MODEL FOR THE CHEMOTACTIC RESPONSE OF A BACTERIAL POPULATION

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ABSTRACT We present a mathematical model for the motion of a bacterial population in prescribed attractant or repellent gradients. The model is suggested by the observations of Mesibov et al. (1973, *J. Gen. Physiol.* **62**:203) and Brown and Berg (1974, *Proc. Natl. Acad. Sci. U.S.A.* **71**:1388) who found that the sensitivity of the chemotactic response depends on the concentration of attractant. Predictions of the theory are in general agreement with the experiments of Dahlquist et al. (1972, *Nat. New Biol.* **236**: 120) and of Mesibov et al. on populations of motile bacteria in fixed attractant gradients. Additional tests of the model are proposed.

INTRODUCTION

Several years ago, Keller and Segel (9) (hereafter referred to as KS) formulated a mathematical description of the motion of large numbers of bacteria in attractant gradients in terms of diffusive and chemotactic currents. Although originally proposed as an explanation of Adler bands (1), their theory permits one to calculate the average translational movement of a bacterial ensemble in prescribed chemical gradients.

Segel and Jackson (15), Nossal and Weiss (13), and Lapidus and Schiller (10) applied this model of chemotaxis to an experiment performed by Dahlquist et al. (7) (hereafter referred to as DLK). The latter observed the space-time variation in the density distribution of a population of *Salmonella typhimurium* in a fixed exponential concentration gradient of chemical attractant. The theoretical predictions based on the Keller-Segel model agreed with significant aspects of DLK's observations. On the other hand, the theory was less successful when applied to bacterial movement in other attractant concentration gradients studied by DLK. Moreover, as already noted by Dahlquist et al. and by Segel and Jackson, the model is deficient in other respects. In particular it does not account for the abundant experimental evidence that bacteria exhibit apparent threshold and saturation responses to prescribed attractant or repellent gradients. Despite these shortcomings, the successful predictions of the KS theory suggested that this phenomenological view of chemotaxis might be sustained with a modified chemotactic current. We have made such a change, and have applied our new model to the gradient experiments of DLK and of Mesibov et al. (12) (hereafter referred to as MOA). The predictions of the theory are in general agreement with the experimental data.

Our model is suggested by the experiments of Brown and Berg (5) who tracked the trajectories of single bacteria moving in time-varying, spatially uniform attractant concentrations. In the Discussion section, we outline the arguments which led us from their experiments to our proposed model.

We have modified the original conjecture of Keller and Segel that bacterial sensing and motor control mechanisms follow a chemotactic version of the Weber-Fechner law, viz., that the chemotactic current is proportional to the gradient of the logarithm of the attractant concentration, because the weight of experimental evidence (5, 7, 12) favors the S-shaped response proposed in our Eq. 2.

Our model is also supported by the simple and plausible receptor model of Mesibov et al. (12) who proposed that the chemotactic behavior of individual cells is initiated by a first order kinetic interaction between molecules of the chemical attractant and those of the membrane receptors. The S-shaped character of the response is assumed to follow from this primary chemical event. As yet there is no direct experimental evidence to confirm this view of the chemotactic mechanism.

CHEMOTACTIC EQUATIONS

Let $b(r, t)$ be the bacterial density, i.e., the number of bacteria per unit volume, and $s(r, t)$ the concentration of attractant. It is useful to introduce the current density, $J(r, t)$, the number of bacteria crossing a unit area per unit time.

In the absence of population growth, the time rate of change of the bacterial density may be written in the general form

$$(\partial b/\partial t) + \nabla \cdot J = 0. \tag{1}$$

Experimental observations of individual bacteria by Berg and Brown (3, 5) suggest that the current density consists of two terms, $J = J_r + J_c$. The first is due to random, diffusion-like motion of cells in the absence of chemotaxis, while the second reflects directed motion in response to a gradient of chemotactic attractant or repellent.

The diffusion current is $J_r = -\nabla(\mu b)$, with the motility μ the analogue of the diffusion constant for molecules in solution.

In general $\mu = \mu(s)$ is a function of the attractant concentration. Such dependency can arise if average bacterial speeds or average step lengths vary in different uniform chemical concentrations. At present, since no consistent dependence of the motility on concentration is suggested by available experimental data, we assume that μ is a constant. However, if this assumption is invalid, experiments designed to investigate chemotaxis must distinguish the chemotactic current from an apparent current arising from the variation of motility.

The Keller-Segel form for the chemotactic current is $J_c^{KS} = \delta b \nabla(\ln s)$, where δ is a constant which characterizes the strength of the chemotactic current, and $s = s(r)$ is the attractant concentration. However, recent reports from several laboratories (5, 7, 12) on the chemotactic sensitivity of bacteria indicate that bacterial current flow due to chemical gradients is not proportional to the derivative of the logarithm of the concentration. Instead, the response declines at low chemical concentrations and

saturates at high concentrations. The evidence strongly suggests that we write the chemotactic current in the form

$$J_c = \delta b \nabla [s/(s + k)] = bv, \tag{2}$$

where the local chemotactic velocity v is given by

$$v = \delta \nabla f = \delta [ks/(s + k)^2] \nabla (\ln s). \tag{3}$$

δ is positive for attractants and negative for repellents.

The function

$$f = s/(s + k) \tag{4}$$

is an S-shaped function on a logarithmic scale and k is a constant. Our current is similar to that of Keller and Segel, except that we replace their constant δ with the sensitivity function $\bar{\delta}(s) = \delta ks/(s + k)^2$. A plot of $\bar{\delta}$ as a function of s is given in Fig. 1.

The local chemotactic speed is proportional to $\bar{\delta}$ with the maximum centered at $s = k$. This response sensitivity presumably reflects underlying molecular and ionic processes linking membrane receptor detection of the attractant molecules to the ultimate mechanical forces responsible for the cell's motility. In the Ordal-Adler model (12), k has a unique value as the dissociation constant for the attractant-receptor molecular interaction.

Finally, we complete this section by writing our chemotactic equation in full:

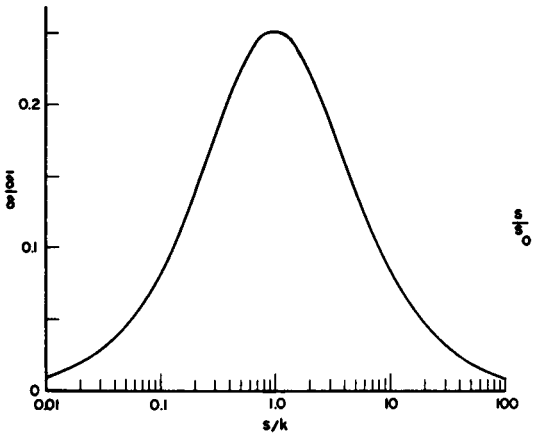

FIGURE 1

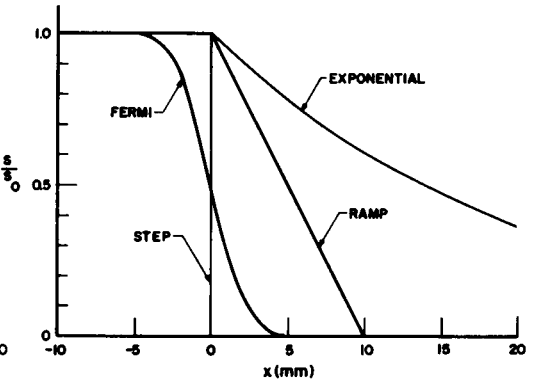

FIGURE 2

FIGURE 1 Plot of $\bar{\delta}(s)/\delta = ks/(s + k)^2$ as a function of s/k.

FIGURE 2 Plots of several fixed gradients of chemotactic attractant. (*a*) Exponential gradient: $s(x)/s_o = 1$ $(x \leq 0)$, $s(x) = s_o \exp(-x/l)$ $(x > 0)$. (*b*) Step gradient: $s(x) = s_o$ $(x \leq 0)$, $s(x) = 0$ $(x > 0)$. (*c*) Step gradient approximated by Fermi function: $s(x) = s_o [\exp(x/l) + 1]^{-1}$. (*d*) Ramp gradient: $s(x) = s_o$ $(x \leq 0)$, $s(x) = s_o (1 - 2x/l)$ $(0 < x \leq l/2)$, $s(x) = 0$ $(x > l/2)$.

$$\partial b/\partial t = \mu \nabla^2 b - \delta \nabla f \cdot \nabla b - \delta \nabla^2 f b. \quad (5)$$

In the remainder of this paper we compare our solutions of Eq. 5 for different attractant concentration gradients to the experimental results of DLK and MOA. We also discuss various methods for determining the values of the parameters μ, δ, and k. We briefly outline the experimental basis of our choice of chemotactic current, Eq. 2, and suggest additional experiments to verify the validity of Eq. 5.

RESULTS

In general, the integration of Eq. 5 by analytic methods is not possible. However, solutions may be determined directly by numerical techniques. We have obtained the space-time development of the bacterial density distribution in several of DLK's one-dimensional attractant concentration gradients. They are described analytically below and illustrated in Fig. 2.

Exponential gradient:

$$s(x) = s_o (x \leq 0); = s_o \exp(-x/l) \qquad (x > 0). \quad (6)$$

Step gradient:

$$s(x) = s_1 (x \leq 0); = s_2 \qquad (x > 0). \quad (7)$$

Step gradient approximated by a Fermi function:

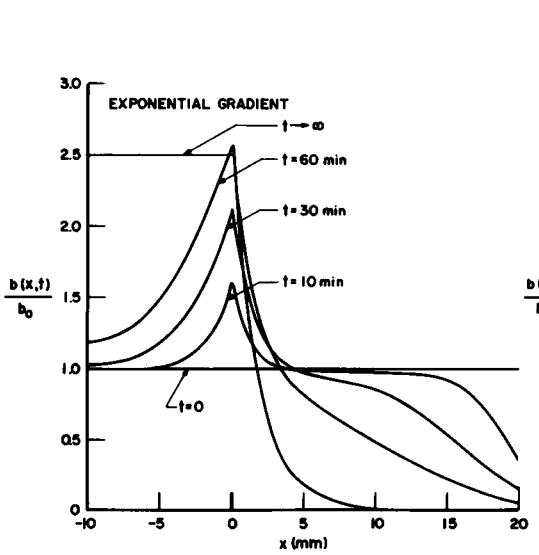

FIGURE 3

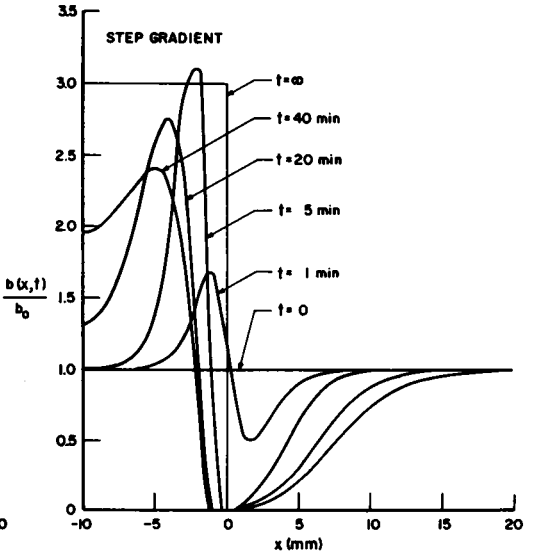

FIGURE 4

FIGURE 3 Distribution of bacteria in an exponential gradient as a function of time with $\mu = 0.33\ \text{mm}^2/\text{min}$, $\delta = 14.0\ \text{mm}^2/\text{min}$, and $k = 0.6 \times 10^{-3}$ M.

FIGURE 4 Distribution of bacteria in a step gradient (approximated by a Fermi function) as a function of time.

$$s(x) = (s_1 - s_2)(e^{x/l} + 1)^{-1} + s_2, \qquad \lim l \to 0. \tag{7A}$$

Ramp gradient:

$$s(x) = s_o(x \leq 0); = s_o(1 - 2x/l) \quad (0 \leq x < l/2); = 0 \quad (x > l/2). \tag{8}$$

We have found the solutions $b(x, t)$ of Eq. 5 in all three cases. They are illustrated in Figs. 3, 4, and 5. (Note that the length of the gradient region in Figs. 3–5, is the same, while in the DLK experiments this value changes in each experiment. Since DLK's published data is incomplete for the step and ramp gradients, we have used the same tube length to facilitate comparison of the three figures.)

For the exponential gradient, DLK found (their Fig. 5) that the area of the central region increases directly with the time, while the height of the peak at the knee grows in proportion to the square root of the time. In Figs. 6 and 7 we have plotted these same quantities from the solutions to Eq. 5 for the exponential gradient. For the 40 min time span of the experiment, the agreement of our theory with the data of DLK is excellent. A similar result was found by Segel and Jackson (15), who solved the KS equation. This is not surprising, for from general arguments (10, 11) one anticipates that under certain conditions, theories with different chemotactic currents could yield similar predictions for these particular observations, and nevertheless be distinguished by other data.

As observed, the attractant gradient draws the bacteria into the central region at a constant rate, so that

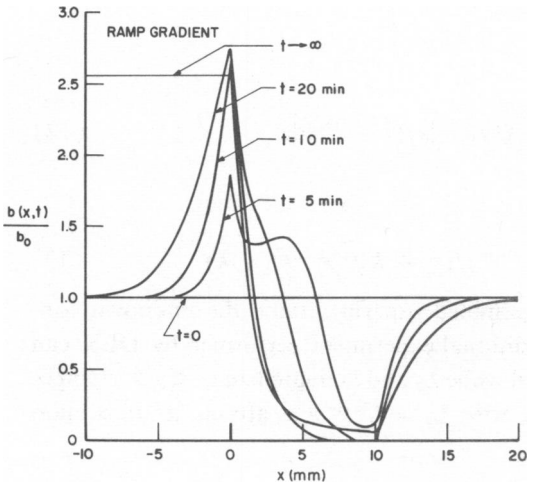

FIGURE 5

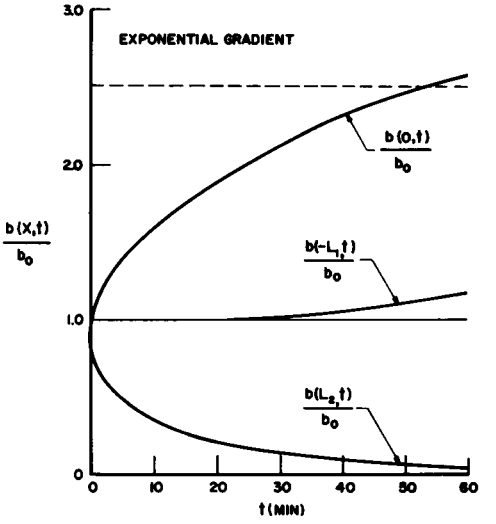

FIGURE 6

FIGURE 5 Distribution of bacteria in a ramp gradient as a function of time.
FIGURE 6 Plots of the quantities $b(0, t)$ the bacterial density at the "knee"; $b(-L_1, t)$, the bacterial density at the left end of the capillary tube; $b(L_2, t)$, the bacterial density at the right end of the capillary tube as functions of time for the exponential gradient.

$$\Delta N = b_o \bar{v} t. \tag{9}$$

ΔN is the increased number of bacteria in the central region, b_o the original uniform linear density of bacteria, and $\bar{v}$ the known rate of flow into the peak area. Segel and Jackson (15) and Nossal and Weiss (13) showed that for a time $t < 4\mu/v^2$ one can predict that the height of the peak at the knee ($x = 0$) should grow as

$$b(0) = b_o \bar{v} t^{1/2} (\pi\mu)^{-1/2}. \tag{10}$$

From Eqs. 9 and 10 and DLK's experimental data, Segel and Jackson found that the motility $\mu = 0.33$ mm^2/min and $\bar{v} = 0.17$ mm/min. This value for μ is in reasonable agreement with other observations based on the known diffusive flow of bacteria in the absence of chemotaxis (2).

Knowledge of $\bar{v}$ allows us to estimate the values of the constants δ and k appearing in the chemotactic current of Eq. 2. For this experiment we assume that for bacterial flow into the central region, diffusion may be neglected for the first 40 min. This assumption will be justified below. Then $\bar{v}$ is approximately the chemotactic velocity evaluated at a point x_o to the right of the origin in our Fig. 3 or DLK's Fig. 6. At x_o, the concentration of bacteria is equal to b_o, the original bacterial density. However x_o varies in time, moving from right to left towards the origin. We therefore approximate $\bar{v}$ by averaging v over the gradient region, i.e.,

$$\bar{v} \simeq \langle v \rangle = (1/L_2) \int_{L_2}^{o} v \, dx. \tag{11}$$

Other approximations for $\bar{v}$ may be used, but they all lead to nearly identical predictions.

From Eq. 3 and Eq. 11 we have

$$\langle v \rangle = (\delta/L_2) \int_{L_2}^{o} (\partial/\partial x)[s/(s + k)] \, dx. \tag{12}$$

With Eq. 6 for $s(x)$,

$$\langle v \rangle = (k\delta/L_2) s_o (1 - e^{-L_2/l})/(s_o + k)(s_o e^{-L_2/l} + k). \tag{13}$$

Since, in principle, $\bar{v}$ has already been determined experimentally, the unknown constants in Eq. 13 are δ and k. A single additional experiment performed by DLK can be used to secure k directly. If s_o is varied while L_2 and l remain fixed, $\langle v \rangle$ changes with s_o as shown in Fig. 8. From Eq. 13, with $L_2 = l$,[1] $\langle v \rangle$ attains its maximum value $\langle v \rangle_{max}$ for $s_o = (s_o)_{max}$,

$$(s_o)_{max} = k e^{L_2/2l} = 1.65 k. \tag{14}$$

From Fig. 8 in DLK, $(s_o)_{max} = 1.0 \times 10^{-3}$ M and $\langle v \rangle_{max} = 0.17$ mm/min. With these values in Eqs. 13 and 14 we find $k = 0.6 \times 10^{-3}$ M and $\delta = 14.0$ mm^2/min.

[1] The actual experimental design in DLK is $L_2 \approx l$.

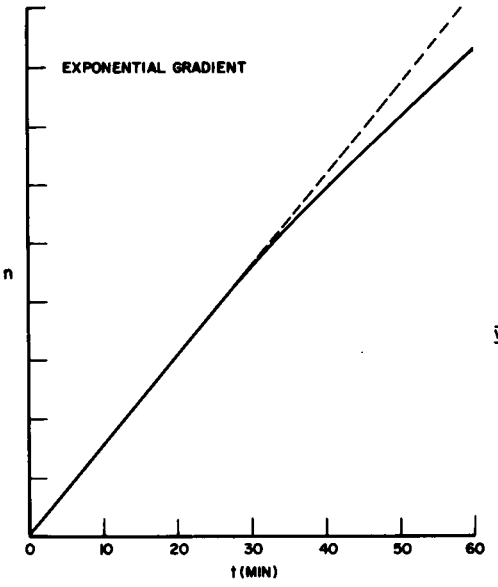

FIGURE 7

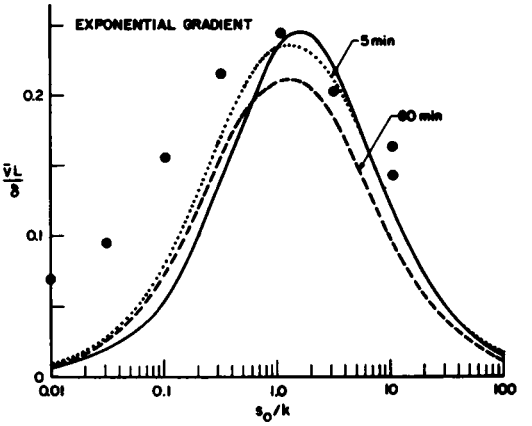

FIGURE 8

FIGURE 7 Plot of the number of bacteria which have migrated into the central region as a function of time for the exponential gradient. For early times the plot is linear in agreement with experiment. The vertical scale is arbitrary.

FIGURE 8 Plot of $<v>$ as a function of s_o/k in Eq. 13 (solid line). Computed sensitivity curves at 5 min (dotted line) and 60 min (dashed line) are shown with the experimental data of DLK (dark circles).

We have also calculated from the solutions to Eq. 5 the sensitivity curve for $\bar{v}$ defined by Eq. 9. The sensitivity is actually a slowly varying function of time, since for long times the chemotactic flow is balanced by the diffusion current. As shown in Fig. 8, there is good agreement between this exact prediction of the theory at 5 min and 60 min and the approximate form for $\bar{v}$ assumed in Eq. 12. This agreement justifies both our neglect of diffusional flow during the early period of bacterial movement into the central region as well as our assumption that $\bar{v}$ is an average chemotactic speed in the gradient region.

In our Fig. 8, we have also reproduced the results of DLK's sensitivity experiment (their Fig. 8). Their data is in reasonable agreement with our predictions at medium and high concentrations but disagree at low concentrations.

The sensitivity experiment distinguishes the model presented here from the Keller-Segel model, and permits a verification of the form of the chemotactic current.

Additional tests of the model could come from the stationary state distribution. For long times, $\partial b/\partial t = 0$ and $\partial J/\partial x = 0$.[2] In addition, $J = 0$ at $x = -L_1, L_2$ so that $J =$

[2]We have neglected diffusion of the chemotactic attractant which is slow compared to the motion of the bacterial population.

0 everywhere. We then have

$$\mu(\partial b/\partial x) = 0, \qquad -L_1 \leq x \leq 0 \tag{15}$$

and

$$\mu(\partial b/\partial x) - \delta b(\partial/\partial x)[s/(s + k)] = 0, \qquad 0 \leq x \leq L_2. \tag{16}$$

Integration of Eq. 15 and Eq. 16 yields

$$b(x) = b_f \qquad -L_1 \leq x \leq 0, \tag{17}$$

$$b(x) = b_f \exp\left[\frac{\delta}{\mu}\left(\frac{s(x)}{s(x) + k} - \frac{s_o}{s_o + k}\right)\right], \quad 0 \leq x \leq L_2, \tag{18}$$

with b_f the final bacterial density at $x < 0$ and s_o the attractant concentration at the origin. The function $s(x)$ depends on the specific attractant gradient employed in the experiment. In this case, $s(x) = s_o e^{-x/l}$. The constant b_f is obtained from the condition that bacterial number is conserved in time,

$$\int_{-L_1}^{L_2} b(x)\,dx = b_o(L_1 + L_2) = N, \tag{19}$$

where N is the total number of bacteria in the capillary at the beginning of the experiment.

The stationary state solution of $b(x)/b(0)$ given by Eqs. 17 and 18 is presented in Fig. 3 as the distribution at time $t \to \infty$. The constants l, δ, μ, and k have values appropriate for the DLK experiment. From the stationary state solution ($t \to \infty$) in Fig. 3, we see that $b_f/b_o = 2.5$, so that in the DLK experiment about 83% of the original bacteria would ultimately be attracted to the region to the left of the origin. At present, there is no evidence to confirm this prediction. We also note that in our Fig. 3 the concentration $b(x, t)$ at 30 min equals b_o at approximately the point 5 mm. This is in rough agreement with DLK's Fig. 6 where the crossover point for $t = 40$ min is about 4 mm.

Other experiments could probe the validity of Eq. 5. For example, with the values of μ, δ, and k secured from DLK's experiments, we plot in Fig. 6 for an exponential gradient the predicted densities as functions of time at the left and right ends of the capillary tube, $b(-L_1, t)$ and $b(L_2, t)$.

The bacterial distributions are shown at various times in Fig. 4 for the Fermi function approximating the step function gradient in Fig. 2. The Fermi function approximation has been used in our computer analysis, since we do not take the actual limit $l \to 0$. Note the correspondence between the experimental data in DLK's Fig. 3, and our predictions in Fig. 4. General arguments similar to those already discussed for the exponential gradient lead to the conclusion that Eq. 9 and Eq. 10 are still valid, but for much shorter times than for DLK's exponential gradient. In addition, we have for $\bar{v}$

the expression in Eq. 12, which in this case becomes

$$\bar{v} \approx (k\delta/l)[s_o(\alpha - 1)(s_o + k)(\alpha s_o + k)]. \tag{20}$$

Here $s_1 \equiv s_o$ and s_2 is chosen to be a constant multiple of s_1, i.e., $s_2 = \alpha s_1 = \alpha s_o$.

If we vary s_o in Eq. 18, we find that $\bar{v}$ peaks at $(s_o)_{max} = k\alpha^{-1/2}$. The plot of $\bar{v}$ as a function of s_o is similar to that shown in Fig. 8. Therefore, if our equations are valid, such an experiment can be used to determine the value of k.

In fact, an experiment similar to the one just suggested has been performed by Mesibov et al. for *E. coli* in a variety of attractants. They have obtained curves which satisfy Eq. 20 and which resemble those in Fig. 8. Since their concentration gradient only approximates a step-function, the value of l in the denominator of Eq. 20 does not become vanishingly small, and in fact may be estimated from the analytical solutions of the gradient calculated by Brokaw (4) and Futrelle and Berg (8). However, provided that the gradient approximates a Fermi function, the precise value of l in Eq. 20 has little relevance in determining the constant k from their sensitivity experiments.

The theory may be subjected to an additional test if we let the bacterial distribution go over to the stationary state. This configuration is shown in Fig. 4 at the time $t \to \infty$. From Eqs. 11 and 12, we have

$$b(x) = b_f \qquad -L_1 \leq x \leq 0 \tag{21}$$

$$b(x) = b_f \exp\left[\left(\frac{\delta}{\mu}\right)\left(\frac{s_2}{s_2 + k} - \frac{s_1}{s_1 + k}\right)\right], \quad 0 \leq x \leq L_2 \tag{22}$$

where b_f is given as

$$b_f = N \Big/ \left\{L_1 + L_2 \exp\left[\left(\frac{\delta}{\mu}\right)\left(\frac{s_2}{s_2 + k} - \frac{s_1}{s_1 + k}\right)\right]\right\}. \tag{23}$$

The plot of the variable $w = \ln[L_2^{-1}(N/b_f - L_1)]$ as a function of s_o with $s_1 = s_o, s_2 = \alpha s_1 = \alpha s_o$, shows that w varies in the same way as $<v>$ in Fig. 8. The function w peaks at $(s_o)_{max} = k\alpha^{1/2}$, so that the final state distribution of bacteria in a step function gradient provides another means to measure k and the ratio δ/μ.

We also have calculated the bacterial distribution for the ramp function gradient of Fig. 2. The bacterial density at various times, including the stationary state, has been plotted in Fig. 5. A noteworthy feature of these solutions appears in the distributions at early times in Fig. 5. A transient relative maximum is recorded, but it disappears at later times. A similar maximum has been detected experimentally by DLK (their Fig. 4).

Finally, in the Appendix we find the unique gradient in our model which plays the equivalent role of the exponential gradient in the Keller-Segel model. If our model is correct, the sensitivity response of the bacteria would vanish in such a gradient, and the final density distribution become independent of the attractant concentration at the knee.

DISCUSSION

Our model for chemotaxis describes the average translational motion of a bacterial distribution in prescribed attractant or repellent concentration gradients. Predictions based on the solution to Eq. 5 are in reasonable agreement with the observations of DLK and MOA. Additional experiments have been suggested to check the validity of our assumptions.

Three parameters, μ, δ, and k, appear in Eq. 5. Their values, which must be secured from experiment, serve to characterize both the motility of an organism and the mechanism for the chemotactic response. We have discussed a variety of methods which may be employed to determine these variables.

Our model is suggested by the work of Brown and Berg (5) who tracked the paths of single bacteria subjected to time varying attractant concentrations. They showed that as the concentration increased continuously in time, the average bacterial path length increased by an amount proportional to the time derivative of the function f of Eq. 4. As Brown and Berg already noted, because the bacterial sensing mechanism detects changes in chemical environment through bacterial movement, the observed increase in path length due to spatial concentration variations must be proportional to the space derivative of f, i.e., $\delta l \propto \mathrm{d}f/\mathrm{d}x = v^{-1}\,\mathrm{d}f/\mathrm{d}t$. Furthermore, the average bacterial translational speed, the magnitude of v, has been observed to remain constant as the concentration of attractant is varied. Finally, if chemotaxis is viewed as a small perturbation of a diffusing system, then the theory of Brownian motion (6, 14) indicates that the chemotactic velocity is proportional to the change in path length and thus to the gradient of the function f. This general argument led us to our Eq. 5, but the detailed calculations will be presented elsewhere.

APPENDIX

There exists a unique attractant concentration function $s(x)$ for which the sensitivity vanishes and our theoretical model becomes identical to that of Keller and Segel for an exponential gradient.

In the KS theory, the chemotactic current is given by

$$J_c^{KS} = \delta b(\partial/\partial x)(\ln s) \tag{24}$$

If $s = s_o e^{-x/l}$ the chemotactic current reduces to a multiple of b, i.e.,

$$J_c^{KS} = -(\delta/l)b = vb, \tag{25}$$

where $v = -(\delta/l)$ is the constant drift velocity of the population.

Similarly, in our theory there is a unique attractant concentration gradient which yields the same result. Our chemotactic current is given by

$$J_c^{LS} = \delta b(\partial/\partial x)[s/(s + k)]. \tag{26}$$

If we choose

$$s = k([ls_o - (s_o + k)x]/[lk + (s_o + k)x]), \quad (27)$$

with s_o the value of s at the coordinate origin, and l a constant chosen so that $ls_o \geq (s_o + k)x$, Eq. 26 goes over into Eq. 25.

Thus, in this special case, the chemotactic response is insensitive to the value of s_o. For the concentration gradient given in Eq. 27 the motion of the bacterial population may be determined analytically if there is no plateau region (11), or numerically if a plateau is included (10).

The above result may be generalized to any model which has a chemotactic current of the form $J_c = \delta b \partial F(s)/\partial x$, with $F(s)$ a known function of s. The condition needed to satisfy Eq. 25 is $F(s) - F(s_o) = x/l$, which in principle, may be solved for s once $F(s)$ is specified.

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

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