Non-Gaussian Fluctuations Resulting from Power-Law Trapping in a Lipid Bilayer

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Anomalous diffusion in lipid bilayers is usually attributed to viscoelastic behavior. We compute the scaling exponent of relative fluctuations of the time-averaged mean square displacement in a lipid bilayer, by using a molecular dynamics simulation. According to the continuous time random walk theory, this exponent indicates non-Gaussian behavior caused by a power-law trapping time. Our results provide the first evidence that a lipid bilayer has not only viscoelastic properties but also trapping times distributed according to a power law.

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Particle motions in overcrowded environments, such as dense colloidal suspensions, cytoplasm, and supercooled liquids, exhibit non-Gaussian behavior, dynamical heterogeneity, and anomalous diffusion [1–7]. Because of molecular crowding, particles become trapped and cannot move smoothly [1–4]. The time-averaged mean square displacement (TAMSD) is derived from a time series of a single-molecule tracking:

$$\overline{\delta_x^2(\Delta;t)} = \frac{1}{t-\Delta}\int_0^{t-\Delta}[x(t'+\Delta)-x(t')]^2 dt'. \quad (1)$$

The diffusion coefficient $D \equiv \overline{\delta_x^2(\Delta;t)}/\Delta^\alpha$ for each TAMSD shows large random deviations from the ensemble average; i.e., *random diffusion coefficient* exists in crowded fluids such as living cells [4–8].

There are two different models for subdiffusive processes. One is fractional Brownian motion (FBM), which is a generalization of Brownian motion [9]. Subdiffusion in FBM originates from an anticorrelation, which emerges in viscoelastic fluids. It is known that subdiffusion in crowded fluids is closely related to FBM, i.e., viscoelasticity [4,7,10,11]. However, FBM cannot account for non-Gaussian behavior of the TAMSD because ergodicity, which holds in FBM, ensures the central limit theorem [12,13].

The other model is a continuous time random walk (CTRW), which is a random walk with random trapping times [14]. When the mean trapping time diverges, a random walker undergoes subdiffusion. By the divergence of the mean trapping time, the trajectory tends to be trapped as time goes on. Unlike FBM, ergodicity, i.e., (time average) = (ensemble average), does not hold in a CTRW. Moreover, it is known that the diffusion coefficients for TAMSDs are intrinsically random in trapped models such as the CTRW and deterministic dynamical systems [15–19]. Intrinsic randomness of the transport coefficient is caused by the divergence of the mean trapping time, which involves the breakdown of the law of large numbers. Even when there is a cutoff in the trapping-time distribution, the transport coefficient for TAMSD shows large fluctuations [20]. In fact, the deviations of TAMSDs from the ensemble average in the diffusion of lipid granules are consistent with a CTRW process with a truncated power-law trapping-time distribution [21,22].

Lipid bilayers are two-dimensional complex fluids. The viscoelasticity of lipid bilayers is still an open problem in experiments [23]. To elucidate anomalous transport properties of lipid bilayers, we consider the relative fluctuations of TAMSD $\overline{\delta^2(\Delta;t)}$, defined by

$$R(t;\Delta) := \frac{\langle|\overline{\delta^2(\Delta;t)} - \langle\overline{\delta^2(\Delta;t)}\rangle|\rangle}{\langle\overline{\delta^2(\Delta;t)}\rangle}, \quad (2)$$

where $\langle\ldots\rangle$ denotes the ensemble average. The relative fluctuations characterize non-Gaussian behavior and ergodicity breaking in time averages [15,24]. Using renewal theory [25], we analytically show that the relative fluctuations $R(t;\Delta)$ decay as $t^{-\gamma}$ in a CTRW. This scaling exponent γ is useful to characterize the anomaly of the transport coefficient caused by a power-law trapping time because $\gamma < 0.5$ implies non-Gaussian fluctuations. By performing a molecular dynamics simulation on a lipid bilayer, we find non-Gaussian fluctuations of TAMSD and viscoelasticity. This non-Gaussian behavior cannot be accounted for by FBM because the relative fluctuations in FBM generating subdiffusion decay as $t^{-0.5}$ [12]. Therefore, we show, for the first time, that a lipid bilayer has not only a viscoelastic property but also a power law in the trapping time.

Relative fluctuations in CTRWs.—TAMSD can be calculated by using renewal theory, because trapping times between successive jumps in CTRW are independently and identically distributed random variables with a probability density function (PDF) $f(x)$ in a manner similar to renewal

processes [17,20]. Let N_t be the total number of jumps until time t, S_r be the time when the rth jump occurs, X_1 be the time when the first jump occurs, and X_n be the time interval between the $n-1$th jump and the nth jump, then we have $S_r = X_1 + \cdots + X_r$. When the mean and variance of X_n exist, denoted by μ and σ^2, respectively, the Laplace transform of $f(x)$ is given by $f^*(s) = 1 - s\mu + \frac{\mu^2+\sigma^2}{2}s^2 + o(s^2)$. Let $r_t = \frac{t}{\mu} + x\sigma\sqrt{t/\mu^3}$. Then, $\Pr[(N_t - t/\mu)/\sigma\sqrt{t/\mu^3}) < x] = \Pr(S_{r_t} > t)$. The central limit theorem states

$$\Pr\left(\frac{N_t - t/\mu}{\sigma\sqrt{t/\mu^3}} < x\right) \to 1 - G(-x), \tag{3}$$

where $G(x)$ is the Gaussian distribution [25]. Therefore, N_t obeys the Gaussian distribution with mean t/μ and variance $\sigma^2 t/\mu^3$, when the mean and the variance exist. On the other hand, N_t does not obey the Gaussian distribution when the variance does not exist. In particular, when the mean exists and the variance does not exist, the Laplace transform of $f(x)$ is given by

$$f^*(s) = 1 - s\mu + C_\beta s^\beta + o(s^\beta), \tag{4}$$

where C_β is a constant and $\beta(<2)$ is the exponent indicating the divergence of the second moment [26]: $\int_0^n x^2 f(x)dx \propto n^{2-\beta}(n \to \infty)$. That is, β characterizes the tail of $f(x)$: $f(x) \propto x^{-1-\beta}(x \to \infty)$. According to the generalized central limit theorem [27], we have

$$\Pr\left(\frac{N_t - t/\mu}{\lambda(t)} < x\right) \to 1 - G_\beta(-x) \qquad (t \to \infty), \tag{5}$$

where $\lambda(t) \sim (t/\mu)^{1/\beta}$ and $G_\beta(x)$ is the stable distribution with index β. Then, the scaling of the fluctuations of N_t is given by

$$\langle |N_t - t/\mu| \rangle \sim \mu_+ \lambda(t) \sim \mu_+ (t/\mu)^{1/\beta}, \tag{6}$$

where μ_+ is the mean of $G_\beta(x)$ with $x > 0$.

In general, there is the useful relation between TAMSD and N_t in a CTRW [15,17,20]:

$$\overline{\delta_x^2(\Delta; t)} \cong \frac{CN_t}{t}, \tag{7}$$

where C is not a random variable but a constant depending on the variance of jump lengths and Δ. It has been shown that $C = \Delta$ when the variance of jump lengths is unity. Even when the mean trapping time diverges, TAMSD shows normal diffusion [15,17,20]. Therefore, diffusion coefficients are given by $D_t = N_t/t$. The distribution of the normalized diffusion coefficients becomes the stable distribution with index β when the PDF of trapping times in CTRW is $f(x) \propto x^{-1-\beta}$ $(1 < \beta < 2)$. Using the relation (7), we obtain the scaling of the relative fluctuations of TAMSD $\overline{\delta^2(t; \Delta)}$ defined by (2):

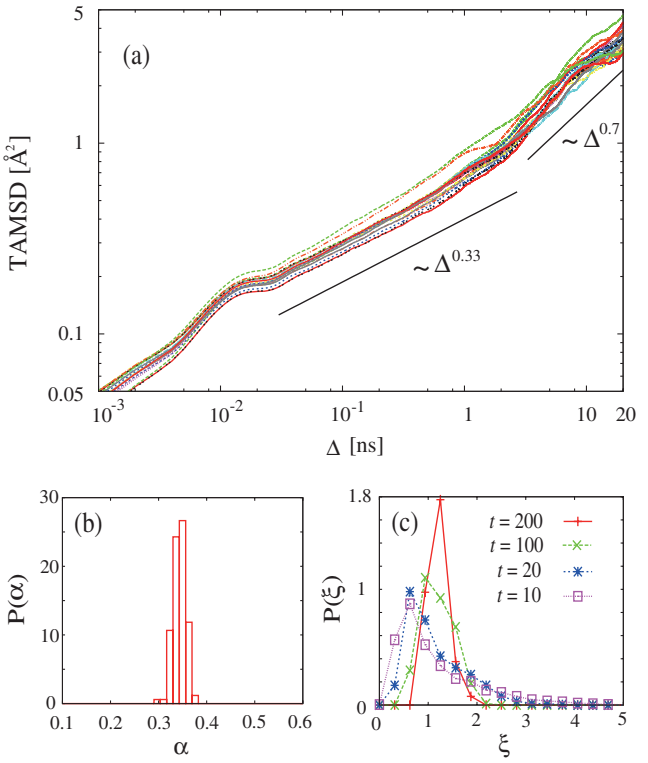

FIG. 1 (color). (a) Lateral TAMSDs for 20 different lipid molecules ($t = 200$ ns). Lines indicate sublinear growths, $\overline{\delta^2(\Delta; t)} \propto \Delta^{0.33}$ and $\Delta^{0.7}$. (b) PDF of the exponent α in small Δ regimes. (c) PDFs of the TAMSDs, $\xi = \overline{\delta^2(5; t)}$, for different measurement times t.

$$R(t; \Delta) \sim \begin{cases} \frac{\sigma}{\sqrt{\mu}} t^{-1/2} & (\beta > 2) \\ \mu_+ (t/\mu)^{-(1-1/\beta)} & (1 < \beta < 2). \end{cases} \tag{8}$$

Thus, non-Gaussian behavior $(1 < \beta < 2)$ can be represented by the scaling exponent of the relative fluctuations. Note that the relative fluctuations do not converge to zero in the case of $\beta \leq 1$ [28].

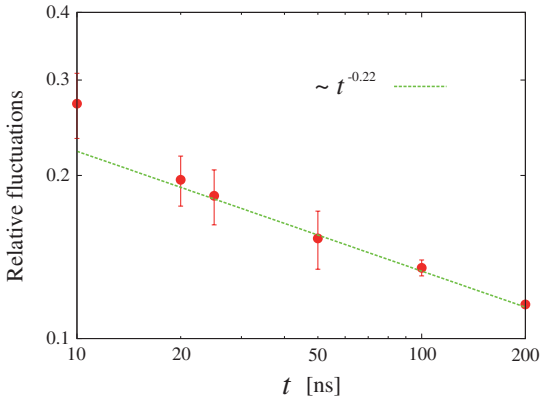

FIG. 2 (color). Relative fluctuations of TAMSD ($\Delta = 5$ ns). Dashed line represents the non-Gaussian scaling, $R(t; \Delta) \propto t^{-0.22}$. Error bars are the standard deviations, where ensembles are obtained by nonoverlapping time intervals.

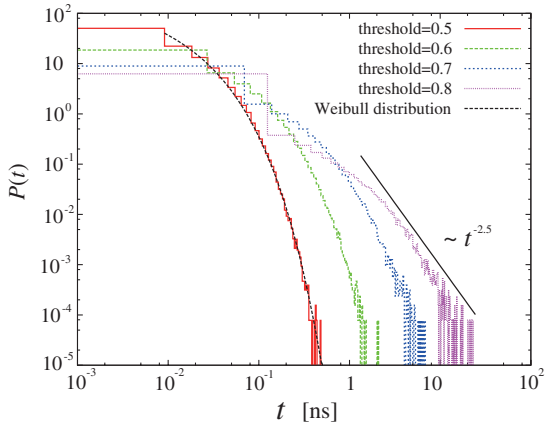

FIG. 3 (color). Probability density function of trapping time. Solid and dashed lines represent a power law $P(t) \propto t^{-2.5}$ and the Weibull distribution with the exponent $a = 0.69$, respectively.

Transient subdiffusion and fluctuations of TAMSD.—To investigate non-Gaussian fluctuations in lipid bilayers, we performed a molecular dynamics simulation on a 1-palmitoyl-2-oleoyl-phosphatidylethanolamine lipid bilayer using the AMBER10 program [29]. We constructed the lipid bilayer by 128 1-palmitoyl-2-oleoyl-phosphatidylethanolamine lipid molecules. The system was solvated by adding 10 004 water molecules to each side of the membrane. After the system was heated at 310 K under ordinary pressure, we performed an *NPT* simulation. After equilibration (100 ns), an additional 200 ns *NPT* simulation for data analysis was performed [30]. In the molecular dynamics simulation, the motion of the lipid bilayer within the systems undergoes Brownian motion because of finite size effects [31]. To eliminate this motion, we analyze a time series of relative motions of lipid molecules. That is, we use the relative motions $x_i(t) = X_i(t) - X_G(t)$, $y_i(t) = Y_i(t) - Y_G(t)$, and $z_i(t) = Z_i(t) - Z_G(t)$, where $(X_G(t), Y_G(t), Z_G(t))$ is the position of the center of mass of a lipid bilayer and $(X_i(t), Y_i(t), Z_i(t))$ is the position of the center of mass of ith lipid molecule ($i = 1, \ldots, 128$).

Lateral TAMSD is defined by $\overline{\delta^2(\Delta; t)} = [\overline{\delta_x^2(\Delta; t)} + \overline{\delta_y^2(\Delta; t)}]/2$, where t is the measurement time. In Fig. 1(a), lateral TAMSDs for 20 different lipid molecules are shown. Lateral TAMSDs exhibit subdiffusion, $\overline{\delta^2(\Delta; t)} \propto \Delta^{\alpha}$, for a small Δ. The subdiffusion exponent for a small Δ is around $\alpha \cong 0.33$ [Fig. 1(b)]. For a large Δ, the exponents for lateral TAMSDs are around 0.7, but fluctuations of lateral TAMSDs for a large Δ are larger than those for a small Δ. Several lateral TAMSDs show the transition from subdiffusion to normal diffusion, consistent with a previous study [32].

The PDFs of lateral TAMSDs at $\Delta = 5$ ns are presented in Fig. 1(c). Fluctuations of lateral TAMSDs are large particularly for a small measurement time t, and the PDFs of lateral TAMSDs are not Gaussian, unlike the expected consequence of the central limit theorem. In a CTRW generating transient subdiffusion, the distribution of lateral TAMSDs is the Mittag-Leffler distribution for a small measurement time t and converges to Gaussian as $t \to \infty$ [20]. Although lateral TAMSDs show large fluctuations, the distribution is neither Mittag-Leffler nor Gaussian.

Non-Gaussian fluctuations of TAMSD.—To elucidate non-Gaussian behavior, we exploit the relative fluctuations of the lateral TAMSD. The ensemble averages are obtained by averaging lateral TAMSDs for 128 different lipid molecules. Figure 2 shows a clear power-law decay of the relative fluctuations except for a small measurement time:

$$R(t; \Delta) \propto t^{-\gamma}, \tag{9}$$

with $\gamma \cong 0.22$, where the point $R(10, 5)$ is ignored to obtain the scaling exponent of relative fluctuations [30]. The relative fluctuations decay more slowly than $t^{-0.5}$, indicating non-Gaussian fluctuations of lateral TAMSDs. Furthermore, the power-law exponent in the trapping-time distribution is estimated as $\beta = 1/(1 - \gamma) \cong 1.28$. Hence, anomalous transport in a lipid bilayer involves a power-law trapping time.

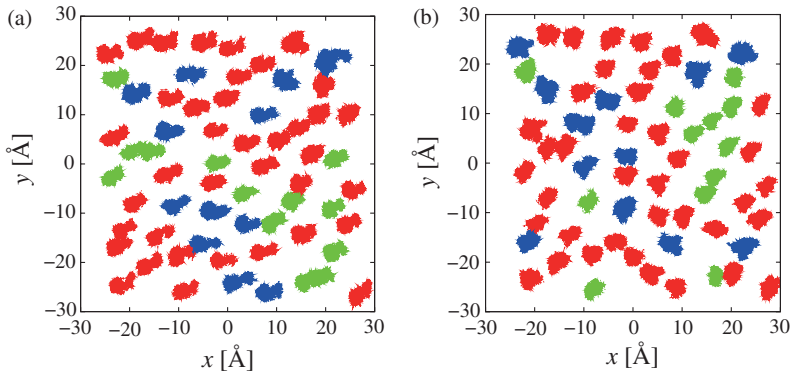

FIG. 4 (color). Trajectories of the center of mass for lipid molecules on the upper layer: (a) time interval from 0 to 10 ns and (b) time interval from 10 to 20 ns. Trajectories with the fastest 20%, the intermediate 60%, and the slowest 20% are represented by blue, red, and green, respectively, where diffusivity is defined as the lateral TAMSD at $\Delta = 5$ ($t = 10$ ns).

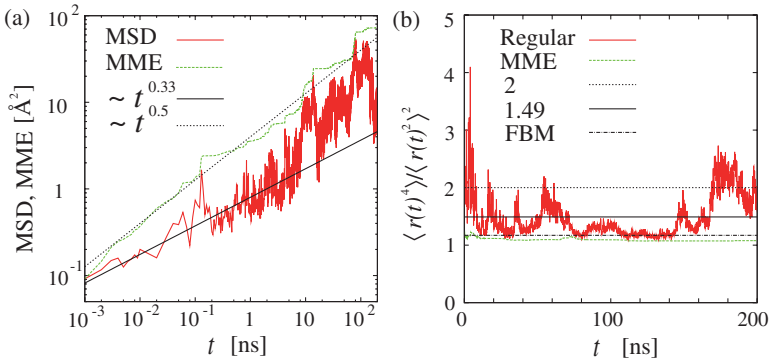

FIG. 5 (color). Mean maximal excursion analysis. (a) MSD and the MME second moment. (b) Moment ratios for regular moment and for the MME moment.

To observe a power-law trapping in a straightforward way, we investigate the distribution of trapping times [30]. The jump is defined as the event that the center of mass of a lipid molecule moves larger than a threshold Δr_c in a unit time interval $\Delta t (= 1$ ps), $\sqrt{\{x(t+\Delta t)-x(t)\}^2+\{y(t+\Delta t)-y(t)\}^2} \geq \Delta r_c$. The trapping time is defined as the time between successive jumps. Changing the threshold, we find that the distribution of the trapping time changes from the Weibull distribution, $F(t) = 1 - \exp[-(t/\tau)^a]$, to a power law, $P(t) = F'(t) \propto t^{-1-\beta}$ (Fig. 3). Moreover, the power-law exponent β is almost the same as 1.28, obtained by the relative fluctuations.

Dynamical heterogeneity and anticorrelation.—Lateral TAMSDs characterize diffusivities of particles. Analyzing the diffusivities of all lipid molecules in different time intervals, we demonstrate that the lipid molecules with low or high diffusivities assemble, and the diffusivities change with time (Fig. 4). Similar to dynamical heterogeneity in colloidal suspensions [1,2], fast particles are spatially correlated. However, unlike usual dynamical heterogeneity, all lateral TAMSDs show transient subdiffusions. We note that our theoretical approach, i.e., renewal theory, holds because spatial correlations are transient.

We found that lateral TAMSDs show transient subdiffusion. Using the mean maximal excursion (MME) method [33], we clarify whether the transient subdiffusion results from an anticorrelation. As shown in Fig. 5, the MSD defined by the ensemble average $\langle r(t)^2\rangle$ and the MME second moment $\langle r(t)^2_{\max}\rangle$ grow sublinearly with time, where $r(t) = \sqrt{x(t)^2 + y(t)^2}$ and $r_{\max}(t) = \max\{r(t'):0 \leq t' \leq t\}$. The subdiffusion exponent of the MSD is smaller than that of the MME second moment. Moreover, the regular moment ratio $\langle r(t)^4\rangle/\langle r(t)^2\rangle^2$ fluctuates around 2 and the MME moment ratio $\langle r(t)^4_{\max}\rangle/\langle r(t)^2_{\max}\rangle^2$ converges to around the estimated value for FBM. These facts are evidence of an anticorrelation. Furthermore, the p variation test also suggests an anticorrelation [30].

Discussion.—We computed the scaling exponent of the relative fluctuations. The non-Gaussian exponent, which is smaller than 0.5, is evidence of a power-law trapping time in anomalous transport. By performing a molecular dynamics simulation on a lipid bilayer, we found non-Gaussian behavior of the lateral TAMSD. Moreover, by the mean maximal excursion method, it was shown that transient subdiffusion originates from an anticorrelation. Our results suggest that molecular crowding leads to an anticorrelation and power-law trapping times. Therefore, a combined model containing FBM and a CTRW could be important.

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