Random death process for the regularization of subdiffusive fractional equations

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The description of subdiffusive transport in complex media by fractional equations with a constant anomalous exponent is not robust where the stationary distribution is concerned. The Gibbs-Boltzmann distribution is radically changed by even small spatial perturbations to the anomalous exponent [S. Fedotov and S. Falconer, Phys. Rev. E **85**, 031132 (2012)]. To rectify this problem we propose the inclusion of the random death process in the random walk scheme, which is quite natural for biological applications including morphogen gradient formation. From this, we arrive at the modified fractional master equation and analyze its asymptotic behavior, both analytically and by Monte Carlo simulation. We show that this equation is structurally stable against spatial variations of the anomalous exponent. We find that the stationary flux of the particles has a Markovian form with rate functions depending on the anomalous rate functions, the death rate, and the anomalous exponent. Additionally, in the continuous limit we arrive at an advection-diffusion equation where advection and diffusion coefficients depend on both the death rate and anomalous exponent.

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I. INTRODUCTION

Anomalous subdiffusion, where the mean squared displacement grows sublinearly with time $\langle x^2(t)\rangle \sim t^{\mu}$, where the anomalous exponent $\mu < 1$, is an observed natural phenomena [1]. It is seen in areas as varied as dispersive charge transport in semiconductors [2], ion movement in spiny dendrites [3], and protein transport on cell membranes [4]. In the classical paper [5], Metzler, Barkai, and Klafter introduced the fractional Fokker-Planck equation (FFPE) that describes anomalous subdiffusion of particles in an external field $F(x)$. This equation for the probability density $p(x,t)$ is written as

$$\frac{\partial p}{\partial t} = \mathcal{D}_t^{1-\mu} L_{FP}\, p(x,t), \tag{1}$$

where

$$L_{FP} = K_{\mu}\left[\frac{\partial^2}{\partial x^2} - \frac{\partial}{\partial x}\frac{F(x)}{k_B T}\right] \tag{2}$$

is the Fokker-Planck operator, K_{μ} is the anomalous diffusion coefficient, and $\mathcal{D}_t^{1-\mu}$ is the Riemann-Liouville fractional derivative of order $1-\mu$, defined as

$$\mathcal{D}_t^{1-\mu} p(x,t) = \frac{1}{\Gamma(\mu)}\frac{\partial}{\partial \tau}\int_0^t \frac{p(x,\tau)d\tau}{(t-\tau)^{1-\mu}}, \tag{3}$$

where $\mu < 1$. It was shown that the external field $F(x)$ leads to a stationary solution to the FFPE in the form of the Gibbs-Boltzmann distribution [6]. However, in a recent paper [7], we have demonstrated that this fundamental result is not structurally stable with respect to spatial variations of the anomalous exponent $\mu(x) = \mu + \delta\mu(x)$. This small perturbation, $\delta\mu(x)$, destroys the Gibbs-Boltzmann distribution as the stationary solution to the FFPE.

The physical explanation for the occurrence of subdiffusion is the distribution of trapping sites throughout the complex media. It is hardly realistic to assume that the distribution, and structure, of the traps is uniform throughout. The main reason for the widespread use of constant μ is the implicit assumption that this is a good approximation. However, we have shown previously that this is not the case. This question is of great importance for the problem of a morphological patterning of embryonic cells, which is controlled by the distribution of signaling molecules known as morphogens [8–10]. To ensure robust pattern formation, the morphogen gradients must be structurally stable with respect to the spatial variations of environmental parameters, including the anomalous exponent.

In fact, even the simple one-dimensional fractional subdiffusion equation with *constant* anomalous exponent and $F(x) = 0$, in the finite domain $[0,L]$ with reflective boundary conditions, is structurally unstable. This equation should yield a uniform stationary distribution over the interval $[0,L]$ in the long-time limit. However, if we use a slightly nonuniform anomalous exponent $\mu(x)$, the probability density $p(x,t)$ will be completely different from the uniform distribution: as $t \to \infty$, it concentrates at the point where $\mu(x)$ has a global minimum on $[0,L]$. We called this phenomenon anomalous aggregation [11]. We should note that there is nothing physically wrong with the fractional equations with space-dependent anomalous exponents and accumulation of particles in a spatial domain with the smallest $\mu(x)$. Note that unusual behavior of subdiffusive transport has been observed in an infinite system with two different values of anomalous exponents [12].

To rectify the structural instability involving unlimited growth of $p(x,t)$, at the point of the minimum of the anomalous exponent $\mu(x)$, we need a regularization of subdiffusive transport. The standard approach to regularize the fractional subdiffusive equations is to temper the power law waiting time distribution in such a way that the normal diffusion behavior in the long-time limit is recovered (see, for example, [13]). In a recent paper [14] the transient anomalous transport has been considered such that this subdiffusive transport becomes normal in the long-time limit. In this paper we suggest a completely different approach, where we do not introduce an exponential cutoff parameter, which is difficult to find experimentally. Instead, we introduce an experimentally measurable death rate. The main idea is to employ a random death process, which is quite natural for many biological applications, for example, the problem of morphogen gradient formation involving morphogen degradation. Although we refer to this as the death process, in fact any reversible or irreversible reaction or conversion to another species ($A \to B$, $A \rightleftharpoons B$) or spontaneous evanescence ($A \to 0$) is valid. For discussion of this, see [15]. We show that as long as a death process is introduced, together with a particle production at the boundary, the stationary solution of the modified fractional master equation is structurally stable whatever the spatial variations of the anomalous exponent might be.

II. SUBDIFFUSIVE MASTER EQUATION

Let us consider a random walk of particles on a semi-infinite lattice with unit length. The particle performs a random walk as follows: it waits for a random time T_k at each point k before making a jump to the right with probability $r(k)$ and left with probability $l(k)$. We consider the anomalous subdiffusive case with the survival probability [16]

$$\Psi(k,t) = \Pr\{T_k > t\} = E_{\mu(k)}\left[-\left(\frac{t}{\tau_0}\right)^{\mu(k)}\right],$$

where $E_\mu[z]$ is the Mittag-Leffler function, τ_0 is a constant with the unit of time, and $\mu(k)$ is the spatially dependent anomalous exponent: $0 < \mu(k) \leqslant 1$. For large t, the survival probability $\Psi(k,t)$ behaves as

$$\Psi(k,t) \sim \left(\frac{t}{\tau_0}\right)^{-\mu(k)}.$$

We assume that during the time interval $(t, t+\Delta t)$ at point k the particle has a chance

$$\theta(k)\Delta t + o(\Delta t)$$

of dying, where $\theta(k)$ is the death rate ($\theta(k) > 0$).

We denote by $p(k,t)$ the average number of particles at point k at time t. The anomalous subdiffusive master equation with the death process can be written as

$$\begin{aligned}\frac{\partial p}{\partial t} &= \nu(k-1)e^{-\theta(k-1)t}\mathcal{D}_t^{1-\mu(k-1)}[p(k-1,t)e^{\theta(k-1)t}]\\ &\quad+\eta(k+1)e^{-\theta(k+1)t}\mathcal{D}_t^{1-\mu(k+1)}[p(k+1,t)e^{\theta(k+1)t}]\\ &\quad-[\nu(k)+\eta(k)]e^{-\theta(k)t}\mathcal{D}_t^{1-\mu(k)}[p(k,t)e^{\theta(k)t}]\\ &\quad-\theta(k)p(k,t), \quad k \geqslant 2,\end{aligned} \tag{4}$$

where

$$\nu(k) = \frac{r(k)}{(\tau_0)^{\mu(k)}}, \quad \eta(k) = \frac{l(k)}{(\tau_0)^{\mu(k)}}$$

are the anomalous rate functions. This fractional equation can be derived from a number of standpoints (see, for example, [17]). In this equation the anomalous exponent depends on the state, which is crucial for what follows. For the case of constant anomalous exponent μ, this reaction-transport equation and its continuous approximations were considered in [15,18–20].

To ensure the existence of stationary structure in the long-time limit, we introduce the constant source term g at the boundary of the semi-infinite lattice ($k = 1$). This is crucial for the problem of morphogen gradient formation, where g models a localized source of morphogens [10]. We assume that the boundary is reflective, so we have the following equation for $p(1,t)$:

$$\begin{aligned}\frac{\partial p(1,t)}{\partial t} &= \eta(2)e^{-\theta(2)t}\mathcal{D}_t^{1-\mu(2)}[p(2,t)e^{\theta(2)t}]\\ &\quad-\nu(1)e^{-\theta(1)t}\mathcal{D}_t^{1-\mu(1)}[p(1,t)e^{\theta(1)t}]-\theta(1)p(1,t)+g.\end{aligned} \tag{5}$$

Note that any nonlinear proliferation term $g(p)$ can be included in the master equation (4).

A. Structural instability of a subdiffusive equation with a constant anomalous exponent

Without the reaction ($\theta = 0$) the fractional master equation (4) with a constant anomalous exponent μ can be written as

$$\begin{aligned}\frac{\partial p(k,t)}{\partial t} &= \nu(k-1)\mathcal{D}_t^{1-\mu}[p(k-1,t)]\\ &\quad+\eta(k+1)\mathcal{D}_t^{1-\mu}[p(k+1,t)]\\ &\quad-[\nu(k)+\eta(k)]\mathcal{D}_t^{1-\mu}[p(k,t)], \quad k \geqslant 2.\end{aligned}$$

The equation for $p(1,t)$ without proliferation term g takes the form

$$\frac{\partial p(1,t)}{\partial t} = \eta(2)\mathcal{D}_t^{1-\mu}[p(2,t)] - \nu(1)\mathcal{D}_t^{1-\mu}[p(1,t)].$$

It follows from here that in the stationary case

$$p_{st}(k) = p_{st}(k-1)\frac{\nu(k-1)}{\eta(k)}, \quad k \geqslant 2. \tag{6}$$

The stationary solution $p_{st}(k) = \lim_{t\to\infty} p(k,t)$ can be found as

$$p_{st}(k) = p_{st}(1)\prod_{j=1}^{k-1}\frac{\nu(j)}{\eta(j+1)}, \quad k \geqslant 2, \tag{7}$$

where

$$p_{st}(1) = \left(1 + \sum_{k=2}^{\infty}\prod_{j=1}^{k-1}\frac{\nu(j)}{\eta(j+1)}\right)^{-1}, \tag{8}$$

provided the sum is convergent. This solution is structurally unstable with respect to partial variations of the anomalous exponent. When the anomalous exponent is not constant, the asymptotic behavior is completely different. Consider point M, at which the anomalous exponent is at a minimum $\mu(M) < \mu(k)$, $\forall\, k \neq M$. Then, one can show [7] that

$$p(M,t) \to 1, \quad p(k,t) \to 0, \quad t \to \infty. \tag{9}$$

See [21] for full details.

B. Stationary solution of master equations (4) and (5)

It is convenient to rewrite the fractional master equation (4) as

$$\frac{\partial p(k,t)}{\partial t} = -I(k,t) + I(k-1,t) - \theta(k)p(k,t), \quad k \geqslant 2, \tag{10}$$

where $I(k,t)$ is the total flux of particles from k to $k+1$,

$$I(k,t) = \nu(k)e^{-\theta(k)t}\mathcal{D}_t^{1-\mu(k)}[p(k,t)e^{\theta(k)t}] - \eta(k+1)e^{-\theta(k+1)t}\mathcal{D}_t^{1-\mu(k+1)}[p(k+1,t)e^{\theta(k+1)t}]. \tag{11}$$

The equation for $p(1,t)$ has the form

$$\frac{\partial p(1,t)}{\partial t} = -I(1,t) - \theta(1)p(1,t) + g. \tag{12}$$

The Laplace transform of the total flux $I(k,t)$,

$$\hat{I}(k,s) = \int_0^\infty I(k,t)e^{-st}dt,$$

takes the form

$$\hat{I}(k,s) = \nu(k)[s+\theta(k)]^{1-\mu(k)}\hat{p}(k,s) - \eta(k+1)[s+\theta(k+1)]^{1-\mu(k+1)}\hat{p}(k+1,s). \tag{13}$$

From here we can find the stationary flux $I_{st}(k) = \lim_{s\to 0} s\hat{I}(k,s)$ as follows:

$$I_{st}(k) = \nu_\mu(k)p_{st}(k) - \eta_\mu(k+1)p_{st}(k+1), \tag{14}$$

where

$$\nu_\mu(k) = \nu(k)[\theta(k)]^{1-\mu(k)}, \quad \eta_\mu(k) = \eta(k)[\theta(k)]^{1-\mu(k)},$$

and $p_{st}(k) = \lim_{s\to 0} s\hat{p}(k,s)$. The main feature of this stationary flux is that it has Markovian form, but the rate functions $\nu_\mu(k)$ and $\eta_\mu(k)$ depend on the anomalous rate $\nu(k)$, $\eta(k)$, the random death rate $\theta(k)$, and the anomalous exponent $\mu(k)$. This unusual form of stationary flux is because of the non-Markovian character of subdiffusion.

Let us find the stationary distribution $p_{st}(k)$ for the simple case where θ is constant. In the long-time limit, at the boundary $k=1$, we then have the following condition:

$$I_{st}(1) = g - \theta p_{st}(1).$$

We are able to obtain a general expression for the stationary flux at location k,

$$I_{st}(k) = g - \theta\sum_{j=1}^{k} p_{st}(j). \tag{15}$$

This has a very simple physical meaning: as $t\to\infty$, $I_{st}(k)$ tends to the difference between the proliferation rate g and the sum of death rates at all states from the boundary up to k. It is clear that as $k\to\infty$, the stationary flux $I_{st}(k)\to 0$ since in the stationary state g should be equal to total death rate,

$$g = \theta\sum_{j=1}^{\infty} p_{st}(j). \tag{16}$$

We obtain

$$\eta(k+1)\theta^{-\mu(k+1)}p_{st}(k+1) = \nu(k)\theta^{-\mu(k)}p_{st}(k) - \left(\frac{g}{\theta} - \sum_{j=1}^{k}p_{st}(j)\right). \tag{17}$$

This equation allows us to find $p_{st}(k)$ for all k. For the symmetrical random walk for which $\nu(k)=\eta(k)=\nu$ and $\mu = \text{const}$, we have

$$p_{st}(k+1) = p_{st}(k) - \frac{\theta^\mu}{\nu}\left(\frac{g}{\theta} - \sum_{j=1}^{k}p_{st}(j)\right). \tag{18}$$

C. Subdiffusive fractional equation with the death process

Now let us obtain the subdiffusive fractional equation with the death process as the continuous limit of the master equation (4). We change the variables $k\to x$, $k\pm 1\to x\pm a$ and obtain from (10)

$$\frac{\partial p(x,t)}{\partial t} = -I(x,t) + I(x-a,t) - \theta(x)p(x,t), \tag{19}$$

where $I(x,t)$ is the flux of particles from x to $x+a$,

$$I(x,t) = \nu(x)e^{-\theta(x)t}\mathcal{D}_t^{1-\mu(x)}[p(x,t)e^{\theta(x)t}] - \eta(x+a)e^{-\theta(x+a)t}\mathcal{D}_t^{1-\mu(x+a)}[p(x+a,t)e^{\theta(x+a)t}]. \tag{20}$$

In the limit $a\to 0$ we find

$$\frac{\partial p(x,t)}{\partial t} = -\frac{\partial}{\partial x}\{a(\nu(x)-\eta(x))e^{-\theta(x)t}\mathcal{D}_t^{1-\mu(x)}[p(x,t)e^{\theta(x)t}]\} + \frac{\partial^2}{\partial x^2}\left\{\frac{a^2}{2}[\nu(x)+\eta(x)]e^{-\theta(x)t}\mathcal{D}_t^{1-\mu(x)}[p(x,t)e^{\theta(x)t}]\right\} - \theta(x)p(x,t). \tag{21}$$

The details of this standard derivation can be found in [15,18–20]. It follows from (14) that the stationary flux $I_{st}(x)$ is

$$I_{st}(x) = \nu(x)\,[\theta(x)]^{1-\mu(x)}\,p_{st}(x) - \eta(x+a)\,[\theta(x+a)]^{1-\mu(x+a)}\,p_{st}(x+a),$$

where $p_{st}(x) = \lim_{t\to\infty}p(x,t)$. From the stationary equation

$$-I_{st}(x) + I_{st}(x-a) = \theta(x)p_{st}(x)$$

in the limit $a\to 0$, we obtain an advection-diffusion equation,

$$-\frac{\partial}{\partial x}\left[v_\mu^\theta(x)\,p_{st}(x)\right] + \frac{\partial^2}{\partial x^2}\left[D_\mu^\theta(x)\,p_{st}(x)\right] = \theta(x)p_{st}(x),$$

where $v_\mu^\theta(x)$ is the drift and $D_\mu^\theta(x)$ is the generalized diffusion coefficient, defined as

$$v_\mu^\theta(x) = \frac{a(r(x)-l(x))[\theta(x)]^{1-\mu(x)}}{(\tau_0)^{\mu(x)}},$$

$$D_\mu^\theta(x) = \frac{a^2\,[\theta(x)]^{1-\mu(x)}}{2(\tau_0)^{\mu(x)}}, \quad 0<\mu(x)\leqslant 1.$$

This result means that in the long-time limit, subdiffusion with the death process becomes standard diffusion with nonstandard drift $v_\mu^\theta(x)$ and diffusion coefficient $D_\mu^\theta(x)$. Both of them depend on the death rate $\theta(x)$ and the anomalous exponent $\mu(x)$. This is due to the non-Markovian character of subdiffusion. Note that the drift term $v_\mu^\theta(x)$ plays an essential role in chemotaxis since $v_\mu^\theta(x)\sim a\frac{\partial C}{\partial x}$, where C is the chemotactic substance. Therefore the dependence of the chemotactic term of the degradation rate θ can be of great importance for the problem of cell aggregation [11,22,23]. For

$\mu(x) = 1$, we have classical drift and a diffusion coefficient independent from $\theta(x)$. It has been found in [19] that the non-Markovian behavior of subdiffusion leads to an effective nonlinear diffusion.

D. Morphogen gradient formation

Let us illustrate our theory in terms of the problem of morphogen gradient formation involving morphogen degradation [8–10]. We consider a random walk with a constant drift $v_\mu^\theta = -v$, diffusion D_μ^θ, and degradation rate θ. We obtain the stationary morphogen profile from the equation

$$v\frac{\partial p_{st}(x)}{\partial x} + D_\mu^\theta \frac{\partial^2 p_{st}(x)}{\partial x^2} - \theta p_{st}(x) = 0. \tag{22}$$

The solution of (22) is the exponential distribution

$$p_{st}(x) = A\exp\left[-\frac{v+\sqrt{v^2+4D_\mu^\theta\theta}}{2D_\mu^\theta}x\right], \tag{23}$$

where A can be found from the condition $g = \theta\int_0^\infty p_{st}(x)dx$:

$$A = \frac{g\left(v+\sqrt{v^2+4D_\mu^\theta\theta}\right)}{2\theta D_\mu^\theta}.$$

When $v_\mu^\theta = 0$, we have the morphogen profile obtained in [10]:

$$p_{st}(x) = \frac{g}{\sqrt{\theta D_\mu^\theta}}\exp\left[-\sqrt{\frac{\theta}{D_\mu^\theta}}x\right]. \tag{24}$$

We now simulate the fractional master equation with a random death process using Monte Carlo techniques. Throughout this we let $\tau_0 = 1$, so that this is the unit of time for the simulation; we take $g = 1$, so that we have a constant birth rate of one particle per unit time. The first particle begins a random walk at $k = 1$, such that at each point k waiting times are power law distributed, and jump probabilities to the left and right of each point k are $r(k)$ and $l(k)$, respectively. A particle completes a random walk from when it is produced until the terminal time $t = T$ or until its random time of death, exponentially distributed as $\psi_D(t) = \theta e^{-\theta t}$. Also note that unlike the waiting time, the death time is not renewed when the particle makes a jump.

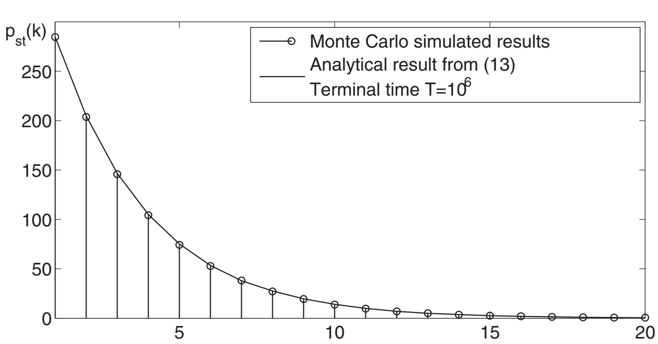

FIG. 1. Stationary profile for the symmetric fractional master equation where $r(k) = l(k) = \frac{1}{2}$, $\mu(k) = \text{const} = 0.5$, $\tau_0 = 1$, and $\theta = 10^{-3}$.

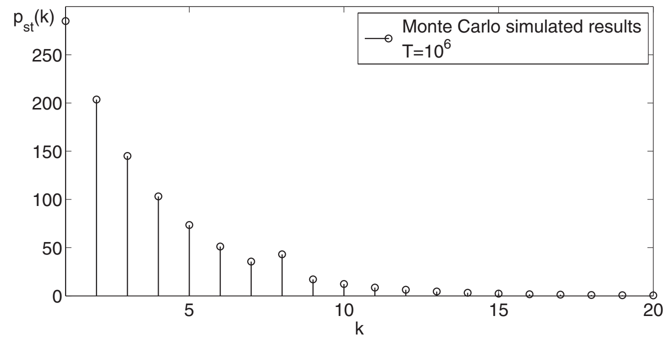

FIG. 2. Stationary profile for the symmetric fractional master equation, with a perturbation to the anomalous exponent at $k = 8$. $\mu(k \neq 8) = 0.5$, $\mu(8) = 0.4$.

First, let us consider the symmetrical random walk, where $r(k) = l(k) = \frac{1}{2}$, $\mu(k) = 0.5$, and $\theta = 10^{-3}$. Figure 1 shows the corresponding stationary density made up of 10^4 realizations of the random walk at time $T = 10^6$. We can see that our simulation is in agreement with the analytical values calculated from the recurrence relation (18).

Next, we show that the model is robust to nonhomogenous spatial perturbations in the anomalous exponent. Analogously to the simulation we presented in the previous work [7], we introduce a small perturbation to the anomalous exponent at one point in the space: all states have $\mu = 0.5$ except for $k = 8$, which has $\mu = 0.4$. From Fig. 2 we can see that although we observe a change to the stationary profile around the point $k = 8$, the stationary profile is structurally stable and exponential in character. We stress the importance of the death process in regulating the behavior of the process to ensure stability, whereas in our previous work, we showed that even a small perturbation in the anomalous exponent like this would lead to a breakdown in the Gibbs-Boltzmann stationary density. Additionally, we considered a nonsymmetrical random walk, which leads to a drift, and found that the profile is stable.

III. CONCLUSIONS

In summary, it was previously thought that as far as the fractional Fokker-Planck equation is concerned, the effect of subdiffusive trapping was just to cause a power law decay to the stationary state, such as the Gibbs-Boltzmann distribution. However, we showed that a nonuniform distribution of traps drastically changes the stationary structure itself and develops singularities like anomalous aggregation. This is a critical problem, especially for morphogen gradient formation, and we introduced the random death process as a natural remedy. Our approach is fundamentally different from tempering [13], which is just the truncation of the power law waiting time distribution by an exponential factor involving a tempering parameter. This parameter is extremely difficult to measure experimentally, but in our case it is quite the opposite. We introduce the death process, and the death rate can be easily measured independently of the transport process. Another advantage of our approach is that it can be easily extended to the case when the death rate depends on the density of particles. So we are not just employing a mathematical trick to overcome the problem of an infinite mean waiting time. We also find the stationary flux of the particles has a Markovian form, with an unusual rate function depending on the anomalous rate functions, the death rate, and the anomalous exponent.

We have shown that the long-time and continuous limit of this regularized fractional equation is the standard advection-diffusion equation that, importantly, is structurally stable with respect to spatial variations of the anomalous exponent μ. Thus we have addressed the problem of applicability to modeling complex biological systems. We have found that the effective advection and diffusion coefficients, v_μ^θ and D_μ^θ, are increasing functions of the death rate θ: $v_\mu^\theta \sim D_\mu^\theta \sim \theta^{1-\mu}$. We have applied a regularized fractional master equation and modified fractional Fokker-Planck equation to the problem of the morphogen gradient formation. We have shown the robustness of the stationary morphogen distribution against spatial fluctuations of anomalous exponent.

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