

## ARTICLE

# Protein Conformational Change Based on a Two-dimensional Generalized Langevin Equation<sup>†</sup>

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A two-dimensional generalized Langevin equation is proposed to describe the protein conformational change, compatible to the electron transfer process governed by atomic packing density model. We assume a fractional Gaussian noise and a white noise through bond and through space coordinates respectively, and introduce the coupling effect coming from both fluctuations and equilibrium variances. The general expressions for autocorrelation functions of distance fluctuation and fluorescence lifetime variation are derived, based on which the exact conformational change dynamics can be evaluated with the aid of numerical Laplace inversion technique. We explicitly elaborate the short time and long time approximations. The relationship between the two-dimensional description and the one-dimensional theory is also discussed.

**Key words:** Protein conformational fluctuation, Two-dimensional generalized Langevin equation, Atomic packing density model, Fractional Gaussian noise

## I. INTRODUCTION

Understanding the role of conformational fluctuation in a protein on its biological functions, such as catalysis and allostery, has been a topic of long standing interest [1, 2]. Single-molecule experiments rapidly developed in recent years provide information about protein dynamics otherwise hidden in ensemble-averaged studies. In particular, investigations have been made for the conformational change of a flavin oxidoreductase [3] and of a protein complex formed between fluorescein and monoclonal anti-fluorescein [4], both of which involve an electron transfer (ET) reaction. The underlying donor-acceptor distance fluctuation  $x(t)$  is inferred from the experimentally accessible variation of fluorescence lifetime  $\gamma^{-1}(t)$ , via the classical ET rate theory [5],

$$\gamma^{-1}(t) = k_0 \exp\{\beta[x^{\text{eq}} + x(t)]\} \quad (1)$$

where  $\beta$  is the single superexchange decay parameter,  $\beta \approx 1.4 \text{ \AA}^{-1}$  for proteins [6],  $k_0$  is a constant, and  $x^{\text{eq}} \approx 4.5 \text{ \AA}$  is the mean donor-acceptor distance of the particular protein complex [7]. The distance fluctuation was observed over a broad range of times ( $10^{-3}$ – $100$  s),

in which protein reactions normally occur. It is therefore responsible for the dynamic disorder of enzymatic rates [8, 9].

Xie and coworkers proposed a one-dimensional generalized Langevin equation, with a harmonic potential, to describe the equilibrium fluctuation of donor-acceptor distance, which is regarded as a one-dimensional coarse-grained stochastic variable [10]. The distance fluctuation autocorrelation function was used to determine the rate kernel  $K(t)$ . It turns out to be  $K \propto t^{-0.51 \pm 0.07}$ , a remarkable power-law decay dependence. This long-time memory is induced by the surrounding protein environment with topological structure, and by the fluctuation-dissipation theorem associated with a fractional Gaussian noise (FGN). Generalized Langevin equation with FGN can account for the slow conformational relaxation dynamics undergoing subdiffusion. As a major class of anomalous diffusion, subdiffusion is featured by a mean-square displacement scaled as  $\langle x^2(t) \rangle \sim t^\alpha$ , where  $0 < \alpha < 1$ , rather than  $\alpha = 1$  of normal diffusion.

One-dimensional generalized Langevin equation is an appropriate theoretical model of distance fluctuation compatible to the single exponential ET rate theory of Eq.(1). It leads to an excellent agreement with the experiments reported in Refs.[3, 4]. Nevertheless, it was found recently some protein-mediated electron transfer processes are sensitive to the protein structure. Examples that deviate simple expression (Eq.(1)) are electron transfers in nine thermally fluctuating cytochrome  $b_{562}$  derivatives [11], and in peptides and proteins in

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the presence of suitable redox intermediates [12]. In contrast to the classical theory, ET rate in these proteins was suggested to be the multi-pathway model [13, 14] or the approximated atomic packing-density model [15, 16]. In particular, the fluorescence lifetime based on the simple atomic packing-density model follows

$$\gamma^{-1}(t) = k_0 \exp\{\beta_b[x_b^{\text{eq}} + x_b(t)]\} \cdot \exp\{\beta_s[x_s^{\text{eq}} + x_s(t)]\} \quad (2)$$

It composes both the through-bond and the through-space tunneling routes, with distinguishable decay parameters  $\beta_b \approx 1.4 \text{ \AA}^{-1}$  and  $\beta_s \approx 2.3 \text{ \AA}^{-1}$ , respectively [16]. It reflects a modification to the classical theory (Eq.(1)) from the contribution of the through-space route, and therefore contains additional information about the protein fold. Accordingly, a two-dimensional description for the conformational change of proteins is required.

Recently we studied explicitly a two-dimensional generalized Langevin equation with coupled FGN and white noise (WN) in respective coordinates. The exact dissipative dynamics as well as the short time and long time behaviors were analyzed [17]. In this work, we extend the achieved results therein to specifically investigate the conformational change for the proteins undergoing electron transfer processes, subject to the aforementioned through-bond and through-space ET rate mechanism.

A two-dimensional generalized Langevin equation with coupled FGN and WN is introduced. Based on it, we derive the general expressions of autocorrelation functions for distance fluctuation and fluorescence lifetime variation. We analyze the short time and long time approximations, and discuss the deviation of the present two-dimensional description to the one-dimensional theory.

## II. TWO-DIMENSIONAL GENERALIZED LANGEVIN EQUATION FOR CONFORMATIONAL CHANGE

To establish a conformational change description compatible to the packing-density model of ET (Eq.(2)), which represent the through-bond and through-space distance fluctuations, respectively, we introduce a coarse-gained stochastic coordinator vector,

$$\mathbf{x}(t) \equiv [\mathbf{x}_b(t), \mathbf{x}_s(t)]^T \quad (3)$$

The superscript T denotes transpose. The dynamics of  $\mathbf{x}(t)$  is analogous to the Brownian motion with two degrees of freedom, described by the following generalized Langevin equation,

$$m\ddot{\mathbf{x}}(t) + \frac{\partial U(\mathbf{x})}{\partial \mathbf{x}} + \int_0^t d\tau \mathbf{K}(t-\tau)\dot{\mathbf{x}}(\tau) = \mathbf{F}(t) \quad (4)$$

here  $m$  is the mass of the Brownian particle,  $U(\mathbf{x})$  is an external potential,  $\mathbf{K}(t)$  represents a dissipative memory kernel matrix, and

$$\mathbf{F}(t) \equiv [F_b(t), F_s(t)]^T \quad (5)$$

which is a random force vector. The classical dissipative kernel  $\mathbf{K}(t)$  is a real symmetric matrix and satisfies also  $\mathbf{K}(-t) = \mathbf{K}(t)$ . It links to the random force  $\mathbf{F}(t)$  by the classical fluctuation-dissipation theorem [18],

$$\langle \mathbf{F}(t)\mathbf{F}(\tau)^T \rangle = k_B T \mathbf{K}(t-\tau) \quad (6)$$

here  $k_B$  is the Boltzmann constant and  $T$  is the temperature.

As suggested in the one-dimensional consideration by Xie and co-workers [10], we also assume the random force  $F_b(t)$  on the coarse-grained through-bond coordinate be a FGN. It is induced by the confined protein structure and related closely to a fractional Brownian motion process [19]. It can generate a stationary sub-diffusive process of equilibrium fluctuation at a broad range of time scales. Its autocorrelation function, defined in the stochastic bath ensembles space, takes a power-law form,

$$\langle F_b(t)F_b(\tau) \rangle = \xi_b k_B T (2-\gamma)(1-\gamma) |t-\tau|^{-\gamma} \quad (7)$$

Note that  $\gamma = 2(1-H)$  in relation to the Hurst parameter  $H$  in Ref.[10]. The memory kernel in this coordinate is

$$K_b(t) = \xi_b (2-\gamma)(1-\gamma) |t|^{-\gamma} \quad (8)$$

which is according to Eq.(6). The physical constraint with quantity which is positive requires  $0 < \gamma < 1$ .

On the other hand, for simplicity, the through-space  $F_s(t)$  is treated as a Gaussian WN, associated with a WN solvent environment,

$$\langle F_s(t)F_s(\tau) \rangle = 2\xi_s k_B T \delta(t-\tau) \quad (9)$$

$\xi_s$  is the measure of the noise strength. It is related to a normal Brownian motion process [20], with  $K_s(t) = 2\xi_s \delta(t)$ .

Furthermore,  $F_b(t)$  and  $F_s(\tau)$  may correlate with each other. The cross correlation function is of  $\langle F_b(t)F_s(\tau) \rangle = \langle F_s(t)F_b(\tau) \rangle$ . It results in identical off-diagonal cross elements between the through-bond and through-space coordinates (denoted by a subscript b-s). In the Fourier frequency domain, it is proposed to be

$$\tilde{K}_{b-s}(\omega) = \epsilon \sqrt{\tilde{K}_b(\omega)\tilde{K}_s(\omega)} \quad (10)$$

where  $\epsilon$  is a parameter to measure the coupling strength between noises. The positivity of spectrum matrix  $\tilde{\mathbf{K}}(\omega)$  requires that  $|\epsilon| \leq 1$ . Thus, we can write down

$$K_{b-s}(t) = \frac{2}{\pi} \epsilon \cos \left[ \frac{(1+\gamma)\pi}{4} \right] \Gamma \left( \frac{1+\gamma}{2} \right) \sqrt{\xi_b \xi_s \Gamma(3-\gamma) \sin \left( \frac{\gamma\pi}{2} \right)} t^{-(\gamma+1)/2} \quad (11)$$

where  $\Gamma$  is the Gamma function.

For the later use, we calculate the Laplace transformation of the memory kernel matrix  $\mathbf{K}(t)$ ,

$$\hat{\mathbf{K}}(s) = \begin{bmatrix} k_\gamma s^{\gamma-1} & \epsilon_\gamma \bar{k}_\gamma s^{(\gamma-1)/2} \\ \epsilon_\gamma \bar{k}_\gamma s^{(\gamma-1)/2} & k \end{bmatrix} \quad (12)$$

$$k_\gamma \equiv \xi_b \Gamma(3-\gamma), \quad k \equiv \xi_s, \quad \bar{k}_\gamma \equiv \sqrt{k_\gamma k} \quad (13)$$

$$\epsilon_\gamma = \epsilon \left[ \frac{2 \sin(\gamma\pi/2)}{1 + \sin(\gamma\pi/2)} \right]^{1/2} \quad (14)$$

Note that  $0 < \epsilon_\gamma / \epsilon < 1$  for  $0 < \gamma < 1$ . It is the effective noise correlation parameter  $\epsilon_\gamma$ , rather than  $\epsilon$  defined in Eq.(10), playing the role in the generalized Langevin Eq.(4), as elaborated soon.

Furthermore,  $U(\mathbf{x})$  assumes a harmonic potential of mean force, as suggested in Refs.[3, 4, 21], following

$$U(\mathbf{x}) = -k_B T \ln P(\mathbf{x}) \quad (15)$$

It can be experimentally determined via the corresponding two-variable Gaussian probability density function of  $\mathbf{x}(t)$  trajectory,

$$P(\mathbf{x}) \approx \exp\left(-\frac{1}{2} \mathbf{x}^T \boldsymbol{\Xi}^{-1} \mathbf{x}\right) \quad (16)$$

where  $\boldsymbol{\Xi}$  is the equilibrium variance matrix defined as

$$\boldsymbol{\Xi} = \begin{bmatrix} \sigma_b & \lambda \sqrt{\sigma_b \sigma_s} \\ \lambda \sqrt{\sigma_b \sigma_s} & \sigma_s \end{bmatrix} \quad (17)$$

$\sigma_b$  and  $\sigma_s$  are the variances in the through bond and through space coordinates respectively. In Eq.(17),  $\lambda$  is introduced to be a measure of the coupling strength between these two variances. As a requirement that the Hessian matrix  $k_B T \boldsymbol{\Xi}^{-1}$  is positive, we have that  $|\lambda| < 1$ . The variance matrix  $\boldsymbol{\Xi}$  can be estimated favorably from the crystal structure data of the average atomic-mean-square displacements.

Under the overdamped condition, the acceleration term in the generalized Langevin (Eq.(4)) is negligible. It then follows

$$k_B T \boldsymbol{\Xi}^{-1} \mathbf{x}(t) = - \int_0^t d\tau \mathbf{K}(t-\tau) \dot{\mathbf{x}}(\tau) + \mathbf{F}(t) \quad (18)$$

The formal solution to Eq.(18) can be obtained by means of the Laplace transformation technique [22, 23], resulting in

$$\mathbf{x}(t) = \bar{\mathbf{x}}(t) + \int_0^t dt' \mathbf{G}(t-t') \mathbf{F}(t') \quad (19)$$

$$\bar{\mathbf{x}}(t) = [\mathbf{I} - k_B T \boldsymbol{\Xi}^{-1} \mathbf{Q}(t)] \mathbf{x}_0 + \mathbf{G}(t) \mathbf{v}_0 \quad (20)$$

Here,  $\mathbf{x}_0 = \mathbf{x}(0)$  is the deterministic initial displacement;  $\mathbf{G}(t)$  is the dissipative Green function for solving  $\mathbf{x}(t)$ , given by the Laplace inversion of

$$\hat{\mathbf{G}}(s) = [s \hat{\mathbf{K}}(s) + k_B T \boldsymbol{\Xi}^{-1}]^{-1} \quad (21)$$

The integral of  $\mathbf{G}(t)$  yields  $\mathbf{Q}(t)$ :

$$\mathbf{Q}(t) = \int_0^t dt' \mathbf{G}(t') \quad (22)$$

Thus, there is also  $\hat{\mathbf{Q}}(s) = \hat{\mathbf{G}}(s)/s$ . From Eqs. (20) and (22), it follows  $\mathbf{G}(0) = 0$  and  $\mathbf{Q}(0) = 0$ .

We proceed to derive the time correlation function of  $\mathbf{x}(t)$  defined as

$$\mathbf{C}_\mathbf{x}(t) \equiv \langle \mathbf{x}(0) \mathbf{x}^T(t) \rangle \quad (23)$$

We convert Eq.(18) to an equation for  $\mathbf{C}_\mathbf{x}(t)$  by multiplying by  $\mathbf{x}(0)$  and averaging over the initial equilibrium condition:

$$k_B T \boldsymbol{\Xi}^{-1} \mathbf{C}_\mathbf{x}(t) + \int_0^t \mathbf{K}(t-\tau) \dot{\mathbf{C}}_\mathbf{x}(\tau) d\tau = 0 \quad (24)$$

The last term  $\langle \mathbf{F}(t) \mathbf{x}(0) \rangle = 0$  because  $\mathbf{F}$  is orthogonal to the initial  $\mathbf{x}$  in the phase space [24–26]. The Laplace transform of Eq.(24) gives

$$\hat{\mathbf{C}}_\mathbf{x}(s) = [s \hat{\mathbf{K}}(s) + k_B T \boldsymbol{\Xi}^{-1}]^{-1} \hat{\mathbf{K}}(s) \mathbf{C}_\mathbf{x}(0) \quad (25)$$

The initial value  $\mathbf{C}_\mathbf{x}(0)$  should be identical to the equilibrium variance matrix  $\boldsymbol{\Xi}$  given by Eq.(17). In view of Eqs. (21) and (22), we can rewrite Eq.(25) as

$$\hat{\mathbf{C}}_\mathbf{x}(s) = \frac{1}{s} \boldsymbol{\Xi} - k_B T \hat{\mathbf{Q}}(s) \quad (26)$$

Then, the inverse Laplace transformation of the above expression yields

$$\mathbf{C}_\mathbf{x}(t) = \boldsymbol{\Xi} - k_B T \mathbf{Q}(t) \quad (27)$$

Finally, we can also obtain the autocorrelation function of fluorescence lifetime variation, defined as

$$C_{\gamma^{-1}}(t) \equiv \frac{\langle \delta\gamma^{-1}(0) \delta\gamma^{-1}(t) \rangle}{\langle \gamma^{-1} \rangle^2} \quad (28)$$

$$\delta\gamma^{-1}(t) = \gamma^{-1}(t) - \langle \gamma^{-1} \rangle \quad (29)$$

and  $\gamma^{-1}(t)$  follows Eq.(2). By virtue of the stationary and Gaussian properties of  $\mathbf{x}(t)$ ,  $C_{\gamma^{-1}}(t)$  is related to  $\mathbf{C}_\mathbf{x}(t)$  by

$$\begin{aligned} C_{\gamma^{-1}}(t) &\equiv \frac{\langle \delta\gamma^{-1}(0) \delta\gamma^{-1}(t) \rangle}{\langle \gamma^{-1} \rangle^2} \\ &= \exp[\beta^T \mathbf{C}_\mathbf{x}(t) \beta] - 1 \end{aligned} \quad (30)$$

where  $\beta \equiv [\beta_b, \beta_s]^T$  is the decay parameter vector. Via this relation, the conformational change characterized by  $\mathbf{C}_\mathbf{x}(t)$  can be detected through the experimental observable  $C_{\gamma^{-1}}(t)$ .

The quantities of interest  $\mathbf{C}_\mathbf{x}(t)$  and  $C_{\gamma^{-1}}(t)$  are now expressed in terms of the equilibrium variance  $\boldsymbol{\Xi}$  and the relaxation function  $\mathbf{Q}(t)$  (Eqs. (27) and (30)). In practice,  $\boldsymbol{\Xi}$  can be measured directly by experiment. The remaining key problem is to evaluate the evolution of  $\mathbf{Q}(t)$ .

### III. SPECIFIC RESULTS AND DISCUSSIONS

In view of Eqs. (21) and (22), we have

$$\hat{\mathbf{Q}}(s) = \frac{1}{k_{\text{B}}T} \left[ \hat{\mathbf{K}}'(s) + \frac{1}{s} \boldsymbol{\Xi}^{-1} \right]^{-1} \quad (31)$$

with the scaled memory kernel matrix,

$$\begin{aligned} \hat{\mathbf{K}}'(s) &\equiv \frac{\hat{\mathbf{K}}(s)}{k_{\text{B}}T} \\ &= \begin{bmatrix} k'_{\gamma} s^{\gamma-1} & \epsilon_{\gamma} \bar{k}'_{\gamma} s^{(\gamma-1)/2} \\ \epsilon_{\gamma} \bar{k}'_{\gamma} s^{(\gamma-1)/2} & k' \end{bmatrix} \end{aligned} \quad (32)$$

where  $k'_{\gamma} \equiv k_{\gamma}/(k_{\text{B}}T)$ ,  $k' \equiv k/(k_{\text{B}}T)$ , and  $\bar{k}'_{\gamma} \equiv \bar{k}_{\gamma}/(k_{\text{B}}T)$ . Plugging Eqs. (17) and (32) into Eq.(31), we can write down explicitly

$$\hat{\mathbf{Q}}(s) = \frac{1}{k_{\text{B}}T\mathcal{D}} \cdot \begin{bmatrix} k's(1-\lambda^2)\sigma_s + 1 & A \\ A & k's^{\gamma}(1-\lambda^2)\sigma_s + \sigma_s/\sigma_b \end{bmatrix} \quad (33)$$

$$A = \lambda\sqrt{\sigma_s/\sigma_b} - \epsilon_{\gamma}\bar{k}'_{\gamma}s^{(\gamma+1)/2}(1-\lambda^2)\sigma_s$$

with the denominator  $\mathcal{D}$  given by

$$\begin{aligned} \mathcal{D} = s \left[ k'_{\gamma}s^{\gamma} + \frac{k'\sigma_s s + 1}{\sigma_b} \right] + 2\lambda\epsilon_{\gamma}\bar{k}'_{\gamma}s^{(\gamma+3)/2} \cdot \\ \sqrt{\sigma_s/\sigma_b} + (1-\epsilon_{\gamma}^2)(1-\lambda^2)k'_{\gamma}k'\sigma_s s^{\gamma+2} \end{aligned} \quad (34)$$

Obviously, due to the finite effective correlation ( $\epsilon_{\gamma} \neq 0$ ) and/or the variance coupling ( $\lambda \neq 0$ ), the self quantities in the through-bond and the through-space coordinates are entangled with each other. Meanwhile, a cross term arises. It is clear that  $\mathbf{Q}(t)$  depends not only on the fluctuations FGN and WN and the equilibrium variances associated to through bond and through space coordinates, but also on the fluctuation correlation  $\epsilon_{\gamma}$  and the variance coupling  $\lambda$ . Straightforwardly, the inverse Laplace transformation of Eq.(33) gives the temporal evolution of  $\mathbf{Q}(t)$ , and then the autocorrelation functions  $\mathbf{C}_{\mathbf{x}}(t)$  and  $C_{\gamma-1}(t)$  can be obtained along with Eqs. (27) and (30). These exact solutions will be obtained with the aid of numerical Laplace transformation technique.

Besides the numerical exact results, we can also deduce the short time and long time behaviors. First of all, by observing the diagonal terms in Eq.(33), it suggests the relevant time scale for short time analysis:

$$\tau^* = \min\{[k'_{\gamma}\sigma_b(1-\lambda^2)]^{1/\gamma}, k'\sigma_s(1-\lambda^2)\} \quad (35)$$

The variance coupling  $\lambda$  shortens this time scale. In the

time regime,  $t < \tau^*$ , Eq.(33) can be reduced to

$$\begin{aligned} \hat{Q}_{\text{b}}(s) &\approx \frac{1}{k_{\text{B}}T} \frac{1/s}{(1-\epsilon_{\gamma}^2)k'_{\gamma}s^{\gamma} + 1/[(1-\lambda^2)\sigma_b]} \\ \hat{Q}_{\text{s}}(s) &\approx \frac{1}{k_{\text{B}}T} \frac{1/s}{(1-\epsilon_{\gamma}^2)k's + 1/[(1-\lambda^2)\sigma_s]} \\ \hat{Q}_{\text{b-s}}(s) &\approx \frac{-1}{k_{\text{B}}T} \frac{\epsilon_{\gamma}\bar{k}'_{\gamma}s^{(\gamma-3)/2}}{(1-\epsilon_{\gamma}^2)k'_{\gamma}k's^{\gamma} + k'/[(1-\lambda^2)\sigma_b]} \end{aligned} \quad (36)$$

Adopting the Laplace inversion formula,

$$\mathcal{L}^{-1} \left\{ \frac{s^{a-b}}{s^a - \alpha} \right\} = t^{b-1} E_{a,b}(\alpha t^a) \quad (37)$$

with  $E_{a,b}(y)$  being a generalized Mittag-Leffler function [27] defined by a series expansion,

$$E_{a,b}(y) = \sum_{n=0}^{\infty} \frac{y^n}{\Gamma(an+b)}, \quad (a, b > 0) \quad (38)$$

it is easy to obtain

$$\begin{aligned} Q_{\text{b}}(t) &\approx \frac{1}{k_{\text{B}}T} \frac{t^{\gamma}}{k'_{\gamma}(1-\epsilon_{\gamma}^2)} E_{\gamma, \gamma+1} \cdot \\ &\quad \frac{-t^{\gamma}}{(1-\epsilon_{\gamma}^2)(1-\lambda^2)k'_{\gamma}\sigma_b} \\ Q_{\text{s}}(t) &\approx \frac{1}{k_{\text{B}}T} \frac{t}{k'(1-\epsilon_{\gamma}^2)} E_{1,2} \cdot \\ &\quad \frac{-t}{(1-\epsilon_{\gamma}^2)(1-\lambda^2)k'\sigma_s} \\ Q_{\text{b-s}}(t) &\approx \frac{-1}{k_{\text{B}}T} \frac{\epsilon_{\gamma}t^{(\gamma+1)/2}}{(1-\epsilon_{\gamma}^2)k'_{\gamma}} E_{\gamma, (3+\gamma)/2} \cdot \\ &\quad \frac{-t^{\gamma}}{(1-\epsilon_{\gamma}^2)(1-\lambda^2)k'_{\gamma}\sigma_b} \end{aligned} \quad (39)$$

Using this approximation, and combining with Eqs. (27) and (30), we finally obtain the short time behavior of autocorrelation functions of distance fluctuation and fluorescence lifetime variation.

Figure 1 presents the short time approximates of  $C_{\gamma-1}(t)$ , versus the corresponding exact results via numerical Laplace inversion of Eq.(33). The figure is obtained under different values of  $\lambda$ , but fixed other parameters. Apparently, the short time solutions show an excellent agreement with the exact ones in  $t < \tau^*$  regime. Moreover, the initial values of this autocorrelation function are in accordance with

$$C_{\gamma-1}(0) = \exp(\beta^{\text{T}} \boldsymbol{\Xi} \beta) - 1 \quad (40)$$

We now turn to the long time behavior, which may be analyzed with  $\epsilon_{\gamma} \approx 0$ , since the equilibrium property of  $\mathbf{Q}(t)$  does not depend on the fluctuation correlation (see also Ref.[17]). Keeping only the relatively lower

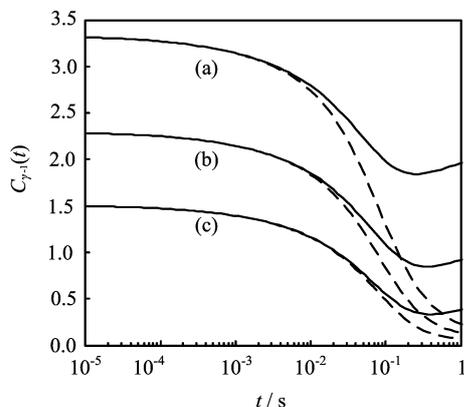


FIG. 1 The short time asymptotic solutions (solid curves) according to Eq.(39) and numerically exact results (dash curves) of autocorrelation function of fluorescence lifetime variation, at fixed parameters:  $\gamma=0.5$ ,  $\sigma_b=0.2 \text{ \AA}^2$ ,  $\xi_b/k_B T=1 \text{ s}^\gamma/\text{\AA}^2$ ,  $\sigma_s=0.1 \text{ \AA}^2$ ,  $\xi_s/k_B T=1 \text{ s}/\text{\AA}^2$  and  $\epsilon_\gamma=0.2$ , but different values of (a)  $\lambda=0.6$  ( $\tau^*=29 \text{ ms}$ ), (b)  $\lambda=0.3$  ( $\tau^*=59 \text{ ms}$ ), and (c)  $\lambda=0$  ( $\tau^*=71 \text{ ms}$ ). The corresponding  $\tau^*$  (Eq.(35)) is specified individually.  $C_{\gamma-1}(0)$  are 3.34 (a), 2.28 (b), and 1.50 (c).

order terms with respect to  $s$  in Eq.(33), we begin with the intermediate expressions

$$\begin{aligned}\hat{Q}_b(s) &\approx \frac{1}{k_B T} \frac{\sigma_b/s}{k'_\gamma \sigma_b s^\gamma + 1} \\ \hat{Q}_s(s) &\approx \frac{1}{k_B T} \frac{\sigma_s/s}{k'_\gamma \sigma_s s + 1} \\ \hat{Q}_{b-s}(s) &\approx \frac{1}{k_B T} \frac{\lambda \sqrt{\sigma_b \sigma_s}/s}{k'_\gamma \sigma_b s^\gamma + 1}\end{aligned}\quad (41)$$

As anticipated, the cross term of Eq.(39) arises from the  $\lambda$ -mixing rather than the fluctuation correlation. The approximate  $\mathbf{Q}(t)$  can be immediately obtained by applying Eq.(37). Inserting the result into Eq.(27), we have, after some algebra,

$$\mathbf{C}_x(t) \approx \begin{bmatrix} \sigma_b E_\gamma[-(t/\tau_b)^\gamma] & B \\ B & \sigma_s \exp(-t/\tau_s) \end{bmatrix} \quad (42)$$

$$\begin{aligned}B &= \lambda \sqrt{\sigma_b \sigma_s} E_\gamma[-(t/\tau_b)^\gamma] \\ \tau_b &= (k'_\gamma \sigma_b)^{1/\gamma}, \quad \tau_s = k'_\gamma \sigma_s\end{aligned}\quad (43)$$

They define two characteristic time scales to measure how fast or slow the autocorrelation function decays to zero.

With the aid of the asymptotic property of the generalized Mittag-Leffler function [30]

$$E_{a,b}(-y) \approx \frac{1}{y\Gamma(b-a)}, \quad (b > a, \quad y > 0) \quad (44)$$

we will get the long time asymptotic approximation of  $\mathbf{C}_x(t)$  for  $t \gg \max\{\tau_b, \tau_s\}$ . Note that  $\exp(-t/\tau_s)$  in Eq.(42) vanishes in this regime. Finally, inserting into

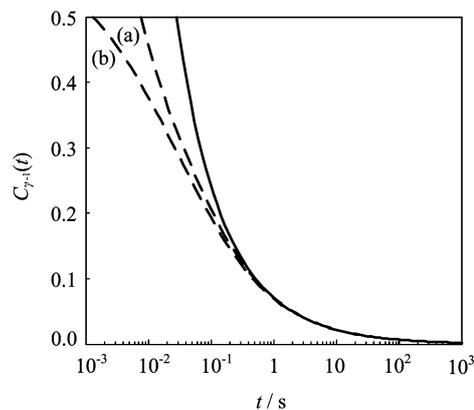


FIG. 2 The long time asymptotic solution (solid curve) according to Eq.(45) and numerically exact results (dash curves) of autocorrelation function of fluorescence lifetime variation, at fixed parameters  $\gamma=0.5$ ,  $\sigma_b=0.2 \text{ \AA}^2$ ,  $\xi_b/k_B T=1 \text{ s}^\gamma/\text{\AA}^2$  ( $\tau_b=71 \text{ ms}$ ), and a common covariance  $\lambda \sqrt{\sigma_s \sigma_b} = \sigma_b/20$ , but different parameter sets  $(\sigma_s, \xi_s/k_B T, \epsilon_\gamma) = (\sigma_b/5, 0.1 \text{ s}/\text{\AA}^2, 0.3)$  (a) ( $\lambda=0.112$ ,  $\tau_s=4.0 \text{ ms}$ ), and  $(\sigma_b/150, 1 \text{ s}/\text{\AA}^2, 0.1)$  (b) ( $\lambda=0.612$ ,  $\tau_s=1.3 \text{ ms}$ ).

Eq.(29) results in

$$C_{\gamma-1}(t) \approx \exp \left[ \frac{\beta_b^2 \sigma_b^2 k'_\gamma}{t^\gamma \Gamma(1-\gamma)} \left( 1 + 2\lambda \frac{\beta_s \sqrt{\sigma_s}}{\beta_b \sqrt{\sigma_b}} \right) \right] - 1 \quad (45)$$

The  $\lambda$ -term in the exponent is the modification to the one-dimensional formula [4, 10], reflecting the influence coming from through space coordinate. This term is determined by the ratio  $\beta_s/\beta_b$ , and also the factor  $\lambda \sqrt{\sigma_s/\sigma_b}$ . The latter one is identical to the ratio between the covariance and the through-bond variance, *i.e.*,  $\lambda \sqrt{\sigma_s \sigma_b}/\sigma_b$ . The fluctuation in through space coordinate characterized by  $k'$  (or  $\xi_s/k_B T$ ) as well as the fluctuation correlation  $\epsilon_\gamma$  can not play a role in this approximate.

Figure 2 presents the long time asymptotic solution of  $C_{\gamma-1}(t)$  according to Eq.(45). And the exact results (dash curves) evaluated based on numerical Laplace inversion of Eq.(33). The figure is obtained under fixed parameters associated to the through bond coordinate and a common covariance, but different parameter sets  $(\sigma_s, \xi_s/k_B T, \epsilon_\gamma)$ .  $\lambda$  takes the value self-consistently. Apparently, the exact solutions degenerate in long times and match well the approximate Eq.(45) in  $t \gg \max\{\tau_b, \tau_s\}$  regime.

Lastly, we discuss in which situation the present two-dimensional description can reproduce the one-dimensional theory reported in Refs.[4, 10]. As mentioned above, the one-dimensional generalized Langevin equation for conformational change is compatible to the classical ET rate theory Eq.(1). In fact, this is a limit case that the through space path is negligible, or more appropriate  $x_s^{\text{eq}} \rightarrow 0$ . Taking into account the fact that the fluctuating donor-accepter distance  $x_s^{\text{eq}} + x_s(t)$  has

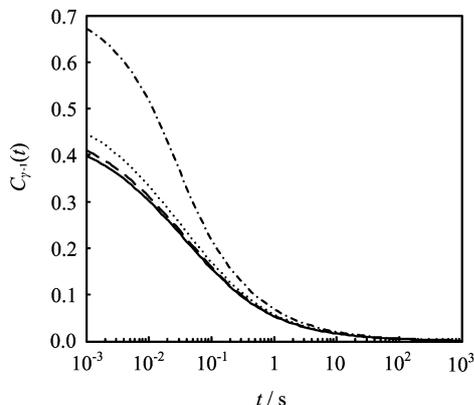


FIG. 3 The one-dimensional approximation (solid curve) according to Eq.(48) and numerically exact results of autocorrelation function of fluorescence lifetime variation, for different ratios  $\sigma_s/\sigma_b=1/1000$  (dash line),  $1/100$  (dot line) and  $1/10$  (dash dot line). The through-bond parameters are adopted the same as those in Ref.[10]:  $\gamma=0.52$ ,  $\sigma_b=0.192 \text{ \AA}^2$ ,  $\xi_b/k_B T=1.04 \text{ s}^\gamma/\text{\AA}^2$ . Other parameters are  $\xi_s/k_B T=1 \text{ s}/\text{\AA}^2$ ,  $\epsilon_\gamma=0.2$  and  $\lambda=0.2$ .

to be positive and  $x_s(t)$  is submitted to a Gaussian distribution at equilibrium state, we deduce that the fluctuation should be confined in a limited range with very small variance  $\sigma_s$  in such a case. Resultantly, the self quantity  $\hat{Q}_b(s)$  as well as the cross quantity  $\hat{Q}_{b-s}(s)$  in Eq.(33) become trivial. Here  $\hat{Q}_b(s)$  is reduced to

$$\hat{Q}_b(s) \approx \frac{1}{k_B T} \frac{\sigma_b/s}{k'_\gamma \sigma_b s^\gamma + 1} \quad (46)$$

Applying Eq.(37) leads to

$$Q_b(t) \approx \frac{1}{k_B T} \sigma_b \left[ 1 - E_\gamma \left( -\frac{t^\gamma}{k'_\gamma \sigma_b} \right) \right] \quad (47)$$

Thus,

$$C_{\gamma-1}(t) \approx \exp \left[ \beta_b^2 \sigma_b E_\gamma \left( -\frac{t^\gamma}{k'_\gamma \sigma_b} \right) \right] - 1 \quad (48)$$

This is just the result given by one-dimensional generalized Langevin equation theory [4, 10]. Therefore, we can see that if only the through space path is significant (with finite  $x_s^{\text{eq}}$  and  $\sigma_s$ ), the two-dimensional description leads to a prominent deviation from the one-dimensional description.

Figure 3 exhibits the exact results of  $C_{\gamma-1}(t)$  for several typical ratios of  $\sigma_s/\sigma_b$ , and also the one-dimensional solution according to Eq.(48). It shows clearly that the larger this ratio is, the farther the exact curve deviates from the one-dimensional approximation.

#### IV. CONCLUSION

In this work, we propose a two-dimensional generalized Langevin equation to describe the protein conformational change, which is appropriate for a protein mediated ET process subject to the atomic packing density model. It is assumed that the through bond and through space coordinates are accompanied with coupled fractional Gaussian noise and white noise. Two types of coupling coming from fluctuations and covariance in equilibrium state are introduced into the model. We derive the general expressions for autocorrelation functions of distance fluctuation and fluorescence lifetime variation, which are expressed in terms of the relaxation function  $\mathbf{Q}(t)$  and the equilibrium variance matrix  $\Xi$ . We specifically analyze the short time and long time approximations, and discuss the relationship between the present two-dimensional description and the one-dimensional theory in previous work [4].

As a conclusion, the short time approximation of the autocorrelation functions takes the form in terms of Mittag-Leffler functions (Eq.(39)), which also includes the effect of fluctuation correlation. While the long time approximation follows Eq.(45), deviating from the one-dimensional approximate by a modification term due to the presence of covariance. The fluctuation in through space coordinate and the fluctuation correlation will not influence the long time asymptotic behavior. In addition to it, we also demonstrate that as the equilibrium variance in through space coordinate becomes negligible compared to that in through bond coordinate, the one-dimensional theory is reproduced. We may expect the present analysis provides a better interpretation to the experimental fluorescence lifetime spectra which are related to the protein-mediated ET processes with structure sensitivity.

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