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Model for Chemotaxis

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The chemotactic response of unicellular microscopic organisms is viewed as analogous to Brownian motion. Local assessments of chemical concentrations made by individual cells give rise to fluctuations in path. When averaged over many cells, or a long time interval, a macroscopic flux is derived which is proportional to the chemical gradient. By way of illustration, the coefficients appearing in the macroscopic flux equations are calculated for a particular microscopic model.

1. Introduction

The chemotactic sensitivity of such one-celled organisms as *Escherichia coli* (Adler, 1966*a,b*) and myxamebae (see, e.g. Bonner, 1967) has been well documented, but the ability of an organism of microscopic dimensions to sense and respond to macroscopic chemical gradients has often been considered a mysterious phenomenon. How can a cell determine either the magnitude or direction of a concentration difference across its body when this difference is so small? A principal purpose of this article is to remove some of the mystery by presenting a description of the chemotactic response which transfers the burden from the detailed behavior of a given cell to its average behavior. In our description, just as in Brownian motion, even though a cell may not be capable of making an accurate assessment of the gradient to which it is exposed at a given time, its *average* behavior can nevertheless reflect the gradient with arbitrary accuracy.

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In Brownian motion, a particle moves in response to the instantaneous difference in impact made by bombarding molecules on different sides of the particle. This difference can be interpreted as a pressure gradient only when averaged over many particles or over a long time interval. The path of the individual particle appears quite erratic, while the average particle flux is proportional to the gradient in pressure. The pressure gradient, in turn, is proportional to the gradient in concentration of the fluid in which the particle is immersed.

In chemotaxis the motion of a cell is influenced by the molecules of the *critical substrate* through a chemical interaction rather than by the direct impact characteristic of Brownian motion. Our basic premise is that the cell responds to fluctuations in estimates made of the concentration of the critical substrate, rather than to the average concentration. This premise becomes plausible, in fact seems necessary, when one considers the extremely small dimensions that a chemical receptor of a microscopic organism must have. The number of molecules in the vicinity of the receptor at any given time would inevitably exhibit a great deal of fluctuation† (although fluctuations would be diminished if the receptor effectively averages its reading of concentration over some time interval).

If the chemotactic event (e.g. pseudopod formation or flagellum activity) is initiated by the local concentration in the vicinity of a chemical receptor, then the path of the individual cell would reflect the fluctuations characteristic of the samples assayed by the chemical receptors. We shall show how such individual cell paths can result in an average cell flux which is proportional to the macroscopic chemical gradient.

2. Formalism

For the sake of simplicity we shall consider here organisms which can take steps of length Δ to the left or right only. (The extension to three-dimensional motion is straightforward.) Receptors are assumed to exist at the extremal portions of the cell. Let α denote the ratio of effective body length (i.e. distance between receptors) to step size, so that the effective length of the organism is $\alpha\Delta$.

We assume that the average frequency of steps in a given direction is influenced only by the mean concentration at the propeling edge. For organisms such as amebae which are propeled by a "pulling" motion, the propeling edge would be the leading edge. For organisms such as flagellated cells which

† In the experiments of Adler (1966*a*), for example, typical concentrations of the critical substrate O_2 are of the order of 10^{-4} M. At this concentration, the average number of substrate molecules in a volume element equivalent to the effective volume of a macromolecule of molecular weight 10^5 would be $N \approx 7$. A rough estimate of the fluctuation is $N^{1/2}$.

are propeled by a "pushing" motion, the propeling edge would be the lagging edge. In the formulas which follow, we assume we are dealing with motion of the pulling kind. Formulae which describe motion of the pushing kind are obtained simply by reversing the sign of α.

Let $f(c)$ denote the average frequency of steps in a given direction, where c is the mean concentration of the critical substrate and is itself a function of position x. The exact function f will be determined by the particular model one assumes. For cells (propeled by pulling) which are centered at x, the average frequency of steps to the right and left will be given by $f[c(x+\frac{1}{2}\alpha\Delta)]$ and $f[c(x-\frac{1}{2}\alpha\Delta)]$, respectively. (We do not indicate dependence on time t explicitly.) Letting $b(x)$ denote the density of cells centered at x, we now wish to find $J(x)$, the net flux of cells per unit time in the direction of increasing x. This is done by multiplying the number of cells $[b(s)\mathrm{d}s]$ in the length element between s and $s+\mathrm{d}s$ by the frequency of steps to the right, integrating over the interval $(x-\Delta, x)$, and then subtracting the corresponding term describing the motion to the left. Explicitly, we have

$$J(x) = \int_{x-\Delta}^{x} f[c(s+\tfrac{1}{2}\alpha\Delta)]b(s)\mathrm{d}s - \int_{x}^{x+\Delta} f[c(s-\tfrac{1}{2}\alpha\Delta)]b(s)\mathrm{d}s. \qquad (1)$$

Using an approximation which is often employed in theoretical studies of Brownian motion (Chandrasekhar, 1943), we keep only the lowest order terms in Δ, so that equation (1) becomes

$$J(x) \approx \Delta^2\{-f[c(x)]b'(x)+(\alpha-1)f'[c(x)]b(x)c'(x)\}. \qquad (2)$$

The first term is the usual "diffusion" term describing the non-chemotactic, random motion of the cells, and the second term describes the chemotactic response. That is

$$J = -\mu(\mathrm{d}b/\mathrm{d}x)+\chi b(\mathrm{d}c/\mathrm{d}x). \qquad (3)$$

The "diffusion" or *motility coefficient*, μ, is given by

$$\mu(c) \equiv \Delta^2/(\Delta t) = f(c)\Delta^2, \qquad (4)$$

where $\Delta t \equiv 1/f(c)$ is the average time interval between steps. Similarly, χ, the *chemotactic coefficient*, is given by

$$\chi(c) = (\alpha-1)f'(c)\Delta^2, \qquad (5)$$

so that

$$\chi(c) = (\alpha-1)\mu'(c). \qquad (6)$$

It is worth noting that while the motility coefficient, μ, is always positive, the chemotactic coefficient χ may be positive or negative, depending on the signs of $(\alpha-1)$ and $f'(c)$. For example, even if the step frequency increases with concentration, $(f' > 0)$, a net flux in the direction of lower concentration may exist if the effective body length is smaller than the step length $(\alpha < 1)$.

The reason for this may be seen from equation (1) by noticing that the average cell in the interval $(x-\Delta, x)$ is centered at $x-\frac{1}{2}\Delta$. The first term may therefore be approximated by

$$f[c(x+\tfrac{1}{2}\Delta(\alpha-1))]b(x-\tfrac{1}{2}\Delta)\Delta.$$

For $\alpha > 1$ the net frequency of steps to the right is thus governed by the concentration to the right of x. For $\alpha < 1$, on the other hand, this frequency is governed by the concentration to the left of x. From this and the corresponding remarks concerning the frequency of steps to the left, the derived dependence on the sign of $(\alpha-1)$ follows easily.

Of special interest (as we were reminded by S. Corrsin) is the case $\alpha = 0$. Here the distance between receptors is zero; chemotaxis occurs because of an *undirected* effect on activity due to the presence of a chemical sensed by a single receptor. From equation (6), $\chi = -\mu'$ and average cell movement is towards (away from) relatively high concentrations of chemical if motility decreases (increases) with concentration.

The dependence of cell density $b(x, t)$ on position and time is described by the differential equation

$$\partial b/\partial \mathrm{t} = -\nabla \cdot \mathbf{J} \tag{7}$$

where the vector flux $\mathbf{J}$ would be given by

$$\mathbf{J} = -\mu \nabla b + \chi b \nabla c. \tag{8}$$

(See Keller & Segel, 1970.) Appropriate initial and boundary conditions must also be prescribed. It we limit ourselves, as above, to consideration of flux in the x direction only, (7) becomes

$$\frac{\partial b}{\partial t} = -\frac{\partial J}{\partial x} = -\frac{\partial}{\partial x}\left(-\mu \frac{\partial b}{\partial x} + \chi b \frac{\partial c}{\partial x}\right). \tag{9}$$

By a slight change of viewpoint, b can be regarded as a probability ω. Equation (9) can then be used to describe the probability of finding a cell at x and t, given a distribution c of critical substrate. In particular, if the initial condition is taken to be

$$\omega(x, 0) = \delta(x-x_0) \tag{10}$$

the solution of equation (9) is the conditional probability function $\omega(x, x_0, t)$. Here δ is the Dirac delta function and $\omega(x, x_0, t)$ gives the probability that the cell is located at point x at time t, given that the cell was at point x_0 at time zero. The boundary condition to be imposed must be determined by the experimental configuration.† Once the conditional probability function has

† See Chandrasekhar (1943) for interesting special solutions of equations (9) and (10). In particular, the solution for the case in which motion of the cells is blocked at one end (e.g. by the bottom of a test tube) and in which μ and χ ($\mathrm{d}c/\mathrm{d}x$) can be taken to be constant can be readily adapted from Chandrasekhar's treatment of the problem of gravitational sedimentation.

been found, the average path of the individual cell can be calculated according to

$$\overline{x(t)} = \int x\omega(x, x_0, t)\mathrm{d}x \tag{11}$$

(where integration is over the entire range of x). Similarly, the mean square deviation is

$$< [x(t) - \overline{x(t)}]^2 > = \int [x - \overline{x(t)}]^2 \omega(x, x_0, t)\mathrm{d}x. \tag{12}$$

3. Prototypic Model

To make further use of the general description given in section 2, we must specify $f(c)$, the dependence of step frequency on mean concentration. In the absence of detailed microscopic observations or of adequate information about biochemical mechanisms, such specification is largely speculative. Nevertheless, in order to clarify and add concreteness to our general description we shall now briefly discuss one specific model. Even if the details of this model should prove inapplicable, the exercise retains its illustrative value.

Let us suppose that the frequency of steps initiated at a given site has one value when the local concentration at that site exceeds a critical value Q, and another value when it is less than Q. That is, let

$$k = \text{frequency of steps initiated at } x \text{ when } \xi(x) > Q, \text{ and} \tag{13}$$

$$k(1-\bar{k}) = \text{frequency of steps initiated at } x \text{ when } \xi(x) < Q,$$
$$0 < \bar{k} \leq 1; \tag{14}$$

where $\xi(x)$ is the estimated or local concentration at x. Then the average frequency of steps taken by a cell at x is

$$f[c(x)] = k\{1 - \bar{k}[\text{prob } \xi(x) < Q]\}. \tag{15}$$

We regard the local concentration at x as a random variable ξ distributed around $c(x)$, the concentration at x, according to the probability distribution function $F(\xi, c)$. Thus

$$[\text{prob } \xi(x) < Q] = \int_0^Q F[\xi, c(x)]\mathrm{d}\xi, \tag{16}$$

so that, using (4) and (15)

$$\mu = \Delta^2 f[c(x)] = \Delta^2 k \{1 - \bar{k} \int_0^Q F[\xi, c(x)]\mathrm{d}\xi\}. \tag{17}$$

It is possible to see certain qualitative features of this formalism before doing any calculations. For example, as $c(x) \to \infty$, it is clear that the local concentration will almost certainly exceed Q, and consequently

$$\mu \to \Delta^2 k. \tag{18}$$

Similarly, as $c(x) \to 0$, the local concentration will almost certainly be less than Q, and we have

$$\mu \to \Delta^2 k(1-\bar{k}). \tag{19}$$

At high concentrations the motion is thus more vigorous than at low concentrations.

We now assume that the level of substrate is governed by the Poisson distribution, so that the probability of finding N molecules at any given time in the effective volume of the receptor is

$$P(N, \bar{N}) = (\bar{N})^N e^{-N}/N!, \tag{20}$$

where $\bar{N}$ is the mean value of N. Let V be the effective volume of the receptor. With $N = \xi V$, $\bar{N} = cV$, equation (20) yields

$$(dN/d\xi)^{-1} F(\xi, c) \equiv P(\xi V, cV) = (cV)^{\xi V} e^{-cV}/(\xi V)!. \tag{21}$$

From equations (4), (17) and (21) we obtain the following expression for the motility coefficient:

$$\mu(c) = k\Delta^2 \left[1 - \bar{k} \sum_{N=0}^{N^*} (cV)^N e^{-cV}/N!\right], \tag{22}$$

where $N^* = QV$ is the threshold number of molecules in the receptor. As anticipated, when considered as a function of c, μ increases monotonically from the value $k\Delta^2(1-\bar{k})$ when $c = 0$ to the value $k\Delta^2$ as $c \to \infty$. Considered as a function of N^* for fixed c, μ decreases monotonically from the value $k\Delta^2[1-\bar{k}\exp(-cV)]$ to the value $k\Delta^2(1-\bar{k})$ as N^* increases from zero to infinity.

Since $\chi(c) = (\alpha-1)\mu'(c)$, we have

$$\chi(c) = -k\bar{k}\Delta^2(\alpha-1)Ve^{-cV}\left[\sum_{N=1}^{N^*} (cV)^{N-1}/(N-1)! - \sum_{N=0}^{N^*} (cV)^N/N!\right] \tag{23}$$

or

$$\chi(c) = -k\bar{k}\Delta^2(\alpha-1)Ve^{-cV}(cV)^{N^*}/(N^*)!. \tag{24}$$

Approximating $(N^*)!$ by Stirling's formula, we can write

$$\chi(c) \approx k\bar{k}\Delta^2(\alpha-1)V(cV/N^*)^{N^*}e^{N^*-cV}(2\pi N^*)^{-1/2}. \tag{25}$$

In this paragraph we suppose, for definiteness, that $\alpha > 1$. Considered as a function of c, χ then increases from zero when $c = 0$ to a maximum $\approx k\bar{k}\Delta^2(\alpha-1)V(2\pi N^*)^{-1/2}$ when $Vc = N^*$, and then decreases to zero as $c \to \infty$. To determine the behavior of χ considered as a function of N^*, we note from equation (23) that χ increases as N^* increases from zero, attains a maximum when $N^* = cV$, and then decreases. Using equation (25), we thus see that χ increases from $k\bar{k}\Delta^2(\alpha-1)V\exp(-cV)$ to a maximum $\approx k\bar{k}\Delta^2(\alpha-1)(2\pi cV)^{-1/2}$ and then decreases to zero as the threshold value N^* increases from zero to infinity.

In particular, in this model $\chi > 0$ and chemotactic response is in the direction of increasing concentration if and only if $\alpha > 1$, i.e. if and only if the "step size" is smaller than the effective body length. The smaller is the threshold N^*, the larger is the maximum chemotactic response. Not surprisingly, the maximum response occurs when the average number of molecules in the receptor equals the threshold number.

4. Discussion

A general prescription has been given for the derivation of the macroscopic equation for the flux of cells whose motion is affected by variations in the ambient concentration of certain chemicals. The theory is based on a Brownian motion model of chemotaxis.

On the basis of general macroscopic arguments, we have previously formulated an equation for the macroscopic flux of cellular slime mold amebae and have used it to describe the initiation of aggregation in that system (Keller & Segel, 1970). Although the essence of the argument was independent of the dependence of the motility μ and the chemotactic coefficient χ on concentration, precise quantitative predictions did depend on such detail. Here we provide a framework for viewing the motion of the amebae which immediately yields the macroscopic flux equation, and which can ultimately be used to obtain the specific form of the motility and chemotactic coefficients.

In describing the motion of an individual slime mold ameba, it is natural to associate the step in the random walk model with the displacement of the organism due to the formation of a single pseudopod. The critical substrate here is acrasin. The degree of wobble in the path of an ameba would then, in our view, reflect the fluctuations in estimates of acrasin density.

It should perhaps be mentioned here that attempts made in the past to characterize the path of a single ameba by such quantities as the "chemotactic index" (Samuel, 1961) are inadequate in that they depend critically on the accuracy of measurement. Only if all movement is recorded in measurement of the total path length is it meaningful to introduce the ratio of forward motion to overall motion as a characteristic parameter. Omission of any motion at all, however slight, leads to an overestimate of the chemotactic index. Since the ameba is not a rigid particle, and since its boundaries are always in a state of flux, the prospect of such complete measurement seems unrealistic. It is not possible to circumvent the difficulty by tracing the succession of a sequence of steps for the result then depends on the definition of "step".

A more adequate characterization of the motion would be provided by examining the progress of a number of amebae and measuring their mean

position as a function of time, and their mean square departure from this mean position. This is a point average, not a path average, and therefore only requires a precise measurement of the position of an ameba at a given time t. Analytically, the average position and the mean square deviation are given by equations (11) and (12) in the one-dimensional case. In general, these are functions of time and cannot be characterized by a single parameter. However, comparison between equations (11) and (12) and the corresponding experimental curves permits one to estimate the parameters μ and χ, for a given c. These, in turn, do provide a parametric characterization of the motion.

Returning to the question of whether the model of section 3 provides a suitable description of the motion of a slime mold ameba, we recall that in this model we have assumed a constant step size and a step frequency determined solely by the mean concentration at the propeling edge. There is some suggestion, however, that the chemotactic response may result from the effect of acrasin concentration on step *size*, or more specifically, on the length of a pseudopod. Shaffer (1965) has observed that some proportion of pseudopods formed at high acrasin levels appear longer than normal.

A simple model which is based on these considerations assumes that steps of length Δ are taken at one frequency $f_1(c)$, while longer steps of length $a\Delta$ are taken at a second frequency $f_2(c)$. The total frequency of steps of either kind can be made concentration-independent by requiring that $f_1+f_2 = F$, a constant. It is quite easy to see that this varying step model leads to equations of exactly the same form as equation (2). In this case one obtains

$$J = \Delta^2[-f_1 b' + (\alpha-1)f_1' c' b] + (\alpha\Delta)^2[-f_2 b' + (\alpha a^{-1}-1)f_2' c' b]$$

or

$$\mu = \Delta^2(f_1 + a^2 f_2), \qquad \chi = \Delta^2[\alpha(f_1' + a f_2') - (f_1' + a^2 f_2')]$$

so (using $f_1+f_2 = \text{constant}$)

$$\chi = [\alpha(a+1)^{-1} - 1]\mu'.$$

The first model assumes that pseudopods have a constant length but their frequency is determined by acrasin concentration while the second assumes that pseudopods are formed at a constant frequency, but that their length is governed by acrasin concentration. Although rather different biochemical machinery would presumably be required to regulate step length or step frequency, both models give rise to the same flux equation (3) with the same simple proportionality between χ and μ'. This insensitivity of macroscopic description to microscopic detail can be of great use in understanding complicated biological phenomena such as aggregation. As in Keller & Segel (1970), one can adopt a phenomenological approach and

proceed without waiting for the unfolding of microscopic detail, particularly as much of this detail does not affect the macroscopic phenomenon.

If both step size and total step frequency were permitted to vary with concentration then χ would no longer be simple proportional to μ' although the basic flux equation would remain. The specific assumptions one should employ can only be decided by direct experimental observation of the influence of concentration on cellular motion. A purpose of our analysis is to demonstrate how such simple assumptions lead to a flux equation in which the motility and chemotactic coefficients have a definite prescribed relationship to each other. Once these coefficients have been assessed experimentally, such relationships are subject to test.

Bacterial chemotaxis can also be viewed in this general framework if the path of the individual bacterium is described as a sequence of steps in which each step corresponds to some unit of flagellar activity. In a study of traveling bands in *E. coli* (Keller & Segel, 1971) based on a flux equation in the form of equation (3), the authors were able to find solutions which seem to be in reasonable accord with observation under the assumptions μ = constant and $\chi = \delta c^{-1}$, δ constant. These assumptions are obviously incompatible with a proportionality between χ and μ'. They therefore cannot be deduced from our general model under the assumptions of constant step size or constant step frequency which were used in our illustrative calculations. [There need be no inconsistency if both step size and step frequency are permitted to vary with concentration, as experimental observation indicates is the case (Weibull, 1960).] On the other hand, the fact that the phenomenological analysis of Keller & Segel (1971) seems to capture the principal features of travelling bands does not demonstrate the validity of the particular assumptions they made concerning the functions μ and χ.

In fact there is no adequate basis at the present time for reaching any conclusions about the dependence of the motility and chemotactic coefficients on concentration. This paper may be considered an exposition of the ways in which such information is useful, and a request for more experimental information on the subject.

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