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The role of ergodicity in anomalous stochastic processes: analysis of single-particle trajectories

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Abstract

Single-particle experiments produce time series $x(t)$ of individual particle trajectories, frequently revealing anomalous diffusion behaviour. Typically, individual $x(t)$ are evaluated in terms of time-averaged quantities instead of ensemble averages. Here we discuss the behaviour of the time-averaged mean squared displacement of different stochastic processes giving rise to anomalous diffusion. In particular, we pay attention to the ergodic properties of these processes, i.e. the (non)equivalence of time and ensemble averages.

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(Some figures may appear in colour only in the online journal)

1. Introduction

In 1908, Jean Perrin, as part of his endeavour to determine Avogadro's number, published his seminal experiments on the Brownian motion of small putty grains in an aqueous solution [1]. Perrin's analysis was based on a large number of such single-particle trajectories. As each trajectory was comparatively short, he used an ensemble average over many trajectories to obtain reliable statistics. The disadvantage was that this ensemble average had to be taken over not completely identical particles, thus adding an error to his results that was difficult to gauge. A few years later, in 1914, it was Ivar Nordlund who came up with the idea to record the Brownian motion of a single mercury drop sedimenting in an aqueous solution through projection on a moving film [2]. His technique allowed him to extract meaningful results from individual single trajectories by performing a *single trajectory time average*.

The key to Nordlund's approach is Boltzmann's ergodic hypothesis, a simplistic explanation of which is given in figure 1. With respect to the single-particle trajectories recorded by Perrin and Nordlund this means that the ensemble average over a large number of particles is equal to the long-time average taken over the trajectory of a single particle. For the concrete example of free Brownian motion ergodicity

can be shown as follows [3]. The ensemble-averaged mean-squared displacement (MSD) is calculated as spatial average

$$\langle x^2(t) \rangle = \int_{-\infty}^{\infty} x^2 P(x, t) dx = 2K_1 t \quad (1)$$

over the probability density function (PDF) $P(x, t)$ to find the particle at position x at time t in an unbounded domain. The diffusion coefficient K_1 has the dimension of length² per time. Here and in the following, for convenience we restrict our discussion to one dimension; generalization to higher dimensions is straightforward. Sampling the position of many particles as a function of time, one may reconstruct the PDF $P(x, t)$ and then calculate the spatial average over x^2 . Alternatively, from the measurement of a single trajectory $x(t)$ one may calculate the time-averaged MSD

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

where Δ is the so-called lag time and T the overall measurement time. To obtain a unique, smooth result also at finite measurement times, one may average $\overline{\delta^2(\Delta, T)}$ over

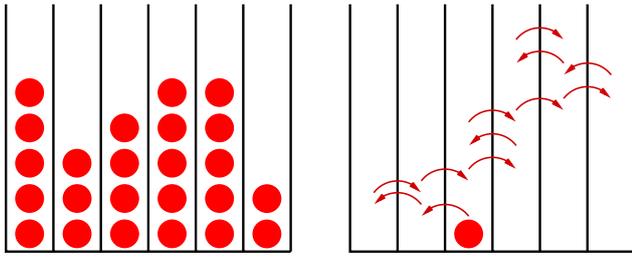


Figure 1. Ergodic hypothesis: distributing a large amount N of identical particles randomly into various boxes, the probability of occupation in box i is given by the ratio $\langle p \rangle_i = N_i/N$ of particles in the box versus N . According to the ergodic hypothesis $\langle p \rangle_i$ is the same as the fraction of time $\bar{p}_i = t_i/t$ during the overall experimental time t spent in a given box by a single particle that is hopping randomly between the boxes: $\lim_{N \rightarrow \infty} \langle p \rangle_i = \lim_{t \rightarrow \infty} \bar{p}_i$. The ensemble mean is the same as the time average if only the number of particles and the averaging time are sufficiently large.

many trajectories,

$$\begin{aligned} \overline{\langle \delta^2(\Delta, T) \rangle} &= \frac{1}{N} \sum_{i=1}^N \overline{\delta_i^2(\Delta, T)} \\ &= \frac{1}{T - \Delta} \int_0^{T-\Delta} \langle [x(t+\Delta) - x(t)]^2 \rangle dt. \end{aligned} \quad (3)$$

We can write the average $\langle [x(t+\Delta) - x(t)]^2 \rangle$ over the square particle position as the typical square length $\langle \delta x^2 \rangle$ of an individual jump times the number of jumps performed during the time interval $(t, t+\Delta)$. On average, the latter is given by the lag time Δ divided by the typical time τ per jump. Then, identifying $K_1 = \langle \delta x^2 \rangle / [2\tau]$ in the typical random walk sense, we find that

$$\overline{\langle \delta^2(\Delta, T) \rangle} = 2K_1\Delta = \langle x^2(\Delta) \rangle. \quad (4)$$

Brownian motion is thus ergodic in the above sense. For long measurements of Brownian motion the number of jumps self-averages and we can write $\overline{\delta^2(\Delta, T)} = \langle x^2(\Delta) \rangle$.

1.1. Single-particle tracking and anomalous diffusion

Today, single-particle tracking has advanced into a standard tool for probing the motion of tracers in a large number of systems, in particular in microscopic systems such as biological cells. In many cases, one observes anomalous diffusion of the subdiffusive form [4, 5]

$$\langle x^2(t) \rangle \simeq K_\alpha t^\alpha, \quad 0 < \alpha < 1, \quad (5)$$

where the physical dimension of the generalized diffusion coefficient is length² per time ^{α} .

Examples of such subdiffusion include the motion of single RNA molecules and DNA chromosomal loci [6, 7], or lipid granules and viruses [8, 9] in the cytoplasm of living bacteria and yeast cells. Similarly, one finds subdiffusion of eukaryotic telomeres [10] or of membrane proteins [11, 12]. Such results are consistent with control experiments in crowded protein or dextran solutions [13, 14], or in reconstituted actin networks [15]. Anomalous diffusion of single particle time averages also occurs in large scale

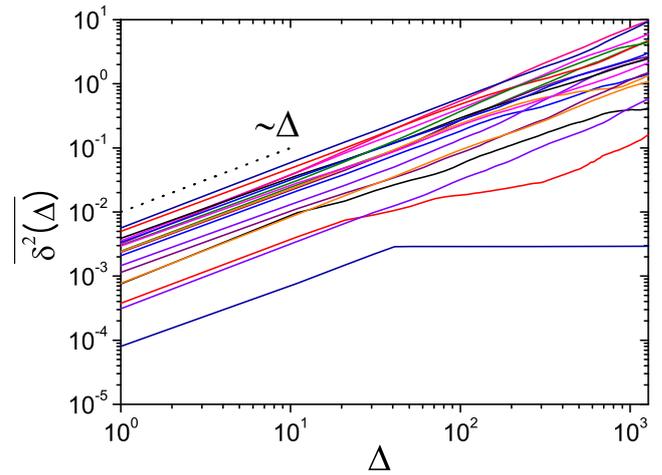


Figure 2. Trajectory–trajectory scatter of the time-averaged MSD for different realizations of a free CTRW process with waiting time distribution (6) with $\alpha = 0.5$. The amplitude scatter as well as local variations in the slope within individual trajectories mirror the influence of a single or a few long waiting times, see text.

computer simulations, see, for instance, [16]. On somewhat larger scales subdiffusion occurs for the motion of single bacteria in a biofilm [17]. Common to most of these examples is, furthermore, a pronounced amplitude scatter between the time-averaged MSD $\overline{\delta^2(\Delta, T)}$ of individual particle trajectories, compare figure 2.

Anomalous diffusion is no longer universally described by a Gaussian PDF of the walker. In fact there exist several classes of stochastic processes giving rise to anomalous diffusion. As shown here the resulting subdiffusive dynamics is not always ergodic.

2. Continuous time random walk (CTRW) subdiffusion: weak ergodicity breaking

One of the best-known theories for describing subdiffusion of form (5) is the Scher–Montroll CTRW [18, 19]. In this model, a random walker after each jump becomes immobilized for a random waiting time t before it is allowed to jump again. The waiting times are independent and identically distributed according to the waiting time PDF $\psi(t)$. If the latter is of power-law form as originally proposed by Scher and Montroll [18],

$$\psi(t) \simeq \frac{\tau^\alpha}{t^{1+\alpha}}, \quad 0 < \alpha < 1, \quad (6)$$

the process possesses a diverging mean waiting time, $\int_0^\infty t\psi(t) dt \rightarrow \infty$. This scale-free property indeed leads to the subdiffusive form of the ensemble averaged MSD (5) [18, 19]. Due to this lack of time scale, one can no longer distinguish the duration of a single or a few jump events from the limit of many jumps, as now extreme events may occur such that single waiting times become of the order of the entire process time. Indeed, for free CTRW subdiffusion the time-averaged MSD for $\Delta \ll T$ becomes [20, 21]

$$\overline{\langle \delta^2(\Delta, T) \rangle} = 2K_\alpha \frac{\Delta}{\Gamma(1+\alpha)T^{1-\alpha}}, \quad (7)$$

which clearly differs from the ensemble result (5). For processes with diverging characteristic waiting time the inequivalence of time and ensemble averages is commonly referred to as weak ergodicity breaking [22, 23]. Interestingly, the lag time dependence deceptively suggests normal diffusion, and the process' anomaly is only visible in the measurement time (T) dependence: on continuation of the process over increasingly long times, longer and longer waiting times occur, leading to increased immobilization of the diffusing particle.

The second effect of the scale-free waiting time distribution is shown in figure 2: indeed the amplitudes of individual trajectories exhibit a pronounced scatter, as seen in experiments. Introducing the dimensionless variable $\xi = \delta^2(\Delta, T) / \langle \delta^2(\Delta, T) \rangle$, the distribution $\phi_\alpha(\xi)$ for CTRW subdiffusion assumes a one-sided Lévy stable form [20]. For instance, for the case $\alpha = 1/2$ it possesses the Gaussian form

$$\phi_{1/2}(\xi) = \frac{2}{\pi} \exp\left(-\frac{\xi^2}{\pi}\right), \quad (8)$$

which implies that there is a finite amount of probability at $\xi = 0$, i.e. there exist realizations for which the particle does not move at all during the measurement. Only in the Brownian limit $\alpha = 1$, we attain ergodic behaviour, $\phi_1(\xi) = \delta(\xi - 1)$ such that for sufficiently long measurements different realizations behave uniformly (self-averaging). Note that an identical result for the scatter distribution $\phi(\xi)$ was found for biased motion [20], and drift-diffusion in a periodic potential [24]. Recently, it was shown that this is a very generic property of CTRW subdiffusion, as the ratio $\delta^2(\Delta, T) / \langle \delta^2(\Delta, T) \rangle$ is proportional to the number $n(T)$ of performed jumps in the corresponding interval, $n(T) / \langle n(T) \rangle$ [27].

For confined CTRW subdiffusion two more remarkable features have been revealed. First, once the particle engages in the confinement of the potential the time-averaged MSD does not converge to a plateau but exhibits the scaling [28] (compare also [29])

$$\overline{\delta^2(\Delta, T)} \sim \left(\langle x^2 \rangle_{\text{B}} - \langle x \rangle_{\text{B}}^2 \right) \frac{2 \sin(\pi\alpha)}{(1-\alpha)\pi\alpha} \left(\frac{\Delta}{T} \right)^{1-\alpha} \quad (9)$$

within the limits $\Delta \ll T$ and $\Delta \gg (1/[K_\alpha \lambda_1])^{1/\alpha}$. Here λ_1 is the lowest non-zero eigenvalue of the Fokker–Planck operator in the external potential, a measure of when the confinement becomes relevant. The above form for the time-averaged MSD is universal in the sense that only the prefactor depends on the specific choice of the external potential $V(x)$, through the moments of the associated Boltzmann distribution, $\langle x^j \rangle_{\text{B}} = \int x^j \exp(-V(x)/[k_{\text{B}}T]) dx / \mathcal{Z}$. Here the normalization is given in terms of the partition $\mathcal{Z} = \int \exp(-V(x)/[k_{\text{B}}T]) dx$. The second remarkable property is that while in a CTRW all jumps are independent and thus for free motion the velocity autocorrelation vanishes, under confinement such correlations do occur [3]: the velocity autocorrelation attains a negative value, with a slow power-law recovery back to zero value, and through fitting from data is practically indistinguishable from the velocity autocorrelation of the fractional Brownian motion (FBM)/fractional Langevin equation (FLE) motion discussed below.

2.1. Ageing behaviour of the time-averaged MSD

CTRW subdiffusion displays ageing effects [25, 26]: ensemble-averaged correlation functions of observables, taken at two times t_2 and t_1 , are no longer solely functions of the time difference, $|t_2 - t_1|$. With this breakdown of stationarity, the statistical properties of such systems are no longer time translation invariant. While many experiments and simulations initiate the system at the same time as they start recording the trajectories, this is not always the case. Assume that the system was prepared at $t = 0$ but the time series $x(t)$ is recorded from $t_{\text{a}} > 0$. Then we can show that the time-averaged MSD experiences a correction in the form of a universal prefactor [27]

$$\Lambda_\alpha(t_{\text{a}}/T) = \left(1 + \frac{t_{\text{a}}}{T}\right)^\alpha - \left(\frac{t_{\text{a}}}{T}\right)^\alpha, \quad (10)$$

which exclusively depends on the ratio of ageing time t_{a} to measurement time T . The entire lag time dependence of the time-averaged MSD remains unaltered by the ageing of the process, this statement remaining valid for a large class of physical observables [27].

A remarkable property of ageing is that the probability that the random walker performs no jumps at all during the measurement time of the process increases with the ageing time. A consequence is that the trajectory–trajectory-averaged time-averaged MSD from experiment does not take into account completely stalled trajectories, and its value would thus differ from the theoretically calculated one [27]. Awareness of this fact is vital to properly extract the anomalous diffusion constant and other quantities from single-particle tracking data falling into the class of CTRW subdiffusion.

3. FBM/FLE motion: ergodic, and still not

3.1. Fractional Brownian motion

In contrast to the CTRW process, in which each jump is independent of the previous one, FBM is strongly correlated. Originally discussed by Kolmogorov [30] and brought to fame by Mandelbrot and van Ness [31], free FBM is defined in terms of the Langevin equation

$$\frac{dx(t)}{dt} = \zeta(t). \quad (11)$$

If the motion occurs in the presence of an external potential $V(x)$, the corresponding force $-V'(x)$ is added to the right-hand side. The process is fuelled by stationary, fractional Gaussian noise $\zeta(t)$ of zero mean and autocorrelation

$$\langle \zeta(t)\zeta(t') \rangle \sim \alpha K_\alpha (\alpha - 1) |t - t'|^{\alpha-2}. \quad (12)$$

For subdiffusion the noise correlator is negative, sometimes referred to as anti-correlation.

FBM is ergodic in the sense that for free motion the time-averaged MSD is

$$\overline{\delta^2(\Delta, T)} = 2K_\alpha \Delta^\alpha, \quad (13)$$

i.e. we find an equivalence to expression (5). The above equality also holds for a single trajectory as long as T is sufficiently large; see also [32]. Under confinement the time-averaged MSD for FBM saturates to a plateau [33]. The distribution of trajectory-to-trajectory amplitude fluctuations of the time-averaged MSD is Gaussian, its width decreasing with increasing measurement time [34].

3.2. Fractional Langevin equation motion

In definition (11) of FBM, the process is fed by external noise, which directly drives the velocity \dot{x} . If the noise is to be considered as internal and consequently the fluctuation dissipation theorem needs to be fulfilled, we arrive at the FLE [35]

$$m \frac{d^2x(t)}{dt^2} = -\gamma \int_0^t |t-t'|^{\alpha-2} \frac{dx(t')}{dt'} dt' + \sqrt{\frac{\gamma k_B \mathcal{T}}{\alpha(\alpha-1)K_\alpha}} \zeta(t), \quad (14)$$

where again $\zeta(t)$ is fractional Gaussian noise, m the particle mass and γ the friction coefficient. To produce subdiffusive motion in the case of the FLE, the noise (12) needs to be positively correlated, with $1 < \alpha < 2$ [36]. FLE motion turns over from ballistic behaviour $\langle x^2(t) \rangle \simeq t^2$ to subdiffusion of form (5) with exponent $2 - \alpha$ in the overdamped limit. In the latter, FLE motion fulfils the same properties as FBM motion [37].

The velocity autocorrelation for an arbitrary time interval δt ,

$$C_{\delta t}(t) = \frac{\langle [x(t+\delta t) - x(t)] \cdot [x(\delta t) - x(0)] \rangle}{\delta t^2} \quad (15)$$

for FBM in free space becomes [3]

$$\frac{C_{\delta t}(t)}{C_{\delta t}(0)} = \frac{|t+\delta t|^\alpha - 2t^\alpha + |t-\delta t|^\alpha}{2\delta t^\alpha}. \quad (16)$$

Here, we used the normalized version, which does not have any free fit parameter, once δt is set and α known from the measurement of the MSD. For free FLE motion a closed-form result involves the generalized Mittag-Leffler functions [37]. However, in the overdamped limit, it reduces exactly to the form (16).

That FBM as well as FLE motion are not entirely benign with respect to their ergodic behaviour was demonstrated recently [38]: accordingly, the relaxation behaviour to the stationary limit under confinement is different for time and ensemble averages of the MSD. While the ensemble average displays the conventional exponential relaxation due to the confinement, the time average relaxes in power-law form. To determine properly the relaxation times from experiment it is imperative to have detailed knowledge about this relaxation behaviour.

4. Correlated CTRW motion

It is not always justified to assume complete independence of successive jumps in a CTRW process. Thus diffusion in inhomogeneous materials, the random walks of humans or

animals or financial market dynamics involve correlations; see, e.g., the recent discussion in [39]. At the same time, fractional Gaussian noise involves a very specific type of correlation. As an alternative one may consider CTRW processes with built-in correlations. A quite flexible way of introducing correlations into CTRW motion was discussed recently. Thus successive waiting times are assumed correlated such that waiting time τ_i corresponds to waiting time τ_{i-1} plus a small increment, ξ_i . The increments may be positive or negative. Successive waiting times are thus correlated, short ones following similarly short ones, and vice versa. The concept in fact corresponds to a random walk in the space of waiting times. We write the current waiting τ_i time as [40–42]

$$\tau_i = \left| \xi_1 + \xi_2 + \dots + \xi_{i-1} \right|. \quad (17)$$

For the distribution of the ξ_i we may choose a symmetric Lévy stable law, defined through its Fourier transform as $\exp(-c_\gamma |k|^\gamma)$. The process then reproduces equation (5) with $\alpha = \gamma/(1 + \gamma)$, whose range spans from 0 to 2/3 [40, 41]. In the limit $\gamma = 2$ the mode relaxation is stretched exponential, $P(k, t) \simeq \exp(-ct^{1/2})$, whereas for $0 < \gamma < 2$ it is of power-law form, $\simeq t^{-\gamma}$ [42].

Due to the absolute value in definition (17), the mean waiting time is constantly growing towards larger values, diverging for long process times. The correlated CTRW process indeed exhibits violation of ergodicity [42],

$$\left\langle \overline{\delta^2(\Delta, T)} \right\rangle \simeq \frac{\Delta}{T^{1-\gamma/(1+\gamma)}}, \quad (18)$$

such that the range of the ageing exponent $1 - \gamma/(1 + \gamma)$ is in between 1/3 and 1, and is thus more pronounced than for the case of uncorrelated CTRW motion. Moreover, the process ages, as shown via the decaying response of the process to a sinusoidal driving force [42].

5. Discussion

Anomalous diffusion processes such as CTRW and FBM/FLE motion have been around for a considerable time. But only now, prompted by single-particle tracking techniques revealing anomalous diffusion, scientists realise the need to understand not only the ensemble average but also time averages of physical quantities. In this paper, we summarized recent findings in this field, some of which are *a priori* quite surprising, in particular, the occurrence of ergodicity breaking in the sense of the inequivalence of ensemble and time averages.

It is important to tell which stochastic mechanism underlies the dynamics of a given system. Thus CTRW subdiffusion leads to increased immobilization and weakly nonergodic volume–surface exchange [43, 44]. The corresponding first passage behaviour, due to the very nature of the waiting time statistics, is characterized by diverging mean first passage times, even in finite domains [5, 45]. However, these diverging characteristic time scales can be mended by the introduction of a cut-off in the distribution of waiting times [8]. Interestingly, while this measure disposes of the ageing and broad scatter properties, it maintains the weakly nonergodic behaviour of the time-averaged MSD [8].

FBM/FLE motion, in contradistinction, has finite mean first passage times on bounded domains (see [46] and references therein). At the same time, it has an increased recurrence and thus samples the volume more efficiently within local domains. Physically, both processes are very different, and so are all the secondary processes predicted from the corresponding stochastic theory. Anomalous diffusion on fractal supports such as critical percolation clusters [47] is not discussed here; however, it shares many common features with FBM/FLE motion [48].

How can one distinguish different stochastic mechanisms? While all of the mechanisms share the same scaling of the MSD (5), complementary quantities may well set the mechanisms apart. Thus one may consider as diagnosis tools the velocity autocorrelation function [3], moment ratios of the form $\langle x^4(t) \rangle / \langle x^2(t) \rangle^2$ for the particle position x and the mean maximal excursions at a given time [49], or the p -variation method [50]. Combining as many such methods as possible increases the likelihood to unambiguously determine a stochastic process for given sets of data.

Subdiffusion does not necessarily mean less efficient dynamics of the associated processes. Thus it has been argued that subdiffusion would foster diffusion-limited chemical reactions, as the reactants after their first encounter do not escape each other too quickly and thus have a chance for additional encounters until the reaction is complete [6, 51]. Moreover, subdiffusion could assist in dynamic localization of objects, making physical separation of domains unnecessary [10]. Finally, recent scenarios show that in more complicated biochemical contexts subdiffusion would indeed be the reasonable choice for the system [52, 53]. Anomalous diffusion in the context of single-particle tracking experiments in biological cells is discussed in [54].

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