A MODEL FOR TRAVELING BANDS OF CHEMOTACTIC BACTERIA

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ABSTRACT A theoretical model is used to study band formation by chemotactic populations of *Escherichia coli*. The model includes the bacterial response to attractant gradients, the chemotactic sensitivity of the bacteria to the concentration of the attractant, and population growth. For certain values of the parameters in the model, traveling bands of bacteria form and propagate with or without growth. Under specific growth conditions the band profile is maintained and the band propagates at constant speed. These predictions are in general agreement with the experimental results of J. Adler and earlier theoretical work by L. Segel and his collaborators. However, our theory differs in several important respects from the latter efforts. Suggestions are made for further experiments to test the proposed model and to clarify the nature of the processes which lead to band formation.

INTRODUCTION

In the last decade the chemotactic responses of microorganisms have become a subject of intensive study. Of special interest is the phenomenon of traveling bands of bacteria, which arise through the metabolism of an attractant by chemotactic bacteria of sufficient density. By consuming the nutrient, the bacteria create a chemical concentration gradient that induces chemotactic movement.

Adler (1966) studied band formation by populations of *Escherichia coli* in capillary tubes. A theoretical model to explain this phenomenon was proposed by Keller and Segel (KS) (1971), and a more detailed computer analysis of a modified version of that model was carried out by Scribner et al. (SSR) (1974). Other contributions to the theory of band propagation based on the work of KS are due to Rosen (1974, 1975), Rosen and Bologa (1975), Nossal (1972), Keller and Odell (1976), and Odell and Keller (1976). Earlier studies of band formation in capillary tubes neglected the growth of the bacterial population. Our model also explicitly uses the observed dependence of the chemotactic motility on attractant concentrations.

Recently we (1976) developed a mathematical model of bacterial chemotaxis that incorporates the observed sensitivity of *E. coli* and other chemotactic microorganisms to attractant concentrations. The theory was used to study the motion of bacterial populations in fixed chemotactic attractant gradients (Lapidus and Schiller, 1976). The predictions were in general agreement with a variety of experiments. In the present paper the model is extended to include population growth and is applied to an analysis

of Adler bands. The results are also compared with those of the KS theory and the numerical analysis by SSR.

As shown in the following sections, the model describes the formation of moving bands of chemotactic bacteria. The growth rate for the bacterial population can be chosen so that the loss of cells from a band due to diffusion is balanced by the increase in cell number arising from population growth. The band appears to propagate as a traveling wave and the model determines the nearly invariant band characteristics of cell number, speed, and density profile. In the absence of growth, bands still form, but they lose cells due to diffusion. There is a consequent decrease in band speed and a broadening of the density profile.

In our model, the number of cells in a band increases with increasing inoculum size, but if other conditions remain fixed, the band population eventually saturates.

We also have studied the dependence of the band speed and the number of cells in the band on the consumption rate and the chemotactic motility. We find that bands form only when the chemotactic current and the bacterial feeding rate or the density of bacteria fall within a specified range of values.

These and other results are presented in detail after a discussion of the model.

MODEL FOR CHEMOTAXIS BY A BACTERIAL POPULATION

A bacterial population in a capillary tube has a volume density given by $b(x, t)$. The number of cells per unit area is $n = \int_{-\Delta L/2}^{\Delta L/2} b(x, t)\,\mathrm{d}x$, where ΔL is a length along the tube. The quantity n is proportional to the number of bacteria in the length ΔL. The total number of cells in the length ΔL is $N = nA$, where A is the cross-sectional area of the tube.

The change in volume density at any position in the tube is given by

$$\partial b/\partial t = -\partial J/\partial x + Rb, \tag{1}$$

where J is the bacterial flux, or current, through a cross-section of the tube, and R is the growth rate per cell. In general, R is a function of the nutrient concentration, the temperature, and other environmental factors. However, it is assumed that except for the nutrient concentration, which varies because of consumption, all other variables are kept constant.

The flux J is composed of two terms, one random and the other chemotactic. This decomposition has been justified by various experimental studies with bacterial populations. Furthermore, Berg and Brown (1972) have confirmed that the motility patterns for individual cells are consistent with a continuum description of the motion of bacterial populations. The random, or diffusive flux is

$$J_R = -\mu\,\partial b/\partial x, \tag{2}$$

where μ, the bacterial random motility, is assumed to be constant. The chemotactic flux is

$$J_c = \delta b \, \partial/\partial x \, [s/(s + k)], \tag{3}$$

where $s(x)$, the chemotactic attractant concentration, is a function of position in the tube. The chemotactic motility, δ, and the sensitivity constant, k, are also assumed to be fixed.

We have discussed the form of Eq. 3 (Lapidus and Schiller, 1976). It is based on the observations of Mesibov et al. (1973) and others indicating that the chemotactic response is proportional to the gradient of a function f of the attractant concentration (the sensitivity function), with $f = s/(s + k)$.

Combining Eqs. 1–3, the equation for the bacterial density becomes

$$\partial b/\partial t = \mu \, \partial^2 b/\partial x^2 - \delta \, (\partial f/\partial x) \, (\partial b/\partial x) - \delta \, (\partial^2 f/\partial x^2) \, b + Rb, \tag{4}$$

where $R(s) = R_0 \, s/(s + s_k)$, with R_0 and s_k constants. $R(s)$ is given this form so that $R(s) \to 0$ when $s \to 0$ and $R(s) \to R_0$ when s is large. In the absence of bacterial diffusion and chemotaxis, $R_0 \tau = \ln 2$, where τ is the doubling time of the population for large concentrations of attractant. The predictions of the model are relatively independent of the precise dependence of $R(s)$ on s.

Since diffusion of the attractant is slow, it is ignored in this analysis. The time rate of change of the nutrient then depends only on the consumption rate, assumed to be proportional to the density of bacteria, i.e.,

$$\partial s/\partial t = - \lambda b, \tag{5}$$

with λ, the time rate of consumption per cell, taken as a constant.

Eqs. 4 and 5 constitute a pair of coupled nonlinear differential equations for the variables b and s. In general these equations do not have analytic solutions, so that we solved them by numerical methods on a digital computer. Our solutions were compared with the experiments of Adler and the theoretical work of SSR. The results are discussed in the next section.

Eqs. 4 and 5 contain six parameters, μ, δ, k, λ, τ, and s_k, which must be deduced from other experiments. Wherever possible, their values have been chosen to correspond to those appearing in SSR.[1] The remaining constants in the calculations are used to set the mathematical boundary values and initial conditions. They are determined from Adler's band experiments and include the initial concentration of bacteria in the inoculum, the size of the inoculum, and the initial concentration of attractant. The values of the constants and parameters used in the model appear in Table I.

[1]Since SSR do not consider the sensitivity of the chemotactic response to the nutrient concentration, our value of δ differs from theirs. For $s \approx k$, $\delta s^2/(s + k)^2 \approx \delta/4 \to \delta^{KS}$, where δ^{KS} is the value of δ used in the above-mentioned references. Thus, the value $\delta/\mu = 13.6/0.33 = 40.8$ used in this paper is equivalent to $\delta^{KS}/\mu = 10.2$.

TABLE I
VALUES OF PARAMETERS

$\mu_0 = 0.333\ mm^2/min$	Random motility.
$\delta_0 = 13.6\ mm^2/min$	Chemotactic motility.
$s_0 = 1\ mM$	Initial attractant concentration.
$\lambda_0 = 1/3 \times 10^{-15}$ mol/min/per cell	Attractant consumption rate.
$b_0 = 4.775 \times 10^5\ cells/mm^3$	Initial cell density.
$L = 80\ mm$	Length of tube.
$A = 0.785\ mm^2$	Cross-sectional area of tube.
$x_0 = 8\ mm$	Inoculum size.
$k = s_0$	Sensitivity constant.
$\tau = 40\ min$	Doubling time.
$s_k = 0.1\ mM$	Attractant concentration at which $R = R_0/2$).

The first eight are equivalent to or the same as those used by Scribner et al. (1974). The last three values are our estimates.

RESULTS

To carry out the numerical calculations, Eqs. 4 and 5 were rewritten as difference equations. The Crank-Nicolson method was used to solve the resulting algebraic equations. In this procedure the ranges of x and t are divided into a grid of points ($x_i = i\Delta x$, $t_j = j\Delta t$; i, j = integers) and the continuous functions $b(x,t)$ and $s(x,t)$ are replaced by the finite sets b_{ij} and s_{ij}, respectively. The differential equations then become a set of implicit difference equations solved by matrix inversion at each time value t_j.

The calculations were carried out on a PDP-10 digital computer (Digital Equipment Corp., Maynard, Mass.) at the Stevens Computer Center. A single pass through the program takes less than 0.1 s. Thus, for an experimental run time of 120 min with $\Delta t = 0.1$ min, the actual computer time is slightly more than 1 min. Compilation of the FORTRAN program takes a few minutes and the program may be run for a number of different values of the parameters during the same execution.

At each time interval ($\Delta t = 0.1$ min), the computer program evaluates the distribution of bacteria $b(x,t)$ and the concentration profile $s(x,t)$. The results are printed at preassigned time intervals (e.g., 1 or 5 min). The program also sums the total number of bacteria, and to measure the round-off error, in the absence of growth evaluates the difference between this sum and the initial number of bacteria in the tube. The errors are small and do not exceed a few percent during hours of "experimental time." Thus, when growth is included in the analysis, changes in time of the total bacterial number primarily reflect population increase.

With the values of the parameters given in Table I, the numerical results presented in Figs. 1 *a–e* demonstrate the initiation and propagation of bands of chemotactic bacteria. The figures indicate the consumption of the chemotactic attractant and the eventual separation of the band from the inoculum.

In the absence of growth, the band profiles widen and the speed of the band decreases. However, with growth and a doubling time of 40 min, a stable traveling band is formed for the parameter values given in Table I. The band profiles are asymmetri-

cal, with the leading edge of the band considerably steeper than the trailing edge. As the band speed increases, the band profile becomes sharper. Our results may be understood as follows: For $s_i = k$ the leading edge of the band is moving in an attractant concentration $\approx s_i$ so that the chemotactic response is maximal. At the trailing edge the chemotactic response is considerably reduced and the diffusive motion becomes more significant. This agrees with some of the profiles found by Keller and Segel (1971) but contrasts with the near symmetry of the bands found by SSR and the reverse asymmetry of some of the steady-state traveling band solutions noted by KS.

Fig. 2 *a* shows, in the absence of growth, the change in time of the number of cells per unit area in the band per standard inoculum size, n/x_0 (x_0 = 8 mm as in the Adler experiments); the density at the peak of the band, b_p; and the width of the band, w, defined as the distance between the point at which the band has consumed all the attractant and the leading edge. Shortly after the band separates from the inoculum, the density peak reaches its maximum value and then decreases in time. The width of the band constantly increases. Initially, the number of cells in the band increases rapidly but then slowly decreases. Fig. 2 *b* shows the results obtained when population growth is included. In contrast to the case of no growth, the density at the peak of band, the number of cells in the band and the band width all assume nearly constant values after an initial transient period.

The results given in Figs. 1 and 2 were obtained with the parameter values in Table I. However, specific parameters can be varied experimentally and the theory can predict the consequences of such changes. Thus the formation and propagation of bands may be studied as a function of the inoculum size, x_i. The results of the analysis are given in Fig. 3 for the case of no growth. A band is formed for all inocula provided that λ, δ, b_0, and s_i fall within a range of values. For small inocula, almost all the bacteria enter the band. With increasing inoculum size, the number of cells in the band increases proportionately. However, after the inoculum reaches a critical size, no additional cells are incorporated into the band. The magnitude of the chemotactic current for the bacteria remaining in the inoculum is too small and they are left behind as the band advances. In time, these inoculum bacteria will diffuse throughout the capillary tube.

The number of cells in a band is a function of the chemotactic motility and the rate of consumption of chemotactic attractant. This dependence is shown in Fig. 4 *a* for fixed δ and variable λ and in Fig. 4 *b* for fixed λ and variable δ. No bands are formed for values of δ or λ significantly beyond the ranges shown in Figs. 4 *a* and *b*, but we have not calculated the exact cut-off values for band formation in each case.

The band speed, defined as the change in position of the density peak per minute, is determined in part by the consumption rate of the attractant and the chemotactic motility. Within the width of the band, the concentration of attractant decreases rapidly from its initial value to zero and the attractant concentration is approximately a step function. The concentration profile has its maximum slope close to the peak of the band. The chemotactic response, which is proportional to the gradient of the concentration, is thus very large at the peak located near the center of the band.

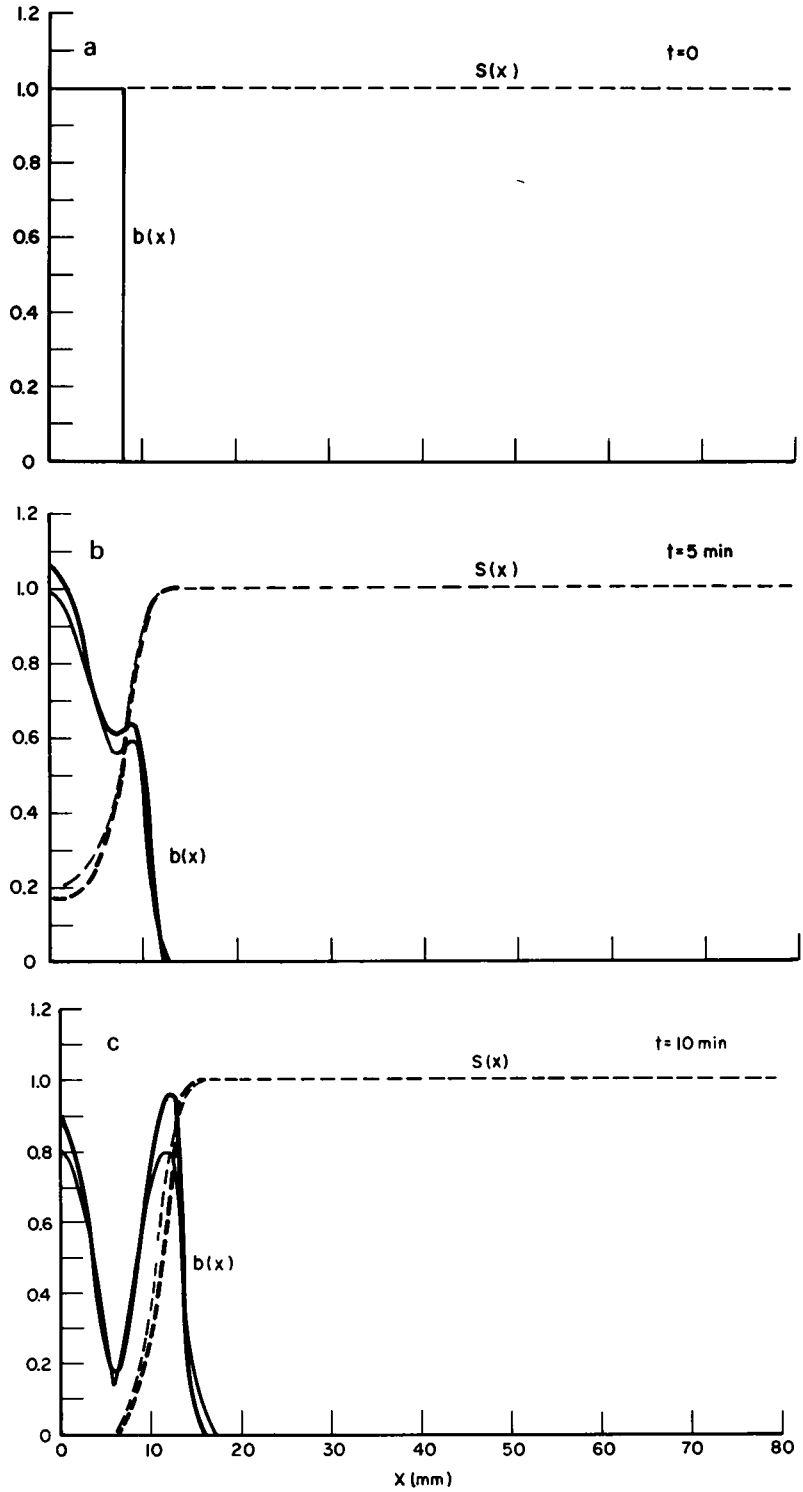

FIGURE 1 See caption on p. 7.

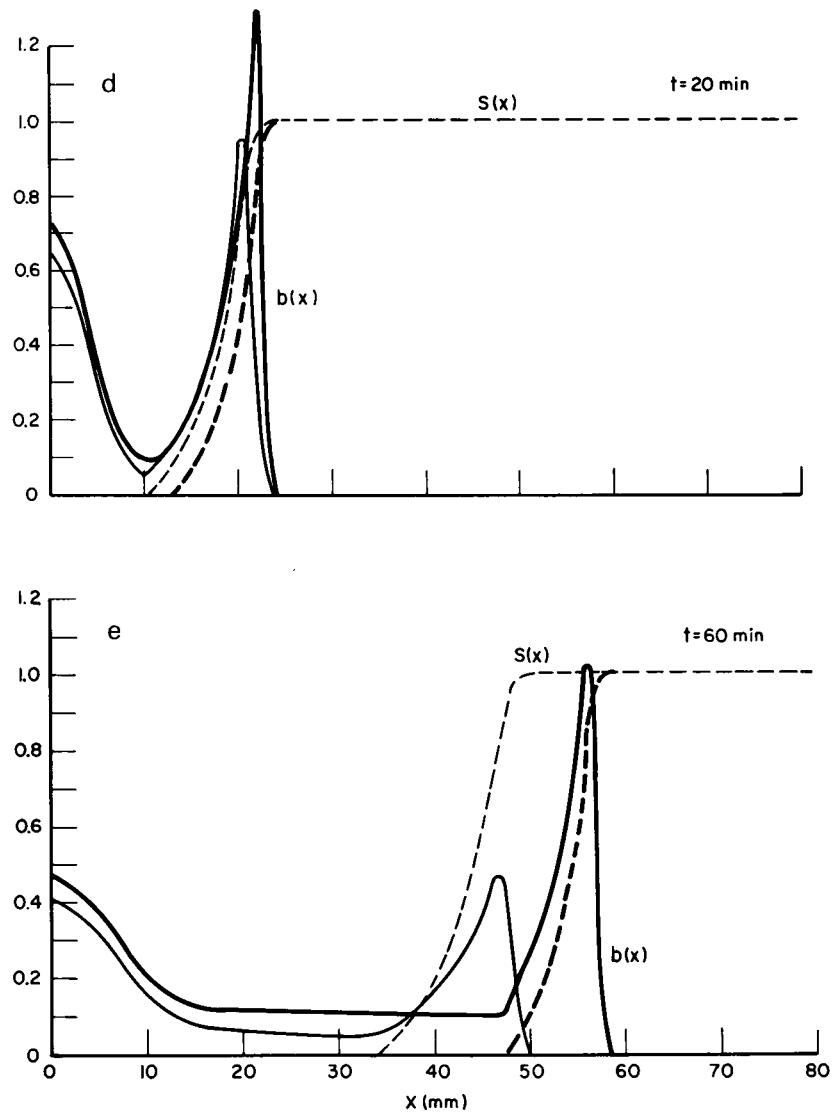

FIGURE 1 Plots of the bacterial density $b(x,t)$ and chemotactic attractant concentration $s(x,t)$ as functions of x for a number of times. The band begins to form within 5 min and separates from the inoculum by 10 min. It reaches the end of the capillary tube at 110 min if there is no growth and at 85 min with growth. After the attractant is completely consumed, the bacteria approach the steady-state uniform distribution. (Light lines are without growth, heavy lines are with growth.) The values of all parameters are given in Table I.

To illustrate the dependence of the band speed on consumption rate and chemotactic motility, Figs. 5 *a* and *b* describe the average speed of the band as a function of time. For the case of no growth, these graphs show the dependence of the speed of the band on a range of consumption rates, λ, and chemotactic motility values, δ. The band speed increases with the consumption rate and with the chemotactic motility.

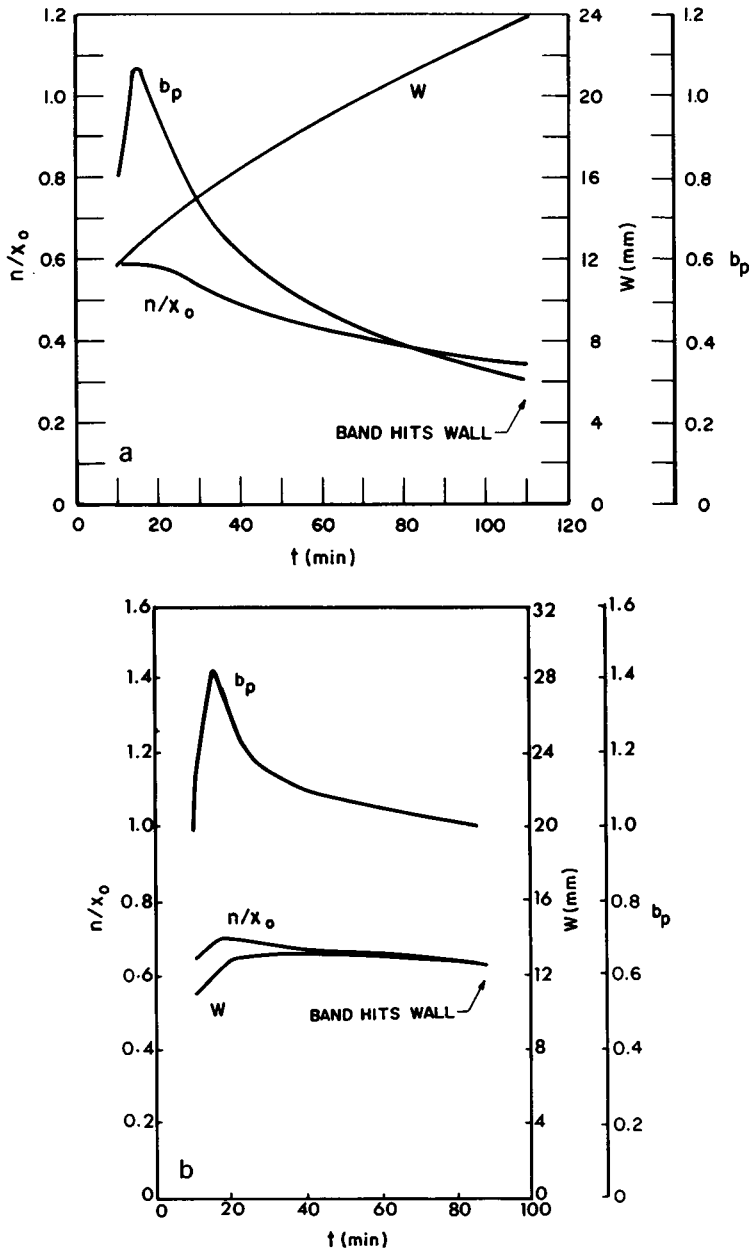

FIGURE 2 Plots, as functions of time, of the number of cells in a band (as a fraction of the standard inoculum size), n/x_0; peak density of the band, b_p; and width of the band, w (*a*) without growth, (*b*) with growth. The values of all parameters are given in Table I. The number of cells in the band was determined as follows: If the attractant concentration is greater than zero at a point x the cells at x are included in the band. This defines the left-hand side of the band. All cells to the right of this point are then included in the band. The width of the band may be noted qualitatively by inspection of the profiles, since the right-hand side has a sharp edge. Quantitatively the leading edge is defined as that point at which the attractant concentration is equal to its original value to an accuracy of 1 part in 10^5.

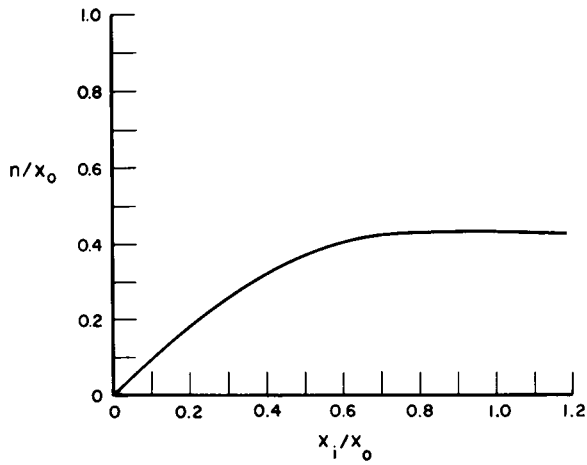

FIGURE 3 Plot of the number of cells in the band, n/x_0, at 60 min as a function of inoculum size, x_i/x_0 without growth. Bands are formed for all inocula. For $x_i/x_0 > 0.75$ the number of cells in the band is independent of inoculum size. Other parameters were fixed at the values given in Table I.

To obtain band formation, the chemotactic current must be comparable to or greater than the diffusion current. Thus, in our model, δ/μ must be much greater than 1. For small values of δ and λ, the chemotactic current is reduced and no band formation is possible. If λ has too large a value, a relatively few cells will consume the attractant, and migrate in a low-density band. If δ is very large, the cells will quickly migrate across the tube without true band formation.

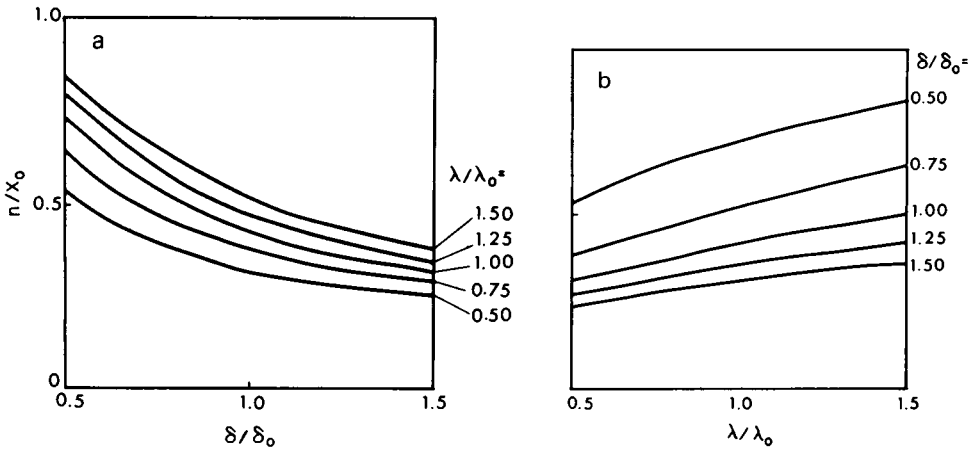

FIGURE 4 Plots of the number of cells in the band, n/x_0, (*a*) as a function of the chemotactic motility, δ (with the rate of consumption of chemotactic attractant, λ, fixed at the indicated value); and (*b*) as a function of the rate of consumption of the chemotactic attractant, λ (with the chemotactic motility, δ, fixed at the indicated value). Other parameters were fixed at the values given in Table I. Growth has been neglected.

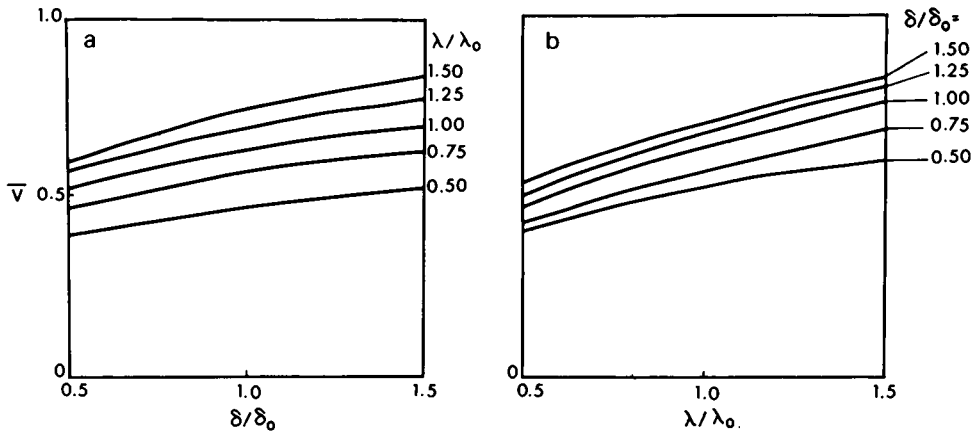

FIGURE 5 Plots of the average band speed, $\bar{v}$, during the time interval 30–60 min (*a*) as a function of the chemotactic motility, δ (with the rate of consumption of the chemotactic attract, λ, fixed at the indicated value); and (*b*) as a function of the rate of consumption of chemotactic attractant, λ (with the chemotactic motility, δ, fixed at the indicated value). Other parameters were fixed at the values given in Table I. Growth has been neglected.

The formation and propagation of bands also may be studied as a function of the initial cell density, b_0. However, this is unnecessary since in our calculations the parameter actually determining the consumption rate of the population is $\Lambda = \lambda b_0/k$. Thus, if we neglect a scale factor, variation of b_0 is equivalent to variation of λ.

The band speed and the number of cells in the band are functions of the initial concentration of chemotactic attractant, s_i. As shown by Mesibov et al. (1973), and Berg and Brown (1972), and discussed in Lapidus and Schiller (1976), the chemotactic response has a maximum sensitivity at a particular concentration of attractant. This sensitivity is also exhibited in our model of the formation of traveling bands. For the cases of no growth and growth, Figs. 6*a* and *b* respectively, graph the average band speed and the number of cells in the band as functions of s_i. The maximum chemotactic response of the bacteria occurs at $s_i \approx k$. The number of cells in the band increases with increasing concentration of attractant.

If $s_i/k \ll 1$ the attractant is rapidly consumed by the few cells which migrate away from the inoculum, but the cells do not form an experimentally observable band. If the value of $s_i/k \gg 1$, the cells consume the attractant very slowly and a band forms only after a long time. The band travels slowly because of the time needed to consume all of the attractant and because at the band's leading edge the chemotactic response is significantly below its maximum value. On this time scale bacterial diffusion becomes important and the band profile cannot be maintained. Thus, no traveling band is observed in this case either.

In the absence of growth the numerical solutions obtained are not traveling waves because the density profile and speed of the band vary slowly as functions of time. However, it is of interest to note that even without growth our solutions satisfy a relation for traveling waves predicted by Eq. 4.

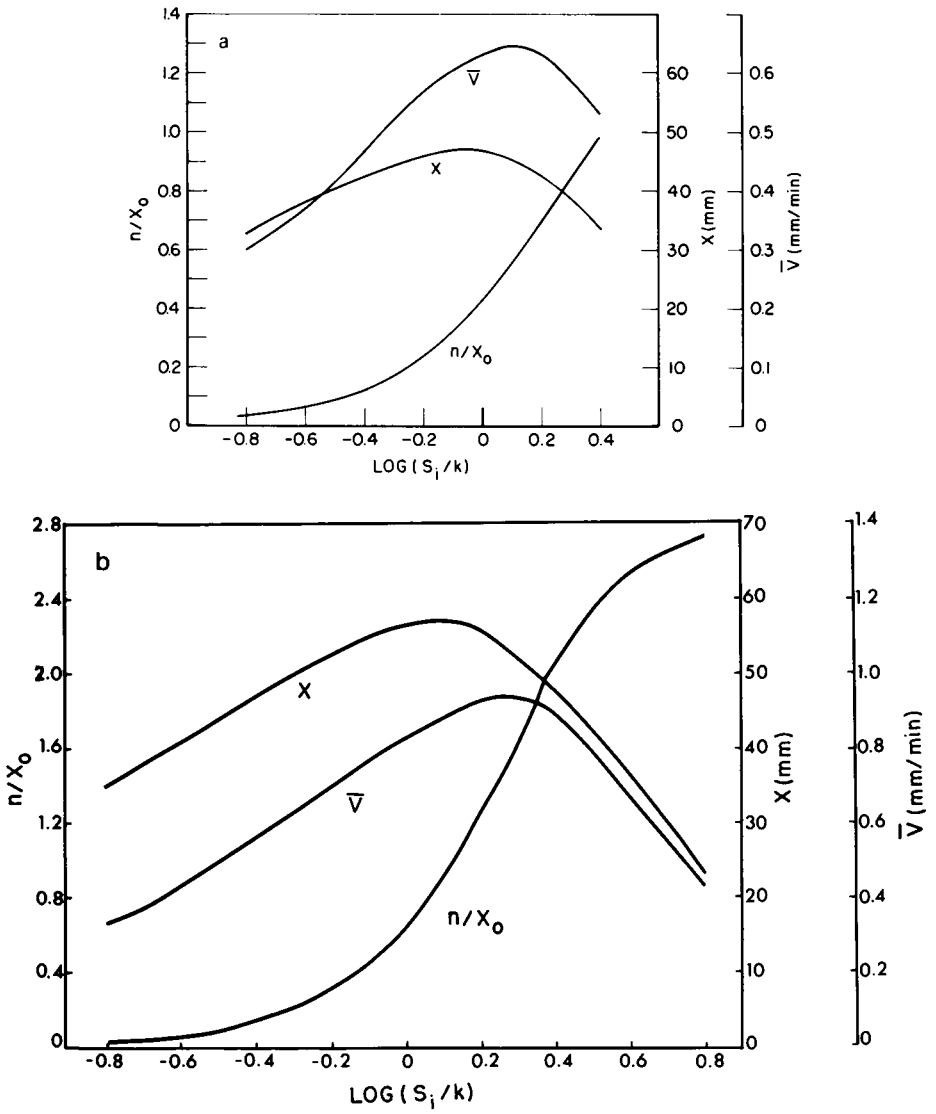

FIGURE 6 Plots of the number of cells in the band (as a fraction of the inoculum), n/x_0, at 60 min; position of the band peak x_p, at 60 min; and average speed of the band, $\bar{v}$, during the time interval 30–60 min as functions of the initial uniform chemotactic attractant concentration, s_i. Other parameters were fixed at the values given in Table I. (*a*) without growth, (*b*) with growth.

For a traveling wave moving with speed v, KS have shown that

$$vs_i = \lambda n, \tag{6}$$

where n is the number of cells per unit area in the band and s_i is the initial uniform concentration in the capillary tube. For a true traveling wave, the two constants v and n are proportional to each other.

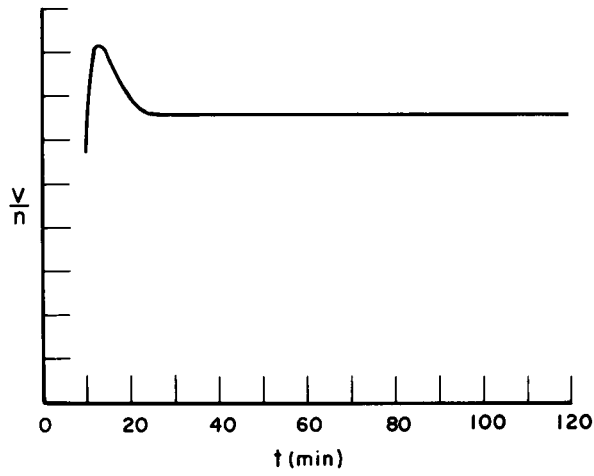

FIGURE 7 Plot of the ratio of the speed of the band to the number of cells per unit area in the band, v/n, as a function of time without growth.

In our calculations s_i and λ are fixed while the number of cells in the band and the speed of the band are dynamic quantities which change as the band propagates along the capillary tube. After an initial transient period, the ratio of v to n remains constant. This is shown in Fig. 7, where, for the bands shown in Fig. 1, v/n is plotted as a function of time.

Furthermore, the quantity $\eta = v\, s_i/\lambda n$ is approximately constant even when the values of s_i and λ are varied. Thus, although the band profile and the number of cells in the band vary slowly in time, the bands still exhibit some features of traveling waves.

The band speeds predicted by our model are larger than those measured by Adler. With an attractant concentration of 0.25 mM galactose, Adler observed a band speed of 0.17 mm/min, while we predict a speed of 0.43 mm/min with growth and a speed of 0.37 mm/min without growth. Given the uncertainty in the measured values of half a dozen different parameters used in our calculations, we do not find the discrepancy a cause for concern, especially since the constancy of $\eta = vs_i/\lambda n$ indicates that we can reduce the predicted value of the band speed by decreasing the feeding rate or the magnitude of the chemotactic motility.

CONCLUSION

The traveling band experiments of Adler (1966) have been analyzed by means of a mathematical model for the chemotactic response of bacteria. This model differs from that proposed by Keller and Segel (1971) and investigated numerically by Scribner et al. (1974). We have incorporated the observed bacterial sensitivity to the concentration of chemotactic attractant as well as population growth. General agreement is obtained with Adler's experimental results. In our model, growth of the bacterial population at a specific rate is necessary for the band to propagate without significant dis-

tortion. In the absence of growth, we find a more pronounced change in the band profile due to loss of cells than SSR found in their calculations.

Our calculations demonstrate that theoretical models of this kind can predict, with reasonable accuracy, a variety of responses of a population of chemotactic bacteria. These range from motion in prescribed chemical gradients to band formation. Although the predicted behavior stems from the sensory and motile characteristics of single cells, a group property such as band formation is dependent on the nature of the ensemble. Conversely, the ability to predict the behavior of a population of microorganisms in prescribed environments may allow reasonable conjectures concerning the cellular mechanisms in individual organisms which lead to the group motions.

We have discussed the results of computer "experiments" in which we varied several parameters of the theory and determined the changes in the band's characteristics. Our predictions on band formation and propagation go beyond the available experimental data, and differ in important details from previous theoretical analyses. We suggest additional experiments to gain a greater understanding of band formation and to test various proposed models of the phenomenon.

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

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