Subdiffusion, superdiffusion and chemotaxis

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We propose two nonlinear random walk models which are suitable for the analysis of both chemotaxis and anomalous transport. We derive the balance 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 anomalous aggregation phenomenon. So we suggest a new explanation of the well-known effect of chemotactic collapse. We develop a non-Markovian "velocity-jump" model and obtain the superdiffusive behavior of bacteria with power law "run" time.

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Continuous time random walks (CTRW) have been widely used in many fields including physics, chemistry and life sciences (see, for example, excellent reviews [1, 2]). Many biological and physical transport processes exhibit anomalous behavior for which walker mean-squared displacement increases as a fractional power of time: $< x^2(t) > \sim t^\mu$ (subdiffusion: $\mu < 1$; superdiffusion: $\mu > 1$). The chemotaxis is a directed migration of cells population toward a more favorable environment. The microscopic theory of the movement of cells or organisms is also based on the random walk theory (see, for example, [3, 4]). Although chemotaxis has a long history and has been studied by researchers for many decades, there is a lack of literature on connection between the anomalous random walk and chemotaxis theory. We should mention recent exception [5] 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]. The main purpose of this paper is to set up the random walk models for both chemotaxis and anomalous transport. These models can be also used in other biological applications of CTRW and chemotaxis as anomalous search strategy [7], cancer cell dichotomy [3], subdiffusion in spiny dendrites [10], embryogenesis and wound healing. Much of the recent literature on chemotaxis has been concerned with movement of bacteria E. coli involving the runs and tumbles. The standard assumption in modeling is that "run" and "tumble" time intervals are exponentially distributed [3]. However it has been found experimentally [11] that the distribution of "run" time intervals might deviate significantly from exponential approximation. It has a power law and leads to superdiffusive behavior of bacteria. One of the purposes of this paper is to examine the effect of long-time tails on bacteria movement in terms of "velocity-jump" model.

We start with "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 $\gamma$ for jumps at point $x$. The standard assumption in CTRW theory is that $\gamma$ depends on the residence time (age) $\tau$. This is a time interval between two successive jumps of the cell. The corresponding waiting time density $\phi(t)$ is related to $\gamma(\tau)$ as $\phi(t) = \gamma(t) \exp \left( \int_0^t \gamma(\tau) d\tau \right)$ [12]. In chemotaxis theory the jump of cells occurs in response to a chemical signal [4]. Therefore the transition rate $\gamma$ should depend on chemotactic substance (external signal) $S(x,t)$ and its spatial and temporal gradient. It also depends on macroscopic population density $\rho(x,t)$. This dependence describes the coupling of the cells density and chemotactic substance and crowding effects. Thus

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

(1)

We introduce the cell density $\xi(x,t,\tau)$ at position $x$ at time $t$ with the residence time $\tau$. The main reason for introduction of the structured density $\xi$ is to make a random walk Markovian. This idea has been used in [3, 12–14]. The density $\xi$ obeys the balance equation

$$\frac{\partial \xi}{\partial t} + \frac{\partial \xi}{\partial \tau} = -\gamma(\tau|S(x,t),\dot{S}(x,t),\rho(x,t),t)\xi.$$  

(2)

We use the initial condition $\xi(x,0,\tau) = \rho_0(x)\delta(\tau)$ for which the residence time of all cells at $t = 0$ equals to 0; $\rho_0(x)$ is the initial density of cells. It is clear that the residence time $\tau$ varies from 0 to $t$. The condition at $\tau = 0$ can be written as

$$\xi(x,t,0) = \int_R \int_0^t \gamma(\tau|x,t)\xi(x-z,t,\tau)w(z|x-z,t) d\tau dz.$$  

(3)

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 $t$

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

(4)

It is assumed that $w$ is independent from $\tau$. On the left hand side of (3) we have a density of cells just arriving at point $x$ at time $t$ (zero residence time). On the right hand side of (3) we have an integration of the rate at which the cells with different age $\tau$ arriving at position $x$ at time $t$ from the different points $x-z$. Our purpose
now is to derive the Master equation for the cell density
\[
\rho(x, t) = \int_0^t \xi(x, t, \tau)d\tau
\]  
(5)
Using the method of characteristics, we find from (2) that
\[
\xi(x, t, \tau) = \xi(x, t - \tau, 0)e^{-\int_{t-\tau}^t \gamma(s-t-\tau)|x,s|ds}.
\]  
(6)
Let us denote the density of cells just arriving at point \( x \) at time \( t \) by \( j(x, t) = \xi(x, t, 0) \). We substitute (6) into (3) and take into account the initial condition for \( \xi \). We get
\[
j(x, t) = \int_{\mathbb{R}} i(x - z, t) w(z|x - z, t) dz,
\]  
(7)
where the \( i(x, t) \) is the density of cells leaving the point \( x \) exactly at time \( t \):
\[
i(x, t) = \int_0^t j(x, u)\phi(x, t, u)du + \rho_0(x)\phi(x, t, 0)
\]  
(8)
\[
\phi(x, t, u) = -\frac{\partial \Psi(x, t, u)}{\partial t} = \gamma(t - u|x, t)e^{-\int_u^t \gamma(s-u|x,s)ds}
\]  
and \( \Psi(x, t, u) \) is the probability that a cell is trapped at point \( x \) from time \( u \) to \( t \) without executing a jump
\[
\Psi(x, t, u) = e^{-\int_u^t \gamma(s-u|x,s)ds}.
\]  
(10)
This is an extension of standard survival function for a nonlinear and nonhomogeneous case when \( \Psi \) depends on chemotactic substance \( S(x, t) \) and population density \( \rho(x, t) \). The balance equation for \( \rho(x, t) \) can be found by substitution of (6) into (5)
\[
\rho(x, t) = \int_0^t j(x, u)\Psi(x, t, u)du + \rho_0(x)\Psi(x, t, 0).
\]  
(11)
The system of balance equations (7), (8) and (11) is a nonlinear generalization of classical CTRW renewal equations \[1, 15\] and CTRW models for inhomogeneous and nonlinear media \[16, 17\]. These equations can serve as a starting point for the analysis of both chemotaxis and anomalous transport for "space-jump" random walk model. If we differentiate \( \rho(x, t) \) in (11) with respect to time, we obtain the nonlinear Master equation
\[
\frac{\partial \rho}{\partial t} = \int_{\mathbb{R}} i(x - z, t) w(z|x - z, t) dz - i(x, t).
\]  
(12)
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 \( \gamma(t|x, t) = \gamma_1(t|S(x)) \). The survival probability \( \Psi \) in (10) must be a function of \( \tau = t - u \) and can be written as
\[
\Psi(\tau|S(x)) = e^{-\int_0^\tau \gamma_1(u|S(x))du}.
\]  
(13)
Using the Laplace transform in (7), (8) and (11), we obtain
\[
i(x, t) = \int_0^t K_x(t - \tau) \rho(x, \tau) d\tau,
\]  
(14)
where \( K_x(t) \) is the memory kernel defined by its Laplace transform
\[
\hat{K}_x(s) = \frac{\hat{\phi}(s|S(x))}{\hat{\Psi}(s|S(x))},
\]  
(15)
where \( s \) is the Laplace variable. Substitution of (14) into (12) gives a generalized Master equation \( \partial \rho/\partial t = L_1\rho \) with the operator \( L_1 \):
\[
L_1\rho = \int_{\mathbb{R}} \int_0^t K_{x-z}(t - \tau) \rho(x - z, \tau) w(z|x - z, t) dz d\tau - \int_0^t K_x(t - \tau) \rho(x, \tau) d\tau.
\]  
(16)
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 movement of bacteria in favorable environment is determined by chemokinesis rather than chemotaxis. In most cases the bacteria or cell "does not feel" a macroscopic gradient of \( S \) \[6\]. That is why it is more important to study the dependence of transition probability \( \gamma \) on chemotactic substance \( S \). To illustrate the general theory we use only a symmetrical dispersal kernel \( w(z) \) as a function of \( z \).

In a Markovian case, when \( \gamma \) does not depend on the residence time variable \( \tau \), we have \( \Psi(x, t, u) = e^{-\gamma_1(S(x))t} \) and \( \hat{K}_x(s) = \gamma_1(S(x)) \). Under the diffusion approximation, the Master equation (16) takes the form
\[
\frac{\partial \rho}{\partial t} = \frac{\sigma^2}{2} \frac{\partial^2}{\partial x^2} (\gamma_1(S(x))\rho(x, t)),
\]  
(17)
where \( \sigma^2 = \int_{\mathbb{R}} z^2 w(z)dz \). It is well known \[4\] that this equation can be rewritten as \( \partial \rho/\partial t + \partial J/\partial x = 0 \) with the flux of cells
\[
J = \chi \frac{\partial S}{\partial x} - \frac{\sigma^2}{2} \frac{\gamma_1(S(x))}{\partial S} \frac{\partial \rho}{\partial x},
\]  
(18)
where \( \chi \) is the chemotactic sensitivity. When the derivative \( \partial \gamma_1/\partial S \) is negative, the advection (taxis) is in the direction of increase in chemotactic substance. In general it follows from (16) that cells flux is not local in time
\[
J = -\frac{\sigma^2}{2} \frac{\partial S}{\partial x} \int_0^t \frac{\partial K_x(t - \tau)}{\partial \tau} \rho(x, \tau) d\tau - \frac{\sigma^2}{2} \int_0^t K_x(t - \tau) \frac{\partial \rho(x, \tau)}{\partial x} d\tau.
\]  
(19)
Instead of \( \chi \) we have a chemotaxis memory kernel \( \partial K_x(t)/\partial S \). Note that the memory kernel for the chemotaxis flux is different form the memory kernel for diffusion term (compare to \[8\]).
Let us consider the anomalous case when the waiting time PDF is heavy-tailed, such that the corresponding mean time is infinite. We assume that the longer cell survives at point x, the smaller the transition probability from x becomes. The rate \( \gamma(x,t) \) is a monotonically decreasing function of residence time \( \tau \). For example, if \( \gamma(x,t) = \mu(S(x)) / (\beta + \tau) \), it follows from [13] that the survival function has a power-law dependence

\[
\Psi(\tau|S(x)) = \left( \frac{\beta}{\beta + \tau} \right)^{\mu(S(x))},
\]

where \( \beta \) is constant. Anomalous case corresponds to \( \mu(S(x)) < 1 \) [1, 13], when \( K_x(s|S(x)) = s^{1-\mu(S(x))} \tau_0^{-\mu(S(x))} \); \( \tau_0 \) is a parameter with units of time. The anomalous cell flux is

\[
J = -\frac{\sigma^2}{2} \frac{\partial S}{\partial x} \frac{1}{\tau_0^{\mu(S(x))}} D_t^{1-\mu(S(x))} \rho(x,t) - \frac{\sigma^2}{2} \frac{\partial^2}{\partial x^2} D_t^{1-\mu(S(x))} \rho(x,t),
\]

where the Riemann-Liouville fractional derivative \( D_t^{1-\mu(S(x))} \) is defined [1, 13] as

\[
D_t^{1-\mu(S(x))} \rho(x,t) = \frac{1}{\Gamma(1-\mu(S(x)))} \frac{\partial}{\partial t} \int_0^t (t-u)^{\mu(S(x))} \rho(x,u) du.
\]

It should be noted that the fractional time derivative of variable order \( \mu(x,t) \) has been considered in [10]. When \( \mu = const. \), we have a classical subdiffusion transport equation for which the mean squared displacement of cell increases with time as \( t^\mu \) with \( \mu < 1 \).

Let us consider the aggregation phenomenon [4]. In a Markovian case, in a finite domain with zero flux of cells on the boundary, there exists a stationary non-uniform solution of [17, 3]. The aggregation of cells is due to the fact that mean waiting time \( \gamma^{-1}(S(x)) \) is decreasing function of the chemotactic substance \( S \). In an anomalous case, the system is not ergodic and there is no stationary distribution. However, one can introduce the anomalous chemotactic sensitivity as a derivative of anomalous exponent: \( \chi_{\mu} = \mu(S(x)) \). When \( \chi_{\mu} < 0 \), the cells will tend to aggregate where the exponent \( \mu \) is small. The anomalous flux [29] leads to \( \rho(x,t) \rightarrow \delta(x-x_{min}) \) as \( t \rightarrow \infty \). Here \( x_{min} \) is the point where the anomalous exponent \( \mu(S(x)) \) has a minimum. It means that all cells aggregate into a tiny region of space forming high density system at the point \( x = x_{min} \). This phenomenon can be referred to as anomalous aggregation. Similar results have been obtained in [18] for a simple two-state system. This effect is known in a literature as chemotactic collapse [4]. Here we suggest an explanation of this effect which is different from the classical one based on Keller-Segel equations. To prevent the occurrence of delta-distribution we need to take into account the crowding effect. In what follows, we consider this effect by assuming that the transition rate depends on both the residence time \( \tau \) and the population density \( \rho \).

If the transition rate \( \gamma \) is independent of residence time \( \tau \), then the system is Markovian. We assume that \( \gamma \) depends on the time \( t \) and the density \( \rho(x,t) \) or non-stationary chemotactic substance \( S(x,t) \), that is \( \gamma(\tau|x,t) = \gamma_1(\rho(x,t), t) \). Then we obtain \( i(x,t) = \gamma_2(\rho(x,t), t) \rho(x,t) \).

The nonlinear evolution equation for \( \rho \) is \( \partial \rho / \partial t = L_2 \rho \), where the operator \( L_2 \) is defined as

\[
L_2 \rho = \int_R \gamma_2(\rho(x-z,t), t) \rho(x-z,t) w(z|x-z,t) dz - \gamma_2(\rho(x,t), t) \rho(x,t).
\]

Now let us consider the case when the transition probability \( \gamma(\tau|x,t) \) depends both on the residence time \( \tau \) and the density \( \rho \) as follows

\[
\gamma(\tau|x,t) = \gamma_1(\tau|S(x)) + \gamma_2(\rho(x,t), t).
\]

From (17), (8) and (11), after lengthy calculations, we obtain

\[
i(x,t) = \int_0^t K_x(t-\tau) e^{-\int_0^t \gamma_2(\rho(x,s), s) ds} \rho(x,\tau) d\tau + \gamma_2(\rho(x,t), t).
\]

It turns out that the nonlocal term in (24) involves the exponential factor with \( \gamma_1(\rho(x,t), t) \). Although \( \gamma_1 \) and \( \gamma_2 \) are separable (see (23)), the corresponding terms in (24) are not separable. This is a non-Markovian memory effect. The generalized Master equation is \( \partial \rho / \partial t = L_\rho \), where

\[
L_\rho = \int_0^t \int_R K_{x-z}(t-\tau) \rho(x-z,\tau) x e^{-\int_0^t \gamma_2(\rho(x-s, s), s) ds} \times w(z|x-z, t) dz d\tau - \int_0^t K_x(t-\tau) \rho(x,\tau) e^{-\int_0^t \gamma_2(\rho(x,s), s) ds} d\tau + L_2 \rho.
\]

It follows from here that \( L_\rho \neq L_1 \rho + L_2 \rho \) despite the fact that \( \gamma = \gamma_1 + \gamma_2 \). Similar phenomena related to chemical reactions has been discussed in [14, 15, 19]. The exponential factor with \( \gamma_2 \) in (25) prevents an anomalous aggregation effect in a long-time limit.

Let us consider now 1-D non-Markovian "velocity-jump" model for bacteria movement. The purpose is to get the superdiffusive behavior [11]. The bacteria moves to the right with the velocity \( v_+ \) and reverses the direction with the rate \( \gamma_+ \). When the bacteria moves to the left with the velocity \( v_- \), the turning rate is \( \gamma_- \). In general, the turning rate depends on run time \( \tau \), on chemotactic substance \( S \) and macroscopic population density \( \rho(x,t) : \gamma_{\pm}(\tau|x,t) = \gamma_{\pm}(\tau|S(x,t), S(x,t), \rho(x,t), t) \).

Let \( \xi_\pm(x,t,\tau) \) be the density of bacteria moving with velocity \( v_\pm \) with run time \( \tau \). The corresponding density of organisms moving with the velocity \( v_- \) is \( \xi_-(x,t,\tau) \). Integration of \( \xi_\pm(x,t,\tau) \) over the run time variable \( \tau \) gives the mean densities \( \rho_\pm(x,t) = \int_0^\infty \xi_\pm(x,t,\tau) d\tau \). The system of equations for \( \xi_\pm(x,t,\tau) \) suggested by Alt [3] are

\[
\frac{\partial \xi_\pm}{\partial t} \pm v_\pm \frac{\partial \xi_\pm}{\partial x} + \frac{\partial \mathcal{K}_\pm}{\partial \tau} = -\gamma_{\pm}(\tau|x,t) \xi_\pm.
\]
Initial conditions are \( \xi_\pm(x,0,\tau) = \rho_0^\pm(x)\delta(\tau) \), where \( \rho_0^\pm(x) \) are the initial densities. Boundary conditions at \( \tau = 0 \):

\[
\xi_\pm(x,t,0) = \int_0^t \gamma_\mp(\tau)S(x,t), \rho(x,t), t\xi_\pm(x,t,\tau)d\tau.
\]

By using method of characteristics we solve (20) and from (27) after lengthy manipulations we find the nonlinear system of equations for \( \rho_\pm(x,t) \) and \( j_\pm(x,t) = \xi_\pm(x,t,0) \):

\[
\rho_\pm(x,t) = \int_0^t j_\pm(x + v_\pm(t - u), u) \Psi_\pm(x,t,u)du + \rho_0^\pm(x + v_\pm t) \Psi_\pm(x,t,0),
\]

\[
j_\pm(x,t) = -\int_0^t j_\mp(x + v_\mp(t - u), u) \Psi_\pm(x,t,u)du - \rho_0^\mp(x + v_\mp t) \Psi_\pm(x,t,0).
\]

Here we introduce the generalized survival function

\[
\Psi_\pm(x,t,u) = e^{-\int_u^\tau \gamma_\pm(s - u)\pm v_\pm(t - s), s)ds}
\]

and its full derivative \( \dot{\Psi}_\pm = \frac{\partial \Psi_\pm}{\partial x} \pm v_\pm \frac{\partial \Psi_\pm}{\partial x} = -\gamma_\pm(\tau)S(x,t), \dot{S}(x,t), \rho(x,t), t \Psi_\pm \). If we differentiate \( \rho_\pm(x,t) \) with respect to time, we obtain the system of nonlinear equations

\[
\frac{\partial \rho_\pm}{\partial t} \pm v_\pm \frac{\partial \rho_\pm}{\partial x} = j_\pm(x,t) - j_\mp(x,t).
\]

If the switching rates \( \gamma_+ \) and \( \gamma_- \) are independent of run time \( \tau \), then \( j_\pm(x,t) = \gamma_\pm(\tau)S(x,t), \dot{S}(x,t), \rho(x,t), t \rho_\pm(x,t) \). This hyperbolic model has been studied by Hillen et al. [2].

Let us illustrate the general theory by considering the case when \( v_\pm = v \) and the run time PDF \( \psi_\pm(\tau) = \gamma_\pm(\tau) \exp \left( \int_0^\tau \gamma_\pm(\tau)d\tau \right) \) behaves like

\[
\psi_\pm(\tau) \sim \left( \frac{\tau_0}{\tau} \right)^{1+\mu}, \quad \mu < 1, \quad \tau \to \infty.
\]

The mean waiting time \( < \tau_\pm > = \int_0^\infty \tau \psi_\pm(\tau)d\tau \) is infinite. The experimental evidence of a power-law distribution like (32) has been reported in [11]. We assume that \( v_+ = v_- = v \) and all bacteria run in a positive direction initially. First we find the Laplace transform of \( \left< x(t) \right> : \left< x(s) \right> = -i \left( \frac{d\rho(k,s)}{dk} \right)_{k=0} \), where \( \rho(k,s) = \rho_+(k,s) + \rho_-(k,s) \) is the Fourier-Laplace transform of the total bacteria density of particles \( \rho = \rho_+ + \rho_- \). In the limit \( s \to 0 \), we find from (28) and (29) a very unusual result that \( \left< x(t) \right> \sim v \tau_0^{\mu}s^{-2+\mu} \). It means that the average position of bacteria is not zero as it should be in Markovian case! It fact \( \left< x(t) \right> \sim v \tau_0^{\mu}t^{-\mu} \) as \( t \to \infty \). The spreading is slower than a ballistic motion \( (x(t) = vt) \) and faster than diffusion for \( 0 < \mu < 0.5 \) (superdiffusion).

In summary, we introduce two nonlinear CTRW models which are suitable for the analysis of both chemotaxis and anomalous 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 derivative 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 anomalous exponent with respect to chemotaxis substance. We find the effect of anomalous aggregation when all bacteria tend to aggregate at the point where power-law exponent has a minimum. So we suggest a new explanation of chemotactic collapse which is different from the classical one based on Keller-Segel equations. Motivated by experiment on run and tumble chemotaxis [11], we set up non-Markovian ”velocity-jump” model and obtain the superdiffusive behavior of bacteria with power law ”run” time.