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Modelling non-Markovian fluctuations in intracellular biomolecular transport

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ABSTRACT

To model non-Markovian fluctuations arising in biomolecular transport, we introduce a stochastic process with memory where Brownian motion is modulated sinusoidally. The probability density function and moments of this non-Markovian process are evaluated analytically as Hida stochastic functional integrals. Comparison of graphs of computed variance vis-á-vis empirical data for protein diffusion coefficients closely match with both exhibiting emergent superdiffusive then subdiffusive behavior for longer proteins.

1. Introduction

We present a Hida stochastic functional integral approach to infer non-Markovian structure of fluctuations generating nonlinear mean square deviations (MSD) of measured diffusion coefficients from estimated values for proteins of varying numbers of component amino acids. This approach allows analytical evaluation of the probability density function (PDF) and moments. Results should be useful for studies of biomolecular transport in complex environments with boundary conditions such as proteins diffusing in crowded cells which has received much attention in view of its role in controlling rates of cell processes [1–7]. For most proteins, a plot of experimental diffusion coefficient D values against protein length, or number of amino acids N, reveals a decreasing mean curve, or best fit curve, of the plotted D values [2,3,6]. Although most proteins yield diffusion coefficient D values near the mean curve, some values however have significant deviations from the mean curve or expected trend based on estimation schemes [2]. Such deviations hamper desired predictability of diffusion coefficients as these depend on different factors such as cell size and density of intracellular structures complicated by variations in intracellular media. It would thus be helpful to recognize a deeper level of mathematical structure in deviations from the empirical mean curve for diffusion coefficients.

Stochastic models have allowed deeper insights into the dynamics of cellular processes since these generally involve vigorous fluctuations. For example, recent work in studies of ion channel fluctuations in cellular membranes involve Markov models [8]. However, when memory or correlation between events is involved, it is necessary to go beyond Markov models. Fractional Brownian motion (fBm) has been used to describe anomalous diffusion in various phenomena including biological processes [9–11]. Nevertheless, this is still insufficient for the study of measured protein diffusion coefficients [2–4], since fBm may not fully capture trends in MSD of diffusion coefficients for varying protein lengths. There could be deviation from the power law time dependence associated with fBm, i.e., $\mathrm{MSD}_{(fBm)} \backsim t^{\alpha}$, which includes ordinary Brownian motion as a special case for $\alpha = 1$.

In this paper, we show that there exists a suitable larger class of stochastic processes with memory for which we can get a closed form for the probability density function and moments. This process is parametrized with a random variable $\xi(L)$,

$$\xi(L) = \xi_0 + B^{SM}(L), \tag{1}$$

where the initial value is $\xi_0 = \xi(0)$ and the fluctuating part $B^{SM}(L)$ is parametrized by a Brownian motion $B(s)$ with sinusoidal modulation of the form,

$$B^{SM}(L) = \exp[b\sin(cL)] \int_0^L (L-s)^{(\nu-1)/2} \frac{\sin^{\frac{1}{2}}(as)}{s^{(1-\nu)/2}} dB(s). \tag{2}$$

In Eq. (2), the factor $\exp[b\sin(cL)]\sin^{\frac{1}{2}}(as)/s^{(1-\nu)/2}$ modulates the Brownian fluctuation $B(s)$, while the term $(L-s)^{(\nu-1)/2}$ serves as a memory kernel for the stochastic process as chain length s progresses from 0 to $L = \pi/a$. The constants a, b, c and ν are determined depending

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on the modelling problem. The parametrization in Eq. (2) gives a larger class that goes beyond anomalous diffusion or fBm given by:

$$B^H(L) = \frac{1}{\Gamma\left(H+\frac{1}{2}\right)}\int_0^L (L-s)^{H-\frac{1}{2}}\, dB(s), \tag{3}$$

in the Riemann-Liouville representation [12]. In Eq. (3), the Hurst index H describes long-memory processes (enhanced diffusion) for $1/2 < H < 1$, short-memory processes (suppressed diffusion) for $0 < H < 1/2$, and ordinary Brownian motion for $H = 1/2$.

As we show in this paper, the expanded class of stochastic processes represented by Eq. (2), closely describes the underlying pattern for nonlinear length-dependent MSD and provides a better fit for the shape and general behavior of empirical graphs for protein transport.

2. PDF and MSD analysis for stochastic process with memory

The probability density function (PDF) for fluctuations with memory given by Eq. (2) can be evaluated using the Hida stochastic functional integral approach which facilitates handling of the nontrivial length dependence ($0 \le s \le L$) of the random variable $\xi(s)$. The approach first considers the ensemble of all possible fluctuations starting at the fixed value ξ_0 at $s = 0$ then determines the probability that ξ ends at a specific value $\xi(L) = \xi_L$ when $s = L$. Following Feynman's sum-over-all histories [13–15], we then consider all possible fluctuations $\xi(L)$ which satisfy the δ-function endpoint constraint,

$$\delta(\xi(L)-\xi_L) = \delta\left(\xi_0 - \xi_L + e^{bsin(cL)}\int_0^L (L-s)^{(\nu-1)/2}\frac{sin^{\frac{1}{2}}(as)}{s^{(1-\nu)/2}}\,\omega(s)ds\right). \tag{4}$$

In Eq. (4), we expressed the Brownian motion differential in terms of white noise $\omega(s)$, i.e., $dB(s) = \omega(s)\, ds$. We can then take $\omega(s)$ as the Hida white noise variable [16] with the Gaussian white noise probability measure $d\mu(\omega)$. The probability density function $P(\xi_L, L; \xi_0, 0)$ can be obtained by simply evaluating the expectation value $E(\delta(\xi(L)-\xi_L))$, i.e.,

$$\begin{aligned} P(\xi_L, L; \xi_0, 0) &= E(\delta(\xi(L)-\xi_L)) \\ &= \int \delta(\xi(L)-\xi_L)\, d\mu(\omega) \\ &= \int \frac{1}{2\pi}\int_{-\infty}^{+\infty} e^{ik(\xi(L)-\xi_L)}dk\; d\mu(\omega). \end{aligned} \tag{5}$$

In Eq. (5), we have written the delta function in terms of its Fourier representation. Using Eq. (2) we can write Eq. (5) as,

$$\begin{aligned} P(\xi_L, L; \xi_0, 0) &= \frac{1}{2\pi}\int_{-\infty}^{+\infty} dk\, \exp\{ik[(\xi_0-\xi_L)]\} \\ &\quad\times \int e^{i\int_0^L \omega(s)\,\zeta(s)\,ds} d\mu(\omega), \end{aligned} \tag{6}$$

where, $\zeta(s) = ke^{bsin(cL)}(L-s)^{(\nu-1)/2}sin^{\frac{1}{2}}(as)/s^{(1-\nu)/2}$. The integral over $d\mu(\omega)$ in Eq. (6) is simply the characteristic functional [16],

$$\int \exp\left\{i\int_0^L \omega(s)\,\zeta(s)\,ds\right\} d\mu(\omega) = \exp\left\{-\frac{1}{2}\int_0^L \zeta^2(s)\,ds\right\}, \tag{7}$$

defined as the Fourier transform of $d\mu(\omega)$. With Eq. (7), we obtain from Eq. (6) the expression,

$$\begin{aligned} P(\xi_L, L; \xi_0, 0) &= \frac{1}{2\pi}\int_{-\infty}^{+\infty} dk\, \exp\{ik[(\xi_0-\xi_L)]\} \\ &\quad\times \exp\left\{\frac{-k^2/2}{e^{-2bsin(cL)}}\int_0^L \frac{[(L-s)s]^{\nu-1}}{csc(as)}ds\right\}. \end{aligned} \tag{8}$$

The integral over dk, recognized as a Gaussian integral, can be evaluated to yield,

$$\begin{aligned} P(\xi_L, L; \xi_0, 0) &= \left(\frac{2\pi}{e^{-2bsin(cL)}}\int_0^L \frac{(L-s)^{\nu-1}sin(as)}{s^{1-\nu}}ds\right)^{-\frac{1}{2}} \\ &\quad\times \exp\left(\frac{-e^{-2bsin(cL)}(\xi_L-\xi_0)^2}{2\int_0^L \frac{(L-s)^{\nu-1}sin(as)}{s^{1-\nu}}ds}\right). \end{aligned} \tag{9}$$

Finally, using Eq. (3.768.7) of reference [17], for Re $\nu > 0$, the integral over ds can be evaluated, i.e.,

$$\begin{aligned} \int_0^L (L-s)^{\nu-1}\frac{sin(as)}{s^{1-\nu}}ds &= \sqrt{\pi}\,\Gamma(\nu)\left(\frac{L}{a}\right)^{\nu-\frac{1}{2}} sin(aL/2) \\ &\quad\times J_{\nu-\frac{1}{2}}(aL/2), \end{aligned} \tag{10}$$

where $\Gamma(\nu)$ and $J_\nu(z)$ are the gamma function and Bessel function, respectively. The result Eq. (10), allows us to write a closed form of the probability density function from Eq. (9) as,

$$\begin{aligned} P(\xi_L, L; \xi_0, 0) &= \left(\frac{2\Gamma(\nu)sin\left(\frac{aL}{2}\right)J_{\nu-\frac{1}{2}}\left(\frac{aL}{2}\right)}{\pi^{-\frac{3}{2}}\left(\frac{L}{a}\right)^{\frac{1}{2}-\nu}e^{-2bsin(cL)}}\right)^{-\frac{1}{2}} \\ &\quad\times \exp\left[\frac{-\left(\frac{L}{a}\right)^{\frac{1}{2}-\nu}e^{-2bsin(cL)}(\xi_L-\xi_0)^2}{\sqrt{4\pi}\,\Gamma(\nu)sin\left(\frac{aL}{2}\right)J_{\nu-\frac{1}{2}}\left(\frac{aL}{2}\right)}\right]. \end{aligned} \tag{11}$$

As shown in the Appendix, the PDF Eq. (11) satisfies a modified diffusion equation.

We next use Eq. (11) to evaluate mean square deviations (MSD) for this stochastic process with, MSD $= \langle(\xi - \langle\xi\rangle)^2\rangle = \langle\xi^2\rangle - \langle\xi\rangle^2$, for the fluctuating variable ξ. An evaluation of the second moment,

$$\langle\xi^2\rangle = \int_{-\infty}^{+\infty} \xi^2\, P(\xi, L; \xi_0, 0)\, d\xi$$

yields,

$$\langle\xi^2\rangle = \xi_0^2 + \frac{\sqrt{\pi}\,\Gamma(\nu)}{e^{-2bsin(cL)}}\left(\frac{L}{a}\right)^{\nu-\frac{1}{2}} sin\left(\frac{aL}{2}\right)J_{\nu-\frac{1}{2}}\left(\frac{aL}{2}\right), \tag{12}$$

where we used Eq. (3.462.8) of reference [17]. With this, the MSD becomes, (with, $\langle\xi\rangle = \xi_0$),

$$\text{MSD} = \sqrt{\pi}\,\Gamma(\nu)\left(\frac{L}{a}\right)^{\nu-\frac{1}{2}} e^{2bsin(cL)} sin\left(\frac{aL}{2}\right)J_{\nu-\frac{1}{2}}\left(\frac{aL}{2}\right). \tag{13}$$

As an illustrative example, plots of Eq. (13) for the Hurst-like diffusive index $\nu = 0.55$, characteristic length $a = 0.0008$, expansion rate $b = 0.35$, characteristic frequency $c = 0.0041$ (solid line) and $c = 0$ (dashed line) are shown in Fig. 1. Application of this sinusoidally modified fluctuation can be done for diffusion coefficients of proteins of various lengths as shown in the next section.

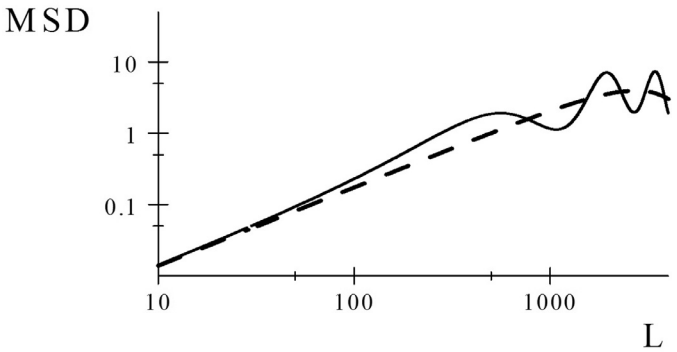

Fig. 1. Log-log graph of MSD versus L for $\nu = 0.55$, $a = 0.0008$, and $b = 0.35$. Solid line: $c = 0.0041$; dash line: $c = 0$.