Narrow-Escape Time Problem: Time Needed for a Particle to Exit a Confining Domain through a Small Window

O. Bénichou and R. Voituriez

Laboratoire de Physique Théorique de la Matière Condensée (UMR 7600), Université Pierre et Marie Curie,
4 Place Jussieu, 75255 Paris Cedex

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The time needed for a particle to exit a confining domain through a small window, called the narrow-escape time (NET), is a limiting factor of various processes, such as some biochemical reactions in cells. Obtaining an estimate of the mean NET for a given geometric environment is therefore a requisite step to quantify the reaction rate constant of such processes, which has raised a growing interest in the past few years. In this Letter, we determine explicitly the scaling dependence of the mean NET on both the volume of the confining domain and the starting point to aperture distance. We show that this analytical approach is applicable to a very wide range of stochastic processes, including anomalous diffusion or diffusion in the presence of an external force field, which cover situations of biological relevance.

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The first-passage time (FPT), namely, the time it takes a random walker to reach a given target site, is known to be a key quantity to quantify the dynamics of various processes of practical interest [1]. Indeed, chemical [2] and biochemical reactions [3], foraging strategies of animals [4,5], and the spread of sexually transmitted diseases in a human social network or of viruses through the world wide web [6] are often controlled by first encounter events.

Among first-passage processes, the case where the target is a small window on the boundary of a confining domain, defined as the narrow-escape problem, has proved very recently to be of particular importance [7,8]. The narrow-escape time (NET) gives the time needed for a random walker trapped in a confining domain with a single narrow opening to exit the domain for the first time (see Fig. 1). The relevance of the NET is striking in cellular biology, since it gives, for instance, the time needed for a reactive particle released from a specific organelle to activate a given protein on the cell membrane. Further examples are given by biochemical reactions in cellular microdomains, like dentritic spines, synapses, or microvesicles to name a few [7,8]. These submicrometer domains often contain a small amount of particles that must first exit the domain in order to fulfill their biological function. In these examples, the NET is therefore a limiting quantity whose quantization is a first step in the modeling of the process.

An important theoretical advance has been made by different groups [7–13], which obtained the leading term of the mean NET in the limit of small aperture in the case of a Brownian particle. However, except for spherically symmetric geometries, these different approaches provide an explicit dependence of the mean NET on the starting point only in a thin boundary layer. Obtaining such information is not only an important theoretical issue, but also a biologically relevant question. As a matter of fact, biomolecules like membrane signaling proteins or transcription factor proteins are generated at specific sites in the cell, whose localization plays an important role in the very function of the biomolecules, as underlined recently in [14]. In addition, the above-mentioned techniques to estimate mean NETs have been limited so far to normal Brownian diffusion, whereas many experimental studies have shown that cellular transport often departs from thermal diffusion due to the complexity of the cellular environment. In particular, crowding effects have proved to induce subdiffusive behavior in many situations [15,16], while the interaction of a tracer particle with molecular motors induces a biased motion.

In this Letter we propose an alternative theory that permits one to get new insights in the narrow-escape problem, as follows: (i) it provides explicitly the scaling dependence of the mean NET on both the volume of the confining domain and the source-aperture distance in the large volume limit, (ii) it applies to a wide range of transport processes, including anomalous diffusion, (iii) it encompasses the case of transport in the presence of a force

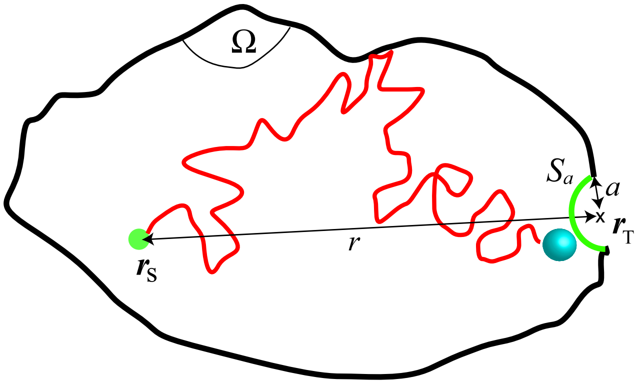

FIG. 1 (color online). The narrow-escape problem: the particle starts from $\mathbf{r}_S$ and evolves in a domain Ω with reflecting walls, except a small aperture S_a of typical radius a centered at $\mathbf{r}_T$.

field. Our formalism partially relies on the method recently proposed in [17], and considerably broadens its scope.

We start by extending the theory developed in [17] to compute the mean FPT of a continuous random motion to a closed surface $S_a(\mathbf{r}_T)$ of typical radius a containing $\mathbf{r}_T$, starting from a source point $\mathbf{r}_S$. We will next give explicit results when $S_a(\mathbf{r}_T)$ is a sphere and show that this approach allows one to tackle the narrow-escape problem. The volume delimited by $S_a(\mathbf{r}_T)$ will be denoted by $B_a(\mathbf{r}_T)$. We consider that the random walker evolves in a bounded domain Ω of volume V of the d-dimensional space $\mathbb{R}^d$. Let $P(\mathbf{r}, t|\mathbf{r}')$ be the propagator, i.e., the density probability to be at $\mathbf{r}$ at time t, starting from $\mathbf{r}'$ at time 0, which satisfies the backward equation [18]:

$$\frac{\partial}{\partial t}P(\mathbf{r}, t|\mathbf{r}') = \Delta_{\mathbf{r}'}P(\mathbf{r}, t|\mathbf{r}'), \tag{1}$$

where $\Delta_{\mathbf{r}}$ denotes the Laplace operator and the diffusion coefficient has been set to 1. Let $F(\mathbf{r}', t|\mathbf{r})dS(\mathbf{r}')$ be the probability that the first-passage time at the infinitesimal surface $dS(\mathbf{r}')$ located at $\mathbf{r}'$, starting from $\mathbf{r}$, is t. By partitioning over the first arrival time t' at a surface element $dS(\mathbf{r}')$ of the sphere $S_a(\mathbf{r}_T)$, one obtains a renewal equation [18]

$$P(\mathbf{r}_T, t|\mathbf{r}_S) = \int_{\mathbf{r}\in S_a(\mathbf{r}_T)} dS(\mathbf{r}) \int_0^t P(\mathbf{r}_T, t-t'|\mathbf{r})F(\mathbf{r}, t'|\mathbf{r}_S)dt'. \tag{2}$$

We next assume $a \ll V^{1/d}$, so that $P(\mathbf{r}_T, t|\mathbf{r} \in S_a(\mathbf{r}_T)) \equiv P(\mathbf{r}_T, t|S_a(\mathbf{r}_T))$ does not depend on $\mathbf{r} \in S_a(\mathbf{r}_T)$. This condition will be fulfilled in the large V limit considered in the following. We denote by $\langle \mathbf{T}\rangle(S_a(\mathbf{r}_T)|\mathbf{r}_S)$ the mean FPT at $S_a(\mathbf{r}_T)$, and write $\lim_{t\to\infty}P(\mathbf{r}_T, t|\mathbf{r}_S) = P_{\mathrm{stat}}(\mathbf{r}_T)$. A first order expansion of the Laplace transform of Eq. (2) in the Laplace variable then yields

$$\langle \mathbf{T}\rangle(S_a(\mathbf{r}_T)|\mathbf{r}_S)P_{\mathrm{stat}}(\mathbf{r}_T) = H(\mathbf{r}_T|S_a(\mathbf{r}_T)) - H(\mathbf{r}_T|\mathbf{r}_S), \tag{3}$$

where $H(\mathbf{r}|\mathbf{r}') = \int_0^\infty[P(\mathbf{r}, t|\mathbf{r}') - P_{\mathrm{stat}}(\mathbf{r})]dt$. Equation (3) is an extension of a similar form given in [17,19]. We then consider the large volume limit of Eq. (3), with the prescription that all points of the domain boundary tend to infinity, and define $\phi_a(\mathbf{r}_T|\mathbf{r}_S) = \lim_{V\to\infty}\langle \mathbf{T}\rangle(S_a(\mathbf{r}_T)|\mathbf{r}_S)P_{\mathrm{stat}}(\mathbf{r}_T)$. As can be checked directly from the definition of H, $\phi_a(\mathbf{r}_T|\mathbf{r}_S)$ satisfies the following boundary value problem in the *infinite* space:

$$\begin{aligned} &\Delta_{\mathbf{r}}\phi_a(\mathbf{r}_T|\mathbf{r}) = 0 \quad \text{for } \mathbf{r} \in \mathbb{R}^d \setminus B_a(\mathbf{r}_T) \\ &\phi_a(\mathbf{r}_T|\mathbf{r}) = 0 \quad \text{for } \mathbf{r} \in S_a(\mathbf{r}_T) \\ &\int_{\mathbf{r}\in S_a(\mathbf{r}_T)} \partial_n\phi_a(\mathbf{r}_T|\mathbf{r})dS(\mathbf{r}) = 1. \end{aligned} \tag{4}$$

Note that here we look only for the physical solutions such that $\phi_a(\mathbf{r}_T|\mathbf{r}_S)$ depends only on the radial coordinate $r = |\mathbf{r}_T - \mathbf{r}_S|$ for $r \gg a$. Equation (4) constitutes the central result of our method as it gives *exactly* the large volume asymptotics of the mean FPT. As we proceed to show on specific examples (see Fig. 2), this formalism provides a very good approximate of the mean FPT for finite volumes of various convex shapes for any value of the source target distance. We stress that the large volume asymptotics differs from the small a limit, which was studied in [7–13], as there are three characteristic lengths in the problem: a, $V^{1/d}$, $r = |\mathbf{r}_T - \mathbf{r}_S|$. In particular, the $r \gg a$ regime is directly accessible with our approach.

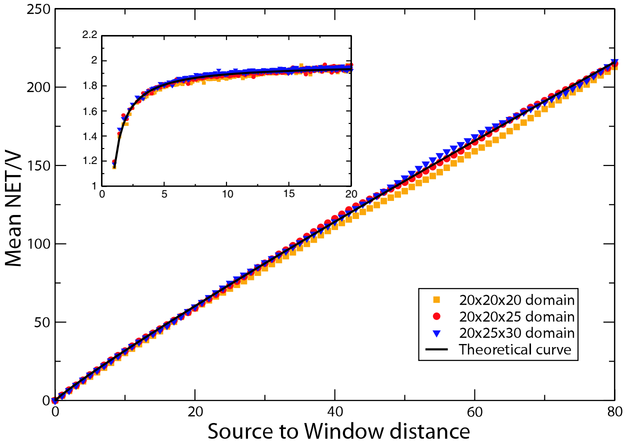

FIG. 2 (color online). The mean narrow-escape time (rescaled by the domain volume) for a diffusing particle on a critical bond percolation cluster embedded in $3d$ parallelepipedic domains of different shapes: the particle starts from a chemical distance r of a square aperture of size 1. The inset gives the same quantity for standard diffusion. Simulations (symbols) are plotted against the theoretical r and V scaling, with $d_w - d_f \simeq 1$ for the critical percolation cluster [23].

It is noteworthy that, rephrased as above, the problem simply amounts to determining an electrostatic potential outside a conducting surface $S_a(\mathbf{r}_T)$ of charge unity, and can therefore be tackled with standard techniques. For example, when $S_a(\mathbf{r}_T)$ is a sphere, the solution is straightforward and yields for the mean FPT:

$$\lim_{V\to\infty}\langle \mathbf{T}\rangle/V = \begin{cases} \frac{1}{2\pi}\ln(r/a) & \text{for } d = 2 \\ \frac{\Gamma(d/2)}{2\pi^{d/2}}\left(\frac{1}{a^{d-2}} - \frac{1}{r^{d-2}}\right) & \text{for } d \geq 3 \end{cases}. \tag{5}$$

This result is compatible with the form found in [20] using a different method.

Besides the very useful analogy with potential theory, we will show in the following that the advantage of the formulation (4) is threefold. (i) First, it can be adapted to other geometries and, in particular, to various examples of extended targets, such as an escape window in the domain boundary. It therefore extends the main result of [17] obtained in discrete space for a pointlike target. (ii) Second, as the derivation of Eq. (4) is independent of the operator Δ, it can be reproduced for any displacement operator $\mathcal{L}$. In the general case, Eq. (4) still holds, but with Δ to be substituted by the adjoint operator $\mathcal{L}^+$, and $\partial_n\phi_a$ to be substituted by the flux of ϕ_a. (iii) Last, and following the previous remark, the formulation (4) can be extended to the case of a random walker experiencing an external force field.

We first show that Eq. (4) can be extended to the example of an escape window $W_a(\mathbf{r}_T)$ of small typical radius a centered at $\mathbf{r}_T \in \partial\Omega$, which is precisely the narrow-escape problem. It will be useful to write $W_a(\mathbf{r}_T) = \partial\Omega \cap B_a^\epsilon(\mathbf{r}_T)$ where $B_a^\epsilon(\mathbf{r}_T)$ is a small volume of typical thickness ϵ. We then set $S_a^\epsilon(\mathbf{r}_T) \equiv \Omega \cap \partial B_a^\epsilon(\mathbf{r}_T)$. We now derive the mean NET through $S_a^\epsilon(\mathbf{r}_T)$, and we will use the fact that $\lim_{\epsilon\to 0} S_a^\epsilon(\mathbf{r}_T) = W_a(\mathbf{r}_T)$ to obtain the mean NET through $W_a(\mathbf{r}_T)$. Following step by step the previous derivation, we obtain

$$\langle \mathbf{T}\rangle(S_a^\epsilon(\mathbf{r}_T)|\mathbf{r}_S)P_{\rm stat}(\mathbf{r}_T) = H(\mathbf{r}_T|S_a^\epsilon(\mathbf{r}_T)) - H(\mathbf{r}_T|\mathbf{r}_S). \quad (6)$$

We now take the infinite volume limit keeping r fixed, with the prescription that Ω tends to the half space $\mathbb{R}_+^d$ delimited by the hyperplane containing $W_a(\mathbf{r}_T)$, and define $\lim_{V\to\infty}\langle \mathbf{T}\rangle(S_a^\epsilon(\mathbf{r}_T)|\mathbf{r}_S)P_{\rm stat}(\mathbf{r}_T) = \phi_a^\epsilon(\mathbf{r}_T|\mathbf{r}_S)$. One can show that $\phi_a^\epsilon(\mathbf{r}_T|\mathbf{r})$ then satisfies:

$$\begin{aligned}
\Delta_{\mathbf{r}}\phi_a^\epsilon(\mathbf{r}_T|\mathbf{r}) &= 0 \quad \text{for } \mathbf{r} \in \mathbb{R}_+^d \setminus B_a^\epsilon(\mathbf{r}_T),\\
\phi_a^\epsilon(\mathbf{r}_T|\mathbf{r}) &= 0 \quad \text{for } \mathbf{r} \in S_a^\epsilon(\mathbf{r}_T),\\
\partial_n\phi_a^\epsilon(\mathbf{r}_T|\mathbf{r}) &= 0 \quad \text{for } \mathbf{r} \in \partial\mathbb{R}_+^d,\\
\int_{\mathbf{r}\in S_a^\epsilon(\mathbf{r}_T)} &\partial_n\phi_a^\epsilon(\mathbf{r}_T|\mathbf{r})dS(\mathbf{r}) = 1.
\end{aligned} \quad (7)$$

This shows that $\phi_a^\epsilon(\mathbf{r}_T|\mathbf{r})$ is the electrostatic potential in a half space delimited by an isolating hyperplane containing a conducting window $S_a^\epsilon(\mathbf{r}_T)$ of charge unity. Taking ϵ to 0 gives the mean NET through $W_a(\mathbf{r}_T)$. In the case of a spherical window $W_a(\mathbf{r}_T)$, the solution of (7) can be exactly given. For $d = 3$, we obtain in oblate spheroidal coordinates [21]:

$$\lim_{V\to\infty}\langle \mathbf{T}\rangle/V = \frac{1}{2\pi a}\arctan\xi = \frac{1}{4a} - \frac{1}{2\pi r} + o\left(\frac{1}{r}\right), \quad (8)$$

where ξ depends on Cartesian coordinates according to $z^2/(a^2\xi^2) + (x^2+y^2)/[a^2(\xi^2+1)] = 1$. For $d = 2$, we use elliptic coordinates and get

$$\lim_{V\to\infty}\langle \mathbf{T}\rangle/V = \frac{\mu}{\pi} \sim_{r\to\infty} \frac{1}{\pi}\ln(r/a), \quad (9)$$

where μ depends on Cartesian coordinates according to $x^2/(a^2\cosh^2\mu) + y^2/(a^2\sinh^2\mu) = 1$. We stress that expressions (8) and (9) of the mean NET are exact for any position of the source point $\mathbf{r}_S$. In particular, they are compatible with the results of [8–13], which give the same small a limit.

We now generalize Eq. (4) to the case of a generic displacement operator $\mathcal{L}$ such that the stationary distribution is *uniform* $P_{\rm stat} = 1/V$, which actually underlies many models of transport in complex media [22]. We here assume that $S_a(\mathbf{r}_T)$ is a sphere, and following [17,23], we further assume that the infinite space propagator P_0 satisfies the standard scaling:

$$P_0(\mathbf{r}, t|\mathbf{r}') \propto t^{-d_f/d_w}\Pi\left(\frac{|\mathbf{r}-\mathbf{r}'|}{t^{1/d_w}}\right), \quad (10)$$

where the fractal dimension d_f characterizes the accessible volume $V_r \propto r_f^d$ within a sphere of radius r, and the walk dimension d_w characterizes the distance $r \propto t^{1/d_w}$ covered by a random walker in a given time t. This formalism, in particular, covers the case of a random walk on a random fractal like critical percolation clusters, which gives a representative example of subdiffusive behavior due to crowding effects [23] and could mimic in a first approximation the cellular environment. Note that we here implicitly require that the trajectories and the medium have length scale invariant properties that ensure the existence of d_w and d_f. Substituting the scaling (10) in the definition of H, we obtain from (3) the large V equivalence for any r:

$$\lim_{V\to\infty}\langle \mathbf{T}\rangle/V = \begin{cases} \alpha(a^{d_w-d_f} - r^{d_w-d_f}) & \text{for } d_w < d_f\\ \alpha\ln(r/a) & \text{for } d_w = d_f,\\ \alpha(r^{d_w-d_f} - a^{d_w-d_f}) & \text{for } d_w > d_f \end{cases} \quad (11)$$

where the constant α does not depend on the confining domain but only on the scaling function Π. Expressions (11) therefore explicitly elucidate the dependence of the mean FPT on the geometrical parameters V and r. As previously Eqs. (11) permit one to obtain the mean NET: if we assume that the exit window $S_a^\epsilon(\mathbf{r}_T)$ is a half sphere of radius a, the mean NET will be exactly given by 2 times the mean FPT (11). For a generic window, the r and V scaling of Eq. (11) is unchanged for $r \gg a$. Figure 2 illustrates the example of a square window and shows that the predicted r and V scaling actually holds for finite volumes of various convex shapes.

Equation (11) highlights two regimes. When the exploration is not compact ($d_w < d_f$), as in the case of a Brownian particle in the three-dimensional space (see Fig. 2 inset), the dependence on the starting point disappears for $r \gg a$. On the other hand, in the case of compact exploration ($d_w \geq d_f$), as for two-dimensional diffusion or subdiffusion on fractals (see Fig. 2), the mean NET diverges at large r and the starting point position is crucial.

Last, we consider the case of a Brownian particle in the presence of a force field $F(\mathbf{r}) = -\nabla_{\mathbf{r}}\Phi(\mathbf{r})$. We assume that the target is a sphere $S_a(\mathbf{r}_T)$, and that the force field is spherically symmetric and centered at $\mathbf{r}_T$. We set the gauge such that $\Phi(\mathbf{r}) = 0$ for $\mathbf{r} \in B_a(\mathbf{r}_T)$. Equation (4) then holds with $\Delta_{\mathbf{r}}$ to be replaced by the adjoint operator $\mathcal{L}^+$ governing the evolution of the propagator [18]:

$$\mathcal{L}^+ = F(\mathbf{r})\nabla_{\mathbf{r}} + \Delta_{\mathbf{r}}. \quad (12)$$

We then solve $\mathcal{L}^+\phi_a(\mathbf{r}_T|\mathbf{r}) = 0$ with the same boundary conditions as in (4), and write the stationary distribution

$$P_{\rm stat}(\mathbf{r}) = \frac{e^{-\Phi(\mathbf{r})}}{\int_\Omega d\Omega(\mathbf{r}')e^{-\Phi(\mathbf{r}')}}. \quad (13)$$

Using Eq. (3), we finally get the large V equivalence of the mean FPT for any r:

$$\langle \mathbf{T} \rangle \sim \frac{\Gamma(d/2)}{2\pi^{d/2}} \left(\int_\Omega d\Omega(\mathbf{r}') e^{-\Phi(\mathbf{r}')} \right) \left(\int_a^r u^{1-d} e^{\Phi(u)} \right). \quad (14)$$

As previously, the mean NET through a spherical window is obtained as 2 times the mean FPT. One should note that the volume dependence entirely lies in the first integral factor of (14), which is suitable for a quantitative analysis. On the other hand, the r dependence is fully contained in the second integral factor and will depend on the specific shape of Φ. The volume dependence of (14) agrees with the one found in [24], where, however, the r dependence was not given.

We now give the explicit example of a divergenceless force. In the context of biological cells, such force can model in a first approximation the coupling of the particle to molecular motors that perform a directional motion along cytoskeletal filaments [25], organized in this example in an aster, if one assumes that the force is proportional to the local concentration of filaments. This situation also describes a Brownian particle advected in an incompressible hydrodynamic flow. For $d = 3$ such force is given by $F(r) = -\gamma/r^2$ and the equivalent potential governing the dynamics can be taken as $\Phi(\mathbf{r}) = \gamma(1/r - 1/a)$. Applying (14), we get

$$\langle \mathbf{T} \rangle \sim \frac{V}{4\pi\gamma} (e^{\gamma(1/a - 1/r)} - 1) \quad (15)$$

for a generic domain shape. Note that the r dependence is modified by the force field, while the V dependence at large V is unchanged for any force intensity γ. For $d = 2$ the force is given by $F(r) = -\gamma/r$ and the equivalent potential can be taken as $\Phi(\mathbf{r}) = \gamma \ln(r/a)$. Applying (14) in the case of a domain whose boundary is parametrized by $R(\theta)$ in polar coordinates, we get the large volume equivalence

$$\langle \mathbf{T} \rangle \sim \frac{1}{\gamma(2-\gamma)} \left(\int_0^{2\pi} \frac{d\theta}{2\pi} R^{2-\gamma}(\theta) - \frac{\gamma}{2} a^{2-\gamma} \right) (r^\gamma - a^\gamma). \quad (16)$$

As opposed to the $d = 3$ case, the V dependence is now modified by the force. Interestingly, we find a transition for $\gamma = 2$. For $\gamma < 2$, the mean FPT will scale like $V^{1-\gamma/2}$ at large V, while the V dependence disappears for $\gamma > 2$. In the case of a target centered in a spherical domain, the results of [1] can be straightforwardly recovered from (14) and are compatible with (15) and (16).

To conclude, we have proposed a general theory that provides explicitly the scaling dependence of the mean NET on both the volume of the confining domain and the source-aperture distance for a wide range of transport processes, including anomalous diffusion and transport in the presence of a force field, which are relevant to biological situations. In particular, we find that the dependence of the mean NET on the source-aperture distance is crucial when the exploration is compact, as is the case for the subdiffusive behavior in the crowded environment that is observed in cells. Our model also permits us to take into account the active transport due to molecular motors.

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