Conditions for self-consistent aggregation by chemotactic particles

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We have numerically studied chemotactic aggregation of microorganisms by introducing a model consisting of elements with intracellular dynamics, random walks with a state-dependent turnover rate, and secretion of attractant. Three phases with and without aggregation, as well as partial aggregation, were obtained as to the diffusion and degradation rates of the attractant, and conditions for cellular aggregation were analyzed. The size of aggregated clusters was shown to be independent of cell density, as is consistent with experiment.

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Chemotaxis is a ubiquitous phenomenon in microorganisms, and has attracted much attention both from the experimental and theoretical sides [1–5]. The external concentration of signal molecules is interpreted by an intracellular signal transduction network, which changes the motility of the cell, so that it moves toward a region with a higher concentration of the attractive signal molecule [3]. The signal pathways governing chemotaxis have been revealed experimentally [6]. The turnover rate for the random walk is modulated by the signal concentration toward the directed motion on average in *Escherichia coli* [7,8] and several other microorganisms as well. From experiments on *Paramecium*, Oosawa and Nakaoka proposed a condition for chemotaxis, which states that the time scale of tumbling must be smaller than that of adaptation and greater than that of sensing [1]. By using a simplified model for internal signal transduction and random turnover, we have recently confirmed that the condition is valid for a variety of environments and for both short- and long-term behavior by suitable renormalization of the parameters for the time scale [9].

Just as the chemotaxis of a single microorganism is of interest, the collective chemotaxis of microorganisms interacting with each other is also of interest [10,11]. For example, *E. coli* aggregate to form a cluster by using chemotaxis [12] or sometimes generate complex patterns [13]. The aggregation is spontaneous, the result of chemotaxis toward a chemical that is secreted by the bacteria themselves. Recently, Mittal *et al.* studied this chemotactic aggregation and found that the size of the bacterial cluster is independent of the number of bacteria therein. They also performed some analysis by imposing the localized signal pattern in advance [12]. However, such a concentrated signal pattern is generated by the aggregating cells themselves, and thus it is essential to obtain a self-consistent condition between the bacterial distribution and the signal field to allow for chemotactic aggregation. In the present paper, we will study a simple model of elements that show chemotaxis and secrete signal molecules, in order to obtain the conditions for chemotactic aggregation. Dependence of the cluster size on the bacterial number will also be examined.

Our model consists of cells with internal chemical reactions showing response to and adaptation against the signal molecule [14]; the turnover rate of the random walk of cells depends on the internal chemical state, while the speed of motion is fixed at v_{speed} for simplicity. Signal molecules are secreted from the cells into the medium, become diffused, and are degraded. The intracellular process for chemical concentration variables c_u and c_v is based on [9,15]. These chemicals respond to the external signal concentration S, and the intracellular adaptive dynamics is represented by

$$\frac{dc_u}{dt} = \frac{S - (c_u + c_v)}{\eta}, \quad \frac{dc_v}{dt} = \frac{S - c_v}{\mu}. \tag{1}$$

Following the increase (decrease) in the signal concentration S, c_u increases (decreases) from its steady-state value ($c_u^*=0$; the concentration here is defined as the deviation from the steady-state value so that it can be negative), but after some time span it returns to the original value c_u^*. The time scale for the response is defined by τ_s, while that for the relaxation to the original value (i.e., adaptation) is defined by τ_a.

Following the experimental result [7,8], we set the tumbling rate to become smaller when $c_u > c_u^*$ and larger when $c_u < c_u^*$. With the average tumbling time interval τ^* and the speed v_{speed}, we set the tumbling probability (per unit time) as

$$P_{tmb}(c_u) = \frac{1.0 - 0.5 \tanh[\kappa_\Delta (c_u - c_u^*)]}{\tau^*}. \tag{2}$$

The tumbling frequency decreases (increases) as S increases (decreases). Unless otherwise mentioned we choose $\kappa_\Delta = 1000.0$, so that the $P_{tmb}(c_u)$ exhibits a threshold behavior. Although the tumbling occurs randomly, this simple model can show chemotaxis: i.e., cells move toward an attractant-rich area under the condition $\tau_s < \tau^* < \tau_a$, which we term the Oosawa condition. (The response time τ_s and adaptation time τ_a need to be properly rescaled depending on the profile of signal concentration [9]).

Now we consider the process of secretion of signal molecules S by the cells, to consider the spontaneous chemotactic aggregation. The chemical is assumed to be secreted continually with a constant rate σ from each cell at its position $p^i(t)$, diffuses through the space with the diffusion coefficient D_s, and is degraded at the rate ν. For simplicity, we assume

that σ, D_s, and ν are constant. According to the above assumptions, the time evolution of the signal concentration $S(x,t)$ is given by

$$\frac{\partial S(x,t)}{\partial t} = \sigma \sum_{i}^{N_{cell}} \delta(x - p^i(t)) + D_s \frac{\partial^2 S(x,t)}{\partial x^2} - \nu S(x,t). \quad (3)$$

When cells are distributed homogeneously in space, the signal concentration approaches a homogeneous steady state $S^* = \sigma\rho/\nu$ with ρ density of cells N_{cell}/L, N_{cell} as the number of cells and L as the system size. By scaling properly, we can fix the value of σ by transforming the parameters $\nu \leftarrow \nu/\sigma$ and $D_s \leftarrow D_s/\sigma$.

In our model, the concentration pattern of the signal chemical changes over time, influenced by the configuration of cells. On the other hand, cells move according to the signal pattern. Cells regulate the signal pattern, which controls the cells' motion. Chemotactic aggregation is possible, when a stationary self-consistent solution between cells' motion and the time evolution of the signal pattern is realized.

At a suitable spatiotemporal scale, it would be possible to make coarse-grained continuum model on cell density and signal concentration, if their spacial variation is sufficiently smooth and each cell's adaptation dynamics can be averaged out. Indeed, a partial differential equation for cell density and signal concentration is derived [15,16], which agrees with the so-called Keller-Segel model [17] in a form often taken as a prototype, originally introduced for the study of chemotactic aggregation of amoeba [18]. By denoting the cell density in space as $N(x,t)$, the derived equation is written as

$$\frac{\partial N}{\partial t} = -\chi \nabla \cdot (N \nabla S) + D_n \nabla^2 N,$$

$$\frac{\partial S}{\partial t} = \sigma N - \nu S + D_s \nabla^2 S, \quad (4)$$

where χ represents the mobility of the cell against the signal gradient, and D_n is the diffusion of cells due to their random walk. In this continuum limit, cells are assumed to show directed motion even at any slight gradient in the signal chemical. From a straightforward linear stability analysis, it is shown that the Keller-Segel model has a steady uniform solution under the condition of $\nu > \nu_c = \sigma\chi\rho/D_n$. In the one-dimensional case, Childress and Percus obtained a nonuniform steady solution with concentrated cell density for $\nu < \nu_c$, which represents the aggregated state [19].

Instead of studying Eq. (4), we consider the cell model in one-dimensional space, without taking a continuum limit, and study the conditions for chemotactic aggregation, in particular dependence on D_s and ν. The parameters for intracellular dynamics, i.e., η, μ, τ^*, are fixed so that they satisfy the Oosawa condition after renormalization of the parameters given by [20]. Although we present simulations of the one-dimensional case only, the preliminary results seem to suggest that the basic results, such as the conditions for aggregation and the cluster size, are applicable for the two-dimensional case [21], as adopted experimentally.

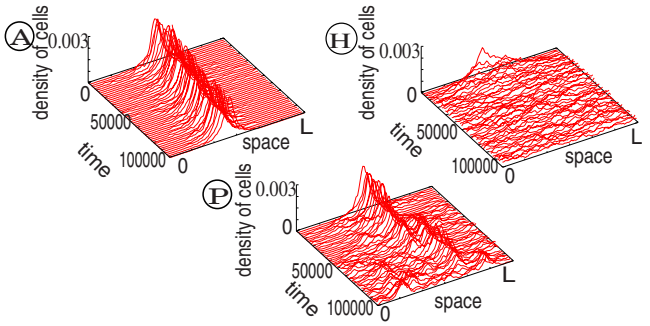

FIG. 1. (Color online) Three characteristic behaviors of cells. The time evolution of the density distribution of cells is plotted. The distribution is computed by averaging over 1000 time units. Parameters are commonly set as $\eta=5.0$, $\mu=50.0$, $\tau^*=70.0$, $\sigma=0.0005$, $N_{cell}=100$, and $L=3000$, while D_s and ν are chosen to be (A) $D_s=300$, $\nu=0.002$, (P) $D_s=0.1$, $\nu=0.002$, and (H) $D_s=300$, $\nu=0.1$.

By fixing the parameter values of the intracellular process, we studied the temporal evolution of distribution by changing the parameter values D_s and ν, and found three distinct types of behavior, i.e., aggregation (A), homogeneous distribution (H), and partial aggregation (P), as shown in Fig. 1.

At the aggregation phase, cells aggregate into a single cluster, which is localized in space and stable in time. This single cluster is formed irrespective of the initial distribution of cells. At the partial-aggregation phase, cells aggregate to form a cluster for some time span, but then this cluster collapses so that cells are broadly scattered until they aggregate again. Intermittent aggregation and collapse is repeated. At the homogeneous phase, cells are distributed uniformly over the space. Tiny fluctuations in cell density are evident from time to time, but on the average the density is uniform in space.

To characterize these behaviors, we computed the following two quantities: d_A, which characterizes the average spatial inhomogeneity of cells at a particular time, and d_V, which characterizes the temporal variation of cell aggregation. These are measured from the average cell-cell distance at each time

$$d(t) = \sqrt{\frac{1}{N_{cell}(N_{cell}-1)} \sum_{i,j}^{N_{cell}} [p^i(t) - p^j(t)]^2}. \quad (5)$$

Then, d_A is defined by the temporal average of $d(t)$ and d_V by its temporal variance. The three phases are characterized by (A) $d_A \ll d_A^{uni}$, $d_V \sim 0$; (P) $d_A \sim d_A^{uni}$, $d_V > 0$; and (H) $d_A \sim d_A^{uni}$, $d_V \sim 0$, where d_A^{uni} is the value when cells are uniformly distributed [22]. The parameter dependence of these quantities is plotted in Fig. 2, from which the phase diagram is obtained. The diagram consists of four regions: i.e., aggregation (A), partial aggregation (P), and two regions of homogeneous phases $(H1, H2)$. Now, we discuss the transitions among these phases.

In the Keller-Segel model, the boundary is given by $\nu = \nu_c$, beyond which the uniform solution of cell density and signal concentration is stable. This boundary line agrees with

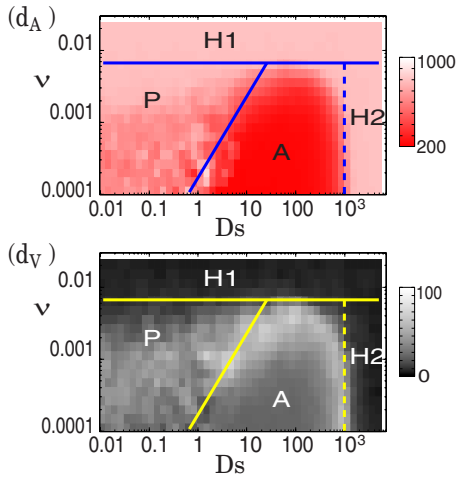

FIG. 2. (Color online) Phase diagram with regards to the diffusion constant of signal chemical D_s (abscissa axis) and its degradation rate ν (ordinate axis). Density plots of d_A (upper) and d_V (lower) are shown. Four phases, $H1$, P, A, and $H2$, were obtained from these values. Parameters other than D_s and ν are identical as adopted in Fig. 1. The values d_A and d_V are computed from the average of 700 000 to 1 000 000 time steps, by starting from a homogeneous distribution.

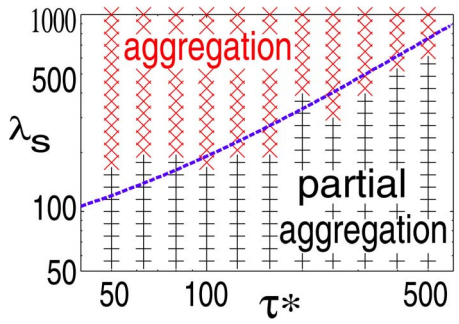

FIG. 3. (Color online) Phase diagram of aggregation and partial aggregation phases, with regards to the cellular tumbling time scale τ^* (abscissa axis) and the parameter $\lambda_s=\sqrt{D_s/\nu}$ (ordinate axis). The symbol $\times$ represents the aggregation phase and + the partial aggregation phase. Fixing $\rho=1/30$ we set $L=3000$ (for $\tau^*\leqslant 100$), $L=6000$ (for $100<\tau^*\leqslant 400$), $L=9000$ (for $400<\tau^*$), while other parameter values are identical with those adopted in Fig. 2. The dashed line represents λ_n (see the text).

that separating the $H1$ phase and the other three phases in our model. In fact, in $H1$, the signal degradation rate is too large to keep a sufficient signal amount for cells to detect. Since the aggregation cluster is always stable under $\nu<\nu_c$ in the Keller-Segel model, the P and $H2$ phases are a result of cell dynamics uncovered by the continuum limit.

The boundary between A and P is given by the straight line of $\nu \propto D_S$. Considering Eq. (3), the spatial scale for a signal molecule to diffuse within its lifetime (λ_s) is given by $\sqrt{D_s/\nu}$. Each cell has to respond to the signal change within this spatial scale. Now, we define the spatial scale for the cell's motility λ_n as the average length a cell moves before it tumbles after it passes the central top of the signal field. This is estimated as follows. The cell's response against the change in signal concentration requires the time delay of τ_s. Up to this time scale, the tumbling frequency does not change and cells seldom tumble. Since the tumbling probability is given by $1/\tau^*$ per unit time, cells show diffusion going straight for the time span of τ^*, on the average. Hence, before the response to the signal the cells travel with the scale $\lambda_n \sim v_{speed}(\tau_s+\sqrt{2}\tau^*)$ on average [23].

For a cell to respond to the change, the spatial scale of the signal change should be larger than the average length of the cell motion before response. Thus, the condition $\lambda_s>\lambda_n$ is imposed. This gives the boundary between the A and P phases in Fig. 2, while we have explicitly confirmed the relationship between λ_s and τ^*, as shown in Fig. 3.

When the aggregation condition in the continuum model ($\nu<\nu_c$) is satisfied, but $\lambda_s<\lambda_n$, the signal field once formed cannot trap cells within, and they wander out so that the original cluster is destabilized. This leads to intermittent formation and collapse of clusters. This is nothing but the behavior in the partial aggregation phase. Note that in the continuous Keller-Segel model, there is always a drift in the cell motion towards a region with higher signal concentration, and the P phase does not exist. By considering each cell as a discrete element with response by internal dynamics, the instability of the aggregated cluster under $\lambda_s<\lambda_n$ is introduced.

The aggregated cluster becomes unstable at large D_s, and chemotactic aggregation is not possible at the $H2$ phase, in contrast to the Keller-Segel model. As the diffusion constant is larger, the gradient of the signal concentration pattern is smaller. If a cell can respond to any small signal gradient, as assumed in the continuum model, cells can aggregate even for any large D_s. On the other hand, in the present model of intracellular dynamics, there exists a minimum value of the gradient in signal concentration required for a cell to respond. Indeed, this value depends on the sharpness of the change of tumbling frequency against c_u, i.e., the value κ_Δ in Eq. (2). As long as κ_Δ is finite, there exists minimum slope, which gives a maximum value of D_s to make aggregation possible. Thus, the $H2$ phase exists as long as κ_Δ is finite.

Finally, we study the dependence of the cluster size upon the number of cells at the aggregation phase. As plotted in Fig. 4, the cluster size (computed by d_A) is independent of the number of cells, as long as it is large enough to form a stable cluster (in the figure, the number is about 50).

Even when the cell number is large, the cellular density in the cluster is sufficiently low (0.01 μm^2 and a single bacterium is about $2\sim3$ μm in length [12]), compared with the colony pattern, and so cells do not collide with each other and move independently. Owing to this independency, the cluster size is determined by the length beyond which the cell returns to the original cluster, given by λ_n, which is independent of the number of cells. In fact, Mittal *et al.* reported that the size of formed bacterial cluster is independent of the number of bacteria contained in it [12]. Our numerical result agrees with their experiment.

In the present paper, we have obtained conditions for chemotactic aggregation. One is the condition for degradation of attractant in the medium, given by $\nu<\nu_c$, which is

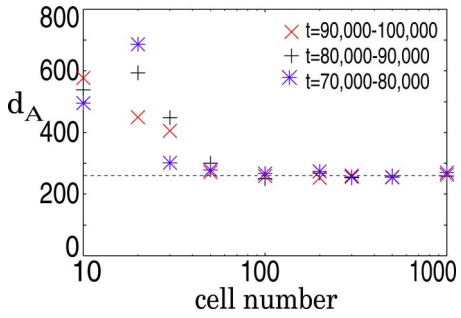

FIG. 4. (Color online) Dependence of the cluster size (estimated by d_A) on the number of cells. Parameters are $\nu=0.002$, $D_s=200$, and others are identical as adopted in Fig. 1. The cluster size is estimated by d_A, computed by the averages from 70 000 to 80 000 ($*$), from 80 000 to 90 000 (+), and from 90 000 to 100 000 ($\times$). Values from three temporal regions are computed to check the stability of the aggregated cluster.

also derived from the continuum limit, Keller-Segel model. The other concerns the inequality between the diffusion scale of the signal molecule within its lifetime and the motility scale of the random walk of cells, $\lambda_s > \lambda_n$. This latter condition, in addition to the condition for diffusion constant of signal molecule to be detected by the signal transduction, is not obtained in the continuum limit model. These conditions, as well as the Oosawa condition for chemotaxis, are general, and can be tested experimentally by varying the nature of the medium and signal molecules and by adopting mutants. As the cluster size constancy against cell density agrees with experimental data, experimental verifications of the predicted phases will be promising. In particular, partial aggregation may underlie intermittent expansion of cellular aggregates [24].

In the present model, the secretion of attractant from cells is independent of the intracellular state. It will be an important future issue to consider state-dependent secretion of chemicals and/or richer intracellular dynamics, to find complex spatiotemporal patterns [13] as well as differentiation of intracellular states [24].

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