On Chemotaxis Models with Cell Population Interactions

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Abstract. This paper extends the volume filling chemotaxis model [18, 26] by taking into account the cell population interactions. The extended chemotaxis models have nonlinear diffusion and chemotactic sensitivity depending on cell population density, which is a modification of the classical Keller-Segel model in which the diffusion and chemotactic sensitivity are constants (linear). The existence and boundedness of global solutions of these models are discussed and the numerical pattern formations are shown. The further improvement is proposed in the end.

Key words: chemotaxis, Keller-Segel model, cell interactions, nonlinear diffusion, blow up, volume filling, chemotactic sensitivity, pattern formation

AMS subject classification: 35K55, 35K57, 35K61, 92C15, 92C17, 92B99

1. Introduction

Chemotaxis is a process by which cells alter their movement reacting to the presence of a chemical substance. The chemotaxis is called attractive (positive) if the chemotactic movement is toward higher concentration of the chemical substance, and repulsive (negative) if the movement direction is opposite. It is a fundamental cellular process in the development of multicellular organisms and particularly plays essential roles in embryonic development, tissue homeostasis, wound healing, immune response, progression of diseases, as well as finding food, repellent action and forming the multicellular body of protozoa [27, 4].

The first mathematical model describing chemotaxis at population level was proposed by Keller-Segel [10] whose model provided a cornerstone for all subsequent mathematical modeling of chemotaxis. The original Keller-Segel model consists of four coupled parabolic equations to de-
scribe the aggregation of cellular slime molds \textit{Dictyostelium discoideum}. Under the quasi-steady-state assumptions for the chemical reaction, the Keller-Segel model reduces to the following two strongly coupled nonlinear parabolic equations

\[
\begin{align*}
\frac{\partial u}{\partial t} &= \nabla \cdot \left( \rho(u, v) \nabla u - \varphi(u, v) \nabla v \right), \quad x \in \Omega \\
\frac{\partial v}{\partial t} &= D_v \Delta v + \mu u - \delta v
\end{align*}
\]  
(KS)

with initial data

\[
\begin{align*}
u(0, x) &= u_0(x), \quad v(0, x) = v_0(x), \quad x \in \Omega
\end{align*}
\] (1.1)

where \(u\) denotes the cell density on a given domain \(\Omega \subseteq \mathbb{R}^N\) and \(v\) represents the chemical concentration. The first equation of (KS) describes the cell dynamics and comprises a diffusive flux modeling random motion of cells, and an advective flux modeling directed cell movement with velocity proportional to the concentration gradient of the chemical. \(\rho(u, v)\) denotes cell diffusion coefficient which is a measure of the vigor of random motion of cells and \(\varphi(u, v)\) represents the chemotactic sensitivity measuring the strength of the influence of the chemical concentration gradient on the flow of cells. The second equation of (KS) is a reaction-diffusion equation describing the chemical kinetics with linear production and degradation with constant rates \(\mu, \delta > 0\). The chemotactic movement described by the Keller-Segel model (KS) is often referred as endogenous chemotaxis [14] meaning that the chemical is emitted by cells themselves such as \textit{E. Coli} and \textit{Dictyostelium discoideum} (see [14] and reference therein).

Since then a large amount of theoretical studies have been performed for various representations of functions \(\rho(u, v)\) and \(\varphi(u, v)\). Among these, the most extensively studied one is the following

\[
\rho(u, v) = d, \quad \varphi(u, v) = \chi u
\] (1.2)

with positive constants \(d, \chi\). Following the nomenclature of Childress and Percus [15], the model (KS) with (1.2) is called the classical (minimal) chemotaxis model which contains the rich dynamics such as finite time blow up behavior, global existence of solutions and spatial pattern formation. The detailed results are summarized in two review articles [8, 9] by Hortsmann and in the text book of Perthame [20].

However the finite time blow up behavior of solutions limits the applicability of model to the real world. So much efforts based on either biological inspiration or mathematical motivation have been made to extend (or improve) the classical model such that the extended models prevent finite time blow up and exhibit the spatial pattern formations. Such an extension is termed regularization and most of results are summarized in a review article [5]. In this paper, we shall pursue this direction further by considering cell population interactions which lead to nonlinear diffusion and chemotactic sensitivity functions.

### 1.1. Motivations

The classical Keller-Segel model (KS), (1.2) describes the aggregation of cells \(u\) to the location with the highest concentration of \(v\). A higher concentration of \(u\) in turn emits more chemical \(v\) through the source term in the second equation of (KS). This forms a positive feedback which
promotes the aggregation of cells and finally raise cell density to blow up. Hence the lack of control of such a positive feedback is the leading reason of resulting in blow up of solutions.

However in chemotactic movement, cells aggregate at the location with the highest chemical concentration where cells will interact each other more often. Hence cell interactions will inevitably come to play an important role and affect both cell random motion and chemotactic movement [19]. Here cell-cell interaction may happen between cells by contact, fusion or junction or between cells and chemical through the signal transmission [3]. Hence intuitively the more appropriate model should be of the following form

\[
\begin{align*}
    u_t &= \nabla \cdot (D(u)\nabla u - \chi u \phi(u)\nabla v) \\
    v_t &= D_v \Delta v + \mu u - \delta v
\end{align*}
\]

(1.3)

where both diffusion coefficient \(D(u)\) and chemotactic sensitivity function \(\phi(u)\) depend on the cell density. The factor \(u\) in the chemotactic term in the first equation of (1.3) comes from the fact that the chemotactic flux must be proportional to their density due to Fick’s law (see [10]).

The majority of chemotaxis models in the literature assumed a constant diffusion coefficient [5] yet it is more likely that the diffusion should nonlinearly depend on the cell density or chemical concentration as described above. There are only few models which phenomenologically incorporate the nonlinear dependencies in cell diffusion. Höfer et al [7] proposed a model describing cell-cell adhesion for Dictyostelium discoideum aggregation by assuming \(D(u) = \mu_1 + \mu_2 u_m^4/(u_m^2 + u^4)\) with \(u_m\) being a critical cell density. In a theoretical study [11] of cross diffusion model, Kuiper and Lung consider a nonlinear diffusion of the form \(D(u) = P(u), \phi(u) = 1\) with condition \(P(u) > c(1 + u)\) for some positive constant \(c\). In another theoretical work [16], Kowalczyk considered the form \(D(u) = u^n, \quad n > 1\). In a recent paper [2], Choi and Wang study a chemotaxis model \(D(u) = 1/(1 - u)^\alpha, \quad \alpha > 0\), which assumes cells can increase their random motility to relieve the crowding. Finally in [13], the form of \(D(u) = (1 + u)/(1 - u + u \ln u)\) was derived as a continuous limit of the stochastic discrete cellular Potts model with extended cell representation.

However in all above nonlinear diffusion chemotaxis models, it was assumed that chemotactic sensitivity function \(\phi(u)\) was a constant. Hence the correlation between the diffusion and chemotactic sensitivity was ignored although they should be intrinsically related each other [10]. The first model that connected \(D(u)\) with \(\phi(u)\) was given in [18] using the volume filling mechanism. The global existence of classical solutions to the model of [18] was shown in [6] and generalized in [28, 29, 26, 30]. The purpose of this paper is to extend the volume filling mechanism by taking into account the cell population interactions and derive some appropriate chemotaxis models with nonlinear diffusion and chemotactic sensitivity. These models are derived from a random walk model instead of using the phenomenological methodology. Furthermore the correlation between cell diffusion and chemotactic sensitivity will be examined.

2. Derivation of the general model

In this section, we will briefly recall the derivation in [18, 26] of the general volume filling chemotaxis model derived from the random walk framework. Then we incorporate the cell interactions
into the model through a transition probability function which will be specified in the subsequent section. The biological implications will be discussed along the study.

The derivation of volume filling chemotaxis model departed with a continuous-time and discrete-space random walk in [25] on a one-dimensional equi-distant discrete lattice

$$\frac{\partial u_i(\tau)}{\partial \tau} = T_{i-1}^+ u_{i-1} + T_{i+1}^- u_{i+1} - (T_i^+ + T_i^-) u_i,$$

(2.1)

where $u_i(\tau)$ is defined as the particle density at lattice point $i \in \mathbb{Z}$ at time $\tau$, and $T_i^\pm$ are the transition rates (or transition probabilities per unit of time) for a one-step jump to the next lattice point $i \pm 1$.

The volume filling mechanism [18] postulates that cells have finite size and cells are limited to move into regions that are already occupied by other cells. This effect is modeled by introducing a function $q(u)$, which represents the probability of finding a neighboring space given a local cell density $u_i$, into the transition rates through

$$T_i^\pm = q(u_{i\pm1})(\alpha + \beta(v_{i\pm1} - v_i))$$

(2.2)

where $\alpha$ and $\beta$ are positive constants.

The function $q(u)$ fulfill the following hypothesis (see [18]):

There is a finite number $\tilde{u}$, called crowding capacity [26], which is the maximal number of cells that can be accommodated at any site (i.e. unit area), such that

$$q(\tilde{u}) = 0, \quad 0 < q(u) \leq 1, \quad q'(u) \leq 0 \text{ for } 0 \leq u < \tilde{u}. \quad (2.3)$$

If furthermore $q(u)$ satisfies an additional condition $q''(u) > 0$ for all $0 \leq u \leq \tilde{u}$, then $q(u)$ is endowed with a special name squeeze probability in [26] to describe the cell elasticity property. Hereafter we shall call $q(u)$ squeeze probability for convenience if no confusion is caused. Now substituting (2.2) into random walk model (2.1) and applying the Taylor expansion to the right hand side of (2.1), one can deduce that

$$\frac{\partial u(x, \tau)}{\partial \tau} = h^2 \alpha \left( q(u) \frac{\partial^2 u}{\partial x^2} - u \frac{\partial^2 q}{\partial x^2} \right) - 2h^2 \beta \frac{\partial}{\partial x} \left( uq(u) \frac{\partial v}{\partial x} \right) + O(h^3),$$

where $h$ is the lattice mesh size such that $x = ih$ and $u(x, t) = u_i(t)$.

Assuming that there is a time scaling constant such that $\tau = \sigma t$ and the following limit

$$\kappa = \lim_{h \to 0, \sigma \to \infty} \sigma h^2$$

(2.4)

exists, one can take the diffusion limit of (2.1) and obtain

$$u_t = (d(q(u) - uq'(u))u_x - \chi uq(u)v_x)_x,$$

(2.5)

with

$$d = \alpha \kappa, \quad \chi = 2 \beta \kappa.$$  

(2.6)
The above derivations extend to higher dimensions without changes. Then if we write (2.5) as a higher dimensional form, and combine it with the dynamical equation for \( v \), we obtain the following volume filling Keller-Segel type model [18]

\[
\begin{align*}
\begin{cases}
u_t = \nabla \cdot (d(q(u) - uq'(u))\nabla u - \chi u q(u) \nabla v) \\
v_t = D_v \Delta u + \mu u - \delta v.
\end{cases}
\end{align*}
\]

(MVF)

In contrast to the previous nonlinear diffusion chemotaxis models where the cell diffusion coefficient has no correlation with the chemotactic sensitivity function, the volume filling model (MVF) not only provides a microscopic origin but also explicitly establishes a communication between the diffusion and chemotactic sensitivity.

3. Squeeze probability with cell population interaction

The specification of the general model (MVF) depends on the representation of squeeze probability function \( q(u) \) which is characterized by the interactions between cells themselves and between cells and chemicals. We shall distinguish them in the following analysis.

3.1. Cell self-interaction

To apply the volume filling model, we need to identify the appropriate forms of squeeze probability function \( q(u) \) which is confined by condition (2.3). For the sake of convenience, we let the crowding capacity \( \bar{u} = 1 \) with loss of generality. Below we first consider the influences of the interactions between cells only. We shall discuss four different squeeze probabilities which are related to cell types.

(I) If cells are fluid, cells can fill all open spaces. Then the cell interactions have no important impact on the squeeze probability which takes the form

\[
q(u) = \begin{cases} 1, & 0 \leq u \leq 1, \\ 0, & u > 1. \end{cases}
\]

(FC)

Substituting it into the volume filling model (MVF), one obtains the following model

\[
\begin{align*}
\begin{cases}
u_t = \nabla \cdot (d\nabla u - \chi u \nabla v) \\
v_t = D_v \Delta u + \mu u - \delta v
\end{cases}
\end{align*}
\]

(MFC)

which is the classical Keller-Segel model (KS), (1.2).

(II) If cells are solid blocks, \( q(u) \) is proportional to the numbers of occupants and hence linearly dependent of cell density (numbers), and has the following representation

\[
q(u) = \begin{cases} 1 - u, & 0 \leq u \leq 1, \\ 0, & u > 1. \end{cases}
\]

(SC)
Substituting it into (MVF), we obtain
\[
\begin{align*}
\frac{\partial u}{\partial t} &= \nabla \cdot (d \nabla u - \chi u (1 - u) \nabla v) \\
\frac{\partial v}{\partial t} &= D_v \Delta v + \mu u - \delta v
\end{align*}
\] (MSC)

which was the model considered in [6].

(III) If cells are elastic (or plastic), they can change (or adapt) their configurations to squeeze into open spaces. As a consequence, the squeeze probability is nonlinear and piecewise higher than that for solid blocks. Hence \( q(u) \) is of the form
\[
q(u) = \begin{cases} 
1 - u^\gamma, & 0 \leq u \leq 1, \gamma > 1 \\
0, & u > 1,
\end{cases}
\]
(EC)

The substitution of (EC) into (MVF) gives rise to the following model
\[
\begin{align*}
\frac{\partial u}{\partial t} &= \nabla \cdot (d (1 + (\gamma - 1) u^\gamma) \nabla u - \chi u (1 - u^\gamma) \nabla v) \\
\frac{\partial v}{\partial t} &= D_v \Delta v + \mu u - \delta v
\end{align*}
\] (MEC)

which was the model discussed in [26].

(IV) As we have seen above, the resulting chemotaxis models (MFC) and (MSC) have linear (constant) diffusion and the model (MEC) has nonlinear diffusion. The mechanism of increasing population diffusion due to population pressure to avoid overcrowding has been widely used in modeling animal dispersal [22, 23, 24], wolf territory formation [14], and population genetics and combustion [17]. However for biological cells, individuals will interact much more often when crowding with an inevitable influences on mobility [19] and chemotactic sensitivity [18]. Typically the crowding or packing effects may hinder both random motion and chemotactic movement of cells. As a consequence nonlinear decreasing diffusion and chemotactic sensitivity may result [14, 1, 21]. With this motivation we thus propose the following squeeze probability
\[
q(u) = \begin{cases} 
(1 - u)^r, & 0 \leq u \leq 1, \ r > 1 \\
0, & u > 1,
\end{cases}
\]
(TC)

Substituting this into (MVF), one gets the following chemotaxis model
\[
\begin{align*}
\frac{\partial u}{\partial t} &= \nabla \cdot (d (1 - u)^{r-1} (1 - u(1 - r)) \nabla u - \chi u (1 - u)^r \nabla v) \\
\frac{\partial v}{\partial t} &= D_v \Delta v + \mu u - \delta v.
\end{align*}
\] (MTC)

It is straightforward to check that both diffusion and chemotactic sensitivity function in (MTC) decrease with respect to cell density \( u \). A numerical plot and comparison of the above four different representations of squeeze probability is given in Fig. 1. Here we see that the squeeze probability function (TC) is smallest, which reflects the fact that the packing effect decreases cell mobility by hindering both cell random and chemotactic movement.
Remark 1. Corresponding to the case of fluid cells, the classical Keller-Segel model becomes a special case of volume filling model.

Remark 2. When cells are solid blocks or fluids, the diffusion coefficient of cells is a constant given by $D$, but the chemotactic motility between solid blocks and fluids is different. Whereas if cells are elastic, the diffusion coefficient of cells is nonlinear and depends on the cell density.

If we write

$$D_1(u) = D_2(u) = d, \quad D_3(u) = d(1 + (\gamma - 1)u\gamma), \quad D_4(u) = d(1 - u)^{r-1}(1 - u(1 - r))$$

(3.1)

and

$$\phi_1(u) = 1, \quad \phi_2(u) = 1 - u, \quad \phi_3(u) = 1 - u\gamma, \quad \phi_4(u) = (1 - u)^r,$$

(3.2)

above four models (MFC), (MSC), (MEC) and (MTC) can be considered as various specific representations of the general model (1.3), where the diffusion coefficients in (MFC), (MSC), (MEC) and (MTC) correspond to $D_1(u), D_2(u), D_3(u)$ and $D_4(u)$, respectively, and the chemotactic sensitivity functions in (MFC), (MSC), (MEC) and (MTC) correspond to $\phi_1(u), \phi_2(u), \phi_3(u)$ and $\phi_4(u)$, respectively.

It is straightforward to verify the following results.

Lemma 3. For any $0 \leq u \leq 1$, it follows that $\frac{d}{du}D_3(u) > 0, \frac{d}{du}D_4(u) < 0, D_4(u) < D_1(u) = D_2(u) < D_3(u)$, and $\phi_4(u) < \phi_2(u) < \phi_3(u) < \phi_1(u)$.  

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The results in Lemma 3 have the following biological implications.

**Remark 4.** The packing effect slows down both the cell diffusive and chemotactic mobility as cell density increases. The cells under packing effect have the lowest diffusion and chemotactic sensitivity. The fluid cells have the largest chemotactic mobility since the packing effect has the least impact on fluid cells. However the elastic cells possess the largest diffusion which can be understood that elastic collision may locally enhance cell random motion.

Next issue to be considered is the global existence of solutions to the chemotaxis models derived above. The typical qualitative feature of the classical Keller-Segel model in two dimensions with zero-flux boundary conditions is the finite time blow up of solutions if the initial cell mass is suitably large such that \( \int_\Omega u_0 dx > \frac{4\pi D}{\mu \chi} \). Most of related results up to 2003 were summarized in review paper [8] and the regularized models (which means the modification of the classical Keller-Segel model such that global solutions exist) were discussed in [5]. The global existence of classical solutions for model (MSC) and (MEC) have been established in paper [6] and [26], respectively, whereby it was shown that \( 0 \leq u \leq 1 \) for all \( t \geq 0 \) if \( 0 \leq u_0 \leq 1 \). However for system (MTC) one generally can not expect the global classical solutions since both the diffusion and chemotactic sensitivity degenerate at the threshold number \( u = 1 \). We observe that the model (MTC) is a special case considered in [12]. To see that we define

\[
D(u) = d(1 - u)^{r-1}(1 - u(1 - r)), \quad h(u) = \chi u(1 - u)^r, \quad r > 1.
\]

It is evident that

\[
D(1) = h(0) = h(1) = 0 \quad \text{and} \quad \begin{cases} D(u) > 0, & u \in [0, 1) \\ h(u) > 0, & u \in (0, 1). \end{cases}
\]

So the condition (7) in [12] is satisfied. Furthermore we define

\[
\mathcal{D}(s) = \int_0^s D(u) du, \quad s \in [0, 1].
\]

Let \( s_1, s_2 \in [0, 1] \) and \( s_1 < s_2 \). Then applying the mean value theorem to \( \mathcal{D}(s) \) on \([s_1, s_2]\), there is a number \( \xi_1 \in (s_1, s_2) \) such that \( \mathcal{D}(s_1) - \mathcal{D}(s_2) = \mathcal{D}'(\xi_1)(s_1 - s_2) \). Applying the mean value theorem again to the function \( h(u) \) on \([s_1, s_2]\), there exists a number \( \xi_2 \in (s_1, s_2) \) so that \( h(s_1) - h(s_2) = h'(\xi_2)(s_1 - s_2) \). Hence

\[
(h(s_1) - h(s_2))^2 = (h'(\xi_2))^2(s_1 - s_2)^2 = \frac{(h'(\xi_2))^2}{\mathcal{D}'(\xi_1)}(s_1 - s_2)(\mathcal{D}(s_1) - \mathcal{D}(s_2))
\]

where we have use the fact that \( \mathcal{D}'(\xi_1) = D(\xi_1) > 0 \) and \( h'(\xi_2) \neq 0 \) for \( \xi_1, \xi_2 \in (s_1, s_2) \). Therefore the condition (9) in [12] is satisfied.

Using the results of [12, Theorem 2], we obtain the following existence theorem for the global weak solutions of system (MTC).
Theorem 5. Let system (MTC) satisfy the zero-flux boundary condition \( \frac{\partial u}{\partial \nu} = \frac{\partial v}{\partial \nu} = 0, \ x \in \partial \Omega \) where \( \nu \) denote the unit outward normal vector at the boundary of \( \Omega \). Assume that \((u_0, v_0) \in L^\infty(\Omega) \) with \( 0 \leq u_0(x) \leq 1, \ v_0(x) > 0 \) for any \( x \in \Omega \). Then there exists a unique global weak solution (in the sense of distribution) to (MTC) such that

\[
0 \leq u(t, x) \leq 1, \ v(t, x) > 0 \ a.e. \ in \ [0, \infty)
\]

and

\[
\begin{align*}
    u & \in L^\infty((0, \infty) \times \Omega) \cap C_w([0, \infty); L^2(\Omega)) \\
v & \in L^\infty((0, \infty) \times \Omega) \cap H^1([0, \infty); L^2(\Omega)) \cap L^2([0, \infty); H^2(\Omega))
\end{align*}
\]

where \( C_w([0, \infty); L^2(\Omega)) \) denotes the set of functions from \([0, \infty)\) in \( L^2(\Omega) \) which are continuous in the weak topology of \( L^2(\Omega) \).

Next we discuss the possibility of the prevention of blow up of solutions for chemotaxis models with nonlinear diffusion and chemotactic sensitivity in a more general sense. In chemotactic movement there are two competitive dynamics: diffusion and directed (chemotactic) movement. When diffusion dominates the overall dynamics, the global bounded solution exists. Whereas if chemotaxis dominates the overall dynamics, the solution will blow up. In the classical Keller-Segel model, the diffusion and chemotactic sensitivity are constant and hence independent. When cells aggregate due to chemotaxis at the site of highest chemical concentration, the increased local density of cells in turn produce more chemical and result in a steeper chemical concentration gradient at the same site. This positive feedback of chemotactic movement finally leads to the blow up of the local cell density. However, in the chemotaxis model (MSC), although the cell diffusion remains a constant, the chemotactic sensitivity decrease with respect to cell density. So the cell aggregation receives control and cell density can not increase continuously. In the chemotaxis model (MEC), diffusion increases and chemotactic sensitivity decreases with respect to cell density, so the diffusion will take more dominance than that of the model (MSC). The model (MTC) describes a distinctive mechanism which assumes that the cell crowding hinder both random and chemotactic motility. The common feature of three models (MSC), (MEC) and (MTC) is that the positive feedback in the classical Keller-Segel model was tuned off, which leads to the existence of global bounded solutions.

The above results and analysis may also deliver us a message that the correlation between diffusion and chemotactic mobility, particularly the property of the ratio of the chemotactic sensitivity \( \phi(u) \) to the diffusion coefficient \( D(u) \), may play a role in determining the solution behavior. Indeed we can readily verify that the function

\[
R_i(u) = \frac{\phi_i(u)}{D_i(u)}, \ i = 2, 3, 4
\]

is decreasing with respect to cell density \( u \) (see also Fig. 2). This means that cell chemotactic mobility relative to random motility declines when cells get crowded. Hence the overcrowding
can be prevented due to the strong dispersive effect. However we observe that in the classical Keller-Segel model

$$R_1(u) = \frac{\phi_1(u)}{D_1(u)} = \frac{1}{d}$$

which is a constant. This leads to the finite-time blow up of solutions. Returning to the general model (1.3), if we define a ratio function

$$R(u) = \frac{\phi(u)}{D(u)}$$

we conjecture that if $R'(u) < 0$, then the classical (or weak) bounded solution of (1.3) may exist globally, and if $R'(u) \geq 0$, the solution may blow up in two dimensional spaces. Here we justify this conjecture by using volume filling models which is a special case of our conjecture. Proving this conjecture however is outside the scope of the present paper and left for the future.

### 3.2. Cell-chemical interaction

The determination of squeeze probability in the preceding subsection ignores the local interactions between cells and chemicals. When cells get crowded during chemotactic movement, the chemical concentration also increases constantly since the chemical is secreted by cells themselves [14]. Although the size of chemicals is smaller than cells, the highly packed chemicals still occupy certain spaces which will prevent cells from penetrating. A simplest way to incorporate this effect into the model is to assume that the squeeze probability depends on the total population density
$u + v$ instead of only $u$. Hence we propose the following \textit{squeeze probability}

$$T_i^\pm = q(w_{i\pm 1})(\alpha + \beta(v_{i\pm 1} - v_i)),$$

(3.3)

where $w$ denotes the total population density under our consideration

$$w = u + v.$$

Then substituting (3.3) into the random walk framework (2.1), using the Taylor expansion and scaling argument as we did in section 2, one obtains the following equation by taking the diffusion limits

$$u_t = (dq(w)u_x - \chi uq(w)v_x)_x - (uq'(w)(w)_x)_x,$$

(3.4)

where $d$ and $\chi$ are the same as in (2.6). Equation (3.4) can be rearranged as

$$u_t = (d(q(w) - uq'(w))u_x - u(dq'(w) + \chi q(w))v_x)_x,$$

(3.5)

which is comparable with the model (2.5). But here the cell-chemical interaction is incorporated.

Writing (3.5) as a multi-dimensional form, we obtain the following Keller-Segel type model

$$\begin{cases}
  u_t = \nabla \cdot (D(u, v)\nabla u - \phi(u, v)\nabla v) \\
  v_t = D_v\Delta v + \mu u - \delta v,
\end{cases}$$

(3.6)

with

$$D(u, v) = d(q(u + v) - uq'(u + v)), \phi(u, v) = u(dq'(u + v) + \chi q(u + v)).$$

Depending on cell types, the specification of $q(w)$ can be the same as $q(u)$ given in the preceding subsection by simply replacing $u$ by $w$. To avoid repetition, we only consider the case that particles are solid blocks. Other cases can be examined analogously. That is

$$q(w) = q(u + v) = \begin{cases} 
1 - (u + v), & 0 \leq u + v \leq 1, \\
0, & u + v > 1.
\end{cases}$$

(3.7)

Note that here the number 1 is the crowding capacity accommodating the total population of cells and chemicals. Substituting (3.7) into model (3.6), we end up with the following chemotaxis model

$$\begin{cases}
  u_t = \nabla \cdot (d(1 - v)\nabla u - (1 - d/\chi - u - v)\nabla v) \\
  v_t = D_v\Delta v + \mu u - \delta v.
\end{cases}$$

(MVFC)

In chemotactic movement, the cell diffusion is small in the system parameters [14]. So we assume that $d/\chi \ll 1$. Then chemotactic mobility will be turned off at $u + v = 1 - d/\chi$ in the model (MVFC), and total population density $u + v$ is bounded by $1 - d/\chi$ if $u_0 + v_0 < 1 - d/\chi$. However the mathematical proof is not straightforward and we only show the numerical results in section 5.
4. Linear stability analysis

The parameter space in which spatial pattern formation arises can be identified by the standard linear stability analysis at the homogeneous steady state of chemotaxis models. Here we briefly show the method for the general Keller-Segel type model (KS) in one dimension and apply the results to the specific models (MFC), (MSC), (MEC), (MTC) and (MVFC).

Let the homogeneous steady state of the model (KS) be \((u_s, v_s) = (u_s, \mu u_s/\delta)\). Define \(w\) as a small perturbation of \((u, v)\), i.e. \(w = (u - u_s, v - v_s)^T\). Then the linearization of the model (KS) about \((u_s, v_s)\) is

\[ \dot{w} = Aw + B\Delta w \] (4.1)

where

\[ A = \begin{pmatrix} 0 & 0 \\ \mu & -\delta \end{pmatrix}, \quad B = \begin{pmatrix} \rho(u_s, v_s) & -\varphi(u_s, v_s) \\ 0 & D_v \end{pmatrix}. \]

Substituting \(w(t, x) = \tilde{w}\exp(\lambda t + ikx)\) into (4.1), after some algebra, we can show that the stability of the homogeneous steady state \((u_s, v_s)\) is determined by the eigenvalue of the following stability matrix (e.g. see [14])

\[ M = \begin{pmatrix} -\rho(u_s, v_s)k^2 & \varphi(u_s, v_s)k^2 \\ \mu & -\delta - D_vk^2 \end{pmatrix}, \]

where \(k \geq 0\) denotes the spatial eigenvalue (mode) of the Laplace operator, i.e. \(\Delta w + k^2w = 0\), on a given bounded domain with zero flux boundary condition, and \(\lambda\) denotes the temporal growth rate as an eigenvalue of \(M\). If the stability matrix \(M\) has eigenvalues with positive real part, then the homogeneous steady state \((u_s, v_s)\) is unstable and the spatial pattern formation can be expected. The eigenvalues of \(M\) are obtained by the determinant-trace formula

\[ \lambda_{1,2} = \frac{\text{tr}\,M}{2} \pm \frac{1}{2} \sqrt{(\text{tr}\,M)^2 - 4 \det\,M}, \]

with

\[ \text{tr}\,M = -\rho(u_s, v_s)k^2 - D_vk^2 - \delta \]

\[ \det\,M = \rho(u_s, v_s)D_vk^4 + (\delta \rho(u_s, v_s) - \mu \varphi(u_s, v_s))k^2. \]

It is helpful to observe that we always have an eigenvalue \(\lambda = 0\) if \(k = 0\). For the homogeneous steady state to be unstable, we require that \(\text{Re}\,\lambda(k) > 0\) for some \(k \neq 0\). Since \(\text{tr}\,M < 0\), \(\text{Re}\,\lambda_{1,2}(k)\) can be positive only if \(\det\,M < 0\), which translates to

\[ \rho(u_s, v_s)D_vk^2 + \delta \rho(u_s, v_s) - \mu \varphi(u_s, v_s) < 0. \]

Then a necessary condition to fulfill the above inequality is

\[ \frac{\delta \rho(u_s, v_s)}{\mu \varphi(u_s, v_s)} < 1. \]
and the corresponding unstable mode satisfies
\[ k^2 < \frac{1}{D_v} \left( \frac{\mu \varphi(u_s, v_s)}{\rho(u_s, v_s)} - \delta \right). \]

Hence the necessary conditions of instability of the homogeneous steady state and corresponding unstable modes to the various volume filling models shown in the present paper can be found using the above two inequalities (see the summary in Table 1).

### 5. Numerical simulations of pattern formation

In this section, we show the numerical simulations of pattern formation for the models (MSC), (MEC), (MTC) and (MVFC). It is well known [8] that the global solution of the classical chemotaxis model (MFC) exist in one dimensional space and may blow up in two dimensional spaces. The numerical solutions have been investigated by various researchers (e.g. see [5]). The typical patterns of chemotaxis model are the merging and emerging aggregations [5, 26] where emerging patterns occurs only when cell kinetics is included in models. However we neglect the cell kinetics in the present paper. So only merging patterns are expected and our numerical simulations will confirm this.

The instability parameter region for each model has been given in Table 1. The initial data are set as the small perturbation of the steady states. It is evident from Table 1 that cell initial density is crucial for pattern formation. At high or low initial cell density, the system tends to be stable to spatial perturbations. Typical numerical pattern formations in one dimension are shown in Fig. 3. All simulations demonstrate similar patterning dynamics: merging process. That is neighboring aggregations join to form a single but wider aggregation resulting in a larger interval of low cell density. Changing the parameter values will result in similar qualitative behavior. Typically we see that cell density is bounded by number 1 which is the maximum cell density.
Figure 3: One dimensional numerical simulation of time evolution of solutions for models (MSC), (MEC), (MTC) and (MVFC). The parameter values are chosen such that the instability conditions in Table 1 are satisfied. (a) $\mu = 1, \delta = 1, d = 0.1, D_v = 1.0, \chi = 20$. (b) $\mu = 1, \delta = 1, d = 0.1, D_v = 1.0, \chi = 20, \gamma = 2$. (c) $\mu = 10, \delta = 1, d = 0.25, D_v = 1.0, r = 2, \chi = 10$. (d) $\mu = 1, \delta = 1, d = 0.5, D_v = 1.0, \chi = 6$. Initial data $u_0 = 0.2$ and $v_0 = \mu u_0/\delta + r(x)$ where $r(x)$ is a 1% random spatial perturbation of the steady state. Domain is $[0, 20]$ with 401 grid points.

The numerical simulation of pattern formation in two dimensional spaces are shown in Fig. 4. The finite element package COMSOL Multiphysics is employed to perform the numerical computations. From the left to the right panels, each row corresponds to the time evolutionary numerical pattern formation for models (MSC) (first row), (MEC) (second row), (MTC) (third row) and (MVFC) (fourth row), respectively. The temporal merging process of pattern formations are shown in these simulations. Initially cells are uniformly distributed with density $u_0$ given in the caption of Fig. 4. After short time, the uniform steady states begin to break into various patterns including strips (first column of the first row), honeycomb (first column of the second and third rows) or spots (first column of the fourth row). When time increases, these small aggregations will merge to form larger ones (patches). All simulations have shown two most common patterning...
Figure 4: Numerical simulation of pattern formation in two dimension for models (MSC) (first row), (MEC) (second row), (MTC) (third row) and (MVFC) (fourth row). The parameters are chosen such that the instability condition in Table 1 are satisfied. (MSC) $\chi = 30$ and $u_0 = 0.4$. (MEC) $\gamma = 20, \gamma = 2$ and $u_0 = 0.5$. (MTC) $\chi = 20$, $r = 2$ and $u_0 = 0.5$. (MVFC)$\chi = 30$ and $u_0 = 0.2$. Other parameter values are $\mu = 1, \delta = 1, d = 0.1, D_v = 1.0$ and $v_0 = u_0 + r(x)$ where $r(x)$ is a 1% random spatial perturbation of the steady state.
dynamics of chemotaxis models: aggregation and merging process.

6. Summary and Outlook

In this paper, we derive and discuss some chemotaxis models with nonlinear diffusion and chemotactic sensitivity that are dependent of cell density or total population density. These models are derived from a random walk model by taking into account volume filling effect as well as cell population interactions. We discuss the existence and boundedness of resulting models and numerically show the pattern formations of these models where the typical aggregations and merging processes are found. We need to point out that model (MTC) only has the global weak solution due to the degeneracy at the crowding capacity number one. The purpose of constructing model (MTC) is to incorporate cell packing effect that slow down both the diffusive and chemotactic mobility. In the model (MTC), the packing effect has the same limiting impact on the cell diffusion and chemotactic sensitivity. That is both diffusion and chemotactic movement cease when cell density reaches the crowding capacity. However the diffusion is a local process and chemotactic movement is a nonlocal process in chemotaxis. The packing effect may influence the diffusion and chemotactic movement in a different way. If this difference is taken into account, the diffusion and chemotactic sensitivity may not be zero concurrently when cell density reach its crowding capacity. We also need to point out that the cell interaction is in general a very complex dynamics and mathematical modeling should be undertaken from various aspects. We will discuss these issues more thoroughly in the future.

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References


