On a Condition for Intracellular Adaptive Dynamics for Chemotaxis

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(Dated: January 21, 2022)

Microorganisms often perform chemotaxis, (i.e., sensing and moving toward a region with a higher concentration of an attractive chemical) by changing the rate of tumbling for random walk. We studied several models with internal adaptive dynamics numerically to examine the validity of the condition for chemotaxis proposed by Oosawa and Nakaoka\textsuperscript{1}, which states that the time scale of tumbling frequency is smaller than that of adaptation and greater than that of sensing. Suitably renormalizing the timescales showed that the condition holds for a variety of environments and for both short- and long-term behavior.

PACS numbers: 87.17.Jj, 82.39.-k, 05.40.-a

I. INTRODUCTION

Chemotaxis is frequently observed in microorganisms. Bacteria move in the direction of a higher concentration of an attractive chemical. Although chemotactic behavior is conserved throughout evolution, bacteria never move toward a goal directly, but instead often tumble by changing direction randomly. By changing the tumbling frequency, bacteria assemble around their goal, the region rich in attractants. Experimental bacterial systems showed that bacteria regulate the rate of tumbling and their speed, but change direction randomly. Bacteria move faster but rarely tumble when located in a region with a high concentration of attractant, whereas they tumble frequently at low speed in a region with a lower concentration. However, this experimental observation seems peculiar if one considers only normal Brownian movement, because a high tumbling frequency should yield a small bacterial diffusion constant in the continuum limit, making the attraction to a high-concentration region impossible.

By assuming an internal state with adaptation dynamics of a certain timescale into the element exhibiting Brownian motion, Oosawa and Nakaoka showed more than 25 years ago that chemotactic behavior is possible\textsuperscript{1}. In other words, the existence of memory in the internal state makes chemotaxis possible. In contrast, de Gennes\textsuperscript{2} noted recently that the elements can move in a favorable direction despite 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\textsuperscript{3}, the steady distribution of long-term behavior is not biased toward a favorable region. A temporal change of tumbling frequency with some memory is required to have a biased steady distribution. By assuming a class of autocorrelation function for the change of tumbling frequency, Clark and Grant showed that the steady distribution of bacteria can be biased toward the favorable region. In addition, by introducing some constraints and optimizing both the short-term and long-term chemotactic behavior, they obtained a beautiful solution to the optimal correlation function.

From a biological viewpoint, the temporal change of the tumbling frequency is a result of intracellular dynamics. For any given intracellular dynamics, arbitrary autocorrelation function is not possible, and we were interested in studying the way that specific intracellular dynamics allow for chemotactic behavior. Such a condition was proposed previously by Oosawa and Nakaoka\textsuperscript{1}, who studied the steady-state distribution of cells with internal adaptive dynamics and the conditions for chemotactic behavior. When the environment changes, bacteria must immediately sense the change and gradually adapt to the new environment by exploiting the dynamics of the internal state. Oosawa and Nakaoka showed that bacteria cannot move toward a region with a higher chemical concentration if the tumbling timescale $\tau$ is faster than the sensing timescale $\tau_s$ to detect the environmental change or slower than the timescale $\tau_a$ for the adaptation. When tumbling faster, bacteria tumble randomly without any directional motion, whereas slower tumbling causes the information about direction to disappear before the tumbling rate changes. The proposed condition, which we call the Oosawa condition, states that the tumbling timescale $\tau$ is greater than the sensing timescale $\tau_s$ and smaller than the adaptation timescale $\tau_a$. The optimal solution by Clark and Grant\textsuperscript{3} satisfies this Oosawa condition.

In this paper, we introduce a model of an explicit internal dynamic system with two degrees of freedom that responds and adapts to the external environment. These internal dynamics correspond to some intracellular reaction process, which exhibits both quick-sensing and slow-adaptive processes where the parameters $\tau_s$ and $\tau_a$ are derived from the parameters characterizing the intracellular reaction dynamics. Using this model, we 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 the renormalization of bare timescales through the bacterial motion within the slope. Using these renormalized timescales, we reconfirm the relevance of the Oosawa condition.

II. MODEL

We first introduced an internal state of a cell that responds and adapts to the external concentration of the signal chemical, and controls the tumbling frequency. This internal variable is denoted by $u$, which might be, for example, the concentration of some protein in the cell that responds to the external chemical and controls the tumbling frequency. This internal chemical responds to the concentration of the attractive chemical component (termed $S$ here) in the field. As the cell moves and the concentration of the external chemical increases, the concentration $u$ increases and returns to the original value, a process known as adaptation $\text{[4]}$. The simplest way to have such adaptation dynamics is by introducing another internal chemical, whose concentration is given by $v$, so that the change of concentrations is governed by

$$
\begin{align*}
\frac{du}{dt} &= f(u, v; S), \\
\frac{dv}{dt} &= g(u, v).
\end{align*}
$$

We assume here that 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 to the original value $u^*$. Here, when the solution $g(u, v) = 0$ involves $u$ but not $v$, the latter constraint is satisfied. For example, $g(u, v) = \beta uv - \gamma v$ satisfies the condition, where $\beta, \gamma$ are positive constants. In this paper, we report our study of such a case, with

$$
\begin{align*}
\frac{du}{dt} &= f(u, v; S) = S - \beta uv - \alpha u, \\
\frac{dv}{dt} &= g(u, v) = \beta uv - \gamma v.
\end{align*}
$$

(2)

corresponding to the reaction process $S \rightarrow u$, $u + v \rightarrow 2v$, and degradation of $u$ and $v$. Another simple example, originally introduced by Othmer $\text{[3]}$ is given by $g(u, v) = (S - v)/\mu$, which gives the linear dynamics

$$
\begin{align*}
\frac{du}{dt} &= \frac{S - (u + v)}{\eta}, \\
\frac{dv}{dt} &= \frac{S - v}{\mu}.
\end{align*}
$$

(3)

with $\eta$ and $\mu$ as positive constants. We also briefly discuss the result of this model. In both models, after $S$ increases, $u$ first increases but later returns to the $S$-independent fixed-point concentration given by $u^* = \gamma/\beta$ 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, following the increase (decrease) of $S$, $u$ first increases (decreases) from $u^*$ and then returns to the original value exponentially with time and shows a peak in time. The sensing time $\tau_s$ is estimated as the time to reach this peak and is given by $\sim 1/2S$. In contrast, the adaptation time $\tau_a$ is estimated by the relaxation time towards the fixed point, given by the 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.

In general, the tumbling frequency is controlled by the internal state $u$, which we assume is given by a continuous function of the concentration $u$. The tumbling occurs randomly in experiments, whereas the rate changes in response to the external signal $S$. Although the speed could also change slightly in bacteria, for simplicity we have changed only the rate of tumbling. 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 for $u$. As an example, we take the form $1/\tau(u) = 1.5 - \text{tanh}(\lambda(u-u_0))$ and choose the parameters so that $\tau(u)$ approaches $2\tau^*$ for $u > u^*$, and $\tau^*/2$ for $u < u^*$, while $\lambda$ is set sufficiently large to respond a change in $u$ by eq.(2). This specific choice is not essential and the results we discuss are valid provided that the rate $1/\tau(u)$ approaches a value sufficiently smaller than $1/\tau^*$ for a large $u$, and sufficiently larger than $1/\tau^*$ for small $u$. This change in the tumbling frequency is consistent with experimental data $\text{[7]}$.

Note that the normal tumbling rate $1/\tau^*$ is independent of the intracellular dynamics, so both are independent of $\tau_s$ and $\tau_a$. This allows us to examine the validity of the Oosawa condition. Hereafter, we take the elements satisfying eq.(2) and insert them into a one-dimensional space, where the external concentration is given as $S(x)$, to examine whether the elements assemble in a region with larger $S(x)$.

III. RESULTS ON THE CONDITION FOR CHEMOTAXIS

A. Case 1: Step change in the chemical field

As a first example, we consider the case with a step-function external field (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 number fraction of cells at $x \geq 0$, numerically obtained for the steady state is plotted in Fig. $\text{[1]}$ by changing the parameter $\tau^*$. In
the simulation, all cells were initially located at \( x < 0 \). The figure shows three examples of different internal timescales \( \tau_a \) and \( \tau_0 \), and the data without internal dynamics are plotted for reference. Table I shows the time scales \((\tau_0, \tau_a, \tau_s)\) (to be defined later)) for the three cases we used in the plot.

As shown, the fraction of cells for \( x \geq 0 \) peaks as \( \tau^* \) changes. For all cases, the most effective tumbling time \( \tau_{\text{peak}} \) that gives a peak for the fraction lies at \( \tau_s \lesssim \tau_{\text{peak}} \lesssim \tau_0 \). All simulations for other parameters show that the elements assemble in the region \( x \geq 0 \), that is, the chemotaxis works well for \( \tau_s \lesssim \tau^* \lesssim \tau_0 \). These results confirm the Oosawa condition. In contrast, as \( \tau^* \) increases for \( \tau^* > \tau_0 \) or decreased for \( \tau^* < \tau_s \), the fraction approaches 0.5, implying that chemotaxis is not possible.

**TABLE I: The parameters and the timescales.**

| Case | \( \alpha \) | \( \gamma = \beta/2 \) | \( \tau_s \) | \( \tau_0 \) | \( \tau_{\text{peak}} \) |
|------|-------|------|-----|------|----------------|
| A    | 0.35  | 0.25 | 0.035 | 0.3  | 10 \( \sim \) 30 |
| B    | 3.5   | 2.5  | 0.015 | 0.3  | 1 \( \sim \) 4   |
| C    | 35.0  | 25.0 | 0.0035| 0.03 | 0.2 \( \sim \) 0.5|

B. Case 2: Chemical gradient with a constant slope

Next, we consider the case with an external chemical concentration at a constant gradient (i.e., \( S(x) = S_0 + x \alpha \)). Again, by initially positioning all cells in the region with small \( x \) with low attractant concentration, we can quantify whether cells move toward the larger \( x \).

In this case, the cells with internal adaptive dynamics move toward the larger \( x \) and stay there, regardless of their tumbling time \( \tau^* \).

The speed for climbing up the slope depends on \( \tau^* \) and the relation between \( \tau^* \) and the internal timescales \( \tau_a \) and \( \tau_0 \). To check the speed, we examined the time \( T \) necessary to reach a specific large \( x \) value, as shown in Fig. 2. As \( \tau^* \) becomes smaller, the time \( T \) increases with \( 1/\tau^* \) for \( \tau^* < \tau^*_c \) with some critical value \( \tau^*_c \) that depends on \( \tau_s \) and \( \tau_0 \). In other words, efficient adaptive motion requires a threshold value \( \tau^* > \tau^*_c \). The next step was to examine whether this range of \( \tau^* \) satisfies the Oosawa condition given by \( \tau_s \) and \( \tau_0 \).

We noted that even if \( \tau^* \gg \tau_0 \), the cells can move to a larger \( x \) efficiently, whereas the critical \( \tau^*_c \) needed to increase \( T \sim 1/\tau^* \) is much larger than \( \tau_0 \). This seemed to violate the original form of the Oosawa condition (\( \tau_s \lesssim \tau^* \lesssim \tau_0 \)).

We note that the actual response and adaptation times for cells moving in the described concentration field are modified from those estimated from the original intracellular dynamics. As the cell continuously moves and senses the change of the external concentration, these timescales ‘renormalize’. To examine this effect, we studied the intracellular dynamics more closely, because the values of \( \tau_s \) and \( \tau_a \) may depend on the dynamics of the internal system \((u, v)\) and \( S \) is changing continuously with time according to the cell’s motion. In our model, as \( S(x) \) continued to change, the equilibrium point of \((u, v)\) also changed, which invalidated the baseline \( u^*, v^* \) to give \( \tau_{\text{s}} \) and \( \tau_{\text{a}} \) obtained by the linear approximation method (Fig. 3).

Instead, by tracking the time series of \( u \) and measuring the time for the peak and relaxation time to \( u^* \), we estimated the renormalized values \( \tau_{\text{s}} \) and \( \tau_{\text{a}} \). 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 \( \tau_0 \) is infinite or at least \( \gg \tau_a \). Accordingly, one part of the Oosawa condition \( \tau^* \lesssim \tau_0 \) is always satisfied.

The sensing time also changes from \( \tau_s \) 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 \( \tau_s \) as cells move before \( u \) reaches the original peak 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 compared \( \tilde{\tau}_s \) with \( \tau^* \), the critical \( \tau^* \) 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 \( T \) maintains a constant value over a wide range for \( \tau^* \gtrsim \tau_c \). Thus, the (renormalized) Oosawa condition \( \tau_s \lesssim \tau^* \lesssim \tau_a \) correctly estimates the condition for chemotaxis. Finally, we note that the renormalized values \( \tilde{\tau}_s \) and \( \tilde{\tau}_a \) are independent of the slope of the concentration of \( S \), and that this condition gives a criterion for chemotaxis for any gradient in the concentration.

The time \( T \), estimated above as the value necessary to reach the region with higher attractant concentration, characterizes the ability of chemotaxis over the long term, as mentioned by Clark and Grant. 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 number 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 \( \tau^* \) 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). By changing the internal timescales \( \tau_a \) and \( \tau_a \), 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 constant slope, and both for short- and long-term behavior.

To perform chemotaxis, the cell’s internal dynamics
have to sense and respond to changes in the external chemical concentration. The timescale of sensing should be smaller than that of the tumbling frequency to induce an effective response. Otherwise, random walks are repeated before the response occurs. Thus, the condition $\tau_s \lesssim \tau^*$ is essential to the short-term response. In contrast, response of 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 $\tau_s \lesssim \tau_s$ is required. Our numerical results suggest that the Oosawa condition $\tau_s \lesssim \tau_s \lesssim \tau_s$ is both necessary and sufficient to explain the chemotactic behavior.

Clark and Grant 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. Our work answers the question about why chemotaxis requires dynamics. 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 $\tau_s$ is estimated from the response function as $R(\tau_s) = 0$, and their solution satisfies $\tau_s \sim \tau^*$, whereas $\tau_a$ is much larger than $\tau^*$.

Although we recognize the importance of their pa-

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**TABLE II: The internal time scales of E. coli. (seconds)**

| Cell          | $\tau^*$ | $\tau_s$ | $\tau_a$ |
|---------------|----------|----------|----------|
| Wild-type     | 1.5      | 0.4      | 4        |
| cheRB*       | 2.3      | 0.6      | 3        |
| cheZ         | 12       | 2.6      | (larger than 15) |
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