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# Gaussianity Fair: The Riddle of Anomalous yet Non-Gaussian Diffusion

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Single particle tracking has become a standard method, especially in biophysics (1,2). With superresolution microscopy, the motions of even individual molecules in a live cell are routinely tracked (1–3). The monitored dynamics provides important clues on the interactions of the probe particle with the intracellular environment.

The results from such studies are quite remarkable. First, they demonstrate the existence of anomalous particle diffusion of the form $\langle \mathbf{r}^2 \rangle \simeq t^\alpha$ with $\alpha \neq 1$ at often macroscopic times (1,2). Second, the observed motion may turn out to be pronouncedly nonstationary: this causes the time-averaged mean squared displacement $\overline{\delta^2}$, typically evaluated from measured time series of the particle trajectories, to behave fundamentally differently from the ensemble analog $\langle \mathbf{r}^2 \rangle$ (4,5). In addition to this, subdiffusive particle motion may exhibit aging, that is, its dynamics changes over time: typically, the particle slows down in the sense that in $\overline{\delta^2}$ the effective diffusivity decays with the trace length $t$ (5,6). However, in the strongly nonequilibrium setting of biological cells, reinforcing aging may also emerge, when the power of the $t$ dependence is positive. The inequivalence $\overline{\delta^2} \neq \langle \mathbf{r}^2 \rangle$ and aging is not universal but is revealed in a growing number of systems.

The observation of anomalous diffusion and the nonstationary behavior of the tracer dynamics in biological systems calls for better strategies to infer the relevant information from measured particle trajectories. Many groups worldwide are working on this point, and many promising, complementary data analysis methods have already been developed; see, for instance, Metzler et al. (2,6).

Concurrently, new surprises keep coming. One phenomenon that is stirring up the field of particle tracking and stochastic process theory is so-called "Brownian yet non-Gaussian dynamics" (7). Reported from a large number of soft matter and biologically relevant systems, this term was coined to classify dynamics combining a linear growth in time of the mean squared displacement, $\langle \mathbf{r}^2 \rangle \simeq t$, with the observation of non-Gaussian probability density functions $P(r,t)$ for the particle spread. Over the whole measured time and spatial range, or intermittently in $r$ or $t$, one extracts the exponential form $P(r,t) \simeq \exp(-r/\lambda(t))$ with the decay length $\lambda(t)$ (7). Note that similar behavior occurs in glassy systems (8).

For a spatially and temporally homogeneous system the central limit theorem enforces the Gaussianity of $P(r,t)$, so this homogeneity needs to be broken somehow. Brownian yet non-Gaussian dynamics was explained theoretically first in terms of an exponential distribution of diffusivities $p(K)$, over which a single Gaussian $G(r,t) = (4\pi K t)^{-d/2} \exp(-r^2/[4Kt])$, $d$ denoting spatial dimension, is averaged, resulting in $P(r,t) = \int_0^\infty p(K) G(r,t) dK$ (7). This is but the by-now classical idea of superstatistics (9). Other approaches to describe this phenomenon assume a diffusing diffusivity, such that on its trajectory the particle experiences a perpetually changing diffusivity (10,11). In this model at longer times the diffusivity averages to an effective value $\langle K \rangle$, and the Gaussianity of the motion is restored, as shown by simulations in Chubynsky and Slater (10). A recent analytical study reconciles the diffusing diffusivity picture with a subordination approach as well as the superstatistical description (12). In particular, it is shown in Chechkin et al. (12) that the distribution $p(K)$ corresponds to the short time behavior of the particle motion, while a crossover to a Gaussian behavior with effective $\langle K \rangle$ is derived.

The careful study by Lampo et al. (3) now examines anomalous yet non-Gaussian dynamics by detailed single particle tracking experiments, tracing the motion of single protein-labeled messenger RNA molecules in living *E. coli* and *S. cerevisiae cells*. The authors collect evidence for the variation of the local diffusion coefficient within individual mRNA trajectories as well as a significant distribution of effective

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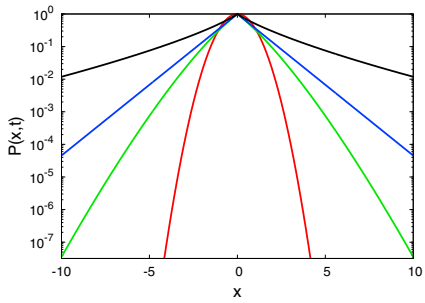


FIGURE 1 Probability density function $P(r,t)$ obtained from the diffusivity distribution $p(K_\alpha)$. (*Top* to *bottom*) The stretching exponent is $\delta = 2$, leading to a superstretched Gaussian (*black line*); $\delta = 1$, producing the Laplace distribution (*blue line*); and $\delta = 1/2$, leading to a stretched Gaussian (*green line*). A Gaussian is also shown, for comparison (*red line*). Plots obtained by numerical integration of $P(r,t)$ for $t = 1$ (a.u.). To see this figure in color, go online.

diffusivities in an ensemble of mRNA trajectories. The surprise here comes from the experimental fact that the motion of labeled mRNA in living cells has been described as "viscoelastic subdiffusion", a Gaussian process with anomalous timescaling, $G_\alpha(r,t) = (4\pi K_\alpha t^\alpha)^{-d/2} \exp(-r^2/[4K_\alpha t^\alpha])$ (6). The characteristic of this motion is the antipersistent displacement correlation shown, e.g., in Fig. S2b in Lampo et al. (3). However, the extended analysis by Lampo et al. (3) at longer times and, in particular, of the probability density $P(r,t)$, reveals that this is not the whole picture: deviations from the pure viscoelastic behavior with constant $K_\alpha$ appear, and $P(r,t)$ is a Laplace distribution. Averaging the Gaussian $G_\alpha(r,t)$ over an exponential distribution $p(K_\alpha)$ of the generalized diffusion coefficient $K_\alpha$, Lampo et al. (3) demonstrate that an exponential (Laplace) distribution for $P(r,t)$ with scaling variable $r/t^{\alpha/2}$ emerges, and indeed fits the data well. Thus, the diffusion of the mRNA is clearly impacted by the inhomogeneity of the medium. This is an important observation that will clearly influence the field and lead experimentalists to reexamine previously studied systems.

The simulations of protein crowded lipid bilayer membranes studied in Jeon et al. (13) demonstrate an even more intricate phenomenology. Namely, contrasting the viscoelastic behavior with Gaussian $G_\alpha(r,t)$ in the pure lipid bilayer, when protein crowding of the membrane becomes significant the resulting probability density of lipids turns out to be a stretched Gaussian, $P_\delta(r,t) \simeq \exp(-c[r/t^{\alpha/2}]^\delta)$, with values for the stretching exponent $\delta$ ranging from 1.3 to 1.6. This behavior can be shown to emerge from a nonexponential diffusivity distribution of the form $p(K_\alpha) \propto \exp(-[K_\alpha/K_\alpha^0]^\kappa)$, which leads to $P_\delta(r,t)$ with $\delta = 2\kappa/[1+\kappa]$ (12).

Fig. 1 shows a numerical evaluation of this scheme. Indeed, for $\kappa = 1$ the Laplace distribution consistently emerges, while for $\kappa$ smaller or larger than unity, the resulting probability density $P_\delta(r,t)$ is a stretched Gaussian or becomes even broader than the Laplace distribution (superstretched Gaussian). Exactly how, on a diffusing diffusivity level, such distributions enter the formalism, remains to be analyzed in detail. More generally, how non-Gaussian distributions come about from a potential conspiration of the central limit theorem and large deviations will be an issue of future research.

Results like those reported on Brownian yet non-Gaussian dynamics from numerous systems (see Wang et al. (7) and the references in Lampo et al. (3)) or generalizations of this effect as explored in Lampo et al. (3) and addressed above, make it clear that with our experimental and numerical resolution we need to consider explicit inhomogeneities in the systems we analyze, especially within biological cells or tissues. The theoretical framework for such inhomogeneous environments is currently being established. However, equally important is the awareness of looking for the right measures to explore the dynamic details of a systems. Just looking at the mean squared displacement is often insufficient. As shown in Lampo et al. (3), the displacement distribution function is an excellent quantity to analyze. There exists by now also a wide range of other analysis tools, for instance, the amplitude distribution of the time-averaged mean squared displacement $\overline{\delta^2}$ between individual trajectories, or the test whether the system is aging, and many others (2,6,13). Only a detailed analysis can guarantee that extracted parameters are physically meaningful.

Biological cells will keep us busy for some time to come. To understand the implications of the massive inhomogeneity of crowders, cytoskeleton, internal and external membranes, and charges (together with the strongly out-of-equilibrium character of many cellular processes), packaging the emerging sub- and superdiffusive patterns into a quantitative model of cells is a demanding task.

When I entered the field of stochastic processes many people thought that we are only left with improving details. However, the opposite is true. In these exciting days, novel experimental insights teach us that theorists actually have to sit down and come up with novel models to explain the richness of the systems of our interest. Experimentalists, keep reporting unexpected behaviors!

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