{\Omega} e^{\Xi(v, w)} \xi(v, w) a^p \psi(a w e^{\Xi(v, w)}) \\ &\quad + \int_{\Omega} e^{\Xi(v, w)} \Xi_v(v, w) a^p v_t - \int_{\Omega} e^{\Xi(v, w)} \xi(v, w) a^p \psi(a w e^{\Xi(v, w)}) \\ &= -p(p-1) \int_{\Omega} e^{\Xi(v, w)} a^{p-2} |\nabla a|^2 \\ &\quad + p(p-1) \int_{\Omega} e^{\Xi(v, w)} (\chi(v, w) - \Xi_v(v, w)) a^{p-1} \nabla a \cdot \nabla v \\ &\quad - (p-1) \int_{\Omega} e^{\Xi(v, w)} \Xi_v(v, w) a^p v_t \\ &\quad + (p-1) \int_{\Omega} e^{\Xi(v, w)} \xi(v, w) a^p \psi(a w e^{\Xi(v, w)}) \quad \text{for all } t \in (0, T_{max}). \end{aligned} \quad (2.72)$$

By Young's inequality, (2.67) and (2.69),

$$p(p-1) \int_{\Omega} e^{\Xi(v, w)} (\chi(v, w) - \Xi_v(v, w)) a^{p-1} \nabla a \cdot \nabla v$$

$$\begin{aligned}
&\leq \frac{p(p-1)}{2} \int_{\Omega} e^{\Xi(v,w)} a^{p-2} |\nabla a|^2 \\
&\quad + \frac{p(p-1)}{2} \int_{\Omega} e^{\Xi(v,w)} (\chi(v,w) - \Xi_v(v,w))^2 a^p |\nabla v|^2 \\
&\leq \frac{p(p-1)}{2} \int_{\Omega} e^{\Xi(v,w)} a^{p-2} |\nabla a|^2 \\
&\quad + \frac{p(p-1)}{2} e^{c_3} (c_5 + c_4)^2 c_7^2 \int_{\Omega} a^p \quad \text{for all } t \in (0, T_{max}),
\end{aligned} \tag{2.73}$$

and due to (2.67) and (2.68),

$$\begin{aligned}
&(p-1) \int_{\Omega} e^{\Xi(v,w)} \xi(v,w) a^p \psi(a w e^{\Xi(v,w)}) \\
&\leq (p-1) e^{c_3} c_2 \int_{\Omega} a^p \cdot \left\{ c_6 \cdot (a w e^{\Xi(v,w)})^{\frac{1}{3}} + c_6 \right\} \\
&\leq (p-1) e^{\frac{4c_3}{3}} c_2 c_1^{\frac{1}{3}} c_6 \int_{\Omega} a^{p+\frac{1}{3}} + (p-1) e^{c_3} c_2 c_6 \int_{\Omega} a^p \quad \text{for all } t \in (0, T_{max}).
\end{aligned} \tag{2.74}$$

Since furthermore an application of the Hölder inequality shows that thanks to (2.67) we have

$$\begin{aligned}
-(p-1) \int_{\Omega} e^{\Xi(v,w)} \Xi_v(v,w) a^p v_t &\leq (p-1) \|v_t\|_{L^4(\Omega)} \cdot \left\{ \int_{\Omega} e^{\frac{4}{3}\Xi(v,w)} |\Xi_v(v,w)|^{\frac{4}{3}} a^{\frac{4p}{3}} \right\}^{\frac{3}{4}} \\
&\leq (p-1) e^{c_3} c_4 \|v_t\|_{L^4(\Omega)} \cdot \left\{ \int_{\Omega} a^{\frac{4p}{3}} \right\}^{\frac{3}{4}} \quad \text{for all } t \in (0, T_{max}),
\end{aligned}$$

and since

$$\int_{\Omega} a^p \leq \int_{\Omega} a^{p+\frac{1}{3}} + |\Omega| \quad \text{for all } t \in (0, T_{max})$$

by Young's inequality, from (2.72)-(2.74) we infer the existence of  $c_9 \in (0, 2)$  and  $c_{10} > 0$  such that for any  $k \geq 1$ ,

$$\begin{aligned}
&\frac{d}{dt} \int_{\Omega} e^{\Xi(v,w)} a^{p_k} + c_9 \int_{\Omega} |\nabla a^{\frac{p_k}{2}}|^2 \\
&\leq c_{10} p_k^2 \int_{\Omega} a^{p_k+\frac{1}{3}} + c_{10} p_k \|v_t\|_{L^4(\Omega)} \cdot \left\{ \int_{\Omega} a^{\frac{4p_k}{3}} \right\}^{\frac{3}{4}} + c_{10} p_k^2 \quad \text{for all } t \in (0, T_{max}).
\end{aligned} \tag{2.75}$$

We now employ the Gagliardo-Nirenberg inequality to fix  $c_{11} \geq 1$  such that

$$\|\varphi\|_{L^{\frac{8}{3}}(\Omega)}^2 \leq c_{11} \|\nabla \varphi\|_{L^2(\Omega)}^{\frac{5}{4}} \|\varphi\|_{L^1(\Omega)}^{\frac{3}{4}} + c_{11} \|\varphi\|_{L^1(\Omega)}^2 \quad \text{for all } \varphi \in W^{1,2}(\Omega), \tag{2.76}$$

and note that due to the Hölder inequality and Young's inequality, this implies that for each  $p \geq 1$ ,

$$\begin{aligned}
\|\varphi\|_{L^{\frac{2(p+\frac{1}{3})}{p}}(\Omega)}^{\frac{2(p+\frac{1}{3})}{p}} &\leq \|\varphi\|_{L^{\frac{8}{3}}(\Omega)}^{\frac{8(p+\frac{2}{3})}{5p}} \|\varphi\|_{L^1(\Omega)}^{\frac{2(p-1)}{5p}} \\
&\leq c_{11}^{\frac{4(p+\frac{2}{3})}{5p}} \cdot \left\{ \|\nabla \varphi\|_{L^2(\Omega)}^{\frac{5}{4}} \|\varphi\|_{L^1(\Omega)}^{\frac{3}{4}} + \|\varphi\|_{L^1(\Omega)}^2 \right\}^{\frac{4(p+\frac{2}{3})}{5p}} \|\varphi\|_{L^1(\Omega)}^{\frac{2(p-1)}{5p}} \\
&\leq 2^{\frac{4(p+\frac{2}{3})}{5p}} c_{11}^{\frac{4(p+\frac{2}{3})}{5p}} \cdot \left\{ \|\nabla \varphi\|_{L^2(\Omega)}^{\frac{p}{5}} \|\varphi\|_{L^1(\Omega)}^{\frac{3(p+\frac{2}{3})}{5p}} \|\varphi\|_{L^1(\Omega)}^{\frac{2(p-1)}{5p}} + \|\varphi\|_{L^1(\Omega)}^{\frac{8(p+\frac{2}{3})}{5p}} \|\varphi\|_{L^1(\Omega)}^{\frac{2(p-1)}{5p}} \right\} \\
&= 2^{\frac{4(p+\frac{2}{3})}{5p}} c_{11}^{\frac{4(p+\frac{2}{3})}{5p}} \cdot \left\{ \|\nabla \varphi\|_{L^2(\Omega)}^{\frac{p}{5}} \|\varphi\|_{L^1(\Omega)}^{\frac{2(p+\frac{1}{3})}{5p}} + \|\varphi\|_{L^1(\Omega)}^{\frac{2(p+\frac{1}{3})}{5p}} \right\} \quad \text{for all } \varphi \in W^{1,2}(\Omega),
\end{aligned}$$

because for any such  $p$  we have  $1 \leq \frac{2(p+\frac{1}{3})}{p} \leq \frac{8}{3}$ . Since, apart from that,  $\frac{4(p+\frac{2}{3})}{5p} \leq \frac{4}{3}$  for all  $p \geq 1$ , this entails that writing  $c_{12} := (2c_{11})^{\frac{4}{3}}$ , for any choice of  $k \geq 1$  we can estimate

$$\|\varphi\|_{L^{\frac{2(p_k+\frac{1}{3})}{p_k}}(\Omega)}^{\frac{2(p_k+\frac{1}{3})}{p_k}} \leq c_{12} \|\nabla \varphi\|_{L^2(\Omega)}^{\frac{p_k}{5}} \|\varphi\|_{L^1(\Omega)}^{\frac{2(p_k+\frac{1}{3})}{5}} \quad \text{for all } \varphi \in W^{1,2}(\Omega). \tag{2.77}$$

With these interpolation properties at hand, we can proceed to estimate the first two summands on the right-hand side of (2.75) by making use of the observation that whenever  $k \geq 1$  and  $T > 0$ ,

$$\int_{\Omega} a^{\frac{p_k}{2}} = \int_{\Omega} a^{p_{k-1}} \leq M_{k-1}(T) \quad \text{for all } t \in (0, T). \quad (2.78)$$

According to (2.77), namely, this firstly implies that due to an application of the Gagliardo-Nirenberg and Young inequalities, relying on the fact that  $\frac{p_k + \frac{2}{3}}{p_k} \leq \frac{5}{3} \leq 2$  for all  $k \geq 1$ ,

$$\begin{aligned} c_{10} p_k^2 \int_{\Omega} a^{p_k + \frac{1}{3}} &= c_{10} p_k^2 \|a^{\frac{p_k}{2}}\|_{L^{\frac{2(p_k + \frac{1}{3})}{p_k}}(\Omega)}^{\frac{2(p_k + \frac{1}{3})}{p_k}} \\ &\leq c_{10} c_{12} p_k^2 \|\nabla a^{\frac{p_k}{2}}\|_{L^2(\Omega)}^{\frac{p_k + \frac{2}{3}}{p_k}} \|a^{\frac{p_k}{2}}\|_{L^1(\Omega)} + c_{10} c_{12} p_k^2 \|a^{\frac{p_k}{2}}\|_{L^1(\Omega)}^{\frac{2(p_k + \frac{1}{3})}{p_k}} \\ &\leq c_{10} c_{12} p_k^2 M_{k-1}(T) \|\nabla a^{\frac{p_k}{2}}\|_{L^2(\Omega)}^{\frac{p_k + \frac{2}{3}}{p_k}} + c_{10} c_{12} p_k^2 M_{k-1}^{\frac{2(p_k + \frac{1}{3})}{p_k}}(T) \\ &= \left\{ \frac{c_9}{2} \int_{\Omega} |\nabla a^{\frac{p_k}{2}}|^2 \right\}^{\frac{p_k + \frac{2}{3}}{2p_k}} \cdot \left( \frac{2}{c_9} \right)^{\frac{p_k + \frac{2}{3}}{2p_k}} c_{10} c_{12} p_k^2 M_{k-1}(T) + c_{10} c_{12} p_k^2 M_{k-1}^{\frac{2(p_k + \frac{1}{3})}{p_k}}(T) \\ &\leq \frac{c_9}{2} \int_{\Omega} |\nabla a^{\frac{p_k}{2}}|^2 + \left( \frac{2}{c_9} \right)^{\frac{p_k + \frac{2}{3}}{p_k - \frac{2}{3}}} (c_{10} c_{12})^{\frac{2p_k}{p_k - \frac{2}{3}}} p_k^{\frac{4p_k}{p_k - \frac{2}{3}}} M_{k-1}^{\frac{2p_k}{p_k - \frac{2}{3}}}(T) \\ &\quad + c_{10} c_{12} p_k^2 M_{k-1}^{\frac{2(p_k + \frac{1}{3})}{p_k}}(T) \quad \text{for all } t \in (0, T), \text{ any } T \in (0, T_{max}) \text{ and each } k \geq 1. \end{aligned}$$

Since  $\frac{p_k + \frac{2}{3}}{p_k - \frac{2}{3}} \leq 5$  and  $1 \leq \frac{p_k}{p_k - \frac{2}{3}} \leq 3$  as well as  $\frac{2(p_k + \frac{1}{3})}{p_k} \leq \frac{2p_k}{p_k - \frac{2}{3}}$  for all  $k \geq 1$ , and since  $M_{k-1}(T) \geq 1$  for all  $k \geq 1$  and  $T \in (0, T_{max})$ , using that  $\frac{2}{c_9} \geq 1$  we thus obtain that if we let

$$c_{13} := \left( \frac{2}{c_9} \right)^5 \cdot (c_{10} c_{12})^3 + c_{10} c_{12},$$

then

$$c_{10} p_k^2 \int_{\Omega} a^{p_k + \frac{1}{3}} \leq \frac{c_9}{2} \int_{\Omega} |\nabla a^{\frac{p_k}{2}}|^2 + c_{13} p_k^{12} M_{k-1}^{\frac{2p_k}{p_k - \frac{2}{3}}}(T) \quad \text{for all } t \in (0, T), T \in (0, T_{max}) \text{ and } k \geq 1. \quad (2.79)$$

We next use (2.78) together with (2.76) to similarly see that again thanks to Young's inequality, whenever  $T \in (0, T_{max})$  and  $k \geq 1$ ,

$$\begin{aligned} c_{10} p_k \|v_t\|_{L^4(\Omega)} \cdot \left\{ \int_{\Omega} a^{\frac{4p_k}{3}} \right\}^{\frac{3}{4}} &= c_{10} p_k \|v_t\|_{L^4(\Omega)} \|a^{\frac{p_k}{2}}\|_{L^{\frac{8}{3}}(\Omega)}^2 \\ &\leq c_{10} c_{11} p_k M_{k-1}^{\frac{3}{4}}(T) \|v_t\|_{L^4(\Omega)} \|\nabla a^{\frac{p_k}{2}}\|_{L^2(\Omega)}^{\frac{5}{4}} + c_{10} c_{11} p_k M_{k-1}^2(T) \|v_t\|_{L^4(\Omega)} \\ &= \left\{ \frac{c_9}{2} \int_{\Omega} |\nabla a^{\frac{p_k}{2}}|^2 \right\}^{\frac{5}{8}} \cdot \left( \frac{2}{c_9} \right)^{\frac{5}{8}} c_{10} c_{11} p_k M_{k-1}^{\frac{3}{4}}(T) \|v_t\|_{L^4(\Omega)} + c_{10} c_{11} p_k M_{k-1}^2(T) \|v_t\|_{L^4(\Omega)} \\ &\leq \frac{c_9}{2} \int_{\Omega} |\nabla a^{\frac{p_k}{2}}|^2 + \left( \frac{2}{c_9} \right)^{\frac{5}{3}} (c_{10} c_{11})^{\frac{8}{3}} p_k^{\frac{8}{3}} M_{k-1}^2(T) \|v_t\|_{L^4(\Omega)}^{\frac{8}{3}} \\ &\quad + c_{10} c_{11} p_k M_{k-1}^2(T) \|v_t\|_{L^4(\Omega)}, \quad \text{for all } t \in (0, T), \end{aligned}$$

so that since  $p_k \geq 1$  for all  $k \geq 1$  and  $\max\{s^{\frac{8}{3}}, s\} \leq s^4 + 1$  for all  $s \geq 0$  by Young's inequality, it follows that

$$c_{10} p_k \|v_t\|_{L^4(\Omega)} \cdot \left\{ \int_{\Omega} a^{\frac{4p_k}{3}} \right\}^{\frac{3}{4}} \leq \frac{c_9}{2} \int_{\Omega} |\nabla a^{\frac{p_k}{2}}|^2 + c_{14} p_k^{\frac{8}{3}} M_{k-1}^2(T) \cdot \left\{ \int_{\Omega} v_t^4 + 1 \right\} \quad (2.80)$$

for any such  $t, T$  and  $k$ , with  $c_{14} := (\frac{2}{c_9})^{\frac{5}{3}} (c_{10} c_{11})^{\frac{8}{3}} + c_{10} c_{11}$ .

We now combine this with (2.79) and (2.75) to infer that as

$$p_k^{\frac{8}{3}} M_{k-1}^2(T) \leq p_k^{12} M_{k-1}^{\frac{p_k - \frac{2}{3}}{2}}(T) \quad \text{and} \quad p_k^2 \leq p_k^{12} \quad \text{for all } T \in (0, T_{max}) \text{ and } k \geq 1,$$

writing  $c_{15} := c_{10} + c_{13} + c_{14}$  and  $\theta_k := \frac{2p_k}{p_k - \frac{2}{3}}$  for  $k \geq 1$ , we have

$$\frac{d}{dt} \int_{\Omega} e^{\Xi(v,w)} a^{p_k} \leq c_{15} p_k^{12} M_{k-1}^{\theta_k}(T) \cdot \left\{ \int_{\Omega} v_t^4 + 1 \right\} \quad \text{for all } t \in (0, T), T \in (0, T_{max}) \text{ and } k \geq 1.$$

Upon an integration this entails that according to (2.70),

$$\int_{\Omega} e^{\Xi(v,w)} a^{p_k} \leq \int_{\Omega} e^{\Xi(v_0,w_0)} a^{p_k}(\cdot, 0) + c_{16} p_k^{12} M_{k-1}^{\theta_k}(T) \quad \text{for all } t \in (0, T), T \in (0, T_{max}) \text{ and } k \geq 1,$$

with  $c_{16} := c_{15} \cdot (c_8 + T_{max})$ . Since by (2.67)

$$e^{-c_3} \int_{\Omega} a^{p_k} \leq \int_{\Omega} e^{\Xi(v,w)} a^{p_k} \leq e^{c_3} \|a\|_{L^\infty(\Omega)}^{p_k} \quad \text{for all } t \in [0, T_{max}] \text{ and } k \geq 1,$$

once more in view of (2.66) this reveals that

$$\begin{aligned} M_k(T) &\leq 1 + e^{c_3} \cdot \left\{ \int_{\Omega} e^{\Xi(v_0,w_0)} a^{p_k}(\cdot, 0) + c_{16} p_k^{12} M_{k-1}^{\theta_k}(T) \right\} \\ &\leq 1 + e^{2c_3} \|a(\cdot, 0)\|_{L^\infty(\Omega)}^{p_k} + e^{c_3} c_{16} p_k^{12} M_{k-1}^{\theta_k}(T) \\ &\leq e^{2c_3} \|a(\cdot, 0)\|_{L^\infty(\Omega)}^{p_k} + c_{17} p_k^{12} M_{k-1}^{\theta_k}(T) \quad \text{for all } T \in (0, T_{max}) \text{ and } k \geq 1, \end{aligned} \quad (2.81)$$

where  $c_{17} := 1 + e^{c_3} c_{16}$ . In light of (2.71), by induction this firstly implies that

$$\bar{M}_k := \sup_{T \in (0, T_{max})} M_k(T)$$

is finite for all  $k \geq 1$ , and that, secondly, these numbers satisfy

$$\bar{M}_k \leq e^{2c_3} \|a(\cdot, 0)\|_{L^\infty(\Omega)}^{p_k} + c_{17} p_k^{12} \bar{M}_{k-1}^{\theta_k} \quad \text{for all } k \geq 1. \quad (2.82)$$

Now if  $\bar{M}_k \leq 2e^{2c_3} \|a(\cdot, 0)\|_{L^\infty(\Omega)}^{p_k}$  for infinitely many  $k \in \mathbb{N}$ , then, since  $p_k \rightarrow \infty$  as  $k \rightarrow \infty$ , it holds that

$$\|a(\cdot, t)\|_{L^\infty(\Omega)} = \liminf_{k \rightarrow \infty} \|a(\cdot, t)\|_{L^{p_k}(\Omega)} \leq \liminf_{k \rightarrow \infty} \bar{M}_k^{\frac{1}{p_k}} \leq \|a(\cdot, 0)\|_{L^\infty(\Omega)} \quad \text{for all } T \in (0, T_{max}).$$

In the opposite case, there exists  $k_0 \in \mathbb{N}$  such that  $e^{2c_3} \|a(\cdot, 0)\|_{L^\infty(\Omega)}^{p_k} \leq \frac{1}{2} \bar{M}_k$  and hence, by (2.82),

$$\bar{M}_k \leq 2c_{17} p_k^{12} \bar{M}_{k-1}^{\theta_k}$$

for all  $k \geq k_0$ . Recalling that  $p_k = 2^k$  for  $k \geq 0$ , we can then fix  $b > 1$  large enough such that

$$\bar{M}_k \leq b^k \bar{M}_{k-1}^{\theta_k} \quad \text{for all } k \geq 1,$$

where by definition of  $(\theta_k)_{k \geq 1}$ ,

$$\frac{\theta_k}{2} - 1 = \frac{p_k}{p_k - \frac{2}{3}} - 1 = \frac{2}{3p_k - 2} = \frac{2}{3 \cdot 2^k - 2} \leq \frac{2}{3 \cdot 2^k - 2^k} = \frac{1}{2^k} \quad \text{for all } k \geq 1.$$

Therefore, according to an elementary estimate derived in [49, Lemma 4.3],

$$\bar{M}_k \leq b^{k+e \cdot 2^{k+1}} \bar{M}_0^{e \cdot 2^k} \quad \text{for all } k \geq 1,$$

so that

$$\limsup_{k \rightarrow \infty} \bar{M}_k^{\frac{1}{p_k}} \leq \limsup_{k \rightarrow \infty} \left\{ b^{k \cdot 2^{-k} + 2e} \bar{M}_0^e \right\},$$

and hence we may conclude that (2.65) also holds in this case.  $\square$

## 2.6 Bounds in $C^{2+\theta}(\bar{\Omega})$ . Proof of Theorem 2.1

Having at hand the above information, and especially  $L^\infty$  bounds for all solution components, we can build our subsequent regularity arguments on the following elementary observation.

**Lemma 2.15.** *We have*

$$\begin{aligned} a_t &= \Delta a + A_1(x, t)\nabla v \cdot \nabla a + A_2(x, t)\nabla w \cdot \nabla a + A_3(x, t)|\nabla v|^2 + A_4(x, t)\nabla v \cdot \nabla w \\ &\quad + A_5(x, t)\Delta v + A_6(x, t)v_t + A_7(x, t) \quad \text{for all } x \in \Omega \text{ and } t \in (0, T_{max}) \end{aligned} \quad (2.83)$$

and

$$\nabla w_t = B_1(x, t)\nabla a + B_2(x, t)\nabla w + B_3(x, t)\nabla v \quad \text{for all } x \in \Omega \text{ and } t \in (0, T_{max}), \quad (2.84)$$

where

$$\begin{aligned} A_1(x, t) &:= 2\Xi_v(v, w) - \chi(v, w), \\ A_2(x, t) &:= \xi(v, w), \\ A_3(x, t) &:= a(-\chi(v, w)\Xi_v(v, w) + \Xi_v^2(v, w) - \chi_v(v, w) + \Xi_{vv}(v, w)), \\ A_4(x, t) &:= a(-\chi(v, w)\xi(v, w) + \Xi_v(v, w)\xi(v, w) - \chi_w(v, w) + \xi_v(v, w)), \\ A_5(x, t) &:= a(-\chi(v, w) + \Xi_v(v, w)), \\ A_6(x, t) &:= a(-\Xi_v(v, w)) \quad \text{and} \\ A_7(x, t) &:= a(\xi(v, w)\psi(awe^{\Xi(v, w)})), \end{aligned} \quad (2.85)$$

as well as

$$\begin{aligned} B_1(x, t) &:= -\psi'(awe^{\Xi(v, w)}) \cdot we^{\Xi(v, w)}, \\ B_2(x, t) &:= -\psi'(awe^{\Xi(v, w)}) \cdot ae^{\Xi(v, w)} \cdot (1 + w\xi(v, w)) \quad \text{and} \\ B_3(x, t) &:= -\psi'(awe^{\Xi(v, w)}) \cdot awe^{\Xi(v, w)} \cdot \Xi_v(v, w) \end{aligned} \quad (2.86)$$

for  $(x, t) \in \Omega \times (0, T_{max})$ .

*Proof.* This can be seen by straightforward differentiation in (2.32).  $\square$

In fact, due to the boundedness features gathered in the previous sections, the latter lemma implies the following.

**Corollary 2.16.** *Assume that  $T_{max} < \infty$ . Then there exists  $C > 0$  such that*

$$|a_t - \Delta a| \leq C \cdot \left\{ |\nabla w \cdot \nabla a| + |\nabla a| + |\nabla w| + |\Delta v| + |v_t| + 1 \right\} \quad \text{in } \Omega \times (0, T_{max}) \quad (2.87)$$

and that

$$|\nabla w_t| \leq C \cdot \left\{ |\nabla a| + |\nabla w| + 1 \right\} \quad \text{in } \Omega \times (0, T_{max}). \quad (2.88)$$

*Proof.* Since (2.22), (2.23), (2.24) and (2.26) together with (2.36), (2.56) and (2.14) warrant boundedness of all the functions  $A_i$  and  $B_j$ ,  $i \in \{1, \dots, 7\}$ ,  $j \in \{1, 2, 3\}$  in (2.85) and (2.86), and since moreover also  $\nabla v$  is bounded in  $\Omega \times (0, T_{max})$  by Lemma 2.13, both inequalities are direct consequences of Lemma 2.15.  $\square$

Once again relying on the planarity of the spatial setting, through an analysis of  $\int_\Omega |\nabla a|^2 + c \int_\Omega |\nabla w|^4$  along trajectories, with suitably chosen  $c > 0$ , we shall next obtain, inter alia, some information on  $a$  at the level of second-order derivatives.

**Lemma 2.17.** *If  $T_{max} < \infty$ , then there exists  $C > 0$  such that*

$$\int_\Omega |\nabla w(\cdot, t)|^4 \leq C \quad \text{for all } t \in (0, T_{max}), \quad (2.89)$$

and moreover we have

$$\int_0^{T_{max}} \int_\Omega |\Delta a|^2 < \infty. \quad (2.90)$$

*Proof.* We employ Young's inequality and Corollary 2.16 to see that with some  $c_1 > 0$ ,

$$\begin{aligned} \frac{1}{2} \frac{d}{dt} \int_\Omega |\nabla a|^2 + \int_\Omega |\Delta a|^2 &= - \int_\Omega \Delta a \cdot (a_t - \Delta a) \\ &\leq \frac{1}{4} \int_\Omega |\Delta a|^2 + \int_\Omega |a_t - \Delta a|^2 \end{aligned}$$

$$\begin{aligned} &\leq \frac{1}{4} \int_{\Omega} |\Delta a|^2 + c_1 \int_{\Omega} |\nabla w|^2 |\nabla a|^2 + c_1 \int_{\Omega} |\nabla a|^2 + c_1 \int_{\Omega} |\nabla w|^2 \\ &\quad + c_1 \int_{\Omega} |\Delta v|^2 + c_1 \int_{\Omega} v_t^2 + c_1 \quad \text{for all } t \in (0, T_{max}). \end{aligned} \quad (2.91)$$

Writing  $c_2 := \|a\|_{L^\infty(\Omega \times (0, T_{max}))} < \infty$  and taking  $c_3 > 0$  such that in accordance with the Gagliardo-Nirenberg inequality and elliptic regularity theory ([23]) we have

$$\int_{\Omega} |\nabla \varphi|^4 \leq c_3 \|\Delta \varphi\|_{L^2(\Omega)}^2 \|\varphi\|_{L^\infty(\Omega)}^2 \quad \text{for all } \varphi \in W^{2,2}(\Omega) \text{ such that } \frac{\partial \varphi}{\partial \nu} = 0 \text{ on } \partial \Omega, \quad (2.92)$$

again by Young's inequality we estimate

$$\begin{aligned} c_1 \int_{\Omega} |\nabla w|^2 |\nabla a|^2 + c_1 \int_{\Omega} |\nabla a|^2 &\leq \frac{1}{4c_2^2 c_3} \int_{\Omega} |\nabla a|^4 + 2c_1^2 c_2^2 c_3 \int_{\Omega} |\nabla w|^4 + 2c_1^2 c_2^2 c_3 |\Omega| \\ &\leq \frac{1}{4c_2^2} \|\Delta a\|_{L^2(\Omega)}^2 \|a\|_{L^\infty(\Omega)}^2 + 2c_1^2 c_2^2 c_3 \int_{\Omega} |\nabla w|^4 + 2c_1^2 c_2^2 c_3 |\Omega| \\ &\leq \frac{1}{4} \int_{\Omega} |\Delta a|^2 + 2c_1^2 c_2^2 c_3 \int_{\Omega} |\nabla w|^4 + 2c_1^2 c_2^2 c_3 |\Omega| \quad \text{for all } t \in (0, T_{max}). \end{aligned}$$

Since Young's inequality moreover entails that

$$c_1 \int_{\Omega} |\nabla w|^2 \leq \frac{1}{2} \int_{\Omega} |\nabla w|^4 + \frac{c_1^2 |\Omega|}{2} \quad \text{for all } t \in (0, T_{max}),$$

from (2.91) we thus obtain the inequality

$$\frac{d}{dt} \int_{\Omega} |\nabla a|^2 + \int_{\Omega} |\Delta a|^2 \leq c_3 \int_{\Omega} |\nabla w|^4 + 2c_1 \int_{\Omega} |\Delta v|^2 + 2c_1 \int_{\Omega} v_t^2 + c_4 \quad \text{for all } t \in (0, T_{max}) \quad (2.93)$$

with  $c_3 := 4c_1^2 c_2^2 c_3 + 1$  and  $c_4 := 4c_1^2 c_2^2 c_3 |\Omega| + c_1^2 |\Omega| + 2c_1$ . In order to appropriately control the growth induced by the first summand on the right-hand side herein, we combine *Corollary 2.16* with Young's inequality to see that with some  $c_5 > 0$  we have

$$\begin{aligned} \frac{d}{dt} \int_{\Omega} |\nabla w|^4 &= 4 \int_{\Omega} |\nabla w|^2 \nabla w \cdot \nabla w_t \\ &\leq c_5 \int_{\Omega} |\nabla w|^3 \cdot \{ |\nabla a| + |\nabla w| + 1 \} \\ &\leq 3c_5 \int_{\Omega} |\nabla w|^4 + c_5 \int_{\Omega} |\nabla a|^4 + c_5 |\Omega| \quad \text{for all } t \in (0, T_{max}), \end{aligned} \quad (2.94)$$

for which once more by (2.92) we estimate

$$c_5 \int_{\Omega} |\nabla a|^4 \leq c_6 \int_{\Omega} |\Delta a|^2 \quad \text{for all } t \in (0, T_{max})$$

with  $c_6 := c_2^2 c_3 c_5$ . Therefore, (2.93) in conjunction with (2.94) show that

$$\begin{aligned} \frac{d}{dt} \left\{ \int_{\Omega} |\nabla a|^2 + \frac{1}{2c_6} \int_{\Omega} |\nabla w|^4 \right\} + \frac{1}{2} \int_{\Omega} |\Delta a|^2 \\ \leq \left( c_3 + \frac{3c_5}{2c_6} \right) \int_{\Omega} |\nabla w|^4 + 2c_1 \int_{\Omega} |\Delta v|^2 + 2c_1 \int_{\Omega} v_t^2 + c_4 + \frac{c_5 |\Omega|}{2c_6} \quad \text{for all } t \in (0, T_{max}), \end{aligned}$$

and that hence the functions given by  $y(t) := \int_{\Omega} |\nabla a(\cdot, t)|^2 + \frac{1}{2c_6} \int_{\Omega} |\nabla w(\cdot, t)|^4$ ,  $g(t) := \frac{1}{2} \int_{\Omega} |\Delta a(\cdot, t)|^2$  and  $h(t) := 2c_1 \int_{\Omega} |\Delta v(\cdot, t)|^2 + 2c_1 \int_{\Omega} v_t^2(\cdot, t) + c_4 + \frac{c_5 |\Omega|}{2c_6}$ ,  $t \in [0, T_{max}]$ , satisfy  $y'(t) + g(t) \leq 2c_6(c_3 + \frac{3c_5}{2c_6})y(t) + h(t)$  for all  $t \in (0, T_{max})$ . Since  $\int_0^{T_{max}} h(t) dt < \infty$  by *Lemma 2.12*, this can readily be seen to firstly imply that  $\sup_{t \in (0, T_{max})} y(t) < \infty$ , and to secondly entail that also  $\int_0^{T_{max}} g(t) dt$  is finite, whereby both (2.89) and (2.90) are established.  $\square$

In order to prepare an extension of the latter to a result in the flavor of that from *Lemma 2.13*, let us draw the following further conclusion of *Corollary 2.16* when combined with maximal Sobolev regularity theory.

**Lemma 2.18.** Suppose that  $T_{max} < \infty$ . Then for all  $p > 1$  one can find  $C(p) > 0$  such that

$$\int_0^{T_{max}} \left\{ \|a(\cdot, t)\|_{W^{2,p}(\Omega)}^p + \|a_t(\cdot, t)\|_{L^p(\Omega)}^p \right\} dt \leq C(p) \cdot \left\{ 1 + \int_0^{T_{max}} \int_{\Omega} |\nabla w|^{2p} \right\}. \quad (2.95)$$

*Proof.* We once again recall a standard result from maximal Sobolev regularity theory ([22]) to fix  $c_1(p) > 0$  such that if  $\varphi \in C^{2,1}(\bar{\Omega} \times [0, T_{max}])$  and  $h \in C^0(\bar{\Omega} \times [0, T_{max}])$  are such that

$$\begin{cases} \varphi_t = \Delta \varphi + h(x, t), & x \in \Omega, t \in (0, T_{max}), \\ \frac{\partial \varphi}{\partial \nu} = 0, & x \in \partial \Omega, t \in (0, T_{max}), \\ \varphi(x, 0) = a(x, 0), & x \in \Omega, \end{cases} \quad (2.96)$$

then

$$\int_0^T \left\{ \|\varphi(\cdot, t)\|_{W^{2,p}(\Omega)}^p + \|\varphi_t(\cdot, t)\|_{L^p(\Omega)}^p \right\} dt \leq c_1(p) \cdot \left\{ 1 + \int_0^T \int_{\Omega} |h|^p \right\} \quad \text{for all } T \in (0, T_{max}). \quad (2.97)$$

To adequately make use of this in the present situation, we once more invoke *Corollary 2.16* to choose  $c_2 > 0$  in such a way that

$$|a_t - \Delta a| \leq c_2 \cdot \left\{ |\nabla w \cdot \nabla a| + |\nabla a| + |\nabla w| + |\Delta v| + |v_t| + 1 \right\} \quad \text{in } \Omega \times (0, T_{max}),$$

and employ the Gagliardo-Nirenberg inequality along with *Lemma 2.14* to see that with some  $c_3(p) > 0$  and  $c_4(p) > 0$  we have

$$\|\nabla a\|_{L^{2p}(\Omega)}^p \leq c_3(p) \|a\|_{W^{2,p}(\Omega)}^{\frac{p}{2}} \|a\|_{L^\infty(\Omega)}^{\frac{p}{2}} \leq c_4(p) \|a\|_{W^{2,p}(\Omega)}^{\frac{p}{2}} \quad \text{for all } t \in (0, T_{max}). \quad (2.98)$$

Therefore, an application of (2.97) to  $\varphi := a$  and  $h := a_t - \Delta a$  shows that due to the Cauchy-Schwarz inequality,

$$\begin{aligned} & \int_0^T \left\{ \|a(\cdot, t)\|_{W^{2,p}(\Omega)}^p + \|a_t(\cdot, t)\|_{L^p(\Omega)}^p \right\} dt \\ & \leq c_1(p) + c_1(p) c_2^p \int_0^T \int_{\Omega} \left\{ |\nabla w \cdot \nabla a| + |\nabla a| + |\nabla w| + |\Delta v| + |v_t| + 1 \right\}^p \\ & \leq c_1(p) + 6^p c_1(p) c_2^p \int_0^T \left\{ \|\nabla w(\cdot, t) \cdot \nabla a(\cdot, t)\|_{L^p(\Omega)}^p + \|\nabla a(\cdot, t)\|_{L^p(\Omega)}^p + \|\nabla w(\cdot, t)\|_{L^p(\Omega)}^p \right. \\ & \quad \left. + \|\Delta v(\cdot, t)\|_{L^p(\Omega)}^p + \|v_t(\cdot, t)\|_{L^p(\Omega)}^p + 1 \right\} dt \\ & \leq c_1(p) + 6^p c_1(p) c_2^p \int_0^T \left\{ \|\nabla w(\cdot, t)\|_{L^{2p}(\Omega)}^p \|a(\cdot, t)\|_{L^{2p}(\Omega)}^p \right. \\ & \quad \left. + |\Omega|^{\frac{1}{2}} \|\nabla a(\cdot, t)\|_{L^{2p}(\Omega)}^p + |\Omega|^{\frac{1}{2}} \|\nabla w(\cdot, t)\|_{L^{2p}(\Omega)}^p \right. \\ & \quad \left. + \|\Delta v(\cdot, t)\|_{L^p(\Omega)}^p + \|v_t(\cdot, t)\|_{L^p(\Omega)}^p + 1 \right\} dt \end{aligned} \quad (2.99)$$

for all  $T \in (0, T_{max})$ . Here, (2.99) together with Young's inequality ensures that if we let  $c_5(p) := \frac{1}{2} \cdot 6^{2p} c_1^2(p) c_2^{2p} c_4^2(p)$ , then

$$\begin{aligned} & 6^p c_1(p) c_2^p \int_0^T \left\{ \|\nabla w(\cdot, t)\|_{L^{2p}(\Omega)}^p \|\nabla a(\cdot, t)\|_{L^{2p}(\Omega)}^p + |\Omega|^{\frac{1}{2}} \|\nabla a(\cdot, t)\|_{L^{2p}(\Omega)}^p \right\} dt \\ & \leq 6^p c_1(p) c_2^p c_4(p) \int_0^T \left\{ \|\nabla w(\cdot, t)\|_{L^{2p}(\Omega)}^p + |\Omega|^{\frac{1}{2}} \right\} \cdot \|a(\cdot, t)\|_{W^{2,p}(\Omega)}^{\frac{p}{2}} dt \\ & \leq \frac{1}{2} \int_0^T \|a(\cdot, t)\|_{W^{2,p}(\Omega)}^p dt + c_5(p) \int_0^T \left\{ \|\nabla w(\cdot, t)\|_{L^{2p}(\Omega)}^p + |\Omega|^{\frac{1}{2}} \right\}^2 dt \\ & \leq \frac{1}{2} \int_0^T \|a(\cdot, t)\|_{W^{2,p}(\Omega)}^p dt + 2c_5(p) \int_0^T \left\{ \|\nabla w(\cdot, t)\|_{L^{2p}(\Omega)}^{2p} + |\Omega| \right\} dt \end{aligned}$$

for all  $T \in (0, T_{max})$ . Since Young's inequality furthermore guarantees that

$$\int_0^T \|\nabla w(\cdot, t)\|_{L^{2p}(\Omega)}^p dt \leq \int_0^T \int_{\Omega} |\nabla w|^{2p} + T_{max} \quad \text{for all } T \in (0, T_{max}),$$

from (2.99) we accordingly infer that

$$\begin{aligned}
& \int_0^T \left\{ \|a(\cdot, t)\|_{W^{2,p}(\Omega)}^p + \|a_t(\cdot, t)\|_{L^p(\Omega)}^p \right\} dt \\
& \leq \left\{ 2c_5(p) + 6^p c_1(p) c_2^p \right\} \int_0^T \int_{\Omega} |\nabla w|^{2p} \\
& \quad + 6^p c_1(p) c_2^p \int_0^T \int_{\Omega} \left\{ |\Delta v|^p + |v_t|^p \right\} \\
& \quad + c_1(p) + 2c_5(p)|\Omega|T_{max} + 6^p c_1(p) c_2^p T_{max} + 6^p c_1(p) c_2^p |\Omega|T_{max} \quad \text{for all } T \in (0, T_{max}),
\end{aligned}$$

and that thus (2.95) holds due to the fact that  $\int_0^T \int_{\Omega} \{|\Delta v|^p + |v_t|^p\} < \infty$  thanks to Lemma 2.12.  $\square$

Here a criterion for boundedness of the expression appearing on the right of (2.95) can be obtained on the basis of (2.84):

**Lemma 2.19.** *Assume that  $T_{max} < \infty$ , and that  $q \geq 1$  is such that*

$$\int_0^{T_{max}} \|\nabla a(\cdot, t)\|_{L^q(\Omega)} dt < \infty. \quad (2.100)$$

*Then there exists  $C > 0$  such that*

$$\|\nabla w(\cdot, t)\|_{L^q(\Omega)} \leq C \quad \text{for all } t \in (0, T_{max}). \quad (2.101)$$

*Proof.* We observe that due to (2.36) and Lemma 2.14 when combined with our overall regularity and boundedness assumptions on  $\psi$  and  $\xi$ , the functions  $B_1$ ,  $B_2$  and  $B_3$  in (2.86) are all bounded in  $\Omega \times (0, T_{max})$ . Since furthermore also  $\nabla v$  is bounded in  $\Omega \times (0, T_{max})$  by Lemma 2.13, from (2.84) and our hypothesis (2.100) we thus infer that with some  $c_1 > 0$  and  $c_2 > 0$  we have

$$\begin{aligned}
\|\nabla w(\cdot, t)\|_{L^q(\Omega)} &= \left\| \nabla w_0 + \int_0^t \nabla w_i(\cdot, s) ds \right\|_{L^q(\Omega)} \\
&\leq \|\nabla w_0\|_{L^q(\Omega)} + \int_0^t \|B_1(\cdot, s) \nabla a(\cdot, s)\|_{L^q(\Omega)} ds \\
&\quad + \int_0^t \|B_2(\cdot, s) \nabla w(\cdot, s)\|_{L^q(\Omega)} ds + \int_0^t \|B_3(\cdot, s) \nabla v(\cdot, s)\|_{L^q(\Omega)} ds \\
&\leq \|\nabla w_0\|_{L^q(\Omega)} + c_1 \int_0^t \|\nabla a(\cdot, s)\|_{L^q(\Omega)} ds \\
&\quad + c_1 \int_0^t \|\nabla w(\cdot, s)\|_{L^q(\Omega)} ds + c_1 \int_0^t \|\nabla v(\cdot, s)\|_{L^q(\Omega)} ds \\
&\leq c_1 \int_0^t \|\nabla w(\cdot, s)\|_{L^q(\Omega)} ds + c_2 \quad \text{for all } t \in (0, T_{max}).
\end{aligned}$$

An application of Gronwall's lemma hence asserts (2.101).  $\square$

Thanks to the fact that the expression on the left of (2.90) essentially dominates the quantity in (2.100) for arbitrary finite  $q > 1$  due to two-dimensional embeddings, from Lemma 2.18 we can immediately draw the following conclusion.

**Lemma 2.20.** *Assume that  $T_{max} < \infty$ . Then there exists  $\theta \in (0, 1)$  such that*

$$a \in C^{1+\theta, \theta}(\bar{\Omega} \times [0, T_{max}]). \quad (2.102)$$

*Proof.* Since Lemma 2.17 implies that  $\int_0^{T_{max}} \|a(\cdot, t)\|_{W^{2,2}(\Omega)}^2 dt < \infty$  and that thus clearly also the integral  $\int_0^{T_{max}} \|\nabla a(\cdot, t)\|_{L^q(\Omega)} dt$  is finite for each  $q \in [1, \infty)$  due to the two-dimensional Sobolev embedding theorem, from Lemma 2.19 it follows that  $\sup_{t \in (0, T_{max})} \|\nabla w(\cdot, t)\|_{L^q(\Omega)} < \infty$  for any such  $q$ . An application of Lemma 2.18 therefore shows that

$$\int_0^{T_{max}} \left\{ \|a(\cdot, t)\|_{W^{2,p}(\Omega)}^p + \|a_t(\cdot, t)\|_{L^p(\Omega)}^p \right\} dt < \infty \quad \text{for all } p \in (1, \infty),$$

so that (2.102) becomes a consequence of the embedding result from [3].  $\square$

We next go back to (2.84) to see that our present information on Hölder regularity of  $a, \nabla a, v$  and  $\nabla v$  implies that if  $T_{max}$  was finite, then actually also  $w$  and  $\nabla w$  must be Hölder continuous in  $\bar{\Omega} \times [0, T_{max}]$ .

**Lemma 2.21.** *If  $T_{max} < \infty$ , then there exists  $\theta \in (0, 1)$  such that*

$$w \in C^\theta(\bar{\Omega} \times [0, T_{max}]) \quad \text{and} \quad \nabla w \in C^\theta(\bar{\Omega} \times [0, T_{max}]; \mathbb{R}^2). \quad (2.103)$$

*Proof.* We first recall that  $\sup_{t \in (0, T_{max})} \|\nabla w(\cdot, t)\|_{L^4(\Omega)}$  is finite by Lemma 2.17, which together with ((2.36)) and a Sobolev embedding theorem ensures that

$$\sup_{t \in (0, T_{max})} \|w(\cdot, t)\|_{C^{\frac{1}{2}}(\bar{\Omega})} < \infty. \quad (2.104)$$

Since also  $\sup_{t \in (0, T_{max})} \|a(\cdot, t)\|_{C^1(\bar{\Omega})}$  is finite by Lemma 2.20, relying on  $\psi' \in C^1([0, \infty))$  and the fact that  $\xi, \Xi$  and  $\Xi_v$  belong to  $C^1([0, \infty)^2)$ , from this we readily infer that there exists  $\theta_1 \in (0, 1)$  such that in (2.86) we have

$$\sup_{t \in (0, T_{max})} \|B_i(\cdot, t)\|_{C^{\theta_1}(\bar{\Omega})} < \infty \quad \text{for } i \in \{1, 2, 3\}.$$

Apart from that, Lemma 2.20 and Lemma 2.12 provide  $\theta_2 \in (0, \theta_1)$  fulfilling

$$\sup_{t \in (0, T_{max})} \|\nabla a(\cdot, t)\|_{C^{\theta_2}(\bar{\Omega})} < \infty \quad \text{and} \quad \sup_{t \in (0, T_{max})} \|\nabla v(\cdot, t)\|_{C^{\theta_2}(\bar{\Omega})} < \infty,$$

so that since  $\|B\varphi\|_{C^{\theta_2}(\bar{\Omega})} \leq \|B\|_{L^\infty(\Omega)} \|\varphi\|_{C^{\theta_2}(\bar{\Omega})} + \|B\|_{C^{\theta_2}(\bar{\Omega})} \|\varphi\|_{L^\infty(\Omega)}$  for all  $B \in C^{\theta_2}(\bar{\Omega})$  and  $\varphi \in C^{\theta_2}(\bar{\Omega})$ , from (2.84) we infer that with some  $c_1 > 0$  we have

$$\begin{aligned} \|\nabla w_t\|_{C^{\theta_2}(\bar{\Omega})} &\leq \|B_1 \nabla a\|_{C^{\theta_2}(\bar{\Omega})} + \|B_2 \nabla w\|_{C^{\theta_2}(\bar{\Omega})} + \|B_3 \nabla v\|_{C^{\theta_2}(\bar{\Omega})} \\ &\leq c_1 + c_1 \|\nabla w\|_{C^{\theta_2}(\bar{\Omega})} \quad \text{for all } t \in (0, T_{max}). \end{aligned} \quad (2.105)$$

Therefore,

$$\|\nabla w(\cdot, t)\|_{C^{\theta_2}(\bar{\Omega})} \leq \|\nabla w_0\|_{C^{\theta_2}(\bar{\Omega})} + c_1 T_{max} + c_1 \int_0^t \|\nabla w(\cdot, s)\|_{C^{\theta_2}(\bar{\Omega})} ds \quad \text{for all } t \in (0, T_{max}),$$

so that Gronwall's lemma ensures the existence of  $c_2 > 0$  fulfilling

$$\|\nabla w(\cdot, t)\|_{C^{\theta_2}(\bar{\Omega})} \leq c_2 \quad \text{for all } t \in (0, T_{max}). \quad (2.106)$$

As a consequence of this, (2.105) now guarantees that also  $c_3 := \|\nabla w_t\|_{L^\infty(\Omega \times (0, T_{max}))}$  is finite, which together with (2.106) shows that

$$\begin{aligned} |\nabla w(x_1, t_1) - \nabla w(x_2, t_2)| &\leq |\nabla w(x_1, t_1) - \nabla w(x_1, t_2)| + |\nabla w(x_1, t_2) - \nabla w(x_2, t_2)| \\ &\leq c_3 |t_1 - t_2| + c_2 |x_1 - x_2|^{\theta_2} \\ &\quad \text{for all } (x_1, t_1) \in \Omega \times (0, T_{max}) \text{ and } (x_2, t_2) \in \Omega \times (0, T_{max}). \end{aligned}$$

Along with a similar argument directly applied to  $w$  on the basis of (2.104) and the evident boundedness of  $w_t$  in  $\Omega \times (0, T_{max})$ , this asserts (2.103).  $\square$

This now warrants accessibility of the first, second and fourth equations from (2.32) to standard parabolic Schauder theory:

**Lemma 2.22.** *If  $T_{max} < \infty$ , then there exists  $\theta \in (0, 1)$  such that*

$$a \in C^{2+\theta, 1+\frac{\theta}{2}}(\bar{\Omega} \times [0, T_{max}]) \quad (2.107)$$

and

$$v \in C^{2+\theta, 1+\frac{\theta}{2}}(\bar{\Omega} \times [0, T_{max}]) \quad (2.108)$$

as well as

$$z \in C^{2+\theta, 1+\frac{\theta}{2}}(\bar{\Omega} \times [0, T_{max}]). \quad (2.109)$$

*Proof.* From Lemma 2.13 together with Lemma 2.20 and Lemma 2.21 we know that in the identity  $z_t = \Delta z + g_1(x, t)z + g_2(x, t)$ , the functions  $g_1 := -v$  and  $g_2 := \phi(u) \equiv \phi(ae^{\Xi(v, w)})$  belong to  $C^{\theta_1, \frac{\theta_1}{2}}(\bar{\Omega} \times [0, T_{max}])$  with some  $\theta_1 \in (0, 1)$ .

Therefore, parabolic Schauder estimates ([30]) provide  $\theta_2 \in (0, 1)$  fulfilling  $z \in C^{2+\theta_2, 1+\frac{\theta_2}{2}}(\bar{\Omega} \times [0, T_{max}])$ , so that, in particular, the coefficients  $h_1 := -\nabla z$  and  $h_2 := -\Delta z$  in  $v_t = \Delta v + h_1(x, t) \cdot \nabla v + h_2(x, t)v$

are Hölder continuous in  $\bar{\Omega} \times [0, T_{max}]$ , and that hence, again by Schauder theory,  $v$  must be an element of  $C^{2+\theta_3, 1+\frac{\theta_3}{2}}(\bar{\Omega} \times [0, T_{max}])$  for some  $\theta_3 \in (0, 1)$ .

Together with the outcomes of *Lemma 2.20* and *Lemma 2.21*, through (2.83) and (2.85) this in turn warrants Hölder continuity of  $a_t - \Delta a$  in  $\bar{\Omega} \times [0, T_{max}]$ , whence the proof can be completed by a third application of parabolic Schauder theory.  $\square$

In consequence, due to (2.84) also  $w$  must remain bounded in  $C^{2+\theta}(\bar{\Omega})$  with some  $\theta \in (0, 1)$  if  $T_{max} < \infty$ :

**Lemma 2.23.** *If  $T_{max} < \infty$ , then there exist  $\theta \in (0, 1)$  and  $C > 0$  such that*

$$\|w(\cdot, t)\|_{C^{2+\theta}(\bar{\Omega})} \leq C \quad \text{for all } t \in (0, T_{max}). \quad (2.110)$$

*Proof.* This can be seen by a straightforward adaptation of the argument from *Lemma 2.21*, based on the result from *Lemma 2.22* and a differentiation of the identity in (2.84).  $\square$

In light of *Lemma 2.2*, our main result thereby becomes obvious:

**PROOF of Theorem 2.1.** As a consequence of *Lemma 2.22* and *Lemma 2.23*, assuming  $T_{max}$  to be finite would yield a contradiction to the extensibility criterion (2.33), so that the claim results from *Lemma 2.2*.  $\square$

### 3 Numerical simulations

We perform numerical simulations of system (1.11), (1.12), (1.18), together with the initial and no-flux boundary conditions from (2.19). For the discretization we use a finite difference approach. We consider a domain  $\Omega = [0, 100] \times [0, 100]$  (in  $\mu\text{m}$ ) and a regular lattice. The standard scheme is improved using for the equations concerning cell motility the method in [46], in order to ensure preservation of non-negativity for the solution. The advection terms are discretized with a first order upwind scheme. The time discretization uses an implicit-explicit IMEX method (see e.g., [5]) which handles the diffusion implicitly, while the drift and reaction terms are treated in an explicit manner. The implementation was performed in MATLAB<sup>5</sup>.

For the functions  $\phi, \psi$  in (1.18) we make the following choices, which satisfy (2.24), (2.25):

$$\phi(u) := \frac{u}{1+u}, \quad \psi(s) := \frac{\beta s}{1+s},$$

where  $K_u > 0$  denotes the tumor carrying capacity and  $\beta > 0$  is a constant.

First we run the simulations for the model (1.11)-(1.18) without source terms for tumor and endothelial cells: this is the situation for which the global existence and uniqueness proof was performed. The initial conditions are as illustrated in the first row of Figure 1. Thus, ECs and tissue are assumed to be uniformly distributed within  $\Omega$ , while the tumor and, correspondingly, the VEGF distribution are more 'localized'. The rest of Figure 1 shows the densities  $u, v, z, w$  of tumor cells (1st column), ECs (2nd column), VEGF (3rd column), and tissue (last column), respectively. The predicted behavior of the solution components is as expected from the corresponding biological processes: in the absence of source terms, the tumor cells spread over the domain, following EC and tissue gradients. They release VEGF, which is relatively fast diffusing. The ECs are chemotactically attracted by VEGF; at the beginning of the simulation they are quickly grouping at areas with abundant VEGF (the latter being produced by the tumor cells), then spread due to diffusion and taxis. The two middle columns show how the EC population is following (with some delay) the VEGF bulk and also the uptake of VEGF at the sites with high EC density. The ECM is degraded by the tumor cells, more substantially at the sites where the tumor bulk is more concentrated, and weaker when the cancer cells have spread and filled the space at densities which are not high enough to noticeably degrade the tissue any further. Tumor, ECs, and VEGF eventually accumulate in the lower right corner, the tissue in the upper left corner is correspondingly spared, and the dynamics is not changing anymore. In fact, all solutions components seem to remain within numerical ranges which are close to certain values. This suggests an asymptotic stabilization of the solution around those values.

Next, we allow for proliferation of tumor cells and ECs. For the rates in (1.11), (1.12) we consider

$$\mu_c(u, v, w) := \frac{\mu_u}{K_u} \left( 1 - \frac{u}{K_u} - \frac{v}{K_v} - \frac{w}{K_w} \right), \quad \mu_e(u, v, z) := \mu_v \frac{z}{K_z} \left( 1 - \frac{v}{K_v} - \frac{u}{K_u} \right), \quad (3.111)$$

with  $K_v, K_w > 0$  representing the carrying capacities for ECs and tissue, respectively,  $\mu_u, \mu_v > 0$  are the growth rates of tumor and EC cells, respectively, and  $K_z > 0$  is a maximally admissible VEGF concentration.

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<sup>5</sup>Version 9.11.0.1769968 (R2021b), The MathWorks Inc.

We do not account for competition of ECs with tissue, as it is negligible when compared to that with fastly growing tumor cells and intraspecific competition. The solution behavior is shown in Figure 2: the tumor is evolving very similarly to the previous case; its growth is limited by all other living components of the tumor environment. The ECs start proliferating and do this more successfully in the areas where they do not infer any competition for space from tumor cells. They are also attracted by VEGF, which, however, they keep uptaking, so the highest EC densities remain in the corners of the domain, where proliferation is stronger. Eventually, the EC bulk in the upper left corner will slowly move towards the lower right corner, where VEGF and tumor cells are accumulating. This is further inhibited by the relatively large density of cancer cells present there.

Finally, we investigate the effect of the taxis cascade by comparing system (1.11), (1.12), (1.18) with the one characterizing cancer cell invasion by performing haptotaxis up tissue gradients and chemotaxis directly following VEGF gradients. Thereby, the equation for EC density is omitted and the degradation term in the  $z$ -equation of (1.18) only features natural decay. Precisely, the new system takes the form

$$\begin{cases} u_t = \Delta u - \nabla \cdot (u\chi(z, w)\nabla z) - \nabla \cdot (u\xi(z, w)\nabla w), \\ w_t = -\psi(uw) \\ z_t = D_z\Delta z - \mu_z z + \phi(u) \end{cases} \quad (3.112)$$

with

$$\chi(z, w) = \frac{\kappa_1}{(B(z, w))^2(1 + B(z, w))}, \quad \xi(z, w) = \frac{\kappa_2}{(B(z, w))^2(1 + B(z, w))}, \quad (3.113)$$

$\kappa_1, \kappa_2 > 0$  constants, and functions  $\phi, \psi, B, \chi$  as previously. We also keep the intial conditions for  $u, w, z$ , and the no-flux boundary conditions for the PDEs for  $u$  and  $z$ . To clearly put in evidence the effect of the taxis cascade we only plot the differences between solution components computed with (1.11), (1.12), (1.18) (without source terms) and those computed with (3.112). The results are shown in Figure 3. The direct following of the chemoattractant yields a faster spread of tumor cells and accumulation at sites with higher VEGF concentration, while locations with less chemoattractant remain populated at relatively large densities and for a longer time. Overall, the model with direct taxis predicts higher cell densities all over the domain - with the correspoding accumulation tendency triggered by the tactic signal and with the largest differences at the sites whose leaving is substantially delayed. More chemoattractant is produced by the cells at their respective locations, and more tissue is degraded by the cells available there. In absence of source terms both model versions suggest that the solution components remain bounded. The simulation outcome in Figure 3 also suggests that direct taxis towards VEGF can lead to a quick accumulation of tumor cells, which in presence of sufficient strong proliferation has explosion potential. Thus, the taxis cascade seems more appropriate in the analyzed context, while direct taxis has a tendency to overestimate tumor spread, accompanied by VEGF production, and slightly underestimate tissue degradation.

## 4 Discussion and outlook

The macroscopic setting (1.11), (1.12), (1.18) deduced in this note aligns to the classification of multiple taxis models given in [28]; more precisely, it belongs to category (iii) therein, which has been far less addressed in literature. Such models with taxis cascade can thus make up a whole subclass of the mentioned category, but they can also be formulated in the simpler context of the population(s) performing just one taxis each. Our model addressing tumor invasion is only a paradigm; the same mathematical framework can accomodate many other applications involving different kinds of populations and their tactic signals, see e.g. [43, 44, 50] and references therein. The mathematical challenges coming with such models are tightly related to the concrete form of taxis and source terms. The hitherto achieved results mainly refer to various versions of forager-scrounger-nutrient taxis cascades under more or less restrictive assumptions on the data of the problem. To our knowledge the model obtained and analyzed in this note is the first one featuring a taxis cascade with chemo- and haptotaxis - with the usual mathematical issues resulting therefrom.

All model versions considered here required the assumptions in Subsection 2.1 to be satisfied. We also chose in Subsection 1.2 very simple turning kernels for both cell populations. This enabled linear diffusions of tumor cells and ECs, with positive and constant diffusion coefficients. A similar meso-to-macro upscaling with more realistic turning kernels which take into account the heterogeneous, often anisotropic structure of the tissue, leads as in [10–13, 15–17, 56] to space-dependent motility coefficients. More detailed microscopic models accounting for mechanical and/or chemical influences can lead as e.g., in [14] to nonlinear (occasionally flux-limited) diffusion. Such nonconstant, possibly solution-dependent and degenerating diffusion and drift terms raise supplementary challenges in terms of well-posedness and long time behavior of solutions, see e.g., [26, 51, 52].

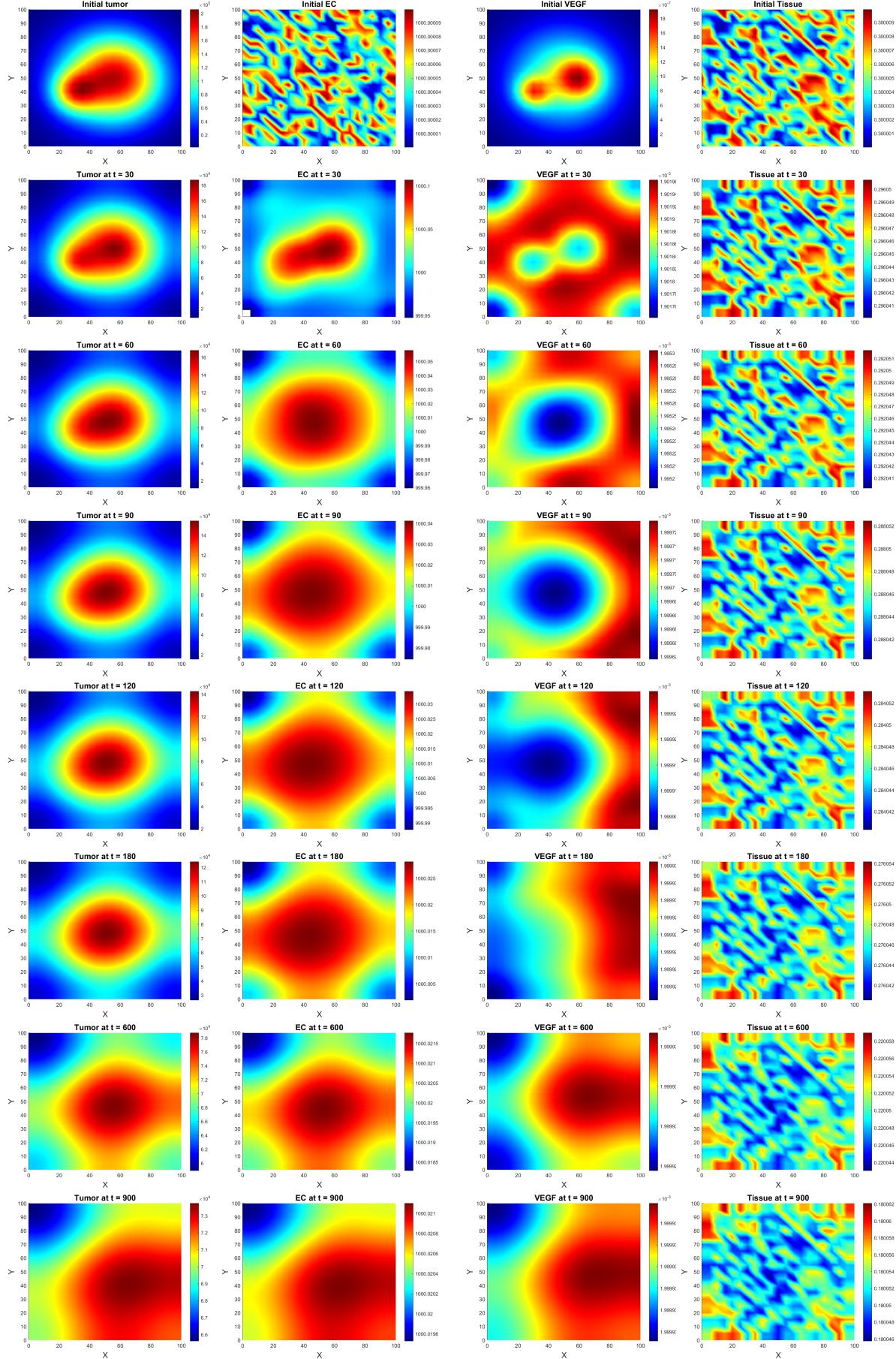


Figure 1: Simulations of model (1.11)-(1.18) without source terms for tumor and endothelial cells.

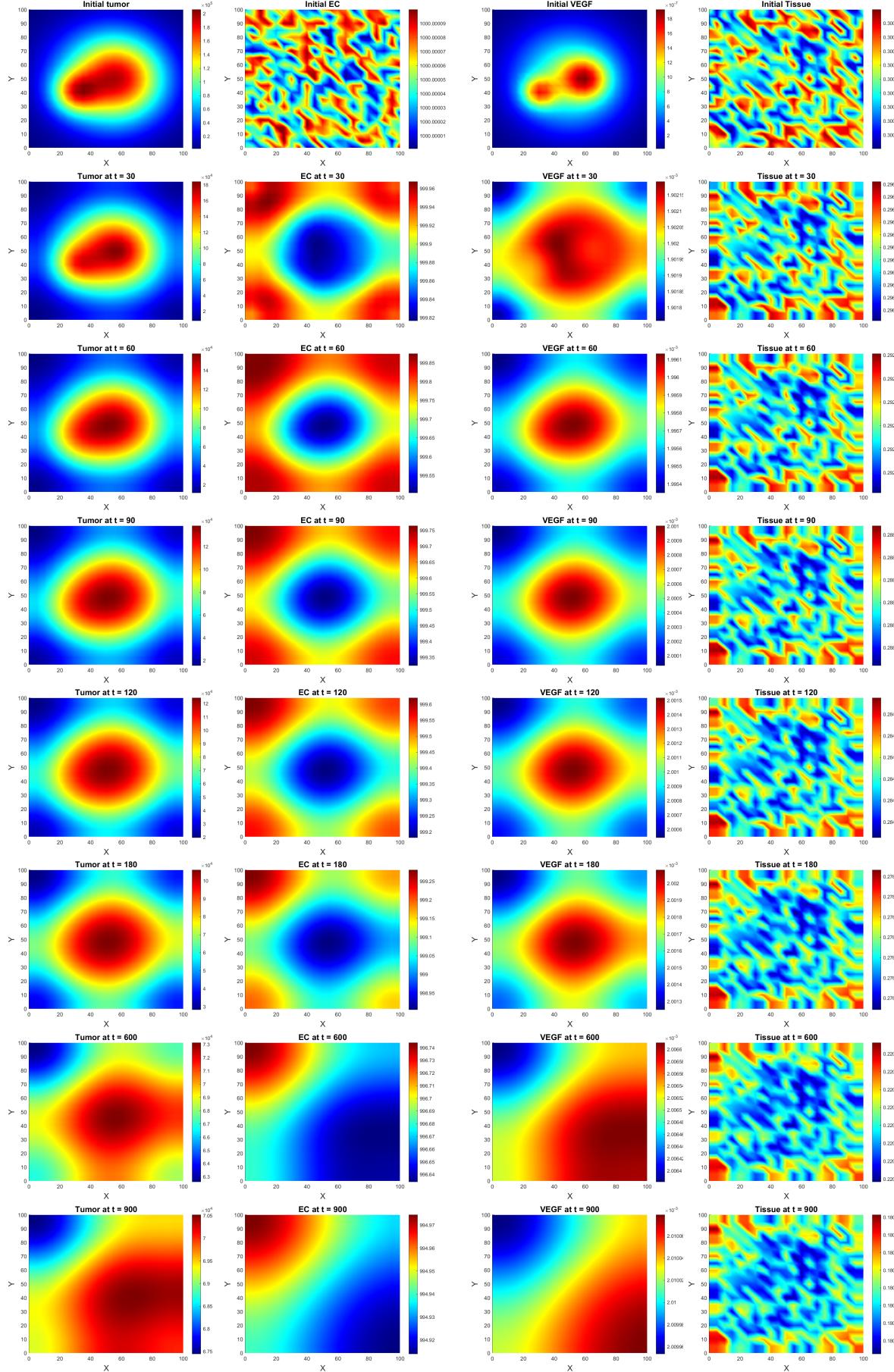


Figure 2: Simulations of model (1.11)-(1.18) with source terms for tumor and endothelial cells as in (3.111).

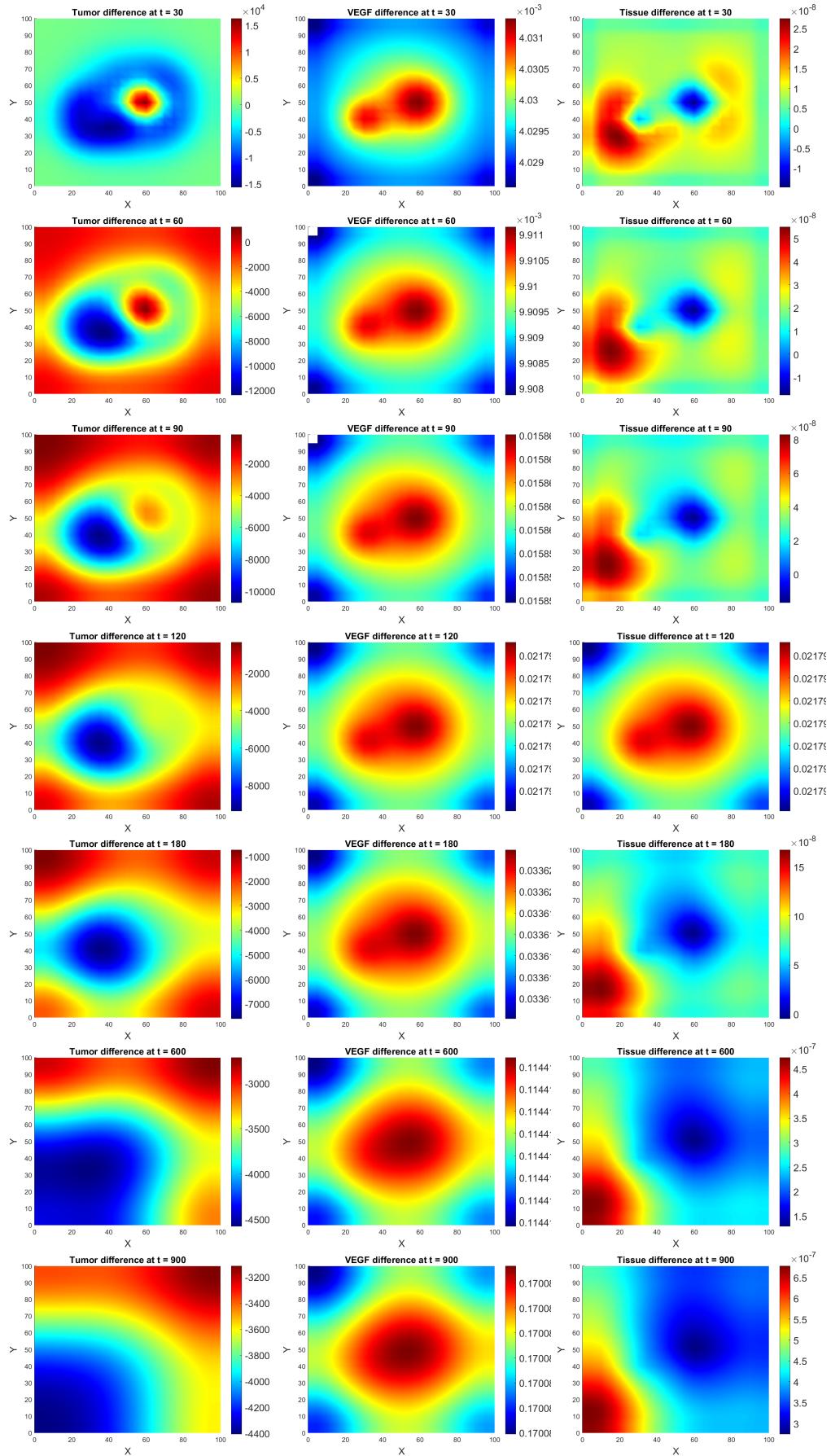


Figure 3: Differences between solution components of (1.11), (1.12), (1.18) and of (3.112).

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