Nonlinear subdiffusive fractional equations and the aggregation phenomenon

Sergei Fedotov

School of Mathematics, University of Manchester, Manchester M13 9PL, UK

In this article we address the problem of the nonlinear interaction of subdiffusive particles. We introduce the random walk model in which statistical characteristics of a random walker such as escape rate and jump distribution depend on the mean density of particles. We derive a set of nonlinear subdiffusive fractional master equations and consider their diffusion approximations. We show that these equations describe the transition from an intermediate subdiffusive regime to asymptotically normal advection-diffusion transport regime. This transition is governed by nonlinear tempering parameter that generalizes the standard linear tempering. We illustrate the general results through the use of the examples from cell and population biology. We find that a nonuniform anomalous exponent has a strong influence on the aggregation phenomenon.

I. INTRODUCTION

Anomalous subdiffusion is a widespread phenomenon in physics and biology [1–3]. It is observed in the transport of proteins and lipids on cell membranes [4], RNA molecules in the cells [5], signaling molecules in spiny dendrites [6], and elsewhere. Apart from fractional Brownian motion, the *linear* fractional equations are the standard models for the description of anomalous subdiffusive transport [2]. In these models the diffusing particles do not interact. The question then arises as to how to extend these equations for the *nonlinear* case, involving particle interactions. These nonlinear effects are typical and very important in cellular and population biology. It is well known that many biophysical processes in microorganisms depend on the their population density. A typical example is the *quorum sensing phenomenon,* in which microorganisms coordinate their behavior according to their local population density [7]. Other examples are a *cellular adhesion,* which involves the interaction between neighboring cells [8–11], and the *volume filling effect,* which describes the dependence of cell motility on the availability of space in a crowded environment [12,13]. The understanding of macroscopic phenomena like cell and microorganism aggregation requires an understanding of how individual species interact through attractive or repulsive forces (see, for example, Ref. [14] and references therein). The attraction between individuals may result from various social interactions such as mating, settlement, defense against predators, etc. While the repulsion may occur due to low resources in highly populated regions [14,15]. Note that microorganisms interact both directly and indirectly via signaling molecules.

The main purpose of this paper is to incorporate these nonlinear effects into subdiffusive equations. Our aim is to take into account the interaction between particles on the mesoscopic level, at which the random walker's characteristics depend on the mean field density of particles. Our intention is to derive the subdiffusive nonlinear fractional equations for the density of particles and apply these equations to the problem of aggregation. In this paper we use two different approaches that are based on the density-dependent dispersal kernels and density-dependent jump rate. Note that several theoretical studies have been devoted to nonlinear generalizations of linear fractional equations. However, most research has been focused

on the problem how to incorporate the nonlinear reactions into subdiffusive equations [16–26]. The aim of this paper is to study the nonlinear subdiffusive transport processes involving the anomalous trapping of particles and their interactions.

In this paper we deal with the random walk model involving a residence time-dependent escape rate and the structural density of particles. This has been used by many authors for the analysis of the non-Markovian random walks [3,16,17,27–29]. It turns out that this linear model is the most suitable for further nonlinear generalizations. We consider a "space-jump" random walk in one space dimension. The particle waits for a random time (residence time) T_x at point x in space before making a jump to another point. The random residence time T_x is determined by the probability density function $\psi(x,\tau) = \Pr\{\tau < T_x < \tau + d\tau\}$. The key characteristic of this random walk is the escape rate γ from the point x. It depends on the residence time τ and the position $x : \gamma = \gamma(x,\tau)$. This rate can be rewritten in terms of the probability density function $\psi(x,\tau)$ and the survival probability $\Psi(x,\tau) = \int_\tau^\infty \psi(x,u)\,du$ as follows [30]:

$$\gamma(x,\tau) = \frac{\psi(x,\tau)}{\Psi(x,\tau)}. \tag{1}$$

It is convenient to write the survival probability $\Psi(x,\tau)$ in terms of $\gamma(x,\tau)$ as follows:

$$\Psi(x,\tau) = e^{-\int_0^\tau \gamma(x,s)\,ds}. \tag{2}$$

Let $\xi(x,\tau,t)$ be the structural density of particles at point x at time t whose residence time lies in the interval $(\tau,\tau + d\tau)$. Here we neglect the aging phenomenon [31] and assume that at $t = 0$ all particles have zero residence time:

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

where $\rho_0(x)$ is the initial density. To consider the aging we need to specify the general distribution for $\xi(x,\tau,0)$.

For the initial condition (3), the density of particles, $\rho(x,t)$, is obtained by integration of the structural density $\xi(x,\tau,t)$ with respect to the residence time variable τ from 0 to t:

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

The number of particles with fixed residence time τ escaping from the point x per unit of time is defined as a product

$\gamma(x,\tau)\xi(x,\tau,t)$. The total escape rate, $i\,(x,t)$, of particles from the point x can be obtained by integration of this product with respect to τ from 0 to t:

$$i(x,t) = \int_0^t \gamma(x,\tau)\xi(x,\tau,t)\,d\tau. \qquad (5)$$

The rate $i\,(x,t)$ is a very useful quantity, since it allows us to write a very simple master equation for the density $\rho\,(x,t)$ as the balance of particles at the point x:

$$\frac{\partial\rho}{\partial t} = \int_{\mathbb{R}} i\,(x-z,t)\,w\,(z|x-z)\,dz - i\,(x,t), \qquad (6)$$

where $w\,(z|x)$ is the dispersal kernel for the jumps. We have assumed here that the jumps of particles are independent from the residence time. One of the main results in the non-Markovian random walk theory is that the mean escape rate $i\,(x,t)$ can be written as a convolution:

$$i\,(x,t) = \int_0^t K\,(x,t-\tau)\,\rho\,(x,\tau)\,d\tau \qquad (7)$$

(see, for example, Ref. [3]). Here $K(x,t)$ is the memory kernel defined by its Laplace transform:

$$\hat{K}\,(x,s) = \frac{\hat{\psi}\,(x,s)}{\hat{\Psi}\,(x,s)}, \qquad (8)$$

where $\hat{\psi}\,(x,s) = \int_0^\infty e^{-s\tau}\psi(x,\tau)\,d\tau$ and $\hat{\Psi}\,(x,s) = \int_0^\infty e^{-s\tau}\Psi(x,\tau)\,d\tau$.

In the anomalous subdiffusive case, the survival probability $\Psi_\mu\,(x,\tau)$ can be modeled by the Mittag-Leffler function [32]:

$$\Psi_\mu\,(x,\tau) = E_\mu\left[-\left(\frac{\tau}{\tau_0(x)}\right)^{\mu(x)}\right], \quad 0 < \mu(x) < 1, \qquad (9)$$

where $\mu(x)$ is the space-dependent anomalous exponent. In what follows we assume for simplicity that τ_0 is constant. The Laplace transform of the memory kernel $K_\mu\,(x,t)$ is $\hat{K}_\mu\,(x,s) = s^{1-\mu(x)}\tau_0^{-\mu(x)}$, and the integral anomalous escape rate $i\,(x,t)$ can be written as

$$i\,(x,t) = \frac{1}{\tau_0^{\mu(x)}}\mathcal{D}_t^{1-\mu(x)}\rho\,(x,t), \qquad (10)$$

where $\mathcal{D}_t^{1-\mu(x)}$ is the Riemann-Liouville derivative with varying anomalous exponent [33]. Substitution of (10) into (6) gives the integral fractional equation with space-dependent anomalous exponent

$$\frac{\partial\rho}{\partial t} = \int_{\mathbb{R}} \frac{1}{\tau_0^{\mu(x-z)}}\mathcal{D}_t^{1-\mu(x-z)}\rho\,(x-z,t)\,w\,(z|x-z)\,dz$$
$$- \frac{1}{\tau_0^{\mu(x)}}\mathcal{D}_t^{1-\mu(x)}\rho\,(x,t). \qquad (11)$$

Note that if $\mu = $ const and $\tau_0 = 1$ one obtains the following equation [34]:

$$\frac{\partial^\mu\rho}{\partial t^\mu} = \int_{\mathbb{R}} \rho\,(x-z,t)\,w\,(z|x-z)\,dz - \rho\,(x,t), \qquad (12)$$

where the Caputo derivative $\partial^\mu\rho/\,\partial t^\mu$ is used instead of the Riemann-Liouville derivative $\mathcal{D}_t^{1-\mu}\rho$.

Using the Taylor series expansion in terms of z, and a symmetric dispersal kernel w for which $\int_{\mathbb{R}} z\,w(z|x)\,dz = 0$,

we obtain the standard fractional subdiffusive equation

$$\frac{\partial\rho}{\partial t} = \frac{\partial^2}{\partial x^2}\big[D_\mu(x)\mathcal{D}_t^{1-\mu(x)}\rho(x,t)\big] \qquad (13)$$

with the fractional diffusion coefficient

$$D_\mu\,(x) = \frac{\sigma^2(x)}{2\tau_0^{\mu(x)}},$$

where $\sigma^2(x) = \int_{\mathbb{R}} z^2 w(z|x)\,dz$.

It has been found recently that subdiffusive fractional equations with constant μ are not structurally stable with respect to the spatial variations of fractal exponent $\mu(x)$ [28,29]. This leads to the anomalous aggregation of particles at the minimum of the function $\mu(x)$. In heterogeneous biological systems, in which the exponent $\mu(x)$ is space dependent, the question arises as to whether this anomalous aggregation of a population can be prevented. Therefore it is an important problem to find the way how to regularize subdiffusive fractional equations. One way is to incorporate random killing, which ensures regular behavior in the long-time limit [35]. The aim of this paper is to address this problem through a nonlinear escape rate that takes into account repulsive forces between particles. In the next section we derive the nonlinear generalization of the fractional equations like (11) and (13).

II. NON-MARKOVIAN AND SUBDIFFUSIVE NONLINEAR FRACTIONAL EQUATIONS

There are two major ways in which nonlinear density-dependence effects can be implemented into non-Markovian and subdiffusive transport equations. The simplest way is to take into account the dependence of jump density w on ρ. This dependence can take into account various nonlinear effects such as adhesion, quorum sensing, volume filling, etc. However, we begin with more complicated case of the random walk model for which the escape rate is a function of the residence time and the local density of particles.

A. Nonlinear escape rate

The main problem with this anomalous escape rate (10) is the phenomenon of anomalous aggregation [27–29]. Nonuniform distribution of the anomalous exponent $\mu(x)$ over the finite domain $[0,L]$ leads to

$$\rho\,(x,t) \to \delta(x - x_M) \quad \text{as} \quad t \to \infty. \qquad (14)$$

Here x_M is the point in space where the anomalous exponent $\mu\,(x)$ has a minimum. The problem is that that the escape rate (10) is a linear functional of the density of particles $\rho\,(x,t)$ and does not take into account nonlinear effects of repulsive forces which, in many situations, can prevent anomalous aggregation. According to (14) all particles aggregate into a small region around the point $x = x_M$ forming a high-density system. To prevent such anomalous aggregation, one can assume that the overcrowding leads to an increase of repulsive forces and a corresponding correction of the anomalous escape rate $\gamma(x,\tau)$.

We assume that the probability of escape due to the repulsive forces is independent from anomalous trapping. We define this probability for a small time interval Δt as

$$\alpha(\rho(x,t))\Delta t + o(\Delta t). \qquad (15)$$

Here $\alpha(\rho)$ is the transition rate which is an increasing function of the particles density ρ. Another interpretation can be given in terms of the quorum sensing phenomenon [7]. The large cell density can lead to the local overdepletion of nutrients and oxygen, and as a result cells can change phenotype from a proliferating state to a migrating one [22]. In another words, when the concentration of cells is low, $\alpha(\rho) = 0$, but if the concentration of cells $\rho(x,t)$ reaches a certain level ρ_{cr} : $\alpha(\rho) \neq 0$ for $\rho \geqslant \rho_{cr}$. Of course, one can assume a nonmonotonic dependence of the transition rate $\alpha(\rho)$ on ρ. For example, at low cell densities $\alpha(\rho)$ could decrease with ρ, while at high densities $\alpha(\rho)$ could be an increasing function: $\alpha(\rho) = \alpha_0(1 - a_1\rho + a_2\rho^2)$ [12,14].

First, we formulate the Markovian model for the random walk of particles with the density-dependent escape rate. Let $\xi(x,\tau,t)$ be the density of particles at time t such that $\xi(x,\tau,t)\Delta x\Delta \tau$ gives the number of particles in the space interval $(x,x + \Delta x)$ whose residence time lies in $(\tau,\tau + \Delta \tau)$. The balance equation for the structural density $\xi(x,\tau,t)$ for $\tau > 0$ takes the form

$$\xi(x,\tau + \Delta\tau,t + \Delta t) = \xi(x,\tau,t)(1 - \gamma(x,\tau)\Delta\tau)$$
$$\times (1 - \alpha(\rho(x,t))\,\Delta t) + o\,(\Delta t),$$

where $1 - \gamma(x,\tau)\Delta\tau$ is the survival probability during $\Delta\tau$ due to the trapping, and $1 - \alpha(\rho(x,t))\Delta t$ is the survival probability during time Δt corresponding to the repulsion forces between particles. Since the residence time τ increases linearly with time t with the rate equals to one ($\Delta\tau = \Delta t$), in the limit $\Delta t \to 0$ we obtain the following equation:

$$\frac{\partial \xi}{\partial t} + \frac{\partial \xi}{\partial \tau} = -\left[\gamma(x,\tau) + \alpha(\rho(x,t))\right]\xi. \qquad (16)$$

Here the effective transition rate is the sum of two escape rates:

$$\gamma(x,\tau) + \alpha(\rho(x,t)). \qquad (17)$$

The second term $\alpha(\rho(x,t))$ can be treated as the correction of the escape rate $\gamma(x,\tau)$ defined by (1). The boundary condition for $\xi(x,\tau,t)$ at zero residence time $\tau = 0$ is

$$\xi(x,0,t) = \int_{\mathbb{R}} i(x - z,t)w\,(z|\rho(x - z,t))\,dz, \qquad (18)$$

where the effective escape rate $i\,(x,t)$ from the point x at time t is defined as

$$i\,(x,t) = \int_0^t [\gamma(x,\tau) + \alpha(\rho(x,t))]\xi(x,\tau,t)\,d\tau. \qquad (19)$$

Equation (18) describes the balance of particles just arriving at the point x from the different positions $x - z$. The jumps of particles are determined by the conditional probability density function (dispersal kernel) $w\,(z|\rho(x - z,t))$. It depends on the total density of particles ρ at the point $x - z$ from which the particles jump at point x (see all details regarding w in Sec. II D). Obviously this dispersal kernel satisfies the normalization condition

$$\int_{\mathbb{R}} w\,(z|\rho(x,t))\,dz = 1.$$

Because of the formula (4), $i\,(x,t)$ can be rewritten as

$$i\,(x,t) = \int_0^t \gamma(x,\tau)\xi(x,\tau,t)\,d\tau + \alpha(\rho)\rho(x,t). \qquad (20)$$

It is convenient to introduce the density of particles $j(x,t)$ just jumping at the point x at time t:

$$j(x,t) = \xi(x,0,t). \qquad (21)$$

We solve (16) for $\xi(x,\tau,t)$ by the methods of characteristics. For $\tau < t$ we find

$$\xi(x,\tau,t) = \xi(x,0,t - \tau)e^{-\int_0^\tau \gamma(x,s)\,ds - \int_{t-\tau}^t \alpha(\rho(x,s))\,ds}. \qquad (22)$$

This solution involves an exponential factor $e^{-\int_0^\tau \gamma(x,s)\,ds}$ that can be interpreted as the survival function $\Psi(x,\tau)$ defined by (2). Therefore the formula (22) for $\xi(x,\tau,t)$ can be rewritten in terms of $j(x,t) = \xi(x,0,t)$ and $\Psi(x,\tau)$ as follows:

$$\xi(x,\tau,t) = j(x,t - \tau)\Psi(x,\tau)e^{-\int_{t-\tau}^t \alpha(\rho(x,s))\,ds} \qquad (23)$$

for $\tau < t$. Taking into account the initial condition (3): $\xi(x,\tau,0) = \rho_0(x)\delta(\tau)$ and the formula $\psi(x,\tau) = \gamma(x,\tau)\Psi(x,\tau)$ [see (1)] and substituting (23) into (20), we obtain

$$i(x,t) = \int_0^t [\psi(x,\tau)j(x,t - \tau)e^{-\int_{t-\tau}^t \alpha(\rho(x,s))\,ds}d\tau$$
$$+ \rho_0(x)\psi(x,t)e^{-\int_0^t \alpha(\rho(x,s))\,ds} + \alpha(\rho)\rho. \qquad (24)$$

Substitution of (23) and (3) into (4) gives

$$\rho(x,t) = \int_0^t [\Psi(x,\tau)j(x,t - \tau)e^{-\int_{t-\tau}^t \alpha(\rho(x,s))\,ds}\,d\tau$$
$$+ \Psi(x,t)\rho_0(x)e^{-\int_0^t \alpha(\rho(x,s))\,ds}. \qquad (25)$$

We should note that the integral with respect to the residence time τ in (24) and (25) is performed over the interval $0 \leqslant \tau < t$, while the integration in (4) and (20) involves also the upper limit $\tau = t$, where we have a singularity due to the initial condition (3).

By using the Laplace transforms one can eliminate $j(x,t)$ from (24) and (25) and express the the *integral* escape rate $i\,(x,t)$ in terms of the density $\rho(x,t)$ as

$$i\,(x,t) = \int_0^t K\,(x,t - \tau)\,e^{-\int_\tau^t \alpha(\rho(x,s))\,ds}\,\rho\,(x,\tau)\,d\tau$$
$$+ \alpha(\rho(x,t))\rho(x,t), \qquad (26)$$

where the memory kernel $K\,(x,t)$ is defined by its Laplace transform (8). The details of this derivation can be found in Ref. [3] (pp. 80–82; see also Ref. [20]). Note that the first term in (26) involves the exponential factor, $e^{-\int_\tau^t \alpha(\rho(x,s))\,ds}$, which can be interpreted as a nonlinear tempering. The main feature of this modified escape rate $i\,(x,t)$ is that although the *local* rates $\gamma(x,\tau)$ and $\alpha(\rho(x,t))$ are additive [see (17)], the corresponding terms in the *integral* escape rate (26) are not additive. This is clearly non-Markovian effect. One of the main aims of this paper is to find out what the implications of this effect on the long-time behavior of the density $\rho(x,t)$ are (see Sec. III).

Note that in the linear homogeneous case, when $\alpha(\rho) = 0$, ψ is independent of x, and w is independent of ρ, we obtain from

$$j(x,t) = \int_{\mathbb{R}} i(x - z,t)w\,(z|\rho(x - z,t))\,dz, \qquad (27)$$

(24) and (25), the classical continuous time random walk (CTRW) equation [1–3]:

$$\rho(x,t) = \int_{\mathbb{R}} \int_0^t \rho(x-z, t-\tau) \psi(\tau) w(z) \, d\tau \, dz + \rho_0(x) \Psi(t).$$

B. Master equation for the mean field density of particles

The master equation for the density $\rho(x,t)$ takes the simple form of the balance of jumping particles:

$$\frac{\partial \rho}{\partial t} = \int_{\mathbb{R}} i(x-z,t) w(z|\rho(x-z,t)) \, dz - i(x,t), \quad (28)$$

where the dispersal kernel w depends on the mean density $\rho(x,t)$. Substitution of the integral escape rate (26) into Eq. (28) gives the closed equation for ρ:

$$\frac{\partial \rho}{\partial t} = \int_{\mathbb{R}} \int_0^t K(x-z, t-\tau) e^{-\int_\tau^t \alpha(\rho(x-z,s)) \, ds}$$
$$\times \rho(x-z, \tau) w(z|\rho(x-z,t)) \, d\tau \, dz$$
$$- \int_0^t K(x, t-\tau) e^{-\int_\tau^t \alpha(\rho(x,s)) \, ds} \rho(x,\tau) \, d\tau$$
$$+ \int_{\mathbb{R}} \alpha(\rho(x-z,t)) \rho(x-z,t) w(z|\rho(x-z,t)) \, dz$$
$$- \alpha(\rho(x,t)) \rho(x,t). \quad (29)$$

One can find various nonlinear diffusion approximations of (29) assuming the particular expressions for the density-dependent dispersal kernels $w(z|\rho(x,t))$ and density-dependent jump rate $\alpha(\rho(x,t))$ [14].

When the escape rate γ does not depend on the residence time variable τ, the survival function $\Psi(x,\tau)$ (2) has an exponential form: $\Psi(x,\tau) = e^{-\gamma(x)\tau}$. In this Markovian case the Laplace transform of the memory kernel, $\hat{K}(x,s)$, does not depend on s: $\hat{K}(x,s) = \gamma(x)$. The integral escape rate $i(x,t)$ takes the standard Markovian form:

$$i(x,t) = [\gamma(x) + \alpha(\rho(x,t))] \rho(x,t). \quad (30)$$

Substitution of this formula into (28) gives the nonlinear Kolmogorov-Feller equation for $\rho(x,t)$ [3]:

$$\frac{\partial \rho}{\partial t} = \int_{\mathbb{R}} [\gamma(x-z) + \alpha(\rho(x-z,t))] \rho(x-z, \tau)$$
$$\times w(z|\rho(x-z,t)) \, dz - \gamma(x)\rho - \alpha(\rho)\rho.$$

Several approximations of this equation and its applications in population biology have been discussed in Ref. [14].

C. Diffusion approximation and chemotaxis

In this subsection we derive from (29) a fractional subdiffusive equation for ρ when $\alpha(\rho) = 0$. The main motivation is to study the chemotaxis which is a directed migration of cells toward a more favorable environment [13,36]. The aim is to illustrate as to how a fractional chemotaxis equation for cell movement can be derived. We consider the random walk in which particle (cell) performing instantaneous jumps in space such that the jump density w involves only two outcomes:

$$w(z|x,t) = r(x,t)\delta(z-a) + l(x,t)\delta(z+a), \quad (31)$$

where a is the jump size, $r(x,t)$ is the jump probability from the point x to $x+a$, $l(x,t)$ is the jump probability from the point x to $x-a$, and

$$r(x,t) + l(x,t) = 1. \quad (32)$$

For the jump kernel (31) the master equation (28) takes the form

$$\frac{\partial \rho}{\partial t} = r(x-a,t)i(x-a,t)$$
$$+ l(x+a,t)i(x+a,t) - i(x,t). \quad (33)$$

In the limit $a \to 0$, we obtain

$$\frac{\partial \rho}{\partial t} = -a \frac{\partial}{\partial x} \{[r(x,t) - l(x,t)]i(x,t)\}$$
$$+ \frac{a^2}{2} \frac{\partial^2 i(x,t)}{\partial x^2} + o(a^2). \quad (34)$$

One can introduce the density of chemotactic substance $U(x,t)$ that induces the movement of the particles (cells) up or down the gradient [13]. The presence of nonzero gradient $\partial U/\partial x$ gives rise to the bias of the random walk when $r(x,t) \neq l(x,t)$ [36,37]. We define the difference $r(x,t) - l(x,t)$ as [37,38]

$$r(x,t) - l(x,t) = -\beta a \frac{\partial U(x,t)}{\partial x} + o(a), \quad (35)$$

where β is the measure of the strength of chemotactic movement. When β is negative, the advection (taxis) is in the direction of increase in the chemotactic substance $U(x,t)$. Equation (34) can be rewritten in terms of $U(x,t)$ as follows:

$$\frac{\partial \rho}{\partial t} = a^2 \frac{\partial}{\partial x} \left[\beta \frac{\partial U}{\partial x} i(x,t) \right] + \frac{a^2}{2} \frac{\partial^2 i(x,t)}{\partial x^2} + o(a^2). \quad (36)$$

Various expressions for the integral escape rate $i(x,t)$ generate the set of the equations for ρ in the diffusion approximations. For example, the Markovian total escape rate

$$i(x,t) = \gamma \rho(x,t)$$

with escape rate $\gamma \to \infty$ and jump size $a \to 0$ gives the standard advection-diffusion equation or classical Fokker-Planck equation

$$\frac{\partial \rho}{\partial t} = 2D \frac{\partial}{\partial x} \left[\beta \frac{\partial U}{\partial x} \rho \right] + D \frac{\partial^2 \rho}{\partial x^2}$$

with finite diffusion coefficient $D = a^2\gamma/2$. Note that if we interpret $U(x,t)$ as the external potential, then $\beta^{-1} = 2kT$ [39]. The anomalous escape rate (10)

$$i(x,t) = \frac{1}{\tau_0^{\mu(x)}} \mathcal{D}_t^{1-\mu(x)} \rho(x,t)$$

generates the subdiffusive advection-diffusion equation or the fractional Fokker-Planck equation [38,39]:

$$\frac{\partial \rho}{\partial t} = 2 \frac{\partial}{\partial x} \left[D_\mu(x) \beta \frac{\partial U}{\partial x} \mathcal{D}_t^{1-\mu(x)} \rho \right]$$
$$+ \frac{\partial^2}{\partial x^2} [D_\mu(x) \mathcal{D}_t^{1-\mu(x)} \rho]. \quad (37)$$

Here $D_\mu(x)$ is the fractional diffusion coefficient defined as

$$D_\mu(x) = \frac{a^2}{2\tau_0{}^{\mu(x)}}, \tag{38}$$

which is finite in the limit $a \to 0$ and $\tau_0 \to 0$.

D. Nonlinear jump distributions

In this subsection we discuss various nonlinear jump distributions leading to nonlinear fractional equations when $\alpha(\rho) = 0$. As we mentioned previously, this is the simplest way to incorporate nonlinearity into subdiffusive fractional equations [28]. As long as the escape rate $i(x,t)$ is determined, we can define "where to jump" through the dispersal kernel w. Let us assume that the dispersal kernel w depends on the density of particles: $w = w(z|\rho(x,t))$. In what follows we restrict ourselves to the subdiffusive case for which the rate $i(x,t)$ is determined by (10). In this case, the starting master equation is

$$\frac{\partial \rho}{\partial t} = \int_{\mathbb{R}} \frac{\mathcal{D}_t^{1-\mu(x-z)}\rho(x-z,t)}{\tau_0{}^{\mu(x-z)}} w(z|\rho(x-z,t))\, dz$$
$$- \frac{\mathcal{D}_t^{1-\mu(x)}\rho(x,t)}{\tau_0{}^{\mu(x)}}. \tag{39}$$

First, we consider the case for which the jump dependence on ρ is local. For example, one can use a Gaussian dispersal kernel with rapidly decaying tails as

$$w(z|\rho) = \frac{1}{\sqrt{2\pi\sigma^2(\rho)}} \exp\left[-\frac{z^2}{2\sigma^2(\rho)}\right].$$

An increasing dispersion $\sigma^2(\rho)$ describes the effect of the local repulsive forces due to overcrowding, while a decaying function $\sigma^2(\rho)$ corresponds to attractive forces. Using the Taylor series expansion in terms of z in the master equation (39), we obtain the subdiffusive equation

$$\frac{\partial \rho}{\partial t} = \frac{\partial^2}{\partial x^2}\left[K_\mu(\rho)\mathcal{D}_t^{1-\mu(x)}\rho(x,t)\right] \tag{40}$$

with the nonlinear fractional diffusion coefficient

$$K_\mu(\rho) = \frac{\sigma^2(\rho)}{2\tau_0{}^{\mu(x)}}$$

One can also introduce the nonlinear drift term generated by Bernoulli jump distribution [14]

$$w(z|\rho) = \tfrac{1}{2}[1 + au(\rho)]\,\delta(z-a)$$
$$+ \tfrac{1}{2}[1 - au(\rho)]\,\delta(z+a),$$

where the positive function $u(\rho)$ takes into account the fact that the jump on the right is more likely than a jump to the left; a is the jump size. It is assumed that $1 - au(\rho)$ is not negative; that is, $u(\rho) \leqslant a^{-1}$. The fractional master equation (39) takes the form

$$\frac{\partial \rho}{\partial t} = \frac{1 + au(\rho(x-a,t))}{2\tau_0{}^{\mu(x-a)}}\mathcal{D}_t^{1-\mu(x-a)}\rho(x-a,t)$$
$$+ \frac{1 - au(\rho(x+a,t))}{2\tau_0{}^{\mu(x+a)}}\mathcal{D}_t^{1-\mu(x+a)}\rho(x+a,t)$$
$$- \frac{1}{\tau_0{}^{\mu(x)}}\mathcal{D}_t^{1-\mu(x)}\rho(x,t). \tag{41}$$

Using the Taylor series expansion in (41) as $a \to 0$, we obtain the nonlinear fractional Fokker-Planck equation

$$\frac{\partial \rho}{\partial t} = -\frac{\partial}{\partial x}\left[2D_\mu(x)u(\rho(x,t))\mathcal{D}_t^{1-\mu(x)}\rho\right]$$
$$+ \frac{\partial^2}{\partial x^2}\left[D_\mu(x)\mathcal{D}_t^{1-\mu(x)}\rho\right] \tag{42}$$

with the *nonlinear* advection term involving $u(\rho(x,t))$ and fractional diffusion coefficient $D_\mu(x)$ defined by (38).

Now let us consider the random jump model when the jump kernel $w(z|\rho)$ depends on the mean density at a neighboring points (nonlocal nonlinearity). This model deals with so-called volume filling effect and cell-to-cell adhesion [9,12]. Instead of considering the jump rates as in Refs. [9,12] we model volume filling and adhesion effects via the jump density

$$w(z|\rho) = r(\rho)\delta(z-a) + l(\rho)\delta(z+a),$$

where $r(\rho(x,t))$ is the probability of jumping right from x to $x+a$ at time t and $l(\rho(x,t))$ is the probability of jumping left from x to $x-a$ at time t. We define these probabilities by using two decreasing functions $f_v(\rho) \geqslant 0$ and $f_a(\rho) \geqslant 0$ as follows:

$$r(\rho(x,t)) = \frac{f_v(\rho(x+a,t))f_a(\rho(x-a,t))}{F(\rho)},$$
$$l(\rho(x,t)) = \frac{f_v(\rho(x-a,t))f_a(\rho(x+a,t))}{F(\rho)}, \tag{43}$$

where the function

$$F(\rho) = f_v(\rho(x-a,t))f_a(\rho(x+a,t))$$
$$+ f_v(\rho(x+a,t))f_a(\rho(x-a,t))$$

makes sure that

$$r(\rho(x,t)) + l(\rho(x,t)) = 1.$$

It follows from (43) that the probabilities $r(\rho)$ and $l(\rho)$ of jumping into a neighboring points are dependent on the densities of particles at these points. The decreasing function $f_v(\rho(x+a,t))$ is used to model volume filling: the jump probability $r(\rho(x,t))$ from the point x to the right $x+a$ is reduced by the presence of particles (cells) at the point $x+a$. The decreasing function $f_a(\rho(x-a,t))$ describes the adhesion effect, which says that the jump probability $r(\rho(x,t))$ from the point x to the right $x+a$ is reduced by the presence of particles (cells) at the point $x-a$.

In the limit $a \to 0$, one can obtain the nonlinear fractional diffusion equation. To illustrate our theory let us consider the particular case involving only volume filling effects (no adhesion):

$$f_v(\rho) = 1 - \rho, \quad f_a(\rho) = 1. \tag{44}$$

In this case, we require the initial density

$$\rho_0(x) < 1.$$

Substitution of (44) into (43) gives the following probabilities:

$$r(\rho(x,t)) = \frac{1 - \rho(x+a,t)}{2 - \rho(x+a,t) - \rho(x-a,t)},$$
$$l(\rho(x,t)) = \frac{1 - \rho(x-a,t)}{2 - \rho(x+a,t) - \rho(x-a,t)}. \tag{45}$$

The master equation (28) for the mean density ρ can be written as

$$\frac{\partial \rho}{\partial t} = r(\rho(x-a,t))i(x-a,t)$$
$$+ l(\rho(x+a,t))i(x+a,t) - i(x,t). \quad (46)$$

To consider the diffusion approximation when $a \to 0$ it is convenient to define the flux of particles $J_{x,x+a}$ from x to $x+a$ as

$$J_{x,x+a} = r(\rho(x,t))i(x,t)a - l(\rho(x+a,t))i(x+a,t)a$$

and the flux of particles $J_{x-a,x}$ from $x-a$ to x as

$$J_{x-a,x} = r(\rho(x-a,t))i(x-a,t)a - l(\rho(x,t))i(x,t)a.$$

The master equation (46) can be rewritten in the form

$$\frac{\partial \rho}{\partial t} = \frac{-J_{x,x+a} + J_{x-a,x}}{a}.$$

In the limit $a \to 0$ we obtain

$$\frac{\partial \rho}{\partial t} = -\frac{\partial J(x,t)}{\partial x}, \quad (47)$$

where

$$J(x,t) = -\frac{a^2}{2}\frac{\partial i}{\partial x} - \frac{a^2 i}{1-\rho}\frac{\partial \rho}{\partial x} + o(a^2). \quad (48)$$

In the Markovian case, when the escape rate $\gamma(x)$ does not depend on the residence time and

$$i(x,t) = \gamma(x)\rho(x,t),$$

we obtain the nonlinear diffusion equation for ρ:

$$\frac{\partial \rho}{\partial t} = \frac{\partial}{\partial x}\left[D(\rho)\frac{\partial \rho}{\partial x}\right] \quad (49)$$

with the nonlinear diffusion coefficient

$$D(\rho) = \frac{a^2 \lambda(x)}{2}\frac{1+\rho}{1-\rho}.$$

In the anomalous subdiffusive case, when the total escape rate from the point x is given by

$$i(x,t) = \frac{1}{\tau_0^{\mu(x)}}\mathcal{D}_t^{1-\mu(x)}\rho(x,t),$$

the flux of particles (48) involves two terms:

$$J(x,t) = -\frac{\partial}{\partial x}\left[D_\mu(x)\mathcal{D}_t^{1-\mu(x)}\rho(x,t)\right]$$
$$-\frac{2D_\mu(x)\mathcal{D}_t^{1-\mu(x)}\rho(x,t)}{1-\rho}\frac{\partial \rho}{\partial x}, \quad (50)$$

where $D_\mu(x)$ is the fractional diffusion coefficient defined by (38). Substitution of (50) into (47) gives a nonlinear fractional equation

$$\frac{\partial \rho}{\partial t} = \frac{\partial^2}{\partial x^2}\left[D_\mu(x)\mathcal{D}_t^{1-\mu(x)}\rho\right]$$
$$+ \frac{\partial}{\partial x}\left[\frac{2D_\mu(x)\mathcal{D}_t^{1-\mu(x)}\rho(x,t)}{1-\rho}\frac{\partial \rho}{\partial x}\right]. \quad (51)$$

The first term on the RHS of (51) is the standard term for the subdiffusive fractional equation, while the second one is the nonlinear term describing the volume filling effect in the subdiffusive case.

III. ANOMALOUS SUBDIFFUSIVE CASE WITH NONLINEAR TEMPERING

The aim of this section is to derive the master equation that describes the transition from subdiffusive transport to asymptotic normal advection-diffusion transport. We consider the subdiffusive case for which the waiting time PDF $\psi(x,\tau)$ has a power law tail: $\psi(x,\tau) \sim (\tau_0/\tau)^{1+\mu(x)}$ with $0 < \mu(x) < 1$ as $\tau \to \infty$. One can use the survival probability $\Psi(x,\tau)$ defined by (9). The advantage of the Mittag-Leffler function (9) is that one can obtain the fractional subdiffusive equation without passing to the long-time limit [34]. The Laplace transforms of $\psi(x,\tau) = -\partial\Psi(x,\tau)/\partial\tau$ and $\Psi(x,\tau)$ are

$$\hat{\psi}(x,s) = \frac{1}{1+(\tau_0 s)^{\mu(x)}}, \quad (52)$$

$$\hat{\Psi}(x,s) = \frac{\tau_0^{\mu(x)}s^{\mu(x)-1}}{1+(\tau_0 s)^{\mu(x)}}, \quad (53)$$

and, therefore, the Laplace transform of the memory kernel $K(x,t)$ is

$$\hat{K}(x,s) = \frac{\hat{\psi}(x,s)}{\hat{\Psi}(x,s)} = \frac{s^{1-\mu(x)}}{\tau_0^{\mu(x)}}. \quad (54)$$

It follows from (26) that instead of (10) we have

$$i(x,t) = \frac{e^{-\Phi(x,t)}}{\tau_0^{\mu(x)}}\mathcal{D}_t^{1-\mu(x)}[e^{\Phi(x,t)}\rho(x,t)] + \alpha(\rho)\rho(x,t), \quad (55)$$

where

$$\Phi(x,t) = \int_0^t \alpha(\rho(x,s))\,ds. \quad (56)$$

This function plays a very important role in what follows. It can be referred as a nonlinear tempering. From (28) and (55) we obtain the subdiffusive master equation for the density $\rho(x,t)$ with the nonlinear tempering $\Phi(x,t)$:

$$\frac{\partial \rho}{\partial t} = \int_{\mathbb{R}} \frac{e^{-\Phi(x-z,t)}}{\tau_0^{\mu(x-z)}}\mathcal{D}_t^{1-\mu(x-z)}[e^{\Phi(x-z,t)}\rho(x-z,t)]$$
$$\times w(z|\rho(x-z,t))\,dz$$
$$- \frac{e^{-\Phi(x,t)}}{\tau_0^{\mu(x)}}\mathcal{D}_t^{1-\mu(x)}[e^{\Phi(x,t)}\rho(x,t)]$$
$$+ \int_{\mathbb{R}} \alpha(\rho(x-z,t))\rho(x-z,t)w(z|\rho(x-z,t))\,dz$$
$$- \alpha(\rho(x,t))\rho(x,t). \quad (57)$$

Using (57) one can obtain various fractional subdiffusive nonlinear equations. In particular, for the jump kernel (31) with (35), in the limit $a \to 0$ we obtain from (57) a nonlinear fractional equation

$$\frac{\partial \rho}{\partial t} = a^2 \frac{\partial}{\partial x}\left(\beta \frac{\partial U}{\partial x}\left\{ \frac{e^{-\Phi}}{\tau_0^{\mu(x)}}\mathcal{D}_t^{1-\mu(x)}[e^{\Phi}\rho] + \alpha(\rho)\rho \right\}\right)$$
$$+ \frac{a^2}{2}\frac{\partial^2}{\partial x^2}\left\{ \frac{e^{-\Phi}}{\tau_0^{\mu(x)}}\mathcal{D}_t^{1-\mu(x)}[e^{\Phi}\rho] + \alpha(\rho)\rho \right\} + o(a^2), \quad (58)$$

where Φ is defined by (56).

A. Transition to asymptotic advection-diffusion transport regime and aggregation phenomenon

In this subsection we discuss a transition from a subdiffusive transport regime to an asymptotically normal advection-diffusion transport regime. This transition is governed by the nonlinear fractional equation (58). It involves the exponential factor $e^{-\Phi(x,t)}$, with $\Phi(x,t) = \int_0^t \alpha(\rho(x,s))\, ds$, that can be considered as a nonlinear tempering. It generalizes the linear tempering, where the power law waiting time distribution is truncated by an exponential factor $\exp(-\alpha t)$ [40]. We expect that in the limit $\Phi(x,t) \to \infty$ we recover the stationary advection-diffusion equation or classical Fokker-Planck equation, while in the intermediate asymptotic regime, when

$$\Phi(x,t) \ll 1, \tag{59}$$

we have a transient subdiffusive transport. If we take the limit $\Phi(x,t) \to 0$ in (58) for a small escape rate $\alpha(\rho)$, nonuniform distribution of the anomalous exponent $\mu(x)$ in (37) leads to the aggregation of particles at the point of minimum of $\mu(x)$ [20,29]. This phenomenon has been observed in experiments on phagotrophic protists when "cells become immobile in attractive patches, which will then eventually trap all cells" [41]. In this case the anomalous exponent $\mu(x)$ dominates and the gradient of the chemotaxis substance (potential field) $U(x)$ is irrelevant to the partial distribution of the density of particles ρ. However, in general, this aggregation of particles around one point is just a transient phenomenon in the time interval

$$\tau_0 \ll t \ll \frac{1}{\bar{\alpha}}, \tag{60}$$

where $\bar{\alpha} = \frac{1}{t} \int_0^t \alpha(\rho(x,s))\, ds$. If we consider the long-time limit $t \to \infty$ such that $\Phi(x,t) \to \infty$, then we obtain the stationary advection-diffusion equations (see the next two subsections on aggregation of particles). The solution of these equations represents ultimate cell aggregation determined by the chemotaxis substance (potential field) $U(x)$ and the spatial distribution of anomalous exponent $\mu(x)$.

1. Aggregation of particles in the linear case

First, we assume that the local escape rate α is independent of time, such that $\Phi(x,t) = \alpha(x)t$. The total escape rate $i(x,t)$ defined by (55) takes the form

$$i(x,t) = \frac{e^{-\alpha(x)t}}{\tau_0^{\mu(x)}} \mathcal{D}_t^{1-\mu(x)} [e^{\alpha(x)t} \rho(x,t)]$$
$$+ \alpha(x)\rho(x,t). \tag{61}$$

Its Laplace transform $\hat{i}(x,s) = \int_0^\infty e^{-st} i(x,\tau)\, d\tau$ is

$$\hat{i}(x,s) = \left\{ \frac{[s + \alpha(x)]^{1-\mu(x)}}{\tau_0^{\mu(x)}} + \alpha(x) \right\} \hat{\rho}(x,s). \tag{62}$$

In the limit $s \to 0$ ($t \to \infty$) one obtains the stationary escape rate $i_{st}(x)$ (if it exists) in terms of the stationary density

$$\rho_{st}(x) = \lim_{s \to 0} s\hat{\rho}(x,s).$$

It follows from (62) that the stationary rate $i_{st}(x)$ can be written in the Markovian form

$$i_{st}(x) = \gamma_\mu(x)\rho_{st}(x),$$

where the effective rate of escape $\gamma_\mu(x)$ is

$$\gamma_\mu(x) = \frac{\alpha(x)}{[\tau_0 \alpha(x)]^{\mu(x)}} + \alpha(x).$$

The essential feature of this rate parameter $\gamma_\mu(x)$ is that it depends on the fractal exponent $\mu(x)$. This escape rate, together with (36), leads to the stationary advection-diffusion equation

$$\frac{\partial}{\partial x}\left[2\beta \frac{\partial U}{\partial x} D(x)\rho_{st}(x)\right] + \frac{\partial^2}{\partial x^2}[D(x)\rho_{st}(x)] = 0, \tag{63}$$

where the diffusion coefficient $D(x) = a^2 \gamma_\mu(x)/2$ depends on $\mu(x)$ and $\alpha(x)$:

$$D(x) = \frac{a^2\{[\tau_0\alpha(x)]^{1-\mu(x)} + \tau_0\alpha(x)\}}{2\tau_0}.$$

When the product $\tau_0\alpha$ is small, the term $(\tau_0\alpha)^{1-\mu(x)}$ is dominant in the anomalous case $\mu(x) < 1$, so $D_\mu(x)$ can be approximated as

$$D(x) = \frac{a^2[\tau_0\alpha(x)]^{1-\mu(x)}}{2\tau_0}, \quad \tau_0\alpha(x) \ll 1.$$

Let us find the solution $\rho_{st}(x)$ to (63) in the interval $[0,L]$. We use the reflective boundary conditions at $x = 0$ and $x = L$ which guarantees the conservation of the total population:

$$\int_0^L \rho(x,t)\, dx = 1.$$

We introduce the new function

$$p(x) = D(x)\rho_{st}(x).$$

It follows from (63) that this function obeys the equation

$$\frac{\partial}{\partial x}\left[2\beta \frac{\partial U(x)}{\partial x} p(x)\right] + \frac{\partial^2 p(x)}{\partial x^2} = 0 \tag{64}$$

with the solution in the form of the Boltzmann distribution

$$p(x) = N^{-1} \exp[-2\beta U(x)].$$

Thus, the steady profile is

$$\rho_{st}(x) = N^{-1} D^{-1}(x) \exp[-2\beta U(x)], \tag{65}$$

where N is determined by the normalization condition $N = \int_0^L D^{-1}(x) \exp[-2\beta U(x)]\, dx$.

To illustrate how the nonhomogeneous anomalous exponent $\mu(x)$ affects the aggregation pattern we consider the steady profile (65) in the interval $[0,1]$ for two cases: (1) $U(x) = 0$ and (2) $U(x) = mx$ for which the anomalous exponent $\mu(x)$ has the form

$$\mu(x) = \mu_0 \exp(-kx),$$

where $0 < \mu_0 < 1$ and $k \geqslant 0$. Figure 1 shows that for the uniform distribution of chemotaxis substance $U(x) = 0$, the particles have the tendency to aggregate in the region of the small values of $\mu(x)$ (dashed line). When the gradient of chemotaxis substance $\partial U(x)/\partial x$ forces the cells (particles)
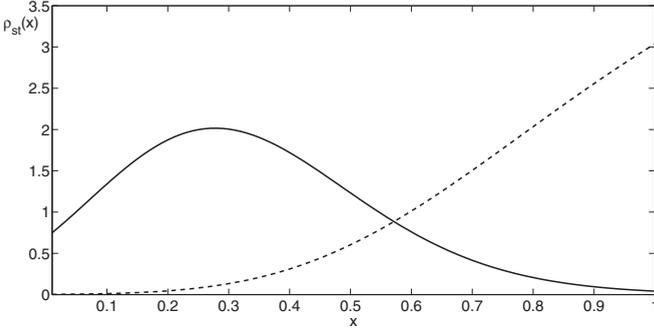
FIG. 1. Stationary profiles $\rho_{st}(x)$ for the linear distribution of the potential $U(x) = 5x$ (solid line) and $U(x) = 0$ (dashed line), $\beta = 1$, $\mu_0 = 0.9, \alpha = 10^{-4}, \tau_0 = 1, k = 2.19$.

to move from the right to the left [$U(x) = 5x$ and $\beta = 1$], the steady profile is not monotonic (solid line).

2. Aggregation in the nonlinear case

Now we consider the nonlinear case when the escape rate α depends on the density ρ. For living systems, this nonlinear dependence results from a coupling between the local density of cells and the intensity of the response of individual cell to external signals. We assume that in the limit $t \to \infty$ the stationary distribution $\rho_{st}(x)$ exists. Then as $t \to \infty$, the tempering factor $e^{-\Phi(x,t)}$ can be approximated by $e^{-\alpha(\rho_{st}(x))t}$. The stationary escape rate $i_{st}(x)$ corresponding to (26) can be written in terms of the Laplace transform $\hat{K}(x,s)$ as follows:

$$i_{st}(x) = [\hat{K}(x,\alpha(\rho_{st})) + \alpha(\rho_{st})]\rho_{st}(x). \quad (66)$$

This steady rate $i_{st}(x)$ has the Markovian form in which the rate parameter consists of two terms $\hat{K}(x,\alpha(\rho_{st}))$ and $\alpha(\rho_{st})$. The dependence of the first term on $\alpha(\rho_{st})$ is due to the non-Markovian character of transport process. This effect does not exist in the Markovian case for which $\hat{K}$ is a function of x only. The effective diffusion coefficient $D(\rho_{st}(x))$ is the function of the mean density, and it depends on the structure of the Laplace transform of the memory kernel K

$$D(\rho_{st}) = \frac{a^2}{2}[\hat{K}(x,\alpha(\rho_{st})) + \alpha(\rho_{st})]. \quad (67)$$

For the subdiffusive case when $\hat{K}(x,s)$ is defined by (54), the stationary escape rate $i_{st}(x)$ is

$$i_{st}(x) = \left(\frac{\{\alpha[\rho_{st}(x)]\}^{1-\mu(x)}}{\tau_0^{\mu(x)}} + \alpha[\rho_{st}(x)] \right) \rho_{st}(x). \quad (68)$$

One can see that the first term on the RHS of (68) is dominant for small $\alpha\tau_0$ and $\mu(x) < 1$. For the jump density (31), in the limit $a \to 0$ we obtain the stationary nonlinear Fokker-Planck equation

$$\frac{\partial}{\partial x}\left[2\beta \frac{\partial U}{\partial x} D(\rho_{st}) \rho_{st}(x) \right] + \frac{\partial^2}{\partial x^2}[D(\rho_{st})\rho_{st}(x)] = 0, \quad (69)$$

where $D(\rho_{st}(x))$ is the nonlinear diffusion coefficient defined as

$$D(\rho_{st}) = \frac{a^2 \{\alpha[\rho_{st}(x)]\}^{1-\mu(x)}}{2\tau_0^{\mu(x)}}, \quad \tau_0\alpha[\rho_{st}(x)] \ll 1.$$

If we assume a zero flux condition at the boundaries of the interval $[0,L]$, then

$$J = -2\beta\frac{\partial U}{\partial x}D(\rho_{st})\rho_{st}(x) - \frac{\partial}{\partial x}[D(\rho_{st})\rho_{st}(x)] = 0,$$

and the stationary profile $\rho_{st}(x)$ can be found from the nonlinear equation

$$\rho_{st}(x) = N^{-1}D^{-1}(\rho_{st}(x))\exp[-2\beta U(x)], \quad (70)$$

where N is determined by the normalization condition $N = \int_0^L D^{-1}[\rho_{st}(x)]\exp[-2\beta U(x)]\,dx$. The time evolution of the density profile $\rho(x,t)$ for the nonlinear fractional equation (58) can be described as follows. At lower values of $\Phi = \int_0^t \alpha[\rho(x,s)]\,ds$, the early evolution is the development of a single peak at the point of the minimum of $\mu(x)$. This can be considered as an intermediate anomalous aggregation of particles. However, incorporating the escape rate $\alpha(\rho)$ and the nonlinear tempering factor $e^{-\Phi}$ provide a regularization of anomalous aggregation. For sufficiently large Φ the density profile $\rho(x,t)$ must converge to a stationary solution (70) as $t \to \infty$.

IV. CONCLUSIONS

The aim in this paper was to derive the macroscopic nonlinear subdiffusive fractional equations for the evolution of a mean density of random walkers by incorporating a nonlinear escape rate and nonlinear jump distributions. The main motivation was to take into account the interaction between particles on the mesoscopic level at which the random walker characteristics depend on the mean density of particles. We illustrated the general results for nonlinear random walk models by using the examples from cell and population biology. We derived nonlinear fractional equations that take into account chemotaxis, volume filling effect, and cell-to-cell adhesion. We showed that the nonlinear escape rate leads to the effective regularization of standard subdiffusive fractional equations. Our modified fractional equations describe the transition from an intermediate subdiffusive regime to an asymptotically normal advection-diffusion transport regime. We showed that this transition is governed by a nonlinear tempering factor that generalize the standard linear tempering. We discussed the aggregation phenomenon and showed the impact of a nonuniform distribution of anomalous exponent on aggregation patterns.

[1] R. Metzler and J. Klafter, Phys. Rep. **339**, 1 (2000).

[2] R. Klages, G. Radons, and I. M. Sokolov, eds., *Anomalous Transport: Foundations and Applications* (Wiley-VCH, Weinheim, 2008).

[3] V. Méndez, S. Fedotov, and W. Horsthemke, *Reaction-Transport Systems* (Springer, Berlin, 2010).

[4] M. J. Saxton, Biophys. J. **81**, 2226 (2001).

[5] I. Golding and E. C. Cox, Phys. Rev. Lett. **96**, 098102 (2006).

[6] F. Santamaria, S. Wils, E. De Schutter, and G. J. Augustine, Neuron **52**, 635 (2006); S. Fedotov and V. Méndez, Phys. Rev. Lett. **101**, 218102 (2008).

[7] M. B. Miller and B. L. Bassler, Annu. Rev. Microbiol. **55**, 165 (2001).

[8] R. A. Weinberg, *The Biology of Cancer* (Garland Science, New York, 2007).

[9] K. Anguige and C. Schmeiser, J. Math. Biol. **58**, 395 (2009).

[10] S. T. Johnston, M. J. Simpson, and R. E. Baker, Phys. Rev. E **85**, 051922 (2012).

[11] E. Khain, M. Katakowski, S. Hopkins, A. Szalad, X. Zheng, F. Jiang, and M. Chopp, Phys. Rev. E **83**, 031920 (2011).

[12] K. Painter and T. Hillen, Can. Appl. Math. Quart. **10**, 501 (2002).

[13] T. Hillen and K. J. Painter, J. Math. Biol. **58**, 183 (2009).

[14] V. Méndez, D. Campos, I. Pagonabarraga, and S. Fedotov, J. Theor. Biol. **309**, 113 (2012).

[15] S. Fedotov, D. Moss, and D. Campos, Phys. Rev. E **78**, 026107 (2008).

[16] M. O. Vlad and J. Ross, Phys. Rev. E **66**, 061908 (2002).

[17] A. Yadav and W. Horsthemke, Phys. Rev. E **74**, 066118 (2006).

[18] Y. Nec and A. A. Nepomnyashchy, J. Phys. A: Math. Theor. **40**, 14687 (2007).

[19] D. Froemberg and I. M. Sokolov, Phys. Rev. Lett. **100**, 108304 (2008).

[20] S. Fedotov, Phys. Rev. E **81**, 011117 (2010).

[21] E. Abad, S. B. Yuste, and K. Lindenberg, Phys. Rev. E **81**, 031115 (2010).

[22] S. Fedotov and A. Iomin, Phys. Rev. Lett. **98**, 118101 (2007).

[23] F. Sagues, V. P. Shkilev, and I. M. Sokolov, Phys. Rev. E **77**, 032102 (2008).

[24] V. P. Shkilev, J. Exp. Theor. Phys. **112**, 711 (2011).

[25] V. A. Volpert, Y. Nec, and A. A. Nepomnyashchy, Phil. Trans. R. Soc. A **371**, 20120179 (2013).

[26] C. N. Angstmann, I. C. Donnelly, and B. I. Henry, Math. Mod. Natural Phen. **8**, 17 (2013).

[27] S. Fedotov, Phys. Rev. E **83**, 021110 (2011).

[28] S. Fedotov and S. Falconer, Phys. Rev. E **85**, 031132 (2012).

[29] S. Fedotov, A. O. Ivanov, and A. Y. Zubarev, Math. Mod. Natural Phen. **8**, 28 (2013).

[30] D. R. Cox and H. D. Miller, *The Theory of Stochastic Processes* (Methuen, London, 1965).

[31] E. Barkai and Y.-C. Cheng, J. Chem. Phys. **118**, 6167 (2003).

[32] E. Scalas, R. Gorenflo, F. Mainardi, and M. Raberto, Fractals **11**, 281 (2003).

[33] A. V. Chechkin, R. Gorenflo, and I. M. Sokolov, J. Phys. A: Math. Gen. **38**, L679 (2005).

[34] F. Mainardi, M. Raberto, R. Gorenflo, and E. Scalas, Physica A **287**, 468 (2000).

[35] S. Fedotov and S. Falconer, Phys. Rev. E **87**, 052139 (2013).

[36] H. G. Othmer and A. Stevens, SIAM J. Appl. Math. **57**, 1044 (1997).

[37] T. A. M. Langlands and B. I. Henry, Phys. Rev. E **81**, 051102 (2010).

[38] B. I. Henry, T. A. M. Langlands, and P. Straka, Phys. Rev. Lett. **105**, 170602 (2010).

[39] E. Barkai, R. Metzler, and J. Klafter, Phys. Rev. E **61**, 132 (2000).

[40] A. Cartea and D. del-Castillo-Negrete, Phys. Rev. E **76**, 041105 (2007); M. M. Meerschaert, Geophys. Res. Lett. **35**, L17403 (2008); A. I. Saichev and S. G. Utkin, J. Exp. Theory Phys. **99**, 443 (2004); A. Stanislavsky, K. Weron, and A. Weron, Phys. Rev. E **78**, 051106 (2008); J. Gajda and M. Magdziarz, *ibid.* **82**, 011117 (2010).

[41] T. Fenchel and N. Blackburn, Protist **160**, 325 (1999).