Condition for Intracellular Adaptive Dynamics for Chemotaxis

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Chemotaxis is ubiquitously performed by bacteria. They sense and move toward a region with a higher concentration of an attractive chemical by changing the rate of tumbling for random walk. We numerically studied several models with internal adaptive dynamics to examine the validity of the condition for chemotaxis proposed by Oosawa and Nakaoka [1], which states that the time scale of tumbling frequency must be smaller than that of adaptation and greater than that of sensing. Suitable renormalization of the timescales showed that the condition holds for a variety of environments and for both short- and long-term behavior.

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I. INTRODUCTION

Chemotaxis is frequently observed in microorganisms and widely studied experimentally and theoretically. For example, bacteria move in the direction of a higher concentration of an attractive chemical. Although such chemotactic behavior has been evolved, bacteria never move toward a goal directly, but instead often tumble by changing direction randomly. By changing the tumbling frequency, they (and some other microorganisms) assemble around a region rich in attractants. Experiments on chemotaxis of bacteria show that they regulate the tumbling frequency while the direction is changed randomly. In fact, the tumbling frequency of bacteria is smaller when they are located in a region with a higher concentration of attractant than in a region with a lower concentration [2, 3].

In particular, *Escherichia coli* is one of the most thoroughly studied organisms with regards to chemotaxis. They respond to external stimulus [4–8] by changing intracellular chemical concentrations temporally through the internal signal transduction pathway [9–12], while the tumbling frequency is changed according to the concentrations. The detailed machinery of signal transduction as well as relevant proteins to it have been elucidated experimentally, while theoretical models on ligand-receptor binding and receptor modification have succeeded in explaining the intra-cellular adaptation process observed experimentally [13–18].

Although intracellular process bridging between the external attractant concentration and the change of tumbling frequency has been clearer both experimentally and theoretically, we need also to understand how the decrease in tumbling frequency at a higher concentration region of attractants makes the cells assemble to the region. Indeed, this experimental observation seems peculiar if one only considers normal Brownian movement, because a high (low) tumbling frequency should yield a small (large) bacterial diffusion constant in the continuum limit respectively, making the attraction to a high-concentration region impossible.

By incorporating an internal state with adaptation dynamics of a certain timescale into an element exhibiting Brownian motion, however, chemotactic behavior is possible, as was discussed by Oosawa and Nakaoka more than 25 years ago [1]. In other words, the existence of memory in the internal state makes chemotaxis possible. In contrast, de Gennes [19] noted recently that the elements can move in a favorable direction albeit not having an internal state to retain some memory. However, this is true only for short-term behavior of chemotaxis. As Clark and Grant reported [20], the steady state distribution of long-term behavior is not biased toward a favorable region. In fact, a temporal change in tumbling frequency with some memory is required to obtain a biased steady state distribution. By assuming a class of autocorrelation function for the change in tumbling frequency, Clark and Grant showed that the steady state distribution of bacteria can be biased toward a favorable region. In addition, by introducing some constraints and optimizing both the short-term and long-term chemotactic behavior, they obtained a solution to the optimal correlation function.

From a biological viewpoint, the temporal change in the tumbling frequency is a result of intracellular dynamics, as mentioned by Koshland [21]. For any given intracellular dynamics, arbitrary autocorrelation function is not possible. Now it is interesting to elucidate the means by which specific intracellular dynamics allow chemotactic behavior. Indeed, a condition on intracellular dynamics for chemotaxis was proposed earlier by Oosawa and Nakaoka [1], who studied the steady-state distribution of cells with internal adaptive dynamics and the required conditions for chemotactic behavior. Indeed, to exhibit chemotaxis, microorganisms must immediately sense the change and gradually adapt to the

new environment by exploiting the dynamics of the internal state, when the environment changes Oosawa and Nakaoka compared the tumbling timescale τ with the sensing timescale τ_s required to detect the environmental change and the timescale τ_a for adaptation. They showed that bacteria cannot move toward a region with a higher chemical concentration when τ is smaller than τ_s, nor when τ is larger than τ_a. When tumbling is fast, bacteria tumble randomly without any directional motion, whereas at a slower tumbling rate information about attractant field disappears before they change directions. The proposed condition, which we call the Oosawa condition, states that the tumbling timescale τ is greater than the sensing timescale (τ_s) and smaller than the adaptation timescale (τ_a).

By using a simple model of an explicit intra-cellular dynamics, and considering the change in the tumbling rate according to the intra-cellular state, one can now examine the validity of the Oosawa condition for chemotaxis. Indeed, examples of such simple models have already been proposed[22–24]. Here we study a simple dynamical system with two degrees of freedom that responds and adapts to the external environment. These internal dynamics correspond to intracellular reaction processes, and are obtained by extracting the essence of adaptation process. They exhibit both quick-sensing and slow-adaptive processes characterized by parameters τ_s and τ_a respectively. Using this model, we have examined the validity of the Oosawa condition for chemotactic behavior. We first demonstrate this condition for a chemical concentration field with a step function in space. Next, using a field with a continuous slope, we describe our observations of chemotactic behavior in a broader regime than originally proposed. We explain this apparent discrepancy from the Oosawa condition by renormalizing bare timescales through the bacterial motion within the attractant gradient. Using these renormalized timescales, we reconfirm the relevance of the Oosawa condition. Consistency of our result with experimental observations on bacteria chemotaxis is briefly discussed.

II. MODEL

To date, several models describing the detailed process of intra-cellular process have been proposed, which explain the adaptation process observed experimentally [13–18]. Our aim in the present paper, however, is not to describe a detailed process for a particular organism. Rather, we intend to study a general condition between intra-cellular dynamics and macroscopic behavior of cells to gather a region with higher attractant concentration. Hence, instead of adopting a detailed intracellular reaction dynamics, we consider a 'minimal' system to show adaptation. By taking this 'simple but general' model, one can study a general condition for chemotaxis, not restricted to *E. coli* or bacteria.

As was first pointed out by Koshland[25], perfect adaptation is possible by considering a system with two variables, which are denoted by u and v, here. When external environment is changed following the motion of a cell, the values of these variables first change, but then they are absorbed only into one of the variables, and the other variable (which is u here) returns to the original value. Indeed, this adaptation dynamics are extracted from intra-cellular reaction dynamics with complex signalling pathway, as long as they show adaptation. An example of such simple models was studied by Erban and Othmer for macroscopic behavior of chemotaxis [22].

Following this general discussion on modeling, we introduce a simple model to examine a condition for chemotaxis. We first introduce an internal state of a cell that responds and adapts to the external concentration of an attractant, and thereby controls the tumbling frequency. This internal variable is denoted by u, which may be considered as, for example, the intracellular concentration of some key protein species (in the case of *E. coli*, CheY) that responds to the external chemical and controls the tumbling frequency. This internal chemical responds to the concentration of the attractant (termed S here) in the field. As the cell moves and the concentration of the external chemical increases, the concentration of u increases and returns to the original value, a process known as adaptation [25]. The simplest way to have such adaptation dynamics is by introducing another internal chemical, whose concentration is given by v, so that the kinetics is governed by

$$\frac{du}{dt} = f(u, v; S), \qquad \frac{dv}{dt} = g(u, v). \tag{1}$$

where the fixed point solution u^*, v^* given by $f(u^*, v^*; S) = 0,\ g(u^*, v^*) = 0$ is stable. If f increases with S and u^* is independent of S, the response to S and adaptation are satisfied because u increases with S first and then returns back to u^*. Here, when the solution $g(u, v) = 0$ involves u but not v, the latter constraint is satisfied. For example, $g(u, v) = \beta uv - \gamma v$, where β, γ are positive constants satisfies the condition. In this paper, we focus our study on such a case,

$$\frac{du}{dt} = f(u, v; S) = S - \beta uv - \alpha u, \qquad \frac{dv}{dt} = g(u, v) = \beta uv - \gamma v. \tag{2}$$

This model corresponds to synthetic reactions $S \to u$, $u + v \to 2v$ and linear degradation of u and v. Another simple example, originally introduced by Othmer [22] is given by the linear dynamics

$$\frac{du}{dt} = \frac{S - (u + v)}{\eta}, \qquad \frac{dv}{dt} = \frac{S - v}{\mu}. \tag{3}$$

when η and μ as positive constants. We also briefly discuss the result of this model later. In both models, after S increases, u first increases but later returns to the S-independent concentration given by fixed-point $u^* = \gamma/\beta$ in the model eq.(2).

We set the parameter values so that the fixed-point solution u^*, v^* is stable. In the model eq.(2), this condition is given by $\alpha\gamma < \beta S$. In this case, provided $S > 0$ following the increase of S, u first increases from u^* and then returns to the original value exponentially with time and shows a peak in time.

From the dynamics of u, we can estimate the sensing time τ_s and adaptation time τ_a. The sensing time τ_s is the time required for the response of u against the increase of S. Hence it is estimated as the time to reach this peak value of u in time after the increase of S. In the model eq.(2), it is given by $\sim 1/2S$. In contrast, the adaptation time τ_a is estimated by the relaxation time towards the fixed point (u^*, v^*). Considering the exponential relaxation to the fixed point, it is given by the inverse of the smaller eigenvalue of the linearized equation of (2) around the fixed point, and is $\sim 1/\gamma$. In this way, the internal timescales are represented by the reaction parameters.

Here we assume that the tumbling frequency is given by a (continuous) function of the concentration of u. The tumbling occurs randomly, however its frequency changes in response to the external signal S. We assume that the cell moves with a constant speed, until it changes direction, whose probability (i.e., the rate of tumbling) $1/\tau(u)$ is given by a function of u. For $u = u^*$, we set the rate as $1/\tau^*$ and assume that $\tau(u)$ is an increasing function of u. As an example, we choose the form $\frac{1}{\tau(u)} = \frac{\sigma_1 - \sigma_2 \tanh(\lambda(u-u_0))}{\tau^*}$ and set the parameters so that $\tau(u)$ approaches $2\tau^*$ for $u > u^*$, and $\tau^*/2$ for $u < u^*$, while λ is kept sufficiently large for respond to a change in u by eq.(2). This specific choice is not essential and the results we discuss remain valid as long as the rate $(1/\tau(u))$ approaches a value sufficiently smaller than $1/\tau^*$ for large u, and sufficiently larger than $1/\tau^*$ for small u. This change in the tumbling frequency is consistent with experimental data [26].

Note that the basal tumbling rate $1/\tau^*$ is given independently of the intracellular dynamics, so that it is independent of τ_s and τ_a. This allows us to examine the validity of the Oosawa condition. Hereafter, we take Brownian particles satisfying eq.(2) and follow their behavior in a one-dimensional space.

The concentration of attractants is set as a fixed function of space, given by $S(x)$. As the particles (cells) move around the space, their position x changes, and the concentration of the attractant they receive changes according to $S(x)$. Hence the cell state is given by a set of ordinary differential equations (2), where the variable S is given by $S(x)$, with the position of the cell as x, while the motion of the cell is given by random walk with the tumbling frequency $\tau(u)$.

III. RESULTS ON THE CONDITION FOR CHEMOTAXIS

A. Case 1: Step change in the chemical field

As a first example, we consider a case where the external field is given by a step function (i.e., $S(x) = S^+$ for $x \geq 0$ and $S(x) = S^-$ for $x < 0$) and examine whether the cells assemble in the region $x \geq 0$. The fraction of cells at $x \geq 0$, numerically obtained for the steady state is plotted against the parameter τ^* in Fig. 1. In the simulations, all cells are initially located at $x < 0$. The figure shows examples from three different internal timescales τ_s and τ_a, and the data without internal dynamics are plotted as a reference. Table. I shows the time scales(τ_s, τ_a, $\tilde{\tau_s}$(to be defined later)) for the three cases we used in the plot.

As shown, the fraction of cells in a region $x \geq 0$ peaks at certain τ^*. For all cases, the most effective tumbling time τ_{peak} lies at $\tau_s \lesssim \tau_{peak} \lesssim \tau_a$. All simulations for other parameters show that the elements assemble in the region $x \geq 0$, that is, chemotaxis works well when $\tau_s \lesssim \tau^* \lesssim \tau_a$. These results confirm the Oosawa condition. In contrast, as τ^* increases for $\tau* > \tau_a$ or decreases for $\tau^* < \tau_s$, the fraction approaches 0.5, implying that chemotaxis is not possible.

TABLE I: The parameters and the timescales.

Case	α	$\gamma(=\beta/2)$	τ_s	τ_a	$\tilde{\tau_s}$
A	0.35	0.25	0.035	4	$10 \sim 30$
B	3.5	2.5	0.015	0.4	$1 \sim 4$
C	35.0	25.0	0.0035	0.04	$0.2 \sim 0.5$

B. Case 2: Chemical gradient with a constant slope

Next, we consider a case where external chemical concentration forms a constant gradient (i.e., $S(x) = S_0 + sx$). Again, by initially positioning all cells in the region with small x with low attractant concentration, we can quantify whether cells move toward larger x. In this case, the cells with internal adaptive dynamics move toward larger x and stay there, regardless of their tumbling time τ^*.

The speed for climbing up the gradient depends on τ^* and the relation between τ^* and the internal timescales τ_s and τ_a. To check the speed, we examined the time T necessary to reach a specific large x value, as shown in Fig. 2. As τ^* becomes smaller, the time T increases with $1/\tau^*$ for $\tau^* < \tau_c^*$ with some critical value τ_c^* that depends on τ_s and τ_a. In other words, efficient adaptive motion requires $\tau^* > \tau_c^*$. The next step was to examine whether this range of τ^* satisfies the Oosawa condition given by τ_s and τ_a.

We note that even if $\tau^* \gg \tau_a$, the cells can move to a

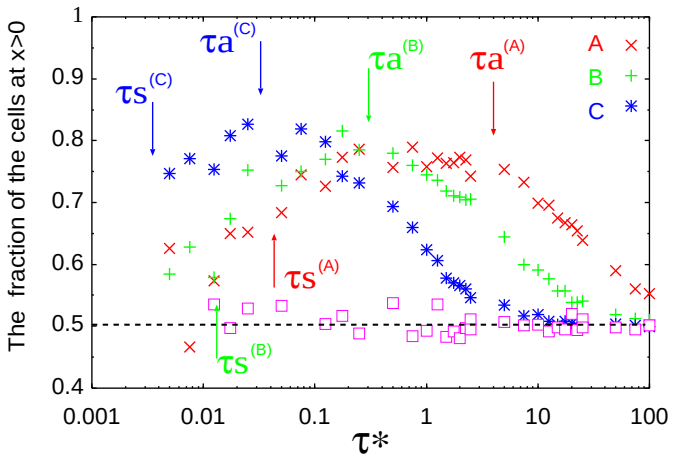

FIG. 1: (Color online) The fraction of the cells located at $x \geq 0$ (i.e., in the S-rich field) are plotted as a function of τ^*. The fraction is obtained from the temporal average for the timespans of 50,000 ($1 \leq \tau^*$), 200,000 ($0.1 \leq \tau^* < 1$), and 300,000 ($\tau^* < 0.1$), after the steady-state distribution is reached over 100 cells. See Table I for the parameters of the model eq.(2) with A, B, and C; the data without internal dynamics are also plotted (□) for reference.

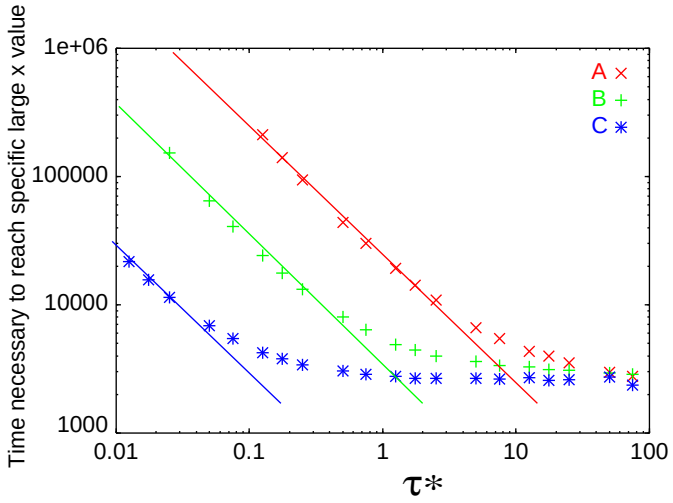

FIG. 2: (Color online) The time T to reach a sufficiently large x value, plotted as a function of τ^*. The parameter values of intracellular dynamics are shown in Table I. The time T was estimated when the center of 100 cells reached $x > 1000$, after positioning 100 cells initially at $x < 10$.

larger x efficiently, whereas the critical τ_c^* needed to increase $T \sim 1/\tau^*$ is much larger than τ_s. The former may suggest the chemotaxis for $\tau^* \gtrsim \tau_a$, and the latter may imply a stronger condition $\tau^* \gtrsim \tau_c > \tau_s$ for chemotaxis. This seemed to violate the original form of the Oosawa condition ($\tau_s \lesssim \tau^* \lesssim \tau_a$).

To resolve this discrepancy, we note that the actual response and adaptation times for cells moving in the

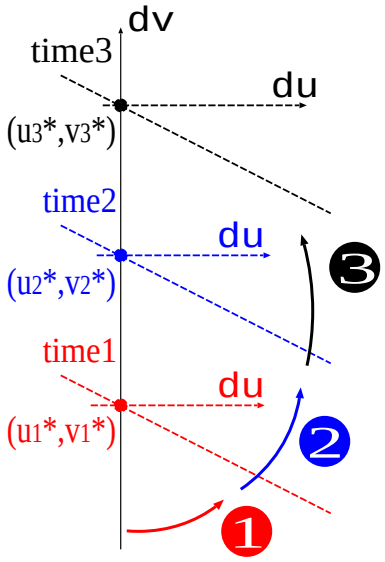

FIG. 3: (Color online) The orbit of (u, v) as S changes continuously. The large points are the equilibrium points (u^*, v^*) for given S values, whereas the dashed lines are stable manifolds at each time. The curved lines with the arrow show the locus of (u, v). Before (u, v) reaches the equilibrium point (u_1^*, v_1^*) for S value of the time 1, the equilibrium point shifts to (u_2^*, v_2^*). Accordingly, (u, v) hardly reaches an equilibrium point.

described concentration field are modified from those estimated from the original intracellular dynamics. As the cell continuously moves and senses the change in the external concentration, these timescales 'renormalized'. To examine this effect, we have studied the intracellular dynamics more closely, keeping in mind that values of τ_s and τ_a may depend on the dynamics of the internal system (u, v) and that S is changing continuously with time according to the cell's motion. In our model, as $S(x)$ continues to change, the equilibrium point for (u, v) also changes, which invalidates the baseline u^*, v^* to give τ_s and τ_a obtained by the linear approximation method (Fig. 3).

Instead, by tracking the time series of u and measuring the time for it to reach the peak and then to u^*, we have estimated the renormalized values $\tilde{\tau_s}$ and $\tilde{\tau_a}$. First, as a cell moves to a region with a higher signal concentration S, the relaxation to the original u^* value hardly occurs because, as S increases, the increase in u occurs before relaxing to u^*. Hence, the renormalized $\tilde{\tau_a}$ is infinite or at least $\gg \tau_a$. Accordingly, one part of the Oosawa condition $\tau^* \lesssim \tau_a$ is always satisfied.

The sensing time also changes from τ_s when cells are placed in a continuously changing field. Although u does not relax to the original u^*, it increases with S and decreases slowly, as shown in Fig. 4. The renormalized sensing time $\tilde{\tau_s}$ can be estimated by the time needed to reach the maximal value. The renormalized $\tilde{\tau_s}$ increases from τ_s as cells move before u reaches the original peak

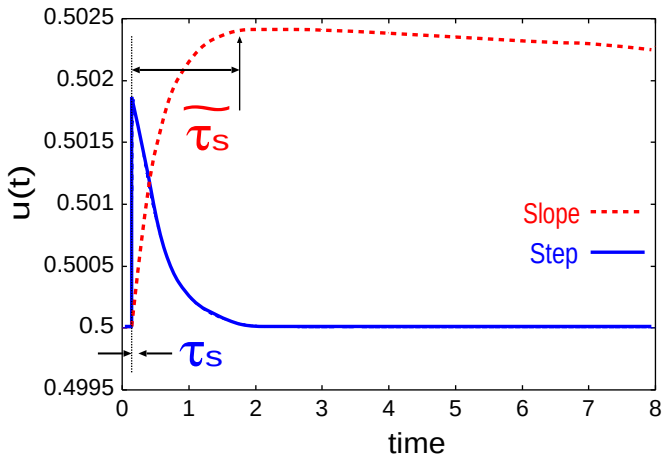

FIG. 4: (Color online) The time series of u for the step chemical field $S(x)$ (solid line) and the gradient with a constant slope (dashed line). The series uses parameter values for the case B in Table I, where the fixed-point value u^* is 0.5. The response to the change of S at $t = 0.15$ is plotted.

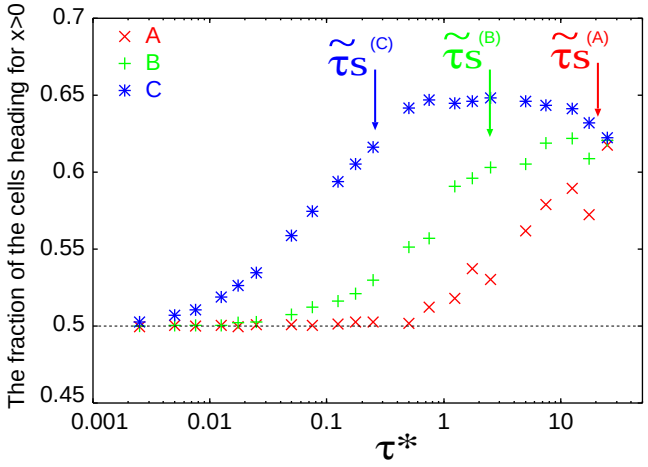

FIG. 5: (Color online) The fraction of cells moving toward the larger x, (i.e., for large $S(x)$) at $T = 100$. The parameters for intracellular dynamics are shown in Table I, in which all conditions are the same as those in Fig 2. The fraction 0.5 indicates the absence of chemotaxis in short-term behavior.

for a given concentration of S, because the fixed point of (u^*, v^*) continuously changes as depicted in Fig. 3.

Now, $\tilde{\tau}_s$, the threshold beyond which the (renormalized) Oosawa condition $\tilde{\tau}_s \lesssim \tau^*$ is satisfied, is expected to give a criterion for chemotaxis. We have compared $\tilde{\tau}_s$ with τ_c^* , the critical τ^* value, to show the increase of $T \sim 1/\tau^*$ (see Fig. 2) and found that the two values agree with each other. We note that $\tau^* \gtrsim \tau_c^* (\sim \tilde{\tau}_s)$ is the only condition for chemotaxis, because T remains constant over a wide range of $\tau^* \gtrsim \tau_c^*$. Thus, the (renormalized) Oosawa condition $\tilde{\tau}_s \lesssim \tau^* \lesssim \tilde{\tau}_a$ correctly estimates the condition for chemotaxis. Finally, we note that the renormalized values $\tilde{\tau}_s$ and $\tilde{\tau}_a$ are independent of the specific value of slope of S, and that this condition gives a criterion for chemotaxis for any given attractant gradient.

The time T, estimated above as the value necessary to reach the region with higher attractant concentration, characterizes the ability of chemotaxis over a long term, as mentioned by Clark and Grant [20]. In contrast, the condition for efficient chemotaxis in a shorter-term is different in general. In our case, however, the chemotactic behaviors in the short and long term are not independent, but are related through intracellular dynamics. We also examined the short-term chemotactic behavior by measuring the fraction of cells that moved toward the higher attractant concentration at $T = 100$, starting from a random distribution of cells. The fraction is plotted as a function of τ^* in Fig. 5, for three examples with different internal timescales. Here again, if $\tau^* \gtrsim \tilde{\tau}_s$, the fraction is much larger than 0.5, whereas for $\tau^* \ll \tilde{\tau}_s$, the fraction is about 0.5, indicating that the cells move randomly. Hence, the Oosawa condition for chemotaxis is also valid for short-term behavior. Because the internal adaptive dynamics satisfy the renormalized Oosawa condition, we conclude that chemotaxis works well over both the short and long term.

IV. DISCUSSION

We have presented a model of chemotaxis that includes internal adaptive dynamics and have shown that the chemotactic behavior appears when the Oosawa condition is satisfied, that is, when the timescale of tumbling is greater than the signal-response time and smaller than the time for the adaptation.

Our conclusion about the condition for chemotaxis applies generally for a system with intracellular adaptive dynamics. For example, we have also studied the linear model given by eq.(3) [22]. By changing the internal timescales τ_s and τ_a, we have examined the validity of the Oosawa condition for chemotaxis. Whether chemotaxis works efficiently is determined by the Oosawa condition for both the chemical concentration field of a step-function and a linear gradient, and both for short- and long-term behavior.

Besides the one-dimensional case, we have also carried out some simulations for a two-dimensional case, where cells move around the two-dimensional space (x, y), with a gradient of attractant concentration along the x direction. In this case, if the change of direction by single tumbling is smaller, it requires a longer time than τ^* for a cell to lose the memory on the direction of motion (for example if the direction change is $\pi/3$ or so, the loss of memory requires 5-10 times of τ^*). Hence we need to 'renormalize' τ^* so that it represents the time for loss of memory. By thus renormalizing τ^*, as well as τ_a and τ_s, we have again confirmed the validity of Oosawa condition, while the chemotaxis works most efficiently when

renormalized τ^* is slightly larger than $\tilde{\tau_s}$, as in Fig.2.

To perform chemotaxis, the cell's internal dynamics must sense and respond to changes in the external chemical concentration. The timescale of sensing should be smaller than that of the tumbling interval to induce an effective response. Otherwise, random walks are repeated before the response occurs. Thus, the condition $\tau_s \lesssim \tau^*$ is essential for the short-term response. In contrast, response in the tumbling frequency without adaptation causes the long-term behavior of cells to be represented by a random walk, so that chemotaxis is not possible. This implies the need for intracellular adaptive dynamics (i.e., relaxation to the original value). However, to induce an effective response to external changes, the tumbling should occur before the relaxation is completed. Hence, the condition $\tau^* \lesssim \tau_a$ is required. Our numerical results suggest that the Oosawa condition $\tau_s \lesssim \tau^* \lesssim \tau_a$ is both necessary and sufficient for the chemotactic behavior.

Clark and Grant [20] recently reported the conditions for the internal response function $R(t)$ to show chemotaxis. In general, the conditions for short- and long-term chemotaxis differ, but by imposing some type of optimization to balance the two behaviors, they were able to obtain a certain condition for the response function, which implies the existence of a form of memory in the autocorrelation function. We can estimate the response function $R(t)$ from our model, which shows that the proper response function in their sense is obtained when the Oosawa condition is satisfied. Similarly, we can define the Oosawa condition in the response function $R(t)$ of Clark and Grant. The sensing time τ_s is estimated from the response function as $R(\tau_s) = 0$, and their solution satisfies $\tau_s \sim \tau^*$, whereas τ_a is much larger than τ^*.

Note, however, that some ambiguity remain concerning the optimization condition that compromises short- and long-term behavior adopted in their paper[20]. In contrast, we have assumed the existence of intracellular dynamics that apply to adaptation after considering the natural properties of intracellular dynamics [25]. By assuming a class of intracellular dynamics, we have shown that chemotaxis occurs in both short- and long-term behavior without requiring an optimization condition, provided that the Oosawa condition is satisfied. Because short- and long-term chemotactic behaviors are satisfied simultaneously, one expects that cells can choose such internal adaptation dynamics that enable efficient chemotaxis for a variety of external conditions. In this sense the optimal condition in [20] is not necessary.

Here we have demonstrated chemotaxis in the two cases: with a constant slope and with a stepwise change. Because most environmental conditions can be represented by the combination of these two cases, the Oosawa condition gives a criterion for chemotaxis in general. Furthermore, we have also confirmed that chemotaxis works when spatial–temporal noise is added in the external environment.

Because the optimal condition in the internal adaptive dynamics depends on the external motility (tumbling time), the validity of the Oosawa condition can be checked experimentally. We estimated the internal timescales for the wild-type and non-chemotactic mutant cells of *E. coli* from [26, 27]. For wild type, which of course performs chemotaxis, $\tau^* \sim 1.5$, $\tau_s \sim 0.4$ and $\tau_a \sim 4$ (seconds). Accordingly the Oosawa condition $\tau_s < \tau^* < \tau_a$ is satisfied. For non-chemotactic mutant cheZ, $\tau^* < 1.5$, $\tau_s \sim 3$ and $\tau_a > 15$ (seconds). Hence, $\tau_s > \tau^*$, and the first inequality in the Oosawa condition is not satisfied, and indeed the mutant does not perform chemotaxis. In addition, the data in [28] suggest that both τ^* and τ_a change in mutants, whereas the relationship $\tau^* \lesssim \tau_a$ is maintained for the mutant with chemotactic ability. In general, different organisms have different timescales for tumbling and internal timescales(τ_s and τ_a). It will be important to check the validity of the condition in different organisms.

Living organisms have many reactions with various timescales, which, when combined, cause adaptive functions to emerge. The proper use of different timescales is important when generating adaptive output behavior in response to changes in external conditions. The process of chemotaxis that we have discussed is one of the simplest mechanisms that takes advantage of the timescale differences, whereas the condition for different timescales can be generalized in a more complex reaction-network system, and in inter-cellular interactions[29–35].

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