

**ANALYSIS AND NUMERICAL SIMULATIONS OF A CHEMOTAXIS
MODEL OF AGGREGATION OF MICROGLIA IN
ALZHEIMER'S DISEASE**

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Abstract

In this paper, we study the well-posedness in scales of Hilbert spaces $E^\alpha, \alpha \in \mathbb{R}$ defined by the non-coupled system partial differential operator of a chemotaxis model of aggregation of microglia in Alzheimer's disease for a perturbed analytic semigroup, which decays exponentially in the large time asymptotic dynamics of the problem to a finite dimensional set $K \subset \mathbb{R}^3$ of the spatial average solutions. Uniform bounds in $\Omega \times (0, T)$ of solutions and gradient solutions to the system of equations are proved. Thus via a bootstrap argument solutions to the problem are shown to be classical solutions. Furthermore, under natural conditions on the coupled elliptic system quasilinear differential operator, we prove the existence of a fundamental solution or evolution operator for the model equations in cited function spaces. In conclusion numerical simulation results are provided.

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1 Introduction

In this paper, we study the well posedness and asymptotic global dynamics of the following chemotaxis system of equations modelling the aggregation of microglia in Alzheimer's disease

$$\begin{cases} U_t + \mathcal{A}U &= P(u)U \\ U(0) &= U_0 \in E^\beta \times E^\gamma \times E^\gamma, \beta \leq \gamma < \beta + 1, \end{cases} \quad (1.1)$$

where $U = (u, v, w)^\top$ with components holding the following meaning

- u := cell density of activated microglia,
- v := chemical concentrations of attractant,
- w := chemical concentrations of repellent,

$$\begin{cases} \mathcal{A} &= \begin{pmatrix} -d_1\Delta & 0 & 0 \\ 0 & -d_2\Delta + \lambda_2 & 0 \\ 0 & 0 & -d_3\Delta + \lambda_3 \end{pmatrix}, \\ P(u)U &= \begin{pmatrix} -\text{Div}(u\vec{d}(\nabla v, \nabla w)) \\ a_2u \\ a_3u \end{pmatrix}, \quad \vec{d}(\nabla v, \nabla w) = \chi_2\nabla v - \chi_3\nabla w, \end{cases} \quad (1.2)$$

of $d_i, \lambda_j, a_j, \chi_j \in \mathbb{R}^+ \setminus \{0\}, i = 1, 2, 3 = j \neq 1$ all different constants with biophysical importance of the following,

- d_1 := motility coefficient,
- d_j := diffusion coefficients,
- χ_2 := chemotactic coefficient towards attractant,
- χ_3 := chemotactic coefficient away from repellent,
- λ_j := rates of decay of chemicals, and
- a_j := rates of production of chemicals.

Let Ω be a smooth open and bounded subset of \mathbb{R}^N with boundary $\partial\Omega = \Gamma$. We consider as domain $D(\mathcal{A})$ for the operator \mathcal{A} in (1.2) given by

$$D(\mathcal{A}) := \left\{ \begin{pmatrix} z_1 \\ z_2 \\ z_3 \end{pmatrix} \in H^2(\Omega) : \begin{pmatrix} d_1\partial_{\vec{n}}z_1 \\ d_2\partial_{\vec{n}}z_2 \\ d_3\partial_{\vec{n}}z_3 \end{pmatrix} = \vec{0} \quad \text{on } \Gamma \right\}, \quad (1.3)$$

where \vec{n} denotes the unit normal vector pointing outwards of Γ . Still in (1.2), $P(u)U$ is a linearly coupled vector function, with the first entry featuring a divergence-0 operator acting on a vector field \vec{d} of concentrations of chemicals, while in the second and third components productive effects on activated microglia cells. At this point we point out that related systems of equations from biomedical chemotaxis have been previously studied from a mathematical view point by many authors [8, 10, 16, 18, 19, 21, 36, 26, 42, 43, 44, 45] among others.

Getting back to the system of equations (1.1)-(1.2) we note that neither proliferation, nor death of cells has been considered. Also, we note that the decay of chemicals follows a simple linear kinetic representing either an uptake by surrounding tissue, or deactivation by some other mechanism. The production of chemicals is taken to be proportional to the density of chemotactic cells. This represents in a non both exclusive manner a constant rate of secretion by the cells or indirect production by other cell types in response to local effects of the motile cells e.g. microglial IL-1 β enhances the processing and production of amyloid by neuronal tissue. The system of equations (1.1)-(1.2) see [13, 16, 20, 31, 32, 36] and other references therein cited is a chemo-attraction and repulsion model of aggregation of microglia in Alzheimer's disease (AD for abbreviation).

This disease is characterized by a progressive decline of cognitive and mental function that eventually leads one to death. It is known that the brain of Alzheimer's disease sufferers develop abnormal foci called senile plaques i.e. lesions composed of extracellular deposits of the β - amyloid protein, degenerating neurons and other nonneuronal cells called glia. Amyloid plaques are the major markers of Alzheimer's disease. According to the amyloid cascade hypothesis initial stages of Alzheimer's disease include local accumulation of soluble β - amyloid protein with levels correlating with severity of the disease. This leads to local deposits called diffuse plaques that over time build up to form relatively insoluble dense plaques which from the view point of other researchers is believed to be the main cause of the pathology with resultant stress and death of neurons in the central nervous system. Alzheimer's disease is known to be associated with inflammation involving cells called microglia and astrocytes. Following activation, these glial nonneuronal cells proliferate and migrate chemotactically to sites of injury where they secrete a host of chemicals including cytokines. The paper by M. Lucas *et al* has treated the role of microglia early in the development of diffusive senile plaques though astrocytes were also implicated in the later stages. On more and most recent biomedical results relating to Alzheimer's disease see [13, 20, 31, 32, 33] and other references therein these given.

Before giving the organization of this paper, it is worthwhile noting that in space dimensions of $\Omega \subset \mathbb{R}^N, N = 2$ it is well known [10, 42] that the solution to the equations in u, v only of (1.1)-(1.2) blow-up in a finite time if $\int_{\Omega} u_0 > \frac{8\pi\chi_2 a_2}{d_2}$ and if $\int_{\Omega} u_0 |x - x_0|^2 \ll 1$ is sufficiently small with $x_0 \in \Omega$. In [36] relating to the system of equations as given in (1.1)-(1.2) in $\Omega \subset \mathbb{R}^N, N = 2$, with $\lambda_2 = \lambda_3$, if attraction dominates repulsion i.e. if $a_3\chi_3 - a_2\chi_2 < 0$ and if $\int_{\Omega} u_0 > \frac{8\pi}{a_2\chi_2 - a_3\chi_3}$ then the solution U to the model system of equations blow- up again in a finite time.

In this paper, we prove in twofolds that the model system of equations (1.1)-(1.2) partial differential operator is an infinitesimal generator of an analytic semigroup acting on $U_0 \in Z_{\delta=\beta+2\gamma} = E^{\beta} \times E^{\gamma} \times E^{\gamma}$ where $E^{\alpha}, \alpha \in \mathbb{R}$ are scales of Banach spaces in $L^2(\Omega)$ defined by the operator in (1.2). In this context Section 2 gives some preliminaries. In Section 3, we prove the system model equations (1.1)-(1.2) defines a perturbed analytic semigroup to the semigroup generated by the operator $-\mathcal{A}$ using from [9, 17, 24, 22, 29] abstract semigroup theory results for semilinear evolution equations. Section 4, is devoted to proving the existence of *a priori* uniform bounds in $\Omega \times (0, T)$ of solutions and gradient solutions to the problem. It concludes using a bootstrap argument in proving that the solutions to the problem are classical solutions.

In Section 5, we revisit the complete system of equations coupled partial differential

operator (i.e. in (1.1) we consider the contribution of the term $P(u)U$ of (1.2) appearing in the left hand side of the equations) to prove that it is an infinitesimal generator of a fundamental solution operator in scales of spaces $Z_\delta, \delta \in \mathbb{R}^+$ in as given by quasilinear partial differential operators. Since we are considering positive time, the results agree with and are much finer to those of Section 3. An immediate consequence, of our results is that the large time asymptotic dynamics of the system of equations (1.1)-(1.2) are well-defined and captured by a subset K in \mathbb{R}^3 of spatial average solutions. This conclusion coincides with other well known results [18, 44, 34, 35, 36] related to the minimal chemotaxis model or Keller-Segel chemotactic problem. In Section 6, we give a much simplified coupled system of equations to (1.1)-(1.2) in which the Div operator in $P(u)U$ is independent of u , an assumption equivalent to studying of the problem (1.1)-(1.2) in case of when *a priori* uniform boundedness of the solution component u in $\Omega \times (0, T)$ is known. Furthermore, given that solutions to the simplified problem are classical solutions results relating to the original problem can be obtained via maximum principle arguments.

In appreciation, it should be highlighted that the results of this paper imply nonlinear diffusion, proliferation and death of cells can be incorporated into the system of equations. A proposition which agrees with the study given in [20], we suppose also that this citation is among others. In Section 7, to visualize the aggregation of microglia as in the model equations, we numerically simulate the equations using a Gradient Weighted Moving Finite Element method. For the simulations shown in this paper we use the code developed in [39] using a set of model parameters found in [16], where the parameters used there are calculated from dimensional values found in Biology, Immunology and Neuroscience publications referenced therein. In Section 8 we discuss the results of the numerical simulations.

Lastly, we point out that throughout the paper we work in a slightly general setup i.e. without loss of particularity we do not immediately assume positivity of the initial data to the system of equations, which naturally imply positivity of the solutions. If positivity of solutions is assumed note that most of the calculations in Section 4 are very much simplified and are relatively easier.

2 Preliminaries

Now for a brief review of the functional setting. To this end, clearly by Lax-Milgram's Theorem [5, 14, 23, 40], \mathcal{A} in (1.2) is a maximal monotone, self adjoint, sectorial operator in $L^2(\Omega)$ with spectrum

$$\sigma(\mathcal{A}) = \bigcup_{i=1}^3 \sigma(-d_i \Delta + \lambda_i) = \{\mu_n = \mu_n(d_i, \lambda_i); n \in \mathbb{N}\} \subset \mathbb{R}^+, \lambda_1 = 0 \quad (2.1)$$

where d_i, λ_i are sufficiently large (see Table 2 in Section 7), such that

$$0 < \mu_1 \leq \mu_2 \leq \dots \leq \mu_n \nearrow \infty \quad \text{as } n \nearrow \infty, \text{ and } 0 \in \sigma(\mathcal{A}). \quad (2.2)$$

As $\mu \in \sigma(\mathcal{A})$ if for some $i = 1, 2, 3 = j \neq 1$, $\mu \in \sigma(-d_i \Delta + \lambda_j)$ we can choose associated eigenfunctions

$$\varphi_n = \varphi_n \cdot \vec{e}_i, \quad \text{where } \{\vec{e}_i; i = 1, 2, 3\} \subset \mathbb{R}^3 \quad (2.3)$$

is a canonic basis of \mathbb{R}^3 , orthonormal in $L^2(\Omega)$ and a Hilbert basis of this function space.

Thus, by [2, 9, 24, 22, 27] the scales of Banach spaces $E^\alpha, \alpha \in \mathbb{R}$ are well defined. Note that the spaces $E^\alpha, \alpha \in \mathbb{R}^-$ define the dual spaces of the scales of spaces $E^\alpha, \alpha \in \mathbb{R}^+$, and in equivalent of norms we can identify the spaces

$$E^1 \equiv D(\mathcal{A}), \quad E^{1/2} \equiv H^1(\Omega) \quad \text{and} \quad E^0 \equiv L^2(\Omega), \quad E^{-1/2} \cong H^{-1}(\Omega).$$

In general, $E^\alpha \cong H^{2\alpha}(\Omega)$ and Sobolev type space embeddings [1, 4, 5, 12, 9, 22, 24],

$$E^\alpha \subset L^r(\Omega) \iff r \begin{cases} \leq \infty & \text{if } N = 1 \\ < \infty & \text{if } N = 2 \\ \leq \frac{2N}{N-4\alpha} & \text{if } N \geq 3 \end{cases} \quad \text{are satisfied.} \quad (2.4)$$

$$\text{Also } E^\alpha \subset C^\theta(\Omega), \quad \theta \in (0, 1) \iff 2\alpha - \frac{N}{2} > \theta. \quad (2.5)$$

In addition, it holds

$$\text{for any } \alpha, \beta \in \mathbb{R} \text{ if } \alpha \geq \beta, \text{ then } E^\alpha \subset E^\beta \quad (2.6)$$

continuously, densely, compactly if $\alpha > \beta$, and constant of the inclusions $i_{\alpha, \beta} := \mu_1^{\beta-\alpha}$. Furthermore, if $\alpha, \beta \in \mathbb{R}$ and $\theta \in [0, 1]$, then for every $u \in E^\gamma, \gamma = \max\{\alpha, \beta\}$ we have

$$\|u\|_{\theta\alpha+(1-\theta)\beta} \leq \|u\|_\alpha^\theta \|u\|_\beta^{1-\theta}. \quad (2.7)$$

Next, for every $\alpha, \varepsilon \in \mathbb{R}, \mathcal{A}^\varepsilon : E^{\alpha+\varepsilon} \rightarrow E^\alpha$ is a surjective isometry with $(\mathcal{A}^\varepsilon)^{-1} = \mathcal{A}^{-\varepsilon}$. Moreover, for every $\alpha, \beta, \gamma \in \mathbb{R}, \mathcal{A}^\alpha \mathcal{A}^\beta = \mathcal{A}^{\alpha+\beta}$ as operators between the spaces $E^{\alpha+\beta+\gamma}$ and E^γ . In particular, for every $\delta \in \mathbb{R}$ we can define the δ - product

$$\langle\langle u, v \rangle\rangle_\delta := \sum_{n=1}^{\infty} \mu_n^\delta u_n v_n \quad (2.8)$$

for every $\varepsilon \in \mathbb{R}, u \in E^{\delta-\varepsilon}, v \in E^\varepsilon$. Clearly, if $\alpha + \beta + 2\gamma = \delta$, then for every $u \in E^{\alpha+\gamma}$ and $v \in E^{\beta+\gamma}$,

$$\langle\langle u, v \rangle\rangle_\delta = \langle \mathcal{A}^\alpha u, \mathcal{A}^\beta v \rangle_\gamma$$

and the 0- product describes all the dualities between the E^α spaces, while the δ - describes among others the scalar product in $E^{\frac{\delta}{2}}$. Occasionally, we will use the notation

$$Z_\delta := E^{\alpha+\beta+2\gamma} = E^{\alpha+\gamma} \times E^{\beta+\gamma} = E^\alpha \times E^\beta \times E^{2\gamma}.$$

If there is no confusion caused we will simply write $\varphi \in E^\alpha$ with understanding that $\nabla \varphi \in E^{\alpha-\frac{1}{2}}$ whenever its derivatives are involved.

It follows as well from [2, 9, 24, 22, 29], that the operator $-\mathcal{A}$ is an infinitesimal generator of an analytic semigroup

$$\{S(t) = e^{-\mathcal{A}t}; t \in \mathbb{R}^+ \setminus \{0\}\} \quad (2.9)$$

in the spaces $E^\alpha, \alpha \in \mathbb{R}$, such that if $\alpha_0, \alpha_1 \in \mathbb{R}, S(t) : E^{\alpha_0} \rightarrow E^{\alpha_1}$ it satisfies that

$$\|S(t)\|_{\alpha_0, \alpha_1} \leq \begin{cases} e^{-\mu_1 t} |\mu_1|^{\alpha_1 - \alpha_0} & \text{if } \alpha_1 \leq \alpha_0 \\ \left\{ \begin{array}{l} \frac{C}{t^{\alpha_1 - \alpha_0}} & \text{for } t \leq t_0 \\ |\mu_1|^{\alpha_1 - \alpha_0} e^{-\mu_1 t} & \text{for } t > t_0 \end{array} \right\} & \text{if } \alpha_1 > \alpha_0, \end{cases} \quad (2.10)$$

where $C = C(\beta - \alpha)$, $C(\sigma) = \sigma^\sigma e^{-\sigma}$, and $t_0 = t_0(\alpha_1 - \alpha_0) = (\alpha_1 - \alpha_0)\mu_1^{-1}$. In particular, for any

$$\omega \in (0, \inf\{\mu; \mu \in \sigma(\mathcal{A})\}),$$

whenever $\alpha_1 > \alpha_0$ we have that

$$\|S(t)\|_{\alpha_0, \alpha_1} \leq \frac{C e^{-\omega t}}{t^{\alpha_1 - \alpha_0}}, \quad \forall t > 0 \quad (2.11)$$

for some $C \in \mathbb{R}^+ \setminus \{0\}$.

Getting, back to (2.1)-(2.2) since $0 \in \sigma(\mathcal{A})$, if we take $V = (1, 1, 1)^\top$ in (1.1)-(1.2) as a test function in the scalar product of $L^2(\Omega)$, i.e. by integrating over Ω then followed by over $(0, t)$, we get as $t \nearrow \infty$ that

$$\begin{aligned} U &= (u, v, w)^\top \in K := \left\{ (\phi, \varphi, \psi) \in [L^1(\Omega)]^3 : \int_{\Omega} \phi dx = \int_{\Omega} \phi_0 = |\Omega| \bar{\phi}_0, \right. \\ &\quad \left. \|(\varphi, \psi)\|_{L^1(\Omega) \times L^1(\Omega)} \leq \left(\frac{a_2}{\lambda_2} + \frac{a_3}{\lambda_3} \right) |\Omega| \bar{\phi}_0 \right\}, \end{aligned} \quad (2.12)$$

which turns out [30, 40, 41] to be a closely approximate limit set for the long time asymptotic dynamics of the system of equations in large diffusion. Throughout this paper all generic constants will be denoted by $C \geq 0$, unless a distinction is necessary.

3 Well posedness of the system of equations

In this section, we first recall some abstract analytic semigroup theory results proved in [9, 17, 22, 24, 27]. Then, we will prove the well posedness of the problem (1.1)-(1.2) in the product scales of Banach spaces $Z_\delta, \delta \in \mathbb{R}^+$.

To this end, consider the following Cauchy problem

$$\begin{cases} \varphi_t + A\varphi &= f(t) \\ \varphi(t_0) &= \varphi_0 \in E^\beta \end{cases} \quad (3.1)$$

where $f : [t_0, t_1) \rightarrow E^\beta$, $\beta \in \mathbb{R}$, A a maximal monotone, self adjoint and sectorial operator with compact resolvent in $L^2(\Omega)$.

Definition 3.1. A function $\varphi(\cdot)$ is a strong solution of (3.1) on $[t_0, t_1)$ if and only if $\varphi : [t_0, t_1) \rightarrow E^\beta$ is a continuous function satisfying that $\varphi_t \in E^\beta$, $\varphi(t) \in E^{\beta+1}$ on (t_0, t_1) , $\varphi(t_0) = \varphi_0$ and the differential equation in (3.1) is verified on the open interval (t_0, t_1) as an equality in $E^\beta, \beta \in \mathbb{R}$.

The the evolution problem (3.1) is well-posed in the sense given by following theorem.

Theorem 3.2. Consider the Cauchy problem (3.1). Assume $f \in L^p(t_0, t_1, E^\beta), 1 \leq p \leq \infty$. Then, the solution to the problem (3.1) given by

$$\varphi(t) = e^{-A(t-t_0)} \varphi_0 + \int_{t_0}^t e^{-A(t-s)} f(s) ds \quad (3.2)$$

satisfies that

(i). $\varphi \in C(t_0, t_1, E^\gamma)$ with $\gamma < \beta + \frac{1}{p'}$ where $\frac{1}{p} + \frac{1}{p'} = 1$. If $\varphi_0 \in E^\gamma$ then $\varphi \in C([t_0, t_1], E^\gamma)$, and the mapping

$$E^\gamma \times L^p(t_0, t_1, E^\beta) \ni (\varphi_0, f) \rightarrow \varphi \in C([t_0, t_1]; E^\gamma)$$

is Lipschitz continuous.

(ii). For any $\beta \in \mathbb{R}$ and $\gamma \in [\beta, \beta + 1)$ the mapping

$$E^\gamma \times L^p(t_0, \infty, E^\beta) \ni (\varphi_0, f) \rightarrow \varphi \in L^p(t_0, \infty; E^\gamma)$$

is Lipschitz continuous. In particular, if $p = 2$, and $\gamma = \beta + \frac{1}{2}$. Then, the mapping,

$$\begin{aligned} E^{\beta+\frac{1}{2}} \times L^2(t_0, t_1, E^\beta) \ni (\varphi_0, f) \\ \rightarrow (\varphi, \varphi_t) \in \left(C([t_0, t_1], E^{\beta+\frac{1}{2}}) \cap L^2(t_0, t_1, E^{\beta+1}) \right) \times L^2(t_0, t_1, E^\beta), \end{aligned}$$

is continuous and the problem (3.1) is verified on (t_0, t_1) a.e.

(iii). If $f : (t_0, t_1) \rightarrow E^\beta$ is locally Hölder continuous of exponent $0 < \theta \leq 1$ and if

$$\int_{t_0}^{t_0+\rho} \|f(s)\|_\beta ds < \infty, \quad \text{for some } \rho > 0.$$

Then, φ in (3.2) is a unique solution of (3.1) such that

$$\varphi \in C([t_0, t_1], E^\beta) \cap C(t_0, t_1, E^{\beta+1}) \cap C^1(t_0, t_1, E^\gamma) \quad \text{for any } \gamma < \beta + \theta.$$

Proof. The proof of the theorem is classical, see [9, 17, 24, 22, 27, 29] where most recently in [29] the Bessel potential function spaces have been used.

Thus in the case of (i) if we consider the formula (3.2) and let $\gamma \geq \beta$, then in estimating from above we get that

$$\|\varphi(t)\|_\gamma \leq \|e^{-A(t-t_0)}\varphi_0\|_\gamma + \int_{t_0}^t \|e^{-A(t-s)}\|_{\beta,\gamma} \|f(s)\|_\beta ds$$

where $\|e^{-A(t-s)}\|_{\beta,\gamma}$ denotes the norm of $\mathcal{L}(E^\beta, E^\gamma)$. Since

$$\|e^{-A(t-s)}\|_{\beta,\gamma} \leq \frac{M}{(t-s)^{\gamma-\beta}}$$

on finite time intervals, it follows with $\gamma = \beta$ if $p = 1$ or with $\beta \leq \gamma < \beta + \frac{1}{p'}$ if $1 < p < \infty$ that

$$\|\varphi(t)\|_\gamma \leq \|e^{-A(t-t_0)}\varphi_0\|_\gamma + b(t) \left(\int_{t_0}^t \|f\|_\beta^p \right)^{\frac{1}{p}}$$

where

$$b(t) = M \left(\int_{t_0}^t (t-s)^{-p'(\gamma-\beta)} ds \right)^{\frac{1}{p'}} \approx t^{\frac{1}{p'} - (\gamma-\beta)}$$

so it is bounded on finite intervals. Consequently, $\varphi(t) \in E^\gamma$ for any $t > 0$. To prove the continuity, fix $t > t_0$ (or even $t = t_0$ if $\varphi_0 \in E^\gamma$). As

$$\begin{aligned} & \|\varphi(t+h) - \varphi(t)\|_\gamma \\ & \leq \|(e^{-Ah} - I)\varphi(t)\|_\gamma + \int_t^{t+h} \|e^{-A(t+h-s)}\|_{\beta,\gamma} \|f(s)\|_\beta ds. \end{aligned}$$

Since the linear semigroup is continuous we have that

$$\|(e^{-Ah} - I)\varphi(t)\|_\gamma \rightarrow 0 \quad \text{as } h \rightarrow 0,$$

while also

$$\begin{aligned} & \int_t^{t+h} \|e^{-A(t+h-s)}\|_{\beta,\gamma} \|f(s)\|_\beta ds \\ & \leq M \left(\int_t^{t+h} (t+h-s)^{-p'(\gamma-\beta)} ds \right)^{\frac{1}{p'}} \left(\int_t^{t+h} \|f\|_\beta^p \right)^{\frac{1}{p}} = O(h^{\frac{1}{p'} - (\gamma-\beta)}) \end{aligned}$$

we obtain the continuity of (3.2). Further on, if $\varphi_0 \in E^\gamma$ we have

$$\|\varphi(t)\|_{C[t_0, t_1], E^\gamma} \leq b(t_1) (\|\varphi_0\|_\gamma + \|f\|_{L^p(t_0, t_1, E^\beta)})$$

which proves the Lipschitz continuity of the mapping $(\varphi_0, f) \rightarrow \varphi$. The proof if $p = \infty$ follows the same lines with obvious modifications and therefore we shall skip it.

To prove (ii) of the theorem, note that for every $\beta \in \mathbb{R}$ and γ such that $\beta \leq \gamma < \beta + 1$ (2.10)-(2.11) holds. Hence,

$$c_{\beta,\gamma}(t) := \|e^{-At}\|_{\beta,\gamma} \leq \frac{Me^{-\omega t}}{t^{\gamma-\beta}}$$

and $c_{\beta,\gamma}(t) \in L^1(0, \infty)$ but unbounded at zero, unless $\gamma = \beta$. Let $p = 1$, $\varphi_0 \in E^\gamma$ and $f \in L^1(t_0, \infty, E^\beta)$. Since

$$e^{-A(t-t_0)}\varphi_0 \in L^1(t_0, \infty, E^\gamma)$$

we just need to prove that

$$\psi(t) := \int_{t_0}^t e^{-A(t-s)} f(s) ds \in L^1(t_0, \infty, E^\gamma) = Z.$$

To this end, set $s = (t-t_0)\sigma + t_0$ to get that

$$\psi(t) = \int_0^1 e^{-A(t-t_0)(1-\sigma)} f((t-t_0)\sigma + t_0)(t-t_0) d\sigma.$$

Therefore,

$$\|\psi\|_Z \leq \int_0^1 \|e^{-A(t-t_0)(1-\sigma)} f((t-t_0)\sigma + t_0)(t-t_0)\|_Z d\sigma.$$

But for any fixed $\sigma \in [0, 1]$,

$$\begin{aligned} & \|e^{-A(t-t_0)(1-\sigma)} f((t-t_0)\sigma + t_0)(t-t_0)\|_Z \\ & = \int_{t_0}^\infty \|e^{-A(t-t_0)(1-\sigma)} f((t-t_0)\sigma + t_0)(t-t_0)\|_\gamma dt. \end{aligned}$$

Consequently, setting $r = (t - t_0)\sigma + t_0$, we find that

$$\|\psi(t)\|_Z \leq \int_0^1 \int_{t_0}^\infty \frac{r-t_0}{\sigma^2} c_{\beta,\gamma} \left((r-t_0) \left(\frac{1-\sigma}{\sigma} \right) \right) \|f(r)\|_\beta dr d\sigma.$$

Again, letting $s = (r - t_0) \frac{(1-\sigma)}{\sigma}$ and integrating over σ we get that

$$\|\psi(t)\|_Z \leq \left(\int_0^\infty c_{\beta,\gamma}(s) ds \right) \left(\int_{t_0}^\infty \|f(r)\|_\beta dr \right),$$

yielding that

$$\|\varphi\|_Z \leq \|c_{\gamma,\gamma}\|_1 \|\varphi_0\|_\gamma + \|c_{\beta,\gamma}\|_1 \|f\|_{L^1(t_0, \infty, E^\beta)}$$

where $\|c_{\beta,\gamma}\|_1 = \|c_{\beta,\gamma}\|_{L^1(0, \infty)}$ and the result is proved.

The case of $p = \infty$, follows exactly as in (i), thus we have that

$$\|\varphi\|_{L^\infty(t_0, \infty, E^\gamma)} \leq \|c_{\gamma,\gamma}\|_\infty \|\varphi_0\|_\gamma + \|c_{\beta,\gamma}\|_1 \|f\|_{L^\infty(t_0, \infty, E^\beta)}.$$

Note that in fact it holds that $\varphi \in C_b([t_0, \infty), E^\gamma)$. Now from what is proved above we get by interpolation that the results are valid for any $1 < p < \infty$. We skip the proof of (iii) as it is exactly as in [9] pp. 50-52, with which the proof of the theorem is complete. \square

Next, we consider the case of perturbations of analytic semigroups, for this assume that $P \in \mathcal{L}_{lip}(E^\alpha, E^\beta)$, $0 \leq \alpha - \beta < 1$ and let the evolution problem

$$\begin{cases} u_t + Au = Pu, \\ u(t_0) = u_0 \in E^\beta, t_0 > 0, \end{cases} \quad (3.3)$$

be given. Then, following [9, 17, 24, 29] abstract semigroup theory results for semilinear equations, let $Y \subset E^\alpha$ and $P : Y \rightarrow E^\beta$ be locally Lipschitz continuous. We define as a solution to (3.3) the following:

Definition 3.3. A continuous function $u : [t_0, t_1) \rightarrow E^\alpha$ satisfying that $u(t) \in E^\alpha$, $u(t_0) = u_0$, $u(t) \in E^{\beta+1}$, $u_t \in E^\beta$ on (t_0, t_1) and the evolution problem (3.3) holds on (t_0, t_1) as an identity in E^β is called a strong solution to the problem.

On existence of solutions to (3.3) we have the following proposition.

Proposition 3.4. Consider in the problem (3.3) with $P \in \mathcal{L}_{lip}(E^\alpha, E^\beta)$, $0 \leq \alpha - \beta < 1$, and let $u \in C([t_0, t_1), E^\alpha)$ verify

$$u(t, u_0) = e^{-A(t-t_0)} u_0 + \int_{t_0}^t e^{-A(t-s)} P u(s) ds. \quad (3.4)$$

Then,

- (i) $u \in C_{loc}^\theta(t_0, t_1, E^\alpha)$ for some $\theta \in (0, 1)$.
- (ii) $u \in C([t_0, t_1), E^\alpha)$ is a solution of the problem (3.3) if and only if (3.4) is verified.
- (iii) $u(t, u_0)$ given by (3.4) is a C^1 strong solution of (3.3) in E^β , and
- (iv) $-A + P$ is an infinitesimal generator of an analytic semigroup $\{S_p(t); t > 0\}$ in the spaces E^β of $\beta \in (\alpha - 1, \alpha]$.

Proof. See [29] Proposition 3.12 and Theorem 3.20, or follow semilinear evolutionary equations results in [9, 17, 22, 29]. It suffices to prove (i) which is classical then apply Theorem 3.2 (iii). Thus it remains only to prove (iv) which follows by using the references cited on perturbations of analytic semigroups. \square

A priori yielding the main theorem of this section, note that following Theorem 3.2 - Proposition 3.4 we look for a solution to the problem (1.1)-(1.2) of the form

$$U(t; U_0) = e^{-\mathcal{A}(t-t_0)} U_0 + \int_{t_0}^t e^{-\mathcal{A}(t-s)} P(u(s)) U(s) ds, \quad (3.5)$$

where

$$P(u) = \begin{pmatrix} 0 & -\text{Div}(u\chi_2\nabla\cdot) & \text{Div}(u\chi_3\nabla\cdot) \\ a_2 & 0 & 0 \\ a_3 & 0 & 0 \end{pmatrix}, \quad \text{and} \quad P(u)U := \begin{pmatrix} \Pi(u)(v, w) \\ a_2 u \\ a_3 u \end{pmatrix} \quad (3.6)$$

of $\Pi(u)(v, w) := -\text{Div}(u\vec{\nabla}(\nabla v, \nabla w))$ as in (1.2) and $U = (u, v, w)^\top$. It is also interesting to note that the system of equations (1.1)-(1.2) have nice regularity features debited to their nature of coupledness, see Remark 3.6. As for the system well-posedness we have the following theorem.

Theorem 3.5. *Consider the system of equations (1.1)-(1.2) for any $\beta, \gamma \in \mathbb{R}$ such that $\beta \leq \gamma < \beta + 1$. Assume that $v_0, w_0 \in E^\gamma$ and $u \in C(t_0, t_1, E^\beta)$. Then, $v, w \in C(t_0, t_1, E^\gamma)$.*

Conversely, for any $\alpha \in \mathbb{R}$ such that $0 \leq \alpha - \beta < 1$, $\alpha' = \alpha + \gamma \geq \frac{1}{2} + \frac{N}{4}$, $2\alpha + \gamma \geq 1 + \frac{N}{4}$, and let $v, w \in C([t_0, t_1], E^\gamma)$. Then,

$$\Pi := \text{Div} : E^{\alpha'} \rightarrow E^\beta \quad \text{is well defined, } \Pi(u) := \text{Div}(u\vec{\nabla}(\nabla\cdot, \nabla\cdot)) \in \mathcal{L}_{lip}(E^{\alpha'}, E^\beta) \quad (3.7)$$

and the solution of (1.1)-(1.2), $u \in C(t_0, t_1, E^\beta)$. Furthermore, if $0 \leq \gamma - \alpha < 1$, the mapping

$$Z_{\alpha(\gamma)} \ni U = (u, v, w)^\top \mapsto P(u)U \in Z_{\beta(\alpha)} \quad (3.8)$$

is well defined and Lipschitz continuous. If $u_0 \in E^\alpha$, then Proposition 3.4 holds in $Z_{\alpha(\gamma)}$ with

$$\|P\|_{\mathcal{L}(Z_{\beta(\alpha)}, Z_{\alpha(\gamma)})} := \sup \left\{ |\langle P(u)U, U \rangle|; \|U\|_{\alpha(\gamma)} \leq 1 \right\} \leq \Lambda \leq 1 \quad (3.9)$$

where $\Lambda = \max \left\{ \{\chi_2, \chi_3\} \mu_1^{\frac{N}{4} - \beta - 2\gamma}, \{a_2, a_3\} \mu_1^{-\beta - \gamma} \right\}$ and $Z_{\delta(\gamma)} := E^\delta \times E^\gamma \times E^\gamma$.

It is worthwhile pointing out that unlike in Proposition 3.4 the converse statements of the theorem require an additional condition to be verified i.e. $\alpha + \gamma \geq \frac{1}{2} + \frac{N}{4}$ for the proper-posedness of the Div operator. Most important is that in view of the experimental data given in the numerical sessions of the paper the last assertion in (3.9) is not restrictive but consistent with that data.

Proof. This first part of the theorem follows by Theorem 3.2-(i). To prove the converse, let $\varphi \in E^\alpha$ be a test function to for example the operator $-\text{Div}(u\chi_2\nabla v)$ in the scalar product of

$L^2(\Omega)$, to conclude using the Sobolev type embeddings (2.4) and Hölder's inequality that the mapping

$$E^\alpha \times E^\gamma \times E^\gamma \ni (u, v, \varphi) \mapsto \langle -\text{Div}(u\chi_2\nabla v), \varphi \rangle = \chi_2 \int_{\Omega} u\nabla v\nabla\varphi \in \mathbb{R} \quad (3.10)$$

is well defined and continuous, provided $\alpha + \gamma \geq \frac{1}{2} + \frac{N}{4}$, $u\nabla v \in L^r(\Omega)$ with $r = 2$ if $\alpha \geq \frac{1}{2}$, and $r > 2$ if $\frac{1}{2} > \alpha$. Also that $-\text{Div}(u\chi_2\nabla v) \in L^p(\Omega)$, of $p \geq \max\{2, \frac{2N}{N+4\alpha}; \alpha \in \mathbb{R}\}$. More concretely, as $u \in E^\alpha \subset L^{r_0}(\Omega)$, $\nabla v \in L^{r_1}(\Omega)$ then $u\nabla v \in L^2(\Omega)$ if and only if

$$\frac{1}{2} = \frac{1}{r_0} + \frac{1}{r_1} \geq \frac{N-4\alpha}{2N} + \frac{N-4\gamma+2}{2N} \Rightarrow N \geq 2N - 4(\alpha + \gamma) + 2 \quad (3.11)$$

of which we obtain $4(\alpha + \gamma) \geq 2 + N$ i.e. $\alpha + \gamma \geq \frac{1}{2} + \frac{N}{4}$. But also $\nabla\varphi \in E^{\alpha-\frac{1}{2}} \subset L^{r_2}(\Omega)$, $r_2 \geq 2$, hence

$$\frac{1}{2} \geq \frac{1}{r_2} \geq \frac{N-4\alpha+2}{2N} \Rightarrow N \geq N - 4\alpha + 2.$$

Consequently $\alpha \geq 1/2$ with from $\alpha + \gamma \geq \frac{1}{2} + \frac{N}{4}$ it is implied that $\gamma \geq \frac{N}{4}$ and in the strict case $E^\gamma \subset L^\infty(\Omega)$ using (2.5). If $r > 2$, as by Hölder's inequality we need $\frac{1}{r_2} + \frac{1}{r} = 1$ we get using (2.4) embeddings that $r \geq \frac{2N}{N+4\alpha-2}$ yielding $2N > 2N + 8\alpha - 4$ of which as a result implies $1/2 > \alpha$. On the other hand replacing $1/2$ by $1/r$ in (3.11) gives $2 < r \leq \frac{2N}{2N-4(\alpha+\gamma)+2}$ with condition $\alpha + \gamma > \frac{1}{2} + \frac{N}{4}$ but as $1/2 > \alpha$ we get $E^\gamma \subset L^\infty(\Omega)$. Thus by taking into account either of the conditions on α leads to $\frac{2N}{N+4\alpha-2} \leq r \leq \frac{2N}{2N-4(\alpha+\gamma)+2}$, the condition in the theorem $2\alpha + \gamma \geq 1 + \frac{N}{4}$ is obtained. The also part follows using (2.4) and Hölder's inequality directly from the inner product expression in (3.11) without passing the partial derivative to the test function.

Now considering (3.6) we get that

$$P(u)U \in Z_{\beta(\alpha)} \cap L^p(\Omega) \times E^\alpha \times E^\alpha,$$

for $p \geq 2, \alpha \geq 0$, and $U = (u, v, w)^\top \in Z_{\alpha(\gamma)} \subset Z_{\beta(\gamma)}$ since $0 \leq \alpha - \beta < 1$. Next if we let $V = (\phi, \varphi, \psi) \in Z_{\alpha(\gamma)}$ in the scalar product of $L^2(\Omega)$, thanks to the space embeddings (2.6) we get by Hölder's inequality that the mapping

$$V = (\phi, \varphi, \psi) \in Z_{\alpha(\gamma)} \mapsto \langle P(u)U, V \rangle \in [L^1(\Omega)]^3 \quad (3.12)$$

is well defined and continuous.

Therefore, the linearity implies for any $U_1, U_2 \in Z_{\alpha(\gamma)}$ of finite norm, $P(u)U \in Z_{\beta(\alpha)}$ is Lipschitz continuous. Thus Proposition 3.4 or abstract semilinear evolution equations results [9, 17, 24, 22, 27] yields the conclusion of the theorem. Moreover, see Theorem 5.1-(5.9)- (5.10) in the next sections (3.9) is true and the solution to the problem (1.1)-(1.2) defines an analytic perturbed semigroup in the scales of spaces $Z_{\delta(\nu)}, \delta(\nu) \in \mathbb{R}$. The proof of the theorem is complete. \square

Now, for some remarks on the main condition yielding Theorem 3.5 we have the following.

Remark 3.6. First we note that in the proof of the Theorem 3.5 if the test functions are taken in E^γ the yielding condition changes to $\alpha + 2\gamma \geq 1 + \frac{N}{4}$ and $E^\alpha \subset L^\infty(\Omega)$ if $\alpha > \frac{N}{4}$ i.e. for $\gamma < 1/2$. Also note that using the minimal yielding condition $\alpha + \gamma \geq \frac{1}{2} + \frac{N}{4}$, if $\alpha, \gamma < 1$ then $2 > \frac{1}{2} + \frac{N}{4}$ and we can solve the problem (1.1)-(1.2) in space dimensions of $\Omega \subset \mathbb{R}^N, N \leq 5$.

In particular, if $\beta = 0$, since we require that $\nabla v, \nabla w \in L^\infty(\Omega)$ i.e. $\gamma > \frac{1}{2} + \frac{N}{4}$ and as $\gamma < 1$ this implies solvability of the problem (1.1)-(1.2) in space dimensions of $\Omega \subset \mathbb{R}^N, N = 1$. Next, if in (3.7) we take $\alpha = \beta$ the necessary condition reads $2\beta + \gamma \geq 1 + \frac{N}{4}$ but $\beta \leq \gamma < \beta + 1$. If we assume $\gamma = \beta > 0$ we get that $3\beta \geq 1 + \frac{N}{4}$ and if $\beta = \frac{1}{2}$ then $N \leq 2$. If $\gamma = \frac{3}{4} > \beta = \frac{1}{2}$ then $N \leq 3$. If $\gamma = \beta = \frac{3}{4}$ then $N \leq 5$. If $\gamma = \frac{5}{4} > \beta = \frac{3}{4}$ then $N \leq 7$. Thus the higher the regularity assumed on that data, the higher the space dimensions in which it is possible to solve the problem (1.1)-(1.2). Lastly, we note that if $2\beta + \gamma > \frac{3N}{4}$ then $Z_{\delta=\beta+\gamma} := E^\beta \times E^\gamma \subset C(\Omega) \times C(\Omega)$ using (2.5) and also if $2\beta + \gamma > \frac{1}{2} + \frac{3N}{4}$, then $Z_{\delta=\beta+\gamma-\frac{1}{2}} = E^\beta \times E^{\gamma-\frac{1}{2}} \subset C(\Omega) \times C(\Omega)$ in both these cases we can solve the problem in any space dimensions.

We conclude this section with the following corollary.

Corollary 3.7. *Consider the system of equations (1.1)-(1.2). Assume the hypotheses of Theorem 3.5 holds within (3.7)*

$$\alpha = \theta\beta + (1 - \theta)(\gamma - \frac{1}{2}), \theta \in [0, 1]. \quad (3.13)$$

Then, (i). Theorem 3.2 holds in $Z_\beta = E^\beta \times E^{\beta+\frac{1}{2}} \times E^{\beta+\frac{1}{2}}$.

(ii). If $2\beta + \gamma > \frac{3N}{4}$, then the solution to the problem (1.1)-(1.2), satisfies

$$U \in C(0, \infty, C^\theta(\Omega)) \cap C(0, \infty, C^{2+\theta}(\Omega)) \cap C^1(0, \infty, C^\theta(\Omega))$$

for some $\theta \in (0, 1)$ and is a classical solution.

Proof. To prove (i) it suffices to note that if α is as given in (3.13) then $\beta > \alpha$ if and only if $\beta > \gamma - \frac{1}{2}$ and also $\alpha > \beta$ if and only if $\gamma - \frac{1}{2} > \beta$. Combining the two we find that $\gamma = \beta + \frac{1}{2}$. We prove (ii) of this corollary in the next section of the paper. An alternative, using a classical approach, since by (2.5), $U_0 \in L^\infty(\Omega)$, the conclusion follows by [2, 17, 10, 25, 36, 44, 45] and Theorem 3.5. The proof of the corollary is complete. \square

4 Uniform bounds of solutions

In this section, we study the existence of *a priori* uniform bounds in $\Omega \times (0, T)$ of solutions to the system of equations (1.1)-(1.2). As an approach to this end, we use the Moser-Nash-De Giorgi [3, 11, 15, 30] technique, and our first lemma is the following:

Lemma 4.1. *Consider the evolution problem (1.1)-(1.2) in context of the Theorem 3.5. Assume that the initial data of the system of equations $U_0 = (u_0, v_0, w_0)^\top \in Z_{\beta(\gamma)} \cap [L^\infty(\Omega)]^3$, and that $u \in L^\infty(0, T, L^r(\Omega))$, for some $r > \frac{N}{2}$ are finitely bounded in norms. Then $v, w \in L^\infty(\Omega \times (0, T))$ are also finitely bounded norms of the given function space.*

Proof. It suffices only to consider one of either of the last two equations of (1.1)-(1.2) in v or w . We adopt here for simplification to use the function space $H^1(\Omega)$. Thus considering the equation in v and taking the inner product of $L^2(\Omega)$ with $|v|^{r-1}v, r > 1$ we get that

$$\begin{aligned} \frac{1}{r+1} \frac{d}{dt} \int_{\Omega} |v|^{r+1} + \left(\frac{2\sqrt{d_2 r}}{r+1} \right)^2 \int_{\Omega} |\nabla |v|^{\frac{r+1}{2}}|^2 + \lambda_2 \int_{\Omega} |v|^{r+1} &\leq a_2 \int_{\Omega} u |v|^{r-1} v \\ &\leq a_2 \left(\int_{\Omega} |v|^{\frac{N(r+1)}{N-2}} \right)^{\Theta_1} \left(\int_{\Omega} |u|^r \right)^{\Theta_2} \left(\int_{\Omega} |v|^{r+1} \right)^{\Theta_3} \\ &\leq a_2 C \left(\int_{\Omega} (|\nabla |v|^{\frac{r+1}{2}}|^2 + (|v|^{\frac{r+1}{2}})^2) \right)^{\frac{N\Theta_1}{N-2}} \left(\int_{\Omega} |u|^r \right)^{\frac{2\Theta_2}{N-2}} \left(\int_{\Omega} |v|^{r+1} \right)^{\Theta_3} \end{aligned} \quad (4.1)$$

where in the second inequality above we have used the Nakao-Hölder -Sobolev inequality [3, 11], since there exists $\vartheta > 0$ such that $r = \frac{N}{2} + \vartheta$ and

$$\Theta_1 = \frac{N-2}{N+\vartheta}, \quad \Theta_2 = \frac{2}{N+\vartheta}, \quad \Theta_3 = \frac{\vartheta}{N+\vartheta},$$

the third inequality is due to Sobolev space embeddings [1, 5, 12, 14, 15] i.e. (2.4) in $\alpha = 1/2$.

In what follows we first note that $2r > r+1 > 2$, hence after multiplying throughout in (4.1) by $r+1$, and using in the right hand side Young's inequality [5, 11] i.e.

$$ab \leq \eta a^s + C_{\eta} b^{s'}, \quad a, b \geq 0, \eta \in (0, 1)$$

since

$$\frac{N\Theta_1}{N-2} = \frac{N}{N+\vartheta}, \quad \frac{N\Theta_1}{N-2} + \Theta_3 = 1$$

we obtain if we let

$$\beta_0 = \inf\{\mu_1, 2d_2 - \eta, 2\lambda_2 - \eta\} > 0, \quad \mu_1 \in \sigma(-\Delta + 1), \quad C_{a_2} = a_2 C$$

that

$$\begin{aligned} \frac{d}{dt} \int_{\Omega} |v|^{r+1} + \beta_0 \left(\int_{\Omega} |\nabla |v|^{\frac{r+1}{2}}|^2 + \int_{\Omega} |v|^{r+1} \right) \\ \leq (2rC_{a_2})^{\frac{1}{\Theta_3}} \left(\sup_{(0,T)} \int_{\Omega} |u|^r \right)^{\frac{4}{\vartheta(N-2)}} \int_{\Omega} |v|^{r+1} \leq (2rC_{a_2})^{\frac{1}{\Theta_3}} \int_{\Omega} |v|^{r+1}, \end{aligned} \quad (4.2)$$

since the term in brackets from the last inequality right to left is finitely bounded from above, and $\frac{1}{\Theta_3} > \frac{4}{\vartheta(N-2)}$ we have incorporated the bounding from above constant with and/or the given $C_{a_2} \geq 0$.

Therefore, if $r_i = 2^i, i \in \mathbb{N}$, and

$$\Theta_i = \frac{2(r_i + 1)}{N(r_i + 1) - (N-2)(r_{i-1} + 1)}, \quad \Theta'_i = 1 - \Theta_i,$$

then by the Hölder's inequality as well as from the Sobolev type inclusions [1, 5, 12, 14, 15] and Young's inequality [5, 11] one obtains

$$\begin{aligned} \int_{\Omega} |v|^{r_i+1} &\leq \left(\int_{\Omega} |v|^{\frac{N(r_i+1)}{N-2}} \right)^{\Theta'_i} \left(\int_{\Omega} |v|^{r_i+1} \right)^{\Theta_i} \\ &\leq C \left(\int_{\Omega} (|v|^{\frac{r_i+1}{2}})^2 + \int_{\Omega} |\nabla |v|^{\frac{r_i+1}{2}}|^2 \right)^{\frac{N\Theta'_i}{N-2}} \left(\int_{\Omega} |v|^{r_i+1} \right)^{\Theta_i}. \end{aligned}$$

Thus from (4.2) while still setting $C_{a_2} = C_{a_2}C$, it follows that

$$\begin{aligned} \frac{d}{dt} \int_{\Omega} |v|^{r_i+1} + \beta_0(\eta) \left(\int_{\Omega} |\nabla |v|^{\frac{r_i+1}{2}}|^2 + \int_{\Omega} |v|^{r_i+1} \right) \\ \leq (2r_i C_{a_2})^{\frac{1}{\Theta_3}} \left(\int_{\Omega} (|v|^{\frac{r_i+1}{2}})^2 + \int_{\Omega} |\nabla |v|^{\frac{r_i+1}{2}}|^2 \right)^{\frac{N\Theta'_i}{N-2}} \left(\int_{\Omega} |v|^{r_i+1} \right)^{\Theta_i} \\ \leq \eta \left(\int_{\Omega} (|v|^{\frac{r_i+1}{2}})^2 + \int_{\Omega} |\nabla |v|^{\frac{r_i+1}{2}}|^2 \right) + (2r_i C_{a_2})^{\frac{N+2}{2\Theta_3}} \left(\int_{\Omega} |v|^{r_{i-1}+1} \right)^{s_i}, \end{aligned}$$

and because $\frac{N\Theta'_i}{N-2} < 1$ we have used Young's inequality [5, 11].

Now set $s_i = \frac{r_i+1}{r_{i-1}+1}$ and since $\frac{N+2}{2} \geq \frac{Nr_{i-1}+r_i+2}{r_i+2}$, therefore

$$\frac{d}{dt} \int_{\Omega} |v|^{r_i+1} + \beta \left(\int_{\Omega} |\nabla |v|^{\frac{r_i+1}{2}}|^2 + \int_{\Omega} |v|^{r_i+1} \right) \leq (2r_i C_{a_2})^{\sigma} \left(\int_{\Omega} |v|^{r_{i-1}+1} \right)^{s_i}$$

where $\sigma = \frac{N+2}{2\Theta_3}$, $\beta = \beta(\mu_1, d_2, \lambda_2, 2\eta) > 0$. Applying Poincaré inequality and defining $y_i(t) = \int_{\Omega} |v|^{r_i+1}$ we obtain

$$\frac{dy_i}{dt} + \beta y_i \leq (r_i C)^{\sigma} (y_{i-1})^{s_i}. \quad (4.3)$$

If $M = M(\|v_0\|_{\infty}) > 0$ is such that $y_i(0) \leq M^{(r_{i-1}+1)s_i}$. Then, solving (4.3) as

$$y_i(t) \leq (r_i C)^{\sigma} \left(y_i(0) + \left(\sup_{t \in (0, T)} y_{i-1}(t) \right)^{s_i} \right)$$

we obtain from $(a+b)^p \leq 2^p(a^p + b^p)$, $a, b, p \geq 0$ with $i = k \geq 1$ that

$$\begin{aligned} y_k(t) &\leq (2C)^{1+2s_k+2s_{k-1}s_k+\dots+2s_2s_3\dots s_k} (2C)^{k\sigma+(k-1)\sigma s_k+\dots+\sigma s_2s_3\dots s_k} M^{2s_1s_2\dots s_k} + \\ &+ (2C)^{1+2s_k+2s_{k-1}s_k+\dots+2s_2s_3\dots s_k} (2C)^{k\sigma+(k-1)\sigma s_k+\dots+\sigma s_2s_3\dots s_k} \left(\sup_{t \in (0, T)} \int_{\Omega} |v|^2 \right)^{s_1s_2\dots s_k} \\ &\leq (2C)^{2A_k} (2C)^{\sigma B_k} M^{2\chi_k} + (2C)^{2A_k} (2C)^{\sigma B_k} \left(\sup_{t \in (0, T)} \int_{\Omega} |v|^2 \right)^{\chi_k} \end{aligned}$$

where $\chi_k = s_k \dots s_1 \leq \frac{r_k+1}{2}$,

$$A_k = 1 + s_k + s_k s_{k-1} + \dots + s_k s_{k-1} \dots s_1 \leq (r_k + 1) \sum_{i=1}^{\infty} \frac{1}{r_i + 1},$$

$$B_k = k + (k-1)s_k + (k-2)s_k s_{k-1} + \dots + s_k s_{k-1} \dots s_1 \leq (r_k + 1) \sum_{i=1}^{\infty} \frac{i}{r_i + 1},$$

and the series in the right hand sides converge since $r_i = 2^i$. Let

$$\omega_1 = \sum_{i=1}^{\infty} \frac{1}{r_i + 1}, \quad \omega_2 = \sum_{i=1}^{\infty} \frac{i}{r_i + 1}$$

to conclude that

$$\begin{aligned} y_k(t) &\leq \left((2C)^{2\omega_1} (2C)^{\sigma\omega_2} M + (2C)^{2\omega_1} (2C)^{\sigma\omega_2} \left(\sup_{t \in (0, T)} \int_{\Omega} |v|^2 \right)^{\frac{1}{2}} \right)^{r_k+1} \\ &\leq \left((2C)^{2\omega_1} (2C)^{\sigma\omega_2} M \left(\sup_{t \in (0, T)} \left(\int_{\Omega} |v|^2 \right)^{\frac{1}{2}} + 1 \right) \right)^{r_k+1}. \end{aligned}$$

This implies

$$\begin{aligned} \sup_{\Omega} |v(t, v_0)| &\leq \lim_{k \rightarrow 0} \left(\int_{\Omega} |v|^{r_k+1} \right)^{\frac{1}{r_k+1}} \\ &\leq (2C)^{2\omega_1} (2C)^{\sigma\omega_2} M \left(\sup_{t \in (0, T)} \left(\int_{\Omega} |v|^2 \right)^{\frac{1}{2}} + 1 \right), \end{aligned}$$

and the proof of the lemma is complete. Note that this proof in general scales of spaces E^α , $\alpha \in \mathbb{R}$ implies the results since $\gamma \geq \beta \geq 1/2$, but this will be more complicated. \square

Next we observe that due to the linearity of the system of equations in v, w and Lemma 4.1 we have as a corollary the following:

Corollary 4.2. *Consider the evolution problem (1.1)-(1.2) in the context of Theorem 3.5 and Lemma 4.1. Assume the initial data $u_0 \in L^\infty(\Omega)$, $\nabla v_0, \nabla w_0 \in [L^\infty(\Omega)]^N$, and that $\nabla u \in L^\infty(0, T, L^r(\Omega))$, $r > \frac{N}{2}$ are finitely bounded in norms of the given spaces. Then, the gradient solutions $\nabla v, \nabla w \in L^\infty(\Omega \times (0, T))$, and $u \in L^\infty(\Omega \times (0, T))$ are also finitely bounded in norms.*

Proof. It suffices to note that from one of v, w system equations of (1.1)-(1.2), if one differentiates these equations with respect to the x variable, and takes as test function say $|\nabla v|^{r-1} \nabla v \in H^1(\Omega)$, $r > 1$. Then, Lemma 4.1 holds due to the linearity of these system equations and weak coupledness.

So we only need to prove that $u \in L^\infty(\Omega \times (0, T))$ is finitely bounded in norm. To this end, consider the u equation of the system (1.1)-(1.2) and take the inner product of $L^2(\Omega)$ with test function $|u|^{r-1} u \in H^1(\Omega)$, $r > 1$ to find that

$$\begin{aligned} \frac{1}{(r+1)} \frac{d}{dt} \int_{\Omega} |u|^{r+1} + \left(\frac{2\sqrt{d_1 r}}{r+1} \right)^2 \int_{\Omega} |\nabla |u|^{\frac{r+1}{2}}|^2 &= \chi_2 r \int_{\Omega} |u|^{r-1} u \nabla u \nabla v - \chi_3 r \int_{\Omega} |u|^{r-1} u \nabla u \nabla w \\ &\leq (C_1 \chi_2 + C_2 \chi_3) r \int_{\Omega} \| |u|^r \nabla u \| = \frac{2(C_1 \chi_2 + C_2 \chi_3) r}{r+1} \int_{\Omega} \| |u|^{\frac{r+1}{2}} \nabla |u|^{\frac{r+1}{2}} \|. \end{aligned}$$

This yields that

$$\begin{aligned} \frac{d}{dt} \int_{\Omega} |u|^{r+1} + 2d_1 \int_{\Omega} |\nabla |u|^{\frac{r+1}{2}}|^2 &\leq 2(C_1\chi_2 + C_2\chi_3)r \int_{\Omega} ||u|^{\frac{r+1}{2}} \nabla |u|^{\frac{r+1}{2}}| \\ &\leq \eta \int_{\Omega} |\nabla |u|^{\frac{r+1}{2}}|^2 + \frac{(C_1\chi_2 + C_2\chi_3)r}{2\eta} \int_{\Omega} |u|^{r+1}, \end{aligned} \quad (4.4)$$

by Young's inequality

$$ab \leq \eta a^s + (\eta s)^{-\frac{s'}{s}} s'^{-1} b^{s'}, \quad a, b \geq 0, \quad \frac{1}{s} + \frac{1}{s'} = 1$$

and if $\beta_0 := 2d_1 - \eta > 0$ or $0 < \eta \ll 1$ is adequately chosen then Poincaré inequality implies that

$$\frac{d}{dt} \int_{\Omega} |u|^{r+1} + \beta \int_{\Omega} |u|^{r+1} \leq \frac{(C_1\chi_2 + C_2\chi_3)r}{2\eta} \int_{\Omega} |u|^{r+1} \quad (4.5)$$

where for $\mu_1 \in \sigma(-\Delta)$, we defined $\beta := \mu_1 \beta_0 > 0$. From this point one can proceed as in the proof of Lemma 4.1 to conclude that $u \in L^\infty(\Omega)$ is finitely bounded in norm.

Alternatively, we notice that by interpolation for $\varphi \in H^1(\Omega)$, it holds that

$$\|\varphi - \bar{\varphi}\|_{L^2(\Omega)}^2 \leq C \|\nabla \varphi\|_{L^2(\Omega)}^{2\theta} \|\varphi\|_{L^1(\Omega)}^{2(1-\theta)} \quad (4.6)$$

where $\theta = \frac{N}{N+2}$, and Young's inequality yields

$$\|\varphi\|_{L^2(\Omega)}^2 \leq \eta_0 \|\nabla \varphi\|_{L^2(\Omega)}^2 + C(1 + \eta_0^{-\frac{N}{2}}) \|\varphi\|_{L^1(\Omega)}^2.$$

Consequently, setting $\varphi = |u|^{\frac{r+1}{2}}$, $\eta_0 = \frac{r}{(r+1)^2 C_\eta}$ with $C_\eta = \frac{(C_1\chi_2 + C_2\chi_3)}{2\eta}$ we obtain that

$$rC_\eta \int_{\Omega} |u|^{r+1} \leq \frac{r}{(r+1)^2} \int_{\Omega} |\nabla |u|^{\frac{r+1}{2}}|^2 + (2^2 C_\eta)^{\frac{N}{2}} C(1 + r^N) \left(\int_{\Omega} |u|^{\frac{r+1}{2}} \right)^2$$

since $r > 1, 2r > r+1$, and $0 < \eta \ll 1$ sufficiently small implies $C_\eta \gg 1$.

Therefore, $C_\eta \geq C$ and because $1 + r^N \leq (1+r)^N$ we obtain from (4.4) the following iterative inequality type of (4.5) with $\beta_0 - \frac{1}{4} > 0$,

$$\begin{aligned} \frac{d}{dt} \int_{\Omega} |u|^{r+1} + \beta \int_{\Omega} |u|^{r+1} &\leq (2C_\eta)^N (1+r)^N \left(\int_{\Omega} |u|^{\frac{r+1}{2}} \right)^2 \\ \implies \int_{\Omega} |u|^{r+1} &\leq \int_{\Omega} u_0^{r+1} + (2C_\eta)^N (1+r)^N \sup_{(0,T)} \left(\int_{\Omega} |u|^{\frac{r+1}{2}} \right)^2. \end{aligned}$$

Next defining

$$K(p) := \max \left\{ \|u_0\|_{L^\infty(\Omega)}, \sup_{(0,T)} \left(\int_{\Omega} |u|^p \right)^{\frac{1}{p}} \right\} \quad (4.7)$$

leads to that

$$K(r+1) \leq [(2C_\eta)^N (1+r)^N]^{\frac{1}{r+1}} K\left(\frac{r+1}{2}\right), \quad \forall r \geq 1,$$

of if we let $r_i + 1 = 2^i, i \in \mathbb{N}^*$ we conclude that

$$\begin{aligned} K(2^i) &\leq (2C_\eta)^{N2^{-i}} (2^i)^{\frac{N}{2^i}} K(2^{i-1}) \leq \dots \leq (2C_\eta)^{N \sum_{k=1}^i 2^{-k}} (2^i)^{2^{-i}N} \dots (1+2)^{2^{-1}N} K(1) \\ &\leq (2C_\eta)^N \left[2^{i2^{-i}N} (2^{-i})^{2^{-i}N} \right] \dots \left[2^{2^{-1}N} (2^{-1})^{2^{-1}N} \right] K(1) \\ &\leq (2C_\eta)^N 2^{N \sum_{k=1}^i k 2^{-k}} \times 2^{N \sum_{k=1}^i 2^{-k}} K(1) \leq C 2^{3N} K(1). \end{aligned}$$

Consequently, taking the limit as $i \rightarrow \infty$ yields

$$\|u\|_{L^\infty(\Omega)} \leq C 2^{3N} K(1) \leq C 2^{3N} \max \{ \|u_0\|_{L^\infty(\Omega)}, \|u_0\|_{L^1(\Omega)} \} < \infty,$$

and the proof of the corollary is complete. \square

The following is a particular converse lemma to Corollary 4.2, since its conclusion holds for all $r \in [2, \infty]$.

Lemma 4.3. *Consider the evolution problem (1.1)-(1.2). Assume the hypotheses of Corollary 4.2 and that $\nabla u_0 \in L^\infty(\Omega)$ is finitely bounded in norm. If $\nabla v, \nabla w \in L^\infty(\Omega \times (0, T))$ are finitely bounded in norm, then $\nabla u \in L^\infty(0, T, L^r(\Omega)), \forall r > \frac{N}{2}$ is also finitely bounded in norm.*

Proof. Differentiate the system equation in u with respect to x . Then, take the inner product of $L^2(\Omega)$ with the test function $|\nabla u|^r \nabla u \in H^1(\Omega), r \geq 0$ to find that

$$\begin{aligned} &\frac{1}{r+2} \frac{d}{dt} \int_{\Omega} |\nabla u|^{r+2} + \frac{4d_1(r+1)}{(r+2)^2} \int_{\Omega} |\nabla(|\nabla u|^{\frac{r+2}{2}})|^2 \\ &= \frac{r+2}{2} \chi_2 \int_{\Omega} \left(|\nabla u|^{\frac{r+2}{2}} \nabla v \Delta u + u |\nabla u|^{\frac{r+2}{2}-2} \nabla u \Delta u \Delta v \right) - \\ &\quad \frac{r+2}{2} \chi_3 \int_{\Omega} \left(|\nabla u|^{\frac{r+2}{2}} \nabla w \Delta u + u |\nabla u|^{\frac{r+2}{2}-2} \nabla u \Delta u \Delta w \right) \\ &\leq \frac{r+2}{2} \chi_2 \left(\int_{\Omega} \|\nabla u\|^{\frac{r+2}{2}} \nabla v \Delta u + \int_{\Omega} |u| |\nabla u|^{\frac{r+2}{2}-2} \nabla u \Delta u \Delta v \right) + \\ &\quad + \frac{r+2}{2} \chi_3 \left(\int_{\Omega} \|\nabla u\|^{\frac{r+2}{2}} \nabla w \Delta u + \int_{\Omega} |u| |\nabla u|^{\frac{r+2}{2}-2} \nabla u \Delta u \Delta w \right) \\ &\leq \frac{r+2}{2} \left(C_\chi \int_{\Omega} |\nabla(|\nabla u|^{\frac{r+2}{2}})| \nabla u + C_u \int_{\Omega} \|\nabla u\|^{\frac{r}{2}} \Delta u (\Delta v + \Delta w) \right), \quad (4.8) \end{aligned}$$

where $C_\chi = (\chi_2 C_{\nabla v} + \chi_3 C_{\nabla w}) \geq 0$, with $C_{\nabla v}, C_{\nabla w}, C_u$ constants for the upper bounds of the variables in $L^\infty(\Omega)$. Multiplying throughout by $r+2$, and since $\frac{1}{2} + \frac{1}{r+2} \leq 1$, for any $r \geq 0$ we get by Holder's inequality that

$$\begin{aligned} &\frac{d}{dt} \int_{\Omega} |\nabla u|^{r+2} + 2d_1 \int_{\Omega} |\nabla(|\nabla u|^{\frac{r+2}{2}})|^2 \\ &\leq \frac{(r+2)^2}{2} \left(C_\chi \int_{\Omega} |\nabla(|\nabla u|^{\frac{r+2}{2}})| \nabla u + C_u \int_{\Omega} \|\nabla u\|^{\frac{r}{2}} \Delta u (\Delta v + \Delta w) \right) \\ &\leq \frac{(r+2)^2}{2} \left(C_\chi \left(\int_{\Omega} |\nabla(|\nabla u|^{\frac{r+2}{2}})|^2 \right)^{\frac{1}{2}} \left(\int_{\Omega} |\nabla u|^{r+2} \right)^{\frac{1}{2}} + \right. \\ &\quad \left. + \frac{2C_u}{r+2} \left(\int_{\Omega} |\nabla(|\nabla u|^{\frac{r+2}{2}})|^2 \right)^{\frac{1}{2}} \left[\left(\int_{\Omega} |\Delta v|^2 \right)^{\frac{1}{2}} + \left(\int_{\Omega} |\Delta w|^2 \right)^{\frac{1}{2}} \right] \right). \quad (4.9) \end{aligned}$$

We recall at this point the Young's inequality

$$ab \leq \eta a^s + \eta^{-\frac{s'}{s}} s'^{-1} b^{s'}, a, b \geq 0, \eta \in (0, 1), \frac{1}{s} + \frac{1}{s'} = 1$$

with which if we let $\eta_1 := \frac{2\eta_2}{(r+2)^2 C_\chi}$ where by [9, 12] Nirenberg-Gagliardo's inequality $0 < \eta_2 \leq 1$ and

$$\int_{\Omega} |\nabla u|^{r+2} \leq \eta_2 \int_{\Omega} |\nabla(|\nabla u|^{\frac{r+2}{2}})|^2 + C_{\Omega} \eta_2^{-m} \left(\int_{\Omega} |\nabla u|^{\frac{r+2}{2}} \right)^2$$

for $m > \frac{N}{2}$, $C_{\Omega} = C(\Omega, m)$, $\eta_3 := \frac{16\eta_2^2}{(r+2)^4 C_\chi^2 |\Omega|^{1-\frac{2}{r+2}}}$ we get that

$$\begin{aligned} \frac{(r+2)^2}{2} C_\chi \int_{\Omega} |\nabla(|\nabla u|^{\frac{r+2}{2}})| \nabla u &\leq \frac{(r+2)^2}{2} C_\chi \left(\int_{\Omega} |\nabla(|\nabla u|^{\frac{r+2}{2}})|^2 \right)^{\frac{1}{2}} \left(\int_{\Omega} |\nabla u|^2 \right)^{\frac{1}{2}} \\ &\leq \frac{(r+2)^2}{2} C_\chi \left(\eta_1 \int_{\Omega} |\nabla(|\nabla u|^{\frac{r+2}{2}})|^2 + (4\eta_1)^{-1} \int_{\Omega} |\nabla u|^2 \right) \\ &\leq \eta_2 \int_{\Omega} |\nabla(|\nabla u|^{\frac{r+2}{2}})|^2 + \frac{(r+2)^2}{2} C_\chi |\Omega|^{1-\frac{2}{r+2}} \left(\frac{8\eta_2}{(r+2)^2 C_\chi} \right)^{-1} \int_{\Omega} |\nabla u|^{r+2} \\ &\leq 2\eta_2 \int_{\Omega} |\nabla(|\nabla u|^{\frac{r+2}{2}})|^2 + \frac{(r+2)^2}{2} C_\chi |\Omega|^{1-\frac{2}{r+2}} \left(\frac{8\eta_2}{(r+2)^2 C_\chi} \right)^{-1} C_{\Omega} (\eta_3)^{-m} \times \\ &\quad \times \left(\int_{\Omega} |\nabla u|^{\frac{r+2}{2}} \right)^2 \\ &= 2\eta_2 \int_{\Omega} |\nabla(|\nabla u|^{\frac{r+2}{2}})|^2 + (r+2)^{4m} \Gamma_1 C_{\Omega} \left(\int_{\Omega} |\nabla u|^{\frac{r+2}{2}} \right)^2, \end{aligned}$$

where $\Gamma_1 = \left(\frac{C_\chi^2 |\Omega|^{1-\frac{2}{r+2}}}{16\eta_2^2} \right)^{m+1}$.

As for the last expression in (4.9) we need a control from above of the integrals involving $-\Delta$ of v, w . To this end multiplying either stationary equations in v or w by $-\Delta$ of the variable one obtains that

$$\begin{aligned} d_2 \int_{\Omega} |\Delta v|^2 + \lambda_2 \int_{\Omega} |\nabla v|^2 &= a_2 \int_{\Omega} \nabla u \nabla v \leq a_2 \left(\int_{\Omega} |\nabla u|^2 \right)^{\frac{1}{2}} \left(\int_{\Omega} |\nabla v|^2 \right)^{\frac{1}{2}} \\ &\leq \eta_4 \int_{\Omega} |\nabla u|^2 + a_2 (4\eta_4)^{-1} \int_{\Omega} |\nabla v|^2 \leq \eta_4 |\Omega|^{1-\frac{2}{r+2}} \int_{\Omega} |\nabla u|^{r+2} + a_2 (4\eta_4) C_{\nabla v}^2 |\Omega| \\ &\leq \eta_4 \frac{|\Omega|^{1-\frac{2}{r+2}}}{\mu_1} \int_{\Omega} |\nabla(|\nabla u|^{\frac{r+2}{2}})|^2 + a_2 (4\eta_4)^{-1} C_{\nabla v}^2 |\Omega|. \end{aligned}$$

Note this remains true even if one had considered the entire equation involving the time derivative, since by Theorem 3.5 the solutions are continuous in time. Let $\eta_4 \leq \eta_5$ and set

$$\eta_6 := \frac{1}{(r+2)C_u} \left(2\eta_5 + \frac{\eta_4}{2\mu_1\eta_5} \left(\frac{1}{d_2} + \frac{1}{d_3} \right) |\Omega|^{1-\frac{2}{r+2}} \right)$$

to find that

$$\begin{aligned}
& (r+2)C_u \left(\int_{\Omega} |\nabla(|\nabla u|^{\frac{r+2}{2}})|^2 \right)^{\frac{1}{2}} \left[\left(\int_{\Omega} |\Delta v|^2 \right)^{\frac{1}{2}} + \left(\int_{\Omega} |\Delta w|^2 \right)^{\frac{1}{2}} \right] \\
& \leq (r+2)C_u \left(2\eta_5 \int_{\Omega} |\nabla(|\nabla u|^{\frac{r+2}{2}})|^2 + \frac{1}{4\eta_5} \left(\int_{\Omega} |\Delta v|^2 + \int_{\Omega} |\Delta w|^2 \right) \right) \\
& \leq (r+2)C_u \left(\left(2\eta_5 + \frac{\eta_4}{2\mu_1\eta_5} \left(\frac{1}{d_2} + \frac{1}{d_3} \right) |\Omega|^{1-\frac{2}{r+2}} \right) \int_{\Omega} |\nabla(|\nabla u|^{\frac{r+2}{2}})|^2 + \right. \\
& \quad \left. + \left(\frac{a_2(C_{\nabla v} + C_{\nabla w})|\Omega|}{16\eta_5\eta_4} \right) \right) \\
& \leq \eta_6 \int_{\Omega} |\nabla(|\nabla u|^{\frac{r+2}{2}})|^2 + \left(\frac{a_2(r+2)(C_{\nabla v} + C_{\nabla w})|\Omega|C_u}{16\eta_4^2} \right).
\end{aligned}$$

Thus, from (4.9) if we let $\eta_7 = 2\eta_2 + \eta_6$, $\Gamma_2 = \frac{a_2(C_{\nabla v} + C_{\nabla w})|\Omega|C_u}{16\eta_4^2}$ and $\Gamma = \max\{\Gamma_1, \Gamma_2\}$ we are led to conclude that

$$\begin{aligned}
& \frac{d}{dt} \int_{\Omega} |\nabla u|^{r+2} + 2d_1 \int_{\Omega} |\nabla(|\nabla u|^{\frac{r+2}{2}})|^2 \\
& \leq \eta_7 \int_{\Omega} |\nabla(|\nabla u|^{\frac{r+2}{2}})|^2 + (r+2)^{4m} \Gamma \left(\left(\int_{\Omega} |\nabla u|^{\frac{r+2}{2}} \right)^2 + 1 \right) \\
& \stackrel{\text{implying}}{\implies} \frac{d}{dt} \int_{\Omega} |\nabla u|^{r+2} + \beta \int_{\Omega} |\nabla u|^{r+2} \leq (r+2)^{4m} \Gamma \left(\left(\int_{\Omega} |\nabla u|^{\frac{r+2}{2}} \right)^2 + 1 \right) \\
& \stackrel{\text{implying}}{\implies} \int_{\Omega} |\nabla u|^{r+2} \leq \int_{\Omega} |\nabla u_0|^{r+2} + (r+2)^{4m} \Gamma \left(\left(\sup_{(0,T)} \int_{\Omega} |\nabla u|^{\frac{r+2}{2}} \right)^2 + 1 \right)
\end{aligned}$$

following from the use of the Poincaré inequality and that $\beta := 2d_1 - \eta_7 > 0$.

Next proceeding as either in proof of Lemma 4.1 or as in proof of Corollary 4.2 yields that $\nabla u \in L^\infty(\Omega \times (0, T))$ is finitely bounded in norm.

To complete the ideas, consider (4.7) in gradient functions and take $p = r+2$ to get that

$$K(r+2) \leq [\Gamma(r+2)^{4m}]^{\frac{1}{r+2}} K\left(\frac{r+2}{2}\right), \forall r \geq 0.$$

Then, let $r_i + 2 = 2^i$, $i \in \mathbb{N}$ to obtain that

$$\begin{aligned}
K(2^i) & \leq \Gamma^{2^{-i}} (2^i)^{4m2^{-i}} K(2^{i-1}) \leq \dots \leq \Gamma^{\sum_{k=1}^i 2^{-k}} (2^i)^{2^{-i}4m} \dots (2)^{2^{-1}4m} K(1) \\
& \leq \Gamma \left[2^{i2^{-i}4m} (2^{-i})^{2^{-i}4m} \right] \dots \left[2^{2^{-1}4m} (2^{-1})^{2^{-1}4m} \right] K(1) \\
& \leq \Gamma 2^{4m \sum_{k=1}^i k 2^{-k}} \times 2^{4m \sum_{k=1}^i 2^{-k}} K(1) \leq C 2^{12m} K(1).
\end{aligned}$$

Thus taking the limit as $i \rightarrow \infty$ yields

$$\|\nabla u\|_{L^\infty(\Omega)} \leq C 2^{12m} K(1) \leq C 2^{12m} \max\{\|\nabla u_0\|_{L^\infty(\Omega)}, \|\nabla u_0\|_{L^1(\Omega)}\} < \infty,$$

and the proof of the lemma is complete. \square

Now we prove (ii) of Corollary 3.7.

Proof. We use a bootstrap argument. By Theorem 3.5 taking into account that the space inclusions (2.5) imply $E^\beta, E^\gamma \subset C(\Omega)$, we get that $u \in C(\Omega \times (0, T))$. Thus, viewing either equations in v or w variables, we get for example that $v_t \in L^\infty(\Omega)$, consequently $g(t) := a_2 u - v_t \in L^p(\Omega)$ for all $p \geq 1$. Thus, $v \in W^{2,p}(\Omega)$ for all $p \geq 1$ and $\nabla v \in W^{1,p}(\Omega)$ for all $p \geq 1$, in particular $\nabla v \in W^{1,p}(\Omega)$ for some $p > N$ yielding $\nabla v \in C^\theta(\Omega)$, for some $\theta > 0$. In fact, if $p < N$, as $\nabla v \in W^{1,p}(\Omega) \subset L^{q_1}(\Omega)$, $q_1 = \frac{pN}{N-p}$ if $p > \frac{N}{2}$ then $q_1 > N$ and the above statements hold. If not we repeat the process, with $W^{1,p}(\Omega) \subset L^{q_2}(\Omega)$, $q_2 = \frac{q_1 N}{N-q_1} = \frac{pN}{N-2p}$ and if $p > \frac{N}{3}$ we are done as $q_2 > N$.

In the otherwise case we repeat the iterative process to find $q_m = \frac{q_{m-1}N}{N-q_{m-1}} = \frac{pN}{N-mp}$ and if $p > \frac{N}{m+1}$ then we are done. Thus in a finite number of steps it is always possible to get $q_m > N$ and the above Hölder smoothness of gradient solutions are obtained.

The next immediate result from Corollary 4.2 is also that $u \in L^\infty(\Omega)$, now if $\nabla u_0 \in L^\infty(\Omega)$, then Lemma 4.3 implies $\nabla u \in L^\infty(\Omega)$. Furthermore, $f(t) = -\operatorname{div}(u\vec{d}(\nabla v, \nabla w)) \in W^{2,p}(\Omega)$ for all $p > 1$. Thus viewing the equation in u as an elliptic problem, we get $\nabla u \in W^{1,p}(\Omega) \subset C^\theta(\Omega)$ for some $\theta > 0$ since in particular using a bootstrap iteration argument as in the above lines $W^{1,p}(\Omega) \subset L^{q_m}(\Omega)$ it is possible to get $q_m > N$ provided $p > \frac{N}{m+1}$. Consequently, $u \in C^{2+\theta}(\Omega)$. Getting back to the v equation, we obtain $g(t) \in C^\theta(\Omega)$ and so $v \in C^{2+\theta}(\Omega)$ for some $\theta > 0$. By similarity, of the equations we also have $w \in C^{2+\theta}(\Omega)$ for some $\theta > 0$. Combining all of the above, we conclude the solution to the problem (1.1)-(1.2) verifies regularity properties given in Corollary 3.7 and is a classical solution. \square

5 Equations in system coupled elliptic differential operator

In this section, we view the problem (1.1)-(1.2) in the form

$$\begin{cases} U_t + \mathcal{A}(t)U &= \vec{0} \\ U(0) &= U_0 \in E^\beta \times E^\gamma \times E^\gamma, \\ 1/2 \leq \beta &\leq \gamma < \beta + 1 \end{cases} \quad (5.1)$$

where $\mathcal{A}(t) = \mathcal{A}(u)$ is the coupled elliptic partial differential operator associated to the problem by passing all terms in the right hand side to the left hand side of the system of equations i.e.

$$\begin{aligned} \mathcal{A}(u) &= \begin{pmatrix} -d_1\Delta & \operatorname{Div}(u\chi_2\nabla\cdot) & -\operatorname{Div}(u\chi_3\nabla\cdot) \\ -a_2 & -d_2\Delta + \lambda_2 & 0 \\ -a_3 & 0 & -d_3\Delta + \lambda_3 \end{pmatrix} \\ &= \begin{pmatrix} -d_1\Delta & 0 & 0 \\ 0 & -d_2\Delta + \lambda_2 & 0 \\ 0 & 0 & -d_3\Delta + \lambda_3 \end{pmatrix} + \begin{pmatrix} 0 & \operatorname{Div}(u\chi_2\nabla\cdot) & -\operatorname{Div}(u\chi_3\nabla\cdot) \\ -a_2 & 0 & 0 \\ -a_3 & 0 & 0 \end{pmatrix} \\ &= \mathcal{A} - P(u). \end{aligned} \quad (5.2)$$

Next if in (5.2) we let the left hand side of the operator be a function of $\Theta \in E^\beta$, and set $U = (u, v, w)^\top$ then

$$\mathcal{A}(\Theta)U = \begin{pmatrix} -d_1\Delta u + \text{Div}(\Theta\chi_2\nabla v) - \text{Div}(\Theta\chi_3\nabla w) \\ -d_2\Delta v + \lambda_2v - a_2u \\ -d_3\Delta w + \lambda_3w - a_3u \end{pmatrix}.$$

Consequently, if we define

$$B : Z_{\beta(\gamma)} \times Z_{\beta(\gamma)} \rightarrow \mathbb{R}, Z_{\beta(\gamma)} := E^\beta \times E^\gamma \times E^\gamma, 2\beta + \gamma \geq 1 + \frac{N}{4} \quad (5.3)$$

by

$$\begin{aligned} B(\Theta; U, V) &:= \langle A(\Theta)U, V \rangle = \langle \mathcal{A}U, V \rangle + \langle P(\Theta)U, V \rangle \\ &= d_1 \int_{\Omega} \nabla u \nabla \phi + d_2 \int_{\Omega} \nabla v \nabla \varphi + d_3 \int_{\Omega} \nabla w \nabla \psi - \chi_2 \int_{\Omega} \Theta \nabla v \nabla \phi + \chi_3 \int_{\Omega} \Theta \nabla w \nabla \phi + \\ &+ \lambda_2 \int_{\Omega} v \varphi + \lambda_3 \int_{\Omega} w \psi - a_2 \int_{\Omega} u \varphi - a_3 \int_{\Omega} u \psi \end{aligned} \quad (5.4)$$

where $V = (\phi, \varphi, \psi)^\top \in Z_{\beta(\gamma)}$, it hence holds the following theorem:

Theorem 5.1. *Let $\Theta \in E^\beta$ be fixed. Then, there exists*

$$\begin{cases} M(\|\Theta\|_\beta) = \max \left\{ d_1\mu_1^{-\frac{1}{2}-\beta}, d_2\mu_1^{-\frac{1}{2}-\gamma} + \lambda_2\mu_1^{-\gamma}, d_3\mu_1^{-\frac{1}{2}-\gamma} + \right. \\ \left. \lambda_3\mu_1^{-\gamma}, \{\chi_2, \chi_3\} \|\Theta\|_\beta \mu_1^{\frac{N}{4}-2\beta-\gamma}, \{a_2, a_3\} \|\Theta\|_\beta \mu_1^{-\beta-\gamma} \right\} > 0, \\ \omega(\|\Theta\|_\beta) = \min \left\{ \{d_1, d_i + \lambda_i\mu_1 : i = 2, 3\} - 2\Lambda_1 \|\Theta\|_\beta \right\} > 0 \end{cases} \quad (5.5)$$

where $\Lambda_1 = \max \left\{ \{\chi_2, \chi_3\} \mu_1^{\frac{N}{4}-2\beta-\gamma}, \{a_2, a_3\} \mu_1^{-\beta-\gamma} \right\} > 0$, and

- (i). $|B(\Theta; U, V)| \leq M(\|\Theta\|_\beta) \|U\|_{\beta(\gamma)} \|V\|_{\beta(\gamma)}$
- (ii). $B(\Theta; U, U) \geq \omega(\|\Theta\|_\beta) \|U\|_{\beta(\gamma)}^2$
- (iii). $\langle \mathcal{A}(\Theta)U - \mathcal{A}(\Theta)V, U - V \rangle > 0, \forall U, V \in Z_{\beta(\gamma)}$.

Moreover, for fixed $(U, F) \in Z_{\beta(\gamma)} \times [Z_{\beta(\gamma)}]^*$ arbitrary and if considered (5.4) for any $V \in Z_{\beta(\gamma)}$ then,

- (iv). $\mathcal{A}(\Theta)U = F \in [Z_{\beta(\gamma)}]^*$ has one and only one solution $U = T_F(\Theta) \in Z_{\beta(\gamma)}$.
- (v). $\mathcal{A}(\Theta)U$ depends continuously on Θ for each $U \in Z_{\beta(\gamma)}$ fixed.
- (vi). $T_F(\cdot) \in \mathcal{L}(Z_{\beta(\gamma)})$ is well-posed and $U = T_F(u)$ is a unique solution of $\mathcal{A}(u)U = F \in [Z_{\beta(\gamma)}]^*$.
- (vii). $T_F(\cdot) \in \mathcal{K}([Z_{\beta(\gamma)}]^*, Z_{\beta(\gamma)})$ is a compact operator.

Proof. First we notice that for any $\beta, \gamma \geq 1/2$, by Sobolev type space embeddings [2, 9, 24, 28, 29] i.e. (2.4) the mapping

$$(U, V) \ni Z_{\beta(\gamma)} \times Z_{\beta(\gamma)} \rightarrow \langle \mathcal{A}U, V \rangle \in L^1(\Omega) \quad (5.6)$$

is well defined and continuous. In fact, it holds that

$$\begin{aligned}
|\langle \mathcal{A}U, V \rangle| &\leq d_1 \|\nabla u\|_{L^1(\Omega)} \|\nabla \phi\|_{L^1(\Omega)} + d_2 \|\nabla v\|_{L^2(\Omega)} \|\nabla \phi\|_{L^2(\Omega)} + d_3 \|\nabla w\|_{L^2(\Omega)} \|\psi\|_{L^2(\Omega)} + \\
&\quad + \lambda_2 \|v\|_{L^3(\Omega)} \|\phi\|_{L^3(\Omega)} + \lambda_3 \|w\|_{L^3(\Omega)} \|\psi\|_{L^3(\Omega)} \\
&\leq d_1 \mu_1^{\frac{1}{2}-\beta} \|u\|_{\beta-\frac{1}{2}} \|\phi\|_{\beta-\frac{1}{2}} + d_2 \mu_1^{\frac{1}{2}-\gamma} \|v\|_{\gamma-\frac{1}{2}} \|\phi\|_{\gamma-\frac{1}{2}} + d_3 \mu_1^{\frac{1}{2}-\gamma} \|w\|_{\gamma-\frac{1}{2}} \|\psi\|_{\gamma-\frac{1}{2}} \\
&\quad + \lambda_2 \mu_1^{-\gamma} \|v\|_{\gamma} \|\phi\|_{\gamma} + \lambda_3 \mu_1^{-\gamma} \|w\|_{\gamma} \|\psi\|_{\gamma} \\
&\leq d_1 \mu_1^{-\frac{1}{2}-\beta} \|u\|_{\beta} \|\phi\|_{\beta} + d_2 \mu_1^{-\frac{1}{2}-\gamma} \|v\|_{\gamma} \|\phi\|_{\gamma} + d_3 \mu_1^{-\frac{1}{2}-\gamma} \|w\|_{\gamma} \|\psi\|_{\gamma} \\
&\quad + \lambda_2 \mu_1^{-\gamma} \|v\|_{\gamma} \|\phi\|_{\gamma} + \lambda_3 \mu_1^{-\gamma} \|w\|_{\gamma} \|\psi\|_{\gamma} \\
&\leq \max \left\{ d_1 \mu_1^{-\frac{1}{2}-\beta}, d_2 \mu_1^{-\frac{1}{2}-\gamma}, \lambda_2 \mu_1^{-\gamma}, d_3 \mu_1^{-\frac{1}{2}-\gamma}, \lambda_3 \mu_1^{-\gamma} \right\} \times \\
&\quad \times \left(\|u\|_{\beta} \|\phi\|_{\beta} + \|v\|_{\gamma} \|\phi\|_{\gamma} + \|w\|_{\gamma} \|\psi\|_{\gamma} \right) \leq \Lambda_0 \|U\|_{\beta(\gamma)} \|V\|_{\beta(\gamma)}, \tag{5.7}
\end{aligned}$$

where $\Lambda_0 \in \mathbb{R}^+ \setminus \{0\}$ is the value expressed in the max argument, and since the norm of $\|W\|_{\beta(\gamma)}$ is greater than or equal to the partial summed norms of elements constituting the product space sum of norms.

Also we have for any $\Theta \in E^{\beta}$, that the mapping

$$(U, V) \ni Z_{\beta(\gamma)} \times Z_{\beta(\gamma)} \rightarrow \langle P(\Theta)U, V \rangle \in L^1(\Omega) \tag{5.8}$$

is well defined and continuous provided $2\beta + \gamma \geq 1 + \frac{N}{4}$ again by Sobolev type space embeddings (2.4). Note that this implies from (5.6) that if $\beta = \gamma = 1/2$ then (5.8) holds only in $N \leq 2$. Now proceeding as above we have that

$$\begin{aligned}
|\langle P(\Theta)U, V \rangle| &\leq \chi_2 |\langle \Theta \nabla v, \nabla \phi \rangle| + |\chi_3| |\langle \Theta \nabla w, \nabla \phi \rangle| + a_2 |\langle u, \phi \rangle| + a_3 |\langle u, \psi \rangle| \\
&\leq \chi_2 \|\Theta\|_{L^4(\Omega)} \|\nabla v\|_{L^2(\Omega)} \|\nabla \phi\|_{L^1(\Omega)} + |\chi_3| \|\Theta\|_{L^4(\Omega)} \|\nabla w\|_{L^2(\Omega)} \|\nabla \phi\|_{L^1(\Omega)} + \\
&\quad + a_2 \|u\|_{L^5(\Omega)} \|\phi\|_{L^3(\Omega)} + a_3 \|u\|_{L^5(\Omega)} \|\psi\|_{L^3(\Omega)} \\
&\leq \chi_2 \mu_1^{\frac{N}{4}+1-2\beta-\gamma} \|\Theta\|_{\beta} \|v\|_{\gamma-\frac{1}{2}} \|\phi\|_{\beta-\frac{1}{2}} + \chi_3 \mu_1^{\frac{N}{4}+1-2\beta-\gamma} \|\Theta\|_{\beta} \|w\|_{\gamma-\frac{1}{2}} \|\phi\|_{\beta-\frac{1}{2}} + \\
&\quad + a_2 \mu_1^{-\beta-\gamma} \|u\|_{\beta} \|\phi\|_{\gamma} + a_3 \mu_1^{-\beta-\gamma} \|u\|_{\beta} \|\psi\|_{\gamma}. \tag{5.9}
\end{aligned}$$

Consequently,

$$\begin{aligned}
|\langle P(\Theta)U, V \rangle| &\leq \chi_2 \mu_1^{\frac{N}{4}-2\beta-\gamma} \|\Theta\|_{\beta} \|v\|_{\gamma} \|\phi\|_{\beta} + |\chi_3| \mu_1^{\frac{N}{4}-2\beta-\gamma} \|\Theta\|_{\beta} \|w\|_{\gamma} \|\phi\|_{\beta} + \\
&\quad + a_2 \mu_1^{-\beta-\gamma} \|u\|_{\beta} \|\phi\|_{\gamma} + a_3 \mu_1^{-\beta-\gamma} \|u\|_{\beta} \|\psi\|_{\gamma}.
\end{aligned}$$

Next if we set

$$\Lambda_1 = \max \left\{ \{\chi_2, \chi_3\} \mu_1^{\frac{N}{4}-2\beta-\gamma}, \{a_2, a_3\} \mu_1^{-\beta-\gamma} \right\},$$

then

$$\begin{aligned}
|\langle P(\Theta)U, V \rangle| &\leq \Lambda_1 \|\Theta\|_{\beta} \left(\|v\|_{\gamma} + \|w\|_{\gamma} \right) \|\phi\|_{\beta} + \left(\|\phi\|_{\gamma} + \|\psi\|_{\gamma} \right) \|u\|_{\beta} \\
&\leq \Lambda_1 \|\Theta\|_{\beta} \left(\|u\|_{\beta} + \|v\|_{\gamma} + \|w\|_{\gamma} \right) \|V\|_{\beta(\gamma)} + \|V\|_{\beta(\gamma)} \|u\|_{\beta} \\
&\leq \Lambda_1 \|\Theta\|_{\beta} \left(\|u\|_{\beta} + \|v\|_{\gamma} + \|w\|_{\gamma} \right) \|V\|_{\beta(\gamma)} + \|V\|_{Z_{\beta(\gamma)}} \|U\|_{\beta(\gamma)} \\
&\leq 2\Lambda_1 \|\Theta\|_{\beta} \|U\|_{\beta(\gamma)} \|V\|_{\beta(\gamma)}. \tag{5.10}
\end{aligned}$$

Combining, this with the estimate from above in (5.7) taking $M := \max\{\Lambda_0, 2\Lambda_1\} \in \mathbb{R}^+ \setminus \{0\}$ we conclude we have proved that (i) holds.

First observing that $Z_{\beta(\gamma)}$ is endowed with the norm $\langle (u, v, w)^\top, (u, v, w)^\top \rangle_{\beta(\gamma)} = \|u\|_\beta^2 + \|v\|_\gamma^2 + \|w\|_\gamma^2$, if we take in (5.3) the scalar product $V = U \in Z_{\beta(\gamma)}$, we get from (5.10) that

$$\begin{aligned} B(\Theta; U, U) &\geq d_1 \|u\|_{\beta-\frac{1}{2}}^2 + d_2 d_3 \left(d_3^{-1} \|v\|_{\gamma-\frac{1}{2}}^2 + d_2^{-1} \|w\|_{\gamma-\frac{1}{2}}^2 \right) + \lambda_2 \mu_1 \|v\|_{\gamma-\frac{1}{2}}^2 \\ &\quad + \lambda_3 \mu_1 \|w\|_{\gamma-\frac{1}{2}}^2 - 2\Lambda_1 \|\Theta\|_\beta \|U\|_{\beta(\gamma)-\frac{1}{2}}^2 \\ &\geq \min\{d_1, d_i + \lambda_i \mu_1 : i = 2, 3\} - 2\Lambda_1 \|\Theta\|_\beta \Big\} \|U\|_{\beta(\gamma)-\frac{1}{2}}^2 \\ &= \omega(\|\Theta\|_\beta) \|U\|_{\beta(\gamma)-\frac{1}{2}}^2, \end{aligned}$$

since $u \in E^\beta \subset E^{\beta-\frac{1}{2}}$, $v, w \in E^\gamma \subset E^{\gamma-\frac{1}{2}}$ using the inclusions (2.4) and (ii) is verified, taking $V = U \in Z_{\beta(\gamma)+1/2}$. From, (ii) if $U \neq V$ it also follows the conclusion (iii) of the theorem. To obtain (iv), it suffices to notice from (i) – (ii) that for each $\Theta \in E^\beta$ fixed, (5.3) defines an isomorphism

$$\mathcal{A}(\Theta)U := B(\Theta; U, \cdot) \in Z_{\beta(\gamma)}^* \text{ for any } U \in Z_{\beta(\gamma)} \text{ by } \langle \mathcal{A}(\Theta)U, V \rangle = \langle F, V \rangle, \quad \forall V \in Z_{\beta(\gamma)},$$

and $F \in Z_{\beta(\gamma)}^*$. This proves (iv) with uniqueness of the solutions being given by (ii).

Also we get using (5.10) that (v) is proved for any two $\Theta_1, \neq \Theta_2 \in Z_{\beta(\gamma)}$ and $U \in Z_{\beta(\gamma)}$ fixed. To prove (vi) we observe that the mapping $F \ni Z_{\beta(\gamma)}^* \rightarrow U \in Z_{\beta(\gamma)}$ by (ii) is continuous. It is also compact since the space inclusions $Z_{\beta(\gamma)} \subset Z_{\beta(\gamma)}^*$ are compact, this proves (vii). Thus, the mapping $F \ni Z_{\beta(\gamma)} \rightarrow T_F(\cdot) = \mathcal{A}^{-1}(\cdot)F \in \mathcal{L}(Z_{\beta(\gamma)})$ and the problem $U = T_F(u) = \mathcal{A}^{-1}(u)U$ by Schauder -Tychonoff theorem (see [5, 4] pp.179, pp.120 respectively) has a unique fixed point $U \in Z_{\beta(\gamma)}$. The rest is trivial, and the proof of the theorem is complete. \square

If in what follows, we let $D(\mathcal{A}(t)) = Z_{\beta(\gamma)+1/2} := E^{\beta+\frac{1}{2}} \times E^{\gamma+\frac{1}{2}} \times E^{\gamma+\frac{1}{2}}$. Then, operator $\mathcal{A}(t) : Z_{\beta(\gamma)+1/2} \subset Z_{\beta(\gamma)} \rightarrow Z_{\beta(\gamma)}^* \subset E^{-1/2} \times E^{-1/2} \times E^{-1/2}$ is closed and densely defined. Also by Theorem 5.1 for each $t \in \mathbb{R}^+$, the resolvent operator

$$R(\mathcal{A}(t), \kappa) = (\mathcal{A}(t) - \kappa I)^{-1} : Z_{\beta(\gamma)}^* \rightarrow Z_{\beta(\gamma)}$$

exists for any $\kappa \in \mathbb{C}$, with $\mathcal{R}e(\kappa) \leq 0$ such that

$$\|R(\mathcal{A}(t), \kappa)\|_{\mathcal{L}(Z_{\beta(\gamma)}^*, Z_{\beta(\gamma)})} \leq \frac{C}{|\kappa| + 1}.$$

Furthermore, by Theorem 3.5 Hölder continuity of the solution for any $0 \leq s \leq \tau \leq t < \infty$ we have that

$$\|[\mathcal{A}(t) - \mathcal{A}(s)]\mathcal{A}^{-1}(\tau)\|_{\mathcal{L}(Z_{\beta(\gamma)}, Z_{\beta(\gamma)}^*)} \leq C(t-s)^\theta \quad (5.11)$$

for $\theta \in (0, 1)$. Consequently, by [2, 6, 7, 12, 9, 24, 28], we obtain that (1.2) is an infinitesimal generator of a fundamental solution operator $\{G(t, s) : t > s\} : Z_{\alpha_0} \rightarrow Z_{\alpha_1}$ satisfying the following:

Lemma 5.2. *Let $J_s := (s, T)$, $s \geq 0$. Then, $G(t, s) \in \mathcal{L}(Z_{\alpha_0}, Z_{\alpha_1})$ uniformly for any $t \in J_s$ verifies that*

$$\|G(t, s)\|_{\alpha_0, \alpha_1} \leq c(\alpha_0, \alpha_1) e^{-\omega(t-s)} (t-s)^{\alpha_0 - \alpha_1} \quad \text{and} \quad G(\cdot, s) \in C^{\beta-\alpha}(J_s, \mathcal{L}(Z_{\alpha_1}, Z_{\alpha_0}))$$

whenever $-1 \leq \alpha_0 \leq \alpha_1 \leq 1$ where $\omega \in \mathbb{R}^+ \setminus \{0\}$ and if

$$U_t + \mathcal{A}(t)U = \vec{0}, \text{ in } J_s, U(s) = U_s \in Z_{\alpha_0} \quad (5.12)$$

then,

$$U(t, s, U_s) = G(t, s)U_s \in C^1(J_s, Z_{\alpha_0}) \cap C^{\alpha_1 - \alpha_0}(J_s, Z_{\alpha_1})$$

is a unique solution of (5.12).

Moreover, if $U_s \in Y$ where either $Y = Z_{\alpha_0}^*$, or $[L^r(\Omega)]^3$ it holds that

$$\|G(t, s)U_s\|_Y \begin{cases} \leq C \frac{e^{-\omega(t-s)}}{(t-s)} \|U_s\|_{Z_{\alpha_0}^*}, & t > s \\ \leq C \frac{e^{-\omega(t-s)}}{(t-s)^{\frac{N}{2}(\frac{1}{q} - \frac{1}{r})}} \|U_s\|_{L^q(\Omega)}, & t > s \end{cases} \quad (5.13)$$

within last estimates $Y = L^r(\Omega)$ following a bootstrap argument for any $1 \leq q \leq r \leq \infty$ and the evolution operator is in $L^q(\Omega)$ for any $1 < q < \infty$.

Remark 5.3. It is not difficult to see that the coupled system of equations (5.1)-(5.2) with initial data $(u_0, v_0, w_0) \in W^{1,p}(\Omega) \times H^1(\Omega) \times H^1(\Omega)$, $p > N$ will be well-posed in a sense similar to Lemma 5.2. Also the long time dynamics of the problem are captured by the set (2.12) given for all this section we assuming that the functions are orthogonal to constant functions and there is decay following the given lemma to null solutions as $t \nearrow +\infty$.

6 A much simplified model of coupled system equations

We conclude this analysis sections by considering a much simplefied system of equations of (1.1)-(1.2), which in view of results of Section 4 is realistic i.e.

$$\left\{ \begin{array}{l} \frac{\partial u}{\partial t} - d_1 \Delta u + \chi_2 \Delta v - \chi_3 \Delta w = 0 \quad \text{in } \Omega \times (0, T) \\ \frac{\partial v}{\partial t} - d_2 \Delta v + \lambda_2 v = a_2 u \quad \text{in } \Omega \times (0, T) \\ \frac{\partial w}{\partial t} - d_3 \Delta w + \lambda_3 w = a_3 u \quad \text{in } \Omega \times (0, T) \\ d_1 \frac{\partial u}{\partial \vec{n}} = d_2 \frac{\partial v}{\partial \vec{n}} = d_3 \frac{\partial w}{\partial \vec{n}} = 0 \quad \text{on } \Gamma \times (0, T) \\ u(0) = u_0, v(0) = v_0, w(0) = w_0 \quad \text{in } \Omega, \end{array} \right. \quad (6.1)$$

where $D_i, \lambda_j, \chi_j = \chi_j(\|u\|_\infty) \in \mathbb{R}^+ \setminus \{0\}$ for $i = 1, 2, 3 = j \neq 1$. Corresponding to the homogeneous system of equations of (6.1) is the matrix

$$\mathcal{A} = \begin{pmatrix} -d_1 \Delta & \chi_2 \Delta & -\chi_3 \Delta \\ -a_2 & -d_2 \Delta + \lambda_2 & 0 \\ -a_3 & 0 & -d_3 \Delta + \lambda_3 \end{pmatrix} \quad (6.2)$$

of which it is not difficult to find more precise conditions for its well-posedness of (5.3)-(5.4) with no restrictive assumption on taking $\beta = \gamma = 1/2$ and $\Theta = 1$ in Theorem 5.1 in nature of (i)–(ii). As clearly, in this case the bilinear form (5.3)-(5.4) is symmetrical, Lax-Milgram's theorem [5, 14, 40], implies \mathcal{A} is a maximal monotone, self-adjoint operator with compact resolvent in $L^2(\Omega)$ and by [9] is a sectorial operator also in $L^2(\Omega)$. Furthermore, the spectrum of (6.2), using [5, 14, 40] can be characterized by real numbers in \mathbb{R} as

$$\sigma(\mathcal{A}) = \{\mu_n; n \in \mathbb{N}^* : 0 < \mu_{n-1} \leq \mu_n \nearrow \infty \text{ as } n \nearrow \infty, \forall n \geq 2\}$$

and we can choose associated eigenfunctions $\Psi_n \in H^1(\Omega)$ orthonormal in and to constitute a basis for the space $L^2(\Omega)$. Since the scales of Hilbert spaces $E^\alpha, \alpha \in \mathbb{R}$ associated with the operator (6.2) are well defined, $-\mathcal{A}$ is an infinitesimal generator of an analytic semigroup as in (2.9) satisfying in operator norm estimates similar to ones given in (2.10)-(2.11). In conclusion, for any initial data in $E^\alpha, \alpha \in \mathbb{R}$ we can solve the coupled systems of equations (6.1) for values in E^β and by (2.11) the long time asymptotic dynamics are determined by the set (2.12) as solutions orthogonal to constant functions will decay to the null state. Lastly, we remark that (6.1) considered in the context of Sections 3 and 4 is much easier to treat directly from the $H^1(\Omega)$ functional setting.

7 Numerical simulation

To visualize the aggregation of microglia as in the model equations, we numerically simulate the equations using a Gradient Weighted Moving Finite Element method.

Gradient Weighted Moving Finite Element methods (GWMFE) are numerical moving mesh methods which are designed for tracking moving shocks and complex structures with a fixed number of mesh nodes. These methods are well suited to modelling aggregation of microglial cells, where the cells aggregate into sharp peaks which need to be resolved. For details of the generalized SGiteWS2. Also see [38] for a comparison of SGWMFE and a Parabolic Moving Mesh Partial Differential Equation method, for solutions of Partial Differential Equations.

In [39] the authors extend the String Gradient Weighted Moving Finite Element (SGWMFE) method in order to include the non-linear diffusion of different variables, necessary for the chemo-attraction-repulsion model equations. For the simulations shown in this paper we use the code developed in [39] using a set of model parameters found in [16].

7.1 Parameter values

The parameter values used in the numerical simulations are calculated from [16], where the parameters used there are calculated from dimensional values found in Biology, Immunology and Neuroscience publications referenced therein. From the set of data found in [16] the corresponding parameter values chosen for the simulations in this paper are summarized in Tables 1 and 2.

The equations are defined on a real and bounded domain Ω , where the boundary is denoted by Γ . Our numerical domain is a two dimensional square of length and width 10. The boundary conditions which hold are zero flux through the boundary Γ . No proliferation or death of microglial cells is considered in this model.

Table 1. Biological parameters from [16], found in literature or calculated therein.

Parameter	Description	Value
μ	Microglia random motility	$33 \frac{\mu \text{ m}^2}{\text{min}}$
$\tilde{\chi}_1$	Chemoattraction	$6 - 780 \frac{\mu \text{ m}^2}{nM \cdot \text{min}}$
$\tilde{\chi}_2$	Chemorepulsion	Not available
D_1	IL- 1β diffusion	$900 \frac{\mu \text{ m}^2}{\text{min}}$
D_2	TNF- α diffusion	$900 \frac{\mu \text{ m}^2}{\text{min}}$
\tilde{a}_1	IL- 1β production rate per microglia cell	$6.25 \times 10^{-6} \frac{\text{pg}}{\text{min}}$
\tilde{a}_2	TNF- α production rate per microglia cell	$8.33 \times 10^{-6} \frac{\text{pg}}{\text{min}}$
b_1	IL- 1β decay rate	$0.003 - 0.03 \text{min}^{-1}$
b_2	TNF- α decay rate	$0.002 - 0.03 \text{min}^{-1}$
L_1	Spatial range for chemoattraction	$\sqrt{D_1/b_1}$
L_2	Spatial range for chemorepulsion	$\sqrt{D_2/b_2}$
\bar{m}	Average microglial cell density	$10^{-6} - 10^{-4} \frac{\text{cells}}{\mu \text{ m}^3}$

The contour plots for the three unknown variables are shown in Fig 1. The corresponding evolving meshes are shown in Fig 2 where we also show a slice of the solutions, where the slice is taken along $y = 7$ of the computational domain.

Summarizing the relation between the non-dimensional variables used in the model equations in this paper and the dimensional variables (as derived from [16]): the characteristic cell density used is the average cell density \bar{m} . One can calculate the dimensional variable for density, from the non-dimensional density u as $u_{dim} = \bar{m}u$. The average chemical concentrations at which production and decay balance, form the characteristic scales for chemical concentrations $\hat{v} = a_1\bar{m}/b_1$ and $\hat{w} = a_2\bar{m}/b_2$. In order to obtain the dimensional chemical concentrations one can then calculate $v_{dim} = \hat{v}v$ and $w_{dim} = \hat{w}w$.

L_2 is close in value to L_1 , and so L_2 is taken as the characteristic length scale of the problem, with $L_2 = \sqrt{900/0.01} = 300\mu \text{ m}$. This value corresponds to the distance over which chemicals spread during the characteristic time of decay. The 10 by 10 non-dimensional domain used for the simulations corresponds to a physical domain of length and width equal to $3,000\mu \text{ m}$.

The characteristic time scale for the problem is $\hat{t} = L_2^2/\mu$, which is the time needed for a cell to move over one unit of the characteristic length scale L_2 [16]. Then in order to calculate the dimensional time t_{dim} , from the non-dimensional time t found in the equations

Table 2. Model parameter values in relation to biological parameters from Table 1.

Dimensionless variable	Expression in terms of variables in Table 1	Variable values from data Set 3, Table 10 in [16]
χ_2	$\frac{\chi_1 \bar{a}_1 \bar{m}}{\mu b_1}$	37.14
χ_3	$\frac{\chi_2 \bar{a}_2 \bar{m}}{\mu b_2}$	27
ϵ_1	$\frac{\mu}{D_1}$	0.0367
ϵ_2	$\frac{\mu}{D_2}$	0.0367
a	$\frac{L_2}{L_1}$	1.1
a_2	$\frac{a^2}{\epsilon_1}$	32.970027248
a_3	$\frac{1}{\epsilon_2}$	27.2479564033
d_2	$\frac{1}{\epsilon_1}$	27.2479564033
d_3	$\frac{1}{\epsilon_2}$	27.2479564033
λ_2	$\frac{a^2}{\epsilon_1}$	32.970027248
λ_3	$\frac{1}{\epsilon_2}$	27.2479564033

of the model, we calculate $t_{dim} = \hat{t}t$. In the simulations shown in this paper, we compute up to a non-dimensional time $t = 0.8$, which corresponds to a dimensional time of

$$t_{dim} = ((300\mu\text{ m})^2 \text{min}/33\mu\text{ m}^2) \times 0.8 = (2.727 \times 10^3 \text{min}) \times 0.8 \approx 1.5 \text{days}$$

i.e. one and a half days.

8 Discussion of results

Fig 1 shows the contour plots of the microglia, attractant and repellent solutions to the equations in system 1.1, at five different times, $t = 0$, $t = 0.2$, $t = 0.4$, $t = 0.6$ and $t = 0.8$. As in the one dimensional results found in [16], we see similar behaviour in that small initial perturbations increase in amplitude and decrease in spatial frequency, so that a few peaks evolve in each of the solutions. We observe that the microglial cells merge locally due to the attractant and form sharp peaks. This feature can also be observed in the slice plot in Fig 2.

The numerical solutions, resulting from the application of SGWMFE, shown in Fig 1, mimic the behavior of microglia observed in both in *vitro* and in *vivo* experiments, specifically the migration in response to chemoattraction.

We show numerical simulations up to a time $t=0.8$, corresponding to a dimensional time computation of 36hrs. This time frame is of interest because studying the early changes in the Alzheimer's disease affected brain is critical, especially given the prospect of new disease-modifying drugs. It should be noted that this time frame is believed to be sufficient to induce early Alzheimer's disease pathology in experimental models, as is recently shown in the development of AD-like pathology at 24hrs in a novel model for sporadic Alzheimer's disease [13].

Fig. 1 below is of contour plots of the numerical solutions of the model equations (1.1)-(1.2) solved with SGWMFE using a mesh of 21 by 21 nodes. At time $t = 0$ the cells and concentrations of attractant and repellent are initialized randomly in the interval (0.998, 1.002).

Fig.2 following after Fig 1 is of mesh plots from (a) to (e) and of slice plots from (f) to (j) corresponding to the numerical solutions in Fig 1. The slice is taken along the line $y = 7$ of the computational domain. The microglia, attractant and repellent are represented by the starred line, the solid line and the dash- dot line respectively.

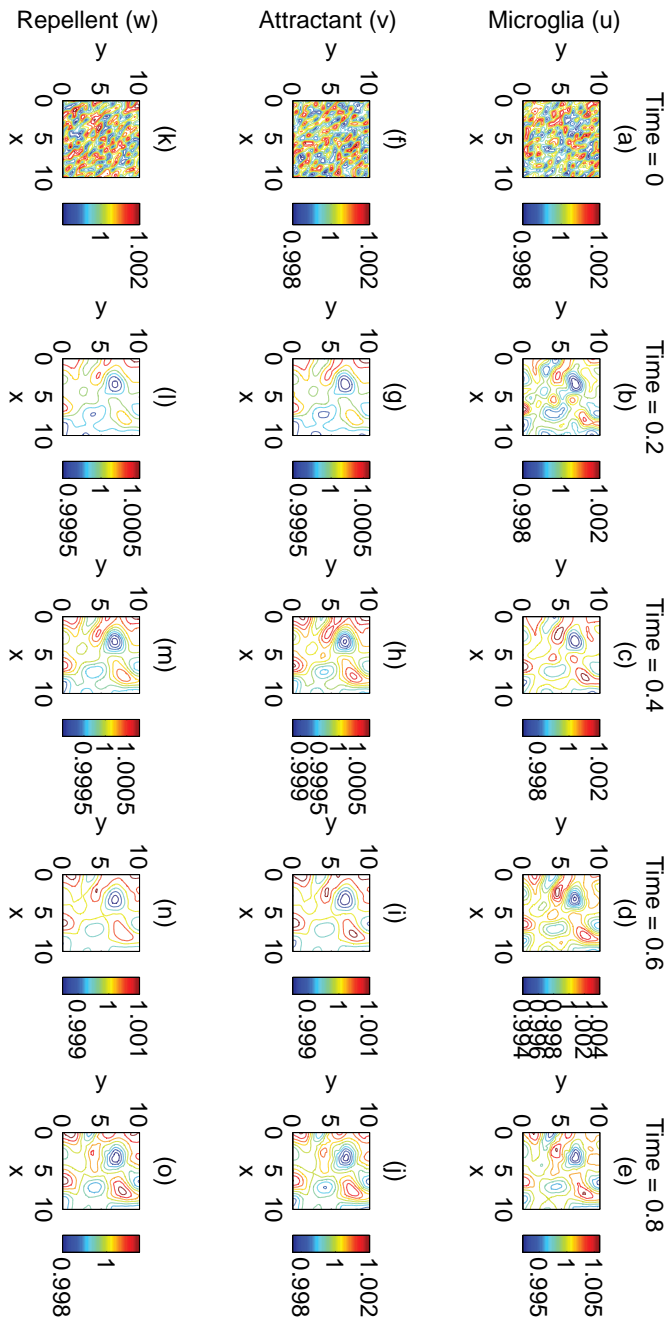


Figure 1. Contour plots.

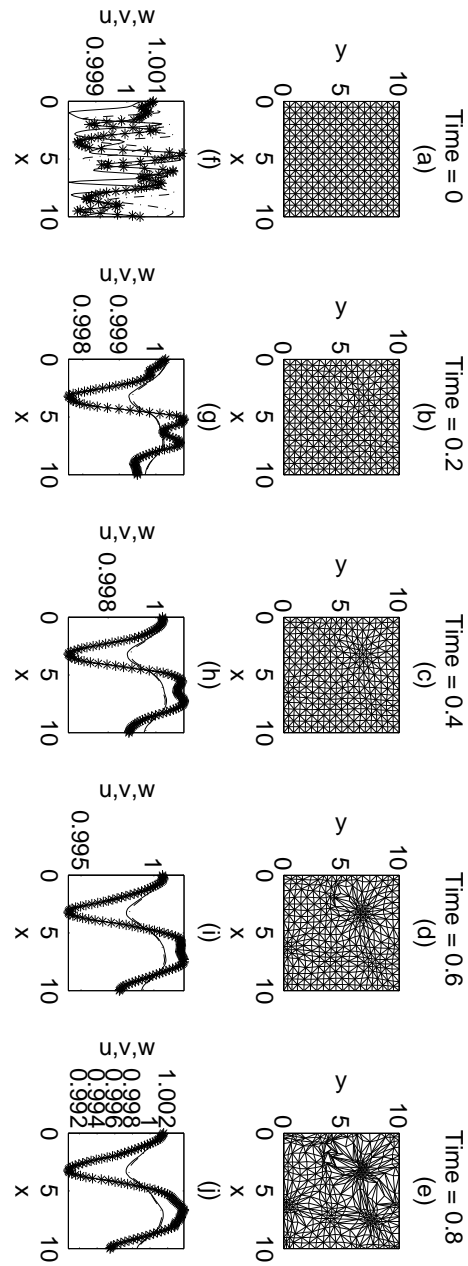


Figure 2. Mesh and slice plots.

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