ANALYSIS OF CHEMOTACTIC BACTERIAL DISTRIBUTIONS IN POPULATION MIGRATION ASSAYS USING A MATHEMATICAL MODEL APPLICABLE TO STEEP OR SHALLOW ATTRACTANT GRADIENTS

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The mathematical model developed by Rivero et al. (1989, Chem. Engng Sci. 44, 2881-2897) is applied to literature data measuring chemotactic bacterial population distributions in response to steep as well as shallow attractant gradients. This model is based on a fundamental picture of the sensing and response mechanisms of individual bacterial cells, and thus relates individual cell properties such as swimming speed and tumbling frequency to population parameters such as the random motility coefficient and the chemotactic sensitivity coefficient. Numerical solution of the model equations generates predicted bacterial density and attractant concentration profiles for any given experimental assay. We have previously validated the mathematical model from experimental work involving a step-change in the attractant gradient (Ford et al., 1991 Biotechnol. Bioengng, 37, 647-660; Ford and Lauffenburger, 1991, Biotechnol. Bioengng, 37, 661-672). Within the context of this experimental assay, effects of attractant diffusion and consumption, random motility, and chemotactic sensitivity on the shape of the profiles are explored to enhance our understanding of this complex phenomenon. We have applied this model to various other types of gradients with successful interpretation of data reported by Dalquist et al. (1972, Nature New Biol. 236, 120-123) for Salmonella typhimurium validating the mathematical model and supporting the involvement of high and low affinity receptors for serine chemotaxis by these cells.

1. Introduction. Bacterial chemotaxis, the ability of bacteria to direct their migration toward increasing concentrations of attractants (e.g. amino acids and sugars) and away from repellents (e.g. alcohols and metabolites) has intrigued many investigators since its first reported observation over a century ago (Engelmann, 1881). An informative method for studying this phenomenon is the population migration assay in which the spatial distribution of cells in stimulus gradients is monitored as a function of time. Examples of this approach include work by Alder (1966), Dalquist et al. (1972, 1976), Holz and Chen (1979), and Boon and Herpigny (1986). However, the distributions observed depend on the specific gradients present in each assay, so the

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experimental results are not generalizable beyond that particular assay. Furthermore, these population observations cannot be simply related to fundamental mechanistic properties of individual cell responses. What is desired is a way to interpret these informative assays in terms of fundamental parameters that are generalizable to bacterial populations in natural environments.

This migratory behavior of bacterial populations is believed to play a significant role in many microbial ecological processes (Chet and Mitchell, 1976) such as nitrogen fixation (Gulash et al., 1984; Armitage et al., 1988), denitrification (Kennedy and Lawless, 1985), pathogenesis of infection (Freter et al., 1979) and the development of biofilms (Chet et al., 1975; Gristina, 1987). A quantitative characterization of the chemotactic response in terms of intrinsic cell properties is necessary for making reliable predictions about the migratory behavior of bacterial populations influencing these processes.

Chemotaxis also plays a critical role in the distribution and dynamic interaction of bacterial populations within the environment. Lauffenburger and co-workers (Lauffenburger et al., 1982; Lauffenburger and Calcagno, 1983; Kelly et al., 1988; Lauffenburger, 1988) have analyzed the effects of motility and chemotaxis on bacterial population growth and competition; they showed that chemotaxis could provide a competitive advantage to a slower growing species allowing it to co-exist and even outgrow species having more favorable growth kinetics. Their approach illustrates the usefulness of mathematical modeling as a tool for interpreting experimental data in terms of intrinsic cell properties that can be used to make predictions of migration behavior outside the controlled environment of the laboratory.

To develop appropriate mathematical models requires understanding how an individual cell senses and responds to chemical gradients which it encounters as it explores its ecological niche. The swimming behavior of peritrichously flagellated bacteria such as *Escherichia coli* and *Salmonella typhimurium* is described as a series of straight line "runs" periodically interrupted by "tumbles" which result in random changes of direction between runs (Berg and Brown, 1972; Macnab and Koshland, 1972; Spudich and Koshland, 1975). Runs last for several seconds while tumbles are only a fraction of a second in duration. For typical cell speeds of 10–30 \( \mu m/sec \), run lengths of 10–20 cell diameters are common (Berg and Brown, 1972). In the absence of a chemical gradient, the path resembles a three-dimensional random walk similar to Brownian motion in molecular diffusion. In the presence of a chemical attractant gradient, cells are able to decrease their frequency of tumbling when moving in a favorable direction (Macnab and Koshland, 1972; Spudich and Koshland, 1975). This increases the run lengths in that direction and results in net migration toward environments more favorable to growth and survival.