A MATHEMATICAL MODEL FOR BACTERIAL CHEMOTAXIS

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ABSTRACT A differential equation describing the chemotactic migration of a bacterial population in a fixed exponential gradient of attractant has been integrated using the appropriate boundary conditions. The solution predicts an initial bacterial accumulation at the concentration "knee" with the final distribution of bacteria approaching a time-independent state. Specific additional experiments to obtain further data for a rigorous test of the theory are suggested.

INTRODUCTION

Modern investigations of bacterial chemotaxis, as well as general taxis behavior in diverse organisms, have followed two complementary lines of development, microscopic and statistical versus biochemical and ultrastructural. The first category is a direct continuation of the pioneering studies of Engelmann (5), Pfeffer (9) and others in the 19th century, with research devoted to the gross or statistical response of bacterial populations to chemical gradients. These gradients, initially set by the experimenter, can be critically modified by bacterial consumption of nutrients, as occurs in the classic work of J. Adler (1) with migrating bands of bacteria. On the other hand, in some bacterial systems, gradients may be imposed and maintained for extended periods of time. Typically these have been spatially varying chemical concentrations essentially stationary in time (4, 11), or spatially uniform concentrations changing in time (3, 7).

In the class of biochemical and ultrastructural investigations we include the nature and distribution of membrane receptor sites, the transport mechanisms which convey information of extracellular gradients into the cell interior, and the intracellular processes which induce and control the flagular rotation, and thus, ultimately, bacterial motion.

Studies in these two broad areas, while significant as distinct scientific efforts, are, of necessity, complementary to one another. We anticipate that our understanding of specific biochemical processes and the details of cell structure pertinent to chemotactic phenomena will be clarified by their relation to behavioral responses. These bacterial motions have been analyzed statistically either through the movement of populations as in the experiments of Adler (1), Dahlquist et al. (4), and Tsang et al. (11), or through the lengthy tracking of individual bacteria as in Berg and Brown (2) and Brown and

Berg (3). A successful phenomenological description of the gross bacterial response to external gradients should prove significant in both probing and comprehending their underlying physical and chemical bases.

The hope that such a description can be achieved is based on the observation that the average behavior of a bacterial population in an attractant gradient is remarkably regular. Simple concentration gradients result in simple bacterial density configurations. In particular, this is true of the experiments of Adler (1) and Dahlquist et al. (reference 4; hereafter referred to as DLK). Their results have inspired new attempts to analyze the bacterial response quantitatively.

One mathematical description of these experiments is based on the diffusion theory of suspended particles in solution. A particular model, that of Keller and Segel (6), has drawn favorable interest, since predictions based on their theory appear to be in agreement with some of the experimental evidence. In this paper we discuss their model and use it to reanalyze one of the experiments of DLK. Our calculations enable us to make several new predictions concerning the bacterial flow which provide a more rigorous test of the theory. These predictions are in qualitative agreement with the experimental data, but more detailed verification is required to check the validity of the model.

EXPERIMENTAL AND THEORETICAL BACKGROUND

Keller and Segel (6) postulated the following equation to describe the density distribution in space and time of bacteria exhibiting chemotaxis without metabolism in a one-dimensional concentration gradient of a given organic attractant:

$$\frac{\partial b}{\partial t} = \mu \frac{\partial^2 b}{\partial x^2} - \delta \frac{\partial}{\partial x}\left(b \frac{\partial \ln(s)}{\partial x}\right). \tag{1}$$

Here $b(x,t)$ is the bacterial density as a function of x and t, s the attractant concentration, μ and δ are constants. The first term on the right represents bacterial diffusion and the second the chemotactic "force" directing bacterial motion. Keller and Segel assumed the form of the force term, and attempted to justify their choice on the basis of the Fechner-Weber law. The claimed connection to that stimulus-response relation is obscure. At this stage their equation only has a pragmatic significance; deductions based on it appear to be in agreement with the band experiments of Adler (1), and aspects of the experiments of DLK (4).

In this paper we restrict our discussion to the experimental work of DLK. They exposed an initial distribution of spatially uniform bacteria, *Salmonella typhimurium,* to various simple concentration gradients of L-serine. Segel and Jackson (10), and later Nossel and Weiss (reference 8; hereafter referred to as NW), have applied the original Keller-Segel equation to one of these experiments where the form of the imposed gradient permits a straightforward mathematical analysis.

In this experiment the concentration gradient of L-serine consists of a plateau followed by an exponential decay. Two important features of the experimental results are

that the peak of the bacterial concentration curve rises approximately as the square root of the time, and the increasing area of the central part of the density curve is directly proportional to the time. Both of these observations are contained in the Segel-Jackson (SJ) solution of Eq. 1 for this problem. An improved solution by NW (8) also agrees with experiment, after these authors recomputed the values of the parameters appearing in the equation.

This agreement, while heartening, is nevertheless questionable. There are two related problems clouding the issue of the validity of the theory. One arises from the analysis in references 10 and 8, the other from the experiment itself. Both conspire to prevent a direct test of the force term assumed by Keller and Segel in their Eq. 1, although both the theory and the experiment provide additional confirmation to the general view that diffusion is an essential element in bacterial motions generally, as well as in chemotaxis. In the analysis carried out in references 10 and 8, it appears that the most significant part of the approximate solutions found by these authors is actually a solution of the ordinary diffusion equation with a singular source at the origin. The source reflects the constant flow of bacteria from the low serine concentration end of the capillary tube into the central region. Given this flow rate, and the assumption that the bacterial distribution remains symmetric about the origin and constant at infinitely distant points for all time, the problem has a unique solution and it is the one presented by SJ, and in the same approximation by NW. For this solution, the central peak in the bacterial distribution rises as the square root of the time and the bacterial number in this region increases as the first power of the time. The chemotactic force is essentially irrelevant to the analysis, since its presence is felt only through a single phenomenological parameter describing the flow of bacteria into the origin.

In reality only a finite number of bacteria move from the low serine concentration end of the tube into the central region. However, in the DLK experiment, the length of the tube, the concentration gradient of serine and the values of the parameters μ and δ are such that this flow is constant for approximately the first 40 min of the experiment. During that time, ordinary diffusion theory with a singular source at the origin provides an adequate description of the bacterial motion. It is also the time span over which DLK observed the flow. At later times, the end of the tube is so depleted of bacteria that the precise form of the chemotactic force becomes significant. The solutions of SJ and NW cannot describe this aspect of the flow. The boundary conditions they have used for their solutions imply an influx of bacteria for all time into the central region, an assumption precluding a description of this new stage in the development of the system, the transition to the stationary state.

In our treatment of the problem we are able to analyze this evolution fully because we have used boundary conditions appropriate to the actual experiment. Since our solutions are valid for all time, we can justify the description of the motion given in the preceding paragraphs, and in addition make detailed predictions concerning the time behavior of several new parameters accessible to measurement. These predictions can be used to test the validity of the assumed chemotactic force. They are discussed in detail in Results and Discussion.

The Keller-Segel equation for one-dimensional bacterial flow is obtained from the "equation of continuity,"

$$(\partial b/\partial t) + (\partial J/\partial x) = 0. \tag{2}$$

Here $b(x,t)$ is the density of bacteria and the "current density" $J(x,t)$ defines the rate at which bacteria pass a unit area perpendicular to the x-axis. Eq. 2 is a statement of "conservation of number" of bacteria, i.e. there are no births and deaths. It is also assumed that the density is sufficiently great so that b may be treated as a continuous variable.

Keller and Segel assume that the current density has the form

$$J = -\mu(\partial b/\partial x) + \delta b[\partial \ln(s)/\partial x], \tag{2A}$$

where $s(x,t)$ is the attractant concentration and μ and δ are constants.

In the DLK (4) experiment $\partial s/\partial t = 0$, and the attractant distribution is a given function of x for all time:

$$s = s_0, \quad -L_1 \leq x \leq 0, \tag{3}$$

$$s = s_0 \exp(-ax), \quad 0 \leq x \leq L_2. \tag{3A}$$

Here $-L_1$ and L_2 are, respectively, the left- and right-hand boundaries of the capillary tube in which the bacteria move.

Eqs. 2 and 2 A become

$$\partial b/\partial t = \mu(\partial^2 b/\partial x^2), \quad -L_1 \leq x \leq 0, \tag{4}$$

$$\partial b/\partial t = \mu(\partial^2 b/\partial x^2) + v(\partial b/\partial x), \quad 0 \leq x \leq L_2, \tag{4A}$$

where the constant $v = \delta a$ represents the mean speed at which bacteria flow up the given concentration gradient.

The appropriate boundary conditions for the solutions of Eqs. 4 and 4 A are

$$b_+(0,t) = b_-(0,t), \tag{5}$$

$$\mu\frac{\partial b_-(0,t)}{\partial x} = \mu\frac{\partial b_+(0,t)}{\partial x} + vb_+(0,t), \tag{5A}$$

$$\mu\frac{\partial b(-L_1,t)}{\partial x} = 0, \tag{6}$$

$$\mu\frac{\partial b(L_2,t)}{\partial x} + vb(L_2,t) = 0. \tag{6A}$$

Here $b_\pm(0,t)$ refers to the limiting value of the bacterial density as the "knee" in

the nutrient concentration is approached from the right or left. The knee is chosen to be at the origin. Eqs. 5 and 5 *A* insure the continuity at the origin of both the bacterial concentration b and the flux J. Eqs. 6 and 6 *A* guarantee that there is no efflux or influx of bacteria at the ends of the tube. These last conditions give rise to the differences between our solutions and those of SJ and NW.

In addition, at $t = 0$

$$b(x,0) = b_0 = \text{constant}, \tag{7}$$

states that initially the bacteria are distributed uniformly in the tube.

An analytical solution to Eqs. 4–7 valid for all times may be sought by the method of Laplace transforms, but the approximate solution we have found through that technique holds only for short times. We therefore have carried out a direct numerical integration of the equations by a finite difference approximation. The results obtained are presented in the next section.

For large values of t the system approaches the steady-state condition and this final bacterial distribution may be obtained directly.

In the steady state

$$\partial b/\partial t = 0. \tag{8}$$

Then,

$$\mu(\partial^2 b/\partial x^2) = 0, \quad -L_1 \leq x \leq 0, \tag{9}$$

$$\mu(\partial^2 b/\partial x^2) + v(\partial b/\partial x) = 0, \quad 0 \leq x \leq L_2. \tag{10}$$

The boundary conditions are given again by Eqs. 5, 5 *A* and 6, 6 *A*. Eqs. 5–10 have the solution

$$b(x) = b_1, \quad -L_1 \leq x \leq 0, \tag{11}$$

$$b(x) = b_1 \exp(-vx/\mu), \quad 0 \leq x \leq L_2 \tag{11 A}$$

where

$$b_1 = \frac{b_0(L_1 + L_2)}{L_1 + (\mu/v)[1 - \exp(-vL_2/\mu)]}. \tag{12}$$

For small values of v

$$b_1 \approx b_0\left(1 + \frac{vL_2^2}{2\mu(L_1 + L_2)}\right), \tag{13}$$

while for large values of v

$$b_1 \approx b_0(L_1 + L_2)/L_1. \tag{14}$$

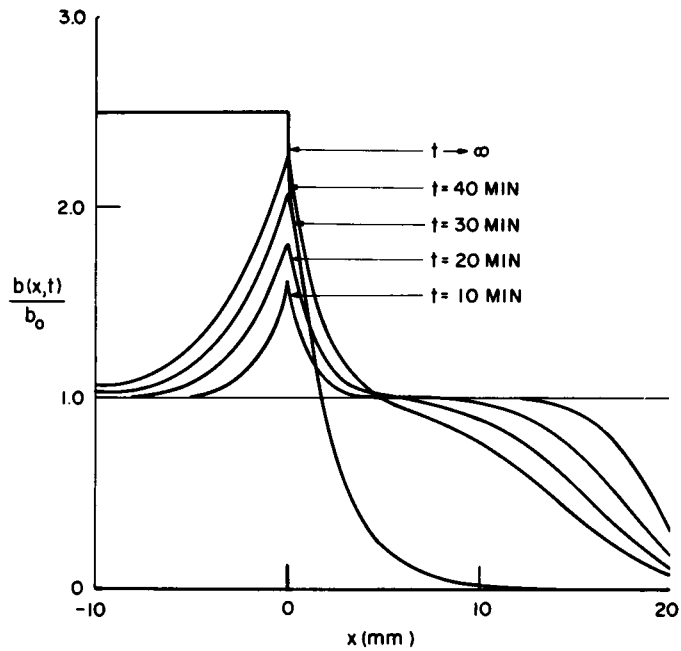

FIGURE 1 Plots of bacterial density distributions at t = 10 min, 20 min, 30 min, 40 min, and $t \to \infty$. The peak of the bacterial density distribution grows with time at the discontinuity in the nutrient (L-serine) gradient located at $x = 0$.

Eq. 11 is plotted in Fig. 1, using the values $\mu = 0.333$ mm^2/min and $v = 0.168$ mm/min from SJ.

Eqs. 11 *A* and 12 may be used to evaluate another experimental quantity, $x_0(\infty)$, the point in the stationary state distribution at which $b(x_0) = b_0$. This is the final "width" of the peak. We find

$$x_0 = L_2\{\ln(1 + L_1/L_2) - \ln[(L_1/L_2) + (\mu/vL_2)(1 - e^{-vL_2/\mu})]\}. \quad (15)$$

For small values of v,

$$x_0 \approx \frac{1}{2} L_2^2/(L_1 + L_2). \quad (16)$$

For large values of v,

$$x_0 \approx (\mu/vL_2) \ln[(L_1 + L_2)/L_1] \to 0. \quad (17)$$

The total number of bacteria which have migrated to the left is given by

$$N = \int_{-L_1}^{x_0} (b(x) - b_0)\,dx = (b_1 - b_0)L_1 + \int_0^{x_0} b_1 \exp(-vx/\mu)\,dx - b_0 x_0$$

$$= (b_1 - b_0)(L_1 + \mu/v) - b_0 x_0, \quad (18)$$

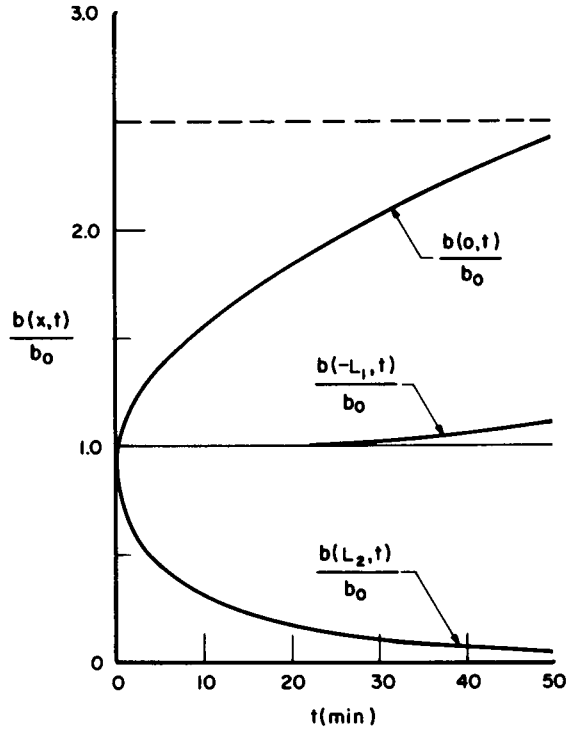

FIGURE 2 Plots of the relative bacterial densities $b(-L_1,t)/b_0$, $b(0,t)/b_0$, and $b(L_2,t)/b_0$ as functions of the time. The points $-L_1$, 0, and l_2 are, respectively, the left-hand end of the capillary tube, the nutrient "knee," and the right-hand end of the capillary tube.

where b_1 is given by Eq. 12 and x_0 by Eq. 15. All the variables on the right hand side of Eq. 18 are determined from the measurable quantities μ, v, L_1, and L_2.

RESULTS AND DISCUSSION

Our numerical solution for the density distribution of bacteria in an attractant gradient is based on a finite difference approximation to the Keller-Segel equation, Eqs. 4 and 4 A and the conditions 5–7. To integrate these equations, the values of various parameters are needed. For *Salmonella typhimurium* in L-serine, Segel and Jackson obtained from DLK the data $\mu = 0.333$ mm^2/min and $v = 0.168$ mm/min. From the same source, we have $L_1 = 10$ mm and $L_2 = 20$ mm.

The most significant results of our calculation are contained in Figs. 1–5. Fig. 1 shows that in the first 40 min of chemotactic movement the density at the knee (origin) increases rapidly, while the density at the right-hand end of the tube decreases. The peak region shows an obvious and growing asymmetry about the origin. There is a movement of density change to the left of the origin, but almost 25 min elapse before any significant deviation from the initial density can be detected at the far left end of the tube.

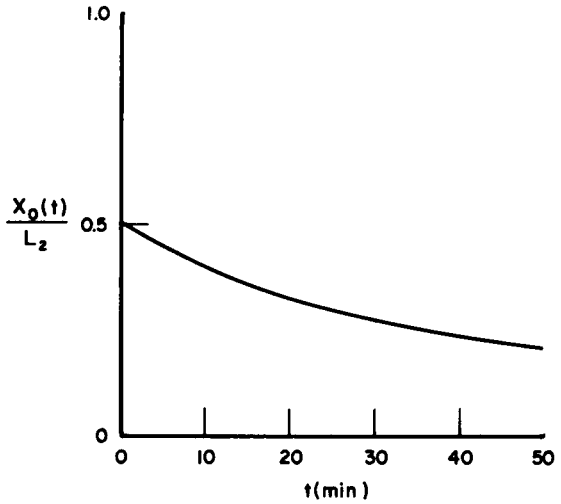

FIGURE 3 Plots of $x_0(t)$ as a function of time. x_0 is the value of x at which the bacterial density is equal to the initial value b_0. x_0 is a measure of the "width" of the peak near the origin.

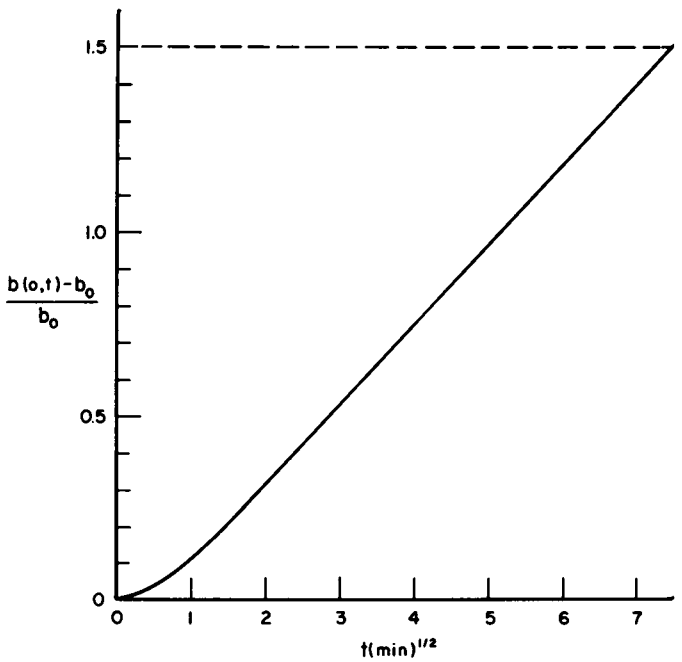

FIGURE 4 Plot of $b(0,t)/b_0$ vs. $t^{1/2}$. The height of the peak grows linearly with $t^{1/2}$ as observed experimentally.

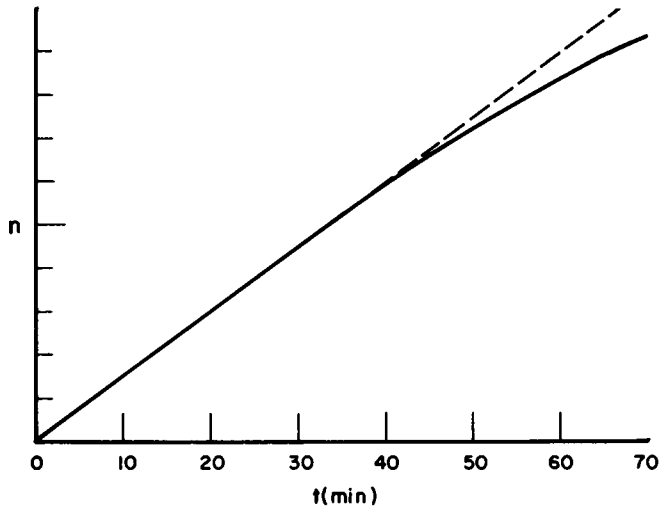

FIGURE 5 Plot of the number, n, of bacteria which migrated into the peak as a function of time. The plot is linear, in agreement with the experimental data. The verticle scale is arbitrary.

During this early period of bacterial flux, the concentration peak rises as the square root of the time, and the area of the central region varies directly with the time. These results are plotted in Figs. 4 and 5, and they agree with the experimental data of DLK and with the predictions of SJ and NW. After 40 min, this flow pattern changes as the bacterial distribution begins to approach its stationary state value. The final distribution is plotted in Fig. 1, and the analytical form of the curve has already been given in Eqs. 11 to 12. There is no experimental data for this later period of flow.

Our work permits us to find the time dependence of three new parameters which can be measured experimentally. These are the bacterial densities at the end points of the observation cell, $b(-L_1,t)$ and $b(L_2,t)$, and the point along the cell axis, $x_0(t)$, where the bacterial density equals the initial density b_0. This time dependence is shown in Figs. 2 and 3. All three parameters approach predicted limiting values. To our knowledge, no experiment has been performed to determine their behaviour.

The qualitative features of the bacterial motion are then as follows: The bacteria are driven up the gradient (from right to left) by the chemotactic force, the second term on the right of Eq. 4 *A*. The first term of the right represents the random, diffusive motion of the bacteria. As the bacterial concentration increases at the knee, the bacteria spill over into the region of the serine plateau and slowly diffuse to the left. The motion proceeds until a time-independent distribution is achieved.

For *Salmonella typhimurium* in L-serine, the bacterial motion may be described in an adequate approximation by ordinary diffusion theory with an apparent source at the origin representing the forced flow of bacteria from the low serine concentration end of the tube. This solution, was first presented by SJ and NW, for times short compared with the time needed to achieve a stationary distribution. However, the description eventually fails, since there are only a finite number of bacteria in the tube. Ultimately,

the bacteria begin their approach to a stationary state, and as the precise nature of the bacterial flow from the low concentration end of the tube becomes increasingly significant, the source description of SJ and NW becomes correspondingly inadequate.

To really test the Keller-Segel equation, it is necessary to follow the evolution of the bacterial distribution to its final state. Hence, the curves of Figs. 1–3 should prove helpful in any future experimental check of the validity of this model. The configuration of the stationary state has special significance, as it provides a direct clue to the nature of the chemotactic force.

The numerical calculations were carried out at the Stevens Computer Center.

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