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Stochastic Aspects of Biological Locomotion

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Various aspects of random walks undertaken by motile bacteria and migrating leukocytes are discussed, including the motions of these cells when responding to gradients of chemoattractants. Brief reference also is made to studies of particle movements within the cytoplasm of eucaryotic cells.

KEY WORDS: Random walks; bacterial motility; leukocyte chemotaxis; cytoplasmic streaming.

1. INTRODUCTION

The purpose of this note is to introduce several areas in cell biology where stochastic motion has been observed and analytically characterized. Most of the discussion concerns the locomotion of flagellated bacteria and motile blood cells, but the intracellular movement of cytoplasmic granules and the ciliary transport of oocytes in the mammalian oviduct also are mentioned. The discussion necessarily is abbreviated, and the interested reader is urged to refer to the several topical reviews which are provided as references.

2. SWIMMING BACTERIA

Many bacterial species have a propulsive apparatus which enables them to swim. Perhaps the best studied examples are the gram negative bacteria *Escherichia coli* and *Salmonella typhimurium*, certain strains of which exhibit altered locomotion when moving in media containing

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gradients of organic substances, such as various sugars and amino acids, which act as "chemoattractants." Excellent reviews recently have been published which discuss aspects of the cellular physiology and behavioral response,[1-3] the genetic determinants of the motile apparatus,[4] and the biochemical mechanism of chemoexcitation[5] of these microorganisms.

Bacteria swim by the action of rigid "flagella," approximately 200 Å in diameter and of the order of 10^4 Å in length, which are helical polymers composed mainly of a structural protein called flagellin. A flagellum is connected to the body of a bacterium by a rotor which turns while the bacterium literally screws its way through the medium in which it is immersed. [A recent paper by Purcell[6] contains an illuminating discussion of the physics of such motion.] Each bacterium usually contains several flagella which, when conditions are favorable, move in a coordinated fashion and form a propulsive bundle. In this instance the helical flagella all rotate with the same "handedness" (e.g., counterclockwise when viewed in a reference frame where the flagella are tethered at their distal ends). At other times, though, some or all of the flagella reverse direction and even undergo conformational changes[3]; the bundle becomes tangled and disorganized, and the bacterium tosses about and tumbles instead of moving forward.

When a bacterium perceives itself to be in an environment where the chemoattractant concentration is temporally increasing, the coordinated rotation of the flagella is sustained for a relatively long interval and the cell's locomotion continues without change.[7,8] If, however, the average chemoattractant concentration is locally constant or decreasing with time, the flagellar bundle has a tendency to come apart; after a few seconds the bundle reforms, but the cell then moves off in a different direction. Consequently, if a bacterium is moving "up a gradient" of chemoattractant, i.e., towards a chemotactic source, it will continue on its path for a longer duration than if it is moving away from the source.

Using an ingeniously designed tracking microscope, Berg *et al.*[9,10] have analyzed the movements of individual bacteria when they were moving in a chemical field. The trajectories were discerned to be essentially straight-line paths separated by discrete turns. The length of the path segments, the angle between turns, and the time spent in tumbling, all are random variables. If the bacteria move towards a source of chemoattractant, they indeed move, on average, for longer intervals before stopping than when they move away from the source. When characterized in this discrete "course-grained" fashion, the run times $\{\tau\}$ appear to be exponentially distributed. The latter can be inferred, also, for a continuous distribution of angles: Using data obtained for the motion of bacteria in spatially uniform, but temporally increasing, chemoattractant concentrations,[8] it

can be shown that the run time distribution is given approximately as[11]

$$P(\tau \mid \varphi, \nu) = \lambda(\varphi, \nu) e^{-\lambda(\varphi,\nu)\tau} \tag{1}$$

where

$$\langle \lambda \rangle^{-1} \cong \begin{cases} \lambda_0^{-1}\left(1 + \dfrac{\alpha K_D}{(K_D + C)^2}\, \boldsymbol{\nu} \cdot \nabla C\right) & \text{if} \quad \varphi < \pi/2 \\ \lambda_0^{-1} & \text{if} \quad \varphi \geqslant \pi/2 \end{cases} \tag{2}$$

In Eq. (2), λ_0 and α are intrinsic mechanistic constants, C is the chemoattractant concentration, K_D is the dissociation constant for binding of chemoattractant to receptors on the surface of the bacteria, $\boldsymbol{\nu}$ is the cell velocity, and φ is the angle between $\boldsymbol{\nu}$ and the chemical field vector.

The turn angle distribution is found to be symmetric with respect to the direction of motion prior to a turn, and uncorrelated with the gradient vector of the chemical field. In the absence of any definitive data to the contrary, mathematical analyses of bacterial trajectories[11–13] have contained assumptions, in addition, that the locomotion of a cell is Markovian (i.e., that the probability of responding to a chemical stimulus depends only on the position and velocity of a cell at a given time), that the speeds exhibited by a cell on successive paths are uncorrelated (which neglects the fact that some individuals may swim faster than others), that the tumbling periods of the cell also are uncorrelated with any other variable, and that the system is stationary (i.e., the bacteria don't get tired!).

The above assumptions and observations allow simple and straightforward mathematical techniques to be used to relate macroscopic transport variables to the stochastic distributions derived from the trajectories of individual cells. Thus, when the timescale of observations of macroscopic motion are long compared with the timescales characterizing the microscopic movement of the cells, the equation of motion for cell density $b(t)$ can be taken to be a modified diffusion equation,[14]

$$\frac{\partial b(\mathbf{r}, t)}{\partial t} = \mu \nabla^2 b - \nabla \cdot \left[\boldsymbol{\nu}_d(\mathbf{r}, t) b\right] + G(\mathbf{r}, t) \tag{3}$$

where μ is a mobility coefficient, $\boldsymbol{\nu}_d$ is the chemotactic drift velocity, and $G(\mathbf{r}, t)$ is a source term which accounts for cell growth. Because $\boldsymbol{\nu}_d(\mathbf{r}, t)$ depends on the chemoattractant gradient, matters become quite complicated mathematically when the gradient is caused by the metabolic activity of the cells. Nonetheless, equations of this nature have been used satisfactorily to describe the growth and motion of "chemotactic bands" and "rings" in laboratory media[14,15] and the accumulation of bacteria in ecological models. Based on studies of the way receptor occupancy affects the

persistence of coordinated motion of bacteria moving in temporally changing media,[8] the function ν_d can be shown to be[11]

$$\nu_d = \frac{\alpha\langle v^2\rangle}{4(1+\lambda_0\tau_w)} \frac{K_D C}{(K_D + C)^2} \nabla \ln C \tag{4}$$

where $\langle v^2\rangle$ is the second moment of the swimming speed distribution and τ_w is the average time spent in tumbling between turns. [The other symbols have the same meaning as in Eq. (2), above.]

Bacteria are very difficult to track because of their small size and relatively large speed. Few laboratories have the necessary equipment, and data on microscopic trajectories of swimming bacteria thus are relatively sparse. It is methodologically much simplier to track large, slowly crawling cells such as PMN leukocytes. The latter have been intensely studied because they show chemotactic response to a variety of chemoattractants which are of great immunological significance, including substances exuded by infectious bacteria.

The locomotory response of amoeboidlike crawling cells will be discussed in the next section. Before continuing, however, we wish to emphasize that the locomotion of flagellated eucaryotic cells (cells which have nuclear membranes), such as spermatozoa and certain algae, swim by a much different mechanism: Propulsion takes place by a 2000-Å-thick flagellum which contains an exquisite interior structure of filaments which slide with respect to each other and generate bending cycles in the flagellum.[16,17] The chemosensory response of such microorganisms recently has been reviewed by Levandowsky and Hauser.[18]

3. POLYMORPHONUCLEAR LEUKOCYTES

The movement of polymorphonuclear leukocytes ("PMN" cells) induced by chemical stimuli is an important factor in an animal's immunological response to infection or injury.[19] Most laboratory assays of PMN chemotaxis involve observations of macroscopic cell accumulation,[11,19] from which attempts frequently are made to deduce physiological mechanisms which underly changes in intrinsic cell behavior. However, the means by which cells change their morphology, extend pseudopods, and thereby move in response to chemical gradients are not yet well understood. Thus, in addition to clarifying the significance of the response noted in macroscopic measurements, studies of the microscopic details of locomotion can provide data necessary for elucidating basic mechanisms of cytoskeletal adaptations.

Here, too, locomotion fundamentally is stochastic in character. Tracks of locomoting PMN cells are determined by following the center of a cell or

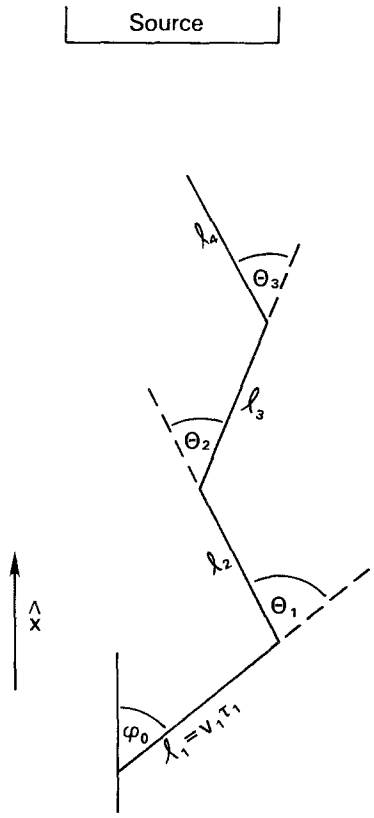

Fig. 1. Parameters used to describe a random walk undertaken by PMN leukocytes migrating towards a chemoattractant source (see text).

the position of the nucleus from a series of successive time-lapse photographs. The trajectories can be represented as in Fig. 1, for which associated probability densities of interest are[20,21] the conditional turn angle distribution $P(\theta \mid \varphi)$, the run length distribution $P(\tau)$, and the speed distribution $p(v)$.

As in the case of bacteria, the turn angle distribution is symmetric when the environment is spatially symmetric.[21,23] However, when leukocytes move in a chemotactic field, the turn angle distribution strongly depends on the direction of locomotion prior to a turn,[20,21] and the cells seem to zig-zag towards the source as they move. If a cell is moving obliquely to a chemotactic gradient, it has a strong tendency to turn towards the source[20,21] and, the greater that a cell's direction vector deviates from the direction of the gradient maximum, the greater the

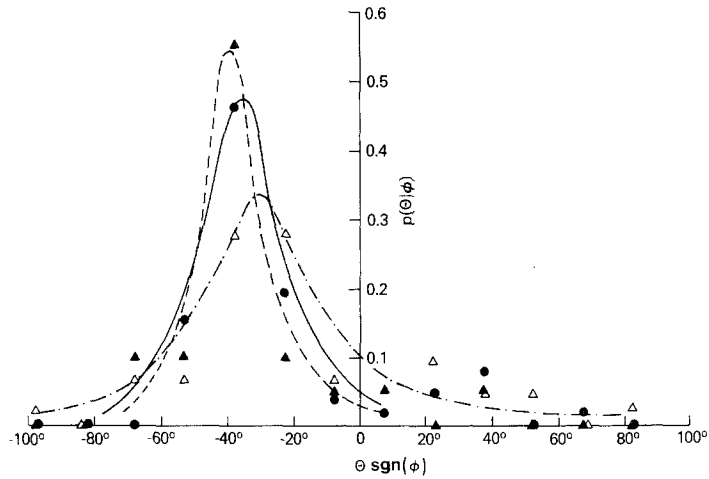

Fig. 2. Conditional turn angle distribution for PMN leukocytes. Cells usually turn towards the chemotactic source and thus undergo zig-zag locomotion. Note that the average angle of turn increases as the angle describing the direction of motion prior to the turn, φ, increases. (Key—△: $0° \leqslant |\varphi| \leqslant 15°$; ●: $15° < |\varphi| \leqslant 30°$; ▲: $30° < |\varphi| \leqslant 45°$.) (See Ref. 21.)

average magnitude of the compensatory turn (see Fig. 2). Also, the run lengths do *not* seem to depend on other stochastic variables.[20]

In order to investigate certain questions concerning the manner in which changes in the stochastic parameters of motion affect the observed macroscopic response of a collection of cells, the turn angle distribution can be characterized as[21,23]

$$p(\theta \mid \varphi) = p(\theta + f(\varphi)) \tag{5}$$

where $p(\theta)$ is the turn angle distribution in the absence of chemoattractant and $f(\varphi)$ is an asymmetric function of φ [e.g., $f(\varphi) \sim \text{sgn}(\varphi)$]. Using Eq. (5), one can examine the dependence of various chemotactic response coefficients on factors such as the offset bias $f(\varphi)$ and the shape of $p(\theta)$.[11,21] For example, one finds that cells can turn too sharply when compensating for their wandering behavior, so net movement towards a source can be less than when more modest turns are made. Cell biologists, who tend to measure chemotactic response by observing cell orientations or accumulations, often explain decreased responsiveness in strong chemoattractant gradients in terms of "saturation of receptors"; however, only by observing the detailed stochastic character of the macroscopic trajectories may other explanations definitely be disregarded.

Very little currently is known about the basic bio*physics* of amoeboid locomotion and chemotactic responsiveness. Many of the various molecules

involved in the polymerization of cytoskeletal structures recently have been isolated and identified,[24–26] but not much is understood yet about the transduction of the chemotactic signal and the way subsequent cell shape changes are related to the dynamic anatomical architecture of the cell. Although microtubules seem to be involved in determining the polarity of cell structural changes,[25,27,28] a substantive mechanistic model needs to be developed and tested. In this regard Alt[29] proposes that the turn angle probability distribution be expressed as

$$p(\theta \mid \varphi) \sim p(\theta) F(s_\theta(\varphi)) \tag{6}$$

where $p(\theta)$ is the turn angle distribution in the absence of chemoattractant. $s_\theta \sim B(C)\cos(\varphi + \theta)\,|\nabla C|$ represents the change in some internal substance in the cell arising from the binding of chemoattractant C at the cell outer membrane, and $F(x)$ is a nonlinear function characterizing a threshold response for pseudopod extension. By slight reinterpretation of the data shown in Fig. 2, Alt's model can be fitted with consistent parameters. Alt[29,30] has also carefully investigated the circumstances under which a diffusionlike equation, rather than a more complicated transport equation, in fact can be used to describe cell migration.

Unfortunately, one of the difficulties in developing mechanistic models for amoeboid chemotaxis is that many complicating details are still being uncovered. These are discussed in recent reviews by Snyderman and Goetzl,[25] Zigmond,[31] and Schiffmann,[32] and include possible degradation of chemoattractant at the cell surface and the "down-regulation" of receptors (i.e., a decrease, perhaps by internalization, in the number of effective receptors after binding). But, an important question which can be profitably examined with only incomplete knowledge of physiological mechanisms is whether a leukocyte senses and responds to a spatial or, rather, a temporal gradient during chemotaxis. Berg *et al.*[8,33] showed that *bacteria* respond to temporal changes, which is logical because thermally induced fluctuations in chemoattractant concentration near the cell surface are comparable to the differences in average concentration which, for typical gradients, occur across the dimensions of a bacterium. Leukocytes, however, are an order of magnitude larger, and therefore might be able to detect spatial gradients directly.[20]

Berg and Purcell[33] and DeLisi, Marchetti, and Del Grosso[34] recently have considered this problem by assuming that a cell recognizes its environment by detecting the fractional occupancy of chemoreceptors distributed over its surface, and averaging the result over some limited time period. The fraction of occupied sites at any given time t is described as[34]

$$I(t) = N_0^{-1} \sum_{i=1}^{N_0} X_i(t) \tag{7}$$

where $X_i(t)$ is a random variable which has a value of 1 if the ith receptor is bound, and 0 otherwise. Assuming that the cell integrates information over a time T (starting at t_1), an estimate of the concentration is obtained as

$$I_T = \frac{1}{T}\int_{t_1}^{t_1+T} I(t)\,dt \tag{8}$$

DeLisi *et al.*[34] then compute the mean-square deviation $\sigma^2 = \langle I_T^2\rangle - \langle I_T\rangle^2$ based on a general model for chemoattractant binding to receptors. They show how the relative error in receptor binding $\sigma^2/\langle I_T\rangle$, which is related to the relative mean square error in detecting mean chemoattractant concentration $\Delta c/\bar{c}$, decreases with increasing measurement time T. When chemoattractant concentration near a cell is unaffected by binding to receptors, the authors conclude that, unless the reaction time between attractant and receptor is diffusion limited, the time required to determine a temporal gradient is much shorter than that necessary to ascertain a spatial gradient. A central point in the argument is the supposition, earlier introduced by Berg and Purcell,[33] that a necessary condition for reliable determination of a temporally varying signal is $(T/\bar{c})(\partial\bar{c}/\partial t) > \sqrt{2}\,\Delta c/\bar{c}$, i.e., that the difference in chemoattractant concentration detected over the measurement time T be greater than the statistical fluctuation in chemoattractant concentration. The analogous criterion for direct spatial detection is that $(a/\bar{c})(\partial\bar{c}/\partial x) > \sqrt{2}\,\Delta c/\bar{c}$, where a is the cell dimension.

4. OTHER CELL MOTIONS

The interior of an amoeboidlike cell is far from quiescent during periods of locomotion. Time lapse photographs of moving PMN cells indicate that the edges of advancing pseudopods are in constant turmoil, from which one infers similar motion in the interior of the cell. Studies of giant amoeboid cells—notably *Chaos carolinensis*, whose lengths can exceed 0.2 mm—show that the motion of cytoplasm is closely linked with locomotion. Birefringence microscopy of the interior of these cells indicates that cytoplasm exists in various states of polymerization in different regions and, by observing the motion of large intracellular particles, one finds that the pattern of interior cytoplasmic flow also depends on details of cytoplasmic morphology.[35]

The motion of granules within the cytoplasm of stationary cells has been studied for many years. Particles within many different types of marine eggs, and in certain types of cells in culture, are readily seen to "saltate": that is, the particles occasionally make large, rapid, jumps in addition to the Brownian motion which is more or less continuously observed. Various aspects of saltatory motion, such as the pauses between

jumps and the speeds and distances moved, have a stochastic character. Descriptions of such movements can be found in the references given by Rebhun[36] in his extensive review of the subject.

This peculiar motion of cytoplasmic granules undoubtedly is related to interactions with the cell cytoskeleton, and by studying granule movement one hopes to gain some insight into the structure and polymerization kinetics of the cytoskeleton. The intracellular movement of particles along nerve axons has been extensively investigated (see the recent review by Grafstein and Forman[37]). Recent cinematographic studies[38] show that movement predominantly is along the longitudinal axis of the axon, indicating the influence of the extensive system of microfilaments and microtubules which extend along the nerve. The movement of mitochondria and large vesicles is saltatory; particles move in both directions, although for each particle there is a preferred direction.

Egg transport in the rabbit oviduct also has been characterized as a one-dimensional random walk with bias,[39] and the overall macroscopic motion of migrating eggs has been described by a Langevin equation. Such statistical observations have been used to test various models of oocyte transport, enabling assessment of the influence of such factors as ciliary movements, viscous forces, and muscular contractions of the oviduct.

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