

A Stochastic Model for Leukocyte Random Motility and Chemotaxis Based on Receptor Binding Fluctuations

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Abstract. Two central features of polymorphonuclear leukocyte chemosensory movement behavior demand fundamental theoretical understanding. In uniform concentrations of chemoattractant, these cells exhibit a persistent random walk, with a characteristic “persistence time” between significant changes in direction. In chemoattractant concentration gradients, they demonstrate a biased random walk, with an “orientation bias” characterizing the fraction of cells moving up the gradient. A coherent picture of cell movement responses to chemoattractant requires that both the persistence time and the orientation bias be explained within a unifying framework. In this paper, we offer the possibility that “noise” in the cellular signal perception/response mechanism can simultaneously account for these two key phenomena. In particular, we

develop a stochastic mathematical model for cell locomotion based on kinetic fluctuations in chemoattractant/receptor binding. This model can simulate cell paths similar to those observed experimentally, under conditions of uniform chemoattractant concentrations as well as chemoattractant concentration gradients. Furthermore, this model can quantitatively predict both cell persistence time and dependence of orientation bias on gradient size.

Thus, the concept of signal “noise” can quantitatively unify the major characteristics of leukocyte random motility and chemotaxis. The same level of noise large enough to account for the observed frequency of turning in uniform environments is simultaneously small enough to allow for the observed degree of directional bias in gradients.

POLYMORPHONUCLEAR neutrophil leukocytes (PMNs)¹ are the class of motile white blood cells that rapidly accumulate at sites of inflammation. The first observations of chemotaxis, the phenomenon in which PMNs crawl towards higher concentrations of soluble stimuli (chemoattractants) which bind to specific surface receptors, were made a century ago (5). A variety of *in vitro* assays have since been developed to study this chemosensory movement, and understanding of its underlying biochemical foundations has continued to grow. However, an examination of leukocyte paths as they crawl in response to chemoattractants raises several open questions.

In uniform chemoattractant concentrations, cell movement continues in the same general direction over the time scale of minutes (1), a phenomenon termed “directional persistence.” On a longer time scale, the cell path has an irregular appearance, and can be adequately described as a random walk (3). The features of this persistent random walk in uni-

form concentrations, termed random motility, are evident in Fig. 1 A.

In concentration gradients of chemoattractant, cells can exhibit biased movement in the direction of the gradient (6). Although the cell paths still feature a noticeable degree of randomness, the gradient evidently presents a directional signal to the cell which results in biased cell movement up a gradient. These features of a biased random walk in a chemoattractant gradient, termed chemotaxis, are evident in Fig. 1 B.

Given these observations, the following critical questions arise. Why do cells change direction randomly in uniform concentrations of chemoattractant? Why do cells sometimes move in the wrong direction in concentration gradients of chemoattractant? Further, is there a relationship between directional persistence in uniform concentrations and accuracy of biased orientation in gradients? We propose that one underlying concept can answer these questions and account for both random and chemotactic movement.

Our fundamental premise is that there exist stochastic elements within the mechanisms by which cells perceive and respond to receptor binding events. That is, random fluctuations arise in the variety of processes involved in the cell response, such as chemoattractant-receptor binding, transduction of intracellular signals, and locomotion generated by

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1. *Abbreviations used in this paper:* FNLLP, *N*-formylnorleucylleucylphenylalanine; PMN, polymorphonuclear neutrophil leukocyte.

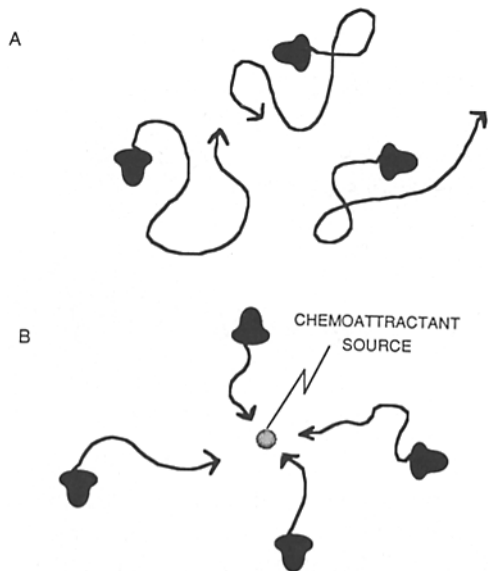


Figure 1. Representative tracings of leukocyte paths in (A) random motility and (B) chemotaxis. Actual tracings can be found in references 1 and 6.

these signals. Although this concept is quite reasonable given the small numbers of molecules involved in cellular phenomena, rigorous assessment of its merits requires a quantitative examination of the effects of putative fluctuations in the various cell sensory and response processes on movement behavior. Such an examination in turn requires quantitative information on the magnitude of fluctuations expected in each process. Presently, the only process understood well enough to do this is the chemoattractant-receptor binding event. Therefore, in this paper we will base our examination of this concept on receptor binding fluctuations.

Because cell receptor binding is inherently a stochastic process, receptor binding fluctuations (which can be thought of as errors in cell perception of chemoattractant concentration) must exist. These fluctuations must then result in fluctuations in the intracellular signals generated by receptor binding, whatever they may be. If these fluctuations are significant relative to the criteria that influence the direction of cell locomotion, then cell movement paths will exhibit some degree of randomness. Therefore, the basic idea behind our stochastic model of this biological guidance system is that noise inherent in receptor-sensing underlies the random directional component of cell paths. As illustrated in

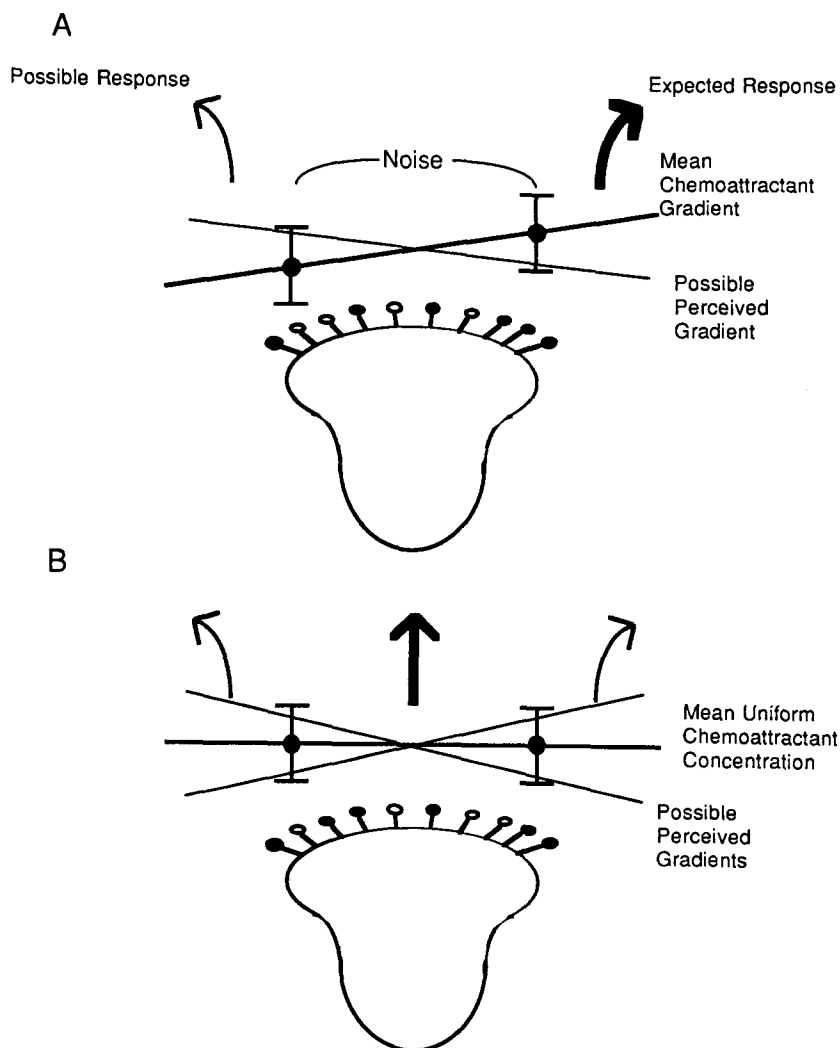


Figure 2. Receptor noise as the unifying concept for the component of directional randomness observed for cell paths in random motility and chemotaxis. The receptor population on the lamellipodium of the cell is divided into two. Each subpopulation perceives fluctuating concentrations (represented by the error bars) around the true local concentration (indicated by the closed circles) in its receptor measurement of concentration. (A) Chemotaxis: the cell is subject to a mean gradient with each subpopulation perceiving, in general, statistically different fluctuations from the true local concentrations. At any instant, the cell perceives some deviation from the true gradient and may even perceive a gradient in the reverse direction. (B) Random motility: each subpopulation is constantly subject to the same mean concentration and perceives the same statistical fluctuations. Thus, the cell perceives fluctuating gradients without a mean reference direction.

Fig. 2, we suggest that the persistent unbiased random walk characteristic of random motility in uniform environments arises from fluctuating perceived gradients in the absence of a mean gradient, whereas the biased random walk observed for chemotactic behavior in gradient environments results from perceived fluctuations around the mean gradient.

Our approach requires conferring the cell with some sort of intracellular response mechanisms through which the receptor signal is transduced and from which directional change occurs. Since the details of these mechanisms are as of yet unclear, it is best at present to be quite general in this respect. This level of abstraction carries the advantage of allowing some fundamental understanding to be gained without dependence on specific assumptions about response mechanisms that may then be proved invalid.

Here, we provide a brief characterization of receptor signal noise and demonstrate its significance, and then assess its consequences by summarizing an analysis of a stochastic model of chemosensory cell movement suggested by Fig. 2. Although we focus on PMNs here, we hope that understanding the salient mechanisms by which these cells bias their movement in chemoattractant gradients may also aid in understanding the chemosensory-directed movement of many chemotactic mammalian cells and, further, elucidate general mechanisms of signal-response coupling in many types of receptor-mediated cell function.

Receptor Signal Noise

We have previously presented a quantitative analysis of receptor binding fluctuations (11), which we summarize here. In the absence of receptor binding fluctuations, the instantaneous fractional occupancy, I , of cell receptors will be equal to the mean fractional occupancy, p . At equilibrium, p is given by the familiar expression

$$p = \frac{C}{K_d + C}, \quad (1)$$

where K_d is the equilibrium dissociation constant for the receptor complex. Thus, in the absence of fluctuations, cells could “measure” the local chemoattractant concentration, C , according to a rearrangement of Eq. 1:

$$C = K_d \frac{p}{1 - p}. \quad (2)$$

This ability could allow it to respond in a directional manner to gradients in C across a cell dimension. However, since receptor-ligand binding is a stochastic process, I will exhibit random deviations from p , so that the perceived concentration will exhibit random fluctuations around C . At $C = K_d$, the relative standard deviation of these fluctuations, estimated from an equilibrium perspective, will be $\sim 2\%$. This result was obtained (11) for 10,000 total receptors for the chemotactic peptide *N*-formylnorleucylleucylphenylalanine (FNLLP) on PMNs (8), which serves as our experimental test system. It must also be demonstrated that this magnitude of receptor signal noise could be of significance. That is quite easy to do given the observation that PMN can orient with high accuracy in FNLLP gradients across their dimension corresponding to a concentration difference of $<1\%$ across a cell dimension (12). Thus, the fluctuations in perceived

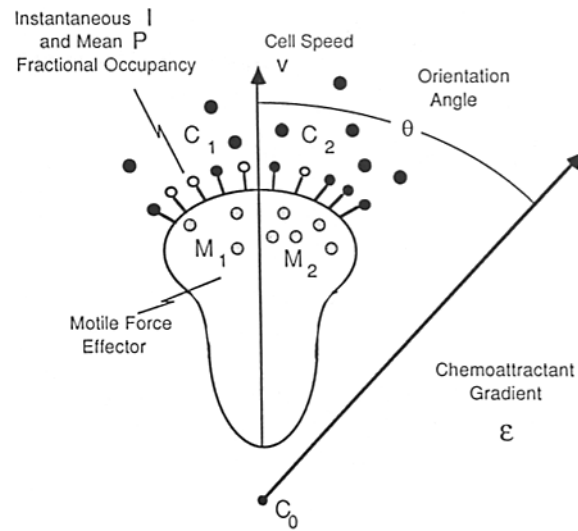


Figure 3. Stochastic model of chemosensory cell movement. The model cell translates along its polarity axis with constant speed and turns in the gradient at a rate proportional to the difference in the motile force effector, M , between the two compartments of the idealized lamellipodium. M is generated with rate proportional to the instantaneous number of bound receptors, $I \cdot N_T$, which fluctuates around the associated mean occupancy, $p \cdot N_T$, determined by the cell path. M also transports between the compartments and is degraded.

concentration due to stochastic receptor binding are of the same magnitude as concentration gradients leading to a directional response. This lends credence to the picture shown in Fig. 2. More complicated mathematical analyses, which estimate the magnitude of fluctuations from a kinetic perspective, also find that the fluctuations are of sufficient size to be capable of influencing orientation behavior (2, 9).

Model Description

The biological basis for the assumptions of the model to be analyzed, illustrated in Fig. 3, has been discussed in detail elsewhere (10, 11). We assume that a cell always maintains its polarity as it makes directional changes and that the constant forward movement of the cell can be uncoupled from the turning behavior. The lamellipodium, where directional changes are assumed to arise, is modeled as two interacting compartments. Considering the transduced receptor signal to be the critical regulator of the motility system, the turning rate of the cell can be related to an imbalance of the transduced receptor signals between the two compartments. The generation of the transduced receptor signal itself is related to the stochastic receptor binding process on the cell surface and, therefore, the response of the cell as it translates and turns in a chemoattractant gradient.

The modeling equations for the specific mechanisms chosen to illustrate the general model based on receptor signal noise are included in the Appendix. For the transduction mechanism, the intracellular messenger, M (i.e., the transduced receptor-signal), which is considered to be the critical regulator of the motility system (e.g., an ion or nucleotide), is generated at a rate proportional to the number of bound receptors, N_b , with first-order transduction rate constant, k_t ,

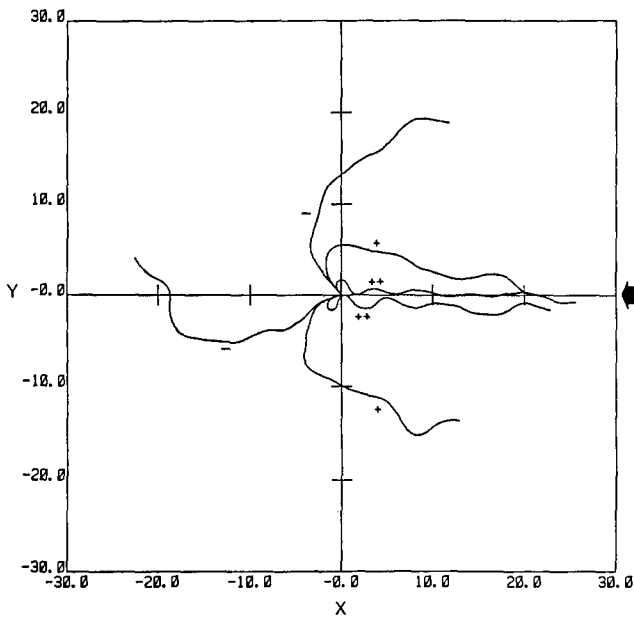


Figure 4. Sample paths for two model cells in the x - y plane. Both cells begin at the origin having one of two initial directions and move for 7.5 min in the absence of a gradient (random motility: -, $\epsilon = 0$), or presence of a small (chemotaxis: +, $\epsilon = 0.008$) or large (chemotaxis: ++, $\epsilon = 0.08$) gradient. The driving noise underlying the paths is constant for each set of the simulations.

decays according to first-order kinetics with decay rate constant, k_d , and is transported between compartments at a rate proportional to the difference in M with diffusive rate constant, D (Eq. A2). The turning rate of the cell due to an imbalance of motile force between the compartments is proportional to the difference in M between the two compartments with turning sensitivity coefficient, κ (Eq. A1). The receptor population of total N_r in each compartment binds chemoattractant at the local bulk concentration, C , determined by the path of the cell through the concentration field (Eq. A5), with binding and dissociation rate constants k_f and k_r . N_b is given by $I \cdot N_r$, where I is described by an Ito stochastic differential equation (Eq. A3), generating a stochastic differential system for the modeling equations. The concentration field is either taken as uniform concentration ($C = K_d$), when random motility of the model cell is considered, or a linear one-dimensional gradient (using $\epsilon = \Delta C/2C$, where ΔC is the absolute concentration difference across the cell diameter, at $C \sim K_d$), when chemotaxis of the model cell is considered. Variables associated with the model cell equations are in **bold type** to denote that they are stochastic processes.

Results

We first illustrate the model behavior with some simulated cell movement paths. Fig. 4 contains two sets of such results. In each set, the cell has the same initial orientation at the origin. Each set represents the migration response of the model cell to one of the infinitely many possible realizations of driving noise, yielding receptor occupancy fluctuations, for each compartment under random motility and chemotaxis condi-

tions. For each set, one path is obtained for the case of random motility conditions (- path, $\epsilon = 0$). The characteristics of the persistent random walk for the real cell behavior are evident. The influence of a moderate gradient on each of these paths indicates a smooth turning response of the model cell in the direction of the gradient (+ paths, $\epsilon = 0.008$). These chemotactic responses correspond to the identical driving noise and same cell parameter values used for the random motility simulation. This gradient is of magnitude typically established in the visual assay system of Zigmond from which quantitative orientation data are obtained (12). Also included is the influence of a ten times steeper gradient on each of the random motility trajectories (++ paths, $\epsilon = 0.08$). A faster turning response with initial oscillatory behavior occurs, along with greater bias toward the gradient later in the simulation. A gradient of this magnitude has yet to be established experimentally, so that it is presently unknown whether oscillatory behavior can be observed or whether it is merely an artifact of our simplified two-compartment picture.

Random Motility

Random motility conditions imply the cell has been exposed to a constant, uniform chemoattractant concentration for effectively an infinite time period, so that binding equilibrium has been established (p is constant). It is possible to solve the covariance matrix of the stochastic differential system (10) for the directional persistence time, P_T , the characteristic time before which a cell significantly changes direction (3):

$$P_T = \lim_{T \rightarrow \infty} \frac{2T}{\langle \theta_T^2 \rangle} = \frac{f_s \tau_R^4 (\rho + 1)^3}{N_r \tau_D^2 \rho}, \quad (3)$$

where T is the observation time, θ_T is the angle formed by the cell polarity axis at time T relative to the initial direction. f_s is considered to be the sampling frequency for a receptor and given simply by $f_s = k_r$. ρ is the dimensionless uniform concentration, C/K_d . By assumption, the model only applies for ρ of order 1, where the cell polarity is greatest. τ_R and τ_D are interpreted as system response and signal decay time constants, respectively, and are defined by

$$\tau_R = \frac{1}{(\kappa k_f)^{1/2}} \quad \tau_D = \frac{1}{(4D^2 + 4Dk_d + k_d^2)^{1/2}}. \quad (4)$$

The dependence of P_T on τ_R and τ_D is consistent with intuition: the larger τ_R (smaller transduction rate constant k_f , small turning sensitivity κ), the slower the cell responds to a receptor signal excursion from the mean value, and the greater the persistence; the smaller τ_D (large decay rate constant k_d , large diffusive rate constant D), the faster the cell eliminates an internal signal (ΔM) created by a receptor signal excursion from the mean value, and, again, the greater the persistence. The dependence of P_T on f_s follows from the result for the relative noise in time-averaged receptor concentration measurement (2): as f_s increases (large dissociation rate constant k_r), the smaller the magnitude of the excursions of I from p , and a greater persistence results. Even though the magnitudes of the excursions also decrease with increasing N_r , the transduction process is amplifying the excursions in proportion to N_r . The net effect of this trade-off from increasing N_r is a decrease in persistence.

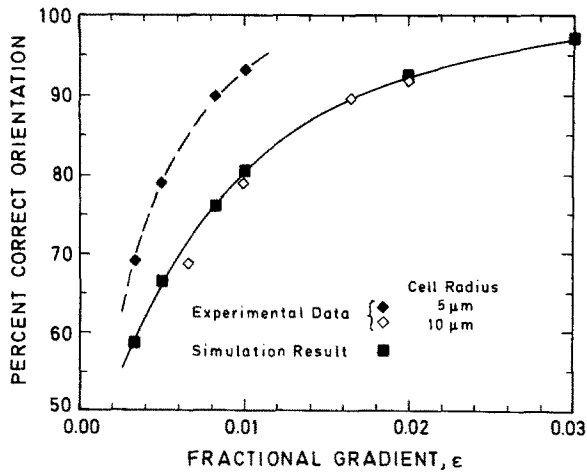


Figure 5. Correct orientation plotted as a function of chemoattractant gradient ϵ ; comparison of simulation results with Zigmond's experimental data for PMN (12). The two compartments of the cell are positioned $5 \mu\text{m}$ (r_c) from the cell center, located at angles relative to the polarity axis of $\pm 45^\circ\text{C}$ (θ_c). A constant translation speed of $20 \mu\text{m}/\text{min}$ (v), and a 100 cell population apply to all simulation results. $N_T = 10,000$, $f_s = 0.4 \text{ min}^{-1}$, $\tau_R = 3.5 \text{ min}$, $\tau_D = 0.11 \text{ min}$. The two sets of experimental data points actually refer to the same experimental observations, but with two different assumed values for the cell radius, 5 and $10 \mu\text{m}$. The fractional concentration difference across the cell, ϵ , is thus the known fractional concentration gradient per unit length multiplied by the assumed cell radius. Uncertainty in cell radius is thus translated into net uncertainty in the fractional concentration difference across the cell.

Chemotaxis

The orientation behavior of the model cell in a constant spatial gradient of chemoattractant is examined in this section. This mathematical system is considerably more complex than the simpler system applicable to random motility and simulation of large populations is the most direct method for characterization (10).

The first finding of significance is that the chemotactic response of the model cell does not depend on the individual cell parameters for a specified ϵ , rather, on the parameters used to characterize the random motility response: f_s , N_T , τ_R , and τ_D . If the identical initial directions and realizations of noise are used, identical paths are obtained for any combination of the intracellular parameters k_i , k_d , D , κ that yield the same values for τ_R and τ_D (for f_s and N_T held constant). Use can be made of Eq. 3 and known values for f_s and N_T (0.4 min^{-1} and 10,000, respectively [7, 8]) and P_T (1–5 min [4, 14]) for the PMN-FNLLP test system to bound the range of values for τ_R^4/τ_D^2 to be $0.312\text{--}1.56 \times 10^4 \text{ min}^2$.

The effect of increasing the fractional gradient, ϵ , on the orientation behavior is first considered. Fig. 5 is a plot of predicted percent correct orientation, the percentage of cells orienting towards higher concentrations, as a function of ϵ . The simulation results shown here incorporate the experimental estimates for N_T and f_s mentioned above, along with choices for k_i , k_d , D , and κ that yield $\tau_R = 3.5 \text{ min}$ and $\tau_D = 0.11 \text{ min}$ (these specifications determine $P_T = 3.9 \text{ min}$, $\tau_R^4/\tau_D^2 = 1.21 \times 10^4 \text{ min}^2$; cf. experimental values above). Also plotted are experimental data points for PMN (12). Comparison with experiment is very satisfying given the

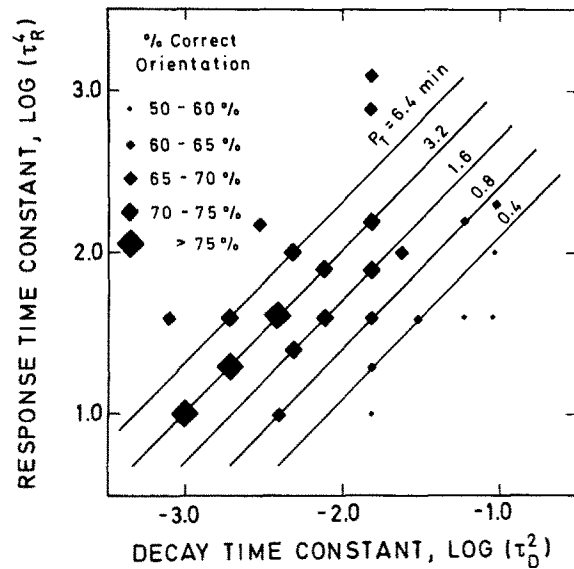


Figure 6. Dependence of orientation accuracy on system response, τ_R , and signal decay, τ_D , time constants (f_s and N_T constant). Notice that a maximal orientation bias occurs for parameters yielding a persistence time of $\sim 3 \text{ min}$.

amount of uncertainty in the estimation of the gradients present experimentally. For example, for this particular choice of parameters, the quantitative agreement ranges from fair to almost perfect depending on the value used for the cell radius in estimating the gradients present in the visual orientation assay. Other sources of similar uncertainty are discussed elsewhere (14).

Given confidence in the ability of our model to represent observed cell behavior in both random motility and chemotaxis modes, we can proceed to explore some of its important predictions. The relationship between directional persistence in random motility and orientation bias in chemotaxis is contained in Figs. 6 and 7. These plots show the dependence of correct orientation as a function of τ_R^4 and τ_D^2 in Fig. 6 (f_s and N_T are constant at 0.4 min^{-1} and 10,000, respectively) and as a function of f_s and N_T in Fig. 7 (τ_R^4 and τ_D^2 constant, corresponding to $\tau_R = 2.5 \text{ min}$ and $\tau_D = 0.124 \text{ min}$ and $\tau_R^4/\tau_D^2 = 0.255 \times 10^4 \text{ min}^2$). Lines of constant P_T are indicated for both plots. The gradient is constant at $\epsilon = 0.008$ for all the simulations.

In crossing lines from small to large P_T in Fig. 6, correct orientation passes through a relatively shallow maximum, with the maximum orientation bias appearing to occur for an optimal $P_T \approx 3 \text{ min}$. Following along any line of constant P_T to smaller values of τ_R^4 and τ_D^2 , correct orientation is seen to increase slightly. Thus, an optimal P_T is suggested; furthermore, one that reflects small time constants τ_R and τ_D , i.e., a cell that rapidly responds to an internal signal and rapidly eliminates an internal signal.

In crossing lines from small to large P_T in Fig. 7, a maximum in correct orientation is again evident, although the maximum does not correspond to an optimal P_T in this case. Following along any line of constant P_T to larger values of f_s and N_T , correct orientation is seen to increase dramatically. It is perhaps more illuminating to observe that for constant f_s , an optimal N_T exists to maximize the orien-

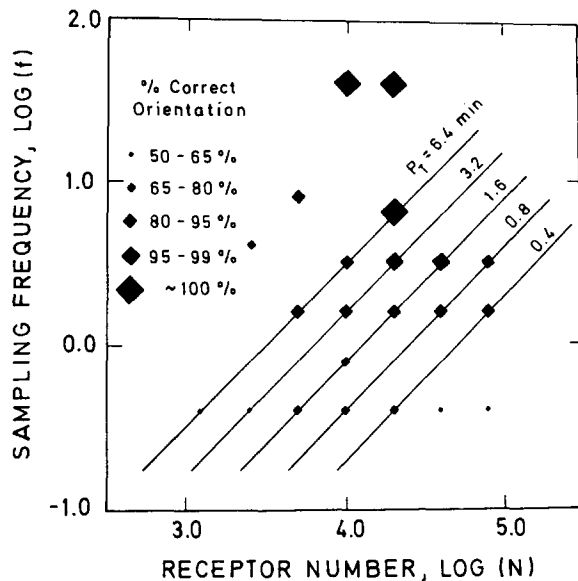


Figure 7. Dependence of orientation accuracy on receptor sampling frequency, f_s , and total receptor number, N_T (τ_D and τ_R constant). Notice that for the value of f_s estimated experimentally for FNLLP, 0.4 min^{-1} , a maximal orientation bias occurs for N_T approximately equal to 20,000.

tation bias ($\approx 20,000$); whereas for a constant N_T correct orientation increases unbounded with f_s . However, a model assumption that receptor-chemoattractant binding is reaction-limited becomes violated for large f_s (as well as large N_T).

Discussion

The goal of this work was to propose a model unifying the two observed modes of PMN migration behavior: random motility, the persistent random walk behavior of cells in uniform concentrations of chemoattractant; and chemotaxis, the biased random walk of cells observed in gradients of chemoattractant. The central concept underlying our model is that the stochastic nature of cell receptor-chemoattractant binding can explain the component of directional randomness observed in both leukocyte random motility and chemotaxis (Fig. 2).

Analysis of a model cell as an integrated system sensing and responding to "noisy" receptor signals (Fig. 3) yields cell paths demonstrating the qualitative features observed experimentally (Fig. 4). In uniform chemoattractant environments, the paths exhibit a persistent random walk behavior, whereas in chemoattractant gradient environments they show biased random walk behavior. Furthermore the quantitative predictions of this model are surprisingly good given its simplicity. Cell random motility behavior, characterized by a directional persistence time, and chemotaxis behavior, characterized by orientation accuracy, are functions of four parameters: the receptor sampling index (equal to the dissociation rate constant for the receptor-chemoattractant complex), the total number of receptors, a system response time constant, and a signal decay time constant. The two time constants are functions of the rate constants associated

with the model mechanisms for receptor signal transduction and turning. It is believed that these dependencies are a feature of the general model irrespective of the particular set of kinetic mechanisms employed. For reasonable values of these parameters, the model can simultaneously predict both the directional persistence time in the absence of a gradient and the orientation bias in the presence of a gradient. Thus, the same amount of noise large enough to account for the observed frequency of turning in uniform environments is also small enough to allow for the observed degree of bias in gradient environments. This consistency, both internally and with respect to experimental data, lends credence to our central concept.

Notice that our general model involves elements of both spatial and temporal gradient sensing, consistent with observations of PMN behavior (13). Alternative formulations may also be examined in the context of our stochastic model framework. As an example, we have also examined the case where the rate of receptor signal transduction was proportional to the fractional receptor occupancy, I , as suggested by an adaptation scheme (9), rather than the number of bound receptors, $I \cdot N_T$, as in this paper. The random motility analysis yields the same result (Eq. 3) except that P_T is now directly rather than inversely proportional to N_T . In addition, chemotaxis simulations analogous to those summarized in Fig. 7 reveal that a maximum in orientation bias corresponding to some optimal N_T does not exist for this "adapting signal" case: orientation bias increases monotonically with N_T over the relevant range for N_T . Thus, the model predicts these alternative candidates for the transducing state of the receptor can be distinguished based on the qualitative dependence of directional persistence and orientation bias on total receptor number.

One major limitation of the present model is that it applies only for chemoattractant concentrations at which the cell retains its morphological polarity. Modeling the cell behavior when the morphology is unstable requires a considerably more complex mechanical model for cell movement than incorporated presently. However, the model based on the high polarity limit analyzed here yields important fundamental insight into the relationships between random motility and chemotaxis.

Clearly, the goal of the cell biologist is to discover the molecular mechanisms by which cells can turn receptor binding events into directional locomotion behavior. We believe that the theoretical model we propose here could prove to be of significant aid in working toward this goal. The values of the time constants for intracellular signal generation and decay, for instance, can serve to suggest quantitative time scales corresponding to the actions of the molecular mechanisms. It is possible that some hypothetical possibilities can be ruled out on the basis of inappropriate rates of operation, according to our model and simulation results.

Appendix

Eq. A1 describes the turning rate of the cell and Eqs. A2-A5 are the kinetic equations for species associated with compartment 1 of the cell for the general case (chemotaxis). For random motility, C and p are constants. Equations for compartment 2 are analogous. W is the normal Weiner process.

$$\frac{d\theta_T}{dt} = \kappa(M_1 - M_2) \quad (\text{A1})$$

$$\frac{dM_1}{dt} = k_i N_T I_1 - k_d M_1 + D(M_2 - M_1) \quad (\text{A2})$$

$$dI_1 = [(k_f C_1(1 - p_1) - k_r p_1) - (k_f C_1 + k_r)(I_1 - p_1)]dt + \frac{1}{N_T^{1/2}} [k_f C_1(1 - p_1) + k_r p_1]^{1/2} dW_1 \quad (\text{A3})$$

$$\frac{dp_1}{dt} = k_f C_1(1 - p_1) - k_r p_1 \quad (\text{A4})$$

$$\frac{dC_1}{dt} = [v \cos \theta_T - r_c \frac{d\theta_T}{dt} \sin(\theta_T + \theta_c)] \frac{\Delta C}{\Delta x} \quad (\text{A5})$$

These equations are discussed in detail elsewhere (10).

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