

## Subdiffusion in time-averaged, confined random walks

Thomas Neusius,<sup>1</sup> Igor M. Sokolov,<sup>2</sup> and Jeremy C. Smith<sup>1,3</sup>

<sup>1</sup>Computational Molecular Biophysics, Universität Heidelberg, Im Neuenheimer Feld 368, D-69120 Heidelberg, Germany

<sup>2</sup>Institut für Physik, Humboldt-Universität zu Berlin, Newtonstraße 15, D-12489 Berlin, Germany

<sup>3</sup>Center for Molecular Biophysics, Oak Ridge National Laboratory, P.O. Box 2008, Oak Ridge, Tennessee 37831-6164, USA

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Certain techniques characterizing diffusive processes, such as single-particle tracking or molecular dynamics simulation, provide time averages rather than ensemble averages. Whereas the ensemble-averaged mean-squared displacement (MSD) of an unbounded continuous time random walk (CTRW) with a broad distribution of waiting times exhibits subdiffusion, the time-averaged MSD,  $\overline{\delta^2}$ , does not. We demonstrate that, in contrast to the unbounded CTRW, in which  $\overline{\delta^2}$  is linear in the lag time  $\Delta$ , the time-averaged MSD of the CTRW of a walker confined to a finite volume is sublinear in  $\Delta$ , i.e., for long lag times  $\overline{\delta^2} \sim \Delta^{1-\alpha}$ . The present results permit the application of CTRW to interpret time-averaged experimental quantities.

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The continuous-time random walk (CTRW), in which the walker waits a time,  $\tau$ , between two successive jumps, taken from a waiting-time probability density (WTD),  $w(\tau)$ , has been studied for many years and has proved useful in describing a variety of diffusive processes in physics [1,2]. A CTRW with a long-tailed waiting-time distribution and a finite jump-length variance is a nonergodic process [3,4] and hence ensemble averages and time averages are, in general, different. Although many types of experimental measurement provide ensemble averages, certain techniques provide time series, such as, for example, molecular dynamics (MD) simulations of a protein molecule or single-particle tracking. Time averages are then required to extract statistically significant properties from the data. Therefore, the question has arisen as to how the time-averaged properties of CTRW processes behave [4–7].

A quantity of principal interest in the context of random walks is the mean squared displacement (MSD),  $\langle x^2(\tau) \rangle$ . A classical unbounded random walker exhibits  $\langle x^2(\tau) \rangle = 2D\tau$ , where  $D$  is the diffusion constant. Random walks with  $\langle x^2(\tau) \rangle \sim \tau^\beta$  (with  $0 < \beta < 1$ ) are said to be *subdiffusive*.

If, at long  $\tau$ , the WTD of a CTRW has a power-law tail, i.e.,  $w(\tau) \sim \tau^{-1-\alpha}$ , with  $0 < \alpha < 1$ , and the variance of jump lengths is finite,  $\langle \delta x^2 \rangle < \infty$ , as is assumed throughout this paper, then the mean value of the WTD diverges, and hence the ensemble-averaged MSD becomes subdiffusive,  $\langle x^2(\tau) \rangle \sim \tau^\alpha$ , where, for analytical simplicity, the first jump is assumed to occur at  $\tau=0$  [2]. In contrast, when the MSD is calculated as a time average over the interval  $[0, t]$ , i.e.,

$$\overline{\delta^2}(\Delta, t) = \int_0^{t-\Delta} \frac{[x(\Delta + \tau_a) - x(\tau_a)]^2}{t - \Delta} d\tau_a, \quad (1)$$

in which  $\Delta$  denotes the lag time, i.e., the time period which elapses during the displacement from a given starting position, then the MSD of the unbounded CTRW is found to have a linear  $\Delta$  dependence as in a classical random walk [5–7]. However, there is a wide variety of physical cases where, rather than unbounded diffusion, distinct boundaries exist, and these can have critical effects on diffusive dynamics [8].

The very active field of single-particle tracking measures the time-averaged MSD. Further, confinement, which is the property investigated here, has been identified throughout the last years as of critical importance in experimental papers on single-particle diffusion in the cytoplasm [9], in the nucleus [10], in membranes [11], and narrow pores [12]. Other experiments and a large number of theoretical papers have also reported the relevance of confinement in diffusion [13].

A considerable body of theoretical work has been recently reported on the use of CTRW as a model for subdiffusion in the above and other experiments [5–7,14]. However, the effects of confinement need to be understood before CTRW can be applied at all to time-averaged quantities, such as those measured in single-particle tracking. This paper closes this conceptual gap.

In recent work, the time-averaged MSD of subdiffusive CTRWs,  $\overline{\delta^2}$ , was examined [5]. Results were presented for the free, unbounded CTRW and simulations performed of a one-dimensional CTRW with WTD exponent  $0 < \alpha < 1$  and reflecting boundary conditions [5]. The present report presents both analytical and extended simulation results that demonstrate that  $\overline{\delta^2}$ , on time scales where the boundary condition becomes important, exhibits a power-law  $\Delta$  dependence and follows  $\overline{\delta^2} \sim \Delta^{1-\alpha}$ , in contrast to  $\overline{\delta^2} \sim \Delta^\alpha$ , as suggested for intermediate time scales in Ref. [5]. Furthermore, the distribution of the random variable  $\overline{\delta^2}$  is discussed, allowing connection to be made with experiments. The critical time,  $\tau_c$ , at which the MSD turns over from linear to sublinear is determined. These findings will be required for any application of CTRW in modeling time-averaged quantities and in particular for the interpretation of single-particle tracking measurements.

Here, we assume the walker to be confined in the spatial interval  $[0, L]$ , and the following WTD is used:

$$w(\tau) = \frac{\alpha/\tau_0}{(1 + \tau/\tau_0)^{1+\alpha}}, \quad \text{with } 0 < \alpha < 1, \quad (2)$$

in which  $\tau_0$  is the unit time. Here, the jump length is a random variable with a standard normal distribution and statistical independence from the waiting time. The results found

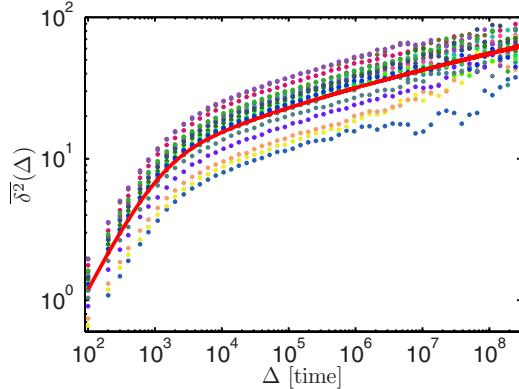


FIG. 1. (Color online) CTRW simulations. The results in Figs. 1–4 were obtained as follows. All CTRW simulations were started at  $x=0$  with an initial jump at  $\tau=0$ . The jump lengths were taken from a Gaussian distribution with variance  $\langle \delta x^2 \rangle = 1$ . The walker moves in the spatial interval  $[-10, 10]$ , i.e.,  $L=20$ , with reflecting boundaries. Uniformly distributed random numbers  $r \in (0, 1)$  were generated with the long-period random number generator of L'Ecuyer with Bays-Durham shuffle and added safeguards [16]. A random variable  $\tau_w$  with the distribution given in Eq. (2) can be obtained from the uniformly distributed  $r$  from the transformation  $\tau_w = r^{-1/\alpha} - 1$  [the time unit in Eq. (2) is  $\tau_0 = 1$  for all simulations]. Simulations were performed for  $\alpha = 0.3, 0.4, 0.5, 0.6, 0.7, 0.8$ , and  $0.9$  on various time scales ranging from  $t = 10^7$  up to  $10^{14}$ . Averages were taken over 1000 realizations for  $t = 10^7 - 10^{11}$  time units and over 100 realizations from  $10^{12}$  to  $10^{14}$  time units. In the figure above, the dotted lines are time-averaged MSD,  $\bar{\delta}^2(\Delta, t)$ , of individual realizations of CTRWs, all with  $\alpha = 0.9$ ,  $t = 10^9$ , and a reflecting boundary ( $L = 20$ ), such that  $\tau_c = 1.3 \times 10^3 \tau_0$ . Full line: mean  $\langle \bar{\delta}^2(\Delta, t) \rangle$  of 1000 of the above simulations.

using  $w(\tau)$  of Eq. (2) can be generalized to other normalizable forms of the WTD that have the same power-law tail; the results are also independent of the exact distribution of the jump lengths, as long as the mean equals zero and the variance is finite. The mean value  $\langle \cdot \rangle$  denotes a simultaneous average over both random variables, waiting time and jump length.

As a consequence of the divergent mean value of  $w(\tau)$ , a CTRW is a nonequilibrium process: there is no typical relaxation time scale. Due to the first jump being at  $\tau=0$ , ensemble-averaged CTRW dynamics are nonstationary and not invariant with time shifts [6,15].

In order to put the following theoretical considerations in this paper to the test, simulations were performed, the details of which are reported in the caption of Fig. 1. Individual  $\bar{\delta}^2$  of a confined CTRW simulation are illustrated in Fig. 1 together with an ensemble average over 1000 such time-averaged MSDs. The individual  $\bar{\delta}^2$  exhibit a common  $\Delta$  dependence, with a spread arising from the fact that time averages obtained from CTRW trajectories are random quantities [4,5]. Later, we also discuss the distribution of the time-averaged MSD,  $\bar{\delta}^2$ ; but first, we analyze the mean value,  $\langle \bar{\delta}^2 \rangle$ .

To understand the behavior of the ensemble averaged  $\langle \bar{\delta}^2 \rangle$  in Fig. 1, consider the displacement undergone between a time  $\tau_a$  and a later time  $\tau_a + \Delta$ . Starting the observation of the

walker at  $\tau_a > 0$  means that an initial waiting time,  $\tau$ , will elapse before the walker moves for the first time. We denote the distribution of these initial waiting times by  $w_1(\tau, \tau_a)$ . The process observed in the time interval  $[\tau_a, \tau_a + \Delta]$  is an *aging* CTRW (ACTRW), i.e., a time-shifted CTRW [15]. The theory of ACTRWs describes the process as a function of  $\tau_a$ . The initial waiting time was derived for  $\tau_a \gg \tau_0$  in Ref. [15] as

$$w_1(\tau, \tau_a) \approx \alpha \kappa_\alpha \frac{\tau_a^\alpha}{\tau^\alpha (\tau + \tau_a)}, \quad (3)$$

with the numerical factor  $\kappa_\alpha = \sin(\pi\alpha)/\pi\alpha$ . After the initial waiting time  $\tau$  has elapsed, the walker makes a first jump at  $\tau_a + \tau$  and its displacement from the present position,  $x(\tau_a)$ , after time  $\tau_a + \tau$  will exhibit the same statistical behavior as the displacement of a CTRW starting at  $\tau=0$  at  $x(0)=0$ . Therefore, the ensemble-averaged MSD in  $[\tau_a, \tau_a + \Delta]$  can be expressed as

$$\langle [x(\Delta + \tau_a) - x(\tau_a)]^2 \rangle = \int_0^\Delta d\tau w_1(\tau, \tau_a) \langle x^2(\Delta - \tau) \rangle, \quad (4)$$

in which  $\langle x^2(\tau) \rangle$  is the ensemble-averaged MSD of a confined CTRW from the origin in the time interval  $[0, \tau]$ . We will use the following approximation for  $\langle x^2(\tau) \rangle$  of a confined CTRW, which can be derived from the fractional diffusion equation (see a detailed derivation in the supplementary material [17])

$$\langle x^2(\tau) \rangle \approx \frac{L^2}{6} \left[ 1 - E_\alpha \left( -\frac{\tau^\alpha}{\tau_c^\alpha} \right) \right], \quad (5)$$

where  $E_\alpha$  is the Mittag-Leffler function and

$$\tau_c = \left( \frac{L^2}{12K_\alpha} \right)^{1/\alpha} \quad (6)$$

is the typical time at which the Mittag-Leffler function crosses from the stretched exponential short- $\tau$  behavior to the power-law long- $\tau$  domain. The generalized diffusion constant is calculated from the unit time  $\tau_0$  in Eq. (2) and the variance of the jump length distribution  $\langle \delta x^2 \rangle$  as  $K_\alpha = \langle \delta x^2 \rangle / 2\Gamma(1-\alpha)\tau_0^\alpha$  for the WTD in Eq. (2) [2]. In Eq. (5),  $\tau_c$  indicates the time after which the boundary condition becomes influential. It is assumed throughout this paper that  $\langle x^2(\tau) \rangle \ll L^2$  so that  $\tau_c \gg \tau_0$ . The approximation in Eq. (5) reproduces both the correct short- and long- $\tau$  asymptotics but is not exact in the crossover region,  $\tau \approx \tau_c$ .

Performing an ensemble average on both sides of Eq. (1) and noting that  $\langle \cdot \rangle$  can be swapped with the  $\tau_a$  integral, we find with Eq. (4)

$$\langle \bar{\delta}^2(\Delta, t) \rangle = \int_0^\Delta \bar{w}_1(\tau) \langle x^2(\Delta - \tau) \rangle d\tau, \quad (7)$$

where the notation  $\bar{w}_1(\tau)$  is used for the initial WTD averaged over  $\tau_a$  in the time interval  $[0, t - \Delta]$ . Assuming  $\Delta \ll t$ , the time averaging over  $\tau_a \in [0, t]$  can be performed in Eq. (3), giving for  $\tau \ll t$

$$\overline{w}_1(\tau) \approx \frac{\kappa_\alpha}{t^{1-\alpha}} \frac{1}{\tau^\alpha}. \quad (8)$$

Upon performing a Laplace transform,  $\Delta \rightarrow u$ , the convolution integral in Eq. (7) can be written as a product of the Laplace transforms of  $\overline{w}_1$  and the ensemble-averaged MSD

$$\langle \overline{\delta^2}(u, t) \rangle = \frac{L^2}{6} \frac{u^{\alpha-2}}{\Gamma(1+\alpha)t^{1-\alpha}} \frac{1}{1+(u\tau_c)^\alpha}, \quad (9)$$

where the Laplace transform,  $z \rightarrow s$ , of the Mittag-Leffler function,  $\mathcal{L}[E_\alpha(-\beta z^\alpha)](s) = 1/(s + \beta s^{1-\alpha})$ , has been used.

The derivation of Eq. (9) involved the approximation of  $\overline{w}_1(\tau)$  in Eq. (8), which is valid for  $\tau_0 \ll \tau \ll t$ , and the approximation of  $\langle x^2(\tau) \rangle$  in Eq. (5), which deviates from the exact behavior mainly around  $\tau_c$ . As an alternative to the above derivation of  $\langle \overline{\delta^2} \rangle$  from the initial WTD,  $\langle \overline{\delta^2} \rangle$  can be obtained also using the approach for continuous time Lévy flights introduced by Fogedby [18], leading to a splitting of the stochastic processes of a CTRW, the jump lengths and waiting times, both being two independent random variables. The supplementary material outlines how  $\langle \overline{\delta^2} \rangle$  can be calculated using such a splitting argument and the exact form of  $\langle \overline{\delta^2}(u, t) \rangle$  is derived [17].

Equation (9) can be evaluated for  $\tau_c^{-1} \gg u \gg t^{-1}$ , corresponding to the long- $\Delta$  behavior, and  $1 \gg u \gg \tau_c^{-1}$ , corresponding to the short- $\Delta$  behavior. In the former, long- $\Delta$  case, we find from  $\langle \overline{\delta^2}(u, t) \rangle \sim u^{\alpha-2}$  that

$$\langle \overline{\delta^2}(\Delta, t) \rangle \approx \frac{L^2}{6} \frac{\kappa_\alpha}{1-\alpha} \left( \frac{\Delta}{t} \right)^{1-\alpha}. \quad (10)$$

This equation describes the  $\Delta > 10^4$  behavior in Fig. 1.  $\langle \overline{\delta^2}(\Delta, t) \rangle$  can be obtained only for  $\Delta \leq t$ , and Eq. (10) is valid only for  $\tau_c \ll \Delta \ll t$ . As can be seen from the simulation results, for  $\Delta \leq t$  the time-averaged MSD does not reach a constant plateau (Fig. 2) and, independent of  $t$ , increases for all  $\Delta < t$ . However,  $\langle \overline{\delta^2} \rangle$  does not exceed  $L^2/6$ , as can be derived from Eq. (7) together with  $\langle x^2(\tau) \rangle \leq L^2/6$  [cf. Eq. (5)]. The inverse  $t$  dependence in Eq. (10), illustrated in Fig. 2, allows for an upper bound without a plateau for any observation time,  $t$ , an entirely nonergodic behavior. In comparison, the ensemble-averaged (not TA) MSD will asymptotically reach a plateau of  $L^2/6$ , according to Eq. (5).

The short- $\Delta$  behavior follows with  $\langle \overline{\delta^2}(u, t) \rangle \sim u^{-2}$  as

$$\langle \overline{\delta^2}(\Delta, t) \rangle \approx \frac{2K_\alpha}{\Gamma(1+\alpha)t^{1-\alpha}} \Delta. \quad (11)$$

Equation (11), valid for  $\tau_0 \ll \Delta \ll \tau_c$ , is the free unbounded CTRW result [5,7]: in the limit of short times (e.g., for  $\Delta < 10^3$  in Fig. 1) a random walker is not affected by the presence of the boundary.

The following interpolation between the short- and long- $\Delta$  domains can be performed

$$\langle \overline{\delta^2} \rangle = \frac{L^2}{6} \frac{\kappa_\alpha}{\bar{\alpha}} \left[ 1 - \exp \left( -\bar{\alpha} \frac{\Delta^\alpha}{\tau_c^\alpha} \right) \right] \frac{\Delta^{\bar{\alpha}}}{t^{\bar{\alpha}}}, \quad (12)$$

where  $\bar{\alpha} = 1 - \alpha$ .

Figures 1–3 illustrate that  $\langle \overline{\delta^2} \rangle$  exhibits free diffusional behavior for small  $\Delta$  but slows down when the walk is af-

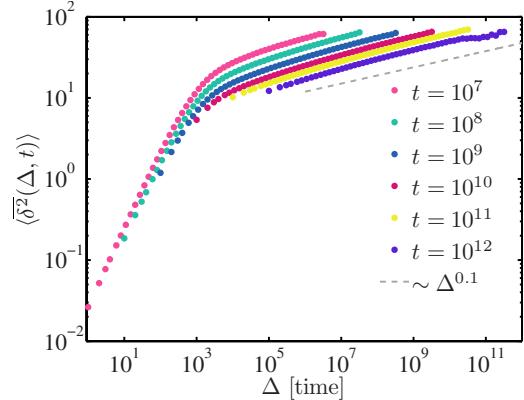


FIG. 2. (Color online) Simulation length ( $t$ ) dependence of  $\langle \overline{\delta^2} \rangle$  of a CTRW with exponent  $\alpha=0.9$  and reflecting boundary ( $L=20$ ). The averages are shown over 1000 CTRWs for total lengths,  $t$ , varying between  $10^7$  and  $10^{11}$  and 100 CTRWs for  $10^{12}$  time units ( $t$  increases from the left to the right). In order that each time series should contain the same number of points ( $10^7$ ), the time resolution of the longer simulations was reduced. Therefore, the short- $\Delta$  behavior of the MSDs of larger  $t$  is absent. The quasifree linear- $\Delta$  behavior breaks down when the boundary becomes sensed at  $\tau_c = 1.3 \times 10^3 \tau_0$ . A  $\Delta$ -sublinear MSD, i.e.,  $\sim \Delta^{1-\alpha}$ , is seen on longer time scales.  $\langle \overline{\delta^2} \rangle$  is bounded by the value  $L^2/6$ . For longer  $t$ ,  $\langle \overline{\delta^2} \rangle$  is shifted to smaller values but does not reach a constant plateau.

fected by the presence of the boundaries. All MSDs cross over from linear to sublinear  $\Delta$  dependence at the critical time,  $\tau_c$ . Figure 2 illustrates that, conforming to Eq. (6), the time  $\tau_c$  does not depend on the length of the simulation,  $t$ . In Fig. 3(A) the scaling with the length of the simulation,  $t$ , becomes apparent. When multiplied by  $t^{1-\alpha}$ , all the MSDs of each particular value of  $\alpha$  coincide and follow Eq. (12) as seen in Fig. 3(B).

The  $\langle \overline{\delta^2} \rangle \sim \Delta^{1-\alpha}$  behavior found in Eq. (10) contrasts with the  $\Delta^\alpha$  behavior found in Ref. [5], which arose from the fact that the time window, in which  $\sim \Delta^\alpha$  was fitted to  $\overline{\delta^2}$  in Ref. [5], was confined to times close to  $\sim \tau_c \approx 27\,000$ .

Experimental measurements provide typically a small number of individual  $\overline{\delta^2}$ , such that the statistics are insufficient to calculate  $\langle \overline{\delta^2} \rangle$ . Therefore, in order to apply the theory of the confined CTRW to experimental results rather than  $\langle \overline{\delta^2} \rangle$ , the distribution of the random variable  $\overline{\delta^2}$  is required. The random nature of  $\overline{\delta^2}$  is due to the fact that in the interval  $[0, t]$ , over which the time average is taken in Eq. (1), the number of jumps  $N$  is a random variable. The mean,  $\langle N \rangle$ , was derived in Ref. [19]. In Ref. [5], the distribution of  $\overline{\delta^2}$  was derived from the distribution of  $N$  for a given  $t$ . Note that the  $t$  scaling of the mean value,  $\langle \overline{\delta^2} \rangle \sim t^{\alpha-1}$  follows from Eq. (9) and is identical to the free unbounded CTRW in all cases [Eqs. (10)–(12)], as was found in [5,7]. Therefore, the same arguments as in Ref. [5] apply to the confined CTRW. In particular, as suggested for the free unbounded CTRW, the relative width of the distribution of  $\overline{\delta^2}$ ,

$$EB = \lim_{t \rightarrow \infty} \frac{\langle (\overline{\delta^2})^2 \rangle - \langle \overline{\delta^2} \rangle^2}{\langle \overline{\delta^2} \rangle^2} = \frac{2\Gamma^2(1+\alpha)}{\Gamma(1+2\alpha)} - 1, \quad (13)$$

measures the violation of the self-averaging property, which causes  $\overline{\delta^2}$  to be different from  $\langle \delta^2 \rangle$  for CTRWs with long-

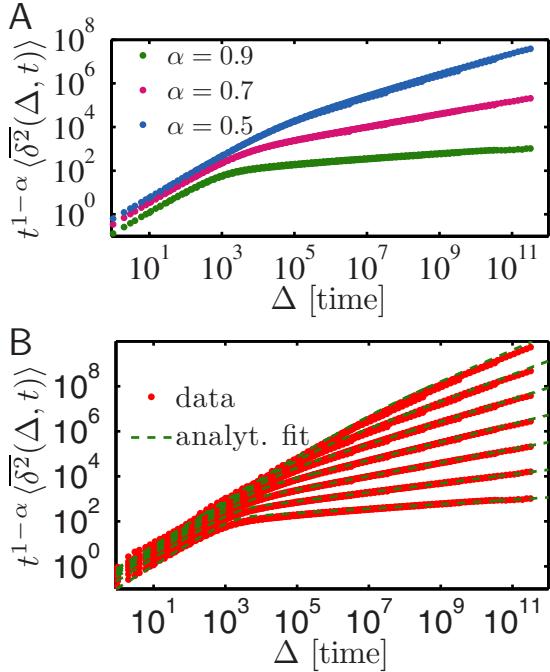


FIG. 3. (Color online) (A) Scaled, TA MSD,  $t^{1-\alpha} \langle \bar{\delta^2} \rangle$  of CTRWs with different  $\alpha=0.5, 0.7, 0.9$  (top down) and reflecting boundaries ( $L=20$ ) such that  $\tau_c$  has the values  $1.4 \times 10^4 \tau_0$ ,  $1.9 \times 10^3 \tau_0$ , and  $1.3 \times 10^3 \tau_0$ , respectively. For each  $t=10^7, 10^8, \dots$  up to  $10^{11}$  and each  $\alpha$ , 1000 simulations, (and for  $t=10^{12}$  to  $10^{14}$ , 100 simulations) were performed. The figure displays the average over the different time-averaged MSDs. (B) Fit of Eq. (12) to data of A (dotted), for the same and further exponents,  $\alpha=0.3, 0.4, 0.5, 0.6, 0.7, 0.8$ , and  $0.9$  (top down). The good fit to the simulation data of the analytical curve (dashed) demonstrates the validity of the approximations made in the derivation of Eqs. (10) and (11) and the usefulness of interpolation formula (12).

tailed WTD [1]: in the literature, the term *weak ergodicity breaking* has been established in recent years [3–5]. In Fig. 4, the simulation results for the parameter EB are shown. There is a good agreement with the prediction of Eq. (13) although the statistics in some cases is poor.

CTRW (or, equivalently, trapping) has been proposed as a model explaining subdiffusion in the internal dynamics of biomolecules [20]. However, in Ref. [6] it was shown that unbounded CTRW cannot account for the subdiffusive  $\bar{\delta^2}$  seen in MD simulations of single biomolecules. The simulations presented in Ref. [6] reach an equilibrium state, i.e.,  $\bar{\delta^2}$  saturates, reaching a constant value. In contrast, in the confined CTRW model,  $\langle \bar{\delta^2} \rangle$  does not saturate to a constant plateau. However, equilibrium would be reached on a time scale  $\tau > \tau_{\max}$ , were the WTD to possess a time,  $\tau_{\max}$ , below which (i.e.,  $\tau < \tau_{\max}$ ) Eq. (2) is followed but beyond which ( $\tau > \tau_{\max}$ ) the WTD decays faster than  $\tau^{-2}$ . In this case, for  $\tau < \tau_{\max}$  the process behaves as a CTRW, whereas for  $\tau > \tau_{\max}$  classical diffusion occurs. Subdiffusion is found on time scales  $\tau_c < \tau < \tau_{\max}$ , (i.e., times shorter than  $\tau_{\max}$  but long enough for the system to explore the accessible volume). For the time-averaged MSD it follows that for  $\Delta < \tau_c$  a linear  $\Delta$  dependence occurs.

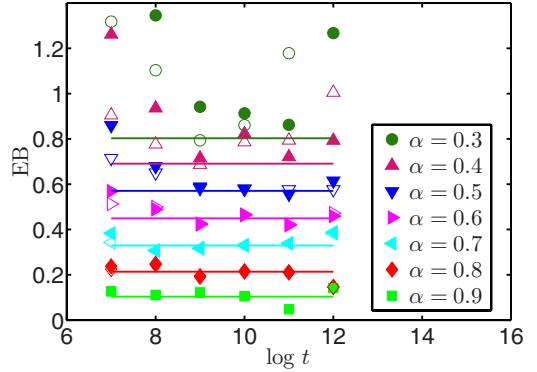


FIG. 4. (Color online) Ergodicity breaking parameter EB as a function of the observation time  $t$  (logarithmic scale) for various  $\alpha$  from 0.3 to 0.9 (top down, see legend). The parameter was calculated for  $\Delta=10^5$  (open markers) and  $\Delta=10^6$  (filled markers; if only filled marker is visible, both values coincide). The full lines indicate the prediction of Eq. (13). The ensemble average was performed over 1000 realizations for  $t=10^7, \dots, 10^{11}$  and 100 realizations for  $t=10^{12}$ .

Given the above considerations, the question arises as to whether the confined CTRW can describe the subdiffusive internal dynamics of biomolecules. To examine this, the time  $\tau_c$  can be estimated from the peptide simulation data in Ref. [6] together with Eq. (6). The required quantities are  $L$  obtained from the converged (equilibrium) value of the MSD,  $K_\alpha$ , estimated from short MD simulations with high time resolution and the exponent  $\alpha$  taken from the subdiffusive part of  $\bar{\delta^2}$ . It was found that  $\tau_c \gtrsim 100$  ns along the most diffusive principal component mode of the simulation [6], a value longer than the time scale (1 ps to 10 ns) over which the MSD is seen to be subdiffusive in the simulation. Hence, the CTRW model with reflecting boundaries cannot account for the subdiffusivity seen. In Ref. [6] an alternative explanation for the subdiffusivity was proposed, involving the fractal geometry of the energy landscape explored.

A CTRW with the WTD from Eq. (2) is inherently a non-equilibrium process due to the absence of a characteristic relaxation time. The present work demonstrates that a CTRW with reflecting boundaries exhibits a  $\langle \bar{\delta^2} \rangle$  with linear  $\Delta$  dependence up to a critical time,  $\tau_c$ , which depends only on the accessible space and the exponent  $\alpha$  in Eq. (2). Beyond  $\tau_c$  the boundary becomes influential and  $\langle \bar{\delta^2} \rangle$  has a sublinear  $\Delta$  dependence, i.e.,  $\langle \bar{\delta^2} \rangle \sim \Delta^{1-\alpha}$ . The theoretical behavior of the  $\langle \bar{\delta^2} \rangle$  is analyzed, the relative width of the distribution of  $\bar{\delta^2}$  is determined, and the results corroborated by extensive computer simulations. The present theory paves the way for the application of CTRW to time-averaged quantities in the presence of distinct boundaries and is therefore expected to be of wide applicability in the analysis and interpretation of experimental and simulation derived time series involving confined diffusive processes.

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