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A Generalized Pearson Random Walk Allowing for Bias

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We calculate asymptotic values of the first two moments of a planar walk in which the step lengths depend on the direction of motion. The model is suggested by experiments on the locomotion of biological cells. Internally induced persistence due to nonuniform turn angle distributions is also accounted for.

KEY WORDS: Planar random walk; cellular locomotion; directed motility.

1. INTRODUCTION

There has been considerable interest recently in the planar motion of biological cells and organisms. Specific applications include the inhibition of macrophage movement by a soluble factor produced by dividing lymphocytes[1,2] and the directed response of leukocytes to gradients of attractive substances released by damaged red blood cells[3] or degraded bacteria.[4]

It would be of some interest to derive quantitative parameters that characterize the motion of such cells. There have been several experimental studies of cellular motion that use the notions of random walk theory to discuss the observed phenomena. These suggest that such diverse cell types as fibroblasts,[5] granulocytes,[6] and flagellated bacteria[7] move in approximately straight line paths separated by discrete changes in direction.

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A recent investigation by Berg and Brown[7] has provided precise data on such random motion for the case of bacteria, and the effects of chemoattractants have been characterized as well. The distribution of times between turns is found by these investigators to be negative exponential. Further, the external chemotactic field has been found to influence the mean run time, apparently without influencing the remaining parameters of the random walk, e.g., the probability of turning through a given angle does not seem to depend on cell orientation with respect to the chemotactic field.

In this paper we calculate the asymptotic average and variance covariance matrix of the displacement in a random walk model suggested by Berg and Brown's experiments. This model is a generalization of that proposed by Pearson[8] and solved by Kluyver[9] allowing for a biasing mechanism appropriate to the bacteria in Berg and Brown's experiments. Patlak[10] has given an exhaustive analysis of biased random walks in the context of problems of biological motion. The assumptions underlying his work are close to our own, but he treats the description of cell motion by an approximate Fokker–Planck equation derived for the case of weak fields. We, on the other hand, treat the dynamics of the process more exactly and can infer the general asymptotic probability distribution for displacements from the central limit theorem.

2. ANALYSIS

Let us consider a two-dimensional random walk of a cell in which the direction of cell movement is measured with respect to a fixed external axis which we choose to be the x axis. At time $t = 0$ the cell is placed at the origin with a uniformly distributed orientation from zero to 2π. We make the following assumptions concerning the subsequent motion of the cell.

1. The motion consists of straight line paths separated by discrete turns. The motion along any path has a constant random speed independent of cell orientation. The distribution of speeds is the same for all paths, and the mean and second moment of the speed are denoted by $\bar{v}$ and $\overline{v^2}$, respectively.

2. At the end of a path the cell turns through a random angle θ, chosen in accordance with a probability density $p(\theta)$. This function is assumed to have the property that the only integer value of n for which

$$\int_{-\pi}^{\pi} p(\theta) e^{in\theta}\, d\theta = 1 \tag{1}$$

is $n = 0$.[2]

[2] It is not difficult to show that if $p(\theta)$ consists of any continuous components, i.e., does not consist solely of delta functions, the above condition is satisfied.

3. Let α be the direction of a given path with respect to a fixed (x) axis The probability density for the duration of a single path is $\lambda(\alpha) \exp[-\lambda(\alpha)t]$. Thus $\lambda(\alpha)$ is the parameter that measures the bias introduced by the chemotactic substance. Symmetry will be assumed for this function, so that $\lambda(\alpha) = \lambda(-\alpha)$.

In addition to the preceding assumptions, we introduce the following notation:

$$\beta_n = \frac{1}{2\pi}\int_{-\pi}^{\pi} \frac{\cos n\theta \, d\theta}{\lambda(\theta)}, \qquad \gamma_n = \frac{1}{2\pi}\int_{-\pi}^{\pi} \frac{\cos n\theta \, d\theta}{\lambda^2(\theta)}$$

$$p_n = \int_{-\pi}^{\pi} p(\theta) e^{in\theta} \, d\theta = c_n + is_n \tag{2}$$

where

$$c_n = \int_{-\pi}^{\pi} p(\theta) \cos n\theta \, d\theta, \qquad s_n = \int_{-\pi}^{\pi} p(\theta) \sin n\theta \, d\theta \tag{3}$$

For the random walk defined above we calculate asymptotic values of the first two moments of the position of the center of the cell at time t, $\mathbf{r}(t) = (x(t), y(t))$. A history of the random walk at time t can be given in terms of (i) the path durations (in time) $\tau_1, \tau_2, \ldots, \tau_{n(t)}$, where $n(t)$ is the number of segments making up a total path at time t, (ii) the initial angle φ, and (iii) the turn angles $\theta_1, \theta_2, \ldots, \theta_{n(t)-1}$. We proceed, in the following, by first fixing $n(t)$, averaging over the cell velocities v, and then averaging over all possible histories. Next the Laplace transform with respect to t is taken, following which the sum over all $n(t)$ is performed. Finally, the angular averages are calculated. An application of a Tauberian theorem for Laplace transforms (11) then allows us to infer the asymptotic values of the averages.

Let us first define the angles

$$\zeta_1 = \varphi, \qquad \zeta_n = \varphi + \theta_1 + \theta_2 + \cdots + \theta_{n-1} \tag{4}$$

to be the angles between the nth path segment and the x axis. Then the value of $x_n(t)$, which is the x displacement at time t conditional on $n - 1$ complete and one incomplete steps having been made, is

$$x_n(t) = \sum_{i=1}^{n} v_i \tau_i \cos \zeta_i \tag{5}$$

where the τ's are nonnegative random variables satisfying

$$\sum_{i=1}^{n} \tau_i = t \tag{6}$$

Thus, the result of averaging with respect to v, and with respect to the τ's subject to this last constraint, can be written

$$
\begin{aligned}
&E_{\tau,v}\{x_n(t)\} \\
&\quad = \lambda_1\lambda_2\cdots\lambda_{n-1}\bar{v}\int_0^\infty d\tau_1\int_0^\infty d\tau_2\cdots\int_0^\infty d\tau_n \\
&\quad\quad \times\left(\sum_{i=1}^{n}\tau_i\cos\zeta_i\right)\exp\left(-\sum_{i=1}^{n}\lambda_i\tau_i\right) \\
&\quad\quad \times\,\delta(\tau_1+\tau_2+\cdots+\tau_n-t)
\end{aligned}
\tag{7}
$$

where the delta function is inserted to satisfy Eq. (6), and we have denoted $\lambda(\zeta_r)$ by λ_r. Since the nth step is incomplete at time t with probability one, λ_n must be omitted as a multiplying factor in the integrand.[3]

If we introduce the notation

$$
F_r = \lambda_r/(\lambda_r + s), \qquad G_r = (\cos\zeta_r)/(\lambda_r + s) \tag{8}
$$

then the Laplace transform of Eq. (7) can be expressed as

$$
\begin{aligned}
&\int_0^\infty \exp(-st)E_{\tau,v}\{x_n(t)\}\,dt \\
&\quad = \lambda_1\lambda_2\cdots\lambda_{n-1}\bar{v}\int_0^\infty d\tau_1\cdots\int_0^\infty d\tau_n \\
&\quad\quad \times\left(\sum_{i=1}^{n}\tau_i\cos\zeta_i\right)\exp\left[-\sum_{i=1}^{n}(\lambda_i+s)\tau_i\right] \\
&\quad = (\bar{v}/s)F_1F_2\cdots F_{n-1}(1-F_n)(G_1+G_2+\cdots+G_n)
\end{aligned}
\tag{9}
$$

since the τ integrations can be performed explicitly, and since

$$
\frac{1}{\lambda_n+s} = \frac{1}{s}\left(1-\frac{\lambda_n}{\lambda_n+s}\right) = \frac{1}{s}(1-F_n) \tag{10}
$$

The next step in the calculation is to perform the summation over n, leading to

$$
\begin{aligned}
&\sum_{n=1}^{\infty}\int_0^\infty e^{-st}E_{\tau,v}\{x_n(t)\}\,dt \\
&\quad = (\bar{v}/s)[G_1+F_1G_2+F_1F_2G_3+F_1F_2F_3G_4+\cdots] = (\bar{v}/s)J(s,\boldsymbol{\theta})
\end{aligned}
\tag{11}
$$

where $J(s, \boldsymbol{\theta})$ is the bracketed sum.

We next turn to the angular averaging. Suppose that a function $H(\boldsymbol{\theta})$ of

[3] That is, since the probability density for the duration of a path is $\lambda e^{-\lambda t}$, it follows that the probability that a path lasts longer than t is

$$
\int_t^\infty \lambda e^{-\lambda t}\,d\tau = e^{-\lambda t}
$$

the angles $\varphi, \theta_1, \theta_2, \ldots, \theta_{n-1}$ is given. Then by our specification of the random walk the angular average of $H(\boldsymbol{\theta})$ is

$$E_\theta\{H(\boldsymbol{\theta})\} = (1/2\pi) \int_{-\pi}^{\pi} d\varphi \int_{-\pi}^{\pi} \cdots \int p(\theta_1)p(\theta_2)\cdots p(\theta_{n-1}) \times H(\boldsymbol{\theta})\, d\theta_1 \cdots d\theta_n \tag{12}$$

Hence we can express the Laplace transform of the average of $x(t)$ as

$$\int_0^\infty e^{-st}\langle x(t)\rangle\, dt = \frac{\bar{v}}{s} E_\theta\{J(s, \boldsymbol{\theta})\} = \frac{\bar{v}}{s} \int_{-\pi}^{\pi} \frac{d\varphi}{2\pi}\, U(\varphi, s) \tag{13}$$

where, if we suppress the s arguments in each of the functions, $U(\varphi)$ is given by

$$\begin{aligned} U(\varphi) &= G(\varphi) + F(\varphi) \int_{-\pi}^{\pi} G(\varphi + \theta)p(\theta)\, d\theta \\ &\quad + F(\varphi) \int_{-\pi}^{\pi} \int F(\varphi + \theta_1)G(\varphi + \theta_1 + \theta_2)p(\theta_1)p(\theta_2)\, d\theta_1\, d\theta_2 \\ &\quad + F(\varphi) \iint_{-\pi}^{\pi} \int F(\varphi + \theta_1)F(\varphi + \theta_1 + \theta_2)G(\varphi + \theta_1 + \theta_2 + \theta_3) \\ &\quad \times p(\theta_1)p(\theta_2)p(\theta_3)\, d\theta_1\, d\theta_2\, d\theta_3 + \cdots \end{aligned} \tag{14}$$

This last equation is a consequence of Eqs. (11)–(13). It is easy to verify from this last expression that $U(\varphi)$ is the solution to the integral equation

$$U(\varphi, s) = G(\varphi, s) + F(\varphi, s) \int_{-\pi}^{\pi} U(\varphi + \theta, s)p(\theta)\, d\theta \tag{15}$$

An equivalent set of equations can be obtained by expanding all functions in a Fourier series,

$$U(\varphi, s) = \sum_{n=-\infty}^{\infty} u_n(s)e^{in\varphi}, \qquad G(\varphi, s) = \sum_{n=-\infty}^{\infty} g_n(s)e^{in\varphi}$$
$$F(\varphi, s) = \sum_{n=-\infty}^{\infty} f_n(s)e^{in\varphi} \tag{16}$$

The right-hand side of Eq. (13) is just $\bar{v}u_0(s)/s$ in terms of these coefficients. From Eq. (15) we see that the Fourier coefficients satisfy

$$u_n(s) = g_n(s) + \sum_{r=-\infty}^{\infty} u_r(s)p_r f_{n-r}(s) \tag{17}$$

for all n. This set of equations is exact and forms the starting point for the asymptotic analysis.

The behavior of $\langle x(t)\rangle$ for large t is related to the small s behavior of

$u_0(s)$. Specifically, we will calculate terms in $u_0(s)$ that either vary as $1/s$ or are constant, as s goes to zero. These terms allow us to infer an expansion of the form $\langle x(t)\rangle \sim \bar{v}(at + b)$ at sufficiently large t.

The definitions in Eqs. (8) and (16) imply that for small $|s|$, $f_n(s)$ and $g_n(s)$ can be expanded as

$$f_n(s) \sim \delta_{n,0} - s\beta_n + s^2\gamma_n - \cdots$$
$$g_n(s) \sim \tfrac{1}{2}(\beta_{n+1} + \beta_{n-1}) - \tfrac{1}{2}s(\gamma_{n+1} + \gamma_{n-1}) + \cdots \tag{18}$$

where $\delta_{n,0}$ is a Kronecker delta and β_n and γ_n are defined in Eq. (2). Hence for small $|s|$ Eq. (17) can be rewritten as

$$(1 - p_n)u_n(s) = \tfrac{1}{2}(\beta_{n+1} + \beta_{n-1}) - \tfrac{1}{2}s(\gamma_{n+1} + \gamma_{n-1}) + \cdots$$
$$- \sum_r u_r(s)p_r[s\beta_{n-r} - s^2\gamma_{n-r} + \cdots] \tag{19}$$

Let us next substitute the expansion

$$u_n(s) = (a_n/s) + b + \cdots \tag{20}$$

into this last equation. (It is easily shown that if higher powers of $1/s$ are included in the expansion, their coefficients will be identically equal to zero; this conclusion is also obvious from probabilistic considerations.) When the terms proportional to $1/s$ are collected it is found that $a_n(1 - p_n)/s = 0$. But this allows us to conclude that

$$a_n = 0, \qquad n \neq 0 \tag{21}$$

by the assumption that $p_n \neq 1$ except for $n = 0$. If we set $s = 0$ in Eq. (19) and collect terms independent of s on the right-hand side, we find that

$$a_0 = \beta_1/\beta_0 \tag{22}$$

Similarly, to calculate the $\{b_n\}$, we collect terms independent of s, finding

$$b_n = [\tfrac{1}{2}(\beta_{n+1} + \beta_{n-1}) - (\beta_1\beta_n/\beta_0)]/(1 - p_n), \qquad n \neq 0 \tag{23}$$

Then, setting $n = 0$ and collecting the coefficients of s, we find that

$$b_0 = \frac{\beta_1\gamma_0}{\beta_0} - \frac{\gamma_1}{\beta_0} - \frac{2}{\beta_0}\sum_{r=1}^{\infty} \beta_r\left[\tfrac{1}{2}(\beta_{r+1} + \beta_{r-1}) - \frac{\beta_1\beta_r}{\beta_0}\right] \operatorname{Re}\left(\frac{p_r}{1 - p_r}\right) \tag{24}$$

The combination of Eqs. (13), (20), (22), and (24) allows us to write, as a final result, the asymptotic relation

$$\langle x(t)\rangle \sim \bar{v}((\beta_1/\beta_0)t + b_0) \tag{25}$$

The term proportional to t depends on $\lambda(\theta)$ but not on the turning angle distribution. The second term includes the turning angle density $p(\theta)$.

A similar, but slightly more elaborate calculation leads to the asymptotic value of elements of the covariance matrix. The analog of Eq. (11) is found to be

$$\int_0^\infty e^{-st}E_{\tau,v}\{x_n^2(t)\}\,dt = (1/s)F_1F_2\cdots F_{n-1}(1-F_n)\Big[2\overline{v^2}\sum_{i=1}^{n} G_i^2 + 2\bar{v}^2\sum_{i=1}^{n}\sum_{j=1}^{i-1} G_iG_j\Big] \tag{26}$$

so that

$$\begin{aligned}\sum_{n=1}^{\infty}\int_0^\infty e^{-st}E_{\tau,v}\{x_n^2(t)\}\,dt = {} & (2/s)\overline{v^2}[G_1^2 + F_1G_2^2 + F_1F_2G_3^2 + \cdots] \\ & + (2\bar{v}^2/s)[F_1G_1(G_2 + F_2G_3 + F_2F_3G_4 + \cdots) \\ & + F_1F_2G_2(G_3 + F_3G_4 + F_3F_4G_5 + \cdots) \\ & + F_1F_2F_3G_3(G_4 + F_4G_5 + F_4F_5G_6 + \cdots)]\end{aligned} \tag{27}$$

The contribution from the first set of bracketed terms to $\sigma_{xx}^2(t)$ is calculated in exactly the same way as $\langle x(t)\rangle$. Details will be omitted, but the resulting term is $\overline{v^2}t(\gamma_0 + \gamma_2)$ plus a constant term that we have not calculated. The average of the second set of bracketed terms can be written

$$(1/2\pi)\int_{-\pi}^{\pi} d\varphi R(\varphi, s) \tag{28}$$

where $R(\varphi, s)$ is the solution to the integral equation

$$\begin{aligned}R(\varphi, s) = {} & G(\varphi, s)[U(\varphi, s) - G(\varphi, s)] \\ & + F(\varphi, s)\int_{-\pi}^{\pi} R(\varphi + \theta, s)p(\theta)\,d\theta\end{aligned} \tag{29}$$

Again confining ourselves to the case of s approaching zero, we can Fourier-analyze $R(\varphi, s)$, finding that

$$(1/2\pi)\int_{-\pi}^{\pi} d\varphi R(\varphi, s) \sim (2/s^2)(\beta_1/\beta_0)^2 + (r_0/\beta_0 s) + \cdots \tag{30}$$

where

$$\begin{aligned}r_0 = {} & \tfrac{1}{2}\sum_{n=-\infty}^{\infty}(\beta_{n+1} + \beta_{n-1})[b_n - \tfrac{1}{2}(\beta_{n+1} + \beta_{n-1}) - (\beta_1/\beta_0)\beta_n] \\ & + (\beta_1\gamma_1/\beta_0) + \beta_1 b_0\end{aligned} \tag{31}$$

the $\{b_n\}$ being given in Eqs. (23) and (24).

If we introduce a function

$$B(\varphi) = \sum_{n=-\infty}^{\infty} b_n e^{in\varphi} \tag{32}$$

then $\sigma_{xx}^2(t) = (\langle x^2(t)\rangle - \langle x(t)\rangle^2)$ goes asymptotically as

$$\sigma_{xx}^2(t) \sim \left[\frac{\sigma_v{}^2}{\beta_0}(\gamma_0 + \gamma_2) + \frac{\bar{v}^2}{\pi\beta_0}\int_{-\pi}^{\pi} B(\varphi)\frac{\cos\varphi}{\lambda(\varphi)}\,d\varphi\right]t \tag{33}$$

plus a constant term. Here we have denoted $(\overline{v^2} - \bar{v}^2)$ by $\sigma_v{}^2$ so that there are two types of contributions, a term due to fluctuations in speed (i.e., this term vanishes if the cells travel at uniform speed), and the remainder combining the effects of fluctuations in path lengths and turn angles.

The other nonzero element of the covariance matrix, $\sigma_{yy}^2(t)$, is calculated in the same way, and we omit details of the computation. If we define

$$B_1(\varphi) = \sum_{n=1}^{\infty}(\beta_{n-1} - \beta_{n+1})\,\mathrm{Im}[e^{in\varphi}/(1 - p_n)] \tag{34}$$

then we find that $\sigma_{yy}^2(t)$ has the asymptotic form

$$\sigma_{yy}^2(t) \sim \left[\frac{\sigma_v{}^2}{\beta_0}(\gamma_0 - \gamma_2) + \frac{\bar{v}^2}{\pi\beta_0}\int_{-\pi}^{\pi} B_1(\varphi)\frac{\sin\varphi}{\lambda(\varphi)}\,d\varphi\right]t \tag{35}$$

plus a constant term. The remaining element, $\sigma_{xy}(t)$, is identically equal to zero as a consequence of symmetry.

An example for which detailed results can be given rather easily is specified by

$$1/\lambda(\alpha) = T(1 + 2\epsilon\cos\alpha) \tag{36}$$

The parameter ϵ is a measure of asymmetry that biases the random walk to move preferably in the positive x direction when $\epsilon > 0$. The parameter T has the dimensions of time and $|\epsilon| < 1/2$. For this case

$$\begin{aligned}\beta_n &= T[\delta_{n,0} + \epsilon(\delta_{n+1,0} + \delta_{n-1,0})]\\ \gamma_n &= T^2[(1 + 2\epsilon^2)\delta_{n,0} + 2\epsilon(\delta_{n+1,0} + \delta_{n-1,0}) + \epsilon^2(\delta_{n+2,0} + \delta_{n-2,0})]\end{aligned} \tag{37}$$

With this set of parameters we see that

$$\begin{aligned}\langle x(t)\rangle &\sim \bar{v}\epsilon t + \bar{v}\epsilon T(2\epsilon^2 - 1)\frac{(1 - c_1)}{(1 - c_1)^2 + s_1{}^2}\\ \sigma_{xx}^2(t) &\sim \left\{\sigma_v{}^2(1 + 3\epsilon^2) + \bar{v}^2\left[(1 - 2\epsilon^2)^2\frac{(1 - c_1)}{(1 - c_1)^2 + s_1{}^2}\right.\right.\\ &\qquad \left.\left. + \frac{\epsilon^2(1 - c_2)}{(1 - c_2)^2 + s_2{}^2}\right]\right\}Tt\\ \sigma_{yy}^2(t) &\sim \left\{\sigma_v{}^2(1 + \epsilon^2) + \bar{v}^2\left[\frac{(1 - c_1)}{(1 - c_1)^2 + s_1{}^2} + \epsilon^2\frac{(1 - c_2)}{(1 - c_2)^2 + s_2{}^2}\right]\right\}Tt\end{aligned} \tag{38}$$

In the limit of long time we expect that the distribution of position in the random walks just described will tend to a Gaussian form. This has not been proved in detail, but at any point in time the cell position is a Markovian random variable, and the asymptotic Gaussian property can probably be proved starting from a form of the central limit theorem for weakly dependent random variables. A generalization of the present calculations which allows random speeds to depend on an external angle is easily made. On the other hand, the generalization of these results to three-dimensional random walks appears to pose much more difficult computational problems.

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