First-Passage Times in d-Dimensional Heterogeneous Media

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Although there are many theoretical studies of the mean first-passage time (MFPT), most neglect the diffusive heterogeneity of real systems. We present exact analytical expressions for the MFPT and residence times of a pointlike particle diffusing in a spherically symmetric d-dimensional heterogeneous system composed of two concentric media with different diffusion coefficients with an absorbing inner boundary (target) and a reflecting outer boundary. By varying the convention, e.g., Itō, Stratonovich, or isothermal, chosen to interpret the overdamped Langevin equation with multiplicative noise describing the diffusion process, we find different predictions and counterintuitive results for the residence time in the outer region and hence for the MFPT, while the residence time in the inner region is independent of the convention. This convention dependence of residence times and the MFPT could provide insights about the heterogeneous diffusion in a cell or in a tumor, or for animal and insect searches inside their home range.

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The first-passage time is an important concept in many fields where complexity and randomness are intricately coupled, including biophysics, ecology, and economics [1–6]. In many cases, the stochasticity originates from the medium in which the system is embedded, e.g., Brownian motion where the noisy driving term arises from the thermal fluctuations of the surrounding environment.

The stochastic process involved can be described in several different equivalent ways, for example, with a stochastic differential equation (SDE) for the random variables or with a (deterministic) partial differential equation of the Fokker-Planck kind for the probability density function (PDF) [7,8].

These two descriptions are equivalent, but for heterogeneous systems the link may not be unique and generally needs to be specified from a phenomenological point of view. This is the so-called Itō-Stratonovich dilemma [7–10]: the position-dependent diffusivity in the overdamped Langevin equation results in a multiplicative noise whose formal integration has several possible interpretations leading to different predictions. More specifically, let us consider the following one-dimensional SDE:

$$x(t+dt) = x(t) + \sqrt{2D(x^*)}dW(t), \tag{1}$$

where $D(x)$ is the position-dependent diffusion coefficient of a Brownian motion, for example, and $dW(t)$ is the increment of a Wiener process of variance proportional to the (small) time increment dt. The position x^* in $D(x^*)$ is an intermediate point between $x(t)$ and $x(t+dt)$ defined by $x^* = \alpha x(t+dt) + (1-\alpha)x(t)$, where $\alpha \in [0,1]$ is part of the system under study and must be chosen on physical grounds [9–11].

Formal integration of Eq. (1) shows that its solutions depend on α, i.e., the anticipating parameter describing the convention chosen to interpret $\sqrt{D(x^*)}dW(t)$. Three conventions are commonly considered: $\alpha = 0$, the Itō convention [12]; $\alpha = 1/2$, the Stratonovich convention [13]; $\alpha = 1$, the isothermal (or kinetic or Hänggi-Klimontovich) convention [14–16].

To each convention corresponds a stochastic calculus and various experimental and theoretical works have shown the relevance of these three different calculi. For example, the nonanticipating property of the Itō calculus is essential for modeling the dynamics of financial assets like stock prices [2], dye diffusion in a fluid with heterogeneous viscosity [17], phase transitions induced by multiplicative noise [18], and some biological processes [19].

In the Stratonovich convention, the anticipating point x^* is located at the midpoint of the interval $[x(t), x(t+dt)]$ and the corresponding stochastic calculus obeys the same rules as normal calculus. It is the correct calculus for the derivation of the Langevin SDE from stochastic systems with inertia [20] or with a small, finite noise correlation time [21]. Experiments show its validity for analogue simulators using electronic devices [22,23] and in stochastic models of pricing with bounded variations [24].

The highly anticipating property of the isothermal convention leads to some counterintuitive behavior, which has recently revived the Itō-Stratonovich dilemma [10,25–27]. Isothermal calculus seems to correspond to the natural framework of Fick's law and some recent experiments tend to confirm its applicability, especially for particles diffusing near a wall [25–29]. One should also mention its important role for generalizing the fluctuation-dissipation relation for equilibrium systems with nonlinear friction [30–32]. In a recent model [33] all three conventions were required to describe the diffusion of a particle in a modulated periodic potential.

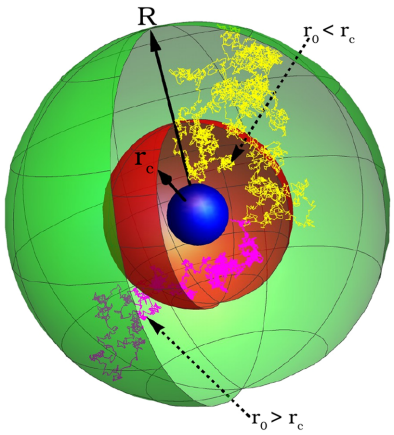

FIG. 1 (color online). Spherically symmetric three-dimensional system composed of two different concentric media with diffusion coefficients D_1 for $a < r < r_c$ and D_2 for $r_c < r < R$. The search begins at $r = r_0$ and ends when the walker reaches the target at $r = a$ (blue). The dashed arrows indicate the starting points of two trajectories, one in $\mathcal{R}_1$ and the other in $\mathcal{R}_2$.

Although many articles address the Itō-Stratonovich dilemma, there is to our knowledge no published work on the effect of the choice of the convention on the first-passage times. Therefore, in this Letter, we examine simple composite systems with spherical symmetry composed of m concentric regions of uniform diffusivities $D_1, D_2, \ldots, D_m$ such that $D(r) = D_i$ for $R_{i-1} < r \leq R_i$ with a target at $r = R_0 = a$ and a reflecting boundary at $r = R_m = R$. We focus on the case $m = 2$, shown in Fig. 1, but give general results where appropriate. We also examine the residence times in each region to help shed light on some recently observed nonintuitive behavior of the mean first-passage time (MFPT) in a particular case [34].

From the SDE (1), one can derive the following (Fokker-Planck) diffusion equation [35]

$$\frac{\partial n(r,t)}{\partial t} = \frac{1}{r^{d-1}} \frac{\partial}{\partial r}\left[r^{d-1} D(r)^{\alpha} \frac{\partial [D(r)^{1-\alpha} n(r,t)]}{\partial r} \right]. \quad (2)$$

By invoking the equation of continuity, $(\partial/\partial t) n(r,t) = -\nabla \cdot \mathbf{j}(r,t)$, we obtain the radial component of the flux

$$j(r,t) = -D(r)^{\alpha} \frac{\partial [D(r)^{1-\alpha} n(r,t)]}{\partial r}. \quad (3)$$

Note that while the flux is continuous whatever the convention α is, the PDF $n(r,t)$ may not be continuous. Indeed, $n(r,t)$ is continuous at $r = r_c$ only for $\alpha = 1$ while $D(r)n(r,t)$ and $\sqrt{D(r)}n(r,t)$ are continuous for $\alpha = 0$ and $\alpha = 1/2$, respectively. As a consequence, for $\alpha \neq 1$, $n(r,t)$ is discontinuous wherever $D(r)$ is discontinuous (see the movie provided in the Supplemental Material [36]). In the present system there is no nontrivial steady state due to the presence of an absorbing boundary. Figure 2 shows the normalized $n(r,t)$ as heat maps obtained by numerical (agent based) simulations of the SDE describing the one-dimensional system [36]. The discontinuity at r_c is evident whenever $\alpha \neq 1$.

The usual strategy to obtain the MFPT consists of solving the (time) Laplace transform of Eq. (2) with appropriate boundary conditions, then finding the flux from which the MFPT and higher moments can be obtained [1]. Here, we employ an alternative, more compact method [46] that, while restricted to systems with reflecting boundary conditions, is particularly well suited when D is piecewise uniform. Since the system under study possesses an absorbing boundary, the MFPT to reach it can be expressed as the sum

$$\tau(r_0) = \sum_{k=1}^{m} \tau_k(r_0), \quad (4)$$

where

$$\tau_k(r_0) = \int_{\mathcal{R}_k} dr r^{d-1} \int_0^{\infty} dt n(r,t;r_0) \quad (5)$$

is the residence time in the region $\mathcal{R}_k = [R_{k-1}, R_k]$, and where the PDF $n(r,t;r_0)$ has been renormalized to absorb the numerical factor $2\pi^{d/2}/\Gamma(d/2)$ coming from the integration of the angular coordinates. The residence times $\tau_k(r_0)$ represent the amount of time the diffusing particle spends in each region before reaching the target at $r = a$. Taking into account the reflecting boundary at $r = R$ and integrating the equation of continuity, we obtain

$$j(r,t) = \frac{1}{r^{d-1}} \int_r^R dr' r'^{d-1} \frac{\partial n(r',t)}{\partial t}. \quad (6)$$

Inserting Eq. (3) in Eq. (6) and integrating over position we obtain

$$n(r,t) = -\frac{1}{D(r)^{1-\alpha}} \int_a^r \frac{dy}{y^{d-1} D(y)^{\alpha}} \int_y^R dx x^{d-1} \frac{\partial n(x,t)}{\partial t}. \quad (7)$$

Inserting this in Eq. (5) with the initial condition $n(r,0) = \delta(r - r_0)/{r_0}^{d-1}$, where $\delta(r)$ is the Dirac delta function, gives

$$\tau_k(r_0) = \int_{R_{k-1}}^{R_k} dz \frac{z^{d-1}}{D(z)^{1-\alpha}} \int_a^z \frac{dy}{y^{d-1} D(y)^{\alpha}} \theta(r_0 - y) \quad (8)$$

as the residence time in $\mathcal{R}_k$ where $\theta(r)$ is the Heaviside step function. One can then check that $\tau(r_0)$ is the solution of the backward Fokker-Planck equation derived by Szabo, Schulten, and Schulten [47] generalized here as $L^{\dagger}\tau(r_0) = D^{1-\alpha}\nabla \cdot [D^{\alpha}\nabla\tau(r_0)] = -1$ where $L^{\dagger}$ is the adjoint operator of $L = \nabla \cdot (D^{\alpha}\nabla D^{1-\alpha})$ appearing in Eq. (2).

We now present explicit results for $m = 2$ layers. For any dimension $d \neq 2$, the residence times appearing in Eq. (4) are given by

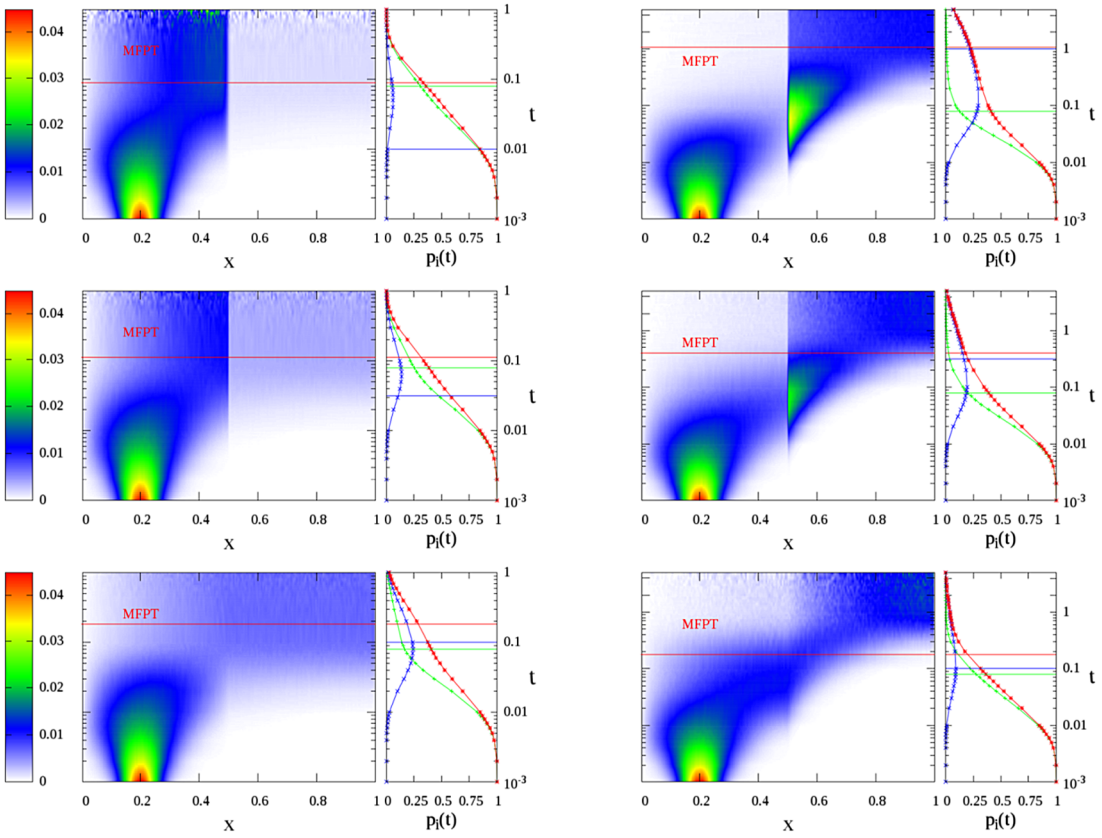

FIG. 2 (color online). Heat maps of the PDF for $d = 1$, $n(x, t)$ where $x = r/R$, in a composite system with either $D_1 = 1$, $x < x_c$ and $D_2 = 10$, $x > x_c$ (left column) or $D_1 = 10$, $x < x_c$ and $D_2 = 1$, $x > x_c$ (right column), where $x_c = r_c/R = 0.5$, for 10^6 different trajectories, each starting at $x_0/R = 0.2$ for the Itō, Stratonovich, and isothermal conventions (from top to bottom). On the right of each heat map is shown the likelihood of presence in $\mathcal{R}_1$ (green), $\mathcal{R}_2$ (blue), and $\mathcal{R}_1 \cup \mathcal{R}_2$ (red) as a function of time. The horizontal lines show the values of the MFPT (red), τ_1 (green), and τ_2 (blue).

$$\tau_1(r_0) = \begin{cases} \frac{1}{D_1}\left[r_c^d \frac{{r_0}^{2-d} - a^{2-d}}{d(2-d)} - \frac{{r_0}^2 - a^2}{2d}\right] & \text{for } r_0 \le r_c, \\ \frac{1}{D_1}\left[r_c^d \frac{r_c^{2-d} - a^{2-d}}{d(2-d)} - \frac{r_c^2 - a^2}{2d}\right] & \text{for } r_0 \ge r_c, \end{cases} \tag{9}$$

$$\tau_2(r_0) = \begin{cases} \frac{R^d - r_c^d}{D_1^\alpha D_2^{1-\alpha}} \frac{{r_0}^{2-d} - a^{2-d}}{d(2-d)} & \text{for } r_0 \le r_c, \\ \frac{R^d - r_c^d}{D_1^\alpha D_2^{1-\alpha}} \frac{r_c^{2-d} - a^{2-d}}{d(2-d)} & \\ \quad + \frac{1}{D_2}\left[R^d \frac{{r_0}^{2-d} - r_c^{2-d}}{d(2-d)} - \frac{{r_0}^2 - r_c^2}{2d}\right] & \text{for } r_0 \ge r_c. \end{cases} \tag{10}$$

The corresponding expressions for $d = 2$ involve logarithms and are given in the Supplemental Material [36]. It is worth noticing that $\tau_2(r_0)$ and $\tau_1(r_0)$, respectively, do and do not depend on the convention and both are always continuous at $r_0 = r_c$. The sum of these quantities also reproduces the MFPT obtained in Refs. [1] and [34] when $\alpha = 1$.

For the homogeneous system, i.e., $D_1 = D_2 = D$, as expected, there is no dependence on the convention and the MFPT expression reduces to $\tau(r_0) = \mathcal{T}(r_0, a, R, D)$, where

$$\mathcal{T}(r_0, a, R, D) = \frac{R^d}{D} \frac{r_0^{2-d} - a^{2-d}}{d(2-d)} - \frac{r_0^2 - a^2}{2dD} \tag{11}$$

gives the MFPT of a particle diffusing in a homogeneous medium between absorbing ($r = a$) and reflecting ($r = R$) concentric (hyper)spheres and starting at r_0. This can be used to write Eqs. (9) and (10) in a more compact form:

$$\tau_1(r_0) = \mathcal{T}(r^<, a, r_c, D_1), \tag{12}$$

$$\tau_2(r_0) = \mathcal{T}(r^<, a, R, D_{\text{eff}}) - \mathcal{T}(r^<, a, r_c, D_{\text{eff}}) + \mathcal{T}(r^>, r_c, R, D_2), \tag{13}$$

where $r^< = \min(r_c, r_0)$, $r^> = \max(r_c, r_0)$, and $D_{\text{eff}} = D_1^\alpha D_2^{1-\alpha}$, i.e., the α-geometric mean of the diffusion coefficients.

The residence time in $\mathcal{R}_1$ is exactly the MFPT of a particle diffusing in a region of volume scaling as $r_c^d - a^d$ with absorbing and reflecting boundaries at a and r_c, respectively, and starting from $\min(r_0, r_c)$.

For $r_0 < r_c$, the residence time in $\mathcal{R}_2$ simply consists of the difference between the MFPTs of a particle exploring the entire system and the residence time in the first region considering an effective diffusion coefficient D_{eff} that depends on the chosen convention. When $r_0 > r_c$, we

can decompose τ_2 into two effective steps: the particle diffuses in $\mathcal{R}_2$ before reaching the interface at r_c, then it diffuses in a medium with the effective diffusion coefficient D_{eff} starting from r_c.

Whatever the convention, τ_1 is independent of D_2 [Eq. (8) actually shows that this result remains valid whatever the r dependence of the diffusion coefficient outside the first region $\mathcal{R}_1$ is], while τ_2 may depend on both diffusion coefficients according to the convention. With the Itō convention τ_2 does not depend on D_1: the time spent in any region does not depend on the diffusivity of the other region, i.e., the diffusive explorations of the two regions can be seen as independent. With the Stratonovich convention, $\alpha = 1/2$, the geometric mean of the diffusion coefficients appears in the expression of τ_2. In general, the more anticipating the jump in r^* is, the more coupled the diffusive explorations of the two regions is. In the extreme case of the isothermal convention this leads to some puzzling results.

First, as noted in Ref. [34], when $\alpha = 1$, $\tau_2(r_0)$, and hence $\tau(r_0)$, are independent of D_2 if $r_0 \leq r_c$, which could mislead one into thinking that the MFPT is independent of the outer region if the particle starts its diffusive movement in region $\mathcal{R}_1$, i.e., close to the target. Actually, τ does depend on $\mathcal{R}_2$ for two reasons, the most obvious one being that Eq. (10) depends on the length of the total system. The other is that the time spent in any subregion of $\mathcal{R}_2$, hence τ_2, is different from zero.

A physical explanation for this surprising result can be obtained by considering the balance between transmission of particles across the interface and the residence times (see the Supplemental Material [36] for more details). For example, particles attempting to pass from $\mathcal{R}_1$ to $\mathcal{R}_2$ when $D_2 < D_1$ see an effective barrier and some are reflected (while in the Itō case there is no reflection and all particles enter $\mathcal{R}_2$) [11,43,44]. This partial reflection is exactly compensated by the increased residence time of particles that do enter $\mathcal{R}_2$.

Another remarkable property is that τ_2 can be greater than τ_1 even when the particle starts infinitely close to the target. For example, in one dimension with $\alpha = 1$ and $a = 0$, the ratio of residence times is $\tau_2(r_0)/\tau_1(r_0) = (R - r_c)/(r_c - r_0/2)$, which is larger than 1 for $r_c = R/2$ and $0 < r_0 < r_c$.

More generally, let us define an interface position r_c^* such that $\tau_2 \geq \tau_1$ for any $r_c < r_c^*$ and any starting point (with the equality applying in the limit $r_0 \to a$). It is straightforward to show that $r_c^* = \{[a^d + R^d(D_1/D_2)^{1-\alpha}]/[1 + (D_1/D_2)^{1-\alpha}]\}^{1/d}$.

For example, in a three-dimensional system with $\alpha = 1$, $a = 0.1R$, $r_c^* = 0.794R$ implying that, when $r_c < r_c^*$, the diffusing particle spends more time in $\mathcal{R}_2$ than $\mathcal{R}_1$ even if the particle starts infinitesimally close to the target. If $\alpha \neq 1$, r_c can be located even further from the target when $D_1/D_2 > 1$, while it must be closer when $D_1/D_2 < 1$, e.g., $r_c^* = 0.969R$ and $r_c^* = 0.451R$, respectively, for $D_1/D_2 = 10$ and 0.1 with $\alpha = 1$ (Itō convention).

In the isothermal convention ($\alpha = 1$) (or in the homogeneous case, $D_1 = D_2$), $r_c^* = [(a^d + R^d)/2]^{1/d}$, dividing the system into equal volumes. As d increases, r_c^* approaches R. So counterintuitively in the isothermal case with $r_c = r_c^*$, for a particle starting very close to the target, τ_2 can still be larger than τ_1 even if $D_2 \gg D_1$ and $R \gg a$. This implies that the particle spends a longer time in region $\mathcal{R}_2$, which is very far from the target if $a \ll R$ and $d > 1$ (for example, when a molecule is injected in a biological cell or a tumor with the aim to reach a small target at its center).

It may be tempting at first sight to link the MFPT and the residence times to the shape of the PDF of the particle for times before the MFPT (marked in red in Fig. 2). However, for example, for very small values of r_0, the MFPT is extremely small and the PDF remains localized around the starting position during all this time. The probabilities of presence in $\mathcal{R}_1$, $\mathcal{R}_2$, and $\mathcal{R}_1 \cup \mathcal{R}_2$, shown in Fig. 2, give additional insight: although the proportion of time spent in $\mathcal{R}_1$ is obviously significant at the beginning of the process, the proportion of time spent in $\mathcal{R}_2$ becomes progressively larger at long times, implying that rare events play an increasingly dominant role in determining the MFPT. In fact, the continuity of $D(r)^{1-\alpha}n(r,t)$ in Eq. (3) creates an imbalance between the time-dependent PDF of the two regions, leading progressively to the appearance of a probability maximum in $\mathcal{R}_2$ (see Fig. 2 and the movie in the Supplemental Material [36]).

The analysis can be readily extended to an m-layer system. One can show, for example, that if $r_0 \in \mathcal{R}_1$ then τ_k depends only on D_1 and D_k. More generally, if $r_0 \in \mathcal{R}_i$ then τ_k depends only on D_k and D_i, $i = 1, \ldots, j$ where $j = \min(i, k)$.

Our theoretical results might be useful for experimentally testing which convention is relevant for a particular application, e.g., by measuring the MFPT or, better, the time spent in any region between r_c and R, it can be possible to determine the correct convention that is needed to model the experimentally investigated system.

Although restricted to spherically symmetric composite systems, our study is relevant for a broad class of physical and biological systems with heterogeneous diffusion. For example, the diffusion of drug molecules inside tumors is currently modeled as obeying Eq. (2) in a spheroidal, layered structure with three principal layers: a necrotic core surrounded by a shell of quiescent, hypoxic cells, and an outer shell of proliferating cells [48,49]. Depending on the cancerous cell density, the diffusion coefficient (of nutrients, waste, or anticancer drugs) can differ from one layer to another by a factor of 3 or more [50].

Two-dimensional stochastic models, with several layers of different diffusivities, are also of great interest in the study of protein diffusion in cellular cytoplasm [51,52], and might help to understand their accumulation in low diffusion membrane microdomains (e.g., lipid rafts) [53].

Likewise, human displacements, search strategies, and foraging of animals and insects in patchy environments can be efficiently modeled with such two-dimensional layered systems [54–58].

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