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.

P ol y m or ph o n u cle ar neu troph il 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 uniform 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

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

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

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**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.
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

\[
p = \frac{C}{K_d + C}.
\]

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:

\[
C = K_d \frac{p}{1 - p}.
\]

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 \( \approx 2\% \). This result was obtained (11) for 10,000 total receptors for the chemotactic peptide N-formylmethionylleucylphenylalanine (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 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, \( k_4 \),

\[
\frac{dN_b}{dt} = k_4 I - k_{4d} N_b,
\]

where \( I \) is the instantaneous receptor fractional occupancy, \( N_b \) is the number of bound receptors, \( k_4 \) is the first-order transduction rate constant, and \( k_{4d} \) is the first-order dissociation rate constant.

In the presence of receptor binding fluctuations, the instantaneous number of receptor complex, \( C(b) \), will exhibit random fluctuations around \( C \). At \( C = K_d \), the relative standard deviation of these fluctuations, estimated from an equilibrium perspective, will be \( \approx 2\% \). This result was obtained (11) for 10,000 total receptors for the chemotactic peptide N-formylmethionylleucylphenylalanine (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 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).
compartment under random motility and chemotaxis condi-
tions, for each set, one path is obtained for the case of ran-
dom motility conditions (-- path, \( \varepsilon = 0 \)). 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, \( \varepsilon = 0.008 \)).
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 Zigmund
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, \( \varepsilon = 0.08 \)).
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 un-
known whether oscillatory behavior can be observed or
whether it is merely an artifact of our simplified two com-
partment 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 equilib-
rium has been established (\( p \) is constant). It is possible to
solve the covariance matrix of the stochastic differential sys-
tem (10) for the directional persistence time, \( P_T \), the charac-
teristic time before which a cell significantly changes direc-
tion (3):

\[
P_T = \lim_{T \to \infty} \frac{2T}{\langle \dot{\theta}_T^2 \rangle} = \frac{f_s^2 \tau_k^4 (\rho + 1)^3}{N_T \tau_d^2 \rho}, \quad (3)
\]

where \( T \) is the observation time, \( \dot{\theta}_T \) 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 \( f_s = k_n \). \( p \) is the dimensionless uniform
concentration, \( C/K_d \). By assumption, the model only ap-
plies for \( p \) of order 1, where the cell polarity is greatest. \( \tau_k \) and \( \tau_d \) are interpreted as system response and signal decay
time constants, respectively, and are defined by

\[
\tau_k = \frac{1}{(k_k)_{1/2}}, \quad \tau_d = \frac{1}{(4D^2 + 4D k_d + k_d^2)^{1/2}}. \quad (4)
\]

The dependence of \( P_T \) on \( \tau_k \) and \( \tau_d \) is consistent with intu-
ition: the larger \( \tau_k \) (smaller transduction rate constant \( k_n \),
small turning sensitivity \( k \)), the slower the cell responds to
a receptor signal excursion from the mean value, and the
greater the persistence; the smaller \( \tau_d \) (large decay rate
constant \( k_n \), large diffusive rate constant \( D \)), the faster the
cell eliminates an internal signal \( (\Delta M) \) 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 dis-
sociation rate constant \( k_n \)), 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 \( N_T \), the transduction process is amplifying
the excursions in proportion to \( N_T \). The net effect of this
trade-off from increasing \( N_T \) is a decrease in persistence.
The two sets of experimental data points actually refer to experimental estimates for \( N_r \) and \( f_{\text{max}} \) mentioned above, along the fractional concentration difference across the cell. The fractional concentration difference across the cell, \( e \), 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 \( e \), rather, on the parameters used to characterize the random motility response: \( f_s \), \( N_r \), \( \tau_s \), and \( \tau_0 \). If the identical initial directions and realizations of noise are used, identical paths are obtained for any combination of the intracellular parameters \( k_i \), \( k_{ii} \), \( D \), \( \kappa \) that yield the same values for \( \tau_s \) and \( \tau_0 \) (for \( f_s \) and \( N_r \) held constant).

Use can be made of Eq. 3 and known values for \( f_s \) and \( N_r \) (0.4 min\(^{-1}\) and 10,000, respectively) and \( P_T \) (1-5 min [4, 14]) for the PMN-FNLLP test system to bound the range of values for \( \tau_s^2/\tau_0^2 \) to be 0.312-1.56 \( \times 10^4 \) min\(^2\).

The effect of increasing the fractional gradient, \( e \), 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 \( e \). The simulation results shown here incorporate the experimental estimates for \( N_r \) and \( f_s \) mentioned above, along with choices for \( k_i \), \( k_{ii} \), \( D \), and \( \kappa \) that yield \( \tau_s = 3.5 \text{ min} \) and \( \tau_0 = 0.11 \text{ min} \) (these specifications determine \( P_T = 3.9 \text{ min} \), \( \tau_s^2/\tau_0^2 = 1.21 \times 10^4 \text{ min}^2 \); cf. experimental values above). Also plotted are experimental data points for PMN (12). Comparison with experiment is very satisfying given the 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 \( \tau_s^2 \) and \( \tau_0^2 \) in Fig. 6 (\( f_s \) and \( N_r \) constant at 0.4 min\(^{-1}\) and 10,000, respectively) and as a function of \( f_s \) and \( N_r \) in Fig. 7 (\( \tau_s^2 \) and \( \tau_0^2 \) constant, corresponding to \( \tau_s = 2.5 \text{ min} \) and \( \tau_0 = 0.124 \text{ min} \) and \( \tau_s^2/\tau_0^2 = 0.255 \times 10^4 \text{ min}^2 \)). Lines of constant \( P_T \) are indicated for both plots. The gradient is constant at \( e = 0.008 \) 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 \( \tau_s^2 \) and \( \tau_0^2 \), correct orientation is seen to increase slightly. Thus, an optimal \( P_T \) is suggested; furthermore, one that reflects small time constants \( \tau_s \) and \( \tau_0 \), 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 \( N_r \), correct orientation is seen to increase dramatically. It is perhaps more illuminating to observe that for constant \( f_s \), an optimal \( N_r \) exists to maximize the orient-
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 - 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.

\[
\frac{d\theta_t}{dt} = \kappa(M_t - M_0) \tag{A1}
\]
\[
\frac{dM_i}{dt} = k_i N_t I_i - k_0 M_i + D(M_2 - M_1)
\]  
(A2)

\[
dI_i = \left[ (k_C(1 - p_t) - k_P I_i) - (k_C + k_p)(I_i - p_t) \right] dt
+ \frac{1}{N_t^{1/2}} [k_C(1 - p_t) + k_P I_i]^{1/2} dW_i
\]  
(A3)

\[
\frac{dp_t}{dt} = k_C(1 - p_t) - k_p I_i
\]  
(A4)

\[
\frac{dC_i}{dt} = [v \cos \theta_t - r_c \frac{d\theta_t}{dt} \sin(\theta_t + \theta_0)] \frac{\Delta C}{\Delta x}
\]  
(A5)

These equations are discussed in detail elsewhere (10).

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