Bulletin of Mathematical Biology (2008) 70: 1570–1607
DOI 10.1007/s11538-008-9322-5

REVIEW ARTICLE

Overview of Mathematical Approaches Used to Model Bacterial Chemotaxis II: Bacterial Populations

M.J. Tindall[a,*], P.K. Maini[a,c], S.L. Porter[b], J.P. Armitage[b,c]

[a] *Centre for Mathematical Biology, Mathematical Institute, 24-29 St Giles', Oxford, OX1 3LB, UK*
[b] *Department of Biochemistry, Microbiology Unit, University of Oxford, South Parks Road, Oxford, OX1 3QU, UK*
[c] *Oxford Centre for Integrative Systems Biology, Department of Biochemistry, University of Oxford, South Parks Road, Oxford, OX1 3QU, UK*

Received: 23 February 2007 / Accepted: 13 June 2007 / Published online: 19 July 2008

Abstract We review the application of mathematical modeling to understanding the behavior of populations of chemotactic bacteria. The application of continuum mathematical models, in particular generalized Keller–Segel models, is discussed along with attempts to incorporate the microscale (individual) behavior on the macroscale, modeling the interaction between different species of bacteria, the interaction of bacteria with their environment, and methods used to obtain experimentally verified parameter values. We allude briefly to the role of modeling pattern formation in understanding collective behavior within bacterial populations. Various aspects of each model are discussed and areas for possible future research are postulated.

Keywords Bacterial chemotaxis · Population modeling · Multi-scale modeling · Review

1. Introduction

Bacteria such as *Escherichia coli*, *Rhodobacter sphaeroides*, and *Bacillus subtilus*[1] respond to extracellular changes in their environment by biased random motion towards attractants or away from repellents. Such movement is commonly referred to as chemotaxis and was first reported as early as the late nineteenth century (Engelmann, 1881a, 1881b; Pfeffer, 1888). In the last 40 years, bacterial chemotaxis has been an area of increasing interest to both experimentalists and theoreticians. This interest has been fueled by ever-increasing experimental insight into the behavior of bacteria, both on the population and individual scale, coupled with insight provided by new and more detailed mathematical

*Corresponding author.
E-mail address: tindallm@maths.ox.ac.uk (M.J. Tindall).
[1] For a comprehensive list of chemotactic bacterial species and the differences between them the reader should consult Eisenbach et al. (2004).

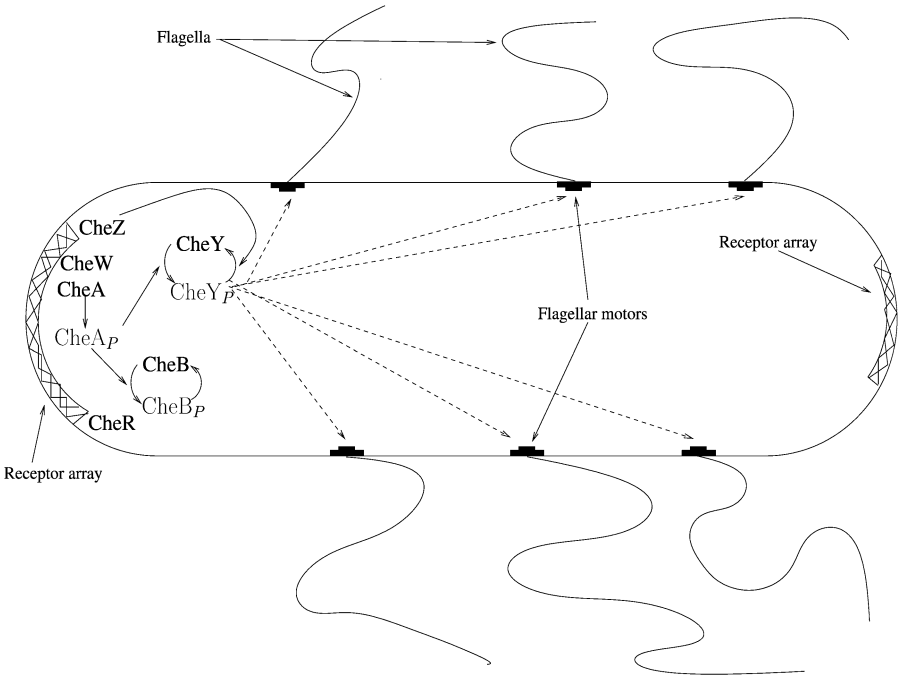


Fig. 1 A schematic representation of the biochemical signaling network between the membrane receptors and flagellar motors within *E. coli* (flagellar not drawn to scale with respect to the cell body). The autophosphorylation of CheA is controlled by the receptor array in response to either gradients of attractant or repellent. In the absence of an attractant or presence of a repellent gradient, the receptors activate CheA autophosphorylation. Phosphotransfer to CheY causes a rise in phosphorylated CheY (CheY$_P$) levels which promotes clockwise rotation of the flagella leading to tumbling. Adaptation is controlled by methylation of the receptors. CheR acts to methylate receptors and phosphorylated CheB (CheB$_P$) demethylates them. In the absence of an attractant gradient, both exist in a dynamic equilibrium. Detection of an attractant gradient leads to cessation of the autophosphorylation of CheA and a decrease in CheY$_P$ concentration causing counter-clockwise rotation of the flagella which leads to chemotactic runs. Simultaneously, a decrease in CheB$_P$ levels allows the receptors to become methylated which leads to activation of CheA autophosphorylation, thus re-setting the system to its pre-stimulus state.

models, at various scales. The fundamental challenges today are in seeking to provide an appropriate description on the macroscale population level while accounting for variation in specific characteristics amongst individual cells.

Individual bacteria are generally 1–3 μm in length; they are too short to detect a change in attractant gradient along their length so they use a well-defined biochemical network to communicate the detected temporal difference in the extracellular environment at the membrane receptors to the flagellar motors (Wadhams and Armitage, 2004; Tindall et al., 2007). Although the biochemical processes are well documented within the cytoplasm of *E. coli* as shown in Fig. 1, the ability of the bacterium to detect small changes in the extracellular concentration over large orders of magnitude has raised a number of challenging and interesting research questions.

In the absence of any stimulus, *E. coli* undergoes a random walk alternating periods of smooth swimming with brief direction changes known as tumbles. Increased attractant

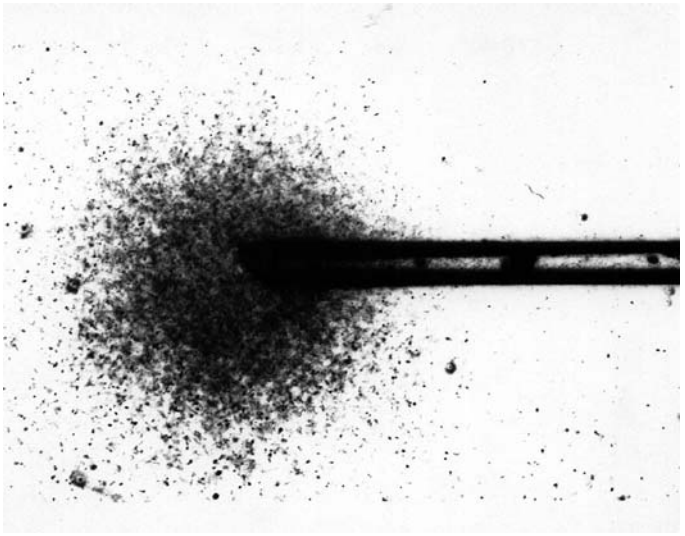


Fig. 2 Aggregation of chemotactic bacteria in regions of high attractant concentration as originally shown by Pfeffer (1888).

concentration suppresses tumbling and leads to biasing of the random walk allowing the bacteria to accumulate in environments containing high attractant concentrations. This results in periods of biased directed motion known as runs. Chemotactic runs generally last on the order of a few seconds while tumbles last approximately tenths of seconds (Berg and Turner, 1990). A combination of runs, allowing directed motion to a response, and tumbles, facilitating a change in direction, allow bacteria to explore and respond to changes in their environment.

Understanding the behavior of chemotactic bacterial populations is interesting for a number of reasons. While bacteria behave independently, populations exhibit collective behavior as shown in Fig. 2. In the natural environment, bacterial populations are generally found to exist in the form of biofilms which can have substantial impact upon industry and medicine (Davey and O'Toole, 2000). Hence, understanding the comparative importance of mechanisms which affect and cause the observed behavior within bacterial populations, for example, chemotaxis and diffusion, would greatly facilitate in the prediction of bacterial behavior in the natural environment.

The focus of our work here is to consider the mathematical modeling work which has aimed to understand the behavior of bacterial populations. Such work has been developed very much in parallel with experimental work over the last 30 years. Experimental results have been used to inform mathematical models and the resulting model solutions have helped in understanding the observed behavior of populations. Much of the *in vitro* experimental work has been undertaken using a number of different experimental assay methods. We provide a brief overview of the more commonly used assays, in particular, those

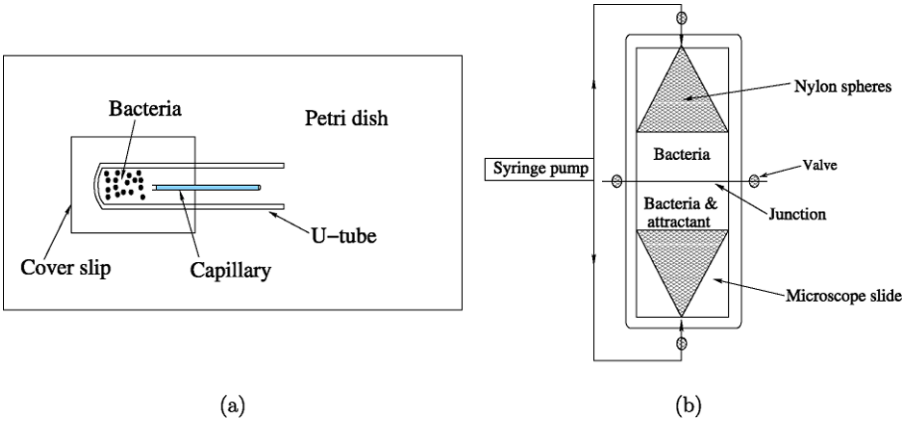


Fig. 3 Schematic representations of: (a) the capillary assay of Adler (1966) as adapted from Rivero-Hudec and Lauffenburger (1986); and (b) the stop flow diffusion chamber (SFDC) method developed by Ford and Lauffenburger (1991b). In (a), an attractant is loaded in the capillary before being placed in the bacterial suspension. The attractant then diffuses out into the bacterial suspension and bacteria are attracted towards it. The figure represents the experimental set-up just after the capillary has been placed in the assay. In (b), dilute bacterial suspensions are initially pumped into the regions above and below (with attractant) the junction point using the syringe pump. Fluid flowing into the top and bottom of the chamber exits through slits at the junction. The impinging flow creates an 'interface' between the two suspensions and maintains the attractant in the lower region of the chamber creating a step profile. When the flow is stopped, the attractant diffuses into the upper region allowing the bacterial response to be measured. The nylon spheres ensure the flow is distributed evenly throughout the chamber. Adapted from the original diagram in Ford and Lauffenburger (1991b).

which have been used to test and parameterize certain mathematical models.[2] Schematic representations of each of the following experimental assays are shown in Fig. 3.

- Adler (1966) developed the capillary assay method in which a capillary tube containing a chemoattractant was placed in a dilute bacterial suspension. The bacteria were then observed to move up the tube in the direction of the attractant gradient forming bands as they did so. This assay has since become one of the most widely used methods for studying the response of bacterial populations to chemoattractants and in testing and validating mathematical models developed to describe bacterial chemotaxis (Lewus and Ford, 2001). A considerable amount of theoretical work has focused on understanding the formation of bacterial bands as detailed in Section 2.2. Difficulties with this assay method include the inability to control the attractant gradient, counting the number of bacteria which have entered the capillary and the large variations in the number of bacteria entering the capillary between measurements.
- Dahlquist et al. (1972) used a laser densitometer assay to study the effect that varying profiles of attractant (exponential, step, and linear) have on the response of the bacterial colony. A helium–neon laser was used to detect the change in density of the bacterial population as it moved through the chamber.

[2] For a more detailed overview of these and other assays, see Ford and Lauffenburger (1991b).

- The stopped flow diffusion chamber (SFDC) was developed by Ford and co-workers (Ford and Lauffenburger, 1991b; Ford et al., 1991) to compare the response of bacteria to well-defined attractant gradients (step) and to obtain improved quantitative estimates of the diffusion and chemotactic coefficients associated with bacterial migration.

This review considers the formulation of early models in understanding Adler's observed bands of chemotactically migrating bacteria in capillary assays through to more recent work on the multiscale modeling of bacterial populations. We note that while chemotaxis is a wide area of research both within the biological and applied mathematical literature, we do not seek to provide an overview of the general modeling of chemotaxis, or the analysis of such models, from either a general biological or mathematical perspective. Our goal is to understand the contribution of mathematical modeling in elucidating the mechanisms responsible for the behavior of chemotactic bacterial populations. Work which has considered modeling the movement of bacteria through porous media (e.g. Reynolds et al., 1989 and Hornberger et al., 1992) or that related specifically to the study of biofilms lies outside our remit and is not considered here.

We begin by considering continuum models of bacterial chemotaxis, in particular, the application of the Keller and Segel (1971a) model of chemotaxis, originally developed in the context of modeling slime molds, in describing the movement and behavior of chemotactic bacteria. Section 2.2 focuses on the various models developed over the past 30 years to understand Adler's observed bands of migrating bacteria within the capillary assay. Early work on modeling bacterial movement right through to more recent attempts have sought to understand the effect that individual bacteria have on the overall response of the bacterial population, often referred to as multiscale modeling. Such work is reviewed in Section 3. Work undertaken in understanding the behavior of more than a colony of one bacterial species is considered in Section 4. Issues regarding the interaction of bacteria populations with their surrounding environment are reviewed in Section 5 and we briefly discuss the importance of modeling pattern formation in bacterial populations in Section 6. An overview of the various mechanisms which have been incorporated in Keller–Segel models of bacterial chemotaxis, and their various mathematical forms, is given in Appendix A. Our work concludes with discussion on the role that mathematical modeling can play in the future research of bacterial chemotaxis.

Our review provides an example of the development of mathematical models: initial modeling efforts are sometimes later viewed as simplistic due to growing knowledge both mathematically and experimentally, which leads to more and more sophisticated models. Various effects within these models are quantified by testing various forms of certain functions (see Appendix A), as clearly demonstrated in the following section on modeling bacterial bands. In essence, different models are tested and those which prove inadequate are discarded. With growing experimental knowledge and the development of new techniques, in particular, those covered in the later stages of our discussion in Section 3, the effects of individual cell behavior on the population scale can be elucidated, likewise the validity of earlier macroscale approaches.

2. Continuum models of a single population

2.1. The Keller–Segel model of chemotaxis

Continuum models (particularly early models of bacterial populations) have generally used the Keller–Segel model of chemotaxis, originally devised by Keller and Segel (1970, 1971a) in modeling the movement of slime molds. Such models have been analyzed using a mix of analytical techniques, for instance, traveling wave and perturbation analysis, and numerical simulations. Numerical solutions have often been employed to allow model predictions to be compared with experimental findings, leading to bounds on model parameters (see Section 7).

For the purposes of this review, we consider a generalized Keller–Segel (K–S) model of the form

$$\frac{\partial b}{\partial t} = \nabla \cdot \big(\mu(s)\nabla b\big) - \nabla \cdot \big(\chi(s) b \nabla s\big) + g(b,s) - h(b,s), \tag{1}$$

$$\frac{\partial s}{\partial t} = D\nabla^2 s - f(b,s), \tag{2}$$

where $b = b(\mathbf{x}, t)$ is the density of the bacterial population, $s = s(\mathbf{x}, t)$ is the attractant concentration at spatial position $\mathbf{x}$ and time t, $\mu(s)$ is the bacterial diffusion coefficient, $\chi(s)$ is the chemotactic coefficient, $g(b,s)$ and $h(b,s)$ are functions describing cell growth and death, respectively, $f(b,s)$ is a function describing attractant degradation, and D is the diffusion coefficient of the attractant. For the remainder of this paper, these symbolic representations will stand unless otherwise stated. Many models have assumed that $\mu(s) = \mu$, i.e. the bacterial diffusion coefficient is considered to be constant. This will be assumed to be the case for all of the models discussed in the forthcoming sections unless otherwise specified.

Equations (1) and (2) are solved for initial bacterial and attractant distributions, denoted here as $b(\boldsymbol{x}, t = 0) = b_0$ and $s(\boldsymbol{x}, t = 0) = s_0$, respectively, and appropriate boundary conditions. Boundary conditions are dependent upon the assay being modeled. In general, Neumann conditions apply at the ends of finite regions for both the bacterial density and attractant concentration. For instance, in modeling chemotactic bands of bacteria in a capillary assay (see the following section), Keller and Segel (1971b) applied such conditions to the bacterial density and attractant concentration at the ends of a tube of length L. For the SFDC experiments, Ford et al. (1991) applied Neumann conditions at the upper and lower ends of the chamber to the bacteria and attractant. These are but some examples and in the following, the reader is directed to the respective references for further details.

In general, growth and death of bacteria occur over a longer timescale than the duration of many *in vitro* experiments. Hence their effects are often ignored when developing mathematical models. However, some authors have considered the effect they may have on the dynamics of the bacterial distribution on both short and long timescales (Lauffenburger et al., 1981).

In referring to Eqs. (1) and (2) as a generalized K–S model, we include any model which assumes bacteria move by chemotaxis and diffusion and where the chemoattractant is described by an equation in the form of (2). Various forms of the K–S model have been used in modeling a wide range of biological systems. Recent reviews by Horstmann (2003a, 2003b) have focused on the contribution the K–S model has made to understanding chemotaxis within biological systems.

2.2. *Modeling chemotactic bands of bacteria*

The formation of chemotactic bands of bacteria[3] is often observed in the capillary assay, as shown in Fig. 4(a). Modeling the formation of such bands has generally explored the effect that the comparative strength of chemotaxis and diffusion of the population and the diffusion and consumption of nutrient have on the overall bacterial density distribution, both dynamically and in steady-state. The effects that the functional form of the bacterial chemotactic $\chi(s)$ and diffusion μ coefficients, and to some degree, the rate of nutrient consumption have on the bacterial distribution has been explored by a number of authors. A full overview of the respective models and a comparison of the different functions is given in Appendix A.

Keller and Segel (1971b) were the first to formulate a model to describe the formation of chemotactic bands as observed by Adler (1966). Using a model of the form given by Eqs. (1) and (2), Keller and Segel (1971b) assumed that the bacteria did not reproduce during the timescale of interest and responded to a single substrate of attractant which did not diffuse. In order to reproduce the observed bands, they assumed a chemotactic coefficient of the form

$$\chi(s) = \frac{\chi}{s}. \tag{3}$$

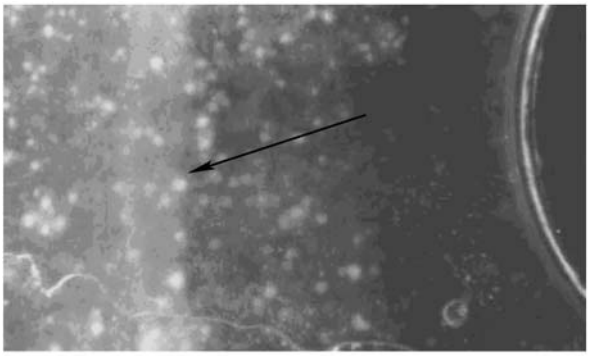
This is singular when $s = 0$ and leads to a peak in the bacterial density. Keller and Segel (1971b) noted this form of the chemotactic coefficient allows the model to predict band behavior (traveling wave solutions) in the bacterial density profiles when the concentration of s is such that a continuum description is no longer adequate, the only condition being that $\chi/\mu > 1$. Holz and Chen (1979) demonstrated that the model of Keller and Segel (1971b) provides an adequate description of bacterial migration in the bacterial response of *E. coli* to serine. They derived estimates for μ and χ when the chemotactic coefficient is of the form in Eq. (3), by comparing the model with their experimental results.

Numerical simulations of the model developed by Keller and Segel (1971b) were undertaken by Scribner et al. (1974). Their motivation was to test whether the model was appropriate for describing bacterial chemotaxis by comparing numerical solutions with the experimental results of Adler (1966). They argued that more biologically realistic forms of the attractant consumption rate, chemotactic and diffusion coefficients should depend upon a critical attractant concentration level a, such that

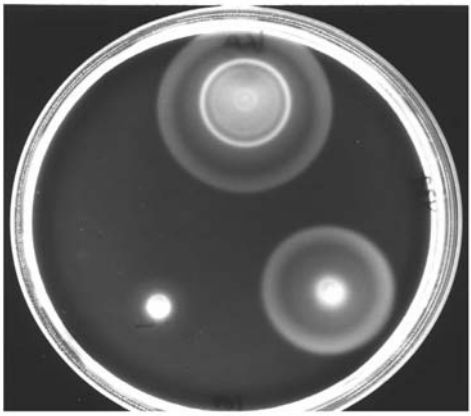
$$\begin{aligned}
&f(b,s) = f_0(as)^m, \quad s \le 1/a; \qquad f(b,s) = f_0, \quad s > 1/a;\\
&\chi(s) = \chi(as)^i/s, \quad s \le 1/a; \qquad \chi(s) = \chi/s, \quad s > 1/a;\\
&\mu(s) = \mu_0(as)^n, \quad s \le 1/a; \qquad \mu(s) = \mu_0, \quad s > 1/a;
\end{aligned} \tag{4}$$

where i, m, and n are all positive real numbers. They further assumed that the attractant was free to diffuse throughout the spatially confined region of interest. Scribner et al. (1974) compared their model solutions with Adler's results for varying initial conditions

[3] Also referred to as 'Adler' bands in recognition of their initial discovery by Adler in the context of the capillary assay method (Adler, 1966, 1969)



(a)



(b)

Fig. 4 (a) The bacterial response of *Rhodobacter sphaeroides* to an oxygen gradient (aerotaxis) (Romagnoli, 2002). The bands of bacteria (marked by the arrow) can be seen on the left of the photo as they move toward an optimal oxygen concentration away from the miniscus of the capillary (and the oxygen source) on the right. Here the tip of the arrow head is 1.3 mm away from the bottom (left hand edge) of the meniscus. (b) Swarm plates of *E. coli* showing the formation of concentric bacterial rings (Armitage Laboratory). The petri dish has a diameter of 90 mm.

and showed that the K–S model predicts both uniform and non-uniform bands of chemotactic bacteria. The experimental data made quantitative comparison with the model difficult due to "fluctations in the number of bacteria" used in each experiment, but qualitative comparisons showed good agreement. Decreasing the chemotactic coefficient meant bands took longer to form and contained fewer bacteria. If the chemotactic exponent i is increased, chemotaxis decreases more rapidly when the attractant concentration drops below the transition level of attractant concentration at $s = 1/a$. Increasing the attractant transition level meant bands took longer to form and contained fewer bacteria. It was noted that the initial bacterial density does not greatly affect the results.

Nossal (1972) modeled the movement of the edges of bacterial colonies growing and moving in soft agar (commonly referred to as swarm plates). Initially, bacteria are placed

at the center of a petri dish which with time migrate outwards, the population increasing at a certain rate, to form concentric chemotactic rings as shown in Fig. 4(b). Nossal formulated a K–S model which included cell growth and obtained various analytical estimates describing the position of the bacterial front, when it is assumed to be smooth, as it moves through the attractant. He noted that exact solutions could be obtained in the case of exponential growth. A general solution was obtained when the bacterial front was assumed to be sharp. We note here that given the difference in timescales of the experiments (capillary assays are of the order of minutes or hours whereas swarm plate assays can be carried out over days) growth terms can in the case of capillary assays be neglected, whereas they may be important when modeling swarm plates.

Segel and Jackson (1973), Nossal and Weis (1973), and Lapidus and Schiller (1974) formulated K–S models to explain the experimental observations of Dahlquist, Lovely, and Koshland (DLK) (Dahlquist et al., 1972) regarding chemotaxis of *Salmonella typhimurium* in an assay analogous to that of the capillary assay. Segel and Jackson (1973) considered the relative strengths of diffusion and chemotaxis on model solutions compared to the DLK experiments. They noted that constant rates of diffusion and chemotaxis were only valid in the case of a population of identical organisms and individual response to chemoattractants would result in a variance in the overall population response. They discussed why chemotaxis leads to wider band formation and noted that analytical solutions, for various asymptotic limits of the governing equations, agreed with most of the DLK experiments. Segel and Jackson (1973) concluded that a chemotactic coefficient of the form (3) was adequate for describing some of the DLK experiments when the variation in s is small and stressed that knowledge of the microscopic behavior is important in macroscopic theories of bacterial chemotaxis.

The model of Nossal and Weis (1973) considered a description of bacteria moving in an exponential, time independent gradient. This simplification allowed analytical solutions for the bacterial density distribution to be derived and values for the chemotactic and diffusion coefficients to be determined from comparison with experimental results.

Lapidus and Schiller (1974) noted that the analysis of Segel and Jackson (1973) and Nossal and Weis (1973) was not able to describe the long term behavior of the bacterial colony and further argued that the chosen boundary conditions were not representative of the experimental set-up. Formulating a similar model to that of Nossal and Weis (1973), with revised boundary conditions, they showed the long time behavior of their revised model agreed well with the experimental data. In particular, the bacterial density curve increased at a rate proportional to the square root of time and bacteria moving into the central region of the assay increased the bacterial density proportional to the elapsed time of the experiment.

Work by Lapidus and Schiller (1975, 1976) continued to focus on the DLK experiments. In 1975, they noted that their previous work (Lapidus and Schiller, 1974) had shown that diffusion theory alone could reproduce the DLK observations and had the experiments been for longer, then the precise form of the chemotactic coefficient would have been important. They discussed the importance of solutions involving chemotaxis matching with experimental observations and posed the question "If after choosing a suitable χ, theory does not match experiment, then is it the choice of χ or the model itself which is inadequate?" Further work (Lapidus and Schiller, 1976) noted that the earlier work of Segel and Jackson (1973), Nossal and Weis (1973) and Lapidus and Schiller (1974) using the original K–S formulation did not successfully predict all of the experiments observed

by Dahlquist et al. (1972). Noting this and considering the experimental work of Mesibov et al. (1973) and Brown and Berg (1974), Lapidus and Schiller (1976) suggested a revised chemotactic coefficient of the form

$$\chi(s) = \frac{\chi K_d}{(K_d + s)^2}, \tag{5}$$

where K_d is the receptor-ligand binding dissociation constant. They modeled the bacterial response to three steady-state attractant gradients; exponential, step and a step-like gradient defined by a Fermi function. By calculating the average number of bacteria which move into the central region of the assay, Lapidus and Schiller (1976) were able to determine values for the chemotactic coefficient, χ, and K_d. Model comparison with experiment showed good agreement.

In Lapidus and Schiller (1978), the authors extended their earlier model to include bacterial growth. They compared numerically determined model solutions with Adler's experimental results and those of Keller and Segel (1971b). The bacterial growth, while generally over a longer timescale than that of the experiment, was chosen to balance the loss of bacteria from the initial distribution due to the formation of bands. It was noted that a lack of bacterial growth did not preclude the formation of bands, but cells were lost to diffusion, resulting in a decrease in band speed and leading to a broadening of the bacterial profile. Considering numerical solutions for different values of the chemotactic coefficient and the rate of attractant consumption, Lapidus and Schiller (1978) also showed that band formation is dependent upon these two parameters and obtained the limits in which these formed.

Using analytical methods, including traveling wave analysis, Green's functions and perturbation analysis, Rosen and colleagues analyzed a number of K–S models, in which variations in the form of the attractant degradation term were considered (Rosen, 1974, 1975, 1976; Rosen and Baloga, 1975, 1976). Their motivation was to determine a K–S model which admitted banded or solitary wave solutions which qualitatively agreed with the work of Adler (1966) and gave unique mathematical solutions.

In Rosen (1974), it was noted that the case of $f(b, s) = kbs$ with $D = 0$ means the K–S model does not admit banded solitary wave solutions, and thus the authors considered

$$\frac{\partial s}{\partial t} = -kbs^p, \quad p \geq 0. \tag{6}$$

This form was found to admit solitary wave solutions for $(1 - (\chi/\mu)) < p < 1$. Traveling wave analysis of the resultant governing equations allowed the speed of the bands to be determined. Rosen further justified this choice by noting that it may be associated with possible physio-chemical and biological mechanisms.

Keller and Odell (1975) considered solutions to the K–S model of Eqs. (1)–(2) in which $\mu(s)$, $\chi(s)$ and $f(b, s)$ are generalized unspecified functions. Using traveling wave analysis, they obtained a set of conditions for which these functions admit traveling wave solutions. In doing so, they verified the earlier finding of Keller and Segel (1971b) that $\chi/\mu > 1$, but refuted that of Rosen that $(1 - (\chi/\mu)) < p < 1$.

In works published in 1975 and 1976, Rosen (1975, 1976), Rosen and Baloga (1975, 1976) focused on the model described by Eqs. (1) and (6) and its ability to admit stable chemotactic band forming solutions. Using a combination of Green function solutions to

the bacteria diffusing only problem and exact solutions to the chemotaxis only case, Rosen (1975) obtained approximate analytical solutions to the full system, noted as an alternative to the numerical solutions of Scribner et al. (1974). Rosen and Baloga (1975) considered a transformation of $\theta = (s/s_\infty)^{(1-p)}$ to combine Eqs. (1) and (2) into a single equation which exhibited solitary traveling wave solutions. Rosen (1976) focused on showing that a K–S model in which the chemoattractant degrades exponentially and does not diffuse gives traveling wave band solutions. He argued that banded solutions can not exist when $\chi(s) = \chi/(s+K)^2$ or $\chi(s) = \chi(K_s + \ln s)/s$ and $f(b,s) = k_f bs$ or $f(b,s) = k_f bs/(s + K_s)$, by obtaining specific conditions on the diffusion and chemotactic coefficients and the nutrient consumption function as $s \to 0$. Rosen and Baloga (1976) considered two-dimensional cylindrically symmetric propagating ring solutions to their model and obtained an asymptotic approximation to the bacterial density in the case of large radii.

Odell and Keller (1976) considered solutions to the K–S model for an extended domain and showed that traveling wave band solutions are possible for all $\chi > 0$. They noted the difference in the bacterial density distributions for $\delta \equiv \chi/\mu < 1/2$ and $\overline{\delta} > 1/2$ and showed that the bands and chemoattractant concentration become steeper as $\overline{\delta} \to 0$. This counterintuitive finding is a result of the chemotactic coefficient being inversally proportional to the attractant gradient: an increase in the gradient leads to a decrease in χ. Bands still form when $\overline{\delta}$ is large and bounded, but the bacterial velocity must be of the order of the band velocity, indicating the attractant gradient has to be small. Odell and Keller (1976) further noted that the Keller and Segel (1971b) requirement $\chi > \mu$ for band formation is still a necessary condition. However, of even greater importance is the chemotactic flux $J = \chi b(\partial s/\partial x)/s$ at the trailing edge of the band, for given any $\mu > 0$, J can become sufficiently large at $s = 0$ to dominate bacterial diffusion, and thus allow bands to form.

The effects of cell death and growth on a K–S model were considered by Kennedy and Aris (1980). Using traveling wave analysis on models both excluding and including chemotaxis (bacterial diffusion being assumed in either case), they showed that certain growth functions (see Appendix A) give traveling wave solutions of constant speed and that the wave speed is increased when chemotaxis is included. This leads to an increase in the size of the population.

Lauffenburger et al. (1981) considered a reaction-diffusion model of a bacterial population whereby cells could only move by diffusion. The work included the effects of bacterial growth and death as well as uptake of the respective attractant substrate. The authors analyzed the effect that each model parameter has on the steady-state form of the population and showed that the random motility of the population depended on the relative magnitude of diffusion coefficient compared to the growth rate. The steady-state population size was found to decrease as the diffusion coefficient increased. Relative changes in the diffusion coefficient were found to have a greater effect on the population size than relative changes in the growth rate.

Lauffenburger et al. (1982) extended their work by including chemotaxis. They considered the effect that varying ratios of diffusion versus chemotaxis have on the population density. As with their previous work, they showed that cell movement outweighs cell growth in terms of affecting the size and growth of the population. Motility effects become more important as the size of the confined growth region increases, but are diminished when the nutrient does not diffuse.

Both works (Lauffenburger et al., 1981, 1982) show that diffusion alone is disadvantageous because it causes the dispersal of the bacteria from high regions of nutrient to

lower regions. Chemotaxis is advantageous because it allows cells to move towards regions where the nutrient concentration is higher.

Further work (Lauffenburger et al., 1984) showed that a chemotactic term was not necessary in order to predict the formation of bands within a capillary assay. By including simple descriptions of bacterial death and growth and assuming the bacteria moved simply by diffusion, Lauffenburger et al. (1984) showed that the governing system of equations produced traveling wave solutions, a common feature of reaction–diffusion systems (Murray, 1993). The speed of the bacterial band, size, and width of the bacterial population were all proportional to the square-root of the diffusion coefficient. The authors noted their model results did not agree as well with experiments as those of previous K–S models, which had included chemotaxis, and observed that these differences may not be observed *in vitro* given the difference in timescales of bacterial death and growth in comparison with the experiment. Thus, the K–S description is appropriate for *in vitro* reported studies, with the diffusion-only model possibly relevant on longer timescales observed ecologically.

Lauffenburger et al. (1984) extended their model to include chemotaxis with a receptor law coefficient of the form given by Eq. (5) and considered this or the reduced cases of χ/K_D ($a \ll K_D$) and χ/a ($a \sim K_D$). The logarithmic law (χ/a) was most effective in increasing the traveling band speed and population size and was 'superior' to the other chemotactic coefficient forms as it always assumes the receptors are acting at maximum sensitivity. A constant chemotactic coefficient was found to be ineffective in increasing the band population with increasing attractant concentration and both the logarithmic and receptor law coefficients are less sensitive to changes in the attractant concentration. Lauffenburger et al. (1984) hypothesized that chemotaxis allows a larger population to exist by moving a small number of bacteria into higher nutrient levels, followed by a larger population density. If the nutrient concentration increases, the bacterial population also increases.

Novick-Cohen and Segel (1984) later analyzed the original model of Keller and Segel (1971a) following the work of Scribner et al. (1974), Keller and Odell (1975) and Alt (1980) and focused on the issue of whether the chemotactic coefficient is required to be singular in order to predict traveling wave solutions in the bacterial density profile. Their traveling wave and asymptotic analysis resolves issues of $\chi(s)$ needing to be singular and decreasing non-linearly to zero in order for the models to produce the experimentally observed bands of migrating bacteria. The work also demonstrates that as the chemotactic band wave velocity decreases this leads to spreading or 'fanning' out at the back of the bacterial distribution.

A transformation by Rosen (1983) of a K–S model, in which the attractant is assumed to diffuse, showed that the resulting equation is the Schrödinger–Block equation. The latter does not include gradient terms of the variable being determined and has well-known solutions given its use in quantum statistical mechanics. Initial value problems in bacterial chemotaxis can thus be readily solved. It was noted that when $\mu/\chi = 2$, the effect of spatial variation in the attractant concentration was removed from the equation describing the evolution of the bacterial distribution. Removal of any gradient in the attractant, except implicitly implied through the Laplacian operator, shows the system of governing K–S equations admits a high level of symmetry for this case.

Rivero-Hudec and Lauffenburger (1986) compared numerical and asymptotic solutions to a K–S model where the diffusion and chemotactic coefficients were of the form

given by Eq. (20) (see Section 3). Bacterial growth and death were ignored as were the effects of nutrient degradation. Transient and steady-state model simulations were compared with the experimental results of Mesibov et al. (1973) and Adler and Dahl (1967), allowing values of the diffusion and chemotactic coefficients to be derived. The derived values agree well with those obtained by Berg and Brown (1972) although Rivero-Hudec and Lauffenburger (1986) note that their model does not account for attractant uptake.

A model accounting for the effect of two chemoattractants (oxygen and glucose) on the motility of *E. coli* within the capillary assay was formulated by Boon and Herpigny (1986). The work was motivated by the experimental results of Herpigny et al. (1984) which showed the formation of more complex, bistable time-dependent spatial patterns of bacteria when *E. coli* are grown in glucose where the surrounding medium is saturated in oxygen. Previous models had only included descriptions of the main chemoattractant and not oxygen. A K–S model showed good agreement with experiment and considered the effect of varying chemoattractant gradients: uniform and steep. The effect of oxygen diffusion from the mouth of the capillary assay allowed the play-off between oxygen diffusion and consumption to be evaluated. When the ratio of consumption to diffusion is large, bacteria accumulate near the mouth of the capillary. However, when diffusion dominates, i.e. when the ratio is small, bacteria still accumulate but not as strongly.

The work of Chen et al. (1998b) considered the effect that interactions between individual bacteria and the walls of the capillary assay have on the overall bacterial distribution. Their work was motivated by the experimental observations of Berg and Turner (1990) and Liu and Papadopoulos (1995) that the bacterial turn angle was related to the diameter of the capillary. The authors considered the symmetrically reduced form of Alt's three-dimensional model (Alt, 1980; Ford and Cummings, 1992) (see Section 3) and solutions from a gas kinetic model of chemotaxis. Their results show that the radius of the tube affects the form of the bacterial distribution; a radius of $r \simeq 10$ μm gives dimensionally reduced diffusion while $r = \simeq 6$ μm results in wave-like motion. Chen et al. (1998b) noted that the gas kinetic model does not give results which agree well with experiment, but by adapting this model to include the bacteria-wall interaction on turning and tumbling, the global turning probability density function is shown to be dependent upon the tube diameter. By defining directional persistence, Chen et al. (1998b) note that a long waiting time leads to a large diffusion coefficient, but when the waiting time is small, wave-like motion is observed. Chen et al. (1998b) conclude that a constant ratio of diffusion coefficients for varying tube diameter implies that: (i) geometrical constraints are universal and independent of receptor saturation by the attractant; and (ii) directional persistence does not increase with varying tumbling angles, but remains at its maximum value even when the diameter is small. The authors noted that their results agreed with experimental observations that bacterial motion is guided by the walls of the tube and propose ways of experimentally testing their theoretical predictions.

Marx and Aitken (1999, 2000) and Pedit et al. (2002) have modeled the response of *Pseudomonas putida* to napthalene. Their work was motivated by experimental results (Grimm and Harwood, 1997) showing this particular bacterial species responds chemotactically in the presence of napthalene. The authors noted, however, that chemotaxis had yet to be shown to be important in describing the bio-degradation of napathelene (or other substrates) in the natural environment. They hence set out to see what effect chemotaxis has on attractant degradation.

In Marx and Aitken (1999), the authors considered the effect that variations in the bacterial and attractant concentrations and incubation time had on the bacterial response. In

particular, they considered the effect that attractant diffusion at the mouth of the capillary assay has on bacterial aggregation as previously considered by Futrelle and Berg (1972) and Ford and Cummings (1992). They noted that while the model of Futrelle and Berg (1972) was more computationally intensive than that of Ford and Cummings (1992), the model does predict bacterial aggregation at the mouth of the capillary assay.

Marx and Aitken (2000) considered the effect that attractant consumption has on the chemotactic response. They noted that earlier work by Rivero-Hudec and Lauffenburger (1986) and Ford and Cummings (1992) had neglected attractant consumption given the bacterial density was low. Using a K–S model, with a chemotactic coefficient described by Eq. (27), Marx and Aitken (2000) showed that for a critical bacterial concentration, the model solutions with and without consumption were identical. However, above this threshold, the attractant becomes depleted thus reducing the later migration of bacteria, following the initial first wave, into the capillary assay.

Pedit et al. (2002) extended the work of Marx and Aitken (2000) and noted that increasing the dissociation constant K_d by an order of magnitude had a significant effect on the rate of removal of napthalene. A four-fold increase had a modest effect on napthalene removal. Overall, the model results agreed well with experiments with diffusion being shown to be insignificant for long time periods in the absence of attractant. By modifying Adler's original capillary assay method, Pedit et al. (2002) extended their model to study the effects that porous media have on bacterial migration. They showed that porous media lead to lower accumulation of bacteria in the capillary, but chemotaxis still occurs in such systems.

Hilpert (2005) has considered two-dimensional numerical solutions, using the Lattice–Boltzmann (LB) numerical method, to a model of bacterial chemotaxis similar to that of Keller and Segel (1971a). The LB method uses quasi-particles to represent individual cells moving across a grid. The model uses the chemotactic velocity description derived by Ford and Cummings (1992) and attractant consumption is based on Monod kinetics. The model can reproduce the chemotactic bands considered by Keller and Segel (1971b) in the case of the bacteria *Pseudomonas putida* and shows changes in the bacterial density of the bands due to loss of bacteria. This result is in contrast to that of Keller and Segel (1971b) which showed constant bacterial density for each band. Hilpert (2005) notes that by assuming the bacterial band is in a quasi-steady state, the original results of Keller and Segel (1971b) can be obtained. Further analysis shows that changes in the initial length of the bacterial population within the capillary does not affect the width of the resultant bacterial bands. The band velocities are also not greatly affected. The article discusses both the advantages and disadvantages of using the Lattice–Boltzmann method in solving bacterial population models.

2.3. Further continuum models of bacterial chemotaxis

The effects of local and non-local cell growth on the dynamics of a well-packed symmetrical bacterial population in an inoculum have been studied by Grimson and Barker (1994). The authors analyze a single reaction–diffusion equation describing the bacterial cell density which includes both diffusion and growth terms. The growth term consists of a local growth term, dependent on the bacterial cell density, plus a non-local term modeled as the gradient of the cell density squared. Grimson and Barker (1994) argue that such a term represents non-local growth given that packing suppresses local growth

and re-organization and growth of the population will generally occur on the periphery of the colony where the concentration of growth medium is greatest. While they do not cite any direct experimental motivation for their work, they note that such a model would not account for bacterial growth and movement "on the surface of a growth medium". They show that the governing equation can be written as a Fisher-type equation, and thus exhibits traveling wave solutions. The importance of the relative strength of local versus non-local growth is considered. Analysis shows that when the growth rate of the population is positive, the population front moves at a non-constant velocity as a result of the non-local population term.

Widman et al. (1997) and Chiu and Hoppensteadt (2001) have modeled the bacterial response to varying forms of attractant gradients generated using the diffusion gradient chamber (DGC) assay as described by Emerson et al. (1994). Widman et al. (1997) undertook their own experiments on *E. coli* and sought to determine values for the diffusion and chemotactic coefficients. These values were then used to parameterize a K–S model, where 2-D numerical simulations were compared with photographic data showing the spatial variation in time of the bacterial distributions within the DGC assay. The model and experimental results agreed well thus verifying the respective parameter values. In formulating their model, Widman et al. (1997) included a description of the two chemoattractants: aspartate and oxygen. The inclusion of oxygen led to results which gave better model fits to the experimental data. The model correctly reproduced the observed dynamical wave of bacteria which moves through the system, but which slows in regions of high attractant concentration. Widman et al. (1997) noted that the observed flattening of circular patterns of bacterial distributions could be explained as either a result of receptor saturation or cells taking longer to consume higher concentrations of chemoattractant near their source. Chiu and Hoppensteadt (2001) also found that a second attractant (oxygen) was required in order for model predictions to match the experimental outcomes. Using a similar model to that of Widman et al. (1997), the authors focused on the effect that nutrient consumption rate and the initial nutrient concentration had on the bacterial response. The model predicted that a large initial nutrient concentration would lead to wider patterns of bacterial aggregation and slower cell movement, results which were confirmed by experiment.

Mazzag et al. (2003) have formulated a model describing the aerotactic response of *Azospirillum brasilense* to varying concentrations of oxygen in a capillary assay. The authors describe the bacterial density along the length of the tube using the one-dimensional telegraph equations (see Section 3). Motivated by the experimental work of Zhulin et al. (1996), they assume cells have a low internal energy when the external oxygen concentration is very low or very high, but the internal energy is maximized and constant at relatively normal oxygen concentrations. An energy function capturing these three states is incorporated into the equations describing the bacterial densities and Mazzag et al. (2003) show that the results from their model agree well with experimental findings reported in Zhulin et al. (1996). They justify their internal energy description by showing that a plot of the energy function versus oxygen concentration compares qualitatively well with a model of phosphorylated CheY regulation in an *E. coli* cell in the absence and presence of oxygen, thus supporting the energy function description in producing the observed motor biasing in the presence of oxygen.

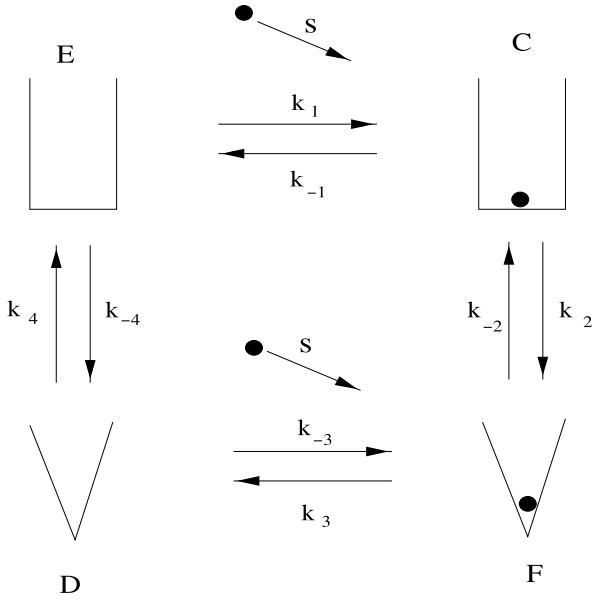


Fig. 5 The bacterial transitions considered by Segel in his 1976 model incorporating receptor dynamics in a population model of bacterial chemotaxis. Here, E represents an open enzyme ligand free receptor, C an open enzyme ligand bound receptor, D an enzyme 'bent' ligand free receptor, F an enzyme bent ligand bound receptor, s is the attractant concentration, and each k_i $(i = \pm 1, \ldots, \pm 4)$ represents the rate of transfer between each state. Adapted from Segel (1976).

3. Microscopic to macroscopic modeling

A growing number of approaches have been taken in modeling and understanding the effect that microscopic (individual) behavior has on the macroscale (population) level. Here, we review approaches which have sought to incorporate 'multiscale' modeling.

Segel (1976) incorporated details of the receptor dynamics into a population model of chemotaxis. By considering the receptors to exist in either an open or 'bent' conformation, he considered a four state model which included the effects of ligand binding as demonstrated in Fig. 5. The total bacterial receptor population was considered to exist in either one of these four states. Considering a one-dimensional region of length L, bacteria which responded positively to the attractant moved in the positive x-direction while negatively responding bacteria moved in the negative x-direction. In the case where spatial variation in the attractant gradient is assumed to be small, he showed that the governing system of equations reduced to the K–S model (Keller and Segel, 1971a).

Segel (1977) extended this earlier work and noted that a much better model fit to experimental data could be obtained when the turning probabilities of the bacteria were assumed to depend on the temporal rate of change of chemoreceptor occupancy, a result not dissimilar to that noted by Block et al. (1983). Segel (1977) used a simplified form of his earlier model in which each receptor could exist in only a ligand bound or unbound

state

$$\frac{\partial E^+}{\partial t} + u\frac{\partial E^+}{\partial x} = k_{-1}C^+ - k_1 s E^+ + \sigma^- E^- - \sigma^+ E^+, \tag{7}$$

$$\frac{\partial C^+}{\partial t} + u\frac{\partial C^+}{\partial x} = -k_{-1}C^+ + k_1 s E^+ + \sigma^- C^- - \sigma^+ C^+, \tag{8}$$

$$\frac{\partial E^-}{\partial t} - u\frac{\partial E^-}{\partial x} = k_{-1}C^- - k_1 s E^- - \sigma^- E^- + \sigma^+ E^+, \tag{9}$$

$$\frac{\partial C^-}{\partial t} + u\frac{\partial C^-}{\partial x} = -k_{-1}C^- + k_1 s E^- - \sigma^- C^- + \sigma^+ C^+, \tag{10}$$

where E^+ (E^-) represents the number density of unbound receptors on right (left) moving bacteria and C^+ (C^-) represents the number density of receptor-ligand bound receptors on right (left) moving bacteria, u is the bacterial velocity, k_1, k_{-1}, σ^-, and σ^+ represent the rate of transfer between each state, and s is the concentration of attractant described by

$$\frac{\partial s}{\partial t} = -k_1 s\left(E^+ + E^-\right) + k_{-1}\left(C^+ + C^-\right) - d + D\frac{\partial^2 s}{\partial x^2}, \tag{11}$$

where D is the diffusion coefficient of the attractant and d represents constant degradation or consumption.

Segel's work also showed that by relating his results to the K–S model the diffusion and chemotactic coefficients could be written in terms of microscopic variables

$$\mu = \frac{u^2}{2\sigma} \quad \text{and} \quad \chi(s) = \frac{u^2}{2\sigma}\frac{\partial \sigma^-}{\partial x}\frac{d}{ds}\left(\frac{s}{K+s}\right). \tag{12}$$

Here, K represents the receptor-ligand binding dissociation constant and $\sigma = (\sigma^+ + \sigma^-)/2$.

It is important to note that a simplified form of the one-dimensional turning model considered by Segel (1976, 1977), in which no distinction between receptor-bound or -unbound states is explicitly included, takes the form

$$\frac{\partial \phi^+}{\partial t} + u\frac{\partial \phi^+}{\partial x} = -k\phi^+ + k\phi^-, \tag{13}$$

$$\frac{\partial \phi^-}{\partial t} - u\frac{\partial \phi^-}{\partial x} = k\phi^+ - k\phi^-, \tag{14}$$

where $\phi^+(x,t)$ represents the density of bacteria moving in the positive x-direction and $\phi^-(x,t)$ is the density of bacteria moving in the negative x-direction with constant velocity u. The turning rates k are assumed here to be constant. This hyperbolic system of equations is often referred to as the telegraph system of equations because they can be written as the single second order partial differential telegraph equation (Othmer et al., 1988; Ockendon et al., 1999)

$$\frac{\partial^2 \phi}{\partial t^2} + 2k\frac{\partial \phi}{\partial t} = u^2\frac{\partial^2 \phi}{\partial x^2}, \tag{15}$$

where $\phi = \phi^+ + \phi^-$. This model system and the resulting telegraph equation have been analyzed by a number of authors both within the context of bacterial chemotaxis and chemotactic theory in general (Othmer et al., 1988; Hillen and Othmer, 2000). Othmer et al. (1988) derived the governing equations whereby a Poisson process governs the discontinuous changes in speed and direction of the bacterium (a velocity jump process). They showed that the governing equations reduced to the telegraph equation when the speed of the bacterium is constant and the spatial flux in cell numbers is the difference in right and left moving cells. Furthermore, the bacteria are assumed to change direction each time they are allowed to do so. Hillen and Othmer (2000) formally showed that the telegraph equation reduces to the diffusion equation for various asymptotic limits, for instance when the turning rate λ and u simultaneously tend to infinity the diffusion coefficient is defined by $D = u^2/\lambda$. Their work also discussed the conditions for an isotropic diffusion tensor and the effect that various external forms of cell motion have on the derived asymptotic equations.

The work of Rosen (1973) considered the connection between descriptions of bacterial chemotaxis using the Fokker–Planck and Langevin equations and K–S models. It was noted that the Langevin description is appropriate for low Reynolds number (Stoke's flow) over short timescales so long as the bacterial propulsive force takes a particular form. In contrast, the Fokker–Planck description is appropriate for macroscopic timescales on the order of the timescale over which the bacterial population evolves. Rosen noted that the bacterial density is given by

$$b(\mathbf{x}, t) = \int_{\Sigma} P(\mathbf{x}, \mathbf{y}; t) b_0(\mathbf{y})\, d^3 y, \tag{16}$$

where $b_0(\mathbf{y})$ is the initial bacterial distribution and $P(\mathbf{x}, \mathbf{y}; t)$ is the probability density function for a bacterium initially at $\mathbf{y}$, to be at spatial point $\mathbf{x}$, at time t, and is governed by a Fokker–Planck equation of the form

$$\frac{\partial P}{\partial t} = \mu \nabla^2 P - \chi \nabla \cdot (P \nabla \ln s) \tag{17}$$

with the initial condition $\lim_{t \to 0^+} P(\mathbf{x}, \mathbf{y}; t) = \delta(\mathbf{x} - \mathbf{y})$. Here μ is a diffusion coefficient and χ a chemotactic coefficient. Rosen notes that certain forms of the Fokker–Planck equation can be transformed into the Schrödinger–Block equation, and this is useful in providing known solutions to specific initial value problems in bacterial chemotaxis as detailed further in his later work (Rosen, 1983) as discussed in Section 2.2.

Lovely and Dahlquist (1975) formulated a three-dimensional model of microscopic behavior of bacteria. Using statistical methods to link experimentally observed parameters to their five defined measures of bacterial motility as shown in Table 1, they derived expressions for: (i) a direction correlation function; (ii) a diffusion constant; (iii) a persistence time; (iv) an average velocity; and (v) an up/down movement ratio in terms of individual cell parameters. In deriving the respective expressions, they assumed that bacterial paths are composed of straight lines, cell trajectories have constant speed, bacteria turn such that their new direction is asymmetric/symmetric about the initial direction, and the angles between and derivation of successive trajectories are governed by probability distributions which are independent of any other information, such as previous trajectories. The probability distribution of each trajectory was assumed to be a decaying exponential distribution.

Table 1 Macroscopic parameters derived in terms of individual microscopic variables (Lovely and Dahlquist, 1975). Here, T is the mean trajectory duration, $T(u)$ is the direction dependent mean trajectory duration, v is the speed of the bacterium, ϕ is the mean turn angle, α is the mean cosine of the turn angle, and $F(x)$ is an expression describing the dependence of T on the attractant concentration and its temporal derivative

Correlation time	$\tau = \frac{T}{1-\alpha}$	Diffusion coefficient	$D = \frac{v^2 T}{3(1-\alpha)} = \frac{1}{3} v^2 \tau$
Persistence time	$t = \frac{\pi}{\phi} \int_0^1 T(u)du = \frac{\pi}{\gamma\phi} \int_0^\gamma F(x)dx$	Average velocity	$V = v \frac{\int_{-1}^1 uT(u)du}{\int_{-1}^1 T(u)du} = \frac{v}{\gamma} \frac{\int_{-\gamma}^\gamma xF(x)dx}{\int_{-\gamma}^\gamma F(x)dx}$
Up/down ratio $R = \frac{\int_0^1 uT(u)du}{\int_0^{-1} uT(u)du} = \frac{\int_0^\gamma xF(x)dx}{\int_0^{-\gamma} xF(x)dx}$			

The derivation of a stochastic description, incorporating individual cell behavior, was the focus of work by Alt (1980). By considering a bacterial density distribution $\sigma = \sigma(t, \mathbf{x}, \theta, \tau)$, which moved through an angle θ when changing direction and with run time τ, he derived the governing stochastic equation

$$\frac{\partial \sigma}{\partial t} + \frac{\partial \sigma}{\partial \tau} + \theta \cdot \nabla(c\sigma) = -\beta\sigma, \quad \tau > 0, \tag{18}$$

where $c = c(\mathbf{x}, t)$ is the mean speed of a run and $\beta = \beta(\mathbf{x}, t, \theta, \tau)$ is the turning or tumbling frequency distribution, with σ defined for a new run in a new direction η by

$$\sigma(\mathbf{x}, t, \eta, 0) = \int_0^\infty \int_S (\beta\sigma) k \, d\theta \, d\tau, \tag{19}$$

where η is the angle through which the bacteria have turned (derived from a turn angle distribution $k = k(\mathbf{x}, t, \theta; \eta)$) and S is the unit sphere in n-dimensional space. When β is independent of the turn angle, the equations reduce to an integral equation which in one dimension reduces to the model of Keller and Segel (1971b). In the presence of a chemoattractant, β is assumed to be of the form $\beta(t, x, \theta) = \beta_0(s(t, x), s(t - T, x - Tc\theta))$, where β_0 is the initial turning frequency and T is the 'memory time' of the bacterium. The main objective of the work is to then derive a diffusion equation approximation, from the governing equations, which is valid in n dimensions.

Alt undertook asymptotic analysis of the governing equations to consider small limits of certain parameters affecting run lengths and turn angles of the bacteria. He showed that in the case of K–S continuum models the diffusion and chemotactic coefficients can be related to microscopic parameters by

$$\mu = \frac{1}{2} T v^2 \quad \text{and} \quad \chi(s) = \frac{K_d T v^2 \sigma}{(K_d + s)^2} = \frac{\gamma_0 K_d}{(K_d + s)^2}, \tag{20}$$

where v is the mean speed of the bacterium, K_d is the receptor-attractant dissociation constant, and σ is the decrease in the change of the mean direction for a specific level of receptor binding. Various estimates of T and v were made by Berg and Brown (1972) for *E. coli*. As noted by Chen et al. (1998a), Alt's three-dimensional model, while comprehensive, is difficult to solve analytically and has for this reason, not received as wide a degree of attention as have the generalized K–S models.

The model of Rivero et al. (1989), more commonly referred to as the RTBL model, links a macroscopic bacterial description by the telegraph process to the individual microscopic variables of cell speed, persistence time and temporal receptor occupation. By first noting the observations of Berg and Brown (1972) that attractant presence stimulates directional change in turning probabilities, and motivated by the work of Segel (1977), Patlak (1953) and Alt (1980), Rivero et al. (1989) note that the tumbling probabilities can be written as

$$p_t^{+/-} = p_0 \exp\left(-\sigma \frac{\mathrm{D}N_b}{\mathrm{D}t}\right), \tag{21}$$

where σ is the chemotactic sensitivity (the change in the mean run time of a bacterium per rate of change of bound receptors) and $\mathrm{D}N_b/\mathrm{D}t$ is the material derivative of the number of bound receptors N_b. The authors show that expressions for the diffusion and chemotactic coefficients of the form

$$\mu(s) = \frac{2v}{p_0(1-\psi)} \exp\left(\sigma \frac{dN_b}{ds}\frac{\partial s}{\partial t}\right) \mathrm{sech}\left(\sigma x \frac{dN_b}{ds}\frac{\partial s}{\partial x}\right) \tag{22}$$

and

$$\chi(s) = v \tanh\left(\sigma v \frac{dN_b}{ds}\frac{\partial s}{\partial x}\right), \tag{23}$$

where in the case of a single receptor it is assumed that

$$\frac{dN_b}{ds} = \frac{R_T K_d}{(K_d + s)^2}, \tag{24}$$

can be derived. Here, ψ is the cosine of the persistence angle, p_0 is the individual bacterial tumbling probability in the absence of a chemoattractant gradient, R_T is the number of receptors per cell, and K_d is the receptor-attractant dissociation constant. Various limits of the expressions are considered and it is noted that in the case of shallow attractant gradients, as analyzed by Keller and Segel (1971a), these expressions reduce to

$$\mu(s) = \frac{v^2}{p_0(1-\psi)}\left(1 + \sigma \frac{dN_b}{ds}\frac{\partial s}{\partial t}\right) \quad \text{and} \quad \chi(s) = \chi v^2 \sigma \frac{dN_b}{ds}. \tag{25}$$

Comparison of model solutions using the diffusion and chemotactic coefficients given by Eqs. (22) and (23) with experimental work (Dahlquist et al., 1976; Mesibov et al., 1973; Berg and Brown, 1972) shows good agreement between the two.

Ford et al. (1991) compared the RTBL model, with non-linear terms for the chemotactic and diffusion coefficients of the form given in Eqs. (22) and (23), with results obtained from SFDC experiments. The model neglects the effects of consumption of the chemoattractant by the bacteria. They noted that the steep attractant gradients which develop in the SFDC assay can not be adequately described by the K–S model, given the assumption by K–S during the derivation of their model that the attractant gradient is small (Keller and Segel, 1971a). They compared model outcomes for the three cases of: (i) constant diffusion and a linear description of chemotaxis; (ii) constant diffusion and the non-linear

description of chemotaxis given by Eq. (23); and (iii) non-linear diffusion and chemotaxis as described by Eqs. (22) and (23). Results showed that while all three forms of the diffusion and chemotactic coefficients converge to the same steady-state cell distributions, the intermediate behavior differs substantially. The case of constant diffusion and non-linear chemotaxis provided the best fit to experimental data indicating the limitations of linear models.

Ford and Lauffenburger continued their work on using the RTBL model to reproduce experimental findings in Ford and Lauffenburger (1991a). Here, the focus was the findings of Dahlquist et al. (1972) (see Section 2.2 for earlier models and details) where steep and smooth attractant gradients were considered. Ford and Lauffenburger (1991a) qualitatively assessed the effect that varying diffusion and chemotactic motility parameters had on the shape of the attractant and bacterial profiles. On fitting the model to the experimental findings of Dahlquist et al., they found that by including expressions for two receptors with different affinities, as part of the chemotactic coefficient, they were able to account for the difference in cell velocities across a range of attractant concentrations.

Ford and Cummings (1992) compared each of the models of Alt (1980), Segel (1977) and Rivero et al. (1989) and considered the various relationships between each model. They noted that Alt's three-dimensional model can be reduced to one dimension when the attractant gradient is assumed to vary in only one spatial dimension and the run times are distributed according to a Poisson distribution. These assumptions lead to the equation

$$\frac{\partial n(x,\theta,t)}{\partial t} = -s_x \frac{\partial (v(x,t)n(x,\theta,t))}{\partial x} - \beta(x,\theta,t)n(x,\theta,t) + \int_0^\pi \beta(x,\theta',t)n(x,\theta',t)K(\theta',\theta)\sin\theta' d\theta', \tag{26}$$

where $n(x,\theta,t)$ is the distribution of cells moving at an angle θ and $K(\theta',\theta)$ is the turn angle distribution (the probability that a particle moving in the θ' direction will tumble to then move in the θ direction). This one-dimensional model reduces to a generic K–S model when the attractant gradient is only considered to vary in one spatial dimension. Ford and Cummings (1992) further noted that Alt's model reduces to Stroock's probabilistic density equation (Stroock, 1974) when bacterial tumbling is assumed to be independent of the run time. They further showed that the governing equations of the RTBL model could be derived from Alt's full three-dimensional model and that the one-dimensional swimming speed is one half the corresponding speed in three-dimensions.

Frymier et al. (1993) discussed the validity of the RTBL model in describing experiments in which the attractant gradient is experimentally three-dimensional, but where the RTBL model has assumed it is one-dimensional. Frymier et al. (1993) compared numerical simulations of the RTBL model with discrete three-dimensional Monte Carlo simulations of Alt's equations. They found that the RTBL assumption that the attractant gradient only varies in one dimension did not make an appreciable difference to solutions. It was noted that it is important to obey the relationship between the one- and three-dimensional chemotactic coefficients of $\chi_0^{3D} = 4\chi_0^{1D}$ as derived by Ford and Cummings (1992).

The work of Frymier and co-workers (Frymier et al., 1994) has compared finite element solutions of the reduced one-dimensional attractant gradient model of Alt (Ford and Cummings, 1992) with model solutions of Frymier et al. (1993) and the author's own experimental data on the chemotaxis of *E. coli* using the SFDC assay. Results from both

models were shown to be in good agreement with experiment. In considering the two cases of bacteria returning to their original tumbling frequency or having an increased rate of tumbling when moving away from attractant gradient, Frymier et al. (1994) showed the former assumption results in fewer bacteria moving to areas of higher concentration. It was further noted that discrepancies in predicted values of the chemotactic coefficient occur when χ is predicted using the one-dimensional attractant case of Ford and Cummings (1992) rather than the three-dimensional, full RTBL, model assumption.

Brosilow et al. (1996) compared one- and two-dimensional numerical solutions of the models of Alt (1980) (in the case where the bacterial running speed is assumed constant) and the RTBL model (Rivero et al., 1989). Solutions from each model were compared with the SFDC experimental observations of Ford and Lauffenburger (1991b) and showed that the discretized Alt model gives similar solutions to a slightly modified version of the RTBL model (the bacterial velocity is assumed to be half that stated in Rivero et al., 1989). Such agreement even occurred when the turning angle was coarsely discretized. Thus, while the Alt model provides a detailed model of chemotactic aggregation and movement, the RTBL model gives an adequate continuum based description of bacterial chemotaxis.

Brosilow et al. do note that although Alt's model is comprehensive, it does not necessarily account for four important features of bacterial chemotaxis. Firstly, the model assumes bacterial runs are straight paths, when in fact they have been observed to drift rotationally. Indeed this difference can be as great as $\theta \sim \sqrt{t}/2$, where θ is the drift angle and t is the run time in seconds. Thus, the model may overestimate the chemotactic response of the cell. Secondly, tumbles are instantaneous and short in comparison to runs. This assumption may somewhat overestimate the bacterial speed of response to any changes in attractant concentration. Thirdly, Alt (1980) assumes that the speed of the bacterial runs is constant when in fact such runs are distributed with a variance of up to 25% from the mean running speed. Finally, the bacterial tumbling process is assumed to obey a Poisson distribution, when as Brosilow et al. note, bacterial tumbling does vary from one bacterium to another. The work furthermore shows that bacterial persistence decreases the rate at which bacteria move towards an attractant. In the case of the RTBL model, persistent random walk behavior leads to a large diffusion coefficient in comparison to when movement is not persistent. This persistence does not affect the chemotactic term of the RTBL model.

Chen et al. (1998c) undertook extensive perturbation analysis of Alt's governing equations and derived a similar expression for the chemotactic coefficient to that of Rivero et al. (1989) (see Eq. (23))

$$\chi(s) = \frac{2v}{3} \tanh\left(\frac{\chi_0}{2v} \frac{K_d}{(K_d + s)^2} \frac{\partial s}{\partial x}\right). \tag{27}$$

This expression has since been used in a number of macroscale continuum models of bacterial chemotaxis (Marx and Aitken, 1999, 2000; Pedit et al., 2002; Hilpert, 2005) (see Section 2.2 for further details), its use motivated by the fact that it allows the effect of important microscopic effects, which affect chemotaxis, to be evaluated on the macroscale, as noted by Ford et al. (1991). For instance, Pedit et al. (2002) noted that in obtaining good agreement between experimental data and model output for the response of *Pseudomonas putida* to naphthaelene, the velocity expression of Eq. (27), and thus the overall macroscopic description of the bacterial density, is particularly sensitive to changes in K_d.

Chen and co-workers (Chen et al., 1998a, 1999) have reduced Alt's three-dimensional model to one dimension, analyzed the resulting equation and it's relation to Segel's work (Segel, 1976, 1977), and the effect of tumbling frequencies. Chen et al. (1998a) considered the effect that individual bacterial turning frequencies have on the overall global population turning frequency, noting the latter is more commonly determined in experiments. Moment analysis of the turning probability distribution function showed that the higher order moments are useful in searching for appropriate angle distributions which are perturbed by the chemoattractant. In Chen et al. (1999), the authors considered a one-dimensional reduction of Alt's model equations and assumed the tumbling frequency switched between different phases dependent upon the strength of the attractant gradient. Their motivation was the observations of Macnab and Koshland (1972) and Berg and Brown (1972) that bacteria only adjust their tumbling frequency slightly when moving down an attractant/repellent gradient versus when moving up an attractant gradient, and the tumbling time is exponentially distributed. It was noted that the bacterial turning angle range was limited when both temporal and spatial gradients of the chemoattractant were considered and that this defines the overall chemotactic response. Undertaking perturbation analysis of the governing equations in the limit of a small attractant gradient, Chen et al. (1999) showed the resultant solutions agreed well with numerical solutions of the full Alt model.

The reduction of Alt's model, in the case of a one-dimensional attractant gradient with a bi-phasic angular distribution function, has been the focus of work by Chen et al. (2003). The authors investigated the effects of assuming planar geometry and showed that the first order angular moment of the turn angle probability distribution function is important in affecting the bacterial response. In converting the angular number density to a bacterial bulk density by integrating the former over the turning angles, the resultant equation can be related to the diffusion equation. The diffusion and chemotactic coefficients in one dimension are found to be three times larger than those in three dimensions if the individual cell swimming speed in one- and three-dimensions remains the same. Perturbation solutions to the reduced model compare well with numerical solutions to Alt's full model equations, both of which compare well with results from SFDC experiments.

Schnitzer et al. (1990) considered the effect that the microscale movement of cells has on the overall macroscale behavior, specifically diffusion. They considered a bacterium moving a distance δ in a time τ and the effect that varying both the distance and speed independently and together has on the derived macroscopic equations. They noted that: (i) varying δ and τ, whilst maintaining a constant speed, leads to a spatially varying diffusion coefficient, but a uniform steady-state bacterial distribution; (ii) keeping δ constant whilst varying τ means $D = \delta^2/4\tau(x)$, the steady-state bacterial distribution is inversely proportional to D and the cells accumulate when the time taken to travel a set distance increases. Here, x is the spatial location of the cell; (iii) varying δ and keeping τ constant gives $D = \delta^2(x)/4\tau$ and leads to an equilibrium distribution where the bacterial density is inversely proportional to the square root of the diffusion coefficient; and (iv) varying δ and τ shows the resultant flux equation can not be written in terms of a diffusion coefficient. The authors note that case (ii) corresponds to the classic K–S model. From Monte Carlo simulations on lattices of varying sizes, Schnitzer et al. (1990) conclude that when the bacterial turning frequency depends solely on the local attractant gradient with a constant cell speed, cells do not accumulate at the crest of the gradient. If the initial bacterial distribution is uniform, it will remain so. Furthermore, when the cell speed depends on the local attractant concentration, bacteria will still aggregate, even when the cell speed is low.

Schnitzer (1993) continued to elucidate the link between microscale behavior and macroscale models of bacterial movement. He argued that bacterial random walks can not be treated on a lattice given the infinite number of distinct directions of motion and the Langevin description is not appropriate as it does not consider individual microscopic collisions. Extending earlier work (Schnitzer et al., 1990) on turning rates and travel time and including analysis of turning angles, he derives the Smoluchowski state equation in the context of bacterial movement based on the assumption that the probability distribution of correlations between directions of motion and after collisions are smooth.

Recently, two further pieces of work (de Gennes, 2004; Clark and Grant, 2005) have considered the effect that internal delays within the intracellular signaling cascade have on the bacterial response. de Gennes (2004) considered the motion of a single bacterium during one run, i.e. a counter-clockwise (CCW) rotation of its flagella, and related the response function (the receptor to motor response) describing the bacterium to the macroscopic scale chemotactic coefficient. de Gennes disagrees with the findings of Schnitzer et al. (1990) that the chemotactic coefficient is zero when the bacterial response is instantaneous. Instead, he notes that by accounting for the internal receptor to motor response delay, the chemotactic coefficient is a sum of the response function, which decreases as the internal delay increases.

Clark and Grant (2005) adopted the model of de Gennes and considered the importance of the response function in describing the difference in short and long bacterial runs. A positive response to short runs should move bacteria up attractant gradients, while long runs should allow bacteria to aggregate in the regions where the attractant concentration is greatest. However, Clark and Grant (2005) find that optimizing one response leads to an unfavorable response in the other. They show that experimental evidence is most likely to be reproduced when a combination of each response is considered (the commonly observed excitation–adaptation response curve), and thus obtain an appropriate expression for the response function.

D'Orsogna et al. (2003) considered the influence of chemokinesis and chemotaxis on the aggregation of *Myxococcus xanthus*. Considering a single bacterium, a one-dimensional model was derived, based on turning probabilities, which accounted for the bacteria releasing and sensing their own attractant. The probability of direction reversal was considered to be a function of the absolute level of chemoattractant under each cell and the gradient sensed along the length of the cell. D'Orsogna et al. (2003) derived a Fokker–Planck equation to describe the bacterial movement of a population and undertook Monte Carlo simulations of the resultant model. They considered the effect that both chemo-attractants and -repellents have on the turning rates when both chemotaxis and chemokinesis are individually included in the model description as well as together. It was shown that various distributions form dependent on the strength of each mechanism.

Agent based models of bacterial chemotaxis have been developed by Kreft et al. (1998), Emonet et al. (2005), and Bray et al. (2007). Such models allow attributes of individual cell behavior to be measured on the population scale and are computational in nature; each cell has a set of defined rules which it follows. Although Kreft et al. (1998) and Emonet et al. (2005) used a similar modeling methodology, their approaches contrast in a number of ways. The simulator developed by Kreft et al. (1998) (BacSim) focused on the cellular metabolism and the effect that cell size and division have on the population. On the single scale, their model accounted for substrate uptake, metabolism, the maintenance of cell biomass, cell volume and surface area, cell diffusion, and the growth

of the colony. In contrast, the simulator developed by Emonet et al. (2005) (AgentCell) included a description of receptor dynamics, the intracellular phosphotransfer network, and the motor and flagellum response.

Kreft et al. (1998) note that random variation in the maximum size of the cell causes the population to become more asynchronous than random variation in cell size at division. The most asynchronous population is obtained when both maximum and division size are chosen to vary randomly. They note that spatial heterogeneity in the available nutrient concentration does not generally cause asynchrony in the population, but results in sub-populations of the main population which grow at different rates, thus giving the appearance of asynchrony. Emonet et al. (2005) considered the effect that stochastic variation in the intracellular signaling pathway may have on the population scale, their work motivated by the experimental evidence of Korobkova et al. (2004). The phosphorylation signal pathway is implemented using the stochastic molecular simulator StochSim (Morton-Firth et al., 1999). AgentCell was used to undertake two simulations. The first considered a population of 1,166 cells swimming in a three-dimensional environment, while the second looked at an individually tethered cell. The single cell behavior compared well with that observed by Korobkova et al. (2004) and details on the diffusion rate of the population compared well with the experimentally known values of Lewus and Ford (2001) and Berg and Turner (1993). Whilst both models have sought to determine the effect that single cell behavior has on the population scale, both models have not systematically studied the effect that individual cell characteristics, such as receptor sensitivity, excitation, adaptation, motor response, and variations in them have on the population scale.

The work of Bray et al. (2007) considers the movement of bacteria in two-dimensional attractant gradients and includes a revised version of their earlier subcellular phosphorylation pathway (incorporating CheR, CheB_P, CheA, CheA_P, CheY, CheY_P, and CheZ) models (Bray et al., 1993; Bray and Bourret, 1995). The individual cell models include only a description of the Tar receptor and the physics of flagella motion are ignored. The authors have developed two graphical representations of the bacterial populations. The *E. solo* model describes individual bacteria in uniform concentration gradients of aspartate, with each cell depicting up to four flagella. The program allows the attractant concentration to be adjusted during the course of a simulation and measurements of the tumbling frequency, adaptation time, turn angle (when tumbling) to be analysed. The *E. pluribus* model allows the movement of bacteria (without flagella) of either wild or mutant types, within a pre-defined fixed attractant gradient, to be analyzed.

Bray et al. (2007) use *E. pluribus* to examine the effect that adaptation and the sensitivity of the phosphorylation network to attractant binding (they define an "infectivity factor") has on bacterial aggregation. Considering various exponential radially static gradients of attractants, they show that the simulated bacteria only accumulate at the maximal of high attractant concentrations when the activity of CheR and CheB are increased 15-fold. At normally predicted activity levels of CheR and CheB (from *in vitro* studies), the cell overshoot in adaptation response is almost non-existent, thus they do not accumulate in regions of high attractant concentration. Bray et al. (2007) note that their work agrees with the findings of Clark and Grant (2005) on how the form of the adaptive response curve of individual bacteria affects their ability to accumulate.

Other recent work on developing multiscale models of bacterial chemotaxis using equation-free methods has been undertaken by Setayeshgar et al. (2005), Erban and Oth-

mer (2004, 2005). Setayeshgar et al. (2005) describe the microscopic behavior of a single bacterium using a system of equations of the form

$$\frac{d\mathbf{y}}{dt} = f(\mathbf{y}, \mathbf{S}), \tag{28}$$

where $\mathbf{y} = (y_1, y_2, y_3, \ldots, y_N) \in \mathbb{R}^N$ are internal state variables of the bacterium describing for instance, the CheY$_P$ concentration, and $\mathbf{S} = (S_1, S_2, S_3, \ldots, S_M) \in \mathbb{R}^M$ are the external signals received by the bacterium. This microscopic description is closed by assuming that the time dependent evolution of the density of the bacterial colony is the relevant macroscopic variable. No equation representing the cell density is actually solved, and hence the method is referred to as "equation-free".

Applying this theory, Setayeshgar et al. (2005) propose a simplified model of excitation and adaptation

$$\frac{du_1}{dt} = \frac{(f(s) - u_2) - u_1}{\tau_\epsilon}, \qquad \frac{du_2}{dt} = \frac{(f(s) - u_2)}{\tau_a}, \tag{29}$$

where u_1 is the deviation in concentration of CheY$_P$ from its steady-state, u_2 is the number of methylated receptors per unit volume per cell and τ_ϵ and τ_a are the excitation and adaptation times, respectively. Here $\tau_\epsilon \ll \tau_a$. The cell response is described by a two-state stochastic model

$$\mathrm{CCW}_i \underset{k_-}{\overset{k_+}{\rightleftharpoons}} \mathrm{CW}_i, \quad i = 1, \ldots, N, \tag{30}$$

where the subscript i denotes the individual bacterium, CCW_i is the counter-clockwise (chemotaxis) state, CW_i is the clockwise (random motion) state, and N is the number of bacteria per colony. The transition rates k_+ and k_- are assumed to depend upon the concentration of CheY$_P$. Monte Carlo simulations of the system show that given the large separation in timescales of an individual bacterium responding to a stimulus (excitation and adaptation) to that of the overall evolving distribution of the bacterial colony, allows coarse graining via the macroscopic description and results in reduced computation time.

Erban and Othmer (2004) incorporated the above microscopic description into a macroscopic description of bacterial chemotaxis as defined by the telegraph process of Eqs. (13) and (14). The turning rates were assumed to depend on the concentration of CheY$_P$. By use of appropriate scalings and moment closure techniques, they derive both a hyperbolic system of equations and the classical parabolic K–S description of chemotaxis. Expressions for the form of the chemotactic coefficient in terms of individual state variables are derived as

$$\chi = f'\big(S(x)\big)\frac{bs^2\tau_a}{\lambda_0(1 + 2\lambda_0\tau_a)(1 + 2\lambda_0\tau_e)}, \tag{31}$$

where s is the speed of the individual bacterium, $\lambda_0 = k(y_1) + by_1$ and f is a prescribed function of the signal $S(x)$. Interestingly, this result shows that the chemotactic response vanishes as the adaptation time tends to zero. Including finite tumbling times shows that the classical chemotaxis equations for both the tumbling and non-tumbling cases only marginally differ. They generalize these results to higher dimensions (Erban and Othmer,

2005) and discuss the importance of using different mathematical techniques to solve the governing equations describing individual cell behavior for a large number of bacteria in a reasonable time.

4. Modeling interactions between bacterial populations

Motivated by their work modeling one bacterial species Lauffenburger et al. (1982) and Lauffenburger and Calcagno (1983) considered a mathematical model to describe the competition between two microbial populations. The authors do not include chemotaxis in their model and consider the effect this has on the spatial and temporal behavior of the bacterial distributions within a defined region. The model exhibits three possible steady-states (one of coexistence, two of either population being excluded) with coexistence shown to be possible even when one population has a smaller growth rate and is less motile. A species with a smaller maximal growth rate in a confined, non-mixed environment may actually grow to a larger population size dependent upon the strength of their motility response to attractants. While they allude to experimental work in the area of mixed populations, they note no direct experimental work exists to verify or refute their findings.

Lauffenburger et al. (1987) considered competition between two bacterial populations and compared model outcomes where bacteria move either by diffusion or chemotaxis or both. Their work began by considering a model in which the tumbling probability depended on the time rate of change of receptor occupancy. They formulated a K–S model and derived the relations between the diffusion and chemotactic coefficients and the microscopic tumbling behavior. They assumed that the number of bound receptors decreases sigmoidally with respect to attractant concentration, as described by Brown and Berg (1974). It was noted that models in which the tumbling probability depends on the change in the total number of bound receptors versus the time rate of change of receptor occupancy leads to models that predict abnormally large attractant gradients. Lauffenburger et al. (1987) undertook experimental work to quantify μ and χ and noted that model solutions, using the derived parameters, agreed well with experimental findings. This model was then extended to the case of two bacterial populations. Simulations showed that cell motility is more important than growth kinetics (in this case Monod kinetics)[4] in governing competition between non-mixed populations. Chemotaxis can help a population to "win", if its growth kinetics are poor, so long as the chemotaxis to diffusion ratio is high (Lauffenburger et al., 1987 note it must be greater than 10 for their chosen parameter values).

Kelly et al. (1988) considered a similar problem to that of Lauffenburger et al. (1987): competition between two bacterial populations in a confined, non-mixed region with a single nutrient supply. They considered transient and steady-state numerical solutions to their governing equations which include descriptions of cell growth and death. They then focused on the role that diffusion and chemotaxis play in the competition between the two populations. As with Lauffenburger et al. (1987) they show that both populations

[4]Monod kinetics is similar to that of Michaelis–Menten, but where an inhibitor complex binds with the enzyme at the same time as the substrate. The inhibitor and substrate are thus in competition for the enzyme. This leads to the additional reaction $I + E \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} IE$.

can co-exist or one population out-competes the other. They note that unlike the case of a well-mixed system, the population in which growth is slower can co-exist so long as its ability to diffuse and chemotact is greater than that of the opposing population. They obtain a lower bound on the chemotactic coefficient in order for a population to be more competitive than an immotile one in a non-mixed environment.

5. Modeling bacteria and their environment

A number of researchers have sought to model the interactions which occur between bacterial populations and their surrounding media. Dillon et al. (1995) considered the interactions which occur between bacteria, the attractant substrate and their surrounding fluid environment. The fluid was modeled by the Navier–Stokes equation, inertial effects being ignored, with an appropriate force term describing the fluid-body interaction for a set number of bacteria, modeled as discrete elastic rings with an associated deformation energy. The chemoattractant was assumed to be consumed according to Michaelis–Menten reaction kinetics and transport was described by an advection-diffusion equation, the velocity being that of the fluid. The derived model also included a simplified model of flagella rotation (Stokelets) as first considered by Lighthill (1975). Numerical simulations showed that hydrodynamic interactions between pairs of swimming bacteria can be important when the distance between them is less than a cell length (including flagella). Nutrient uptake was shown to depend not only on the Peclet number (the ratio of advective to diffusive effects), but also on uptake rate. Simulations showed that if the uptake rate is low, then swimming has negligible effect on the quantity of attractant consumed, but if attractant consumption is high, then slow swimming cells, moving up attractant gradients, can consume nutrient faster than either non-motile cells or those swimming down the gradient. Dillon et al. (1995) concluded that models which ignore bacterial-fluid interactions can give poor predictions on nutrient uptake.

Other researchers have focused in more detail on modeling the hydrodynamic interactions which occur between bacteria and the surrounding fluid (Lighthill, 1975; Pedley and Kessler, 1992; Ramia et al., 1993; Goto et al., 2005; Lauga et al., 2006). Unlike Dillon et al. (1995), such work does not consider macroscale descriptions of bacterial distributions, the surrounding fluid environment, the transport of chemoattractant, or interactions between them.

6. Pattern formation and bacterial chemotaxis

While our work here has focused primarily on models which have directly elucidated the behavior of bacterial populations, we briefly mention work which has considered modeling pattern formation in bacterial colonies. A more comprehensive list of papers relevant to pattern formation in bacterial chemotactic systems can be found in Erban and Othmer (2005).

Pattern formation is a result of self-organization within the species being studied and many biological systems exhibit such behavior (Murray, 1993). In the case of bacterial chemotaxis, such patterns are often observed in petri dishes (Budrene and Berg, 1991; Ben-Jacob et al., 1994, 1995; Berg, 1996). Indeed pattern formation models have generally been based on K–S models. Such work often considers the effect of varying reaction-kinetics on the generated patterns and parameter limits which lead to instabilities (Zhu

Table 2 Various model parameters used in continuum models of bacterial populations. Here, the data are for *E. coli*. Adapted from Ford and Lauffenburger (1991b)

Parameter description	Notation	Value
Initial bacterial density	b_0	10^8 cells/ml
Initial attractant concentration	s_0	0.1 mM
Bacterial diffusion coefficient	μ	1.5^{-5} cm^2/s
Bacterial chemotactic coefficient	χ	1.5–75^{-5} cm^2/s
Attractant diffusion coefficient	D	10^{-5} cm^2/s
Individual cell swimming speed	v	10 μm/s

and Murray, 1995; Maini et al., 1991). Hillesdon et al. (1995) considered the effect that varying forms of the cell swimming speed, Heaviside or exponential, have on the movement of *B. subtilis* in petri dishes of varying vertical depths. Work has also focused on the effect that secretion of chemoattractant by the bacteria has on the formation of bacterial patterns (Brenner et al., 1998).

7. Parameter values

Many of the models reviewed here have relied on using parameter values determined by the various experimental assays detailed in the Introduction. As noted, mathematical models have been developed to reproduce both qualitatively and quantitatively the experimentally observed behavior. By iterating between model and experimental comparison, improvements to model fits of experimental data have been made by adjusting the various model parameters. This general methodology has allowed estimates to macroscopic parameters such as diffusion and chemotactic coefficients, bacterial growth, and death rates and chemoattractant consumption rates to be made. Once accurate predictions of parameter values have been made, these can then be used to make model predictions and simulations of the behavior of bacterial populations in the natural environment.

A brief list of common macro- and micro-scopic parameters is provided in Table 2. The papers of Ford and Lauffenburger (1991b) and Ford et al. (1991) are but two examples of authors who have focused on determining parameter values through comparison of model outcomes with experimental data. For a summary of diffusion and chemotactic coefficients derived by comparison with experiments for different chemotactic species, discussion on the various assay methods used to determine these and their various sources, the reader is referred to Lewus and Ford (2001). As noted there, the differences in reported values for the chemotactic and diffusion coefficients of up to two orders of magnitude is a result of "differences in bacterial species/strains, growth medium, growth conditions, experiment type, and experimental conditions."

8. Summary and discussion

The development of mathematical models within the field of bacterial chemotaxis has allowed the importance of macroscopic and microscopic mechanisms which affect the spatio-temporal behavior of bacterial populations to be elucidated.

Our review work here has covered a range of models. A number of continuum models, based upon that originally devised by Keller and Segel (1971b), have been developed to

understand the bacterial response to chemoattractants using a number of *in vitro* assay methods. Such work has often been carried out in parallel with experiment allowing good estimates of model parameters to be made. The ability of the Keller–Segel equations to accurately reproduce experimental findings has meant that this generic model framework is still widely used today in the study, not only of bacterial chemotaxis populations, but also of other biological systems which exhibit chemotaxis (Murray, 1993).

Modeling work has also continued to incorporate individual cell behavior into overall macroscopic descriptions of bacterial distributions. The initial work of Segel (1976, 1977) simply considered the change in distributions generated by bacteria with differential receptor confirmations moving along a one-dimensional line. Alt's seminal work (Alt, 1980) sought to obtain descriptions including more individual effects such as turn angle and individual run time. Since analyzed in detail, the comparison between various K–S models and reduced forms of Alt's original equations have allowed macroscopic parameters such as the diffusion and chemotactic coefficients to be expressed in terms of individual microscopic ones. More recently equation-free methods have been used to predict macroscopic behavior from microscopic descriptions of single cell intracellular biochemistry without the need for explicit derivation of equations describing macroscopic behavior. Such methods have been shown to be computationally less intensive than other multiscale schemes. We note that in developing macroscale population descriptions, it is important that these are based upon the correct assumptions. For instance, the density of cells and concentration of chemoattractant is large enough to warrant a continuum description such as that developed by Keller and Segel. In cases where these assumptions do not hold the K–S theory of chemotaxis is no longer valid and other methods must be employed (Newman and Grima, 2004).

Experimentally, a number of questions regarding the response of individual bacteria to changes in extracellular attractant concentration remain, as yet, unanswered. Such questions relate to small changes which bacteria can sense over the large order range of attractant concentration, specifically sensitivity, gain, and adaptation. The importance such mechanisms have on the macroscale behavior of bacterial populations is as yet unclear, although recent work has elucidated the importance of adaptation in the bacterial response on bacterial aggregation (Bray et al., 2007). In order to incorporate such microscale mechanisms at the macroscale level, further use of multiscale modeling methods is required.

There remain a number of important questions to be answered on the single cell scale as we have noted in a recent review on modeling within individual bacteria (Tindall et al., 2007). Improved understanding on the individual cell scale, combined with new modeling techniques to incorporate such affects on the population scale, will ensure comprehensive, but tractable models are developed, thereby aiding our understanding of bacterial cell populations.

Acknowledgements

We thank Julie Simons for comments on earlier versions of this manuscript. This work (MJT and SLP) was funded by a grant (BB/C513350/1) from the Biotechnology and Biological Sciences Research Council (BBSRC), UK. PKM was partially supported by a Royal Society Wolfson Merit Award. The authors are particularly grateful to the referees for their comments and careful reading of the manuscript.

Appendix A: Comparison of K–S models of bacterial chemotaxis

The generic K–S system of equations is given by

$$\frac{\partial b}{\partial t} = \nabla \cdot \big(\mu(s)\nabla b\big) - \nabla \cdot \big(\chi(s) b \nabla s\big) + g(b,s) - h(b,s) \quad \text{and} \quad \frac{\partial s}{\partial t} = -f(b,s) + D\nabla^2 s.$$

The table below provides a summary of the above terms included in the cited references and lists the functional forms used where necessary.

Reference	$\mu(s)$	$\chi(s)$	$g(b,s)$	$h(b,s)$	$f(b,s)$	D
Keller and Segel (1971b)	√	χ/s	0	0	$k_f b$	√
Segel and Jackson (1973)[b]	√	χ/s	0	0	0	0
Nossal and Weis (1973)	√	χ/s	0	0	0	0
Lapidus and Schiller (1974)[b]	√	χ/s	0	0	0	0
Lapidus and Schiller (1975)	√	χ/s	0	0	$k_f b$	0
Lapidus and Schiller (1976)[c]	√	$\frac{\chi}{(K_d+s)^2}$	0	0	0	0
Lapidus and Schiller (1978)	√	$\frac{\chi}{(K_d+s)^2}$	$k_g b$	0	0	0
Rosen (1974)	√	χ/s	0	0	$k_f b s^p$	√
Rosen (1975)	√	χ/s	0	0	$k_f b s^p$	√
Rosen and Baloga (1975)	√	χ/s	0	0	$k_f b s^p$	0
Rosen (1976)	√	χ	0	0	$k_f b$	0
Rosen and Baloga (1976)	√	χ/s	0	0	$k_f b s^p$	0
Kennedy and Aris (1980)	√	0	$\frac{k_g b s^p}{K^p+s^p}$	$k_f b$	$\frac{k_f b s^p}{K^p+s^p}$	√
Lauffenburger et al. (1982)	√	χ	$\frac{k_g b s}{K+s}$	$k_h b$	$\frac{k_g b s}{K+s}$	√
Lauffenburger et al. (1984)	√	χ, χ/s and $\frac{\chi K_d}{(K_d+s)^2}$	$\frac{k_g b s}{K+s}$	$k_h b$	$\frac{k_f b s}{K_s+s}$	√

Reference	$\mu(s)$	$\chi(s)$	$g(b,s)$	$h(b,s)$	$f(b,s)$	D
Rosen (1983)	$\surd$	χ/s	0	0	$k_f b$	$\surd$
Novick-Cohen and Segel (1984)	$\surd$	$\frac{\chi}{(K_d+s)}$	0	0	$k_f b$	$\surd$
Boon and Herpigny (1986)[d]	$\surd$	$\frac{\chi 2 s_i K_d}{(K_d+s_i)^2}$	0	0	$\frac{k_{f1} b s_1}{(K_{s1}+s_1)(K_{s2}+s_2^4)} + \frac{k_{f2} b s_1 s_2}{(K_{s1}+s_1)(K_{s2}+s_2)}$	D_i
Rivero-Hudec and Lauffenburger (1986)	$\frac{1}{2} T v^2$	$\frac{\chi_0 K_d}{(K_d+s)^2}$	0	0	0	$\surd$
Ford and Lauffenburger (1991b)	$\frac{v^2}{(1-\vartheta)p_0} \exp(\sigma \frac{dC}{ds} \frac{\partial s}{\partial t}) \times \operatorname{sech}(\sigma v \frac{dC}{ds} \frac{\partial s}{\partial x})$	$v \tanh(\sigma v \frac{dC}{ds} \frac{\partial s}{\partial x})$	0	0	$\frac{k_f b s}{K_s+s}$	$\surd$
Ford et al. (1991)	$\mu_0 \exp\big(\sigma \frac{R_T K_d}{(K_d+s)^2} \frac{\partial s}{\partial t}\big) \times \operatorname{sech}\big(\sigma \frac{R_T K_d}{(K_d+s)^2} \frac{\partial s}{\partial x}\big)$	$\frac{\chi_0 K_d}{(K_d+s)^2}$	0	0	$\frac{k_f b s}{K_s+s}$	$\surd$
Widman et al. (1997)[a]	$\surd$	$\frac{\chi_0 K_d}{(K_d+s)^2}$	$\frac{k_g N b}{K+N}$	0	$\frac{k b s}{K_s+s}$	$\surd$
Chiu and Hoppensteadt (2001)[a]	$\surd$	$\frac{\chi_0 K_d}{(K_d+s)^2}$	$\frac{k_g N b}{K+N}$	0	$\frac{k b s}{K_s+s}$	$\surd$
Marx and Aitken (1999)	$\surd$	$\frac{2v}{3} \tanh\big(\frac{\chi_0}{2v} \frac{K_d}{(K_d+s)^2} \lvert\nabla s\rvert\big)$	0	0	0	$\surd$
Marx and Aitken (2000)	$\surd$	$\frac{2v}{3} \tanh\big(\frac{\chi_0}{2v} \frac{K_d}{(K_d+s)^2} \lvert\nabla s\rvert\big)$	0	0	$\frac{k b s}{K_s+s}$	$\surd$
Pedit et al. (2002)	$\surd$	$\frac{2v}{3} \tanh\big(\frac{\chi_0}{2v} \frac{K_d}{(K_d+s)^2} \lvert\nabla s\rvert\big)$	$\frac{k_g b s}{K+s}$	$k_h b$	$\frac{k s b}{K_s+s}$	$\surd$
Hilpert (2005)	$\surd$	$\frac{2v}{3} \tanh\big(\frac{\chi_0}{2v} \frac{K_d}{(K_d+s)^2} \lvert\nabla s\rvert\big)$	$\frac{k_g b s}{K+s}$	0	$\frac{k_f b s}{K_s+s}$	$\surd$

Parameter and variable definitions

$b = b(x, t)$ Bacterial density
$s = s(x, t)$ Chemoattractant concentration
$\mu(s)$ Bacterial diffusion coefficient
$\chi(s)$ Bacterial chemotaxis coefficient
$g(b, s)$ Function describing bacterial growth
$h(b, s)$ Function describing bacterial death
$f(b, s)$ Function describing attractant decay
D Diffusion coefficient of the attractant
v Speed of an individual bacterium
K_d Receptor-attractant dissociation constant
p Hill coefficient
K Bacterial Michaelis–Menten constant for bacterial reproduction
K_s Chemoattractant Michaelis–Menten constant
T Mean persistence time
ϑ Directional persistence
N Concentration of a non-chemoattractant nutrient
C Concentration of attractant bound receptors
σ Fractional change in cell run time per rate of change of receptor occupancy
p_0 Individual bacterial tumbling probability in the absence of a chemoattractant gradient

Notes

$\surd$ Indicates value is constant
[a]Model description includes two chemoattractants and a non-consumable nutrient. Chemotaxis coefficients are of the same form for both chemoattractants
[b]$s = s_0 e^{-ax}$, with s_0 and a constant
[c]Considers three time-independent functions of concentration (exponential, Heaviside and Fermi)
[d]Includes chemotactic response to two chemoattractants (oxygen and glucose—$i = 1, 2$) and respective diffusion and depletion of these. $f(b, s)$ stated is that for the depletion of oxygen. Glucose has similar form with concentration subscripts interchanged

References

Adler, J., 1966. Chemotaxis in bacteria. Science 153, 708–716.

Adler, J., 1969. Chemoreceptors in bacteria. Science 166(3913), 1588–1597.

Adler, J., Dahl, M., 1967. A method for measuring the motility of bacteria and for comparing random and non-random motility. J. Gen. Microbiol. 46(2), 161–173.

Alt, W., 1980. Biased random walk models for chemotaxis and related diffusion approximations. J. Math. Biol. 9, 147–177.

Ben-Jacob, E., Schochet, O., Tenenbaum, A., Cohen, I., Czirok, A., Vicsek, T., 1994. Generic modelling of cooperative growth patterns in bacterial colonies. Nature 368, 46–49.

Ben-Jacob, E., Cohen, I., Schochet, O., 1995. Complex bacterial patterns. Nature 373, 566–569.

Berg, H., 1996. Symmetries in bacterial motility. Proc. Natl. Acad. Sci. 93, 14225–14228.

Berg, H., Brown, D., 1972. Chemotaxis in *Escherichia coli* analyzed by three-dimensional tracking. Nature 239, 500–504.

Berg, H., Turner, L., 1990. Chemotaxis of bacteria in glass capillary assays. Biophys. J. 58, 919–930.

Berg, H., Turner, L., 1993. Torque generated by the flagellar motor of *Escherichia coli*. Biophys. J. 65, 2201–2216.

Block, S., Segall, J., Berg, H., 1983. Adaptation kinetics in bacterial chemotaxis. J. Bacteriol. 154, 312–323.

Boon, J.-P., Herpigny, B., 1986. Model for chemotactic bacterial bands. Bull. Math. Biol. 48, 1–19.

Bray, D., Bourret, R., 1995. Computer analysis of the binding reactions leading to a transmembrane receptor-linked multiprotein complex involved in bacterial chemotaxis. Mol. Biol. Cell 6, 1367–1380.

Bray, D., Bourret, R., Simon, M., 1993. Computer simulation of the phosphorylation cascade controlling bacterial chemotaxis. Mol. Biol. Cell 4, 469–482.

Bray, D., Levin, M., Lipkow, K., 2007. The chemotactic behavior of computer-based surrogate bacteria. Curr. Biol. 17, 12–19.

Brenner, M., Levitov, L., Budrene, E., 1998. Physical mechanisms for chemotactic pattern formation by bacteria. Biophys. J. 74(4), 1677–1693.

Brosilow, B., Ford, R., Sarman, S., Cummings, P., 1996. Numerical solution of transport equations for bacterial chemotaxis: Effect of discretization of directional motion. SIAM J. Appl. Math. 56(6), 1639–1663.

Brown, D., Berg, H., 1974. Temporal stimulation of chemotaxis in *Escherichia coli*. Proc. Natl. Acad. Sci. 71(4), 1388–1392.

Budrene, E., Berg, H., 1991. Complex patterns formed by motile cells of *Escherichia coli*. Nature 349, 630–633.

Chen, K., Ford, R., Cummings, P., 1998a. The global turning probability density function for motile bacteria and its applications. J. Theor. Biol. 195, 139–155.

Chen, K., Ford, R., Cummings, P., 1998b. Mathematical models for motile bacterial transport in cylindrical tubes. J. Theor. Biol. 195, 481–504.

Chen, K., Ford, R., Cummings, P., 1998c. Perturbation expansion of Alt's cell balance equations reduces to Segel's one-dimensional equations for shallow chemoattactant gradient. SIAM J. Appl. Math. 59, 35–57.

Chen, K., Ford, R., Cummings, P., 1999. Spatial effect of tumbling frequences for motile bacteria on cell ball equations. Chem. Eng. Sci. 54, 593–617.

Chen, K., Ford, R., Cummings, P., 2003. Cell balance equation for chemotactic bacteria with a biphasic tumbling frequency. J. Math. Biol. 47(6), 518–546.

Chiu, C., Hoppensteadt, F., 2001. Mathematical models and simulations of bacterial growth and chemotaxis in a diffusion gradient chamber. J. Math. Biol. 42, 120–144.

Clark, D., Grant, L., 2005. The bacterial chemotactic response reflects a compromise between transient and steady-state behaviour. Proc. Natl. Acad. Sci. 102(26), 9150–9155.

Dahlquist, F., Elwell, R., Koshland, D., 1976. Studies of bacterial chemotaxis in defined concentration gradients. J. Supramol. Struct. 4, 329–342.

Dahlquist, F., Lovely, P., Koshland, D., 1972. Quantitative analysis of bacterial migration in chemotaxis. Nat. New Biol. 236, 120–123.

Davey, M., O'Toole, G., 2000. Microbial biofilms: from ecology to molecular genetics. Mol. Microbiol. 64(4), 847–867.

de Gennes, P., 2004. Chemotaxis: the role of internal delays. Eur. Biophys. J. 33(8), 691–693.

Dillon, R., Fauci, L., Gaver, D., 1995. A microscale model of bacterial swimming, chemotaxis and substrate transport. J. Theor. Biol. 177, 325–340.
D'Orsogna, M., Suchard, M., Chou, T., 2003. Interplay of chemotaxis and chemokinesis mechanisms in bacterial dynamics. Phys. Rev. E 68, 1–10.
Eisenbach, M., Lengeler, J., Varon, M., Gutnick, D., Meili, R., Firtel, R., Segall, J., Omann, G., Tamada, A., Murakami, F., 2004. Chemotaxis. Imperial College Press, London.
Emerson, D., Worden, R., Breznak, J., 1994. A diffusion gradient chamber for studying microbial behavior and separating microorganism. Appl. Environ. Microbiol. 60(4), 1269–1278.
Emonet, T., Macal, C., North, M., Wickersham, C., Cluzel, P., 2005. Agentcell: A digital single-cell assay for bacterial chemotaxis. Bioinformatics 21(11), 2714–2721.
Engelmann, T., 1881a. Neue methode zur untersuchung der sauerstoffaussheidung pflanzlicher und thierischer organismen. Pflugers Arch. Gesamte Physiol. Menschen Tiere 25, 285–292.
Engelmann, T., 1881b. Zur biologie der schizomyceten. Pflugers Arch. Gesamte Physiol. 26, 537.
Erban, R., Othmer, H., 2004. From individual to collective behaviour in bacterial chemotaxis. SIAM J. Appl. Math. 65, 361–391.
Erban, R., Othmer, H., 2005. From signal transduction to spatial pattern formation in *E. coli*: A paradigm for multiscale modelling in biology. Multiscale Model. Simul. 3(2), 362–394.
Ford, R., Cummings, P., 1992. On the relationship between cell balance equations for chemotaxis cell populations. SIAM J. Appl. Math. 52(5), 1426–1441.
Ford, R., Lauffenburger, D., 1991a. Analysis of chemotactic bacterial distributions in population migration assays using a mathematical model applicable to steep or shallow or gradients. Bull. Math. Biol. 53, 721–749.
Ford, R., Lauffenburger, D., 1991b. Measurement of bacterial random motility and chemotaxis coefficients I : Stopped-flow diffusion chamber assay. Biotech. Bioeng. 37, 647–660.
Ford, R., Quinn, J., Philips, B., Lauffenburger, D., 1991. Measurement of bacterial random motility and chemotaxis coefficients II: Application of single cell-based mathematical model. Biotech. Bioeng. 37, 661–672.
Frymier, P., Ford, R., Cummings, P., 1993. Cellular dynamics simulation of bacterial chemotaxis. Chem. Eng. Sci. 48(4), 687–699.
Frymier, P., Ford, R., Cummings, P., 1994. Analysis of bacterial migration: I. Numerical solution of balance equation. AIChE J. 40(4), 704–715.
Futrelle, R., Berg, H., 1972. Specification of gradients used for studies of chemotaxis. Nature 239, 517–518.
Goto, T., Nakata, K., Baba, K., Nishimura, M., Magariyama, Y., 2005. A fluid-dynamic interpretation of the asymmetric motion of singly flagellated bacteria swimming close to a boundary. Biophys. J. 89(6), 3771–3779.
Grimm, A., Harwood, C., 1997. Chemotaxis of *Pseudomonas spp.* to the polayaromatic hydrocarbon, napthalene. Appl. Environ. Microbiol. 63, 4111–4115.
Grimson, M., Barker, G., 1994. Continuum model for the spatiotemporal growth of bacterial colonies. Phys. Rev. E 49(2), 1680–1684.
Herpigny, B., Boon, J., Lavalle, R., 1984. Bacterial chemotaxis and band formation: Response to the simultaneous effects of two attractants. Unpublished experimental results.
Hillen, T., Othmer, H., 2000. The diffusion limit of transport equations derived from velocity-jump processes. SIAM J. Appl. Math. 61, 751–775.
Hillesdon, A., Pedley, T., Kessler, J., 1995. The development of concentration gradients in a suspension of chemotactic bacteria. Bull. Math. Biol. 57(2), 299–334.
Hilpert, M., 2005. Lattice-Boltzman model for bacterial chemotaxis. J. Math. Biol. 51(3), 302–332.
Holz, M., Chen, S., 1979. Spatio-temporal structure of migrating chemotactic band of *Escherichia coli*. I. Travelling band profile. Biophys. J. 26, 243–261.
Hornberger, G., Mills, A., Herman, J., 1992. Bacterial transport in porous media: Evaluation of a model using laboratory observations. Water Resour. Res. 28(3), 915–938.
Horstmann, D., 2003a. From 1970 until present: The Keller–Segel model in chemotaxis and its consequences I. Jahresber. DMV 105(3), 103–165.
Horstmann, D., 2003b. From 1970 until present: the Keller–Segel model in chemotaxis and its consequences II. Jahresber. DMV 106(2), 51–69.
Keller, E., Odell, G., 1975. Necessary and sufficient conditions for chemotactic bands. Math. Biosci. 27, 309–317.

Keller, E., Segel, L., 1970. Initiation of slime mold aggregation viewed as an instability. J. Theor. Biol. 26, 399–415.
Keller, E., Segel, L., 1971a. Model for chemotaxis. J. Theor. Biol. 30(2), 225–234.
Keller, E., Segel, L., 1971b. Travelling bands of chemotactic bacteria: A theoretical analysis. J. Theor. Biol. 30(2), 235–248.
Kelly, F., Dapsis, K., Lauffenburger, D., 1988. Effect of bacterial chemotaxis on dynamics of microbial competition. Microb. Ecol. 16(2), 115–131.
Kennedy, C., Aris, R., 1980. Travelling waves in a simple population model involving growth and death. B. Math. Biol. 42, 397–429.
Korobkova, E., Emonet, T., Vilar, J., Shimizu, T., Cluzel, P., 2004. From molecular noise to behavioural variability in a single bacterium. Nature 428, 574–578.
Kreft, J., Booth, G., Wimpenny, J., 1998. Bacsim, a simulator for individual-based modelling of bacterial colony growth. Microbiology 144, 3275–3287.
Lapidus, R., Schiller, R., 1974. A mathematical model for bacterial chemotaxis. Biophys. J. 14, 825–834.
Lapidus, R., Schiller, R., 1975. Bacterial chemotaxis in a fixed attractant gradient. J. Theor. Biol. 53, 215.
Lapidus, R., Schiller, R., 1976. Model for the chemotactic response of a bacterial population. Biophys. J. 16, 779–789.
Lapidus, R., Schiller, R., 1978. A model for travelling bands of chemotactic bacteria. J. Theor. Biol. 22, 1–13.
Lauffenburger, D., Calcagno, B., 1983. Competition between two microbial populations in a nonmixed environment: Effect of cell random motility. Biotech. Bioeng. 25, 2103–2125.
Lauffenburger, D., Aris, R., Keller, K., 1981. Effects of random motility on growth of bacterial populations. Microb. Ecol. 7(3), 207–227.
Lauffenburger, D., Aris, R., Keller, K., 1982. Effects of cell motility and chemotaxis on microbial populations growth. Biophys. J. 40, 209–219.
Lauffenburger, D., Kennedy, C., Aris, R., 1984. Traveling bands of chemotactic bacteria in the context of population growth. B. Math. Biol. 46(1), 19–40.
Lauffenburger, D., Rivero, M., Kelly, F., Ford, R., DiRienzo, J., 1987. Bacterial chemotaxis. cell flux model, parameter measurement, population dynamics, and genetic manipulation. Ann. NY Acad. Sci. 506, 281–295.
Lauga, E., DiLuzio, W., Whitesides, G., Stone, H., 2006. Swimming in circles: motion of bacteria near solid boundaries. Biophys. J. 90(2), 400–412.
Lewus, P., Ford, R., 2001. Quantification of random motility and chemotaxis bacterial transport coefficients using individual-cell and population-scale assays. Biotech. Bioeng. 75(3), 292–304.
Lighthill, J., 1975. Flagellar hydrodynamics: The John von Neumann lecture 1975. SIAM Rev. 18(2), 161–230.
Liu, Z., Papadopoulos, K., 1995. Unidirectional motility of *Escherichia coli* in restrictive capillaries. Appl. Environ. Microbiol. 61(10), 3567–3572.
Lovely, P., Dahlquist, F., 1975. Statistical measures of bacterial motility and chemotaxis. J. Theor. Biol. 50, 477–496.
Macnab, R., Koshland, D., 1972. The gradient-sensing mechanism in bacterial chemotaxis. Proc. Natl. Acad. Sci. 69(9), 2509–2512.
Maini, P., Myerscough, M., Winters, K., Murray, J., 1991. Bifurcating spatially heterogenous solutions in a chemotaxis model for biological pattern formation. Bull. Math. Biol. 53(5), 701–719.
Marx, R., Aitken, M., 1999. Quantification of chemotaxis to naphthalene by *Pseudomonas putida* G7. Appl. Environ. Microbiol. 65(7), 2847–2852.
Marx, R., Aitken, M., 2000. A material balance approach for modelling bacterial chemotaxis to a consumable substrate in the capillary assay. Biotech. Bioeng. 63, 308–315.
Mazzag, B., Zhulin, I., Mogilner, A., 2003. Model of bacterial band formation in aerotaxis. Biophys. J. 85, 3558–3574.
Mesibov, R., Ordal, G., Adler, J., 1973. The range of attractant concentrations for bacterial chemotaxis and the threshold size of response over this range. J. Gen. Phys. 62, 203–223.
Morton-Firth, C., Shimizu, T., Bray, D., 1999. A free-energy based stochastic simulation of the Tar receptor complex. J. Mol. Biol. 286, 1059–1074.
Murray, J., 1993. Mathematical Biology, 2nd edn. Springer, New York.
Newman, T., Grima, R., 2004. Many-body theory of chemotactic cell-cell interactions. Phys. Rev. E 70, 051916.
Nossal, R., 1972. Boundary movement of chemotactic bacterial populations. Math. Biosci. 13, 397–406.

Nossal, R., Weis, G., 1973. Analysis of a densitometry assay for bacterial chemotaxis. J. Theor. Biol. 41(1), 143–147.
Novick-Cohen, A., Segel, L., 1984. A gradually slowly travelling band of chemotactic bacteria. J. Math. Biol. 19, 125–132.
Ockendon, J., Howison, S., Lacey, A., Movchan, A., 1999. Applied Partial Differential Equations. Oxford University Press, Oxford.
Odell, G., Keller, E., 1976. Travelling bands of chemotactic bacteria revisited. J. Theor. Biol. 56, 243–247.
Othmer, H., Dunbar, S., Alt, W., 1988. Models of dispersal in biological systems. J. Math. Biol. 26, 263–298.
Patlak, C., 1953. Random walk with persistence and external bias. Bull. Math. Biophys. 15, 311–338.
Pedit, J., Marx, R., Miller, C., Aitken, M., 2002. Quantitative analysis of experiments on bacterial chemotaxis to naphthalene. Biotech. Bioeng. 78(6), 626–634.
Pedley, T., Kessler, J., 1992. Hydrodynamic phenomena in suspensions of swimming microorganisms. Annu. Rev. Fluid Mech. 24, 313–358.
Pfeffer, W., 1888. Uber chemotaktische bewegungen von bacterien, flagellaten and volvocineen. Untersuch. Bot. Inst. Tübingen 2, 582.
Ramia, M., Tullock, D., Phan-Thien, N., 1993. The role of hydrodynamic interaction in the locomotion of microorganisms. Biophys. J. 65, 755–778.
Reynolds, P., Sharma, P., Jenneman, G., McInerney, M., 1989. Mechanisms of microbial movement in subsurface materials. Appl. Environ. Microbiol. 55(9), 2280–2286.
Rivero, M., Tranquillo, R., Buettner, H., Lauffenburger, D., 1989. Transport models for chemotactic cell populations based on individual cell behaviour. Chem. Eng. Sci. 44(12), 2881–2897.
Rivero-Hudec, M., Lauffenburger, D., 1986. Quantification of bacterial chemotaxis by measurement of model parameters using the capillary assay. Biotech. Bioeng. 28, 1178–1190.
Romagnoli, S., 2002. Role of redoc sensing in controlling *Rhodobacter sphaeroides* swimming behaviour. PhD thesis, Department of Biochemistry, University of Oxford.
Rosen, G., 1973. Fundamental theoretical aspects of bacterial chemotaxis. J. Theor. Biol. 41, 201–208.
Rosen, G., 1974. On the propagation theory for bands of chemotactic bacteria. Math. Biosci. 20, 185–189.
Rosen, G., 1975. Analytical solution to the initial value problem for traveling bands of chemotactic bacteria. J. Theor. Biol. 49, 311–321.
Rosen, G., 1976. Existence and nature of band solutions to generic chemotactic transport equations. J. Theor. Biol. 59, 243–246.
Rosen, G., 1983. Theoretical significance of the condition $\delta = 2\mu$ in bacterial chemotaxis. Bull. Math. Biol. 45(2), 151–153.
Rosen, G., Baloga, S., 1975. On the stability of steadily propagating rings of chemotactic bacteria. Math. Biosci. 24, 273–279.
Rosen, G., Baloga, S., 1976. On the structure of steadily propagating rings of chemotactic bacteria. J. Mechanochem. Cell Motility 3, 225–228.
Schnitzer, M., 1993. Theory of continuum random walks and application to chemotaxis. Phys. Rev. E 48(4), 2553–2568.
Schnitzer, M., Block, S., Berg, H., Purcell, E., 1990. Strategies for chemotaxis. Symp. Soc. Gen. Microbiol. 46, 15–34.
Scribner, T., Segel, L., Rogers, E., 1974. A numerical study of the formation and propagation of travelling bands of chemotactic bacteria. J. Theor. Biol. 46, 189–219.
Segel, L., 1976. Incorporation of receptor kinetics into a model for bacterial chemotaxis. J. Theor. Biol. 57, 23–42.
Segel, L., 1977. A theoretical study of receptor mechanisms in bacterial chemotaxis. SIAM J. Appl. Math. 32(3), 653–665.
Segel, L., Jackson, L., 1973. Theoretical analysis of chemotactic movements in bacteria. J. Mechanochem. Cell Motility 2, 25–34.
Setayeshgar, S., Gear, C., Othmer, H., Kevrekidis, I., 2005. Application of coarse integration to bacterial chemotaxis. Multiscale Model. Simul. 4(1), 307–327.
Stroock, D., 1974. Some stochastic processes which arise from a model of the motion of a bacterium. Z. Wahrsch. Verw. Geb. 28, 305–315.
Tindall, M., Porter, S., Maini, P., Gaglia, G., Armitage, J., 2007. Overview of mathematical approaches used to model bacterial chemotaxis I: The single cell. Bull. Math. Biol., submitted.
Wadhams, G., Armitage, J., 2004. Making sense of it all: bacterial chemotaxis. Nat. Rev. Mol. Cell Biol. 5(12), 1024–1037.

Widman, M., Emerson, D., Chiu, C., Worden, R., 1997. Modelling microbial chemotaxis in a diffusion gradient chamber. Biotech. Bioeng. 55(1), 191–205.
Zhu, M., Murray, J., 1995. Parameter domains for generating spatial pattern: A comparison of reaction-diffusion and cell-chemotaxis models. Int. J. Bifurc. Chaos 5(6), 1503–1524.
Zhulin, I., Bespalov, V., Johnson, M., Taylor, B., 1996. Oxygen taxis and proton motive force in *Azospirillum brasilense*. J. Bacteriol. 178, 5199–5204.