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A dual-gradient chemotaxis system modeling the spontaneous aggregation of microglia in Alzheimer's disease

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In this paper, we consider the following dual-gradient chemotaxis model

$$\begin{cases} u_t = \Delta u - \nabla \cdot (\chi u \nabla v) + \nabla \cdot (\xi f(u) \nabla w), & x \in \Omega, t > 0, \\ \tau_1 v_t = \Delta v + \alpha u - \beta v, & x \in \Omega, t > 0, \\ \tau_2 w_t = \Delta w + \gamma u - \delta w, & x \in \Omega, t > 0, \end{cases}$$

with $f(u) = u^m$ for $m \geq 1$ and $f(u) = u(u+1)^{m-1}$ for $0 < m < 1$, where Ω is a bounded domain in $\mathbb{R}^n (n \geq 2)$ with smooth boundary, $m > 0, \chi \geq 0, \xi > 0, \alpha, \beta, \gamma, \delta > 0$ and $\tau_1, \tau_2 \in \{0, 1\}$. The model was proposed to interpret the spontaneous aggregation of microglia in Alzheimer's disease due to the interaction of attractive and repulsive chemicals released by the microglia. It has been shown in the literature that, when $m = 1$, the solution of the model with homogeneous Neumann boundary conditions either blows up or asymptotically decays to a constant in multi-dimensions depending on the sign of $\theta = \chi\alpha - \xi\gamma$, which means there is no pattern formation. In this paper, we shall show as $m > 1$, the uniformly-in-time bounded global classical solutions exist in multi-dimensions and hence pattern formation can develop. This is significantly different from the results for the case $m = 1$. We perform the numerical simulations to illustrate the various patterns generated by the model, verify our analytical results and predict some unsolved questions. Biological applications of our results are discussed and open problems are presented.

Keywords: Dual-gradient; spontaneous aggregation; chemotaxis; attraction–repulsion; boundedness; higher dimensions; pattern formation.

Mathematics Subject Classification 2010: 35A01, 35B40, 35B44, 35K57, 35Q92, 92C17

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1. Introduction and Main Results

Alzheimer's disease (AD) is a devastating neurodegenerative disease characterized by the presence of numerous senile plaques in the brain tissue [41], whose major components are extracellular deposits of β-amyloid protein that build up in the spaces between nerve cells. It was found in the brains of patients with AD that activated microglia, which are the most abundant of the resident macrophage populations in the central nerve system [39], are associated with β-amyloid deposit and concentrated in regions of compact amyloid deposit, where they surround and infiltrate into the β-amyloid plaques [37]. When activated from resting state upon environment stimulation (like injury, infection and inflammation of the nervous system), microglia will secrete proteases, cytokines, and reactive oxygen species which cause the production of β-amyloid and encourage the aggregation of β-amyloid [37]. The growing size of these plaques in turn triggers the action of even more microglia, which then secrete more cytokines, proteases, and oxygen species, thus amplifying the neurodegeneration [22].

Despite enormous efforts and progress made in the past, the mechanism of pathogenesis of AD still remains poorly understood. While conventional experimental approaches have been unable to identify critical underlying causes for AD due to its highly complex and dynamic interactions occurring among multiple cell types throughout the aging process, mathematical models can serve as powerful tools to help understand the molecular and cellular processes regulating complex diseases [6]. Indeed, there have been a few mathematical approaches to model the formation of senile plaques (marker of AD) such as PDE approach in [7] and kinetic method in [24, 26], and the intertwined cross-talks among microglia, astroglia and neurons by ODE approach in [40]. Recently, an integral–differential model describing the progression of AD with focus on the role of prions in memory impairment was proposed and analyzed in [10].

While the cause of Alzheimer's disease is incompletely known to date, it has been widely accepted that microglial activation has a central role in the formation of β-amyloid plaques [7, 9, 39]. Among other things, this paper will be devoted to understanding the dynamics of microglia whose density in the brains of patients with AD has been found to be much higher than those in the brains of healthy individuals [16]. Particularly, microglia density distribution of the midbrain substantia nigra compacta is uneven and significantly higher than other regions [21]. Since microglia cells are strongly associated with β-amyloid deposit in the central nerve system as mentioned above, understanding the mechanism of aggregates of microglia will be an essential step to untangle the pathogenesis of AD. It is generally believed that high density of microglia results from spontaneous aggregation rather than proliferation [30]. One hypothesis is that chemicals (cytokines) secreted by microglia including chemoattractant (i.e. Interleukin-1β protein) and chemorepellent (i.e. tumor necrosis factor-α) might interact to produce the localized aggregates of microglia. Hence a key question is what type of interactions between microglia and their secreted chemical factors would lead to localized aggregates of microglia. Our present work will be concentrated on this question and explore the possible mechanism leading to aggregates of microglia as a result of the combined interaction of attraction and repulsion with microglia.

Toward the question raised above, Luca, Chavez-Ross, Edelstein-Keshet and Mogilner proposed the following dual-gradient system in [30]:

$$\begin{cases} u_t = \Delta u - \nabla \cdot (\chi u \nabla v) + \nabla \cdot (\xi u \nabla w), \\ \tau_1 v_t = \Delta v + \alpha u - \beta v, \\ \tau_2 w_t = \Delta w + \gamma u - \delta w, \end{cases} \tag{1.1}$$

where u denotes the density of microglia, v denotes the concentration of chemoattractant (like Interleukin-1β) and w accounts for the concentration of chemorepellent (like Tumor necrosis factor-α); $\chi \geq 0$ and $\xi \geq 0$ are chemotactic coefficients measuring the strength of attraction and repulsion, respectively. α/γ and β/δ are positive constants denoting production and degradation rates of chemoattractant/chemorepellent, respectively. Here, $\tau_1, \tau_2 \geq 0$ are nonnegative scaling constants (see more details in [30]).

The main goal of proposing the model (1.1) in [30] is to examine whether the combined chemicals (chemoattractant and chemorepellent) may interact to produce aggregates of microglia. Linear stability analysis was performed in [30] to identify the parameter regime for the local instability of constant steady states of (1.1) in an interval with Neumann boundary conditions, where numerical simulations of the model shows the possible periodic patterns. Later the existence of periodic solutions in one dimension was rigorously proved using Hopf bifurcation theorems in [29] by Liu, Shi and the second author. However, these analytical and numerical results are inadequate to support the model to interpret the aggregation of microglia in Alzheimer's disease. Deeper and more exhaustive analysis, particularly in the physical two or three dimensions, is highly desired. Recently, Tao and the second author made a comprehensive investigation for the model (1.1) in a bounded domain with homogeneous Neumann boundary condition in [45] and first found that the solution behavior of (1.1) essentially depends on the sign of parameter $\theta := \chi\alpha - \xi\gamma$, which interprets the competing effect between attraction and repulsion as follows:

- $\theta < 0 \Leftrightarrow$ repulsion dominates;
- $\theta = 0 \Leftrightarrow$ repulsion cancels attraction;
- $\theta > 0 \Leftrightarrow$ attraction dominates.

The analysis in [45] reveals that the mathematical techniques used for the case $\beta = \delta$ and $\beta \neq \delta$ are very different. Since then a series of works have been developed further for the model (1.1) in a bounded domain with homogeneous Neumann boundary conditions which will be assumed in the sequel without mention anymore. We outline the existing results briefly in the following. For the case $\beta = \delta$, the results of [45] asserted that: (1) if $\theta \leq 0$, then the model (1.1) with $\tau_1 = \tau_2 = 0$ has a unique global classical solution which converges to a unique constant steady state asymptotically in two or higher dimensions. The same result holds for $\tau_1 = \tau_2 = 1$ in two dimensions; (2) if $\theta > 0$, then there exists a threshold number $\sigma = \frac{8\pi}{\theta}$ such that the solution of (1.1) with $\tau_1 = \tau_2 = 0$ or $\tau_1 = \tau_2 = 1$ may blow-up (or globally exists) in two dimensions if initial cell mass is larger (or smaller) than the threshold number σ. These results together provided a basic picture for the behavior of solutions of (1.1) with $\beta = \delta$: for large initial cell mass, the solution of (1.1) either blows up or converges to a constant steady state asymptotically, which implies aggregation pattern does not exist. For the case $\beta \neq \delta$, the available results are the following: (i) if $\theta \leq 0$, it was shown in [45] that for any large initial cell mass, the model (1.1) admits a unique global classical solution which is uniformly bounded in time for $\tau_1 = \tau_2 = 0$ and time-dependent for $\tau_1 = \tau_2 = 1$. This result was improved recently in [18, 25] showing that if $\theta \leq 0$, the global solution of (1.1) with $\tau_1 = \tau_2 = 1$ is also uniformly bounded in time. Furthermore in [27, 28], the convergence of solutions to constant steady states is established for small initial cell mass; (ii) if $\theta > 0$, it was shown in [8, 53] that there is a threshold number same as σ mentioned above such that the solution of (1.1) with $\tau_1 = \tau_2 = 0$ may blow up (or globally exists) in two dimensions if the cell mass is larger (or smaller) than σ. The same result was extended to the case $\tau_1 = 1, \tau_2 = 0$ in [20] by the authors. The boundedness, blow-up and large time behavior of solutions have been recently carried over to the whole space in [19, 42]. We find from the existing results that the solution behavior of (1.1) for $\beta = \delta$ is the same as for $\beta \neq \delta$ except the case $\tau_1 = \tau_2 = 1$ remain unjustified. In the last section of this paper, we shall confirm this case numerically. Hence one can conclude that for large cell mass, the solution of the model (1.1) either blows up or converges to a constant asymptotically for any parameter values. The bounded but not asymptotically constant solutions are ruled out from the system (1.1). This entails that the model (1.1) cannot fully interpret the aggregates of microglia observed in Alzheimer's disease.

Due to the failure of generating aggregation patterns, the model (1.1) is unable to testify the hypothesis that the interaction of chemotactic attraction and repulsion with microglia may lead to the aggregates of microglia in the brains of patients with Alzheimer's disease [30]. Naturally, one will ask whether this failure comes from the model or the hypothesis. If we presume that it is due to the model, we need to modify the model (1.1). In this paper, we consider a modification of the model (1.1) as follows:

$$\begin{cases} u_t = \Delta u - \nabla \cdot (\chi u \nabla v) + \nabla \cdot (\xi f(u) \nabla w), \\ \tau_1 v_t = \Delta v + \alpha u - \beta v, \\ \tau_2 w_t = \Delta w + \gamma u - \delta w, \end{cases} \tag{1.2}$$

where

$$f(u) = \begin{cases} u^m & \text{for } m \geq 1, \\ u(u+1)^{m-1} & \text{for } 0 < m < 1. \end{cases} \tag{1.3}$$

When $m = 1$, the model (1.2) becomes (1.1) which says that the chemotactic response of microglia to both chemoattractant and chemorepellent is linear. When $m \neq 1$, the model (1.2) implies that the chemotactic response of microglia to the chemorepellent is nonlinear, different from the linear response to the chemoattractant. To formulate our problem completely, we prescribe the following initial and boundary conditions

$$\begin{cases} \dfrac{\partial u}{\partial \nu} = \dfrac{\partial v}{\partial \nu} = \dfrac{\partial w}{\partial \nu} = 0, & x \in \partial\Omega,\ t > 0, \\ u(x,0) = u_0(x), \tau_1 v(x,0) = \tau_1 v_0(x), \tau_2 w(x,0) = \tau_2 w_0(x), & x \in \Omega, \end{cases} \tag{1.4}$$

where Ω is a bounded domain in $\mathbb{R}^n (n \geq 2)$ with smooth boundary and ν denotes the outward normal vector of the boundary $\partial\Omega$.

We shall show that the modified model (1.2)–(1.4) with $m > 1$ has a unique global classical solution which is uniformly bounded in time for any large initial cell mass and parameter values. Numerical simulations will be performed to show that this solution is not an asymptotic constant and the aggregation pattern can be generated. When $\xi = 0$ and w-equation is decoupled, the model (1.2) reduces to the classical attractive chemotaxis model which has been widely studied over the past several decades (e.g. see [4, 11, 13, 14, 31, 33, 34, 49, 52] and references therein). Hereafter, we shall assume that $\xi > 0$ and our first main results on the boundedness of solutions is as follows.

Theorem 1.1. *Let Ω be a bounded domain in $\mathbb{R}^n$ with smooth boundary. Assume that $\xi, \alpha, \beta, \gamma, \delta > 0$ and $\chi \geq 0$. Then the following results hold*:

(i) *If $\tau_1 = \tau_2 = 0$ and $0 \leq u_0 \in W^{1,\infty}(\Omega)$, then the system* (1.2)–(1.4) *has a unique global classical solution (u, v, w) in $C^0(\bar{\Omega} \times [0,\infty)) \cap C^{2,1}(\bar{\Omega} \times (0,\infty))$ for any $m > 1, n \geq 2$.*

(ii) *If $\tau_1 = 1, \tau_2 = 0$ and $0 \leq (u_0, v_0) \in [W^{1,\infty}(\Omega)]^2$, the system* (1.2)–(1.4) *has a unique global classical solution (u, v, w) in $C^0(\bar{\Omega} \times [0,\infty)) \cap C^{2,1}(\bar{\Omega} \times (0,\infty))$ for either $m > 1$ and $n = 2$ or $m \geq 2$ and $n \geq 3$.*

Furthermore, for both cases (i) *and* (ii), *there exists a constant C independent of t such that*

$$\|u(\cdot,t)\|_{L^\infty} \leq C.$$

If $\chi = 0$, the v-equation can be decoupled from the system (1.2), and hence the first and third equations of (1.2) with (1.4) become the following repulsive chemotaxis system:

$$\begin{cases} u_t = \Delta u + \xi \nabla \cdot (f(u) \nabla w), & x \in \Omega,\ t > 0, \\ \tau_2 w_t = \Delta w + \gamma u - \delta w, & x \in \Omega,\ t > 0, \\ \dfrac{\partial u}{\partial \nu} = \dfrac{\partial w}{\partial \nu} = 0, & x \in \partial\Omega,\ t > 0, \\ u(x,0) = u_0(x),\ \tau_2 w(x,0) = \tau_2 w_0(x), & x \in \Omega, \end{cases} \tag{1.5}$$

where $f(u)$ satisfies (1.3). The repulsive chemotaxis system (1.5) has not been completely understood to date. The first result was obtained for $m = 1$ in [5] where the existence of global classical solutions for $n = 2$ and weak solutions for $n = 3, 4$ of (1.5) with $\tau_2 = 1$ was obtained. The existence of global classical solutions for $n \geq 3$ still remains open. As $m \neq 1$ it was shown in [43] if m is suitably small such that $0 < m < \frac{4}{n+2}$, then (1.5) with $\tau_2 = 1$ has a unique global classical solution for $n \geq 2$. As $m \geq \frac{4}{n+2}$, it is conjectured that the same result would hold. In this paper, we shall show for the simplified parabolic–elliptic version of (1.5), global classical solutions exist with uniform-in-time bound for any $m > 0$ and $n \geq 2$. Precisely, we have the following results.

Proposition 1.2. *Let Ω be a bounded domain in $\mathbb{R}^n$ with smooth boundary. Assume $0 \leq u_0 \in W^{1,\infty}(\Omega)$. Then for any $m > 0$ and $n \geq 2$, the system (1.5) with $\tau_2 = 0$ admits a unique global classical solution $(u, w) \in C^0(\bar{\Omega} \times [0, \infty)) \cap C^{2,1}(\bar{\Omega} \times (0, \infty))$ which is uniformly bounded in time.*

The results for the full parabolic model (1.2) (i.e. $\tau_1 = \tau_2 = 1$) with $\chi, \xi > 0$ largely remain open. However, if $\beta = \delta$ and $\frac{v_0}{\alpha} \equiv \frac{w_0}{\gamma}$, we can reduce the model (1.2) into a volume-filling chemotaxis model [36, 47] and the following result is established.

Theorem 1.3. *Let Ω be a bounded domain in $\mathbb{R}^n$ with smooth boundary. Assume $\beta = \delta$ and $0 \leq (u_0, v_0, w_0) \in [W^{1,\infty}(\Omega)]^3$ with $\frac{v_0}{\alpha} = \frac{w_0}{\gamma}$. Then for any $m > 1$ and $n \geq 2$, the system (1.2)–(1.4) with $\tau_1 = \tau_2 = 1$ has a unique classical solution $(u, v, w) \in C^0(\bar{\Omega} \times [0, \infty)) \cap C^{2,1}(\bar{\Omega} \times (0, \infty))$. Moreover, if $0 \leq u_0 \leq (\frac{\chi\alpha}{\xi\gamma})^{\frac{1}{m-1}}$, it follows that*

$$0 < u \leq \left(\frac{\chi\alpha}{\xi\gamma}\right)^{\frac{1}{m-1}} \quad \textit{for all } t > 0.$$

2. Local Existence and Preliminaries

In this section, we shall present some basic facts and results that will be used later. The existence of local solutions of the problem (1.2)–(1.4) can be proved by the fixed point theorem and maximum principle along the same lines shown in [45, 46]. Hence we only present the local existence result without proof below.

Lemma 2.1. *Assume that $0 \leq (u_0, \tau_1 v_0, \tau_2 w_0) \in [W^{1,\infty}(\Omega)]^3$. Then there exists $T_{\max} \in (0, \infty]$ such that the model (1.2)–(1.4) has a unique nonnegative classical solution $(u, v, w) \in C(\bar{\Omega} \times [0, T_{\max}); \mathbb{R}^3) \cap C^{2,1}(\bar{\Omega} \times (0, T_{\max}); \mathbb{R}^3)$. Moreover, $u > 0$ in $\Omega \times (0, T_{\max})$ and*

$$\textit{if } T_{\max} < \infty, \quad \textit{then } \|u(\cdot, t)\|_{L^\infty} \to \infty \quad \textit{as } t \nearrow T_{\max}. \tag{2.1}$$

Integrating equations in (1.2) and using the boundary condition in (1.4), the following results can be readily obtained.

Lemma 2.2. *The solution* (u, v, w) *of* (1.2)–(1.4) *satisfies the following properties*:

$$\begin{aligned}
&\|u(\cdot,t)\|_{L^1} = \|u_0\|_{L^1},\\
&\|v(\cdot,t)\|_{L^1} \le \tau_1\|v_0\|_{L^1} + \frac{\alpha}{\beta}\|u_0\|_{L^1},\\
&\|w(\cdot,t)\|_{L^1} \le \tau_2\|w_0\|_{L^1} + \frac{\gamma}{\delta}\|u_0\|_{L^1}.
\end{aligned}$$

The following inequalities are well known. We present them here for the convenience of quotation later.

Lemma 2.3 ([23]). *Let* Ω *be a bounded domain in* $\mathbb{R}^n$ *with smooth boundary. Assume there is a constant* $C > 0$ *such that*

$$\|u\|_{L^s} \le C \quad \textit{for all } t \in (0, T).$$

If $v_0 \in W^{1,\infty}(\Omega)$, *then there exists some constant* C_q *such that for every* $t \in (0, T)$ *and* $1 \le s < n$, *the solution of the problem*

$$v_t = \Delta v + \alpha u - \beta v \quad \textit{in } \Omega, \frac{\partial v}{\partial \nu} = 0 \quad \textit{on } \partial\Omega$$

satisfies

$$\|v(t)\|_{W^{1,q}} \le C_q \tag{2.2}$$

for all $q < \frac{ns}{n-s}$. *If* $s = n$, *then* (2.2) *holds for all* $q < \infty$, *and if* $s > n$, (2.2) *holds for* $q = \infty$.

Lemma 2.4 (Gagliardo–Nirenberg inequality). *Let* Ω *be a bounded domain in* $\mathbb{R}^n$ *with smooth boundary. Let* $1 \le p, q \le \infty$ *satisfying* $(n - kq)p < nq$ *for some* $k > 0$ *and* $r \in (0, p)$. *Then, for any* $h \in W^{k,q}(\Omega) \cap L^r(\Omega)$, *there exist two constants* c_1 *and* c_2 *depending only on* Ω, q, k, r *and* n *such that*

$$\|h\|_{L^p} \le c_1\|D^k h\|^a_{L^q}\|h\|^{1-a}_{L^r} + c_2\|h\|_{L^r}, \tag{2.3}$$

where $a \in (0, 1)$ *fulfilling*

$$\frac{1}{p} = a\left(\frac{1}{q} - \frac{k}{n}\right) + (1 - a)\frac{1}{r}.$$

We should remark the original Gagliardo–Nirenberg inequality (e.g. see [35]) is stated only for $r \ge 1$, but this condition can be easily relaxed to $r \in (0, p)$ by using the Hölder's inequality (cf. [48, Lemma 3.2] or [45]).

3. Proof of Theorem 1.1(i)

From the blow-up criterion given in Lemma 2.1, it suffices to derive $\|u\|_{L^\infty} < \infty$ for all $t > 0$ to extend the local solution to the global one. To this end, we first show the boundedness of $\|u\|_{L^p}$ for $p > n$ as a starting point. Hereafter, we use c_i to denote a generic constant which may vary in the context.

We first give an inequality that will be frequently used later. The proof of this inequality is inspired from [45]. For completeness, we present it here.

Lemma 3.1. *Let Ω be a bounded domain in $\mathbb{R}^n$ with smooth boundary. For any $\varepsilon > 0$ and $p > 1$, there exists a constant $C > 0$ such that for each $u \in L^1(\Omega)$, the solution of the problem*

$$-\Delta w + \delta w = \gamma u \quad in\ \Omega, \qquad \frac{\partial w}{\partial \nu} = 0 \quad on\ \partial\Omega \tag{3.1}$$

satisfies

$$\int_\Omega w^p dx \le \varepsilon \int_\Omega u^p dx + C.$$

Proof. First, we apply the Agmon–Douglis–Nirenberg L^p-estimates [1, 2] to the linear elliptic problem (3.1) with zero Neumann boundary condition, and find a constant $c_1 > 0$ such that

$$\|w(\cdot,t)\|_{W^{2,p}} \le c_1 \|u(\cdot,t)\|_{L^p}. \tag{3.2}$$

Then we use the Gagliardo–Nirenberg inequality in Lemmas 2.2 and 2.4 and (3.2) to get some constants $c_2 > 0$ and $c_3 > 0$ such that

$$\begin{aligned}\int_\Omega w^p dx = \|w\|_{L^p}^p &\le c_2 \|D^2 w\|_{L^p}^{p\theta} \|w\|_{L^1}^{p(1-\theta)} + c_2 \|w\|_{L^1}^p \\ &\le c_3 \|u\|_{L^p}^{p\theta} + c_3,\end{aligned}$$

where

$$\theta := \frac{1 - \dfrac{1}{p}}{1 + \dfrac{2}{n} - \dfrac{1}{p}} \in (0,1)$$

due to $p > 1$. Furthermore, noting the fact $\theta \in (0,1)$, the Young inequality entails that

$$\int_\Omega w^p dx \le c_3 \|u\|_{L^p}^{p\theta} + c_3 \le \varepsilon \textstyle\int_\Omega u^p dx + c_4(\varepsilon), \tag{3.3}$$

which completes the proof. □

Lemma 3.2. *Let $m > 1$. Then for any $p > \max\{\frac{n}{2}, 1\}$, there exists a constant $C > 0$ such that the solution of* (1.2)–(1.4) *with $\tau_1 = \tau_2 = 0$ satisfies*

$$\int_\Omega u^p dx \le C \quad for\ all\ t \in (0, T_{\max}).$$

Proof. Multiplying the first equation of (1.2) by pu^{p-1}, integrating by parts and employing the second and the third equations in (1.2) with $\tau_1 = \tau_2 = 0$, we end up with

$$\frac{d}{dt}\int_\Omega u^p dx + p(p-1)\int_\Omega u^{p-2}|\nabla u|^2 dx + \frac{p(p-1)\xi\gamma}{p-1+m}\int_\Omega u^{p+m}dx$$
$$\leq (p-1)\chi\alpha\int_\Omega u^{p+1}dx + \frac{p(p-1)\xi\delta}{p-1+m}\int_\Omega u^{p-1+m}wdx. \tag{3.4}$$

Since $m > 1$, then using the Young's inequality, we have

$$(p-1)\chi\alpha\int_\Omega u^{p+1}dx \leq \frac{p(p-1)\xi\gamma}{4(p-1+m)}\int_\Omega u^{p+m}dx + c_1. \tag{3.5}$$

Furthermore, by the Hölder inequality and the Young's inequality, we can find two constants $c_2, c_3 > 0$ such that

$$\begin{aligned}\frac{p(p-1)\xi\delta}{p-1+m}\int_\Omega u^{p-1+m}wdx &\leq \frac{p(p-1)\xi\gamma}{4(p-1+m)}\int_\Omega u^{p+m}dx + c_2\int_\Omega w^{p+m}dx\\ &\leq \frac{p(p-1)\xi\gamma}{2(p-1+m)}\int_\Omega u^{p+m}dx + c_3,\end{aligned} \tag{3.6}$$

where Lemma 3.1 has been used. Then substituting (3.5) and (3.6) into (3.4), one has

$$\frac{d}{dt}\int_\Omega u^p dx + p(p-1)\int_\Omega u^{p-2}|\nabla u|^2 dx + \frac{p(p-1)\xi\gamma}{4(p-1+m)}\int_\Omega u^{p+m}dx \leq c_1 + c_3. \tag{3.7}$$

With the following inequality resulting from the Young's inequality

$$\int_\Omega u^p dx \leq \frac{p(p-1)\xi\gamma}{4(p-1+m)}\int_\Omega u^{p+m}dx + c_4, \tag{3.8}$$

we have from (3.7) and (3.8) that

$$\frac{d}{dt}\int_\Omega u^p dx + \int_\Omega u^p dx \leq c_5.$$

This, together with Gronwall's inequality, yields

$$\int_\Omega u^p dx \leq \int_\Omega u_0^p dx + c_5.$$

Then the proof of Lemma 3.2 is completed. □

Similarly, for the system (1.5) with $\tau_2 = 0$, we have the following results.

Lemma 3.3. *Let $m > 0$. Then for any $p > \max\{\frac{n}{2}, 1\}$, there exists a constant $C > 0$ such that the solution of (1.5) with $\tau_2 = 0$ satisfies*

$$\int_\Omega u^p dx \leq C \quad \textit{for all } t \in (0, T_{\max}). \tag{3.9}$$

Proof. We first consider the case $m \geq 1$ and hence $f(u) = u^m$. In this case, we multiply the first equation of (1.5) by pu^{p-1}, integrate by parts and then use the second equation of (1.5) with $\tau_2 = 0$. Then we get

$$\begin{aligned}
&\frac{d}{dt}\int_\Omega u^p dx + p(p-1)\int_\Omega u^{p-2}|\nabla u|^2 dx \\
&\quad = -p(p-1)\xi\int_\Omega u^{p-2+m}\nabla u\cdot\nabla w dx \\
&\quad = \frac{p(p-1)\xi\delta}{p-1+m}\int_\Omega u^{p-1+m} w dx - \frac{p(p-1)\xi\gamma}{p-1+m}\int_\Omega u^{p+m}dx. \qquad (3.10)
\end{aligned}$$

Then substituting (3.6) into (3.10), one can find a constant $c_1 > 0$ such that

$$\frac{d}{dt}\int_\Omega u^p dx + p(p-1)\int_\Omega u^{p-2}|\nabla u|^2 dx + \frac{p(p-1)\xi\gamma}{2(p-1+m)}\int_\Omega u^{p+m}dx \le c_1,$$

which together with (3.8) gives

$$\frac{d}{dt}\int_\Omega u^p dx + \int_\Omega u^p dx \le c_2. \qquad (3.11)$$

Then applying Gronwall's inequality to (3.11), one has (3.9) in the case of $m \ge 1$.

On the other hand, if $0 < m < 1$ one has $f(u) = u(u+1)^{m-1}$. In this case, multiplying the first equation of (1.5) by $p(u+1)^{p-1}$, and using the similar argument as the case $m \ge 1$, we end up with

$$\begin{aligned}
&\frac{d}{dt}\int_\Omega (u+1)^p dx + p(p-1)\int_\Omega (u+1)^{p-2}|\nabla u|^2 dx \\
&\quad = -p(p-1)\xi\int_\Omega [(u+1)^{p+m-2} - (u+1)^{p+m-3}]\nabla u\cdot\nabla w dx \\
&\quad = \frac{p(p-1)\xi}{p-1+m}\int_\Omega (u+1)^{p-1+m}(\delta w - \gamma u)dx \\
&\qquad - \frac{p(p-1)\xi}{p-2+m}\int_\Omega (u+1)^{p-2+m}(\delta w - \gamma u)dx \\
&\quad \le \frac{p(p-1)\xi\delta}{p-1+m}\int_\Omega (u+1)^{p-1+m} w dx - \frac{p(p-1)\xi\gamma}{p-1+m}\int_\Omega (u+1)^{p+m}dx \\
&\qquad + \frac{p(p-1)(2p+2m-3)\xi\gamma}{(p-1+m)(p-2+m)}\int_\Omega (u+1)^{p+m-1}dx \\
&\quad \le -\frac{p(p-1)\xi\gamma}{2(p-1+m)}\int_\Omega (u+1)^{p+m}dx + c_3 \\
&\quad \le -\int_\Omega (u+1)^p dx + c_4,
\end{aligned}$$

which together with the Gronwall's inequality gives (3.9). Hence the proof of Lemma 3.3 is completed. □

We are now in a position to prove Theorem 1.1(i) and Proposition 1.2.

Proof of Theorem 1.1(i). We apply the Agmon–Douglis–Nirenberg L^p-estimates [1, 2] to the following linear elliptic equations under zero Neumann boundary conditions:

$$\begin{cases} -\Delta v + \beta v = \alpha u, & x \in \Omega, \quad t \in (0, T_{\max}), \\ -\Delta w + \delta w = \gamma u, & x \in \Omega, \quad t \in (0, T_{\max}), \\ \dfrac{\partial v}{\partial \nu} = \dfrac{\partial w}{\partial \nu} = 0, & x \in \partial\Omega, \quad t \in (0, T_{\max}), \end{cases}$$

where $\beta, \delta > 0$. Then there exists a constant $c_1 > 0$ such that

$$\|(v, w)(\cdot, t)\|_{W^{2,p}} \leq c_1 \|u(\cdot, t)\|_{L^p}, \tag{3.12}$$

which together with Lemma 3.2 gives

$$\|(v, w)(\cdot, t)\|_{W^{2,p}} \leq c_2. \tag{3.13}$$

Choosing $p > n$ in (3.13) and using the Sobolev embedding theorem, we can find a constant $c_3 > 0$ such that

$$\|(\nabla v, \nabla w)(\cdot, t)\|_{L^\infty} \leq c_3.$$

Then by the well-known Moser–Alikakos iteration procedure (cf. [3, 45]), one can find a constant $c_4 > 0$ such that

$$\|u(\cdot, t)\|_{L^\infty} \leq c_4 \quad \text{for all } t \in (0, T_{\max}). \tag{3.14}$$

Then Theorem 1.1(i) immediately follows from (3.14) and Lemma 2.1. □

Proof of Proposition 1.2. The combination of Lemma 3.3 and (3.12) gives

$$\|w(\cdot, t)\|_{W^{2,p}} \leq c_1. \tag{3.15}$$

We choose $p > n$ in (3.15) and use the Sobolev embedding theorem to obtain

$$\|\nabla w(\cdot, t)\|_{L^\infty} \leq c_2.$$

Similarly, by the well-known Moser–Alikakos iteration procedure (cf. [3, 45]), we can obtain

$$\|u(\cdot, t)\|_{L^\infty} \leq c_3 \quad \text{for all } t \in (0, T_{\max}). \tag{3.16}$$

Then the proof of Proposition 1.2 is completed by combining (3.16) and Lemma 2.1. □

4. Proof of Theorem 1.1(ii)

4.1. *Basic energy estimates for $n \geq 2$*

With $\tau_1 = 1$, $\tau_2 = 0$ and $m > 1$, the system (1.2)–(1.4) reads as

$$\begin{cases} u_t = \Delta u - \nabla \cdot (\chi u \nabla v) + \nabla \cdot (\xi u^m \nabla w), & x \in \Omega,\ t > 0, \\ v_t = \Delta v + \alpha u - \beta v, & x \in \Omega,\ t > 0, \\ 0 = \Delta w + \gamma u - \delta w, & x \in \Omega,\ t > 0, \\ \dfrac{\partial u}{\partial \nu} = \dfrac{\partial v}{\partial \nu} = \dfrac{\partial w}{\partial \nu} = 0, & x \in \partial\Omega,\ t > 0, \\ u(x,0) = u_0(x), v(x,0) = v_0(x), & x \in \Omega. \end{cases} \tag{4.1}$$

Lemma 4.1. *Assume that $0 \leq (u_0, v_0) \in [W^{1,\infty}(\Omega)]^2$. If there exists a constant $c_1 > 0$ such that*

$$\|u\|_{L^p} \leq c_1 \quad \textit{for all } p > n, \tag{4.2}$$

then there exists a unique triple (u, v, w) of nonnegative functions belonging to $C(\bar{\Omega} \times [0,\infty)) \cap C^{2,1}(\bar{\Omega} \times (0,\infty))$ which solves (4.1) classically such that $\|u(\cdot,t)\|_{L^\infty} \leq c_2$, where c_2 is a constant independent of t.

Proof. If (4.2) holds, from Lemma 2.3, we can find a constant $c_1 > 0$ such that

$$\|\nabla v\|_{L^\infty} \leq \|v\|_{W^{1,\infty}} \leq c_1. \tag{4.3}$$

Furthermore, the combination of (3.12) and (4.2) gives

$$\|w\|_{W^{2,p}} \leq c_2 \quad \text{for all } p > n,$$

which together with the Sobolev embedding theorem gives

$$\|\nabla w\|_{L^\infty} \leq c_3. \tag{4.4}$$

Then it follows from (4.3), (4.4) and the well-known Moser–Alikakos iteration procedure (cf. [3]) that there exists a constant $c_4 > 0$ such that

$$\|u(\cdot,t)\|_{L^\infty} \leq c_4 \quad \text{for all } t \in (0, T_{\max}). \tag{4.5}$$

This completes the proof of Lemma 4.1 by combining (4.5) and Lemma 2.1. □

Now, it is the key to show (4.2) holds in order to prove Theorem 1.1(ii). Inspired by [43, 44], we shall establish a combined estimate of $\int_\Omega u^p dx + \int_\Omega |\nabla v|^{\frac{2(p+m)}{m}} dx$ for $t > 0$ to obtain the boundedness of solutions, instead of $\int_\Omega u^p dx$ alone. As a starting point toward this aim, we shall use the condition $m > 1$ to derive the boundedness of $\|\nabla v\|_{L^2}$.

Lemma 4.2. *Let $m > 1$ and $0 \le (u_0, v_0) \in [W^{1,\infty}(\Omega)]^2$. Then the solution of* (4.1) *satisfies*

$$\int_\Omega |\nabla v|^2 \, dx \le C, \tag{4.6}$$

where $C > 0$ is a constant independent of t.

Proof. Multiplying the first equation of (4.1) by $\ln u$ and integrating the result over Ω yield that

$$\frac{d}{dt}\int_\Omega u \ln u dx + \int_\Omega \frac{|\nabla u|^2}{u} dx = \chi \int_\Omega \nabla u \cdot \nabla v dx - \xi \int_\Omega u^{m-1} \nabla u \cdot \nabla w dx. \tag{4.7}$$

We multiply the second equation of (4.1) by $-\Delta v$ and integrate the resulting equation by part over Ω to obtain

$$\frac{1}{2}\frac{d}{dt}\int_\Omega |\nabla v|^2 \, dx + \int_\Omega |\Delta v|^2 \, dx + \beta \int_\Omega |\nabla v|^2 \, dx = \alpha \int_\Omega \nabla u \cdot \nabla v dx. \tag{4.8}$$

Furthermore, using the third equation of (4.1) and boundary conditions, we can derive that

$$-\xi \int_\Omega u^{m-1} \nabla u \cdot \nabla w dx = \frac{\xi}{m}\int_\Omega u^m \Delta w dx = \frac{\xi\delta}{m}\int_\Omega u^m w dx - \frac{\xi\gamma}{m}\int_\Omega u^{m+1} dx. \tag{4.9}$$

The combination of (4.7), (4.8) and (4.9) gives

$$\begin{aligned}
&\frac{d}{dt}\int_\Omega \left(u \ln u + \frac{1}{2}|\nabla v|^2\right) dx + \int_\Omega \frac{|\nabla u|^2}{u} dx \\
&\quad + \int_\Omega |\Delta v|^2 \, dx + \beta \int_\Omega |\nabla v|^2 \, dx + \frac{\xi\gamma}{m}\int_\Omega u^{m+1} dx \\
&= -(\chi + \alpha)\int_\Omega u \Delta v dx + \frac{\xi\delta}{m}\int_\Omega u^m w dx \\
&\le \frac{(\chi+\alpha)^2}{2}\int_\Omega u^2 dx + \frac{1}{2}\int_\Omega |\Delta v|^2 dx + \frac{\xi\delta}{m}\int_\Omega u^m w dx,
\end{aligned}$$

which, together with the inequality $2\beta \int_\Omega u \ln u dx \le 2\beta \int_\Omega u^2 dx$, yields that

$$\begin{aligned}
&\frac{d}{dt}\int_\Omega \left(u \ln u + \frac{1}{2}|\nabla v|^2\right) dx + \int_\Omega \frac{|\nabla u|^2}{u} dx + \frac{1}{2}\int_\Omega |\Delta v|^2 dx \\
&\quad + \beta \int_\Omega |\nabla v|^2 \, dx + 2\beta \int_\Omega u \ln u dx + \frac{\xi\gamma}{m}\int_\Omega u^{m+1} dx \\
&\le \frac{(\chi+\alpha)^2 + 4\beta}{2}\int_\Omega u^2 dx + \frac{\xi\delta}{m}\int_\Omega u^m w dx.
\end{aligned} \tag{4.10}$$

With $m > 1$, using the Young's inequality, we have

$$\frac{(\chi+\alpha)^2 + 4\beta}{2}\int_\Omega u^2 dx \le \frac{\xi\gamma}{4m}\int_\Omega u^{m+1} dx + c_1. \tag{4.11}$$

Furthermore, applying the Hölder inequality and Young's inequality to the last term in (4.10), one has

$$\begin{aligned}\frac{\xi\delta}{m}\int_\Omega u^m w dx &\le \frac{\xi\gamma}{4m}\int_\Omega u^{m+1}dx + c_2\int_\Omega w^{m+1}dx\\ &\le \frac{\xi\gamma}{2m}\int_\Omega u^{m+1}dx + c_3,\end{aligned}\tag{4.12}$$

where Lemma 3.1 has been used due to $m+1>1$. Set $y(t) := \int_\Omega (u\ln u + \frac{1}{2}|\nabla v|^2)dx$. Substituting (4.11) and (4.12) into (4.10), one has

$$y'(t) + 2\beta y(t) \le c_1 + c_3,$$

which implies

$$y(t) \le y(0) + c_4 \quad \text{for all } t\in(0,T_{\max}).\tag{4.13}$$

Noting the facts $-u\ln u \le \frac{1}{e}$ for all $u>0$ and the definition of $y(t)$, then from (4.13), we have

$$\begin{aligned}\frac{1}{2}\int_\Omega |\nabla v|^2 dx &\le \int_\Omega u_0\ln u_0 dx + \frac{1}{2}\int_\Omega |\nabla v_0|^2 dx - \int_\Omega u\ln u dx + c_4\\ &\le \int_\Omega u_0\ln u_0 dx + \frac{1}{2}\int_\Omega |\nabla v_0|^2 dx + \frac{|\Omega|}{e} + c_4,\end{aligned}$$

which gives (4.6). Then we complete the proof of this lemma. □

Lemma 4.3. *Let $p>1, q\ge 2$. Then there exist two constants $C_1>0$ and $C_2>0$ such that for all $t\in(0,T_{\max})$, the solution of (4.1) satisfies*

$$\begin{aligned}&\frac{d}{dt}\left(\int_\Omega u^p dx + \int_\Omega |\nabla v|^{2q}dx\right) + \frac{2(p-1)}{p}\int_\Omega |\nabla u^{\frac{p}{2}}|^2 dx\\ &\quad + \frac{2(q-1)}{q}\int_\Omega |\nabla|\nabla v|^q|^2 dx + \frac{p(p-1)\xi\gamma}{2(p-1+m)}\int_\Omega u^{p+m}dx\\ &\le \frac{p(p-1)\chi^2}{2}\int_\Omega u^p|\nabla v|^2 dx + C_1\int_\Omega u^2|\nabla v|^{2q-2}dx + C_2.\end{aligned}\tag{4.14}$$

Proof. Multiplying the first equation of (4.1) by pu^{p-1}, and integrating the equation with respect to x over Ω, one has

$$\begin{aligned}&\frac{d}{dt}\int_\Omega u^p dx + p(p-1)\int_\Omega u^{p-2}|\nabla u|^2 dx\\ &= p(p-1)\chi\int_\Omega u^{p-1}\nabla u\cdot\nabla v dx + \frac{p(p-1)\xi}{p-1+m}\int_\Omega u^{p-1+m}(\delta w - \gamma u)dx\\ &\le \frac{p(p-1)}{2}\int_\Omega u^{p-2}|\nabla u|^2 dx + \frac{p(p-1)\chi^2}{2}\int_\Omega u^p|\nabla v|^2 dx\\ &\quad + \frac{p(p-1)\xi\delta}{p-1+m}\int_\Omega u^{p-1+m}w dx - \frac{p(p-1)\xi\gamma}{p-1+m}\int_\Omega u^{p+m}dx,\end{aligned}$$

which yields

$$\frac{d}{dt}\int_\Omega u^p dx + \frac{p(p-1)}{2}\int_\Omega u^{p-2}|\nabla u|^2 dx + \frac{p(p-1)\xi\gamma}{p-1+m}\int_\Omega u^{p+m}dx \le \frac{p(p-1)\chi^2}{2}\int_\Omega u^p|\nabla v|^2 dx + \frac{p(p-1)\xi\delta}{p-1+m}\int_\Omega u^{p-1+m}w dx. \tag{4.15}$$

Furthermore, we can use Young's inequality and Lemma 3.1 to estimate the last term in (4.15) as

$$\begin{aligned}\frac{p(p-1)\xi\delta}{p-1+m}\int_\Omega u^{p-1+m}w dx &\le \frac{p(p-1)\xi\gamma}{4(p-1+m)}\int_\Omega u^{p+m}dx + c_1\int_\Omega w^{p+m}dx \\ &\le \frac{p(p-1)\xi\gamma}{2(p-1+m)}\int_\Omega u^{p+m}dx + c_2.\end{aligned} \tag{4.16}$$

Substituting (4.16) into (4.15), one has

$$\frac{d}{dt}\int_\Omega u^p dx + \frac{2(p-1)}{p}\int_\Omega |\nabla u^{\frac{p}{2}}|^2 dx + \frac{p(p-1)\xi\gamma}{2(p-1+m)}\int_\Omega u^{p+m}dx \le \frac{p(p-1)\chi^2}{2}\int_\Omega u^p|\nabla v|^2 dx + c_2. \tag{4.17}$$

We differentiate the second equation of system (4.1) and multiply the results by $2\nabla v$ to obtain

$$\begin{aligned}(|\nabla v|^2)_t &= 2\nabla v\cdot\nabla\Delta v + 2\alpha\nabla u\cdot\nabla v - 2\beta|\nabla v|^2 \\ &= \Delta|\nabla v|^2 - 2|D^2v|^2 + 2\alpha\nabla u\cdot\nabla v - 2\beta|\nabla v|^2,\end{aligned} \tag{4.18}$$

where we have used the identity $\Delta|\nabla v|^2 = 2\nabla v\cdot\nabla\Delta v + 2|D^2 v|^2$. Multiplying the equation (4.18) by $q|\nabla v|^{2q-2}(q\ge 2)$, integrating the result by parts, one has

$$\begin{aligned}&\frac{d}{dt}\int_\Omega |\nabla v|^{2q}dx + q(q-1)\int_\Omega |\nabla v|^{2q-4}|\nabla|\nabla v|^2|^2 dx \\ &\quad + 2q\int_\Omega |\nabla v|^{2q-2}|D^2 v|^2 dx + 2q\beta\int_\Omega |\nabla v|^{2q}dx \\ &= q\int_{\partial\Omega}|\nabla v|^{2q-2}\frac{\partial|\nabla v|^2}{\partial\nu}dS + 2q\alpha\int_\Omega |\nabla v|^{2q-2}\nabla u\cdot\nabla v dx \\ &\le \frac{q(q-1)}{4}\int_\Omega |\nabla v|^{2q-4}|\nabla|\nabla v|^2|^2 dx + 2q\alpha\int_\Omega |\nabla v|^{2q-2}\nabla u\cdot\nabla v dx + c_3,\end{aligned} \tag{4.19}$$

where we have used the following estimate (see [15, inequality, (3.10)] for details) due to (4.6)

$$q\int_{\partial\Omega}|\nabla v|^{2q-2}\frac{\partial|\nabla v|^2}{\partial\nu}dS \le \frac{q(q-1)}{4}\int_\Omega |\nabla v|^{2q-4}|\nabla|\nabla v|^2|^2 dx + c_3.$$

Next, we estimate the second term on the right-hand side of (4.19) as follows

$$\begin{aligned}
&2q\alpha\int_\Omega |\nabla v|^{2q-2}\nabla u\cdot\nabla v dx\\
&\quad= -2q(q-1)\alpha\int_\Omega u|\nabla v|^{2q-4}\nabla v\cdot\nabla|\nabla v|^2dx - 2q\alpha\int_\Omega u|\nabla v|^{2q-2}\Delta v dx\\
&\quad\le \frac{q(q-1)}{4}\int_\Omega |\nabla v|^{2q-4}|\nabla|\nabla v|^2|^2dx + 4q(q-1)\alpha^2\int_\Omega u^2|\nabla v|^{2q-2}dx\\
&\qquad+\frac{2q}{n}\int_\Omega |\nabla v|^{2q-2}|\Delta v|^2dx + \frac{nq\alpha^2}{2}\int_\Omega u^2|\nabla v|^{2q-2}dx. \qquad (4.20)
\end{aligned}$$

Substituting (4.20) into (4.19), one has

$$\begin{aligned}
&\frac{d}{dt}\int_\Omega |\nabla v|^{2q}dx + \frac{q(q-1)}{2}\int_\Omega |\nabla v|^{2q-4}|\nabla|\nabla v|^2|^2dx\\
&\quad\le \frac{2q}{n}\int_\Omega |\nabla v|^{2q-2}|\Delta v|^2dx - 2q\int_\Omega |\nabla v|^{2q-2}|D^2v|^2dx\\
&\qquad+\left(\frac{nq\alpha^2}{2}+4q(q-1)\alpha^2\right)\int_\Omega u^2|\nabla v|^{2q-2}dx + c_3\\
&\quad\le \left(\frac{nq\alpha^2}{2}+4q(q-1)\alpha^2\right)\int_\Omega u^2|\nabla v|^{2q-2}dx + c_3, \qquad (4.21)
\end{aligned}$$

where we have used the inequality

$$\frac{2q}{n}\int_\Omega |\nabla v|^{2q-2}|\Delta v|^2dx \le 2q\int_\Omega |\nabla v|^{2q-2}|D^2v|^2dx,$$

by noting the fact $|\Delta v|^2 \le n|D^2v|$. The combination of (4.17) and (4.21) yields (4.14). Then we complete the proof of this lemma. □

Next, we will show the boundedness of solutions of system (4.1). To this end, we only need to show the boundedness of $\|u\|_{L^p}$ for $p > n$ by Lemma 4.1. We proceed with cases $n = 2$ and $n \ge 3$ separately in the following.

4.2. *Boundedness for $n = 2$*

We first present the L^2-estimate as follows.

Lemma 4.4. *Let $m > 1$ and $n = 2$. Then there exists a constant $C_3 > 0$ such that the solution of* (4.1) *satisfies*

$$\|u(\cdot,t)\|_{L^2} \le C_3 \quad \text{for all } t\in(0,T_{\max}). \qquad (4.22)$$

Proof. Choosing $p=2, q=2$ in Lemma 4.3, one has

$$\frac{d}{dt}\left(\int_\Omega u^2dx+\int_\Omega |\nabla v|^4dx\right)+\int_\Omega |\nabla u|^2dx+\int_\Omega |\nabla|\nabla v|^2|^2dx+\frac{\xi\gamma}{1+m}\int_\Omega u^{2+m}dx$$
$$\leq c_1\int_\Omega u^2|\nabla v|^2dx+c_2. \tag{4.23}$$

Using the Hölder inequality and Young's inequality, and noting the fact $m>1$, we have

$$\begin{aligned} c_1\int_\Omega u^2|\nabla v|^2dx &\leq c_1\left(\int_\Omega u^3dx\right)^{\frac{2}{3}}\left(\int_\Omega |\nabla v|^6dx\right)^{\frac{1}{3}} \\ &\leq \mu\|\nabla v\|_{L^6}^6+c_3\|u\|_{L^3}^3 \\ &\leq \mu\|\nabla v\|_{L^6}^6+\frac{\xi\gamma}{2(1+m)}\int_\Omega u^{2+m}dx+c_4. \end{aligned} \tag{4.24}$$

Furthermore, we can use the Gagliardo–Nirenberg inequality and the fact $\||\nabla v|^2\|_{L^1}=\|\nabla v\|_{L^2}^2\leq C$ in (4.6) to obtain that

$$\begin{aligned} \|\nabla v\|_{L^6}^6=\||\nabla v|^2\|_{L^3}^3 &\leq c_5\|\nabla|\nabla v|^2\|_{L^2}^2\||\nabla v|^2\|_{L^1}+c_5\||\nabla v|^2\|_{L^1}^3 \\ &\leq c_6\|\nabla|\nabla v|^2\|_{L^2}^2+c_7. \end{aligned} \tag{4.25}$$

Substituting (4.24) and (4.25) into (4.23), and taking $\mu=\frac{1}{2c_6}$, one has

$$\frac{d}{dt}\left(\int_\Omega u^2dx+\int_\Omega |\nabla v|^4dx\right)+\int_\Omega |\nabla u|^2dx$$
$$+\frac{1}{2}\int_\Omega |\nabla|\nabla v|^2|^2dx+\frac{\xi\gamma}{2(1+m)}\int_\Omega u^{2+m}dx\leq c_8. \tag{4.26}$$

Using the Gagliardo–Nirenberg inequality and Young's inequality together with Lemma 2.2 and (4.6) give

$$\int_\Omega u^2dx\leq c_9(\|\nabla u\|_{L^2}\|u\|_{L^1}+\|u\|_{L^1}^2)\leq \|\nabla u\|_{L^2}^2+c_{10} \tag{4.27}$$

and

$$\int_\Omega |\nabla v|^4dx\leq c_{11}(\|\nabla|\nabla v|^2\|_{L^2}\||\nabla v|^2\|_{L^1}+\||\nabla v|^2\|_{L^1}^2)\leq \frac{1}{2}\|\nabla|\nabla v|^2\|_{L^2}^2+c_{12}. \tag{4.28}$$

Let $z(t)=\int_\Omega u^2dx+\int_\Omega |\nabla v|^4dx$. Then the combination of (4.26), (4.27) and (4.28) gives

$$z'(t)+z(t)\leq c_{13},$$

which implies there exists a constant $c_{14}>0$ such that

$$z(t)=\int_\Omega u^2dx+\int_\Omega |\nabla v|^4dx\leq c_{14}. \tag{4.29}$$

Then the proof of Lemma 4.4 is completed. □

Lemma 4.5. *Let $m > 1, n = 2$. For $p > 2$, there exists a constant C independent of t such that the solution (u, v, w) of (4.1) satisfies*

$$\|u\|_{L^p} \leq C. \tag{4.30}$$

Proof. Multiplying the first equation of (4.1) by pu^{p-1}, and integrating the equation with respect to x over Ω, we arrive at the following inequality (see also (4.17))

$$\begin{aligned} &\frac{d}{dt}\int_\Omega u^p dx + \frac{2(p-1)}{p}\int_\Omega |\nabla u^{\frac{p}{2}}|^2 dx + \frac{p(p-1)\xi\gamma}{2(p-1+m)}\int_\Omega u^{p+m} dx \\ &\quad \leq c_1 \int_\Omega u^p |\nabla v|^2 dx + c_2. \end{aligned} \tag{4.31}$$

Using the Hölder inequality and Young's inequality, we have

$$\begin{aligned} c_1 \int_\Omega u^p |\nabla v|^2 dx &\leq c_1 \left(\int_\Omega u^{p+m} dx\right)^{\frac{p}{p+m}} \left(\int_\Omega |\nabla v|^{\frac{2(p+m)}{m}} dx\right)^{\frac{m}{p+m}} \\ &\leq \frac{p(p-1)\xi\gamma}{4(p-1+m)}\int_\Omega u^{p+m} dx + c_3 \int_\Omega |\nabla v|^{\frac{2(p+m)}{m}} dx. \end{aligned} \tag{4.32}$$

Combining Lemma 2.3 and (4.22) and noting $n = 2$, we can find a constant $c_4 > 0$ such that

$$\int_\Omega |\nabla v|^{\frac{2(p+m)}{m}} dx \leq c_4. \tag{4.33}$$

The combination of (4.31), (4.32) and (4.33) gives

$$\frac{d}{dt}\int_\Omega u^p dx + \int_\Omega u^p dx \leq c_5, \tag{4.34}$$

where we have used the following inequality:

$$\int_\Omega u^p dx \leq \frac{2(p-1)}{p}\int_\Omega |\nabla u^{\frac{p}{2}}|^2 dx + c_6,$$

which is obtained by the Gagliardo–Nirenberg inequality. Integrating (4.34) yields (4.30) and the proof of Lemma 4.5 is completed. □

4.3. *Boundedness for $n \geq 3$*

Lemma 4.6. *Let $m \geq 2$ and $n \geq 3$. Then for all $m \leq p < \infty$, there exists a constant $C > 0$ independent of t such that the solution of (4.1) satisfies*

$$\|u(\cdot, t)\|_{L^p} \leq C, \quad \textit{for all } t \in (0, T_{\max}) \tag{4.35}$$

and

$$\|\nabla v(\cdot, t)\|_{L^{\frac{2(p+m)}{m}}} \leq C, \quad \textit{for all } t \in (0, T_{\max}). \tag{4.36}$$

Proof. For $2 \le m \le p < \infty$ and $q = \frac{p+m}{m} > 2$, from Lemma 4.3, we can find two constants $c_1 > 0$ and $c_2 > 0$ such that

$$\begin{aligned}\frac{d}{dt}\left(\int_\Omega u^p dx + \int_\Omega |\nabla v|^{2q} dx\right) &+ \frac{2(p-1)}{p}\int_\Omega |\nabla u^{\frac{p}{2}}|^2 dx \\ &+ \frac{2(q-1)}{q}\int_\Omega |\nabla|\nabla v|^q|^2 dx + \frac{p(p-1)\xi\gamma}{2(p-1+m)}\int_\Omega u^{p+m} dx \\ &\le c_1\int_\Omega u^p|\nabla v|^2 dx + c_1\int_\Omega u^2|\nabla v|^{2q-2} dx + c_2. \end{aligned} \tag{4.37}$$

Using the Hölder inequality, we can choose $q = \frac{m+p}{m} > 2$ and $\lambda = \frac{p+m}{p+m-2} > 1$ such that

$$\int_\Omega u^p|\nabla v|^2 dx \le \left(\int_\Omega u^{p+m} dx\right)^{\frac{p}{p+m}} \cdot \left(\int_\Omega |\nabla v|^{2q} dx\right)^{\frac{1}{q}} \tag{4.38}$$

and

$$\int_\Omega u^2|\nabla v|^{2q-2} dx \le \left(\int_\Omega u^{p+m} dx\right)^{\frac{2}{p+m}} \cdot \left(\int_\Omega |\nabla v|^{2(q-1)\lambda} dx\right)^{\frac{1}{\lambda}}. \tag{4.39}$$

Moreover, we use the Gagliardo–Nirenberg inequality to obtain

$$\left(\int_\Omega |\nabla v|^{2q} dx\right)^{\frac{1}{q}} = \||\nabla v|^q\|_{L^2}^{\frac{2}{q}} \le c_3\|\nabla|\nabla v|^q\|_{L^2}^{\frac{2\theta_1}{q}} \cdot \||\nabla v|^q\|_{L^{\frac{2}{q}}}^{\frac{2(1-\theta_1)}{q}} + c_3\||\nabla v|^q\|_{L^{\frac{2}{q}}}^{\frac{2}{q}}, \tag{4.40}$$

where

$$\theta_1 = \frac{\frac{q}{2} - \frac{1}{2}}{\frac{q}{2} + \frac{1}{n} - \frac{1}{2}} \in (0,1).$$

The combination of (4.6) and (4.40) gives

$$\left(\int_\Omega |\nabla v|^{2q} dx\right)^{\frac{1}{q}} \le c_4\left(\int_\Omega |\nabla|\nabla v|^q|^2 dx\right)^{\frac{1}{q}\cdot\frac{\frac{q}{2}-\frac{1}{2}}{\frac{q}{2}+\frac{1}{n}-\frac{1}{2}}} + c_4. \tag{4.41}$$

Similarly, defining $\theta_2 = \frac{\frac{q}{2} - \frac{p+m-2}{2p}}{\frac{q}{2}+\frac{1}{n}-\frac{1}{2}}$, and using the Gagliardo–Nirenberg inequality and (4.6), we can find a constant $c_5 > 0$ such that

$$\begin{aligned}\left(\int_\Omega |\nabla v|^{2(q-1)\lambda} dx\right)^{\frac{1}{\lambda}} &= \||\nabla v|^q\|_{L^{\frac{2(q-1)\lambda}{q}}}^{\frac{2(q-1)}{q}} \\ &= \||\nabla v|^q\|_{L^{\frac{2p}{p+m-2}}}^{\frac{2(q-1)}{q}} \\ &\le c_5\|\nabla|\nabla v|^q\|_{L^2}^{\frac{2(q-1)\theta_2}{q}} \cdot \||\nabla v|^q\|_{L^{\frac{2}{q}}}^{\frac{2(q-1)(1-\theta_2)}{q}} + c_5\||\nabla v|^q\|_{L^{\frac{2}{q}}}^{\frac{2(q-1)}{q}}\end{aligned}$$

$$\leq c_5 \|\nabla|\nabla v|^q\|_{L^2}^{\frac{2(q-1)\theta_2}{q}} \cdot \|\nabla v\|_{L^2}^{2(q-1)(1-\theta_2)} + c_5\|\nabla v\|_{L^2}^{2(q-1)}$$
$$\leq c_6 \left(\int_\Omega |\nabla|\nabla v|^q|^2 dx\right)^{\frac{(q-1)}{q}\cdot\frac{\frac{q}{2}-\frac{p+m-2}{2p}}{\frac{q}{2}+\frac{1}{n}-\frac{1}{2}}} + c_6. \tag{4.42}$$

The combination of (4.38), (4.39), (4.41) and (4.42) entails that

$$c_1\int_\Omega u^p|\nabla v|^2 dx + c_1\int_\Omega u^2|\nabla v|^{2q-2}dx$$
$$\leq c_1c_4\left(\int_\Omega u^{p+m}dx\right)^{\frac{p}{p+m}}\left(\int_\Omega |\nabla|\nabla v|^q|^2dx\right)^{\frac{1}{q}\cdot\frac{\frac{q}{2}-\frac{1}{2}}{\frac{q}{2}+\frac{1}{n}-\frac{1}{2}}}$$
$$+ c_1c_4\left(\int_\Omega u^{p+m}dx\right)^{\frac{p}{p+m}} + c_1c_6\left(\int_\Omega u^{p+m}dx\right)^{\frac{2}{p+m}}$$
$$\times\left(\int_\Omega |\nabla|\nabla v|^q|^2dx\right)^{\frac{(q-1)}{q}\cdot\frac{\frac{q}{2}-\frac{p+m-2}{2p}}{\frac{q}{2}+\frac{1}{n}-\frac{1}{2}}} + c_1c_6\left(\int_\Omega u^{p+m}dx\right)^{\frac{2}{p+m}}. \tag{4.43}$$

Since $q = \frac{p+m}{m}$, one can check that

$$\frac{p}{p+m} + \frac{1}{q}\cdot\frac{\frac{q}{2}-\frac{1}{2}}{\frac{q}{2}+\frac{1}{n}-\frac{1}{2}} = \frac{p}{p+m} + \frac{m}{p+m}\cdot\frac{\frac{q}{2}-\frac{1}{2}}{\frac{q}{2}+\frac{1}{n}-\frac{1}{2}} < 1. \tag{4.44}$$

Moreover, if $q = \frac{p+m}{m}$ and $m \geq 2$, it holds that

$$\frac{2}{p+m} + \frac{q-1}{q}\cdot\frac{\frac{q}{2}-\frac{p+m-2}{2p}}{\frac{q}{2}+\frac{1}{n}-\frac{1}{2}} < 1. \tag{4.45}$$

By the Young's inequality, one can readily derive that for any $\varepsilon > 0$ and $X, Y \geq 0$ there exists a constant $C > 0$ such that

$$X^aY^b \leq \varepsilon(X+Y) + C, \tag{4.46}$$

where $a > 0$ and $b > 0$ are constants such that $a + b < 1$. Applying (4.46) to (4.43) with the facts (4.44) and (4.45), we have

$$c_1\int_\Omega u^p|\nabla v|^2dx + c_1\int_\Omega u^2|\nabla v|^{2q-2}dx \leq \varepsilon\left(\int_\Omega u^{p+m}dx + \int_\Omega |\nabla|\nabla v|^q|^2dx\right) + c_7. \tag{4.47}$$

Substituting (4.47) into (4.37) and choosing $\varepsilon = \min\{\frac{q-1}{q}, \frac{p(p-1)\xi\gamma}{4(p-1+m)}\}$, one has

$$\frac{d}{dt}\left(\int_\Omega u^pdx + \int_\Omega |\nabla v|^{2q}dx\right) + \frac{2(p-1)}{p}\int_\Omega |\nabla u^{\frac{p}{2}}|^2dx + \frac{(q-1)}{q}\int_\Omega |\nabla|\nabla v|^q|^2dx$$
$$+ \frac{p(p-1)\xi\gamma}{4(p-1+m)}\int_\Omega u^{p+m}dx \leq c_8. \tag{4.48}$$

Using the Gagliardo–Nirenberg inequality, we have

$$\int_\Omega |\nabla v|^{2q} dx = \||\nabla v|^q\|_{L^2}^2 \le c_9 \|\nabla |\nabla v|^q\|_{L^2}^{2\theta_3} \cdot \||\nabla v|^q\|_{L^{\frac{2}{q}}}^{2(1-\theta_3)} + c_9 \||\nabla v|^q\|_{L^{\frac{2}{q}}}^2, \tag{4.49}$$

where

$$\theta_3 = \frac{\frac{q}{2} - \frac{1}{2}}{\frac{q}{2} + \frac{1}{n} - \frac{1}{2}} \in (0,1).$$

Noting $\||\nabla v|^q\|_{L^{\frac{2}{q}}} = \||\nabla v|\|_{L^2}^q \le c_{10}$ (see (4.6)), we have from (4.49) that

$$\int_\Omega |\nabla v|^{2q} dx \le \tfrac{(q-1)}{q} \|\nabla |\nabla v|^q\|_{L^2}^2 + c_{11}. \tag{4.50}$$

Furthermore, using the Hölder inequality and Young's inequality, we can derive that

$$\int_\Omega u^p dx \le \frac{p(p-1)\xi\gamma}{4(p-1+m)} \int_\Omega u^{p+m} dx + c_{12}. \tag{4.51}$$

Substituting (4.49), (4.50) and (4.51) into (4.48) gives

$$\frac{d}{dt}\left(\int_\Omega u^p dx + \int_\Omega |\nabla v|^{2q} dx\right) + \int_\Omega u^p dx + \int_\Omega |\nabla v|^{2q} dx \le c_{13},$$

which implies there exists a constant c_{14} such that

$$\int_\Omega u^p dx + \int_\Omega |\nabla v|^{2q} dx \le c_{14},$$

which gives (4.35) and (4.36) by noting that $q = \frac{p+m}{m}$. Then we complete the proof of Lemma 4.6. □

4.4. *Proof of Theorem* 1.1(ii)

Theorem 1.1(ii) is a direct consequence of Lemmas 4.1, 4.5 and 4.6.

5. Proof of Theorem 1.3

In this section, we will study the model (1.2)–(1.4) with $\tau_1 = \tau_2 = 1$. With the conditions given in Theorem 1.3, we can transform the system (1.2)–(1.4) into a generalized volume-filling chemotaxis model. We are now in a position to prove Theorem 1.3.

Proof of Theorem 1.3. Letting $s = \frac{v}{\alpha} - \frac{w}{\gamma}$ and using the conditions $\beta = \delta$, $\tau_1 = \tau_2 = 1$ and $\frac{v_0}{\alpha} = \frac{w_0}{\gamma}$, from the second and third equations of (1.2)–(1.4), we can derive that

$$\begin{cases} s_t = \Delta s - \beta s, & x \in \Omega,\ t > 0, \\ \dfrac{\partial s}{\partial \nu} = 0, & x \in \partial\Omega,\ t > 0, \\ s(x,0) = s_0(x) := \dfrac{v_0}{\alpha} - \dfrac{w_0}{\gamma} = 0, & x \in \Omega, \end{cases}$$

which implies $s = \frac{v}{\alpha} - \frac{w}{\gamma} = 0$ by the maximum principle. Substituting the identity $w = \frac{\gamma v}{\alpha}$ into the first equation of system (1.2), one has

$$\begin{cases} u_t = \Delta u - \kappa \nabla \cdot (u(l - u^{m-1})\nabla v), & x \in \Omega,\ t > 0, \\ v_t = \Delta v + \alpha u - \beta v, & x \in \Omega,\ t > 0, \\ \dfrac{\partial u}{\partial \nu} = \dfrac{\partial v}{\partial \nu} = 0, & x \in \partial\Omega,\ t > 0, \\ u(x,0) = u_0(x), v(x,0) = v_0(x), & x \in \Omega, \end{cases} \tag{5.1}$$

where $l = \frac{\chi\alpha}{\xi\gamma}, \kappa = \frac{\chi}{l}$. The reduced model (5.1) is a type of the volume-filling chemotaxis model proposed in [36] and generalized in [47]. As $m = 2$, the existence of global classical solutions of (5.1) has been studied in [50], where the boundedness of solutions was proved in [12] by energy estimates and in [50] by a sophisticated constructive approach. The asymptotic behavior of solutions was later studied in [17, 51]. Although the method of [12, 50] is applicable to the case $m > 1$, here we shall present a much simpler method *maximum principle* to derive the boundedness of solutions to (5.1) for any $m > 1$. To this end, we first note that the strong maximum principle employed to the first equation of (5.1) gives that $u(x,t) > 0$ for all $t > 0$ since $u_0(x) \geq 0$. Then we set $U = l - u^{m-1} < l$ and substitute it into the first equation of (5.1). After some tedious calculations, we find that $U(x,t)$ satisfies the equation

$$\begin{aligned} U_t = \Delta U + \frac{m-2}{m-1}\frac{1}{l-U}|\nabla U|^2 + \kappa(m-1)U(l-U)\Delta v \\ + \kappa(m-1)(l-U)\nabla U \nabla v - \kappa U \nabla U \nabla v. \end{aligned} \tag{5.2}$$

Noting that $U_0(x) = l - u_0^{m-1} \geq 0$ by the condition $u_0 \leq (\frac{\chi\alpha}{\xi\gamma})^{\frac{1}{m-1}} = l^{\frac{1}{m-1}}$ and U satisfies the Neumann boundary conditions. Then the strong maximum principle and Hopf's lemma applied Eq. (5.2) yield $U(x,t) > 0$ for all $t > 0$. That is $0 < u(x,t) < l^{\frac{1}{m-1}}$. Finally, we remark that the local existence of classical solutions of the generalized volume-filling chemotaxis model (5.1) can be proved by the standard fixed point theorem (e.g. see [12, 47] for $m = 2$). This, together with the boundedness derived above, finishes the proof of Theorem 1.3. □

Remark 5.1. With the conditions given in Theorem 1.3, the system (1.2) is transformed into the system (5.1). Furthermore, if $m = 1$, the system (5.1) become the classical attractive (or repulsive) chemotaxis model if $\alpha\chi > \xi\gamma$ (or $\alpha\chi < \xi\gamma$). Hence there is no pattern formation for the system (5.1) with $m = 1$ in multi-dimensions (e.g. see [5, 49]). However, if $m > 1$, the system (5.1) is a generalized volume-filling chemotaxis model and pattern formation can be generated, see [36] for the simulation results of (5.1) with $m = 2$. This entails that substantial differences exist between $m > 1$ and $m = 1$ for the system (1.2).

6. Simulations, Implications and Open Questions

In this paper, we prove that the model (1.2)–(1.4) with $m > 1$ has a unique global classical solution which is uniformly bounded in time for the case $\tau_1 = \tau_2 = 0$ or $\tau_1 = 1, \tau_2 = 0$. It takes the first step to show that the model can generate pattern formation. In order to prove the model (1.2)–(1.4) is capable of producing the aggregation pattern to interpret the aggregates of microglia due to its interaction with both chemoattractant and chemorepellent, one needs to prove the existing global solution is not a constant asymptotically. However, this appears to a very challenging question and we have to leave it open by far. Then the numerical simulation become a necessary and important tool. In this section, we shall numerically illustrate that the model (1.2)–(1.4) truly produces nonconstant bounded solutions (i.e. pattern formation), which implies that the modified model (1.2)–(1.4) provides a possible mechanism to explain the aggregates of microglia in Alzheimer's disease. Here, we will achieve two primary goals through the numerical simulations. One is to show that the pattern formation of the model (1.2)–(1.4) with $m > 1$ does not depends on the sign of $\theta = \chi\alpha - \xi\gamma$ and hence the dynamics of the model substantially differs from the case $m = 1$ studied before. The other is to find under what conditions, the aggregation patterns can be generated from the model (1.2)–(1.4). The numerical computations will be performed by the computing package *COMSOL Multiphysics* based on the finite element scheme.

In the following, we first perform the linear stability analysis to find the necessary conditions on parameters for the instability of the homogeneous steady state of (1.2)–(1.4) with $m \geq 1$, and then show various numerical pattern formations and discuss their implications.

6.1. *Linearized stability analysis*

Let $(\bar{u}, \bar{v}, \bar{w})$ denote the homogeneous (i.e. constant) steady state of the system (1.2)–(1.4) satisfying $\bar{u} > 0, \bar{v} = \frac{\alpha}{\beta}\bar{u}, \bar{w} = \frac{\gamma}{\delta}\bar{u}$. We linearize the full chemotaxis model (1.2) with $\tau_1 = \tau_2 = 1$ and $m \geq 1$ around $(\bar{u}, \bar{v}, \bar{w})$ to get

$$\begin{cases} \Theta_t = A\Delta\Theta + B\Theta, & x \in \Omega,\ t > 0, \\ (\nu \cdot \nabla)\Theta = 0, & x \in \partial\Omega,\ t > 0, \\ \Theta(x, 0) = \Theta_0(x) := (u - u_0, v - v_0, w - w_0)^{\mathcal{T}}, & x \in \Omega, \end{cases} \tag{6.1}$$

where $\mathcal{T}$ denote the transpose and

$$\Theta = \begin{pmatrix} u-\bar{u} \\ v-\bar{v} \\ w-\bar{w} \end{pmatrix}, \quad A = \begin{pmatrix} 1 & -\chi\bar{u} & \xi\bar{u}^m \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix}, \quad B = \begin{pmatrix} 0 & 0 & 0 \\ \alpha & -\beta & 0 \\ \gamma & 0 & -\delta \end{pmatrix}.$$

Let $Y_k(x)$ denote the eigenfunction of the following eigenvalue problem:

$$\Delta Y_k(x) + k^2 Y_k(x) = 0, \quad (\nu\cdot\nabla)Y_k(x) = 0,$$

where k is called the wavenumber. Since the problem (6.1) is linear, we look for solutions $\Theta(x,t)$ in the form of

$$\Theta(x,t) = \sum_{k\geq 0} c_k e^{\lambda t} Y_k(x). \tag{6.2}$$

Substituting (6.2) into (6.1), for each $k \geq 0$, we have

$$\lambda Y_k(x) = -k^2 A Y_k(x) + B Y_k(x).$$

This implies λ is the eigenvalue of the following matrix:

$$M_k = \begin{pmatrix} -k^2 & \chi\bar{u}k^2 & -\xi\bar{u}^m k^2 \\ \alpha & -k^2-\beta & 0 \\ \gamma & 0 & -k^2-\delta \end{pmatrix}.$$

After some algebra, one can find that the eigenvalue λ of the matrix M_k satisfies

$$\lambda^3 + a_2(\chi,k^2)\lambda^2 + a_1(\chi,k^2)\lambda + a_0(\chi,k^2) = 0, \tag{6.3}$$

where

$$\begin{aligned} a_2(\chi,k^2) &= 3k^2 + \beta + \delta, \\ a_1(\chi,k^2) &= 3k^4 + [2(\beta+\delta) + \xi\gamma\bar{u}^m - \alpha\chi\bar{u}]k^2 + \delta\beta, \\ a_0(\chi,k^2) &= k^6 + [\beta+\delta+\xi\gamma\bar{u}^m - \alpha\chi\bar{u}]k^4 + [\beta\delta + \beta\xi\gamma\bar{u}^m - \delta\alpha\chi\bar{u}]k^2. \end{aligned}$$

If the matrix M_k has eigenvalues with positive real part, then the homogeneous steady state $(\bar{u},\bar{v},\bar{w})$ is unstable and the spatial pattern formation can be expected. In fact, using the well-known Routh–Hurwitz criterion (see [32]), we have the following results on the stability/instability of $(\bar{u},\bar{v},\bar{w})$.

Proposition 6.1. *Let $(\bar{u},\bar{v},\bar{w})$ be the homogeneous steady state of* (1.2)–(1.4), *where $\alpha,\beta,\gamma,\delta,\xi > 0$. Then the following results hold.*

(1) *$(\bar{u},\bar{v},\bar{w})$ is locally asymptotically stable with respect to the system* (1.2)–(1.4) *if $\chi \geq 0$ and satisfies*

$$\chi \leq \frac{\xi\gamma}{\alpha}\bar{u}^{m-1}\min\left\{\frac{\beta}{\delta},\frac{\delta}{\beta}\right\}. \tag{6.4}$$

(2) *$(\bar{u},\bar{v},\bar{w})$ is unstable with respect to* (1.2)–(1.4) *if $\alpha\chi$ is large enough.*

Proof. From the Routh–Hurwitz criterion, we can derive that the homogeneous steady state $(\bar{u}, \bar{v}, \bar{w})$ is locally asymptotically stable with respect to (1.2) if and only if for every $k \geq 0$, it holds that

$$a_0(\chi, k^2) > 0 \quad \text{and} \quad a_2(\chi, k^2)a_1(\chi, k^2) - a_0(\chi, k^2) > 0. \tag{6.5}$$

A direct calculation shows that (6.5) will hold if the following inequalities are satisfied

$$\xi\gamma\bar{u}^m - \chi\alpha\bar{u} \geq 0 \quad \text{and} \quad \beta\xi\gamma\bar{u}^m - \delta\chi\alpha\bar{u} \geq 0,$$

which are ensured by (6.4). Hence the homogeneous steady state $(\bar{u}, \bar{v}, \bar{w})$ is locally asymptotically stable under the conditions (6.4). From the definition of $a_0(x, k^2)$, we know that for any fixed $k > 0$, $a_0(\chi, k^2) < 0$ when $\alpha\chi$ is large enough, which implies $(\bar{u}, \bar{v}, \bar{w})$ is unstable. □

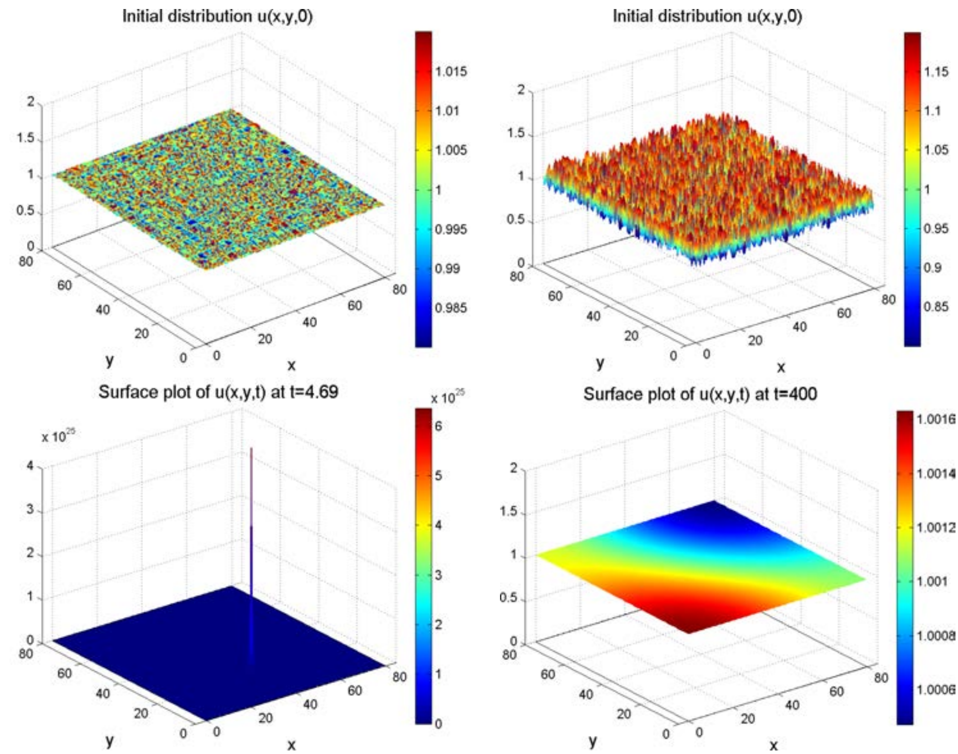
6.2. *Numerical Simulations*

The linear stability result shown above implies that a necessary condition for the instability of the homogeneous steady state $(\bar{u}, \bar{v}, \bar{w})$ is

$$\chi > \frac{\xi\gamma}{\alpha}\bar{u}^{m-1}\min\left\{\frac{\beta}{\delta}, \frac{\delta}{\beta}\right\}. \tag{6.6}$$

If $m = 1$, the instability condition (6.6) becomes $\chi\alpha > \xi\gamma\min\{\frac{\beta}{\delta}, \frac{\delta}{\beta}\}$ which explains why the sign of $\theta = \chi\alpha - \xi\gamma$ is important if $\beta = \delta$ irrespective of the value of the homogeneous steady states. It has been shown in [8, 45] that for any $\beta, \delta > 0$ and $\tau_1 = \tau_2 = 0$ or $\beta = \delta$ and $\tau_1 = \tau_2 = 1$, the solution of (1.2)–(1.4) with $m = 1$ may blow- up if $\theta > 0$ and is asymptotically a constant if $\theta \leq 0$. For $\beta \neq \delta$ and $\tau_1 = \tau_2 = 1$, it is conjectured that same results will hold but it remains to verify analytically. Here, we confirm this conjecture by the numerical simulations shown in Fig. 1. The initial data are set to be a small and large perturbation of the homogeneous steady states $(1, 1, 1)$ in Figs. 1(a) and 1(b), respectively. This indicates that whether the solution of (1.2)–(1.4) with $m = 1$ blows up or is an asymptotic constant is determined by the sign of θ, not caused by the initial values. This verifies the analytical results obtained in [8, 45].

If $m > 1$, for given $\chi, \xi, \alpha, \beta, \gamma, \delta > 0$, one can select the value of $\bar{u}$ such that (6.6) holds and pattern formation can be generated regardless of the sign of θ. We show the patterns formed by the solution component $u(x, y, t)$ of (1.2)–(1.4) with $m > 1$ for the case $\theta > 0$ in Fig. 2 where it is seen that no blow-up occurs and pattern formation arises. This is essentially different from the case $m = 1$ as shown in Fig. 1(a). More interestingly, we find that three different classes of patterns (aggregates, strips and reversed aggregates) are formed by the model (1.2)–(1.4) depending on the magnitude of the background states $(\bar{u}, \bar{v}, \bar{w}) = (\bar{u}, \frac{\alpha}{\beta}\bar{u}, \frac{\gamma}{\delta}\bar{u})$, where the initial values are set as a small perturbation of $(\bar{u}, \bar{v}, \bar{w})$. In the simulations, we deliberately

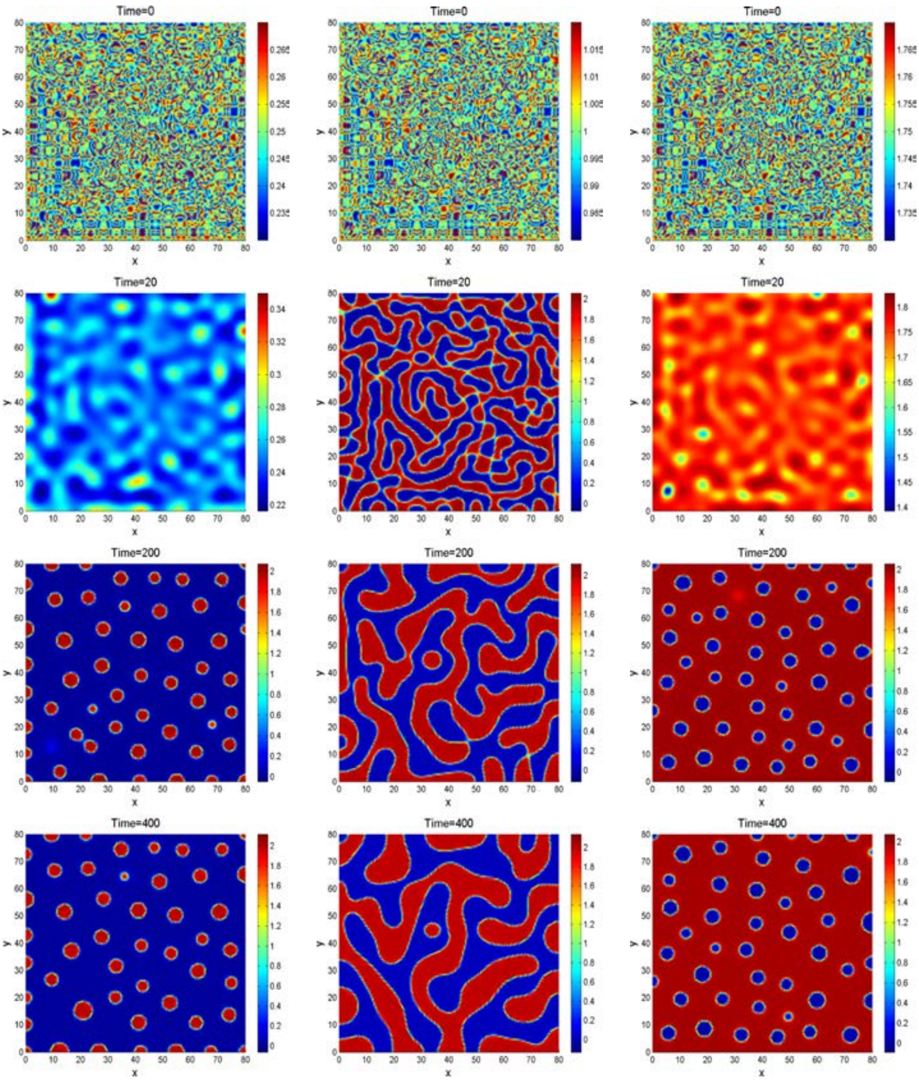


(a) $\theta > 0$ (b) $\theta < 0$

Fig. 1. Numerical illustration of solution component $u(x, y, t)$ of the system (1.2)–(1.4) with $m = 1$ and $\tau_1 = \tau_2 = 1$ in two dimensions for the case $\theta > 0$ and $\theta < 0$ where $\theta = \chi\alpha - \xi\gamma$. The initial data is set as a perturbation of the homogeneous background state $(\bar{u}, \bar{v}, \bar{w}) = (\bar{u}, \frac{\alpha}{\beta}\bar{u}, \frac{\gamma}{\delta}\bar{u})$, namely $u_0 = \bar{u} + r, v_0 = \bar{v} + r, w_0 = \bar{w} + r$, where r is a 2% small perturbation of the background state $(\bar{u}, \bar{v}, \bar{w})$ in (a) and a 20% perturbation of the background state $(\bar{u}, \bar{v}, \bar{w})$ in (b). The parameter values are: (a) $\bar{u} = 1, \chi = 8, \xi = 4, \alpha = \gamma = \beta = 1, \delta = 2$; (b) $\bar{u} = 1, \chi = 8, \xi = 10, \alpha = \gamma = \beta = 1, \delta = 2$.

choose $\beta = \delta$ and $\frac{v_0}{\alpha} = \frac{w_0}{\gamma}$ to make the numerical results comparable with the theoretical results obtained in Theorem 1.3. From the parameter values chosen in Fig. 2, one derives that the solution component $u(x, y, t)$ satisfies that $0 < u \leq 2$ according to the results in Theorem 1.3. This is exactly verified by our numerical results shown in Fig. 2. We remark if $\beta \neq \delta$, the model (1.2)–(1.4) will generate the qualitatively same pattern formations as for the case $\beta = \delta$ (not shown here for brevity).

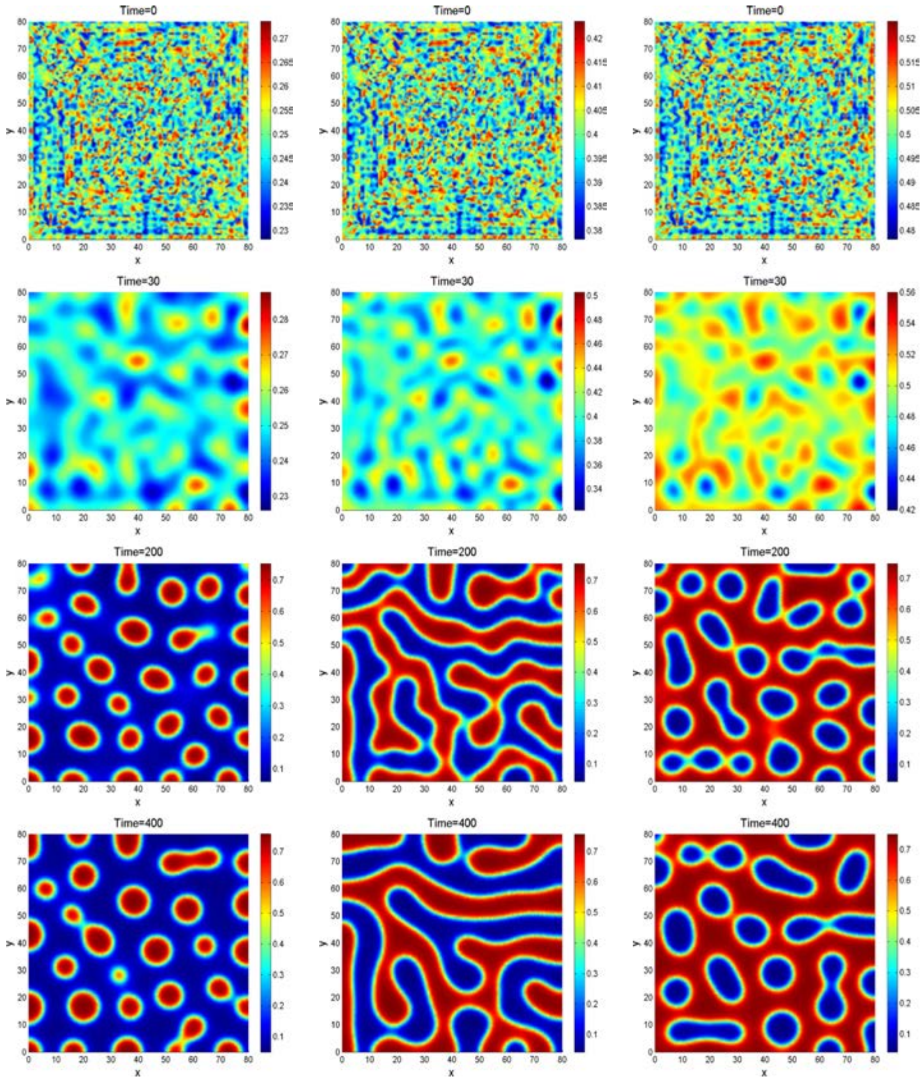
Next, we examine the possible pattern formations generated from the case $m > 1$ and $\theta < 0$. The numerical patterns of the solution component $u(x, y, t)$ were shown in Fig. 3. It is found the solution does not converge to a constant, which is significantly different from the case $m = 1$ and $\theta < 0$ shown in Fig. 1(b). Furthermore, the pattern variety is similar to the case $\theta > 0$ where three classes of patterns



(a) (b) (c)

Fig. 2. Numerical patterns formed by the solution component $u(x, y, t)$ to the system 1.2–(1.4) with $m > 1$ in two dimensions for the case $\theta = \chi\alpha - \xi\gamma > 0$. The initial data is set as a perturbation of the homogeneous background state $(\bar{u}, \bar{v}, \bar{w}) = (\bar{u}, \frac{\alpha}{\beta}\bar{u}, \frac{\gamma}{\delta}\bar{u})$, namely $u_0 = \bar{u} + r, v_0 = \bar{v} + r, w_0 = \bar{w} + r$, where r is a 2% small perturbation of the homogeneous background state $(\bar{u}, \bar{v}, \bar{w})$. The parameter values are $m = 2, \chi = 8, \xi = 4, \alpha = \gamma = \beta = \delta = 1$ and $\bar{u} = 0.25$ in (a), $\bar{u} = 0.5$ in (b) and $\bar{u} = 0.75$ in (c).

(aggregates, strips and reversed aggregates) are also generated depending on the value of the background states $(\bar{u}, \bar{v}, \bar{w})$ around which the initial data is prescribed. By a simple calculation, it is easy to see that the results of Theorem 1.3 are consistent with the numerical results. We furthermore stress that the numerical results



(a) (b) (c)

Fig. 3. Numerical patterns of the solution component $u(x, y, t)$ to the system (1.2)–(1.4) with $m > 1$ and $\tau_1 = \tau_2 = 1$ in two dimensions for the case $\theta = \chi\alpha - \xi\gamma < 0$. The initial data is set as a perturbation of the homogeneous background state $(\bar{u}, \bar{v}, \bar{w}) = (\bar{u}, \frac{\alpha}{\beta}\bar{u}, \frac{\gamma}{\delta}\bar{u})$, namely $u_0 = \bar{u} + r, v_0 = \bar{v} + r, w_0 = \bar{w} + r$, where r is a 2% small perturbation of the homogeneous background state $(\bar{u}, \bar{v}, \bar{w})$. The parameter values are $m = 2, \chi = 8, \xi = 10, \alpha = \gamma = \beta = \delta = 1$ and $\bar{u} = 0.25$ in (a), $\bar{u} = 0.4$ in (b) and $\bar{u} = 0.5$ in (c).

for the remaining case $\theta = 0$ are qualitatively same as the case $\theta \neq 0$ and they are not shown here to avoid the repetition. In summary, except verifying our analytical results on the boundedness of solutions in Theorems 1.1 and 1.3, we can draw the following conclusions from our numerical results that are not yet proved analytically:

(a) The pattern formation of the modified model (1.2)–(1.4) with $m > 1$ exists for any model parameter values irrespective of the sign of $\theta = \chi\alpha - \xi\gamma$ and solutions will neither blow up nor asymptotically converge to a constant. This is essentially different from the case $m = 1$;

(b) The variety of patterns is determined by the magnitude of homogeneous background states $(\bar{u}, \bar{v}, \bar{w})$, where the initial data is set as a small perturbation of $(\bar{u}, \bar{v}, \bar{w})$. The patterns change from aggregates to reserved aggregates as the initial value is increased and the strips are the intermediate patterns between them. In other words, the aggregates form only if the magnitude of background states $(\bar{u}, \bar{v}, \bar{w})$ of initial values is small. If the magnitude of $(\bar{u}, \bar{v}, \bar{w})$ is large, the model will generate patterns like stripe or reversed aggregates instead of aggregates.

Related to the biological relevance, our results imply that (1.2)–(1.4) with $m > 1$ is able to interpret the spontaneous aggregation of microglia due to its interaction with the combined attractive and repulsive chemicals. Specifically, if microglia interact with both chemoattractant and chemorepellent linearly (namely $m = 1$), then the aggregation cannot occur. However, if microglia interact with chemoattractant linearly but with chemorepellent super-linearly (namely $m > 1$), the aggregation pattern will arise if the background states $(\bar{u}, \bar{v}, \bar{w})$ of initial values are suitably small.

As $\xi = 0$ (i.e. no repulsion), the model (1.2) becomes the classical Keller–Segel model which does not admit pattern formation in multi-dimensions due to its blow-up nature (e.g. see [11, 13, 14, 31, 33, 34, 49]). As $\chi = 0$ (i.e. no attraction), the model (1.2) becomes the repulsive chemotaxis model (1.5) which has no pattern formation either since its solution asymptotically converges to a constant (see [5, 43, 45]). Therefore, the modified model (1.2) with $m > 1$ (super-linear repulsive sensitivity) offers us a possible mechanism to test the hypothesis that the aggregate of microglia is due to the combined interaction of attraction and repulsion, and neither of them is dispensable. However, we should remark that our revision might not be the only (or unique) way to modify the attraction–repulsion chemotaxis model (1.1) to generate pattern formation from the modeling point of view. For instance, one can try incorporating the volume-filling effect [36, 47] into the model (1.1) as done in [38]. However, if so, the resulting model can generate aggregates without repulsion and hence the repulsion becomes dispensable for the aggregation pattern formation. This, however, is not desirable for testing the hypothesis. In this sense, our revision $m > 1$ for the model provides a valuable perspective to model the aggregation caused by the combined interaction of attraction and repulsion although experiment results or date have not been available to support it by far. This in turn reflects the role of mathematical modeling for complex biology. But we by no means exclude other possible ways to modify the model such as the sensitivity related to attraction, which indeed imposes an interesting question for the further study but exceeds the scope of this paper.

From the analytical point of view, there are various unsolved questions remaining in our study due to the technical difficulty as listed below:

(1) The boundedness of solutions for the full model (1.2)–(1.4) with $m > 1$ and $\tau_1 = \tau_2 = 1$ in two or higher dimensions;
(2) The existence of nonconstant stationary solutions of the system (1.2)–(1.4) with $m > 1$;
(3) The large time behavior of solutions of the system (1.2)–(1.4) with $m > 1$;

In the paper, we only consider the model (1.2)–(1.4) for the case $m > 1$. The case for $m < 1$ is not investigated in this paper. But we conjecture the solution of the system (1.2)–(1.4) with $m < 1$ will blow-up regardless of the sign of θ. However, this is a challenging problem and will be left for future pursue.

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