Generalized Langevin Equation with Fractional Gaussian Noise: Subdiffusion within a Single Protein Molecule

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By introducing fractional Gaussian noise into the generalized Langevin equation, the subdiffusion of a particle can be described as a stationary Gaussian process with analytical tractability. This model is capable of explaining the equilibrium fluctuation of the distance between an electron transfer donor and acceptor pair within a protein that spans a broad range of time scales, and is in excellent agreement with a single-molecule experiment.

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The ubiquitous Brownian diffusion has been the cornerstone for statistical mechanics and is well understood. However, Brownian motion theory cannot account for the so-called anomalous diffusion processes. A major class of anomalous diffusion is subdiffusion, in which the mean-squared displacement is $\langle \Delta x(t)^2 \rangle \sim t^\alpha$ ($0 < \alpha < 1$, instead of $\alpha = 1$ as in Brownian diffusion). This subdiffusion phenomenon is widespread in condensed phased systems [1]. For example, it was recently found that the distance between a donor and an acceptor of electron transfer within a single protein molecule undergoes subdiffusion [2]. This fluctuation of protein conformation results in dynamic disorder of enzymatic rates [3,4]. Despite much effort [5], the underpinning of subdiffusion is not well understood. Here we report a theoretical model for subdiffusion based on the generalized Langevin equation (GLE) with fractional Gaussian noise (FGN). Under a harmonic potential, this model describes a stationary Gaussian process of equilibrium fluctuation at a broad range of time scales. The model is tested in the context of the single-molecule experiment.

Brownian motion is well described by the Langevin equation: $m\, dv/dt = -\zeta v + F(t)$, where v is the velocity of a Brownian particle with a mass m, ζ is the frictional constant, and the random fluctuation force $F(t)$ is assumed to be white noise $\langle F(t) \rangle = 0$, ($\langle\rangle$ denoting trajectory averaging), with the autocorrelation function

$$\langle F(t)F(t') \rangle = 2\zeta k_B T \delta(t - t'), \tag{1}$$

where k_B is the Boltzman constant and T is absolute temperature. Equation (1) is a consequence of the fluctuation-dissipation theorem, which relates the amplitude of $F(t)$ to the frictional constant. It follows that the velocity autocorrelation function is $\langle v(0)v(t) \rangle = (k_B T/m) \exp(-t\zeta/m)$. For the displacement $\Delta x(t) = \int_0^t v(s)ds$ one obtains the mean-squared displacement of a Brownian particle at large t: $\langle \Delta x(t)^2 \rangle = (2k_B T/\zeta)t$, which is the Einstein formula for Brownian motion.

If $F(t)$ is not white noise, the motion of the particle is described by GLE [6]:

$$m\frac{dv}{dt} = -\zeta \int_{-\infty}^{t} v(u)K(t-u)du + F(t) \tag{2}$$

where the fluctuation-dissipation theorem links the memory kernel $K(t)$ with the autocorrelation function of $F(t)$: $\langle F(t)F(t') \rangle = k_B T \zeta K(t - t')$. If $F(t)$ is a Gaussian process, $v(t)$ will also be Gaussian, which can be fully described if its mean and autocorrelation function are known.

The key point of this Letter is to introduce a Gaussian noise known as fractional Gaussian noise to the GLE. The FGN is closely related to the fractional Brownian motion (FBM) process [7], which is defined as a Gaussian process $B_t^{(H)}$ with an index $H \in (0, 1)$, mean $\langle B^{(H)}(t) \rangle = 0$, and the autocorrelation function, $\langle B^{(H)}(t)B^{(H)}(s) \rangle = (|t|^{2H} + |s|^{2H} - |t - s|^{2H})/2$ for any $t, s \geq 0$. When $H = 1/2$, FBM reduces to normal Brownian motion. The FBM process has two unique properties: self-similarity and stationary increments [8]. Self-similarity means that if a time segment is taken from the FBM trajectory, after proper normalization, the segment has the same behavior as any segments of other time scales. Stationary increment means that the distribution of $B^{(H)}(t) - B^{(H)}(s)$ does not depend on the starting time s, but only on the time lag $t - s$. FGN is defined as $\frac{dB^{(H)}(t)}{dt}$. We take $F(t)$ to be $F^{(H)}(t) = \sqrt{2k_B T\zeta}\frac{dB^{(H)}(t)}{dt}$, which is Gaussian and stationary. The autocorrelation function of FGN [9] is the memory kernel $K(t)$:

$$\begin{aligned} K(t) &= 2\langle \frac{dB^{(H)}(0)}{dt}\frac{dB^{(H)}(t)}{dt} \rangle \\ &= 2H(2H-1)|t|^{2H-2} + 2(1+2H)(1-H)\delta(t)^{2-2H} \end{aligned} \tag{3}$$

The physical constraint that $K(0)$ has to be positive requires $1/2 \leq H \leq 1$. The spectral density of the FGN is

$$\tilde{K}(\varpi) = \int_{-\infty}^{\infty} e^{i\varpi t}K(t)dt = 2\Gamma(2H+1)\sin(H\pi)|\varpi|^{1-2H} \tag{4}$$

which corresponds to the well known $1/f^\alpha$ noise [10].

Although GLE has been applied to many systems, most studies to date have not been concentrating on situations with long-tailed memory kernels. Introducing FGN into the GLE provides an appropriate physical description for equilibrium fluctuation with a long memory in a closed system [11].

Taking the memory kernel in the GLE to be the FGN autocorrelation, we can apply Fourier transform to solve the equation. The velocity autocorrelation function

$$C(t) = \langle v(0)v(t)\rangle = \frac{1}{2\pi}\int_{-\infty}^{\infty} e^{it\varpi}\tilde{C}(\varpi)d\varpi \qquad (5)$$

is given through its Fourier transform $\tilde{C}(\varpi) = k_B T\zeta\tilde{K}(\varpi)/|\zeta\tilde{K}_+(\varpi) - im\varpi|^2$, where

$$\begin{aligned}\tilde{K}_+(\varpi) &= \int_0^{\infty} e^{i\varpi t}K(t)dt \\ &= \Gamma(2H+1)|\varpi|^{1-2H}[\sin(H\pi) \\ &\quad - i\cos(H\pi)sgn(\varpi)] \end{aligned} \qquad (6)$$

For large t, the mean-squared displacement is

$$\begin{aligned}\langle \Delta x(t)^2\rangle &= \left\langle \left[\int_0^t v(s)ds\right]^2\right\rangle \\ &= \frac{k_B T}{\zeta}\frac{\sin(2H\pi)}{\pi H(2H-1)(2H-2)}t^{2-2H}. \end{aligned} \qquad (7)$$

Therefore, subdiffusion ($H > 1/2$) is a consequence of a GLE with FGN. When $H = 1/2$, both Eq. (5) and (7) recover the Brownian diffusion results.

So far we have only considered diffusion without external forces. In the presence of an external potential $U(x)$, the force $-U'(x)$ is added to the right side of Eq. (2), which is $-m\omega^2 x(t)$ for a harmonic potential:

$$m\ddot{x}(t) = -\zeta\int_{-\infty}^{t}\dot{x}(u)K(t-u)du - m\omega^2 x(t) + F^{(H)}(t). \qquad (8)$$

GLE in Eq. (8) can be derived from the Hamiltonian of a harmonically bounded particle interacting with a heat bath via the projection operator approach [6].

Under the overdamped condition, the particle has negligible acceleration. The GLE thus reads

$$m\omega^2 x(t) = -\zeta\int_{-\infty}^{t}\dot{x}(u)K(t-u)du + F^{(H)}(t), \qquad (9)$$

whose solution $x(t)$ is a stationary Gaussian process. Using the Fourier transform method we obtain the autocorrelation function $C_x(t) = \langle x(0)x(t)\rangle$ of $x(t)$,

$$\begin{aligned}C_x(t) &= \frac{k_B T\sin(H\pi)}{\pi(1-H)} \\ &\quad\times\int_0^{\infty}\frac{\cos(t[\zeta\Gamma(2H+1)/\eta]^{-1/(2-2H)})}{m^2\omega^4 - 2m\omega^2\cos(H\pi)\eta + \eta^2}d\eta \end{aligned} \qquad (10)$$

At time 0, $C_x(0) = k_B T/(m\omega^2)$, which is independent of H. Equation (10) is reduced to the Brownian diffusion result, $C_x(t) = k_B T/(m\omega^2)\exp[-(m\omega^2/\zeta)t]$, when $H = 1/2$.

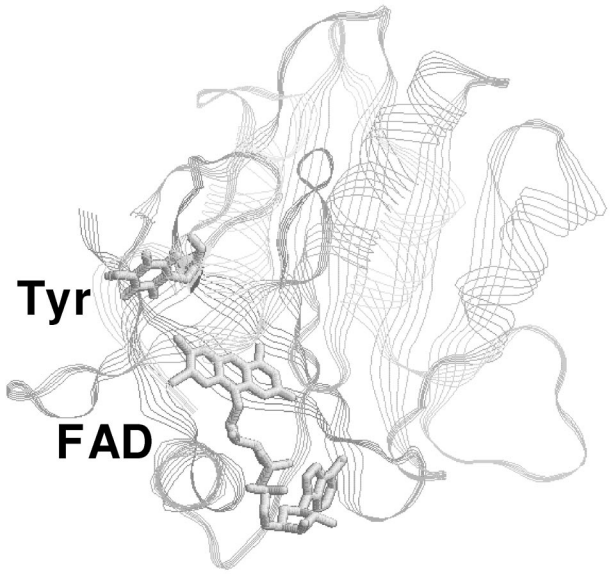

FIG. 1. Schematics of the structure of Fre protein [14]. The Tyr donor and FAD acceptor for the photo-induced electron transfer reaction are shown.

We now consider the conformational dynamics of a protein, flavin:NADH oxidoreductase (Fre) containing a flavin adenine dinucleotide (FAD) and a nearby tyrosine (Tyr), as shown in Fig. 1. A recent experiment shows that the distance between FAD and Tyr in a single Fre molecule fluctuates at a broad range of time scales (10^{-4}–1 s) [2]. This spontaneous distance fluctuation was observed through the variation of the fluorescence lifetime of the

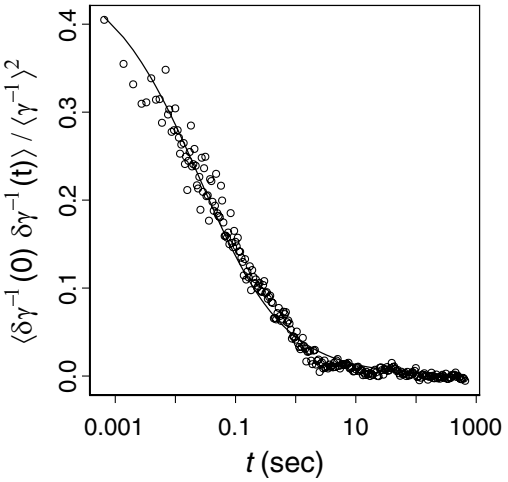

FIG. 2. Autocorrelation function of fluorescence lifetime fluctuation of a FAD within a single Fre protein molecule, plotted in logarithmic scale in time (from Ref. [2]). The decay spanning a broad range of time scales results from the fluctuation of the distance between FAD and Tyr, and is fit well with the result of GLE with FGN (solid line).

excited state of FAD, which receives an electron from the Tyr [2]. Determined by the photo-induced electron transfer reaction, the fluorescence lifetime γ^{-1} of FAD has an exponential dependence on the distance, $x_{\rm eq} + x$, between the electron transfer donor (Tyr) and acceptor (FAD) [12]:

$$\gamma^{-1}(t) = [k_0 e^{-\beta(x_{\rm eq}+x(t))}]^{-1} \quad (11)$$

where k_0 is a constant, $x_{\rm eq} \sim 4.5$ Å is the mean distance [13], $\beta \sim 1.4$ Å^{-1} for proteins [14]. Therefore, the distance fluctuation $x(t)$ is an experimentally accessible one-dimensional variable.

We model $x(t)$ by the GLE with FGN and a harmonic bound under the overdamped condition. It then follows that autocorrelation function of the lifetime fluctuation, $\delta\gamma^{-1}(t) = \gamma^{-1}(t) - \langle\gamma^{-1}\rangle$, is given by

$$\langle\delta\gamma^{-1}(0)\delta\gamma^{-1}(t)\rangle = k_0^{-2} e^{2\beta x_{\rm eq} + \beta^2 C_x(0)}(e^{\beta^2 C_x(t)} - 1) \quad (12)$$

Figure 2 shows the autocorrelation from experimental data [2], which spans a broad range of time scales. Also shown is an excellent fit to our model with the parameters of $H = 0.74$, $\zeta/m\omega^2 = 0.20$ s, $\beta^2 k_B T/(m\omega^2) = 0.81$.

We note that the experimentally measured $\langle\delta\gamma^{-1}(0)\delta\gamma^{-1}(t)\rangle$ also fits well [2,15] with the fractional Fokker-Planck equation (FFPE) describing subdiffusion in a potential. However, the FFPE [16] builds on the assumption that the trapping time at a particular position has a power law distribution with an infinite mean, which implies a nonstationary (nonequilibrium) process [17]. In contrast, the process governed by the GLE with FGN have finite moments of all orders for the first passage time, since it is known that for stationary Gaussian processes all moments of the first passage time are finite [18] if the autocorrelation eventually vanishes [as in Eq. (10)].

Higher order correlation functions of the fluorescence lifetime should be more sensitive in testing different models. We computed the three-time and four-time correlation functions $\langle\delta\gamma^{-1}(0)\delta\gamma^{-1}(t_1)\delta\gamma^{-1}(t_1+t_2)\rangle$ and $\langle\delta\gamma^{-1}(0)\delta\gamma^{-1}(t_1)\delta\gamma^{-1}(t_1+t_2)\delta\gamma^{-1}(t_1+t_2+t_3)\rangle$ from the experimental data and compared them with the theoretical values from our model:

$$\langle\delta\gamma^{-1}(0)\delta\gamma^{-1}(t_1)\delta\gamma^{-1}(t_1+t_2)\rangle = k_0^{-3} e^{3\beta x_{\rm eq} + 3\beta^2 C_x(0)/2}(e^{\beta^2[C_x(t_1)+C_x(t_2)+C_x(t_1+t_2)]} - e^{\beta^2 C_x(t_1)} - e^{\beta^2 C_x(t_2)} - e^{\beta^2 C_x(t_1+t_2)} + 2). \quad (13)$$

$$\begin{aligned}\langle\delta\gamma^{-1}(0)\delta\gamma^{-1}(t_1)\delta\gamma^{-1}(t_1+t_2)\delta\gamma^{-1}(t_1+t_2+t_3)\rangle &= k_0^{-4} e^{4\beta x_{\rm eq} + 2\beta^2 C_x(0)}\{e^{\beta^2[C_x(t_1)+C_x(t_1+t_2)+C_x(t_1+t_2+t_3)+C_x(t_2)+C_x(t_2+t_3)+C_x(t_3)]} - e^{\beta^2[C_x(t_1)+C_x(t_1+t_2)+C_x(t_2)]} \\ &- e^{\beta^2[C_x(t_1)+C_x(t_1+t_2+t_3)+C_x(t_2+t_3)]} - e^{\beta^2[C_x(t_1+t_2)+C_x(t_1+t_2+t_3)+C_x(t_3)]} - e^{\beta^2[C_x(t_2+t_3)+C_x(t_3)+C_x(t_2)]} + e^{\beta^2 C_x(t_1)} \\ &+ e^{\beta^2 C_x(t_1+t_2)} + e^{\beta^2 C_x(t_1+t_2+t_3)} + e^{\beta^2 C_x(t_2)} + e^{\beta^2 C_x(t_2+t_3)} + e^{\beta^2 C_x(t_3)} - 3\}. \end{aligned} \quad (14)$$

Figure 3 shows the three-time and four-time correlations $\langle\delta\gamma^{-1}(0)\delta\gamma^{-1}(t)\delta\gamma^{-1}(2t)\rangle/\langle\gamma^{-1}\rangle^3$ and $\langle\delta\gamma^{-1}(0)\delta\gamma^{-1}(t)\delta\gamma^{-1}(2t)\delta\gamma^{-1}(3t)\rangle/\langle\gamma^{-1}\rangle^4$; the overlaid theoretical curves are calculated using the same parameters obtained from fitting the data to Eq. (12) (Fig. 2). The excellent agreement provides additional proof that $x(t)$ is well described by our model. The fact that the fluctuation of $x(t)$ appears to be stationary Gaussian is intriguing, and could arise from the fact the bounded donor-acceptor pair

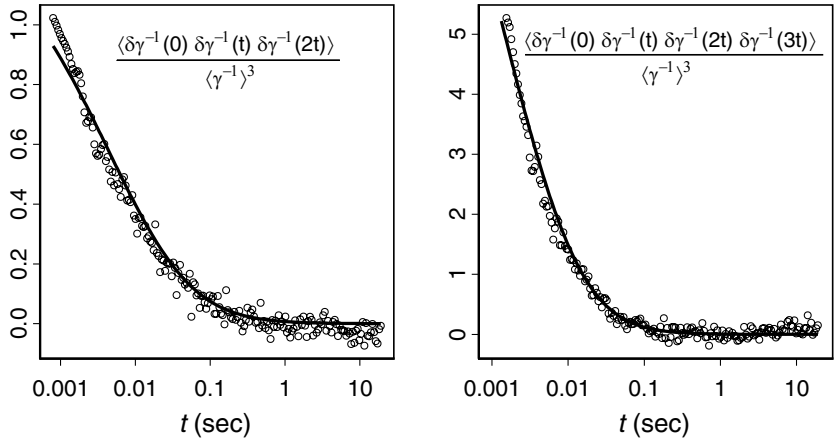

FIG. 3. Three-time and four-time correlation functions of fluorescence lifetime fluctuation of the same Fre molecule as in Fig. 2, which agree well with the predictions from the GLE with FGN (solid lines according to Eq. (13) and (14) respectively) using the same parameters obtained from the data fitting in Fig. 2.

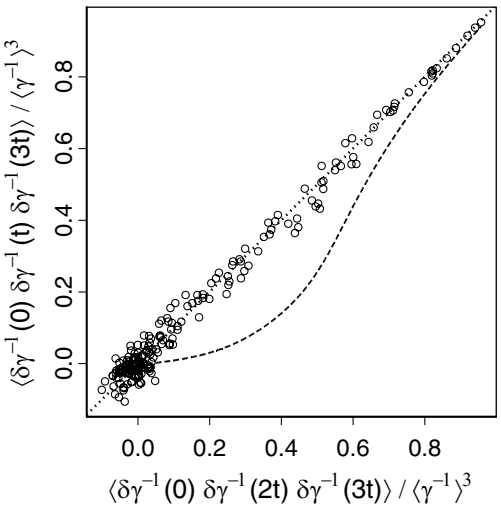

FIG. 4. Three-time fluorescence lifetime correlations $\langle \delta\gamma^{-1}(0)\delta\gamma^{-1}(t)\delta\gamma^{-1}(3t)\rangle/\langle\gamma^{-1}\rangle^3$ and $\langle \delta\gamma^{-1}(0)\delta\gamma^{-1}(2t)\times \delta\gamma^{-1}(3t)\rangle/\langle\gamma^{-1}\rangle^3$ of the same Fre molecule plotted against each other for various t. The diagonal experimental data indicates time reversibility, which is consistent with the prediction from the GLE with FGN [diagonal dotted line and Eq. (15)]. In contrast, FFPE results in the nondiagonal dashed line using the parameters obtained by fitting $\langle \delta\gamma^{-1}(0)\delta\gamma^{-1}(t)\rangle$ with FFPE; see Ref. [2] for details of the FFPE parameters.

interacts with a large density of quasi-independent oscillators in the protein bath.

Equation (13) predicts an interesting time-symmetry: For any t_1 and t_2

$$\langle \delta\gamma^{-1}(0)\delta\gamma^{-1}(t_1)\delta\gamma^{-1}(t_1+t_2)\rangle = \langle \delta\gamma^{-1}(0)\delta\gamma^{-1}(t_2)\delta\gamma^{-1}(t_1+t_2)\rangle. \quad (15)$$

Taking $t_1 = t$, $t_2 = 2t$, Fig. 4 plots the experimental $\langle \delta\gamma^{-1}(0)\delta\gamma^{-1}(t)\delta\gamma^{-1}(3t)\rangle/\langle\gamma^{-1}\rangle^3$ versus $\langle \delta\gamma^{-1}(0)\delta\gamma^{-1}(2t)\delta\gamma^{-1}(3t)\rangle/\langle\gamma^{-1}\rangle^3$ for various t. The diagonal experimental data is consistent with the prediction from our model [Eq. (15) and the diagonal dotted line]. In contrast, for a process described by the FFPE, the time symmetry does not hold. The third order correlation functions of γ^{-1} based on FFPE have been derived [17], which resulted in the nondiagonal dashed curve. Therefore, the experimental data indicates the stationary Gaussian nature of x fluctuation and the adequacy of our model in describing equilibrium fluctuation within a protein over FFPE. We note that FFPE proved to be able to describe non-Gaussian subdiffusion processes [16].

In summary, our model in the framework of GLE and FGN is capable of explaining subdiffusion dynamics, in particular, equilibrium fluctuation of protein conformation at a broad range of time scales. The microscopic origin of FGN is currently under investigation. Applications of this model to other chemical and biological problems are underway.

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Note added in proof.—An identical but simpler expression of Eq. (10) has been found to be

$$C_x(t) = \frac{k_B T}{m\omega^2} E_{2-2H}\left(-\frac{m\omega^2}{\zeta\Gamma(2H+1)} t^{2-2H}\right),$$

where $E_a(z) = \sum_{k=0}^{\infty} z^k/\Gamma(ak+1)$ is the Mittag-Leffler function [19].

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