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Heterogeneous anomalous diffusion in view of superstatistics

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ABSTRACT

It is experimentally known that virus exhibits stochastic motion in cytoplasm of a living cell in the free form as well as the form being contained in the endosome and the exponent of anomalous diffusion of the virus fluctuates depending on localized areas of the cytoplasm. Here, a theory is developed for establishing a generalized fractional kinetics for the infection pathway of the virus in the cytoplasm in view of superstatistics, which offers a general framework for describing nonequilibrium complex systems with two largely separated time scales. In the present theory, the existence of a large time-scale separation in the infection pathway is explicitly taken into account. A comment is also made on scaling nature of the motion of the virus that is suggested by the theory.

1. Introduction

In recent years, the infection pathway of adeno-associated viruses in living *HeLa* cells has experimentally been studied by making use of the technique of real-time single-molecule imaging [1,2]. (Here, the adeno-associated virus is a small virus particle, and the *HeLa* cell is a line of human epithelial cells.) Remarkably, an exotic phenomenon has been observed in cytoplasm of the living cell. In the experiments [1,2], the virus solution of low concentrations was added to a culture medium of the living cells. Then, the trajectories of the viruses, each of which is labeled with fluorescent dye molecule, in the cytoplasm were analyzed. The experiments show that the fluorescent viruses exhibit stochastic motion in the free form as well as the form being contained in the endosome (i.e., a spherical vesicle).

Let us denote the mean square displacement in stochastic motion by $\overline{x^2}$. It behaves as

$$\overline{x^2} \sim t^{\alpha}, \tag{1}$$

for large elapsed time, t, in general. Normal diffusion leads to $\alpha = 1$, while $0 < \alpha < 1$ ($\alpha > 1$) corresponds to subdiffusion (superdiffusion). The experimental result shows that the mean square displacement of the fluorescent virus exhibits not only normal diffusion but also subdiffusion in the form of Eq. (1). However, what is truly remarkable is the fluctuations of α in the case of subdiffusion [1]: α fluctuates between 0.5 and 0.9, depending on localized areas of the cytoplasm. This may be due to existence of obstacles in the cytoplasm, not the forms of existence of the virus (i.e., being free or contained in the endosome) [1,2]. Thus, this phenomenon is seen to manifest the *heterogeneous* structure of the cytoplasm as a medium for stochastic motion of the virus.

The phenomenon mentioned above is in marked contrast to traditional anomalous diffusion [3] discussed for a variety of physical systems, examples of which are particle motion in turbulent flow [4], charge carrier transport in amorphous solids [5], the flow of contaminated vortex in fluid [6], chaotic dynamics [7], porous glasses [8]. On the other hand, in biology, a lot of efforts have been devoted to understanding the virus infection process in order to both design antiviral drug and develop efficient gene therapy vectors.

The purpose of this paper is to develop a theoretical framework for establishing a generalized fractional kinetics proposed in Ref. [9], where the infection pathway of the adeno-associated virus in the cytoplasm of the living *HeLa* cell is studied by generalizing traditional fractional kinetics [10]. For this purpose, we base our consideration on the idea of superstatistics. Superstatistics, which has been introduced in Ref. [11] after some preliminary works in Refs. [12–14], is "statistics of statistics" with two largely separated time scales and offers a unified theoretical framework for describing nonequilibrium complex systems with two such time scales. A prototype system in superstatistics [11,13] is a Brownian particle moving through a fluid environment with varying temperature on a large spatial scale. This system is divided into many small spatial "cells", each of which is in local equilibrium characterized by each value of temperature. So, the Brownian particle in a given cell moves to neighboring ones. Then, variation of the local fluctuations of temperature is slow, whereas relaxation of the Brownian particle in a cell to a local equilibrium state with a given value of temperature is fast. Consequently, the system on a long

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time scale is described by a superposition of two statistics associated with these different dynamics. The situation we consider here is that the virus moves through the cytoplasm with varying local fluctuations of the exponent, α, in Eq. (1). We assume that there is a large separation of two time scales in the infection pathway: the time scale of variation of exponent fluctuations is much larger than that of stochastic motion of the virus in a localized area of the cytoplasm. This is in analogy with the existence of two largely separated time scales in superstatistics. From the viewpoint of superstatistics, we describe the motion of the virus by a superposition of two different statistics: one is statistics concerning stochastic motion of the virus in a localized area of the cytoplasm, and the other is one associated with variation of exponent fluctuations. For the virus in each localized area, we apply fractional kinetic theory, which generalizes Einstein's approach to Brownian motion [15]. Proposing the statistical form of the fluctuations of the exponent based on the experimental data as well as the maximum entropy principle [16], we show that the present framework yields the generalized fractional kinetic theory. We also make a comment on a scaling law for the motion of the virus that is suggested by the theory.

2. Stochastic motion of the virus in the cytoplasm and superstatistics

Let us start our discussion with considering 1-dimensional stochastic motion of the virus in the cytoplasm with slowly varying local fluctuations of the exponent, α. We describe it in view of superstatistics. To do so, we regard the cytoplasm as a medium for stochastic motion of the free virus as well as the virus contained in the endosome. Then, we imaginarily divide the medium into many small blocks, each of which is identified with a localized area of the cytoplasm. As already mentioned in the Introduction, the time scale of variation of the fluctuations is supposed to be much larger than that of stochastic motion of the virus in each local block. In other words, α is approximately constant while the virus moves through the blocks. For the virus in a local block with a given value of α, we describe the probability of finding the virus in the interval $[x, x+dx]$ at time t by $f_\alpha(x,t)dx$. Denoting the statistical distribution of the fluctuations of α by $P(\alpha)$, we describe the probability of finding the virus on a long time scale by the average of $f_\alpha(x,t)dx$ with respect to $P(\alpha)$:

$$f(x,t)dx = dx \int d\alpha\, P(\alpha) f_\alpha(x,t). \tag{2}$$

Eq. (2) clearly shows that the statistical property of the virus in the cytoplasm is given by the superposition of $f_\alpha(x,t)dx$ with respect to $P(\alpha)$ in conformity with the viewpoint of superstatistics.

In what follows, we first formulate a generalized fractional kinetic theory, in which the statistical fluctuation of the exponent is incorporated, based on Eq. (2).

We express $f_\alpha(x,t)dx$ in Eq. (2) in terms of $f(x,t)dx$ based on the scheme of continuous-time random walks [17]:

$$f_\alpha(x,t)dx = dx \int_{-\infty}^{\infty} d\Delta \int_0^t d\tau\, f(x+\Delta, t-\tau)\phi_\tau(\Delta)\psi_\alpha(\tau) + \delta(x)R(t)dx. \tag{3}$$

Here, the first term on the right-hand side stands for all of possible probabilities that the virus moves into the interval from outside or stays in the interval. The second term is a partial source guaranteeing the initial condition, $f(x,0)=\delta(x)$, and $R(t)$ describes a time-dependent partial source with the condition, $R(0)=1$. Then, $\phi_\tau(\Delta)$ is the normalized probability density distribution for a displacement, Δ, in a finite time step, τ. This distribution is sharply peaked at $\Delta=0$ and satisfies the condition, $\phi_\tau(\Delta)=\phi_\tau(-\Delta)$. $\psi_\alpha(\tau)$ is the normalized probability density distribution for τ, which is treated as a random variable, and satisfies the condition, $\psi_\alpha(0)=0$. As will be seen below, it is implied that this distribution decays as a power law characterized by $\alpha \in (0,1)$ for long time step [see the discussion after Eq. (6) below]. From the normalization condition on $f(x,t)$, it is found that $R(t)$ is connected to $\psi_\alpha(\tau)$ through the relation: $R(t) = 1 - \int_0^t d\tau\, \psi_\alpha(\tau)$ [from which $R(t)$ depends on α]. In our later discussion, we shall show how the present theory yields traditional fractional kinetics [10], which turns out to reproduce both normal diffusion and subdiffusion with a fixed exponent observed in the experiments.

Now, it seems that the nature of subdiffusion observed in the experiments comes from $\psi_\alpha(\tau)$, not $\phi_\tau(\Delta)$. Therefore, we assume in what follows that $\phi_\tau(\Delta)$ is actually independent of time steps: $\phi_\tau(\Delta)=\phi(\Delta)$. To formulate the generalized fractional kinetic theory, we employ the Laplace transforms of Eqs. (2) and (3) with respect to time:

$$\tilde{f}(x,u) = \int d\alpha\, P(\alpha)\tilde{f}_\alpha(x,u), \tag{4}$$

$$\tilde{f}_\alpha(x,u) = \int_{-\infty}^{\infty} d\Delta\, \tilde{f}(x+\Delta,u)\phi(\Delta)\tilde{\psi}_\alpha(u) + \delta(x)\frac{1-\tilde{\psi}_\alpha(u)}{u}, \tag{5}$$

where $\tilde{f}(x,u)$, $\tilde{f}_\alpha(x,u)$, and $\tilde{\psi}_\alpha(u)$ are the Laplace transforms of $f(x,t)$, $f_\alpha(x,t)$, and $\psi_\alpha(\tau)$, respectively, provided that $\mathcal{L}(g)(u) = \tilde{g}(u) = \int_0^\infty dt' g(t') e^{-ut'}$.

In analogy with the discussions in Refs. [18,19], where the separation of the time scales in superstatistics is explicitly implemented by the use of conditional concepts, we notice here the following point: in Eq. (4), the averaging over the slow variable, i.e., α, is taken after the integration over the fast variable, i.e., Δ, is performed. This procedure is opposite to that discussed in Ref. [9], where the integration over the fast variable is performed after the elimination of the slow variable. Thus, the existence of a large time-scale separation in the infection pathway is explicitly taken into account in the present procedure.

In Eq. (5), we suppose that $\tilde{\psi}_\alpha(u)$ takes the following form:

$$\tilde{\psi}_\alpha(u) \sim 1 - (su)^\alpha \tag{6}$$

with a characteristic constant, s, which has the dimension of time. This characteristic time is an indicative one, at which the virus is displaced. We also impose the condition that $\psi_\alpha(\tau)$ has the divergent first moment, which requires the exponent α to be in the interval $(0,1)$. Eq. (6) implies that $\psi_\alpha(\tau)$ decays as a power law like, $\psi_\alpha(\tau) \sim s^\alpha/\tau^{1+\alpha}$, for the long time step, $\tau \gg s$, as mentioned earlier.

We expand $\tilde{f}$ up to the second order of Δ after substituting Eq. (5) into Eq. (4). Then, neglecting the term $\langle\Delta^2\rangle \int d\alpha P(\alpha)(su)^\alpha$ with $\langle\Delta^2\rangle \equiv \int_{-\infty}^{\infty} d\Delta \Delta^2 \phi(\Delta)$ (u being small in the long time behavior), we have

$$\tilde{f}(x,u) = \frac{\langle\Delta^2\rangle}{2\int d\alpha\, P(\alpha)(su)^\alpha}\frac{\partial^2 \tilde{f}(x,u)}{\partial x^2} + \delta(x)\frac{1}{u}. \tag{7}$$

Performing the inverse Laplace transform of Eq. (7), we obtain the following generalized fractional diffusion equation:

$$\int d\alpha\, P(\alpha) s^{\alpha-1} {}_0\mathcal{D}_t^{-(1-\alpha)} \frac{\partial f(x,t)}{\partial t} = D\frac{\partial^2 f(x,t)}{\partial x^2}, \tag{8}$$

where the diffusion constant, D, is calculated to be $D = \langle\Delta^2\rangle/(2s)$ and a mathematical fact of fractional operator [10], $\mathcal{L}({}_0\mathcal{D}_t^{-\alpha} g(x,t))(u) = u^{-\alpha}\tilde{g}(x,u)$, has been used. For the virus in a given local