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Diffusion with a broad class of stochastic diffusion coefficients

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In many physical or biological systems, diffusion can be described by Brownian motions with stochastic diffusion coefficients (DCs). In the present study, we investigate properties of the diffusion with a broad class of stochastic DCs with an approach that is different from subordination. We show that for a finite time, the propagator is non-Gaussian and heavy tailed. This means that when the mean square displacements are the same, for a finite time, some of the diffusing particles with stochastic DCs diffuse farther than the particles with deterministic DCs or exhibiting a fractional Brownian motion. We also show that when a stochastic DC is ergodic, the propagator converges to a Gaussian distribution in the long time limit. The speed of convergence is determined by the autocovariance function of the DC.

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I. INTRODUCTION

Diffusion in physical systems or in biological systems is often described by Brownian motions with stochastic diffusion coefficients (DCs). For example, ligands often fluctuate between different conformational states. In the models of ligand diffusion, different DCs are given for the different states [1–3]. An experimental observation of subdiffusion of a certain receptor on a cell membrane is also explained by a model of a Brownian motion with a stochastic DC [4]. In this model, the stochasticity of the DC comes from the dynamic heterogeneity of the cell membrane [4].

It has been shown that for a specific class and specific models of Brownian motions with stochastic DCs, the propagators are heavy tailed for short times [5–7]. When a DC is described by the square of an Ornstein-Uhlenbeck process (minimal diffusing-diffusivity model), the propagator is a Laplace-like distribution with exponential tails for short times [5,6]. When the DC fluctuates between two states and the distributions of sojourn time in each state are given by power-law distributions (two-state model with power-law distributions), the propagator is heavy tailed for short times [7]. However, unlike continuous time random walk (CTRW) where the exponential decay is shown to be a common property of propagators [8], it remains unknown whether a heavy-tailed propagator is a common property of Brownian motions with stochastic DCs.

There is another open question about diffusion with stochastic DCs. For specific models of stochastic DCs, theoretical studies have shown that at long times, heavy-tailed propagators cross over to Gaussian propagators. When a DC follows a certain random walk, the propagator is exponential at short times and Gaussian at long times [9]. For the minimal diffusing-diffusivity model, it has been shown that at times longer than some correlation time of the DC, a crossover from a heavy-tailed propagator to a Gaussian propagator occurs [5]. However, as with a property of propagators for short times, it remains unknown for how broad a class of stochastic DCs the crossover occurs.

In the present study, we investigate properties of the diffusion with a broad class of stochastic DCs, with a particular focus on the propagator. In Sec. II, we describe an overdamped Langevin equation with a stochastic DC. The diffusion with a stochastic DC can be described by an overdamped Langevin equation with a stochastic DC. In Sec. III, we present an approach to find an expression for the propagator. We derive the diffusion equation corresponding to the overdamped Langevin equation with a stochastic DC and then derive an expression for the propagator by solving the diffusion equation. In Sec. IV, we reveal properties of the diffusion through properties of the propagator. In Sec. V, we discuss the relation of our approach to other approaches and compare our results with those of other models.

II. MODEL

The overdamped Langevin equation with a stochastic DC is given by

$$\frac{d\boldsymbol{x}(t)}{dt} = \sqrt{2D(t)}\boldsymbol{\xi}(t), \tag{1}$$

where $\boldsymbol{x}(t)$ is the n-dimensional position of the diffusing particle and $\boldsymbol{x}(t) = [x_1(t), x_2(t), \dots, x_n(t)]^T$. In Eq. (1), $D(t)$ is a stochastic process and represents a DC. In Eq. (1), $\boldsymbol{\xi}(t)$ is a vector of Gaussian white noises and $\boldsymbol{\xi}(t) = [\xi_1(t), \xi_2(t), \dots, \xi_n(t)]^T$: $\langle \boldsymbol{\xi}(t)\rangle = \boldsymbol{0}$ and $\langle \xi_i(t)\xi_j(t')\rangle = \delta_{ij}\delta(t-t')$ $(i, j = 1, 2, \dots, n)$. We assume that $D(t)$ and $\xi_i(t)$ are statistically independent.

III. DIFFUSION EQUATION

A. Derivation

Here, we derive the diffusion equation corresponding to Eq. (1). The stochastic integral equation corresponding to Eq. (1) is given by

$$\boldsymbol{x}(t) = \boldsymbol{x}_0 + \int_0^t \sqrt{2D(t')}d\boldsymbol{B}(t'), \tag{2}$$

where $\boldsymbol{x}_0 = \boldsymbol{x}(0)$, $\boldsymbol{B}(t)$ is a vector of Wiener processes, and $\boldsymbol{B}(t) = [B_1(t), B_2(t), \ldots, B_n(t)]^T$: $\langle d\boldsymbol{B}(t)\rangle = \boldsymbol{0}$ and $\langle dB_i(t)dB_j(t)\rangle = \delta_{ij}dt$.

Equation (1) is just a formal equation. If $D(t)$ is deterministic and $\int_0^t D(t')dt' < \infty$, the integral on the right-hand side of Eq. (2) is the Wiener integral. If $D(t)$ is a stochastic process defined on the measurable space on which $\boldsymbol{B}(t)$ is defined, the integral on the right-hand side of Eq. (2) can be the stochastic integral. However, in this study, $D(t)$ is neither. Thus, for further calculations, we need to give an interpretation of Eq. (1).

One natural interpretation of Eq. (1) is given by the equations

$$\boldsymbol{x}(t;\omega) = \boldsymbol{x}_0 + \int_0^t \sqrt{2D(t',\omega)}d\boldsymbol{B}(t')\ (\omega \in \Omega), \tag{3}$$

$$\int_0^t D(t',\omega)dt' < \infty, \tag{4}$$

where Ω represents the sample space for $D(t)$, ω represents a sample, $D(t,\omega)$ represents a sample path of $D(t)$, and $\boldsymbol{x}(t;\omega)$ is the position of the diffusing particle for a given sample path $D(t,\omega)$. Each sample path of $D(t)$ is deterministic. Thus, the integral in the right-hand side of Eq. (3) is the Wiener integral. The condition given by Eq. (4) is natural because $0 \leqslant D(t) < \infty$.

The diffusion equation corresponding to Eq. (3) is given by

$$[\partial_t - D(t;\omega)\nabla^2]G(\boldsymbol{x},t,\boldsymbol{x}_0;\omega) = \delta(\boldsymbol{x}-\boldsymbol{x}_0)\delta(t)\ (\omega \in \Omega), \tag{5}$$

where $G(\boldsymbol{x},t,\boldsymbol{x}_0;\omega)$ represents the propagator for a given sample path $D(t;\omega)$.

B. Propagator

Here, we solve Eq. (5) and derive the propagator. Under the natural boundary condition, the solution of Eq. (5) is given by [10]

$$G(\boldsymbol{x},t,\boldsymbol{x}_0;\omega) = \frac{1}{[4\pi S(t;\omega)t]^{n/2}} \exp\left[-\frac{|\boldsymbol{x}-\boldsymbol{x}_0|^2}{4S(t;\omega)t}\right], \tag{6}$$

where $S(t;\omega)$ represents the time average of $D(t;\omega)$ and is given by

$$S(t;\omega) = \frac{1}{t}\int_0^t D(t';\omega)dt'. \tag{7}$$

The propagator $G(\boldsymbol{x},t,\boldsymbol{x}_0;\omega)$ depends on ω only through $S(t;\omega)$. Thus, the propagator for the diffusion described by Eq. (1) $G(\boldsymbol{x},t,\boldsymbol{x}_0)$ is given by

$$G(\boldsymbol{x},t,\boldsymbol{x}_0) = \int_0^\infty \frac{p(S,t)}{(4\pi St)^{n/2}} \exp\left(-\frac{|\boldsymbol{x}-\boldsymbol{x}_0|^2}{4St}\right)dS, \tag{8}$$

where $p(S,t)$ is the probability distribution of the time average of the DC (TADC), $S(t)$.

From Eq. (8), we can see that the propagator is unimodal and the peak is at $\boldsymbol{x} = \boldsymbol{x}_0$. In addition, when $0 < D(t)$, the propagator is differentiable at $\boldsymbol{x} = \boldsymbol{x}_0$. When $D(t)$ can take the value of zero, the propagator can be nondifferentiable at $\boldsymbol{x} = \boldsymbol{x}_0$ if t is smaller than the time that characterizes the change of $D(t)$ (see Ref. [11] for an example). However, even if $D(t)$ can take the value of zero, the propagator is differentiable at $\boldsymbol{x} = \boldsymbol{x}_0$ if t is larger than the time that characterizes the change of $D(t)$. The differentiability at the peak means that the peak is not sharp. The smoothness of the peak is important in comparing with other diffusion models (see Sec. V).

IV. PROPERTIES OF THE DIFFUSION

A. General theory

Here, we reveal properties of the diffusion with a broad class of stochastic DCs through properties of the propagator. From Eq. (8), we can derive expressions for the moments of all orders. From Eq. (8), we have

$$\int_{\boldsymbol{x}} \exp(\lambda|\delta\boldsymbol{x}|^2)G(\boldsymbol{x},t,\boldsymbol{x}_0)d\boldsymbol{x} = \int_0^\infty \frac{p(S,t)}{(1-4St\lambda)^{n/2}}dS, \tag{9}$$

where $\delta\boldsymbol{x}$ represents the displacement and is given by $\delta\boldsymbol{x} = \boldsymbol{x} - \boldsymbol{x}_0$, and $\int_{\boldsymbol{x}} d\boldsymbol{x} = \int_{-\infty}^{\infty}\cdots\int_{-\infty}^{\infty} dx_1\cdots dx_n$. For the left-hand side of Eq. (9), substituting $\lambda = 0$ into the kth-order derivative of λ leads to

$$\frac{d^k}{d\lambda^k}\int_{\boldsymbol{x}} \exp(\lambda|\delta\boldsymbol{x}|^2)G(\boldsymbol{x},t,\boldsymbol{x}_0)d\boldsymbol{x}\bigg|_{\lambda=0} = \langle|\delta\boldsymbol{x}(t)|^{2k}\rangle, \tag{10}$$

where k is a positive integer. In this study, the ensemble average $\langle\,\rangle$ is taken over the ensemble that is appropriate for the stochastic variable to be averaged. For example, in Eq. (10), $\langle|\delta\boldsymbol{x}(t)|^{2k}\rangle$ is given by

$$\langle|\delta\boldsymbol{x}(t)|^{2k}\rangle = \int_{\boldsymbol{x}} |\delta\boldsymbol{x}|^{2k}G(\boldsymbol{x},t,\boldsymbol{x}_0)d\boldsymbol{x}. \tag{11}$$

For the right-hand side of Eq. (9), substituting $\lambda = 0$ into the kth-order derivative of λ leads to

$$\frac{d^k}{d\lambda^k}\int_0^\infty \frac{p(S,t)}{(1-4St\lambda)^{n/2}}dS\bigg|_{\lambda=0} = (2t)^k n(n+2)\cdots(n+2k-2)\langle S^k(t)\rangle. \tag{12}$$

From Eqs. (9), (10), and (12), we obtain

$$\langle|\delta\boldsymbol{x}(t)|^{2k}\rangle = (2t)^k n(n+2)\cdots(n+2k-2)\langle S^k(t)\rangle. \tag{13}$$

In addition, from Eq. (8), we have

$$\langle|\delta\boldsymbol{x}(t)|^{2k-1}\rangle = 0. \tag{14}$$

From Eq. (13), we have

$$\langle|\delta\boldsymbol{x}(t)|^2\rangle = 2nt\langle S(t)\rangle. \tag{15}$$

This equation has already been derived for a broad class of stochastic DCs using the Langevin formalism (Eq. (24) in Ref. [7]).

From Eq. (15), we can see that the mean square displacement (MSD) $\langle|\delta\boldsymbol{x}(t)|^2\rangle$ does not reflect fluctuations in DCs. From Eq. (8), we can see that for a finite time, the propagator is non-Gaussian if a DC is stochastic. This suggests that the non-Gaussian parameter reflects fluctuations in a DC. The non-Gaussian parameter [7,12,13] $A(t)$ is given by

$$A(t) = \frac{\langle[\delta\boldsymbol{x}^T(t)\Sigma^{-1}(t)\delta\boldsymbol{x}(t)]^2\rangle}{n(n+2)} - 1, \tag{16}$$

where $\Sigma(t)$ represents the variance-covariance matrix. When the propagator is Gaussian, $A(t) = 0$. From Eq. (13), we have

$$\Sigma(t) = 2t\langle S(t)\rangle I_n, \tag{17}$$

where I_n is the nth-order identity matrix. From Eqs. (15) and (17), we obtain

$$\Sigma(t) = \frac{\langle|\delta\boldsymbol{x}(t)|^2\rangle}{n} I_n. \tag{18}$$

Thus, we have

$$A(t) = \frac{n\langle|\delta\boldsymbol{x}(t)|^4\rangle}{(n+2)\langle|\delta\boldsymbol{x}(t)|^2\rangle^2} - 1. \tag{19}$$

On the other hand, from Eq. (13), we can obtain the variance of the TADC,

$$\begin{aligned}\langle[S(t) - \langle S(t)\rangle]^2\rangle &= \langle S^2(t)\rangle - \langle S(t)\rangle^2 \\ &= \frac{\langle|\delta\boldsymbol{x}(t)|^4\rangle}{4t^2 n(n+2)} - \langle S(t)\rangle^2.\end{aligned} \tag{20}$$

From Eqs. (15) and (20), we have

$$\begin{aligned}\frac{\langle[S(t) - \langle S(t)\rangle]^2\rangle}{\langle S(t)\rangle^2} &= \frac{\langle|\delta\boldsymbol{x}(t)|^4\rangle}{4t^2 n(n+2)\langle S(t)\rangle^2} - 1 \\ &= \frac{n\langle|\delta\boldsymbol{x}(t)|^4\rangle}{(n+2)\langle|\delta\boldsymbol{x}(t)|^2\rangle^2} - 1.\end{aligned} \tag{21}$$

Thus, from Eqs. (19) and (21), we obtain

$$A(t) = \frac{\langle[S(t) - \langle S(t)\rangle]^2\rangle}{\langle S(t)\rangle^2}. \tag{22}$$

From this equation, we can see that the non-Gaussian parameter is equal to the square of the coefficient of variation of the TADC.

When t is sufficiently smaller than the time that characterizes the change in $D(t)$, from Eq. (7), we have an approximation,

$$S(\omega) \approx D(0; \omega). \tag{23}$$

Thus, for sufficiently small t, we have

$$A(t) \approx \frac{\langle[D(0) - \langle D(0)\rangle]^2\rangle}{\langle D(0)\rangle^2}. \tag{24}$$

Here, using Eq. (22), we show that for a finite time, the propagator is heavy tailed relative to a Gaussian distribution when a DC is stochastic. From Eq. (22), we can see that for a finite time, the non-Gaussian parameter is positive when a DC is stochastic. The non-Gaussian parameter is essentially equivalent to the kurtosis of the propagator. The kurtosis is a measure of whether a distribution is heavy tailed or light tailed relative to a Gaussian distribution. The kurtosis $\beta(t)$ and the non-Gaussian parameter have the relation (for the kurtosis, see [14])

$$\beta(t) = n(n+2)[A(t) + 1]. \tag{25}$$

From this equation, for a finite time, we have

$$\beta(t) > n(n+2), \tag{26}$$

because $A(t) > 0$ for a finite time. The kurtosis is equal to $n(n+2)$ for a Gaussian distribution. Thus, from Eq. (26), we can see that for a finite time, the propagator is heavy tailed relative to a Gaussian distribution. This means that when the MSDs are the same, some of the diffusing particles with stochastic DCs diffuse farther than the particles with deterministic DCs for a finite time. Note that from Eq. (8), the propagators are Gaussian for deterministic DCs.

From Eq. (6), we have

$$\langle|\delta\boldsymbol{x}(t;\omega)|^2\rangle = 2ntS(t;\omega). \tag{27}$$

From this equation, we can see that the MSD is a stochastic variable. From Eqs. (22) and (25), we can also see that even if the values of $\langle S(t)\rangle$ are equal, the stochastic process $D(t)$ with the larger variance of the TADC gives the larger value of the kurtosis. This is natural because a large variance in a TADC leads to a large variance in an MSD and thus some particles diffuse farther.

Variation in a TADC comes from fluctuations in a DC. What properties of a DC lead to larger TADC variance? From Eq. (7), we have

$$\langle[S(t) - \langle S(t)\rangle]^2\rangle = \frac{1}{t^2}\int_0^t\int_0^t C(t', t'')dt'dt'', \tag{28}$$

where $C(t', t'')$ represents the autocovariance function of $D(t)$ and is given by

$$C(t', t'') = \langle\delta D(t')\delta D(t'')\rangle. \tag{29}$$

In this equation, $\delta D(t)$ is given by $\delta D(t) = D(t) - \langle D(t)\rangle$. From Eq. (28), we can see that the larger the variance of $D(t)$ and the longer the correlation lasts, the larger the variance of a TADC.

B. Normal diffusion

When $\langle D(t)\rangle$ is a constant, from Eq. (15), we have

$$\langle|\delta\boldsymbol{x}(t)|^2\rangle = 2n\mu t, \tag{30}$$

where $\mu = \langle D(t)\rangle$. The diffusion is normal.

When $D(t)$ is a stationary process, $\langle D(t)\rangle$ is a constant. Thus, when $D(t)$ is a stationary process, the diffusion is normal. When $D(t)$ is a stationary process, it can be seen more clearly that the variance of the DC plays an important role in determining the magnitude of the fluctuation of TADC and, in turn, the value of $A(t)$. When $D(t)$ is a stationary process, we can find the upper limit of $A(t)$. From Eq. (22), when $D(t)$ is a stationary process, we have

$$A(t) = \frac{\langle[S(t) - \mu]^2\rangle}{\mu^2}. \tag{31}$$

In addition, we have

$$\int_0^t\int_0^t C(t', t'')dt'dt'' \leqslant \int_0^t\int_0^t \sigma^2 dt'dt'' = \sigma^2 t^2, \tag{32}$$

where σ represents the standard deviation of $D(t)$ and is given by $\sigma = \sqrt{\langle[D(t) - \mu]^2\rangle}$. Thus, from Eqs. (28) and (31), we have

$$A(t) \leqslant \left(\frac{\sigma}{\mu}\right)^2. \tag{33}$$

From this equation, we can see that when $D(t)$ is a stationary process, $A(t)$ is less than or equal to the square of the coefficient of variation of $D(t)$. In addition, for a sufficiently small t, we have

$$A(t) \approx \left(\frac{\sigma}{\mu}\right)^2. \quad (34)$$

When $D(t)$ is ergodic, $\lim_{t\to\infty} S(t) = \mu$. Thus, from Eq. (8), when $t \to \infty$, we have

$$G(\boldsymbol{x}, t, \boldsymbol{x}_0) \sim \frac{1}{(4\pi\mu t)^{n/2}} \exp\left(-\frac{|\boldsymbol{x} - \boldsymbol{x}_0|^2}{4\mu t}\right). \quad (35)$$

In addition, from Eq. (31), the non-Gaussian parameter $A(t)$ converges to zero.

Conversely, if we have Eq. (35) in the long time limit, $D(t)$ is ergodic. When Eq. (35) holds, from Eq. (8) we have $\lim_{t\to\infty} p(S,t) = \delta(S-\mu)$. Thus, we have $\lim_{t\to\infty} S(t) = \mu$.

In general, even if $\lim_{t\to\infty} A(t) = 0$, it does not necessarily mean that the propagator converges to a Gaussian distribution. However, for stationary stochastic DCs, the convergence of the non-Gaussian parameter to zero means that the propagator converges to a Gaussian distribution. From Eq. (31), when $\lim_{t\to\infty} A(t) = 0$, we have $\lim_{t\to\infty} S(t) = \mu$. When $\lim_{t\to\infty} S(t) = \mu$, $\lim_{t\to\infty} p(S,t) = \delta(S-\mu)$. Thus, from Eq. (8), we have Eq. (35).

C. Anomalous diffusion

As shown in the previous section (Sec. IV B), when $D(t)$ is a stationary process, the diffusion is normal. Thus, anomalous diffusion can occur only when $D(t)$ is a nonstationary process. In particular, it is necessary that the process is a nonstationary process in which the ensemble average of the DC is time dependent.

Here, we assume that the ensemble average of the DC is given by

$$\langle D(t)\rangle = \alpha D_c t^{\alpha-1} \ (0 < \alpha < 1, 1 < \alpha), \quad (36)$$

where D_c is a positive constant. From Eq. (36), we have

$$\langle S(t)\rangle = D_c t^{\alpha-1}. \quad (37)$$

Substituting this equation into Eq. (15) leads to

$$\langle|\delta\boldsymbol{x}(t)|^2\rangle = 2nD_c t^{\alpha}. \quad (38)$$

Thus, the diffusion is anomalous.

Substituting Eq. (37) into Eq. (22) leads to

$$A(t) = \frac{\langle[S(t) - D_c t^{\alpha-1}]^2\rangle}{D_c^2 t^{2(\alpha-1)}} \quad (39)$$

$$= \frac{\langle[S_s(t) - t^{\alpha-1}]^2\rangle}{t^{2(\alpha-1)}}, \quad (40)$$

where $S_s(t) = \frac{1}{t}\int_0^t D(t')/D_c dt'$.

D. Case study

In this section, we investigate properties of the propagators for two specific models of $D(t)$. One is a simple model for which we can find an analytical expression for $A(t)$, and the other is a realistic model. In the simple model, we assume that $D(t)$ is described by a two-state Markov process. The realistic model is a model of diffusion of a molecule in cell membranes. The simple model shows normal diffusion, while the realistic model shows anomalous diffusion. For simplicity, the dimension is assumed to be one.

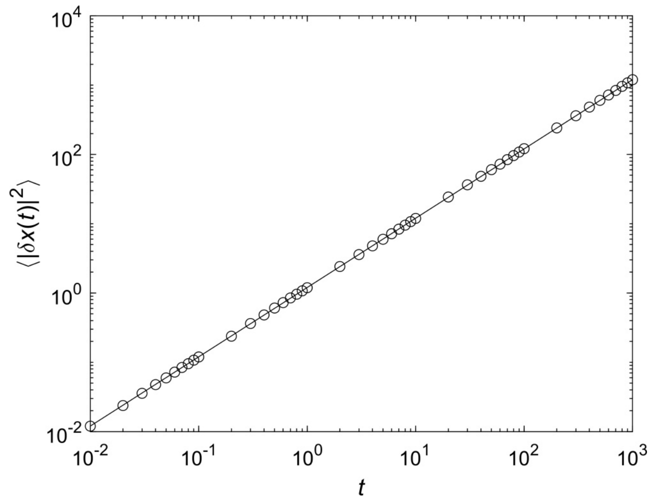

FIG. 1. Time dependence of the MSD. The solid line shows the time dependence estimated from Eq. (45), and the open circles show the time dependence estimated from simulations. $\lambda_+ = 0.5$, $\lambda_- = 0.5$, $D_+ = 1$, $D_- = 0.2$. Time is normalized by t_0 and the DC is normalized by D_+.

1. Two-state Markov model for $D(t)$

Here, we assume that $D(t)$ is described by a two-state Markov process. We also assume that the process is stationary. We label one state + and the other state −. The DC is equal to D_+ at the + state and is equal to D_- at the − state. The distribution of sojourn time in each state is given by

$$\psi_+(\tau) = \lambda_- e^{\lambda_- \tau}, \quad (41)$$

$$\psi_-(\tau) = \lambda_+ e^{\lambda_+ \tau}, \quad (42)$$

where $\psi_+(\tau)$ and $\psi_-(\tau)$ are the distributions of sojourn time in the + state and the − state, respectively. In Eqs. (41) and (42), λ_- represents the transition probability from the + state to the − state and λ_+ represents the transition probability from the − state to the + state. The initial distribution of the DC is the equilibrium distribution.

For this model, we have

$$\mu = \frac{D_+\lambda_+ + D_-\lambda_-}{\lambda_+ + \lambda_-}, \quad (43)$$

$$\sigma^2 = \lambda_+\lambda_-\left(\frac{D_+ - D_-}{\lambda_+ + \lambda_-}\right)^2. \quad (44)$$

Thus, from Eq. (30), we have

$$\langle|\delta\boldsymbol{x}(t)|^2\rangle = 2\frac{D_+\lambda_+ + D_-\lambda_-}{\lambda_+ + \lambda_-}t. \quad (45)$$

Figure 1 demonstrates an excellent agreement between this result and the result estimated from simulations (see the Appendix for the details of the simulations).

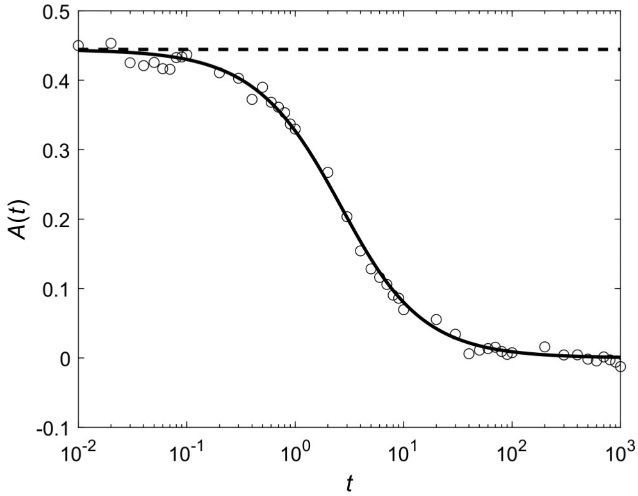

FIG. 2. Time dependence of the non-Gaussian parameter. The solid line shows the time dependence estimated from Eq. (48), the open circles show the time dependence estimated from simulations, and the dashed line shows the upper limit estimated from Eq. (33).

For the model, we can derive an analytical expression for $A(t)$. For the model, we have the autocovariance function $C(\Delta t)$,

$$C(\Delta t) = \sigma^2 e^{-\frac{\Delta t}{t_0}}, \tag{46}$$

where Δt is the time difference, and t_0 is the time constant and is given by $t_0 = 1/(\lambda_+ + \lambda_-)$. Substituting Eq. (46) into Eq. (28) leads to

$$\langle [S(t) - \mu]^2 \rangle = \frac{2\sigma^2 t_0^2 \left(\frac{t}{t_0} - e^{-\frac{t}{t_0}} - 1\right)}{t^2}. \tag{47}$$

By substituting this equation and Eq. (43) into Eq. (31), we have

$$A(t_s) = \frac{2C_v^2(t_s + e^{-t_s} - 1)}{t_s^2}, \tag{48}$$

where $t_s = t/t_0$, and C_v represents the coefficient of variation and is given by $C_v = \sigma/\mu$. Figure 2 shows the time dependence of $A(t)$. From this figure, we can see that the time dependence of the non-Gaussian parameter estimated from Eq. (48) is in good agreement with that estimated from simulations. We can also see that for short times, the value of the non-Gaussian parameter is nearly equal to C_v^2, which is predicted from Eq. (34), but rapidly decreases to around zero on the timescale of one. This result indicates that on the timescale of one, a heavy-tailed propagator crosses over a distribution that is very close to a Gaussian distribution. Figure 3 shows that this is true. The timescale at which the crossover occurs is equal to the timescale of the correlation time of the DC.

2. Subdiffusion in cell membranes

Here, we examine the propagator of the model that describes subdiffusion of a molecule on living-cell membranes. The molecule is dendritic cell-specific intercellular adhesion molecule 3-grabbing nonintegrin (DC-SIGN), which is a receptor with unique pathogen-recognition capabilities. The model explains the experimental data well [4]. The fluctuation of the DC comes from the dynamic heterogeneity of the cell membrane.

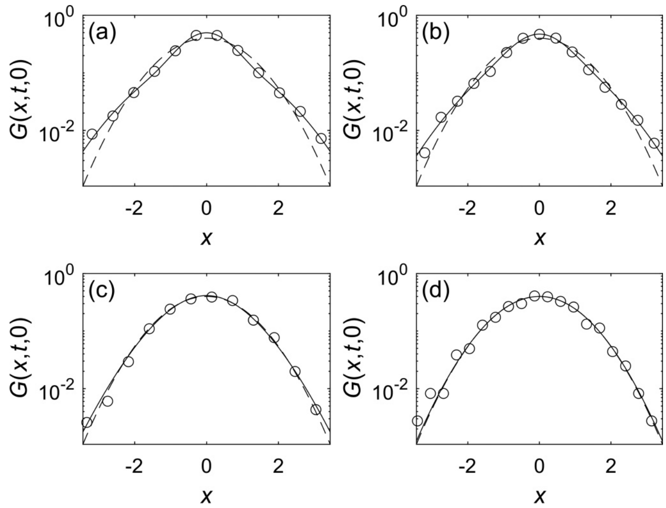

FIG. 3. Propagators at different times. The solid lines show the propagators estimated from Eq. (8), the open circles show the propagators estimated from simulations, and the dashed lines show the Gaussian distribution with the variance of one. The propagators are normalized so that their variances equal one. (a) $t = 0.1$, (b) $t = 1$, (c) $t = 10$, (d) $t = 100$.

In the model, the distribution of the DC is given by a Γ distribution,

$$P_D(D) = \frac{D^{\zeta-1} e^{-D/b}}{b^\zeta \Gamma(\zeta)}, \tag{49}$$

where $P_D(D)$ represents the distribution of the DC, $\Gamma(y)$ is the Gamma function, ζ is the shape parameter, and b is the scale parameter. In addition, the conditional distribution of transit times τ (the time when a molecule moves with a given D) is

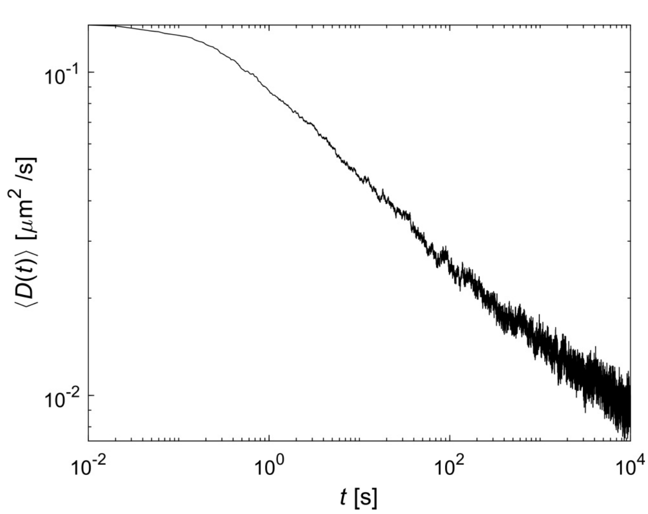

FIG. 4. Time dependence of the ensemble average of the DC. $\zeta = 1.16$, $\gamma = 1.38$, $b = 0.12\ \mu\mathrm{m}^2/\mathrm{s}$, $l = 0.10\ \mu\mathrm{m}^{2\gamma}\mathrm{s}^{\gamma+1}$.

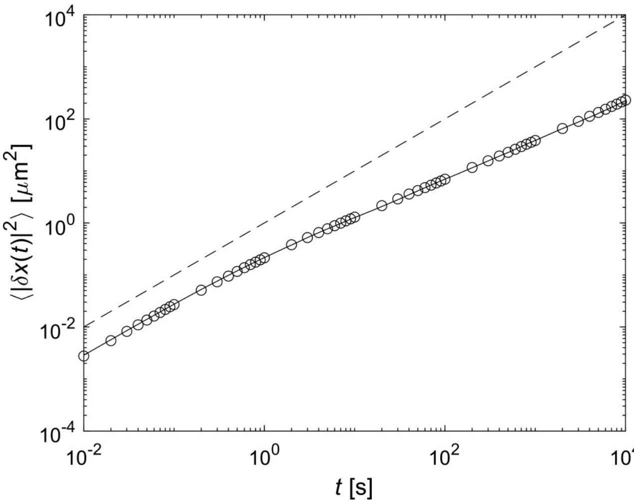

FIG. 5. Time dependence of the MSD. The solid line shows the time dependence estimated from Eq. (15), the open circles show the time dependence estimated from simulations, and the dashed line shows the line with the slope of one.

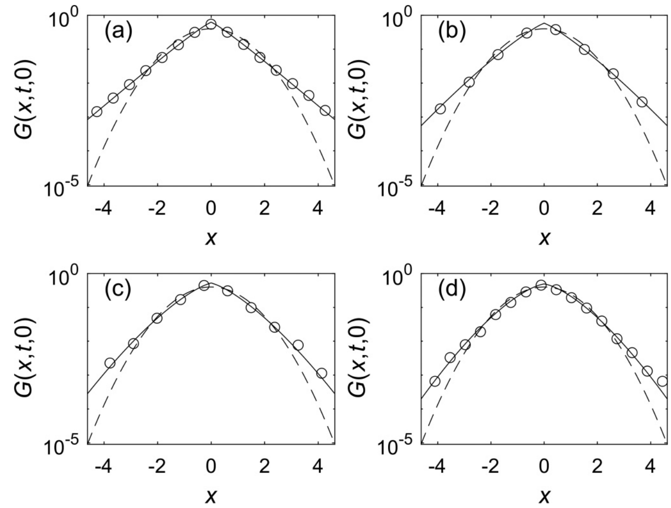

FIG. 7. Propagators at different times. The solid lines show the propagators estimated from Eq. (8), the open circles show the propagators estimated from simulations, and the dashed lines show the Gaussian distribution with the variance of one. The propagators are normalized so that their variances equal one. (a) $t = 0.1$ s, (b) $t = 1$ s, (c) $t = 10$ s, (d) $t = 100$ s.

given by an exponential distribution,

$$P_\tau(\tau|D) = \frac{D^\gamma}{l} e^{-\tau D^\gamma / l}, \tag{50}$$

where γ and l are constants. The initial distribution of the DC is $P_D(D)$. In this model, the DC is a nonstationary process in which the ensemble average of the DC is time dependent. Figure 4 shows the time dependence of $\langle D(t)\rangle$. From this figure, we can see that the time dependence of $\langle D(t)\rangle$ is given by Eq. (36) with $0 < \alpha < 1$, although the value of α changes around $t = 1$ s. This result indicates that diffusion is anomalous. Figure 5 shows the time dependence of $\langle|\delta \boldsymbol{x}(t)|^2\rangle$. We can see that the time dependence of $\langle|\delta \boldsymbol{x}(t)|^2\rangle$ is given by Eq. (38) with $0 < \alpha < 1$, although the value of α changes around $t = 1$ s. Thus, the diffusion is anomalous. From Fig. 5, we can also see that the time dependence of $\langle|\delta \boldsymbol{x}(t)|^2\rangle$ estimated from Eq. (15) is in good agreement with that estimated from the simulations. Figure 6 shows the time dependence of $A(t)$. From this figure, we can see that the time dependence of the non-Gaussian parameter estimated from Eq. (22) is in good agreement with that estimated from the simulations. In addition, for short times, the value of the non-Gaussian parameter is nearly equal to $1/\zeta$, which is predicted from Eq. (24). From Fig. 6, we can also see that as in the two-state Markov model, the value of the non-Gaussian parameter rapidly decreases on the timescale of one. However, unlike the two-state Markov model, the non-Gaussian parameter continues to decrease slowly after reaching a certain positive value. This result indicates that the tails of the propagator become lighter on the timescale of one, but the tails still remain heavy. Figure 7 shows that this is true.

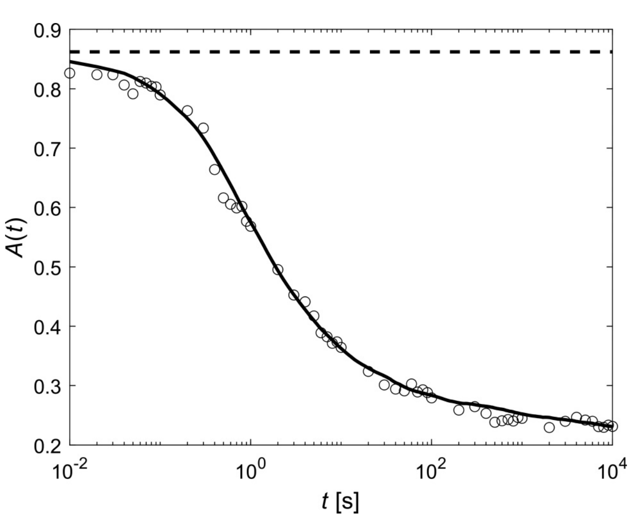

FIG. 6. Time dependence of the non-Gaussian parameter. The solid line shows the time dependence estimated from Eq. (22), the open circles show the time dependence estimated from simulations, and the dashed line shows the value for short times estimated from Eq. (24).

V. DISCUSSION

In the present study, we investigated properties of the diffusion with a broad class of stochastic DCs, focusing on the propagator. We showed that the propagator for the diffusing particle is unimodal and the peak is not sharp. We also showed that for a finite time, the propagator is non-Gaussian and the non-Gaussian parameter of the propagator is positive: the propagator is heavy tailed relative to a Gaussian distribution. In addition, we showed that when a stochastic DC is ergodic, the propagator converges to a Gaussian distribution in the long time limit.

An equation equivalent to Eq. (8) can be derived using subordination [5]. However, subordination has a different view than our approach. The essence of subordination is time change: subordination is the change of the time variable from real time to some kind of stochastic process. In the subordination approach, the superensemble consists of ensembles with the same DC, but different time flows. On the other hand, in our approach, the superensemble consists of ensembles with the same time flow, but different time evolutions of TADC, which can be regarded as an effective DC.

In a short time limit, Eq. (8) has a relation with the propagator obtained by the superstatistical approach. In the superstatistical approach, the propagator $G_s(\boldsymbol{x}, t, \boldsymbol{x}_0)$ is given by

$$G_s(\boldsymbol{x}, t, \boldsymbol{x}_0) = \int_0^\infty \frac{r(D)}{(4\pi Dt)^{n/2}} \exp\left(-\frac{|\boldsymbol{x}-\boldsymbol{x}_0|^2}{4Dt}\right) dD, \quad (51)$$

where $r(D)$ is the probability distribution of D [15–17]. When t is sufficiently smaller than the time that characterizes the change in $D(t)$, from Eq. (7), we have an approximation,

$$S(\omega) \approx D(0; \omega). \quad (52)$$

Thus, we have

$$G(\boldsymbol{x}, t, \boldsymbol{x}_0) \approx \int_0^\infty \frac{p(D, 0)}{(4\pi Dt)^{n/2}} \exp\left(-\frac{|\boldsymbol{x}-\boldsymbol{x}_0|^2}{4Dt}\right) dD. \quad (53)$$

This is an approximation of the propagator by the superstatistical formula. For the minimal diffusing-diffusivity model, it has already been shown that when the time is sufficiently smaller than the correlation time of $D(t)$, the propagator obtained from the subordination formula is equal to the propagator obtained by the superstatistical approach [5].

Our approach is a natural extension of the superstatistical approach. This is because our approach includes the superstatistical approach as a special case. In Eq. (1), if the DC is described by a special stochastic process in which each sample path of the DC is time independent, we can easily obtain Eq. (51) by our approach.

In the present study, we showed that for a finite time, the propagator is heavy tailed for stochastic DCs. The propagators of the anomalous diffusion described by CTRWs have a similar property: the propagators show exponential decay [8]. It has also been reported that anomalous diffusion described by CTRWs and anomalous diffusion with stochastic DCs have similar properties other than propagators [7,18]. Thus, it is difficult to distinguish between anomalous diffusion described by CTRWs and anomalous diffusion with stochastic DCs. However, there is a case where there is a difference between the propagators of the diffusion with stochastic DCs and CTRWs. For one-dimensional subdiffusion, the propagators of CTRWs often have a cusp at the origin and are not differentiable at the origin [19,20]. On the other hand, when $x_0 = 0$ and t is larger than the time that characterizes the change of $D(t)$, as we showed in Sec. III B, the propagator in the Brownian motion with a stochastic DC has a smoother shape at the origin and is differentiable at the origin. In this sense, subdiffusion with stochastic DCs is different from that described by CTRWs.

Convergence of the propagators to Gaussian distributions in the long time limit has been shown for specific stochastic models of DCs. For example, convergence of a heavy-tailed propagator to a Gaussian propagator has been shown for the minimal diffusing-diffusivity model with the equilibrium distribution of the DC as the initial condition [5,21]. Convergence to a Gaussian distribution has also been demonstrated for the two-state model with power-law distributions with the equilibrium distribution of the DC as the initial condition [7]. Our results suggest that the convergence in these models comes from the ergodicity of the models rather than characteristics unique to each model.

In the present study, we showed that when DCs are ergodic, the propagators converge to Gaussian distributions in the long time limit. However, this does not necessarily mean that it takes an infinitely long time for the propagators to approach Gaussian distributions. From Eqs. (28) and (31), we can see that it actually depends on how fast the autocovariance functions of the DCs decay. In fact, when autocovariance functions decay exponentially, as in the simple model we used, $A(t)$ approaches zero on the same timescale as the correlation time of the DC. On the other hand, if autocovariance functions decrease with power laws $(\Delta t)^{-\kappa} (0 < \kappa < 1)$, $A(t)$ approaches zero at a rate of $t^{-\kappa}$.

In the present study, we showed that in a realistic model, the propagator does not converge to a Gaussian distribution even after 10 000 s. However, it is unknown whether this has any physical meaning. This is because the consistency of the model with experimental data has been shown only up to a few seconds [4], and it is unclear whether the model accurately describes diffusion of a molecule over longer times.

In the present study, we showed that heavy-tailed propagators can be commonly observed in diffusion with stochastic DCs. This result may be important for triggered reactions in physics, chemistry, and biology. The result means that when a DC is described by a stationary process, some particles diffuse farther than in diffusion due to a Brownian motion with the constant DC that is equal to the mean of the fluctuating DC. In addition, if the MSDs are the same, some particles diffuse farther in anomalous diffusion with stochastic DCs than in anomalous diffusion due to a fractional Brownian motion, whose propagator is Gaussian [22]. The property that some particles are transported farther in the same time is obviously important in diffusion-limited reactions triggered by single molecules.

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APPENDIX: SIMULATIONS

We used the Euler method for numerical integration of the Langevin equation [23],

$$x(t+h) = x(t) + \sqrt{2D(t)h}\,\xi(t), \quad (A1)$$

where h represents the time step in simulations. For the simple model, the time step in simulations is 0.001 up to time 1, and 0.1 after that. The number of trajectories that we simulated is 40 000. For the realistic model, the time step in simulations is 0.001 s up to 1 s, and 0.1 s after that. The number of trajectories that we simulated is 40 000 for Figs. 5 and 7 and 80 000 for Fig. 6.

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