Subdiffusion, chemotaxis, and anomalous aggregation

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We propose a nonlinear random walk model which is suitable for the analysis of both chemotaxis and anomalous subdiffusive transport. We derive the master equations for the population density for the case when the transition rate for a random walk depends on residence time, chemotactic substance, and population density. We introduce the *anomalous chemotactic sensitivity* and find an *anomalous aggregation* phenomenon. So we suggest a different explanation of the well-known effect of *chemotactic collapse.*

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I. INTRODUCTION

Continuous time random walks (CTRW) have been widely used in many fields including physics, chemistry, and life sciences (see, for example, reviews [1,2]). Many biological and physical transport processes exhibit anomalous behavior for which walker mean-squared displacement increases as a fractional power μ of time: $\langle x^2(t)\rangle \sim t^\mu$ (subdiffusion: $\mu < 1$; superdiffusion: $\mu > 1$). The chemotaxis is a directed migration of cells toward a more favorable environment [3]. The microscopic theory of the movement of cells or organisms is also based on the random walk theory (see, for example, [4–7]). Although chemotaxis has a long history and has been studied by researchers for many decades, there is a lack of literature on the connection between the anomalous random walk and chemotaxis theory. We should mention the recent exception [8] where biased CTRW has been analyzed. One of the reasons for this gap is that the chemotaxis is essentially nonhomogeneous in space and time random process, while the standard anomalous CTRW model involves the spatial and temporal invariance [1,2]. Much of the recent literature on chemotaxis has been concerned with the movement of bacteria *E. coli* involving the runs and tumbles [5]. The theory is based on the "velocity-jump" model in which the "run" and "tumble" time intervals are exponentially distributed [9]. However, it has been found experimentally [10] that the distribution of run time intervals might deviate significantly from exponential approximation. It might have a power law which leads to anomalous superdiffusive behavior of bacteria.

The main purpose of this paper is to set up the "space-jump" model for both chemotaxis and non-Markovian random walk, including subdiffusive transport. In particular, we consider the phenomenon of cell aggregation by chemotaxis [3,5,11,12]. The aim is to show that the subdiffusive transport might lead to the *anomalous aggregation* when all cells aggregate into a very small region of space. Our model can also be used in other biological applications such as anomalous search strategy [13], cancer cell dichotomy [14], subdiffusion in spiny dendrites [15], invasions through patchy environments [16], and embryogenesis and wound healing.

II. RESIDENCE TIME STRUCTURED MODEL

We start with a space-jump random walk model in one space dimension. The cell performs a random walk as follows: it waits for a random time at each point in space before making a jump to another point. The most important characteristic of this walk is the transition rate γ for jumps at point x. The standard assumption in CTRW theory is that γ depends on the residence time (age) τ. This is a time interval between two successive jumps of the cell. The corresponding waiting time density $\phi(\tau)$ is related to $\gamma(\tau)$ as $\phi(\tau) = \gamma(\tau)\exp[\int_0^\tau \gamma(u)du]$ [17]. In chemotaxis theory the jump of cells occurs in response to a chemical signal [5]. For swimming bacteria the transition rate from the running mode to the tumbling mode is the functional of the chemotactic substance $S(x,t)$ [6]. This memory effect reflects the bacterial response to the time history of chemotactic substance. For the space-jump random walk model, we assume that the transition rate γ depends on S and possibly on its spatial and temporal gradient $\dot{S}$. We also assume that γ depends on the macroscopic population density $\rho(x,t)$. This dependence describes the crowding effects. Thus

$$\gamma(\tau|x,t) = \gamma(\tau|S(x,t),\dot{S}(x,t),\rho(x,t),t). \tag{1}$$

We introduce the cell density $\xi(x,t,\tau)$ at position x at time t with the residence time τ. The main reason for introduction of the structured density ξ is to make a random walk Markovian. This idea has been used in [4,17–20]. The density ξ obeys the balance equation

$$\frac{\partial \xi}{\partial t} + \frac{\partial \xi}{\partial \tau} = -\gamma(\tau|x,t)\xi. \tag{2}$$

For simplicity we use the initial condition

$$\xi(x,0,\tau) = \rho_0(x)\delta(\tau) \tag{3}$$

for which the residence time of all cells at $t = 0$ equals 0; $\rho_0(x)$ is the initial density of cells. It is clear that the residence time τ varies from 0 to t.

Our purpose is to derive the master equation for the cell density defined as

$$\rho(x,t) = \int_0^t \xi(x,t,\tau)\,d\tau. \tag{4}$$

The boundary condition for $\xi(x,t,\tau)$ at $\tau = 0$ is

$$\xi(x,t,0) = \int_0^t \int_{\mathbb{R}} \gamma(\tau|x,t)\xi(x-z,t,\tau)w(z|x-z,t)\,dz\,d\tau. \tag{5}$$

Here $w(z|x,t)$ is the dispersal kernel for jumps z which also depends on chemotactic substance and its gradient, density $\rho(x,t)$ and t,

$$w(z|x,t) = w(z|S(x,t),\dot{S}(x,t),\rho(x,t),t). \tag{6}$$

It is assumed that w is independent from τ. On the left-hand side of Eq. (5) we have a density of cells just arriving at point x at time t (zero residence time). On the right-hand side of Eq. (5) we have an integration of the rate at which the cells with different age τ arrive at position x at time t from the different points $x-z$. Using the method of characteristics, we find from Eq. (2) that

$$\xi(x,t,\tau) = \xi(x,t-\tau,0)\exp\left\{-\int_{t-\tau}^{t}\gamma[s-(t-\tau)|x,s]\,ds\right\}. \tag{7}$$

Let us denote the density of cells just arriving at point x at time t by

$$j(x,t) = \xi(x,t,0). \tag{8}$$

We also introduce the density of cells $i(x,t)$ leaving the point x exactly at time t. We substitute Eq. (7) into Eq. (5), use the initial condition for ξ (Eq. (3)), and obtain

$$j(x,t) = \int_{\mathbb{R}} i(x-z,t)w(z|x-z,t)\,dz, \tag{9}$$

$$i(x,t) = \int_0^t j(x,u)\phi(x,t,u)\,du + \rho_0(x)\phi(x,t,0), \tag{10}$$

where

$$\phi(x,t,u) = -\frac{\partial\Psi(x,t,u)}{\partial t} = \gamma(t-u|x,t)\exp\left[-\int_u^t \gamma(s-u|x,s)\,ds\right]. \tag{11}$$

Here $\Psi(x,t,u)$ is the probability that a cell is trapped at point x from time u to t without executing a jump (survival probability)

$$\Psi(x,t,u) = \exp\left[-\int_u^t \gamma(s-u|x,s)\,ds\right]. \tag{12}$$

This is an extension of standard survival function for a nonlinear and nonhomogeneous case when Ψ depends on chemotactic substance $S(x,t)$ and population density $\rho(x,t)$. The balance equation for $\rho(x,t)$ can be found by the substitution of Eq. (7) into Eq. (4),

$$\rho(x,t) = \int_0^t j(x,u)\Psi(x,t,u)\,du + \rho_0(x)\Psi(x,t,0). \tag{13}$$

The system of balance equations (9), (10), and (13) is a nonlinear generalization of CTRW renewal equations [1,2,20] and CTRW models for inhomogeneous and nonlinear media [21,22]. These equations can serve as a starting point for the analysis of both chemotaxis and anomalous subdiffusive transport for the space-jump random walk model.

If we differentiate $\rho(x,t)$ in Eq. (13) with respect to time, we obtain the nonlinear master equation

$$\frac{\partial\rho}{\partial t} = \int_{\mathbb{R}} i(x-z,t)w(z|x-z,t)\,dz - i(x,t). \tag{14}$$

For a simple linear homogeneous case, when ϕ and Ψ are independent of x and depend on $t-u$ only, we can obtain from Eqs. (9), (10), and (13) the classical CTRW equation

$$\rho = \int_0^t\int_{\mathbb{R}} \rho(x-z,u)\phi(t-u)w(z)\,dz\,du + \rho_0(x)\Psi(t). \tag{15}$$

A. Non-Markovian random walk in a stationary field of chemotactic substance

Now we are in a position to analyze the chemotaxis and anomalous effects in more detail. First we consider the case when a cell performs a random walk in a stationary environment with the distribution of chemotactic substance $S(x)$. In this case

$$\gamma(\tau|x,t) = \gamma_1(\tau|S(x)). \tag{16}$$

The survival probability Ψ in Eq. (12) must be a function of $\tau = t-u$ and can be written as

$$\Psi(\tau|S(x)) = \exp\left[-\int_0^\tau \gamma_1(u|S(x))\,du\right]. \tag{17}$$

The waiting time probability density function $\phi(\tau|S(x)) = -\partial\Psi(\tau|S(x))/\partial\tau$ is

$$\phi(\tau|S(x)) = \gamma_1(\tau|S(x))\exp\left[-\int_0^\tau \gamma_1(u|S(x))\,du\right]. \tag{18}$$

Using the Laplace transform in Eqs. (9), (10), and (13), we obtain

$$i(x,t) = \int_0^t K_x(t-\tau)\rho(x,\tau)\,d\tau. \tag{19}$$

Here $K_x(t)$ is the memory kernel defined by its Laplace transform

$$\hat{K}_x(s) = \frac{\hat{\phi}(s|S(x))}{\hat{\Psi}(s|S(x))}, \tag{20}$$

where s is the Laplace variable. The generalized master equation is

$$\frac{\partial\rho}{\partial t} = L_1\rho, \tag{21}$$

where the evolution operator L_1 can be written as

$$L_1\rho = \int_0^t\int_{\mathbb{R}} K_{x-z}(t-\tau)\rho(x-z,\tau)w(z|x-z,t)\,dz\,d\tau - \int_0^t K_x(t-\tau)\rho(x,\tau)\,d\tau. \tag{22}$$

The case when the dispersal kernel $w(z|x,t)$ depends on chemotactic substance S has been considered by Langlands and Henry [8]. It has been pointed out by Erban and Othmer that the movement of bacteria in a favorable environment is determined by chemokinesis rather than chemotaxis. In most cases the bacteria or cells are too small to "feel" a macroscopic gradient of S [7,11]. That is why it is more important to study the dependence of transition probability γ on chemotactic substance S. To illustrate the general theory in what follows we use only a symmetrical dispersal kernel $w(z)$.

In a Markovian case, when γ_1 does not depend on the residence time variable τ, we obtain from Eq. (17) that the survival probability is

$$\Psi(\tau|S(x)) = e^{-\gamma_1(S(x))\tau}. \tag{23}$$

The memory kernel $K_x(t) = \gamma_1(S(x))\delta(t)$ and $i(x,t) = \gamma_1(S(x))\rho(x,t)$. If jump lengths are small, the even kernel $w(z)$ is a rapidly decaying function for large z. In this case, one can use the Taylor series in Eq. (22) expanding $\rho(x-z,\tau)$ in z and truncate the series at the second moment. So under this diffusion approximation, the master equation (21) takes the form

$$\frac{\partial \rho}{\partial t} = \frac{\sigma^2}{2}\frac{\partial^2}{\partial x^2}[\gamma_1(S(x))\rho(x,t)], \tag{24}$$

where

$$\sigma^2 = \int_{\mathbb{R}} z^2 w(z)\, dz. \tag{25}$$

It is well known [5] that this equation can be rewritten as

$$\frac{\partial \rho}{\partial t} + \frac{\partial J}{\partial x} = 0$$

with the flux of cells

$$J = \chi \frac{\partial S}{\partial x}\rho - \frac{\sigma^2 \gamma_1(S(x))}{2}\frac{\partial \rho}{\partial x} \tag{26}$$

and the chemotactic sensitivity

$$\chi(S(x)) = -\frac{\sigma^2}{2}\frac{\partial \gamma_1}{\partial S}. \tag{27}$$

When the derivative $\partial\gamma_1/\partial S$ is negative, the advection (taxis) is in the direction of increase in the chemotactic substance.

In the general non-Markovian case, it follows from Eq. (22) that in the diffusion approximation, cell flux is nonlocal in time

$$J = -\frac{\sigma^2}{2}\frac{\partial S}{\partial x}\int_0^t \frac{\partial K_x(t-\tau)}{\partial S}\rho(x,\tau)\, d\tau - \frac{\sigma^2}{2}\int_0^t K_x(t-\tau)\frac{\partial \rho(x,\tau)}{\partial x} d\tau. \tag{28}$$

Here, instead of the sensitivity χ defined in Eq. (27) we have a chemotactic memory kernel $\partial K_x(t)/\partial S$. Note that the memory kernel for the chemotaxis flux is different from the memory kernel for the diffusion term.

Let us consider the situation when the longer cell survives at point x, the smaller the transition probability from x becomes. In this case the rate $\gamma_1(\tau|S(x))$ is a decreasing function of residence time τ. We assume that

$$\gamma_1(\tau|S(x)) = \frac{\mu(S(x))}{\tau_0 + \tau},$$

where τ_0 is a parameter with units of time. It follows from Eq. (17) that the survival function has a power-law dependence

$$\Psi(\tau|S(x)) = \left(\frac{\tau_0}{\tau_0+\tau}\right)^{\mu(S(x))},$$

where the exponent μ depends on the stationary distribution of chemotactic substance $S(x)$. The corresponding waiting time density is

$$\phi(\tau|S(x)) = -\frac{\partial \Psi}{\partial \tau} = \frac{\mu(S(x))/\tau_0}{(1+\tau/\tau_0)^{1+\mu(S(x))}}. \tag{29}$$

The anomalous subdiffusive case with infinite mean residence time corresponds to $\mu(S(x)) < 1$ [1,2,20]. The asymptotic approximation for the Laplace transform of the waiting time density can be found from the Tauberian theorem [23]

$$\hat{\phi}(s|S(x)) \simeq 1 - g_\mu(x)s^{\mu(S(x))} \tag{30}$$

with $g_\mu(x) = \Gamma[1-\mu(S(x))]\tau_0^{\mu(S(x))}$ as $s \to 0$. Since $\hat{\Psi}(s|S(x)) = [1-\hat{\phi}(s|S(x))]/s$, we obtain from Eq. (20) the Laplace transform of the memory kernel

$$\hat{K}_x(s) \simeq \frac{s^{1-\mu(S(x))}}{g_\mu(x)} \tag{31}$$

for $s \to 0$. The cell flux (28) takes the form

$$J = -\frac{\sigma^2}{2}\frac{\partial S}{\partial x}\frac{\partial \mu}{\partial S}\frac{\partial}{\partial \mu}g_\mu^{-1}(x)\mathcal{D}_t^{1-\mu(S(x))}\rho(x,t) - \frac{\sigma^2}{2}g_\mu^{-1}(x)\mathcal{D}_t^{1-\mu(S(x))}\frac{\partial \rho(x,t)}{\partial x}. \tag{32}$$

Here we introduce the *anomalous chemotactic sensitivity* $\partial\mu/\partial S$ as a derivative of the anomalous exponent μ. $\mathcal{D}_t^{1-\mu(S(x))}$ is the Riemann-Liouville fractional derivative:

$$\mathcal{D}_t^{1-\mu(S(x))}\rho(x,t) = \frac{1}{\Gamma[\mu(S(x))]}\frac{\partial}{\partial t}\int_0^t \frac{\rho(x,u)\, du}{(t-u)^{1-\mu(S(x))}} \tag{33}$$

for $0 < \mu(S(x)) < 1$ [1,20]. It should be noted that the fractional derivative of variable order $\mu(x)$ has been considered in [21]. When $\mu = \text{const}$, we have a classical subdiffusion transport equation for which the mean-squared displacement of cell increases with time as t^μ with $\mu < 1$.

B. Anomalous cell aggregation

Let us consider the phenomenon of cell aggregation by chemotaxis [3,5,11,12]. In a Markovian case, in a finite domain with zero flux of cells on the boundary, there exists a stationary nonuniform solution of Eq. (24) [5]. This steady distribution represents cell aggregation. In the anomalous case, the system is not ergodic and there is no steady state distribution. When anomalous chemotactic sensitivity $\partial\mu/\partial S \neq 0$, the cells will tend to aggregate where the exponent μ is small. The anomalous flux (32) leads to

$$\rho(x,t) \to \delta(x - x_M) \quad \text{as} \quad t \to \infty. \tag{34}$$

Here x_M is the point in space where the anomalous exponent $\mu(S(x))$ has a minimum. It means that all cells aggregate into a tiny region of space forming a high density system at the point $x = x_M$. This phenomenon can be referred to as anomalous aggregation. This behavior has been observed in experiments on phagotrophic protists when "cells become immobile in attractive patches, which will then eventually trap all cells" [11]. Another example of dense aggregation is the formation of nodules on the roots of nitrogen-fixing plants that contain the colony of nitrogen-fixing bacteria [3]. Many

pathogenic species have a tendency to colonize at some loci (for example, a wound in the skin).

To understand the phenomenon of anomalous aggregation mathematically, let us consider a coupled map lattice approximation. We divide a finite space domain $[0,l]$ into an N subinterval and denote the density in each subinterval i by ρ_i.

Thus the density field $\rho(x,t)$ is approximated by the vector $\rho(t) = (\rho_1, \rho_2, \ldots, \rho_N)$. Now we assume that cells jump on the right and the left with equal probability $1/2$. The transition rate of the cells is regulated by the local concentration of chemotactic substance S_i, say, by foods [11]. We denote the corresponding anomalous exponent by $\mu_i = \mu(S_i)$. Then it follows from the master equation (21) that the governing equation for $\rho(t)$ is

$$\frac{d\rho_i}{dt} = \frac{1}{2}\int_0^t [K_{i-1}(t-\tau)\rho_{i-1}(\tau) + K_{i+1}(t-\tau)\rho_{i+1}(\tau) - 2K_i(t-\tau)\rho_i(\tau)]\,d\tau \quad (35)$$

for $i = 3, \ldots, N-2$. It should be noted that this equation has been derived earlier by Chechkin *et al.* [21]. In the subdiffusive case, the memory kernel K_i is defined by its Laplace transform:

$$\hat{K}_i(s) \simeq \frac{s^{1-\mu_i}}{\Gamma(1-\mu_i)\tau_0^{\mu_i}} \quad (36)$$

for $s \to 0$ [see Eq. (31)]. Since there is no flux of cells outside the domain $[0,l]$, the lattice master equation (35) should be modified for the subintervals $1,2$ and $N-1,N$. For example,

$$\frac{d\rho_1}{dt} = \frac{1}{2}\int_0^t [K_2(t-\tau)\rho_2(\tau) - 2K_1(t-\tau)\rho_1(\tau)]\,d\tau. \quad (37)$$

Let us assume that the maximum food's concentration is inside the interval $i = M$, and, therefore, $\mu_M < \mu_i$ for all $i \neq M$. If we apply the Laplace transform to Eq. (35) and use the law of conservation of mass: $\sum_{i=1}^N \hat{\rho}_i(s) = 1/s$, we obtain $s\hat{\rho}_i(s) \to 0$ for $i \neq M$ and $s\hat{\rho}_M(s) \to 1$ as $s \to 0$ or $\rho_M(t) \to 1$ and $\rho_i(t) \to 0$ for $i \neq M$ as $t \to \infty$. It means that all cells are trapped inside the subinterval $i = M$ with the maximum food's concentration as $t \to \infty$ [see Eq. (34) for the distributed case]. This result should be valid for high dimensions too. A similar effect has been discussed in a different context for a simple two-state system [24] and a composite system of two separated regions with different anomalous exponents [21,25]. Sometimes such aggregation is referred to as *chemotactic collapse* [5]. However, our explanation of this effect is different from the classical one based on the Patlak-Keller-Segel (PKS) model [12]. In the PKS theory chemotactic collapse means the growth of cell density to infinity in finite time.

C. Markov model with nonlinear transition rate

To prevent the occurrence of delta distribution (34), one can take into account the crowding effect. We assume that the transition rate γ depends on the density $\rho(x,t)$ and time t, that is,

$$\gamma(\tau|x,t) = \gamma_2(\rho(x,t),t). \quad (38)$$

If the transition rate γ is independent of residence time τ, then the system is Markovian. In this case the density of cells $i(x,t)$ leaving the point x exactly at time t is $i(x,t) = \gamma_2(\rho(x,t),t)\rho(x,t)$. The nonlinear evolution equation for ρ is $\partial\rho/\partial t = L_2\rho$ with the operator L_2:

$$L_2\rho = \int_{\mathbb{R}} \gamma_2(\rho(x-z,t),t)\rho(x-z,t)w(z|x-z,t)\,dz - \gamma_2(\rho(x,t),t)\rho(x,t). \quad (39)$$

In a diffusion approximation for the symmetric dispersal kernel $w(z)$, we obtain

$$\frac{\partial\rho}{\partial t} = \frac{\sigma^2}{2}\frac{\partial^2(\gamma_2(\rho,t)\rho)}{\partial x^2}, \quad (40)$$

where σ^2 is defined in Eq. (25). Note that Eq. (40) can be rewritten as a classical diffusion equation

$$\frac{\partial\rho}{\partial t} = \frac{\partial}{\partial x}\left(D(\rho)\frac{\partial\rho}{\partial x}\right) \quad (41)$$

with the density dependent diffusivity $D(\rho) = \frac{\sigma^2}{2}(\frac{\partial\gamma_2}{\partial\rho} + \gamma_2)$. If $\gamma_2(\rho,t)$ is the decreasing function of ρ and $\rho\partial\gamma_2/\partial\rho + \gamma_2 < 0$, $D(\rho)$ becomes negative. The pattern formation due to this effect has been studied in [26] where a transport operator similar to L_2 has been suggested (see also [27]).

D. Non-Markovian random walk with nonlinear transition rate

Now let us consider the case when the transition rate $\gamma(\tau|x,t)$ depends on the residence time τ, chemotactic substance $S(x)$, and the density ρ as follows:

$$\gamma(\tau|x,t) = \gamma_1(\tau|S(x)) + \gamma_2(\rho(x,t),t). \quad (42)$$

From Eqs. (9), (10), and (13), after lengthy calculations, we obtain

$$i(x,t) = \int_0^t K_x(t-\tau)\exp\left[-\int_\tau^t \gamma_2(\rho(x,s),s)\,ds\right]\rho(x,\tau)\,d\tau + \gamma_2(\rho(x,t),t), \quad (43)$$

where the memory kernel $K_x(t)$ is defined in Eq. (20). The nonlocal term in Eq. (43) involves the exponential factor with $\gamma_2(\rho(x,t),t)$. Although γ_1 and γ_2 are separable [see Eq. (42)], the corresponding terms in Eq. (43) are not separable. This is a non-Markovian memory effect. The generalized master equation is $\partial\rho/\partial t = L\rho$, where

$$L\rho = \int_0^t\int_{\mathbb{R}} K_{x-z}(t-\tau)\rho(x-z,\tau) \times \exp\left[-\int_\tau^t \gamma_2(\rho(x-z,s),s)\,ds\right]w(z|x-z,t)\,dz\,d\tau - \int_0^t K_x(t-\tau)\rho(x,\tau). \quad (44)$$

It follows from here that $L\rho \neq L_1\rho + L_2\rho$ despite the fact that $\gamma = \gamma_1 + \gamma_2$ [see Eq. (42)]. A similar phenomenon related to chemical reactions has been discussed in [19,20,28]. The exponential factor with γ_2 in Eq. (44) prevents an anomalous aggregation effect in a long-time limit.

III. CONCLUSIONS

We introduce a nonlinear CTRW model which is suitable for the analysis of both chemotaxis and anomalous subdiffusive transport. We consider the case when the transition rate for a random walk depends not only on residence time, but also on chemotactic substance, its derivatives, and macroscopic population density. We manage to derive the balance equations for the population density and corresponding nonlinear master equations. We introduce the concept of anomalous chemotactic sensitivity as a derivative of the anomalous exponent with respect to chemotaxis substance. We find the effect of anomalous aggregation when all bacteria tend to aggregate at the point where the power-law exponent has a minimum. So we suggest an explanation of *chemotactic collapse* which is different from the classical one based on the PKS model. It should be noted that we did not explicitly include the power law for a waiting time distribution. It occurs naturally as a result of the assumption that the longer the cell survives at point x, the smaller the transition probability from x becomes. We assume that the transition probability is inversely proportional to the large residence time.

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[1] R. Metzler and J. Klafter, Phys. Rep. **339**, 1 (2000).
[2] R. Metzler and J. Klafter, J. Phys. A **37**, R161 (2004).
[3] G. Wadhams and J. Armitage, Nat. Rev. Mol. Cell Biol. **5**, 1024 (2004).
[4] W. Alt, J. Math. Biol. **9**, 147 (1980); H. G. Othmer, S. R. Dunbar, and W. Alt, *ibid.* **26**, 263 (1988).
[5] H. G. Othmer and A. Stevens, SIAM J. Appl. Math. **57**, 1044 (1997).
[6] P. G. de Gennes, Eur. Biophys. J. **33**, 691 (2004); D. A. Clark and L. C. Grant, Proc. Natl. Acad. Sci. USA **102**, 9150 (2005); A. Celani and M. Vergassola, *ibid*. **107**, 1391 (2010).
[7] R. Erban and H. G. Othmer, Multiscale Model Simul. **3**, 362 (2005).
[8] T. A. M. Langlands and B. I. Henry, Phys. Rev. E **81**, 051102 (2010).
[9] T. Hillen, Math. Models Meth. Appl. Sci. **12**, 1 (2002); T. Hillen and A. Stevens, Nonlinear Analysis: Real World Appl. **1**, 409 (2000).
[10] E. Korobkova *et al.*, Nature (London) **428**, 574 (2004).
[11] T. Fenchel and N. Blackburn, Protist **160**, 325 (1999).
[12] B. Perthame, Appl. Math. **49**, 539 (2004); M. Herrero and J. Velazquez, J. Math. Biol. **35**, 177 (1996).
[13] G. Viswanathan *et al.*, Nature (London) **401**, 911 (1999).
[14] S. Fedotov and A. Iomin, Phys. Rev. Lett. **98** 118101 (2007); Phys. Rev. E **77**, 031911 (2008).
[15] S. Fedotov and V. Méndez, Phys. Rev. Lett. **101**, 218102 (2008).
[16] D. Campos, V. Méndez, and V. Ortega-Cejas, Bull. Math. Biol. **70**, 1937 (2008).
[17] D. R. Cox and H. D. Miller, *The Theory of Stochastic Processes* (Methuen, London, 1965).
[18] M. O. Vlad and J. Ross, Phys. Rev. E **66**, 061908 (2002).
[19] A. Yadav and W. Horsthemke, Phys. Rev. E **74**, 066118 (2006).
[20] V. Méndez, S. Fedotov, and W. Horsthemke, *Reaction-Transport Systems* (Springer, Berlin, 2010).
[21] A. V. Chechkin, R. Gorenflo, and I. M. Sokolov, J. Phys. A **38**, L679 (2005).
[22] R. Sanchez, B. A. Carreras, and B. Ph. van Milligen, Phys. Rev. E **71**, 011111 (2005).
[23] W. Feller, *An Introduction to Probability Theory and Its Applications*, (Wiley, New York, 1971), Vol. 2.
[24] D. Campos, S. Fedotov, and V. Méndez, Phys. Rev. E **77**, 061130 (2008).
[25] N. Korabel and E. Barkai, Phys. Rev. Lett. **104**, 170603 (2010).
[26] S. Fedotov, D. Moss, and D. Campos, Phys. Rev. E **78**, 026107 (2008).
[27] M. E. Cates, D. Marenduzzo, I. Pagonabarraga, and J. Tailleur, Proc. Natl. Acad. Sci. USA **107**, 11715 (2010).
[28] B. I. Henry, T. A. M. Langlands, and S. L. Wearne, Phys. Rev. E **74**, 031116 (2006); S. Fedotov, *ibid*. **81**, 011117 (2010). S. Fedotov *et al.*, *ibid*. **82**, 041103 (2010).