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Langevin equation in heterogeneous landscapes: how to choose the interpretation

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The Langevin equation is a common tool to model diffusion at a single-particle level. In non-homogeneous environments, such as aqueous two-phase systems or biological condensates with different diffusion coefficients in different phases, the solution to a Langevin equation is not unique unless the interpretation of stochastic integrals involved is selected. We analyze the diffusion of particles in such systems and evaluate the mean, the mean square displacement, and the distribution of particles, as well as the variance of the time-averaged mean-squared displacements. Our analytical results provide a method to choose the interpretation parameter from single particle tracking experiments.

Keywords: Heterogeneous diffusion process, Brownian motion, Liquid phase separation, Aqueous two-phase systems, Itô, Stratonovich

Diffusion is a fundamental process that is ubiquitous in physics, chemistry, and biology. The first successful attempts to understand such motion came from Einstein and, independently, from Smoluchowski, who described the probabilistic nature of Brownian motion [1, 2]. Shortly after these seminal works, Langevin introduced a single-particle formalism equivalent to Newton's second law of motion in the context of statistical physics [3]. The Langevin equation is a differential equation for the position $X(t)$ of a tracer particle that includes a random force $\xi(t)$ related to the interactions of the tracer with the particles forming the medium [4–6]. The strength of the random force is proportional to the square root of the diffusion coefficient D. Thus, a heterogeneous environment involving variations in local diffusivity yields local fluctuations in the random forces.

During the last decade, heterogeneous processes have received increased attention due to the broad use of single particle tracking methods and their sensitivity to probe local diffusive properties [7–22]. In particular, systems having a boundary that separates two liquid phases where particles have different diffusivities are gaining technological interest in food science, chemical synthesis, and biomedical engineering [23–25]. Aqueous two-phase systems are spontaneously formed by the separation of two incompatible polymers above a critical concentration. Their key property is that small molecules can diffuse across the interface. Currently, they are employed in the separation and purification of biomolecules [26], carbon nanotubes [27], and metal ions [28]. Furthermore, liquid phase separation has been recently found to play fundamental roles in cellular processes, such as genetic regulation [29] and signaling cascades [30]. In the life sciences, these compartments are thought of as membraneless organelles composed of dense assemblies of proteins and nucleic acids and are termed biological condensates [31, 32]. Thus, modeling the diffusion of molecules across these boundaries has importance both from scientific and technological perspectives. In addition to two-phase systems, heterogeneous diffusion has been probed in a wide variety of systems, including porous media [33], supercooled liquids [34], and micropillar matrices [35].

The Langevin equation for a particle in a homogeneous environment is well-defined [36]. However, for heterogeneous environments, the integrals appearing when solving the Langevin equation are not uniquely defined. The lack of uniqueness is rooted in the integrand function having a random nature. The problem becomes severe when the diffusivity landscape has abrupt changes, such as those encountered in a two-phase system. In practice, stochastic integrals are defined as sums over infinitesimal rectangles, and, contrary to the case of smooth functions, the integral depends on the position of the points where the function is evaluated. This dependence, thus, requires additional information known as interpretation [37–43]. Due to its lack of a unique solution, some authors prefer to term the Langevin equation a pre-equation [39].

The first approach to solving the Langevin equation via stochastic integration was introduced by Itô, employing the initial point of the infinitesimal interval to compute the integrals [44]. Then, Stratonovich introduced an alternative method by which the midpoint of the interval is selected [45, 46]. Finally, Hänggi and Klimontovich introduced yet another prescription, taking the last point of the infinitesimal interval [47–50]. Such freedom at selecting an interpretation gives rise to the problem of choosing the *'correct'* interpretation [51]. Thus, when developing models to describe dynamics in heterogeneous environments a choice is made *a priori*, typically employing ei-

ther Itô [52], Stratonovich [8], or Hänggi-Klimontovich (HK) [53] prescriptions.

Nowadays, it is accepted that the choice of interpretation depends on the underlying mechanisms that dictate the fluctuations of the physical system [36, 39]. However, methods that assign an interpretation of Langevin equation to experimental physical systems are still missing. Given the broad interest in diffusion in heterogeneous media, this problem and its implications need careful consideration. Particularly, tools to infer the interpretation parameter from physical observables can help guide experimentalists and theoreticians in the use of Langevin equation.

In this letter, we study the diffusion of particles in a heterogeneous environment that mirrors a two-phase system, namely, having different diffusion coefficients on each side of an interface. We consider the interpretation as a parameter, focusing on the Itô, Stratonovich, and HK interpretations. The simple situation considered here elucidates significant variations between solutions associated with different interpretations and leads to distinctive experimental predictions. We observe that typical characterizations, such as the mean, the mean square displacement (MSD), and the displacement probability density function (PDF) for different interpretations have different forms. Our results provide a tool to infer the interpretation parameter in experimental settings from the measured density of particles at both sides of an interface.

We start by considering a Langevin equation with position-dependent diffusion coefficient $D(x)$ [54],

$$dX(t) = \sqrt{2D[X(t)]}\, dB(t), \tag{1}$$

where $B(t)$ is standard Brownian motion. In the mathematical literature, such a process is said to have *multiplicative noise*, as opposed to *additive noise* where the diffusion coefficient is either constant or a function of time [54]. To integrate this equation, one splits the time interval $[0, t]$ into N subintervals of size $\Delta t = t/N$, leading to N integrals that are Riemann approximated,

$$\int_{t_n}^{t_{n+1}} \sqrt{2D[X(s)]}\, dB(s) \approx \sqrt{2D[X(t')]}\, \xi_n, \tag{2}$$

where $t_n = n\Delta t$, $n = 0, \ldots, N$, $t' \in [t_n, t_{n+1}]$, and $\xi_n = B(t_{n+1}) - B(t_n)$ are the increments of Brownian motion, i.e., independent and identically distributed Gaussian random variables with variance Δt. In contrast to additive noise, the choice of t' alters the evolution of the system because different times within $[t_n, t_{n+1}]$ can give different diffusion coefficients.

Let us express t' as $t' = t_n + \alpha(t_{n+1} - t_n)$, with $\alpha \in [0, 1]$ known as the interpretation parameter. Performing a Taylor expansion to first order of $X(t')$ around t_n, we find $X(t') \approx X(t_n) + \alpha \Delta X_n$, with $\Delta X_n = X(t_{n+1}) - X(t_n)$, and by replacing this expression in Eq. (2),

$$X(t) = \sum_{n=0}^{N-1} \sqrt{2D\left[X(t_n) + \alpha \Delta X_n\right]}\, \xi_n. \tag{3}$$

The Langevin equation with multiplicative noise (Eq. (1)) is associated with a Fokker-Planck equation for the PDF $p(x, t)$ of the particle's position at time t [36, 54]

$$\frac{\partial p(x,t)}{\partial t} = \frac{\partial}{\partial x}\left\{ D^{\alpha}(x) \frac{\partial}{\partial x}\left[D^{1-\alpha}(x) p(x,t) \right] \right\}, \tag{4}$$

where α is the interpretation parameter.

To numerically study this Fokker-Planck equation, we consider a discrete space with lattice constant a. Eq. (4) becomes

$$\begin{aligned} \frac{dp_i(t)}{dt} = {} & \frac{D^{\alpha}_{i-1/2} D^{1-\alpha}_{i-1}}{a^2}\, p_{i-1}(t) - \\ & - \frac{D^{\alpha}_{i+1/2} D^{1-\alpha}_{i} + D^{\alpha}_{i-1/2} D^{1-\alpha}_{i}}{a^2}\, p_i(t) + \\ & + \frac{D^{\alpha}_{i+1/2} D^{1-\alpha}_{i+1}}{a^2}\, p_{i+1}(t), \end{aligned} \tag{5}$$

where $p_i(t)$ is the probability to find the particle on site i at time t, that is $p_i(t) = p(x = ia, t)$, and $D_{i\pm 1/2} = D[x = (i \pm 1/2)a]$. This equation has the form of a master equation [55] with transition rates $\omega_{i \to j}$ from position i to j,

$$\omega_{i \to j} = \frac{D^{1-\alpha}_{i} D^{\alpha}_{k}}{a^2}, \tag{6}$$

with $k = (i + j)/2$ for $j = i \pm 1$.

We consider the master equation using a simple diffusion coefficient function of the form

$$D(x) = \begin{cases} D_- & \text{if } x < 0, \\ \\ D_+ & \text{if } x \geq 0, \end{cases} \tag{7}$$

with $D_{\pm} > 0$. This function represents a two-phase system with a diffusivity change at the boundary. Setting $a = 1$, we use a fourth-order Runge-Kutta integration scheme [56] with an integration step of $\Delta t = 0.01$ to numerically solve the above master equation for different values of the interpretation parameter α. We found that the PDF for any α is described by a *generalized* two-piece Gaussian distribution [57]

$$p(x, t; \alpha) = \begin{cases} \dfrac{2\beta(\alpha)}{\sqrt{4\pi D_- t}} \exp\left(-\dfrac{x^2}{4D_- t} \right), & x < 0, \\ \\ \dfrac{2[1 - \beta(\alpha)]}{\sqrt{4\pi D_+ t}} \exp\left(-\dfrac{x^2}{4D_+ t} \right), & x \geq 0, \end{cases} \tag{8}$$

where $\beta(\alpha)$ is the probability that the particle is in the negative part of the axis, i.e. $\beta = \mathbb{P}[X(t) < 0]$, which is

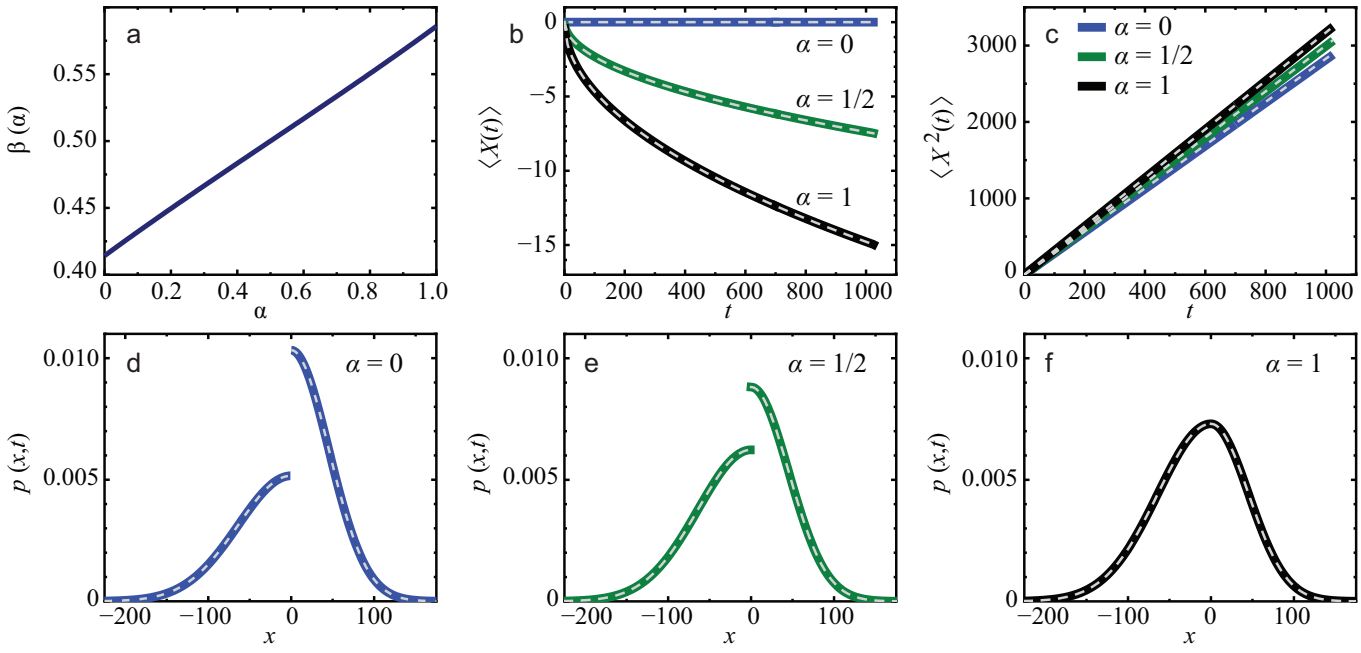


FIG. 1. Characterization of heterogeneous Brownian motion with $D_- = 2$ and $D_+ = 1$. (a) Probability β of finding the tracer in the left half plane as a function of α, as found analytically (Eq. (9)). (b) Mean $\langle X(t)\rangle$ for three interpretation parameters $\alpha = 0, 1/2$, and 1, corresponding, respectively to Itô, Stratonovich, and Hänggi-Klimontovich. Thick lines are numerical simulations and thin dashed lines are analytical solutions. (c) MSD $\langle X^2(t)\rangle$ for the interpretation parameter $\alpha = 0, 1/2$, and 1. Thick lines are simulations and thin dashed lines are analytical solutions. (d-f) PDF at time $t = 1024$ for the three interpretations. Thick lines are numerical simulations of the master equation (Eq. (5)) and thin dashed lines are analytical solutions given by Eq. (8).

independent of time. We verified that the identified PDF (Eq. (8)) is the solution to the Fokker-Planck equation (Eq. (4)) [57]. Then, using matching conditions on both sides of the origin, we find the probability β [57],

$$\beta(\alpha) = \left[1 + \left(\frac{D_-}{D_+}\right)^{(1/2-\alpha)}\right]^{-1}. \tag{9}$$

We focus on the first two moments, corresponding to the mean position and the MSD,

$$\langle X(t)\rangle = \frac{2}{\sqrt{\pi}}\left[\sqrt{D_+} - \beta(\alpha)\left(\sqrt{D_-} + \sqrt{D_+}\right)\right] t^{1/2}, \tag{10}$$

and

$$\langle X^2(t)\rangle = 2\left[D_+ + \beta(\alpha)(D_- - D_+)\right] t. \tag{11}$$

For any interpretation, the MSD is linear, i.e., it resembles normal diffusion with an effective diffusion coefficient that depends on α. However, except for $\alpha = 0$, the process is not centered and the mean scales as $t^{1/2}$. A summary of the results for the Itô, Stratonovich, and HK interpretations is shown in Table I.

To visualize the role of the interpretation, we analyze a process with $D_- = 2$ and $D_+ = 1$, via analytical solutions and numerical simulations. The probability of finding the tracer in the region $x < 0$, following Eq. (9), is presented in Fig. 1(a). Figures 1(b) and 1(c) show the mean $\langle X(t)\rangle$ and MSD $\langle X^2(t)\rangle$ for the three considered interpretations ($\alpha = 0, 1/2, 1$). Next, the PDFs of the position at $t = 1024$ are shown in Fig. 1(d)-(f). In the three cases, the numerical integration of the master equation (Eq. (5)) agrees with the analytical expression (Eqs. (8), (9)).

Often, trajectories of individual particles are analyzed in terms of the time-averaged MSD (TAMSD) [9, 58, 59], defined in an observation time T, at lag-time τ, as

$$\overline{\delta^2(\tau)} = \frac{1}{T-\tau}\int_0^{T-\tau} [X(\tau + t) - X(t)]^2\, dt. \tag{12}$$

This quantity is often suitable for the analysis of experimental data, with a limited number of trajectories.

Brownian motion is an ergodic process where the TAMSD is $\overline{\delta^2(\tau)} = 2D\tau$. In the two-phase system, the time a tracer spends on one side before switching to the other is the first return time of a standard Brownian motion. The occupation time fraction in the region $x < 0$ is a random variable f_α, and its mean yields the mean of the TAMSD [57],

$$\left\langle \overline{\delta^2(\tau)} \right\rangle \sim 2\left[D_+ + (D_- - D_+)\beta(\alpha)\right]\tau, \tag{13}$$

which shows that $\left\langle \overline{\delta^2(\tau)} \right\rangle = \langle X^2(\tau)\rangle$, in contrast to most non-stationary processes. However, the TAMSD remains

TABLE I. Summary of the probabilistic analyses for the Itô ($\alpha = 0$), Stratonovich ($\alpha = 1/2$), and HK ($\alpha = 1$) interpretations.

	Mean $\langle X(t)\rangle$	MSD $\langle X^2(t)\rangle$	β
Itô	0	$2\sqrt{D_+D_-}\,t$	$\left(1+\sqrt{D_-/D_+}\right)^{-1}$
Stratonovich	$\frac{1}{\sqrt{\pi}}\left(\sqrt{D_+}-\sqrt{D_-}\right)t^{1/2}$	$(D_+ + D_-)\,t$	$1/2$
HK	$\frac{2}{\sqrt{\pi}}\left(\sqrt{D_+}-\sqrt{D_-}\right)t^{1/2}$	$2\left(D_+ + D_- - \sqrt{D_+D_-}\right)t$	$\left(1+\sqrt{D_+/D_-}\right)^{-1}$

a random variable at long realization times, a signature of weak ergodicity breaking. We consider the coefficient of variation (CV) of the TAMSD, defined as the ratio between the standard deviation σ_{δ^2} and the mean, i.e., $\mathrm{CV} = \sigma_{\delta^2}/\langle\overline{\delta^2(\tau)}\rangle$.

The ergodicity breaking parameter is the square of the CV, which is often used in the study of weak non-ergodicity [60]. By computing the variance of f_α [57], we obtain

$$\mathrm{CV} \sim \frac{|D_- - D_+|\sqrt{\beta(\alpha)[1-\beta(\alpha)]/2}}{D_+ + (D_- - D_+)\beta(\alpha)}. \tag{14}$$

as shown in Supplementary Fig. 1.

A natural question that arises is, given a physical system, how should experimental measurements in the vicinity of an interface guide the choice of the interpretation parameter? The most detailed measurements of particle dynamics are obtained using single-particle tracking. Using this method, diffusion coefficients and the PDF of localization can be obtained on both sides of the two-phase system. For proper initial conditions, trajectories should start when the tracer is at the interface. A continuous density indicates $\alpha = 1$ (HK prescription, Fig. 1(f)). Otherwise, a discontinuity in the PDF at the interface indicates $\alpha \neq 1$, and the interpretation is dictated by the measured probability of being on one side (β). By inverting Eq. (9),

$$\alpha = \frac{1}{2} - \frac{\ln(\beta^{-1}-1)}{\ln(D_-/D_+)}. \tag{15}$$

To illustrate the proposed methodology, we employ simulations that represent an experimental system. Our model system is bovine serum albumin (BSA) labeled with AlexaFluor fluorophores within two aqueous phases containing dextran and polyethylene glycol (PEG) [23]. The left phase contains 13.2 wt% dextran 500000, and the right phase contains 7.1 wt% PEG 6000, yielding diffusion coefficients for BSA of 14 and 24 μm^2/s, respectively. For these simulations, we assume the system follows the Stratanovich interpretation ($\alpha = 1/2$), and data are collected every 0.1 s. 2000 trajectories of 100 data points each are obtained. This combination of trajectory number and length is experimentally realistic in single-particle tracking [59]. Figure 2(a) shows representative simulations of BSA trajectories.

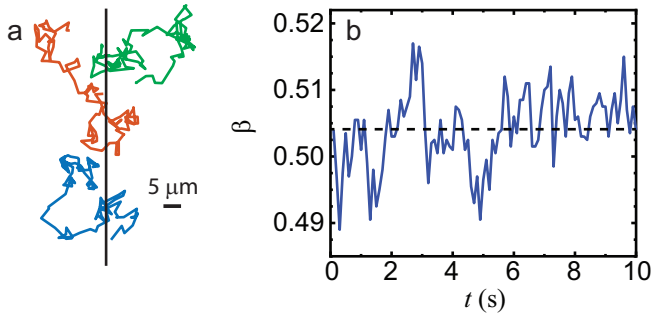


FIG. 2. Inference of the interpretation from a set of trajectories in a two-phase system. (a) Representative simulated two-dimensional trajectories of BSA in dextran-rich and PEG-rich phases. The black vertical line delineates the interface. (b) Fraction of trajectories for which the tracer is found on the left yields $\beta(t)$. In this case, the time-average of $\beta(t)$ for 100 data points is $\overline{\beta} = 0.504$, shown as a dashed line.

While it is possible to use the mean, MSD, or TAMSD CV to infer the interpretation α, we showcase a simplified method using only the fraction of trajectories to the left of the interface at a given time. If the selected interpretation is correct, the predictions for MSD and CV should ensue. Figure 2(a) presents $\beta(t)$ obtained as the fraction of points to the left of the interface. The time average for this dataset is $\overline{\beta} = 0.504$, which yields an interpretation $\alpha = 0.470$, according to Eq. (15). To assess estimation error, we repeated the described procedure 100 times. The statistical results are $\overline{\beta} = 0.501 \pm 0.007$ and, in turn, $\alpha = 0.49 \pm 0.06$ (mean $\pm$ standard deviation). Histograms of $\overline{\beta}$ and α are presented in Supplementary Fig. 2.

The simplicity of a system with a single interface allows us to obtain analytical results and highlights the differences between interpretations. Even though our approach is for the general case, we focus our analysis on the three most widely used interpretations. Each of these

prescriptions has appealing strengths: with the Itô interpretation, the mean is always zero, a consequence of this process being a martingale, that is, the conditional expectation of the next value in a sequence equals the current value, regardless of its history [5]. While the Itô interpretation maintains a constant mean position (martingale property), the Stratonovich one preserves the median in the two-phase system. With the Stratonovich interpretation, a tracer has equal probabilities of being on either side of the origin, i.e., $\mathbb{P}[X(t) < 0] = 1/2$. With the HK interpretation, the Fokker-Planck equation coincides with that obtained from combining Fick's first law of diffusion and the continuity equation, and the PDF of displacements is continuous at the origin. The Fokker-Planck equations for the three interpretations are listed in Supplementary Table I.

To make sense of the results for different interpretations in inhomogeneous systems, we briefly consider a system in a box with reflecting boundary conditions. As this system equilibrates, the distribution converges to $p(x) \sim D^{\alpha-1}(x)$ [57]. From this Boltzmann distribution, we obtain an effective potential $U(x) = -k_B T \ln p(x)$ of the form

$$U(x) = k_B T(1-\alpha) \ln D(x) + \text{const}, \qquad (16)$$

which has a discontinuity, except for the HK case. Overall, the changes in D imply changes in the interactions between the tracer and its surroundings. The properties of the non-equilibrium PDFs follow from the discontinuity in the potential, i.e. from an unbalanced force in the vicinity of the boundary towards the domain with a lower diffusion coefficient.

The process treated in the main part of this work (Fig. 1) is not confined and, as such, it describes an out-of-equilibrium system that does not reach a steady state. Due to the absence of confinement, a so-called infinite density emerges [61, 62]. Several statistical properties of these processes and their relation with infinite ergodic theory have been previously analyzed [63, 64]. Despite these complexities, the probability β does not depend on time, facilitating the analysis of experimental results. Given the interpretation, using infinite ergodic theory formalism, it is possible to obtain thermodynamical properties of the system and relations between time- and ensemble-averaged observables.

One interesting aspect is that Brownian motion with alternating diffusivities maintains the linear time behavior of the MSD, regardless of the interpretation. However, the effective diffusion coefficient depends on the interpretation. With the Itô interpretation, the effective diffusivity is equal to the geometric mean of the two diffusion coefficients, while with the Stratonovich interpretation, the effective diffusivity is equal to their arithmetic mean.

Throughout the study of a simple two-phase heterogeneous environment, we have shown how the overall characterization of the motion depends on the interpretation parameter. This result encourages researchers modeling diffusion in heterogeneous environments to consider which interpretation suits best the physics of their system. These results do not imply one interpretation is better than the others, or that choosing one makes the others incorrect. Selecting an interpretation simply states how the Langevin equation will be treated.

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[1] A. Einstein, Über die von der molekularkinetischen Theorie der Wärme geforderte Bewegung von in ruhenden Flüssigkeiten suspendierten Teilchen, Annalen der Physik **322**, 549 (1905).
[2] M. von Smoluchowski, Zur kinetischen Theorie der Brownschen Molekularbewegung und der suspensionen, Annalen der Physik **326**, 756 (1906).
[3] P. Langevin, Sur la thérie du mouvement Brownien, C. R. Acad. Sci. (Paris) **146**, 530 (1908).
[4] I. Karatzas and S. Shreve, *Brownian Motion and Stochastic Calculus*, Graduate Texts in Mathematics (Springer, New York, 2012).
[5] B. Oksendal, *Stochastic Differential Equations: An Introduction with Applications*, Universitext (Springer, Berlin, 2003).
[6] C. Braumann, *Introduction to Stochastic Differential Equations with Applications to Modelling in Biology and Finance* (Wiley, Hoboken, 2019).
[7] B. P. van Milligen, P. D. Bons, B. A. Carreras, and R. Sánchez, On the applicability of Fick's law to diffusion in inhomogeneous systems, European Journal of Physics **26**, 913 (2005).
[8] A. G. Cherstvy, A. V. Chechkin, and R. Metzler, Anomalous diffusion and ergodicity breaking in heterogeneous diffusion processes, New Journal of Physics **15**, 083039 (2013).
[9] C. Manzo and M. F. Garcia-Parajo, A review of progress in single particle tracking: from methods to biophysical insights, Reports on Progress in Physics **78**, 124601 (2015).
[10] A. Weron, K. Burnecki, E. J. Akin, L. Solé, M. Balcerek, M. M. Tamkun, and D. Krapf, Ergodicity breaking on the neuronal surface emerges from random switching between diffusive states, Scientific Reports **7**, 5404 (2017).
[11] K. Tsekouras, A. Siegel, R. Day, and S. Pressé, Inferring diffusion dynamics from FCS in heterogeneous nuclear environments, Biophysical Journal **109**, 7 (2015).
[12] H. Shen, L. J. Tauzin, R. Baiyasi, W. Wang, N. Moringo, B. Shuang, and C. F. Landes, Single particle tracking: from theory to biophysical applications, Chemical Reviews **117**, 7331 (2017).
[13] K. Norregaard, R. Metzler, C. M. Ritter, K. Berg-Sørensen, and L. B. Oddershede, Manipulation and motion of organelles and single molecules in living cells, Chemical Reviews **117**, 4342 (2017).

[14] A. V. Chechkin, F. Seno, R. Metzler, and I. M. Sokolov, Brownian yet non-Gaussian diffusion: From superstatistics to subordination of diffusing diffusivities, Physical Review X **7**, 021002 (2017).

[15] D. Krapf and R. Metzler, Strange interfacial molecular dynamics, Physics Today **72**, 48 (2019).

[16] E. B. Postnikov, A. Chechkin, and I. M. Sokolov, Brownian yet non-Gaussian diffusion in heterogeneous media: from superstatistics to homogenization, New Journal of Physics **22**, 063046 (2020).

[17] J. Janczura, M. Balcerek, K. Burnecki, A. Sabri, M. Weiss, and D. Krapf, Identifying heterogeneous diffusion states in the cytoplasm by a hidden Markov model, New Journal of Physics **23**, 053018 (2021).

[18] A. Pacheco-Pozo and I. M. Sokolov, Convergence to a Gaussian by narrowing of central peak in Brownian yet non-Gaussian diffusion in disordered environments, Physical Review Letters **127**, 120601 (2021).

[19] P. Singh, Extreme value statistics and arcsine laws for heterogeneous diffusion processes, Physical Review E **105**, 024113 (2022).

[20] G. Muñoz, H. Bachimanchi, J. Pineda, B. Midtvedt, M. Lewenstein, R. Metzler, D. Krapf, G. Volpe, and C. Manzo, Quantitative evaluation of methods to analyze motion changes in single-particle experiments, arXiv preprint arXiv:2311.18100 (2023).

[21] A. Pacheco-Pozo and I. M. Sokolov, Random walks in correlated diffusivity landscapes, The European Physical Journal B **96**, 152 (2023).

[22] N. Korabel and E. Barkai, Paradoxes of subdiffusive infiltration in disordered systems, Physical Review Letters **104**, 170603 (2010).

[23] G. Münchow, F. Schönfeld, S. Hardt, and K. Graf, Protein diffusion across the interface in aqueous two-phase systems, Langmuir **24**, 8547 (2008).

[24] Y. Chao and H. C. Shum, Emerging aqueous two-phase systems: from fundamentals of interfaces to biomedical applications, Chemical Society Reviews **49**, 114 (2020).

[25] C. D. Keating and R. V. Pappu, Liquid–liquid phase separation: A widespread and versatile way to organize aqueous solutions, The Journal of Physical Chemistry Letters **12**, 10994 (2021).

[26] P.-Å. Albertsson, G. Johansson, and F. Tjerneld, Aqueous two-phase separations, in *Separation Processes in Biotechnology*, edited by J. A. Asenjo (CRC Press, 2020) pp. 287–328.

[27] X. Yang, C. Zhu, L. Zeng, W. Xue, L. Zhang, L. Zhang, K. Zhao, M. Lyu, L. Wang, Y.-Z. Zhang, *et al.*, Polyoxometalate steric hindrance driven chirality-selective separation of subnanometer carbon nanotubes, Chemical Science **13**, 5920 (2022).

[28] M. R. Rahimipoor and A. Hamta, Investigation of the effect of different parameters on the separation of lead, arsenic, and cadmium ions from wastewater using aqueous two-phase systems, Journal of Advanced Materials and Technologies **12**, 29 (2023).

[29] J. E. Henninger, O. Oksuz, K. Shrinivas, I. Sagi, G. LeRoy, M. M. Zheng, J. O. Andrews, A. V. Zamudio, C. Lazaris, N. M. Hannett, *et al.*, RNA-mediated feedback control of transcriptional condensates, Cell **184**, 207 (2021).

[30] A. S. Lyon, W. B. Peeples, and M. K. Rosen, A framework for understanding the functions of biomolecular condensates across scales, Nature Reviews Molecular Cell Biology **22**, 215 (2021).

[31] S. Bo, L. Hubatsch, J. Bauermann, C. A. Weber, and F. Jülicher, Stochastic dynamics of single molecules across phase boundaries, Physical Review Research **3**, 043150 (2021).

[32] L. Hubatsch, L. M. Jawerth, C. Love, J. Bauermann, T. D. Tang, S. Bo, A. A. Hyman, and C. A. Weber, Quantitative theory for the diffusive dynamics of liquid condensates, eLife **10**, e68620 (2021).

[33] B. Berkowitz, J. Klafter, R. Metzler, and H. Scher, Physical pictures of transport in heterogeneous media: Advection-dispersion, random-walk, and fractional derivative formulations, Water Resources Research **38**, 9 (2002).

[34] R. Yamamoto and A. Onuki, Dynamics of highly supercooled liquids: Heterogeneity, rheology, and diffusion, Physical Review E **58**, 3515 (1998).

[35] I. Chakraborty and Y. Roichman, Disorder-induced Fickian, yet non-Gaussian diffusion in heterogeneous media, Physical Review Research **2**, 022020(R) (2020).

[36] I. Sokolov, Ito, Stratonovich, Hänggi and all the rest: The thermodynamics of interpretation, Chemical Physics **375**, 359 (2010), Stochastic processes in Physics and Chemistry (in honor of Peter Hänggi).

[37] H. W. de Haan, M. V. Chubynsky, and G. W. Slater, Monte Carlo approaches for simulating a particle at a diffusivity interface and the "Ito–Stratonovich dilemma" (2012), arXiv:1208.5081 [cond-mat.stat-mech].

[38] C. Escudero and H. Rojas, Itô versus Hänggi-Klimontovich (2023), arXiv:2309.03654 [math-ph].

[39] N. G. van Kampen, Itô versus Stratonovich, Journal of Statistical Physics **24**, 175 (1981).

[40] J. M. Sancho, Brownian colloidal particles: Ito, Stratonovich, or a different stochastic interpretation, Physical Review E **84**, 062102 (2011).

[41] R. Tsekov, Stochastic equations for thermodynamics, Journal of the Chemical Society, Faraday Transactions **93**, 1751 (1997).

[42] O. Farago and N. Grønbech-Jensen, Langevin dynamics in inhomogeneous media: Re-examining the Itô-Stratonovich dilemma, Physical Review E **89**, 013301 (2014).

[43] L. Menon Jr, M. dos Santos, and C. Anteneodo, Random-search efficiency in a bounded interval with spatially heterogeneous diffusion coefficient, Journal of Statistical Mechanics: Theory and Experiment **2023**, 123203 (2023).

[44] K. Itô, Stochastic integral, Proceedings of the Imperial Academy **20**, 519 (1944).

[45] R. Stratonovich, A new form of representing stochastic integrals and equations, Vestnik Moskov. Univ. Ser. I Mat. Meh **1**, 3 (1964).

[46] R. L. Stratonovich, A new representation for stochastic integrals and equations, SIAM Journal on Control **4**, 362 (1966).

[47] P. Hänggi, Stochastic processes. I, Asymptotic behaviour and symmetries, Helvetica Physica Acta **51**, 183 (1978).

[48] P. Hänggi, Connection between deterministic and stochastic descriptions of nonlinear systems, Helvetica Physica Acta **53**, 492 (1980).

[49] P. Hänggi and H. Thomas, Stochastic processes: Time evolution, symmetries and linear response, Physics Reports **88**, 207 (1982).

[50] Y. L. Klimontovich, Nonlinear Brownian motion, Physics-Uspekhi **37**, 737 (1994).

[51] B. West, A. Bulsara, K. Lindenberg, V. Seshadri, and K. Shuler, Stochastic processes with non-additive fluctuations: I. Itô and Stratonovich calculus and the effects of correlations, Physica A: Statistical Mechanics and its Applications **97**, 211 (1979).

[52] A. Cumberworth and P. R. ten Wolde, Constriction of actin rings by passive crosslinkers, Physical Review Letters **131**, 038401 (2023).

[53] A. G. Cherstvy, A. V. Chechkin, and R. Metzler, Particle invasion, survival, and non-ergodicity in 2D diffusion processes with space-dependent diffusivity, Soft Matter **10**, 1591 (2014).

[54] V. L. Thibaut Arnoulx de Pirey, Leticia F. Cugliandolo and F. van Wijland, Path integrals and stochastic calculus, Advances in Physics **71**, 1 (2022).

[55] J. Klafter and I. M. Sokolov, *First Steps in Random Walks: From Tools to Applications* (Oxford University Press, 2011).

[56] W. Press, S. Teukolsky, B. Flannery, and W. Vetterling, *Numerical Recipes in FORTRAN 77: The Art of Scientific Computing, Volume 1 of Fortran Numerical Recipes* (Cambridge University Press, 1992).

[57] See Supplemental Material available online for mathematical details and Supplementary Figures. The Supplemental Material includes Ref. [55, 65–72].

[58] G. Muñoz-Gil, G. Volpe, M. A. Garcia-March, E. Aghion, A. Argun, C. B. Hong, T. Bland, S. Bo, J. A. Conejero, N. Firbas, *et al.*, Objective comparison of methods to decode anomalous diffusion, Nature Communications **12**, 6253 (2021).

[59] A. Sabri, X. Xu, D. Krapf, and M. Weiss, Elucidating the origin of heterogeneous anomalous diffusion in the cytoplasm of mammalian cells, Physical Review Letters **125**, 058101 (2020).

[60] R. Metzler, J.-H. Jeon, A. G. Cherstvy, and E. Barkai, Anomalous diffusion models and their properties: non-stationarity, non-ergodicity, and ageing at the centenary of single particle tracking, Physical Chemistry Chemical Physics **16**, 24128 (2014).

[61] J. Aaronson, *An introduction to infinite ergodic theory* (American Mathematical Society, Providence, 1997).

[62] E. Aghion, D. A. Kessler, and E. Barkai, Infinite ergodic theory meets Boltzmann statistics, Chaos, Solitons & Fractals **138**, 109890 (2020).

[63] E. Aghion, D. A. Kessler, and E. Barkai, From non-normalizable Boltzmann-Gibbs statistics to infinite-ergodic theory, Physical Review Letters **122**, 010601 (2019).

[64] N. Leibovich and E. Barkai, Infinite ergodic theory for heterogeneous diffusion processes, Physical Review E **99**, 042138 (2019).

[65] K. F. Wallis, The two-piece normal, binormal, or double Gaussian distribution: Its origin and rediscoveries, Statistical Science **29**, 106 (2014).

[66] M. Balcerek, A. Wyłomańska, K. Burnecki, R. Metzler, and D. Krapf, Modelling intermittent anomalous diffusion with switching fractional Brownian motion, New Journal of Physics **25**, 103031 (2023).

[67] J. Krug, H. Kallabis, S. N. Majumdar, S. J. Cornell, A. J. Bray, and C. Sire, Persistence exponents for fluctuating interfaces, Physical Review E **56**, 2702 (1997).

[68] G. M. Molchan, Maximum of a fractional Brownian motion: probabilities of small values, Communications in Mathematical Physics **205**, 97 (1999).

[69] L. P. Sanders and T. Ambjörnsson, First passage times for a tracer particle in single file diffusion and fractional Brownian motion, The Journal of Chemical Physics **136** (2012).

[70] A. Rebenshtok and E. Barkai, Occupation times on a comb with ramified teeth, Physical Review E **88**, 052126 (2013).

[71] A. Lejay and P. Pigato, Statistical estimation of the oscillating Brownian motion, Bernoulli **24**, 3568 (2018).

[72] W. Rüemelin, Numerical treatment of stochastic differential equations, SIAM Journal on Numerical Analysis **19**, 604 (1982).