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Deviation of the statistical fluctuation in heterogeneous anomalous diffusion

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HIGHLIGHTS

- The statistical fluctuation in heterogeneous anomalous diffusion is discussed.
- Assumption on the blocks in the medium regarded as cytoplasm of a cell is examined.
- The deviation of the statistical fluctuation from a Poisson-like one is considered.
- Behavior of the deviation is studied in view of Einstein's theory of fluctuations.
- The deviation obeys the multivariate Gaussian distribution in a class of deviations.

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ABSTRACT

The exponent of anomalous diffusion of virus in cytoplasm of a living cell is experimentally known to fluctuate depending on localized areas of the cytoplasm, indicating heterogeneity of diffusion. In a recent paper (Itto, 2012), a maximum-entropy-principle approach has been developed in order to propose an *Ansatz* for the statistical distribution of such exponent fluctuations. Based on this approach, here the deviation of the statistical distribution of the fluctuations from the proposed one is studied from the viewpoint of Einstein's theory of fluctuations (of the thermodynamic quantities). This may present a step toward understanding the statistical property of the deviation. It is shown in a certain class of small deviations that the deviation obeys the multivariate Gaussian distribution.

There exists a remarkable phenomenon, which is exotic from the traditional perspective of the physics of diffusion. Such a phenomenon has experimentally been observed in the infection pathway of adeno-associated viruses in living *HeLa* cells by the use of the technique of real-time single-molecule imaging [1–3]. (Here, the adeno-associated virus is a small virus particle, whereas the *HeLa* cell is a line of human epithelial cells.) The experiments show that, in cytoplasm of the cell, the virus, which is labeled with fluorescent dye molecule, exhibits stochastic motions in both the free form and the form being contained in the endosome (i.e., a spherical vesicle). There, the mean square displacement in stochastic motion, which is denoted here by $\overline{x^2}$, is evaluated based on analysis of the trajectories of the fluorescent viruses. Then, $\overline{x^2}$ scales for large elapsed time, t, as

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

The experimental results show not only normal diffusion, leading to $\alpha = 1$, but also subdiffusion, corresponding to $0 < \alpha < 1$. Remarkably, subdiffusion of the virus exhibits a novel feature [2] that the exponent, α, fluctuates depending

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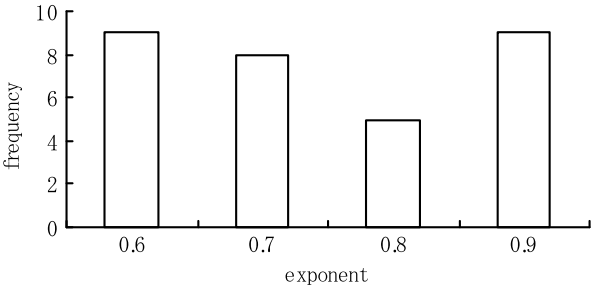

Fig. 1. The frequency of the exponent in the case of subdiffusion. The histogram is made based on Fig. 7.44 in Ref. [1].

on localized areas of the cytoplasm: $\alpha \in (0.5, 0.9)$. This may not be due to the forms of existence of the virus (i.e., the free or endosomal forms) [2] and, thus, highlights its *heterogeneity*, in marked contrast to anomalous diffusion widely discussed over the years, for example, in Refs. [4–10] (see Ref. [11] for a recent review).

In recent works [12,13], a kinetic theory has been developed in order to describe the infection pathway of the virus over the cytoplasm by generalizing fractional kinetics [14] modeling anomalous diffusion in a unified way. There, the statistical distribution of the fluctuations of α over the cytoplasm plays a central role. According to the experiment [2], 113 trajectories of the viruses are analyzed. The result of the analysis is as follows. In the form in Eq. (1), 53 trajectories show $\alpha = 1$, and 51 exhibit α varying between 0.5 and 0.9. On the other hand, the mean square displacement in 9 trajectories has a parabolic form for the elapsed time, indicating diffusion with drift. The number of these trajectories is seen to be less compared to those in the case of normal diffusion and subdiffusion (a relevant discussion can be found in Ref. [3]). Therefore, the result in 9 trajectories has been neglected in the discussions in Refs. [12,13]. (Following Refs. [12,13], the result is also not taken into account in the present discussion.) From the above result on 104 trajectories, as the statistical property of the fluctuations of α, it is considered [12,13] that normal diffusion is often to be realized, whereas subdiffusion with the exponent near $\alpha = 0$ may seldom be the case. This consideration is also motivated by the property [2] that the virus tends to reach the nucleus of the cell. In addition, the exponents found in both the free and endosomal forms are supposed to be different from each other only slightly. Consequently, as an *Ansatz* for the statistical distribution of the fluctuations, the following Poisson-like distribution, which is expressed here in the case of discrete values of the exponent for convenience in our later discussion, has been proposed:

$$P_{\alpha_i} \propto \mathrm{e}^{\lambda\alpha_i} \quad (i = 1, 2, \ldots, A), \tag{2}$$

where A is the total number of different values of the exponent, α_i is the ith value of the exponent, and λ is a positive constant.

We here wish to mention the following. The distribution in Eq. (2) has property of monotonic increase with respect to the exponent. On the other hand, as can be seen in Fig. 1, in which the experimental data of the frequency of the exponent in the case of subdiffusion is presented, the weights of the exponents decrease at $\alpha = 0.8$. This indicates that the statistical distribution of fluctuations to be suggested by the weights has no property of monotonic increase in the whole range of α described there, although it is seen to have such a property in the range near $\alpha = 1$. Therefore, one might think that Eq. (2) does not well explain the distribution based on the weights. Regarding this point, however, it seems necessary to clarify if each trajectory is taken from each of different localized areas in the cytoplasm. Then, the distribution in Eq. (2) is supposed to describe the statistical fluctuation on a large spatial scale in the cytoplasm, not limited to the localized areas studied in the experiments. Accordingly, it seems fair to say that this distribution is yet to be carefully examined with further information on the fluctuations. In Refs. [12,13], it has been shown that it is in fact possible to theoretically derive the distribution in Eq. (2) (which is continuous there) in a consistent manner (see the later discussion), supporting its realization. Therefore, we suppose that this is the distribution of relevance, here.

Now, a fundamental premise in the discussions in Refs. [12,13] is that the time scale of variation of exponent fluctuations is much larger than that of stochastic motion of the virus in each localized area: that is, the exponent slowly varies. The exponent is then assumed to be approximately constant during the motion of the virus over the cytoplasm.

Here, a natural question arises. If this assumption is relaxed, then the statistical distribution of the fluctuations to be observed on a long time scale may deviate from that in Eq. (2) due to variation of the fluctuations, in general, although the deviation seems to be small. Accordingly, the question is how the behavior of such a deviation can be determined.

In this short note, we wish to answer this question for a certain class of deviations. For it, from the viewpoint of Einstein's theory of fluctuations [15–17], we examine the approach proposed in Refs. [12,13], where it is shown that the Poisson-like distribution of exponent fluctuations can be derived by the maximum entropy principle. Since the deviation should not be so large due to slow variation of the fluctuations, we consider, as the statistical distribution of the fluctuations to be observed, a distribution that can deviate from the Poisson-like distribution in Eq. (2) only slightly. Specifically, we focus our attention on a class of deviations in the following situation: the expectation values of the exponent with respect to both this distribution and that in Eq. (2) are equal to each other. Such a class is of physical interest in accordance with the above approach. Then, we show that the deviation in this class obeys the multivariate Gaussian distribution. The present discussion can be seen as a step toward understanding the statistical property of the deviation.

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