Asymptotics for the fastest among $N$ stochastic particles: role of an extended initial distribution and an additional drift component

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We derive asymptotic formulas for the mean exit time $\bar{\tau}_N$ of the fastest among $N$ identical independently distributed Brownian particles to an absorbing boundary for various initial distributions (partially uniformly and exponentially distributed). Depending on the tail of the initial distribution, we report here a continuous algebraic decay law for $\bar{\tau}_N$, which differs from the classical Weibull or Gumbell results. We derive asymptotic formulas in dimension 1 and 2, for half-line and an interval that we compare with stochastic simulations. We also obtain formulas for an additive constant drift on the Brownian motion. Finally, we discuss some applications in cell biology where a molecular transduction pathway involves multiple steps and a long-tail initial distribution.

1. INTRODUCTION

Transient molecular activation in many cellular processes, such as gene transcription [1], calcium activity in neuronal protrusion [2] or biochemical pathways associated with a secondary messenger transduction [3] often occur in geometrical restricted micro-compartments, where the initial distribution of the source is well separated from the target site. To guarantee a reliable and fast activation, these processes are carried out by multiple redundant particles [4–6]. The multiplicity or redundancy has two effects: it increases the probability of finding a small target and, in parallel, decreases the mean activation time. Because it is usually costly to produce many copies of the same object, there is usually a compromise between the number of produced copies and the ultimate time scale of activation. In addition, for molecular processes involving multiple time steps, as we shall see here, any possible spreading of the initial distribution can affect the final activation time.

For example, calcium ions enter in less than a few milliseconds inside a dendrite or neuronal synapses through few channels located on the membrane. After channels are closed, the calcium concentration has already spread, with a characteristic distribution, approximated as Gaussian in the diffusion limit (Fig. 1A). But other initial distributions are possible because cellular crowding could slow down diffusion, leading to anomalous diffusion profiles. Starting with such long-tail instantaneous distribution, calcium ions can fulfill several functions such as activating buffer located at a certain distance away from the calcium channels. This step is necessary for the activation of a secondary messenger that can lead to change in the physiology. Indeed, it has been known for decades that calcium concentration is a key factor for the induction of long-term synaptic changes [8], but the exact reasons is still unclear: it could be to activate enough molecules quickly. We recently reported [2] that the initial distribution of injected calcium ions can modulate the probability of a calcium avalanche known as calcium-induced-calcium release, fundamental for the induction of physiological changes underlying learning and memory. Another generic example is the secondary biochemical messenger pathway (Fig. 1B): molecules such as cGMP, IP$_3^+$ or cAMP are generated near receptors and need to travel a certain distance away to activate a second pathway. In all these cases, the initial concentration of these molecules is critical for the genesis of rhythmic oscillations or the amplification of a single molecular events. As we shall see, the initial number and their distribution can be critical for the determination of the activation time of a transduction cascade.

We recall that changing the initial number on the search time by the fastest has been quantified as follows: when there are $N$ i.i.d. particles, generated at a specific point location (entrance of a channel or a receptor), then the Mean Fastest Arrival Time (MFAT), which is the mean time it takes for the first one to arrive decays with $1/\log N$ (a classical property of the Gumbell distribution) [2 3 11], but the decays can be much faster $1/N^2$ when the
Fig. 1: Two examples of fast molecular signalling where the initial distribution has a long tails. A. Calcium ions enter very quickly through a channel or a cluster of channels. This fast entrance is associated to an initial distribution that can intersect at the tail with calcium sensitive receptors (such as Ryanodine receptors). B. IP$_3^+$ molecules, generated very quickly from PIP$_2$ at the cell membrane, that need to bind to IP$_3$-receptor.

Initial distribution of particles is uniformly distributed [12–14]. Computing how the first arrival time depends on the initial numbers $N$ is key to formulate biophysical laws of activation by the fastest diffusing particles to reach a target. The type of motion could matter, as revealed for spermatozoa to arrive to the ovule location, modeled as persistent motion switching direction after hitting the surface [15]. In general we are still missing the law of arrival for anomalous diffusion and many classical random motion such as for the full Langevin.

We compute here the mean arrival time $\bar{\tau}_N$ for the fastest among $N$ identical Brownian particles using short-time asymptotic of the diffusion equation. In particular, we consider the case of extended initial conditions. Indeed, as mentioned above, after a molecule is generated at a specific location, additional chemical processes are involved to provide the molecular activity required to interact with a given target. Specific reactions are phosphorylations in case of transcription factor or methylations [16]. Indeed in some cases, transcription factors need to be phosphorylated or other molecules are needed, creating re-modeler complexes [17]. During these specific activation, the initial molecule can move by small drift or diffuse away allowing the initial concentration to spread a bit, a situation that we are interested in here.

The manuscript is organized as follow. First, we recall the framework and derive explicit expressions for the MFAT when the initial distribution is uniform, intersecting or not with the target site for half a line $R_+$ and for a segment $\Omega = [0, a]$. We study initial distributions of the form $p_1(x) = \frac{2 b e^{-b x^2}}{\Gamma(\frac{\alpha + 1}{2})} x^{\alpha} e^{-b x^2}$ with $b > 0$ and $\alpha \geq 0$ and obtain the general formula (relation (11))

$$\bar{\tau} \sim \frac{C_\alpha}{N^{\frac{1}{\alpha+1}}} \frac{1}{4 D b} \text{ for } N \gg 1,$$

(1)
where $\Gamma$ is the Gamma function and
\[ C_\alpha = \Gamma \left( \frac{\alpha + 3}{\alpha + 1} \right) \left( \frac{\sqrt{\pi} (\alpha + 1) \Gamma \left( \frac{\alpha + 1}{2} \right)}{2 \Gamma \left( \frac{\alpha + 2}{2} \right)} \right)^{\frac{\alpha}{2+\alpha}}. \] (2)

This formula reveals a large spectrum of possible decay that depends on the analytical expression of the local overlap between the initial distribution and the target location. In addition, we provide an equivalent formula in two dimensions. Finally, we study the influence of a constant drift on the escape time $\bar{\tau^N}$.

2. GENERAL FRAMEWORK FOR THE FIRST ARRIVAL TIME

The shortest arrival time for $N$ non-interacting i.i.d. Brownian trajectories (molecules, proteins, ions) moving in a domain $\Omega$ to a small target (binding site) is defined as
\[ \tau^1 = \min(t_1, ..., t_N), \]
where $t_i$ are the i.i.d. arrival times of the $N$ particles. The complementary cumulative density function of $\tau^1$ is given by
\[ Pr\{\tau^1 > t\} = [Pr\{t_1 > t\}]^N, \]
where $Pr\{t_1 > t\}$ is the survival probability of a single particle prior to reaching the target. This probability can be computed from solving the diffusion equation
\[ \frac{\partial p(x,t)}{\partial t} = D \Delta p(x,t) \text{ for } x \in \Omega, \ t > 0 \]
\[ p(x,0) = p_0(x) \text{ for } x \in \Omega \]
\[ \frac{\partial p(x,t)}{\partial n} = 0 \text{ for } x \in \partial \Omega_r \]
\[ p(x,t) = 0 \text{ for } x \in \partial \Omega_a \]
where $D$ is the diffusion coefficient and, the boundary $\partial \Omega$ contains $R$ binding sites $\partial \Omega_i \subset \partial \Omega$ with $i = 1, .., R$, we have then
\[ \partial \Omega_a = \bigcup_{i=1}^R \partial \Omega_i \]
and $\partial \Omega_r = \partial \Omega - \partial \Omega_a$. The survival probability is
\[ Pr\{t_1 > t\} = \int_{\Omega} p(x,t)dx \] (3)
so that the probability density function (pdf) for the arrival of the first particle is
\[ Pr\{\tau^1 = t\} = \frac{d}{dt} Pr\{\tau^1 < t\} = N(Pr\{t_1 > t\})^{N-1} Pr\{t_1 = t\}, \] (4)
where the instantaneous probability is given by the probability flux
\[ Pr\{t_1 = t\} = \oint_{\partial \Omega^a} \frac{\partial p(x,t)}{\partial n} dS_x. \]
The Mean Fastest Arrival Time (MFAT) is defined as the mean time for the first among $N$ i.i.d. Brownian paths to reach the target and is obtained by computing the integral
\[ \tau^N = \int_0^\infty Pr\{\tau^1 > t\} \, dt = \int_0^\infty [Pr\{t_1 > t\}]^N \, dt. \] (5)
3. ARRIVAL TIMES FOR MULTIPLE INITIAL DISTRIBUTIONS IN DIM 1

3.1. Arrival from a ray for multiple initial distributions

We start with the case of a ray $\Omega = \mathbb{R}_+$, for which the solution of the diffusion equation

$$\frac{\partial p(x, t)}{\partial t} = D \frac{\partial^2 p(x, t)}{\partial x^2} \quad \text{for } x > 0, t > 0$$

(6)

$$p(x, 0) = \delta (x - y) \quad \text{for } x > 0$$

$$p(0, t) = 0 \quad \text{for } t > 0$$

is given by

$$p(x, t) = \frac{1}{\sqrt{4Dt}} \exp \left\{ -\frac{(x - y)^2}{4Dt} \right\} - \exp \left\{ -\frac{(x + y)^2}{4Dt} \right\}. \quad (7)$$

For a general initial condition, the solution of (6) is the convolution of the initial pdf $p(x, 0)$ with the elementary function presented in (7). We previously treated the case of the Dirac delta function in dimension 1, 2 and 3 \cite{13, 18, 19} and also for initial distributions spread over a perpendicular segment in a cusp \cite{20}. When the initial distribution of particles is uniform in a small portion of the ray, $[0; y_0]$, $p(x, 0) = \frac{1}{y_0} \mathbb{1}_{[x \in [0, y_0]]}$, then the solution is

$$p(x, t) = \int_0^{y_0} \frac{1}{y_0 \sqrt{4Dt}} \left[ \exp \left\{ -\frac{(x - y)^2}{4Dt} \right\} - \exp \left\{ -\frac{(x + y)^2}{4Dt} \right\} \right] dy.$$ 

The survival probability given by relation (3) is

$$Pr \{t_1 > t\} = \int_0^\infty p(x, t) dx = 1 - \frac{2}{\pi} \int_0^\infty e^{-u^2} du + \sqrt{\frac{4Dt}{y_0 \sqrt{\pi}}} \exp \left\{ -\frac{y_0^2}{4Dt} \right\} - 1.$$ \quad (8)

For small time asymptotic $t \ll 1$, $Pr \{t_1 > t\} \sim 1 - \frac{\sqrt{4Dt}}{y_0 \sqrt{\pi}}$ and thus using relation (4),

$$\mathcal{N} \sim \int_0^\infty \exp \left\{ -\mathcal{N} \frac{\sqrt{4Dt}}{y_0 \sqrt{\pi}} \right\} dt = \frac{y_0^2 \pi}{2DN^2}. \quad (9)$$

This result shows that as soon as the initial condition overlaps with the target, the MFAT decay with order $1/N^2$. We now consider a local initially uniform distribution in the shifted interval $[y_1; y_2]$ where $y_1 > 0$, not overlapping with the target site. The initial normalized distribution function is thus $p_0(x) = \frac{1}{y_2 - y_1} \mathbb{1}_{[x \in [y_1, y_2]]}$ with $y_2 > y_1 > 0$. We now compute the pdf for particle to reach the boundary. It is given by

$$Pr \{t_1 > t\} = \int_0^\infty \int_{y_1}^{y_2} \frac{1}{(y_2 - y_1) \sqrt{4Dt}} \left[ \exp \left\{ -\frac{(x - y)^2}{4Dt} \right\} - \exp \left\{ -\frac{(x + y)^2}{4Dt} \right\} \right] dy \ dx$$

$$= 1 - \frac{y_2}{y_2 - y_1} \left( \frac{2}{\pi} \int_{y_1}^{y_2} e^{-u^2} du \right) + \frac{y_1}{y_2 - y_1} \left( \frac{2}{\pi} \int_{y_1}^{y_2} e^{-u^2} du \right)$$

$$+ \frac{\sqrt{4Dt}}{(y_2 - y_1) \sqrt{\pi}} \left[ e^{-\frac{y_2^2}{4Dt}} - e^{-\frac{y_1^2}{4Dt}} \right].$$

Expanding the complementary error function, we obtain for small $t$ asymptotic the relation

$$S(t) = Pr \{t_1 > t\} \sim 1 - \frac{(\sqrt{4Dt})^3}{2(y_2 - y_1) \sqrt{\pi}} \left[ e^{-\frac{y_2^2}{4Dt}} y_1^2 + e^{-\frac{y_1^2}{4Dt}} y_2^2 \right]. \quad (9)$$
Note that expression (9) contains two exponentially small terms. It is however possible to recover the case of an initial Dirac function by making the expansion \( y_2 = y_1 (1 + \varepsilon) \) and studying the limit when \( \varepsilon \) goes to zero in equation (9). In that case, we have

\[
S_\varepsilon(t) \sim 1 - \frac{(\sqrt{4Dt})^3 e^{-\frac{y_1^2}{4Dt}}}{2y_1\varepsilon \sqrt{\pi}} \left[ 1 - \frac{e^{-\frac{y_1^2(2x+\varepsilon)^2}{4D(t)}}}{(1+\varepsilon)^2} \right].
\]

A Taylor expansion in \( \varepsilon \) and \( \frac{1}{t} \) leads to

\[
S_\varepsilon(t) = 1 - \frac{(\sqrt{4Dt})^3 e^{-\frac{y_1^2}{4Dt}}}{\sqrt{\pi}y_1^3} \left[ 1 + \frac{y_1^2}{4Dt} - \varepsilon\left( 1 + \frac{3y_1^2}{2 \cdot 4Dt} + \frac{2y_1^4}{(4Dt)^2} \right) + O(\varepsilon^2) + O\left( \frac{\varepsilon}{t} \right) \right].
\]

When \( \varepsilon \to 0 \), the survival probability \( S_\varepsilon(t) \) converges to \( S_0(t) \) corresponding to an initial condition for the Dirac delta function at position \( y_1 \). However, the convergence is not uniform in \( t \) in the interval \( [0, \infty] \), preventing to use this expansion to estimate the MFAT for the case of an interval. Thus to leading order, using that

\[
\lim_{y_2 \to y_1} \Pr\{t_1 > t\} \sim 1 - \frac{\sqrt{4Dt}}{\sqrt{\pi}} \left[ \frac{e^{-\frac{y_1^2}{4Dt}}}{y_1} \right],
\]

we obtain to leading order the asymptotic formula for \( N \gg 1 \)

\[
\tau N \approx \frac{y_1^2}{4D \log \left( \frac{A_1}{\sqrt{\pi}} \right)} + A_x,
\]

where \( A_x = A_0 + \varepsilon A_1 + ... \), where \( A_k \) are constants. Here \( y_1 \) is the shortest distance to the absorbing boundary. To conclude, to leading order, the MFAT for a small interval is the same as a Dirac delta function at the minimum point of the interval where the particles are uniformly distributed.

### 3.2. MFAT for an initial distribution asymptotically touching the target site

For an initial normalized distribution \( p_1(x) = K x^\alpha e^{-bx^2} \) with \( \alpha \geq 0 \) and \( b > 0 \), we have

\[
K = \frac{2b^{\frac{\alpha+1}{2}}}{\Gamma\left(\frac{\alpha+1}{2}\right)}.
\]

The survival probability of the diffusion process is given by relation (5) leading to

\[
\Pr\{t_1 > t\} = \frac{2b^{\frac{\alpha+1}{2}}}{\Gamma\left(\frac{\alpha+1}{2}\right)} \int_0^\infty \text{erf}\left(\frac{y}{\sqrt{4Dt}}\right) y^\alpha \cdot \exp\{-by^2\} dy
\]

\[= \frac{\Gamma\left(\frac{\alpha+2}{2}\right)}{\Gamma\left(\frac{\alpha+1}{2}\right) \cdot (4Dbt)^{\frac{\alpha+1}{2}} \sqrt{\pi}^{\frac{\alpha+2}{2}}} 2F_1\left[\frac{1}{2},\frac{\alpha+2}{2},\frac{3}{2},\frac{-1}{4Dbt}\right].\]

where \( 2F_1\left[a, b, c, z\right] \) is the Gauss hyper-geometric function. The expansion for \( z \to \infty \) (\( t \) small), gives

\[
2F_1\left[\frac{1}{2},\frac{\alpha+2}{2},\frac{3}{2},\frac{-1}{4Dbt}\right] = \frac{\sqrt{\pi} \cdot \Gamma\left(\frac{\alpha+2}{2}\right) \cdot (4Dbt)^{\frac{\alpha+2}{2}}}{2\Gamma\left(\frac{\alpha+3}{2}\right)} - \frac{(4Dbt)^{\frac{\alpha+2}{2}}}{\alpha+1} + O(t^{\frac{\alpha+4}{2}}).
\]

Thus for \( t \) small, we have

\[
\Pr\{t_1 > t\} \sim 1 - \frac{2\Gamma\left(\frac{\alpha+2}{2}\right)}{(\alpha+1)\sqrt{\pi} \Gamma\left(\frac{\alpha+3}{2}\right)(4Dbt)^{\frac{\alpha+1}{2}}}
\]
and the MFAT is
\[
\tau^N \sim \int_0^\infty \exp \left\{ -\frac{2NT(a+2)}{(a+1)\sqrt{\pi} \Gamma\left(\frac{a+1}{2}\right)} (4Dt)^{\frac{a+1}{2}} \right\} \, dt
\]
\[
\sim \left( \frac{\sqrt{\pi}(a+1)\Gamma\left(\frac{a+1}{2}\right)}{2NT\left(\frac{a+1}{2}\right)} \right)^{\frac{1}{a+1}} \cdot \frac{1}{4Dd} \cdot \Gamma\left(\frac{\alpha+3}{\alpha+1}\right). \tag{11}
\]
When \(\alpha = 0\), the initial distribution becomes \(p_0 = \frac{2\sqrt{\pi}}{\sqrt{2\pi}} \exp \left\{ -by^2 \right\}\), we recover the same behavior as the case where the Brownian particles are uniformly distributed in \([0, y_0]\). For \(\alpha = 1\), we obtain that the MFAT decays with \(1/N\). For \(\alpha = 2\), we obtain that MFAT decays like \(\frac{1}{N^{\frac{1}{2}}t}\).

### 3.3. MFAT inside the interval \([0, a]\)

In this part, we present asymptotic computation for the MFAT to one of the extremities of an interval. We start with the solution of the diffusion equation
\[
\frac{\partial p(x, t)}{\partial t} = D \frac{\partial^2 p(x, t)}{\partial x^2} \quad \text{for } x > 0, t > 0
\]
\[
p(x, 0) = \delta(x - y) \quad \text{for } x > 0
\]
\[
p(0, t) = p(a, t) = 0 \quad \text{for } t > 0
\]
which is given by the infinite sum
\[
p(x, t) = \frac{1}{\sqrt{4Dt\pi}} \sum_{n=-\infty}^{+\infty} \left[ \exp \left\{ -\frac{(x - y + 2na)^2}{4Dt} \right\} - \exp \left\{ -\frac{(x + y + 2na)^2}{4Dt} \right\} \right]. \tag{13}
\]
To compute the MFAT, we shall use only the first terms associated with \(n = \pm 1\). For an initial uniformly distributed particles in the interval \([0, a]\) of the form \(p_0(x) = \frac{1}{a} \mathbb{1}_{\{x \in [0, a]\}}\) with \(0 < b < a\), the approximated solution of equation (12) is given by
\[
p(x, t) = \int_0^b \frac{1}{\sqrt{4Dt\pi}} \left[ \exp \left\{ -\frac{(x - y)^2}{4Dt} \right\} - \exp \left\{ -\frac{(x + y)^2}{4Dt} \right\} \right] \, dy.
\]
The survival probability is
\[
Pr\{t_1 > t\} = \int_0^a p(x, t) \, dx = \frac{1}{b} \left[ b \cdot \text{erf} \left( \frac{b}{\sqrt{4Dt}} \right) - (a + b) \cdot \text{erf} \left( \frac{a + b}{\sqrt{4Dt}} \right) + 2a \cdot \text{erf} \left( \frac{a}{\sqrt{4Dt}} \right) \right. \\
- \left. (a - b) \cdot \text{erf} \left( \frac{a - b}{\sqrt{4Dt}} \right) + (2a + b) \cdot \text{erf} \left( \frac{2a + b}{\sqrt{4Dt}} \right) - 4a \cdot \text{erf} \left( \frac{2a}{\sqrt{4Dt}} \right) \right. \\
+ \left. (2a - b) \cdot \text{erf} \left( \frac{2a - b}{\sqrt{4Dt}} \right) - \frac{(3a - b)}{2} \cdot \text{erf} \left( \frac{3a - b}{\sqrt{4Dt}} \right) - \frac{(3a + b)}{2} \cdot \text{erf} \left( \frac{3a + b}{\sqrt{4Dt}} \right) \right. \\
+ \left. 3a \cdot \text{erf} \left( \frac{3a}{\sqrt{4Dt}} \right) + \frac{\sqrt{4Dt}}{\pi} \left[ a^{-\frac{12}{4D}} - 1 - e^{\frac{(a-b)^2}{4Dt}} - 2e^{\frac{a^2}{4Dt}} - e^{\frac{(a+b)^2}{4Dt}} \right. \\
- \left. 2e^{\frac{(2a)^2}{4Dt}} + e^{\frac{(2a-b)^2}{4Dt}} - \frac{1}{2} e^{\frac{(3a-b)^2}{4Dt}} + e^{\frac{(3a+b)^2}{4Dt}} - \frac{1}{2} e^{\frac{(3a+b)^2}{4Dt}} \right].
\]
In the small $t$ limit, we have the approximation

$$S(t) = Pr \{ t_1 > t \} \sim 1 - \frac{\sqrt{4Dt}}{b\sqrt{\pi}}.$$  

Note that using equation (4), we can compute the distribution of arrival times. In that case, we have

$$Pr \{ \tau^1 = t \} = \frac{d}{dt} \Pr \{ \tau^1 > t \} = N(Pr \{ t_1 > t \})^{N-1}Pr \{ t_1 = t \} \sim \frac{N\sqrt{D}}{b\sqrt{\pi} \cdot t} \exp \left\{ -\frac{\sqrt{4Dt}N}{b\sqrt{\pi}} \right\}. \tag{14}$$

This formula leads to the asymptotic expression for the MFAT

$$\tau^N \sim \frac{b^2\pi}{2DN^2}. \tag{15}$$

When the initial distribution intersect the right hand-side of the interval $p_0(x) = \frac{1}{a-x}[x \in [b,a)]$ with $0 < b < a$, we obtain a similar expression:

$$\tau^N \sim \frac{(a-b)^2\pi}{2DN^2}.$$  

When the Brownian particles are initially uniformly distributed in an interval $[b,c]$ contained inside $[0,a]$, $p_0(x) = \frac{1}{c-b}[x \in [b,c)]$ with $0 < b < c < a$, the solution of the diffusion equation becomes

$$p(x,t) = \int_b^c \frac{1}{(c-b)\sqrt{4Dt\pi}} \left[ \exp\left\{ -(x-y)^2 \frac{4D}{4Dt}\right\} - \exp\left\{ -(x+y)^2 \frac{4D}{4Dt}\right\} + \exp\left\{ -(x+y-2a)^2 \frac{4D}{4Dt}\right\} \right] dy$$

and the survival probability is

$$Pr \{ t_1 > t \} = \frac{1}{c-b} \left[ c-b + \frac{(\sqrt{4Dt})^3}{\sqrt{\pi}} \left[ e^{-\frac{c^2}{4D}} - e^{-\frac{b^2}{4D}} - \frac{e^{-\frac{(a+b)^2}{4D}}}{2(c+a)^2} \frac{c}{2} - \frac{e^{-\frac{(a+c)^2}{4D}}}{2(b+c)^2} \frac{c}{2} \right] \right. \left. + \frac{e^{-\frac{(a+2b)^2}{4D}}}{2(c+2a)^2} + \frac{e^{-\frac{(a-2b)^2}{4D}}}{2(c-2a)^2} + \frac{e^{-\frac{(2a+c)^2}{4D}}}{2(2a+c)^2} e^{-\frac{(2a-c)^2}{4D}} + \frac{e^{-\frac{(3a-c)^2}{4D}}}{2(3a-c)^2} \right] .$$

The distribution for the arrival time is given by

$$Pr \{ \tau^1 = t \} = -\frac{d}{dt} S(t) |_{N} \sim -\frac{d}{dt} \left[ \exp\left\{ -\frac{N(\sqrt{4Dt})^3 e^{-\frac{(b_0+b-a)^2}{4Dt}}}{2(c-b)(b_0)(a-c)^2\sqrt{\pi}} \right\} \right]$$

$$\sim \frac{\sqrt{4Dt}^3 \exp\left\{ \frac{-\min^2(b,a-c)}{4Dt} \right\}}{2(c-b) \cdot \min(b,a-c)\sqrt{\pi} \cdot t} \times \exp\left\{ -\frac{(\sqrt{4Dt})^3 N}{2(c-b)\sqrt{\pi}} \frac{\min^2(b,a-c)}{\min^2(b,a-c)} \right\}$$

$$\times \frac{\min(b,a-c)}{4Dt^2} + \frac{3}{2t}. \tag{16}$$
Using a Taylor expansion when \( c \to b \) in the form \( c = b(1 + \epsilon) \) when \( \epsilon \to 0 \), the survival probability \( S_\epsilon(t) \) converges to the survival probability \( S_0(t) \) in the case that the initial condition is a Dirac delta function. However, as shown above, the convergence is not uniform in time \( t \) in the interval \([0, \infty)\[, preventing to use this expansion to estimate the MFAT for the case of an interval. Thus to leading order, we have

\[
\lim_{c \to b} \Pr \{ t_1 > t \} \sim 1 - \frac{\sqrt{4Dt}}{\sqrt{\pi}} \left[ e^{-\frac{\text{min}(b,a-c)^2}{4Dt}} \right],
\]

and thus the leading order term for the asymptotic formula for \( N \gg 1 \) is given by

\[
\tau_N \sim \frac{\text{min}(b,a-c)^2}{4D \log \left( \frac{N}{\sqrt{\pi}} \right)} + A_\epsilon,
\]

where \( A_\epsilon = A_0 + \epsilon A_1 + \ldots \), where \( A_k \) are constants. Here \( \text{min}(b,a-c) \) is the shortest distance to the absorbing boundaries. To conclude, at leading order, the MFAT when the initial distribution of particles falls inside a small interval is the same as the one obtained for a Dirac delta function where the main parameter is the minimal distance to the boundaries of the interval where the particles are uniformly distributed.

### 3.4. MFAT for particles initially distributed following a long tail inside the interval \([0,c]\)

We consider the MFAT when the initial distribution is given by \( p_1(x) = \frac{2b}{1-e^{-bc}}xe^{-x^2\frac{\epsilon}{4}} \text{1}_{[x \in [0,c]} \) with \( a > c > 0 \). Then, the solution of the diffusion equation is given by the following expression

\[
p(x,t) = \frac{2b}{1-e^{-bc}} \int_0^a \frac{1}{\sqrt{4Dt\pi}} \left[ \exp \left\{ -(x-y)^2/4Dt \right\} - \exp \left\{ -(x+y)^2/4Dt \right\} + \exp \left\{ -(x-y-2a)^2/4Dt \right\} \right] \left[ \exp \left\{ -(x+y-2a)^2/4Dt \right\} \right] y \exp \left\{ -bc^2 \right\} dy.
\]

For \( t \) small, the survival probability can be approximated by the formula

\[
S(t) = \Pr \{ t_1 > t \} \sim 1 - \frac{2Dbt}{1-e^{-bc^2}}.
\]

The distribution for the first arrival time in this case is

\[
\Pr \{ \tau^1 = t \} = -\frac{d}{dt}S^N(t) \sim -\frac{d}{dt} \left[ \exp \left\{ -\frac{2NDbt}{1-e^{-bc^2}} \right\} \right] = \frac{2bDN}{1 - \exp\{-bc^2\}} \exp \left\{ -\frac{2DbN}{1 - \exp\{-bc^2\}} \right\}.
\]

Thus, we have the asymptotic formula

\[
\tau^N \sim \frac{1 - e^{-bc^2}}{2DbN^2},
\]

We decided to compare the asymptotic distribution we obtained with stochastic simulations (see Appendix for the description of the algorithm). We generated trajectories before the reach the origin and selected the fastest (green in Fig. 2A). We chose several initial distributions (Fig. 2B) and we compare the histogram of arrival time for the fastest with
FIG. 2: Arrival times for the fastest Brownian particles for various initial distributions. 

A. Examples of 5 independent Brownian trajectories starting at $x = 0.5$ and absorbed at $x = 0$ and the fastest is green. 

B. Three initial distributions: the exponential distribution $p_1(x) = \frac{2b^{\alpha+1}}{\Gamma(\frac{\alpha+1}{2})}x^{\alpha-1}e^{-bx^2}$ and two uniform distributions $p_2(x) = \frac{1}{y_2-y_1}I_{\{y_1 \leq x \leq y_2\}}$ and $p_3(x) = \frac{1}{y_2-y_1}I_{\{y_2 \leq x \leq y_1\}}$. 

C. Distribution of the arrival time $\tau_N$: analytical (equation (14)) in red vs stochastic simulations (blue histogram) for particles distributed with respect to $p_0(x) = \frac{1}{b}I_{\{x \in [0,b]\}}$ for $0 < b < a$ with $b = 4$ and $a = 5$ for $N = 100$ (left) and $N = 500$ (right) with 1000 runs. 

D. Distribution of the arrival time $\tau_N$: analytical (equation (16)) in red vs stochastic simulations (blue) for particles distributed with respect to $p_0(x) = \frac{1}{c-b}I_{\{x \in [b,c]\}}$ with $0 < b < c < a$, $b = 1$ and $c = 4$. 

E. Distribution of the arrival time $\tau_N$: analytical (equation (18)) in red vs stochastic simulations (blue) for particles distributed with respect to $p_1(x) = \frac{2b^{\alpha+1}}{1-e^{-b^2}}xe^{-bx^2}I_{\{x \in [0,c]\}}$ with $a > c > 0$ with $b = 0.5$, $\alpha = 1$ and $c = 4$. 


FIG. 3: Mean fastest arrival time vs the number of particles $N$. A. Probability $Pr\{\tau^1 = t\}$ of arrival times in an interval computed from equations (14), (16), and (18) for a total number $N = [3, 5, 10, 100, 500]$ and the three initial distributions, presented in Fig. 2B). B. MF AT vs $N$ comparing stochastic simulations (colored disks) and the asymptotic formulas (continuous lines). The asymptotic expression for the MF AT when the particles are initially uniformly distributed in $[y_1, y_2]$ (blue curve) is of the form $y_2^2 \frac{4D}{2DN^2}$. An optimal fit gives $\alpha = -0.3075$. Parameters of the simulations are described in Fig. 2C, D and E when the domain of simulation is the interval $[0, a]$. We found a very good agreement between the analytical distributions and the empirical histogram for the arrival times of the fastest for the the three initial distributions associated to the pdf of the fastest given by expressions (14), (16), and (18) respectively. We plotted the analytical pdfs for the shortest arrival time (14), (16), (18) and for various values of $N$ (Fig. 3A). The MFAT decreases with the number of particles (Fig. 3B) as predicted by equations (15) red, (17) blue and (19) green. Note that in this case, we used $b = 1$ and $c = 3$, for which the distribution (16) and the MFAT (17) show a good agreement with the stochastic simulations (Fig. 2D and Fig. 3B in blue, respectively). We summarized in the next table the main asymptotic formulas associated with different initial conditions.
Asymptotics formula for the MFAT

| Initial Distribution | \( \Omega = \mathbb{R}^+ \) | Initial Distribution | \( \Omega = [0, a] \) |
|----------------------|-----------------|----------------------|-----------------|
| \( p_0(x) = \delta(x-x_0) \) | \( \sim \frac{x^2}{4D \log \left( \frac{r}{x} \right)} \) | \( p_0(x) = \delta(x-x_0) \) | \( \sim \frac{x^2}{16D \log \left( \frac{r}{x} \right)} \) |
| \( p_0(x) = \frac{1}{\sqrt{2\pi}} e^{-\frac{x^2}{2}} \) | \( \sim \frac{\sqrt{2\pi}}{4D} \) | \( p_0(x) = \frac{1}{\sqrt{2\pi}} e^{-\frac{x^2}{2}} \) | \( \sim \frac{\sqrt{2\pi}}{4D} \) |
| \( p_0(x) = \frac{1}{\sqrt{2\pi}} e^{-\frac{x^2}{2}} \) | \( \sim \frac{\sqrt{2\pi}}{4D} \) | \( p_0(x) = \frac{1}{\sqrt{2\pi}} e^{-\frac{x^2}{2}} \) | \( \sim \frac{\sqrt{2\pi}}{4D} \) |
| \( p_0(x) = 2kxe^{-kx^2} \) | \( \sim \frac{\sqrt{2\pi}}{4Dk} x^2 e^{-kx^2} \) | \( p_0(x) = 2kxe^{-kx^2} \) | \( \sim \frac{\sqrt{2\pi}}{4Dk} x^2 e^{-kx^2} \) |
| \( p_0(x) = \frac{4\pi}{4D(2N)^2} \) | \( \sim \frac{\pi}{4D(2N)^2} \Gamma \left( \frac{5}{4} \right) \) | - | - |

To conclude, when there are \( N \) i.i.d. Brownian particles initially uniformly distributed in an interval that does not contain the escape points, either the real semi-axis or a bounded interval, then the MFAT has a similar decay with \( N \) for a Dirac delta function or a locally constant initial distribution.

4. MFAT IN DIM 2

4.1. MFAT for a uniform initial distribution

We study here \( N \) i.i.d. Brownian particles in a bounded domain in two dimension \( \Omega \subset \mathbb{R}^2 \) (Fig. 4). The particles are initially uniformly distributed in the region

\[
\Omega^* = \{ B_{r_2}(A) \setminus B_{r_1}(A) : \theta_1 \leq \theta \leq \theta_1 + \theta_2 \},
\]

where \( B_r(A) \) is a disk of radius \( r \) centered at \( A \). They can bind to a single small absorbing arc \( \partial \Omega_r \) in the boundary \( \partial \Omega \) of \( \Omega \) of length \( 2c \) and centered at a point \( A \). Here we consider the initial distribution of i.i.d Brownian particles

\[
p(x, 0) = \frac{1}{A(\Omega^*)} 1_{\{x \in \Omega^*\}}
\]

(21)

where the area of the region is \( A(\Omega^*) = \frac{r^2 - r_1^2}{2} \theta_2 \). The solution of the diffusion equation with a general initial condition is the convolution of the elementary solution for the Dirac delta function with the initial condition \( p(x, t) \):

\[
p(x, t) = \int_{\Omega} p(y-x,t) * x p(y,0)dy.
\]

(22)

Using the asymptotic solution computed in [18] for dimension two, we have

\[
S(t) = Pr \{ t_1 > t \} = \frac{1}{A(\Omega^*)} \int_{\Omega^*} \left( 1 - \sqrt{\pi D} t \exp \left( -\frac{|A-y|^2}{4Dt} \right) \right) dy
\]

\[
= 1 - \sqrt{\pi D} t \frac{1}{A(\Omega^*)} \int_{\Omega^*} \exp \left( -\frac{|z|^2}{4Dt} \right) \frac{dy}{|z|^2}.
\]

Note now, \( \Omega^* - A = \{ B_{r_2}(0) \setminus B_{r_1}(0) : \theta_1 \leq \theta \leq \theta_1 + \theta_2 \} \), then \( |z|^2 = r^2 \), where \( r \) is the distance to the point \( A \) chosen as the origin of coordinates. Then we can rewrite the integral
FIG. 4: Schematic of the two-dimensional domain to study the MFAT to a small arc. The bounded domain $\Omega$ is delimited by the blue curve. The initial distribution of the Brownian particles is given by $p(x,0) = \frac{1}{A(\Omega^*)} \mathbb{1}_{x \in \Omega^*}$, where the region $\Omega^* = \{B_{r_2}(A) \setminus B_{r_1}(A) : \theta_1 \leq \theta \leq \theta_1 + \theta_2\}$ is delimited by the red curves.

above as

$$S(t) = 1 - \frac{\sqrt{2}D\pi t}{2\log \left(\frac{1}{\varepsilon}\right) A(\Omega^*)} \int_{r_1}^{r_2} \int_{\theta_1}^{\theta_1 + \theta_2} \frac{\exp \left\{-\frac{r^2}{4Dt}\right\}}{r^2} r d\theta dr$$

$$= 1 - \frac{\sqrt{2}D\pi t}{2\log \left(\frac{1}{\varepsilon}\right) (r_2^2 - r_1^2)} \left( \text{ei} \left( -\frac{r_2^2}{4Dt} \right) - \text{ei} \left( -\frac{r_1^2}{4Dt} \right) \right), \quad (23)$$

where $\text{ei}(x) = -\int_{-\infty}^{\infty} \frac{e^{t}}{t} dt$ is the exponential integral. For $t$ small, we expand this function and we get

$$S(t) \sim 1 - \frac{\sqrt{2}D\pi t}{2\log \left(\frac{1}{\varepsilon}\right) (r_2^2 - r_1^2)} \left( \frac{4Dt}{r_2^2} e^{-\frac{r_2^2}{4Dt}} - \frac{4Dt}{r_1^2} e^{-\frac{r_1^2}{4Dt}} \right). \quad (24)$$

Scaling $r_2 = (1 + \gamma)r_1$ and making an expansion when $\gamma \to 0$, we get

$$S(t) \sim 1 - \frac{\sqrt{2}\pi (4Dt) e^{-\frac{r_2^2}{4Dt}}}{8 \log \left(\frac{1}{\varepsilon}\right) r_1^2} \left( 1 + \frac{4Dt}{r_1^2} - 2\gamma \left( 1 + \frac{r_1^2}{4Dt} \right) + O(\gamma^2) + O \left( \frac{\gamma}{t} \right) \right). \quad (25)$$

To conclude, when $\gamma \to 0$, the survival probability $S(t)$ is recovered for the case with the Dirac delta function at the points with $r = r_1$ as the initial condition. Thus to leading order, using that

$$\lim_{r_2 \to r_1} Pr \{ t_1 > t \} \sim 1 - \frac{\sqrt{2}\pi (4Dt) e^{-\frac{r_2^2}{4Dt}}}{8 \log \left(\frac{1}{\varepsilon}\right) r_1^2}, \quad \text{Pr} \{ t_1 > t \} \sim 1 - \frac{\sqrt{2}\pi (4Dt) e^{-\frac{r_2^2}{4Dt}}}{8 \log \left(\frac{1}{\varepsilon}\right) r_1^2},$$
we obtain to leading order the asymptotic formula for \( N \gg 1 \)

\[
\bar{T}_N \approx \frac{r_1^2}{4D \log \left( \frac{\sqrt{2\pi N}}{N \log(b)} \right) + A_\varepsilon},
\]

(26)

where \( A_\varepsilon = A_0 + \varepsilon A_1 + \ldots \), where \( A_k \) are constants as before and \( r_1 \) is the shortest distance to the absorbing boundary. The MFAT for this case has a similar behavior as for the Dirac delta function.

### 4.2. MFAT in two dimensions for an initial distribution asymptotically intersecting the target site

We study here the consequence of an initial distribution asymptotically intersecting the target site. For that goal, we consider the algebraic distribution modulated by a global exponential

\[
p_{\varepsilon}(x) = K|x - A|^\varepsilon e^{-b|x - A|^2}.
\]

(27)

The function \( p_{\varepsilon}(x) \) is the initial distribution for the diffusion equation (6), where the normalization constant is approximated on most of the domain where we added the small triangle at the summit between the dashed and the blue lines in Fig. 3 (the area of which is \( O(\varepsilon^2) \)).

Thus we approximate normalization constant is

\[
K_{\varepsilon}^{-1} \approx \int |x - A|^\varepsilon e^{-b|x - A|^2} dx = \int_0^R \int_{\theta_1}^{\theta_2} r^\alpha e^{-br^2} r d\theta dr,
\]

where \( R \) is the largest radius of the circular sector centered in \( A \) that can be inscribed in \( \Omega \). This leads to the expression

\[
K_{\varepsilon}^{-1} = \frac{\theta_2 - \theta_1}{2b^{\varepsilon+2}} \left( \Gamma \left( 1 + \frac{\alpha}{2} \right) - \Gamma \left( 1 + \frac{\alpha}{2}, bR^2 \right) \right),
\]

(28)

where \( \Gamma(z) \) is the Gamma function and \( \Gamma(z, t) \) is the incomplete Gamma function. We can now estimate the survival probability

\[
S(t) = \text{Pr}\{t_1 > t\} = \int \int_\Omega \tilde{p}(x, t) K_{\varepsilon}^{-1} |y - A|^\varepsilon e^{-b|y - A|^2} dy dx
\]

\[
= \int_\Omega K_{\varepsilon}^{-1} \left( 1 - \frac{\sqrt{2D\pi t}}{2\log \left( \frac{b}{2} \right)} \exp \left\{ -\frac{|y - A|^2}{4Dt} \right\} \right) |y - A|^\varepsilon e^{-b|y - A|^2} dy
\]

\[
= 1 - \frac{\sqrt{2D\pi t}}{2\log \left( \frac{b}{2} \right)} K_{\varepsilon} \int_\Omega |y - A|^\varepsilon e^{-b|y - A|^2} dy,
\]

\[
= 1 - \frac{\sqrt{2D\pi t} \theta_2}{2\log \left( \frac{b}{2} \right)} \int_0^R r^\alpha e^{-bR^2} r d\theta dr,
\]

\[
= 1 - \frac{\sqrt{2\pi(4Dbt)^{\frac{\alpha+2}{2}}} \left( \Gamma \left( \frac{\alpha}{2} \right) - \Gamma \left( \frac{\alpha}{2} + \frac{4Dbt + 1}{D}, bR^2 \right) \right)}{8\log \left( \frac{b}{2} \right) \Gamma \left( 1 + \frac{\alpha}{2} \right) - \Gamma \left( 1 + \frac{\alpha}{2}, bR^2 \right)}.
\]

Thus for \( t \) small, we have

\[
S(t) \sim 1 - \frac{\sqrt{2\pi} \Gamma \left( \frac{\alpha}{2} \right)}{8\log \left( \frac{b}{2} \right) \Gamma \left( 1 + \frac{\alpha}{2} \right) - \Gamma \left( 1 + \frac{\alpha}{2}, bR^2 \right)} (4Dbt)^{\frac{\alpha+2}{2}},
\]
and the MFAT is
\[ \tau^N \sim \int_0^\infty \exp \left\{ -\frac{\sqrt{2N\pi\Gamma\left(\frac{\alpha}{2}\right)}}{8\log\left(\frac{1}{\varepsilon}\right)\left(\Gamma\left(\frac{\alpha+2}{2}\right) - \Gamma\left(\frac{\alpha+2}{2}, bR^2\right)\right)} (4Db)^{\frac{\alpha+2}{\alpha+2}} \right\} \, dt \]
\[ \sim \left( \frac{8\log\left(\frac{1}{\varepsilon}\right)\left(\Gamma\left(\frac{\alpha+2}{2}\right) - \Gamma\left(\frac{\alpha+2}{2}, bR^2\right)\right)}{\sqrt{2N\pi\Gamma\left(\frac{\alpha}{2}\right)}} \right)^{\frac{\alpha+2}{2}} \cdot \frac{1}{4Db} \cdot \Gamma\left(\frac{\alpha+4}{\alpha+2}\right). \] (29)

We can rewrite this formula as
\[ \tau^N \sim \frac{C_{\alpha,\Omega}}{N^{\frac{\alpha}{2}} 4Db} \quad \text{for} \quad N \gg 1, \] (30)
where
\[ C_{\alpha,\Omega} = \Gamma\left(\frac{\alpha+4}{\alpha+2}\right) \left( \frac{8\log\left(\frac{1}{\varepsilon}\right)\left(\Gamma\left(\frac{\alpha+2}{2}\right) - \Gamma\left(\frac{\alpha+2}{2}, bR^2\right)\right)}{\sqrt{2\pi\Gamma\left(\frac{\alpha}{2}\right)}} \right)^{\frac{\alpha+2}{\alpha+2}}. \] (31)

To conclude, we propose that the present formula could be generalized to any dimension \( d \), that would lead to a spectrum of possible decay of the MFAT with respect to the variable \( N \) depending in the algebraic decay \( x^{\alpha} \) of the initial distribution at the target located at 0:
\[ \tau^N \sim \frac{C_{\alpha,\Omega}}{N^{\frac{\alpha}{2}} 4Db} \quad \text{for} \quad N \gg 1, \] (32)
where \( d \) is the dimension of \( \Omega \).

5. EFFECT OF A CONSTANT DRIFT ON EXTREME ARRIVAL

In half-a-line, we consider now the first arrival time of the \( N \) independent processes \((X_1(t), \ldots, X_N(t))\), solution of
\[ \dot{X}_k = -a + \sqrt{2D}\dot{W}_k, \]
where \( a \) is a constant velocity and \( D \) the diffusion coefficient.

5.1. Effect of a constant drift when the initial distribution is a Dirac delta function

The Fokker-Planck Equation (FPE) is
\[ \frac{\partial p(x,t)}{\partial t} = D \frac{\partial^2 p(x,t)}{\partial x^2} + a \frac{\partial p(x,t)}{\partial x} \quad \text{for} \quad x > 0, t > 0 \]
\[ p(x,0) = p_0(x) = \delta(x-y) \]
\[ p(0,t) = 0. \] (33)

To solve equation (33), we change the variable \( p = q \exp\left\{ -\frac{a(x+y)^2}{2D} t \right\} \), so that \( q \) satisfies the diffusion equation \[ \frac{\partial q(x,t)}{\partial t} = D \frac{\partial^2 q(x,t)}{\partial x^2}. \] Thus the solution is given by equation (17) and
\[ p(x,t) = \frac{\exp\left\{ -\frac{a(x+y)^2}{2D} t \right\}}{\sqrt{4D\pi t}} \left[ \exp\left\{ -\frac{(x-y)^2}{4Dt} \right\} - \exp\left\{ -\frac{(x+y)^2}{4Dt} \right\} \right]. \]
The extreme escape time is given by relation (34)

$$\tau^N = \int_0^\infty S(t)^N dt,$$

where the survival probability is

$$S(t) = \int_0^\infty \exp\left\{ -\frac{(x-y)^2}{4Dt} \right\} dV,$$

and

$$S_1(t) = \frac{1}{\sqrt{\pi}} \int_{-\infty}^{\infty} \exp(-u^2)du \quad \text{and} \quad S_2(t) = \frac{1}{\sqrt{\pi}} \int_{\infty}^{\infty} \exp(-u^2)du.$$

We re-write the sum

$$S(t) = H_1(t) + H_2(t),$$

where

$$H_1(t) = \frac{1}{2} \left( \text{erfc} \left( -\frac{y + at}{\sqrt{4D\pi t}} \right) - \text{erfc} \left( \frac{y + at}{\sqrt{4D\pi t}} \right) \right)$$

and

$$H_2(t) = \frac{1}{2} \left( 1 - \exp \left\{ \frac{ay}{D} \right\} \right) \text{erfc} \left( \frac{y + at}{\sqrt{4D\pi t}} \right).$$

We obtain for short-time asymptotic,

$$H_1(t) \sim 1 - \sqrt{4Dt} \frac{e^{-\frac{y^2}{4Dt}}}{y\sqrt{\pi}}$$

and

$$H_2(t) \sim \left( 1 - \exp \left\{ \frac{ay}{D} \right\} \right) \sqrt{Dt} \frac{e^{-\frac{y^2}{4Dt}}}{y\sqrt{\pi}}.$$

Thus, $S(t) = 1 - \sqrt{4Dt} \left( 1 + \exp \left\{ \frac{ay}{D} \right\} \right) \frac{e^{-\frac{y^2}{4Dt}}}{y\sqrt{\pi}}$ leading to,

$$Pr \{ \tau = t \} = -\frac{d}{dt} S(t) \sim -\frac{d}{dt} \left[ \exp \left\{ -N\sqrt{4Dt} \left( 1 + \exp \left\{ \frac{ay}{D} \right\} \right) \frac{e^{-\frac{y^2}{4Dt}}}{y\sqrt{\pi}} \right\} \right]$$

and

$$\tau^N = \int_0^\infty S(t)^N dt \sim \int_0^\infty \exp \left\{ -N\sqrt{4Dt} \left( 1 + \exp \left\{ \frac{ay}{D} \right\} \right) \frac{e^{-\frac{y^2}{4Dt}}}{y\sqrt{\pi}} \right\} dt.$$

Using the asymptotic computation of [18], we obtain

$$\tau^N \sim \frac{y^2}{4D \log \left( N \left( 1 + \exp \left\{ \frac{ay}{D} \right\} \right) \right)}.$$
To conclude, in the large $N$ limit, adding a negative drift $a < 0$, leads to a small increase in the extreme arrival time. Formula (37) reveals how adding a drift can be equivalent to reducing the number of initial particles by a factor \( \exp\left(\frac{a y}{D}\right) < 1 \).

Finally, we tested the quality of the analytical approximation of the pdfs with the stochastic simulations for the shortest arrival time (35) with drifts $a = 1$ and $a = -1$ respectively and for different values of $N$ (Fig. 5A and B). The MFAT decreases with $N$ (Fig. 5C) according to equation (36) for $a = -1$ in red and $a = 1$ in blue.

![Diagram](image)

**FIG. 5**: Mean fastest arrival time vs the number of particles $N$ with a drift. A. Distribution of the arrival time $\bar{\tau}_N$: analytical represented by equation (36) (in red) vs stochastic simulations (blue histogram) for particles distributed with respect to $p_0(x) = \delta(x - y_0)$ with $y_0 = 0.25$ and a drift $a = 1$ for $N = 500$ (left) and $N = 500$ (right) with 1000 runs. B. Distribution of the arrival time $\bar{\tau}_N$: analytical expression (35) (in red) vs stochastic simulations (blue histogram) with drift $a = -1$. C. MFAT vs $N$ obtained from stochastic simulations (colored disks) and the asymptotic formulas (continuous lines) with $y_0 = 0.25$ and 1000 runs.

**5.2. Effect of a constant drift for a uniform initial distribution**

When the particles are initially uniformly distributed in a small portion of the ray, $[0; y_0]$, the initial condition is given by formula $p(x, 0) = \frac{1}{y_0} \mathbb{1}_{[x \in [0,y_0]]}$, and the solution of the diffusion
equation with a drift is given by

\[
p(x, t) = e^{-ax - a^2 t/2} \int_0^{y_2} \exp \left\{ \frac{ay}{2Dr} \right\} \left[ \exp \left\{ -\frac{(x - y)^2}{4Dt} \right\} - \exp \left\{ -\frac{(x + y)^2}{4Dt} \right\} \right] dy
\]

Thus, making the asymptotic for \( t \) small, we have

\[
S(t) \sim 1 - \frac{\sqrt{4Dt}}{\sqrt{\pi}y_0}
\]

leading to

\[
\pi^N = \frac{y_0^2 \pi}{2DN^2}.
\]

This result is the one obtained in the case of no drift, showing that the drift does not affect the extreme arrival time when the absorbing point overlap with the interval where the particles are initially uniformly distributed.

### 5.3. Effect of a constant drift for a uniform initial distribution not intersecting the target

When the particles are uniformly distributed in the interval \([y_1, y_2]\) with \( y_2 > y_1 > 0 \), the initial distribution is of the form \( p_0(x) = \frac{1}{y_2 - y_1} \mathbb{1}_{[x \in [y_1, y_2]]} \). The solution of the diffusion equation is given by

\[
p(x, t) = e^{-ax - a^2 t/2} \int_0^{y_2} \exp \left\{ \frac{ay}{2Dr} \right\} \left[ \exp \left\{ -\frac{(x - y)^2}{4Dt} \right\} - \exp \left\{ -\frac{(x + y)^2}{4Dt} \right\} \right] dy
\]

Then, using the change of variable \( u = \frac{x - y_0 + at}{\sqrt{4Dt}} \), the survival probability is

\[
S(t) = \frac{1}{2y_0} \left[ \text{erfc} \left( \frac{x - y_0 + at}{\sqrt{4Dt}} \right) - \text{erfc} \left( \frac{x + at}{\sqrt{4Dt}} \right) \right] dx
\]

Using the change of variable \( u = \frac{x - y_0 + at}{\sqrt{4Dt}} \) we can obtain,

\[
S_1(t) = \frac{1}{2y_0} \left[ -at \cdot \text{erf} \left( \frac{at}{\sqrt{4Dt}} \right) + \frac{\sqrt{4Dt}}{\sqrt{\pi}} e^{-\frac{(y_0 - at)^2}{4Dt}} - y_0 \cdot \text{erf} \left( \frac{at - y_0}{\sqrt{4Dt}} \right) \right]
\]

Then, using the change of variable \( u = \frac{x - y_0 + at}{\sqrt{4Dt}} \) and integrating by parts, we obtain

\[
S_2(t) = \frac{D}{2ay_0} \left[ -2 \cdot \text{erf} \left( \frac{at}{\sqrt{4Dt}} \right) + \text{erfc} \left( \frac{y_0 - at}{\sqrt{4Dt}} \right) - \text{erfc} \left( \frac{y_0 + at}{\sqrt{4Dt}} \right) e^{\frac{y_0^2}{4Dt}} \right]
\]

Thus, making the asymptotic for \( t \) small, we have

\[
S(t) \sim 1 - \frac{\sqrt{4Dt}}{\sqrt{\pi}y_0}
\]
and we can compute the survival probability as

\[
S(t) = \frac{1}{2(y_2 - y_1)} \int_0^\infty \left( \text{erfc} \left( \frac{x - y_2 - at}{\sqrt{4Dt}} \right) - \text{erfc} \left( \frac{x - y_1 - at}{\sqrt{4Dt}} \right) \right) dx
- \frac{1}{2(y_2 - y_1)} \int_0^\infty e^{-\frac{x^2}{4Dt}} \left( \text{erfc} \left( \frac{x + y_2 - at}{\sqrt{4Dt}} \right) - \text{erfc} \left( \frac{x + y_1 - at}{\sqrt{4Dt}} \right) \right) dx
= S_1(t) + S_2(t).
\]

And, proceeding as before, we obtain

\[
S_1(t) = \frac{1}{2(y_2 - y_1)} \left( 2(y_2 - y_1) - (y_2 - at) \text{erfc} \left( \frac{y_2 - at}{\sqrt{4Dt}} \right) + (y_1 - at) \text{erfc} \left( \frac{y_1 - at}{\sqrt{4Dt}} \right) + \frac{\sqrt{4Dt}}{\sqrt{\pi}} \exp \left\{ -\frac{(y_2 - at)^2}{4Dt} \right\} - \frac{\sqrt{4Dt}}{\sqrt{\pi}} \exp \left\{ -\frac{(y_1 - at)^2}{4Dt} \right\} \right)
\]

and

\[
S_2(t) = \frac{-D}{2a(y_2 - y_1)} \left( \text{erfc} \left( \frac{y_1 - at}{\sqrt{4Dt}} \right) - \text{erfc} \left( \frac{y_2 - at}{\sqrt{4Dt}} \right) + e^{\frac{y_2}{D}} \text{erfc} \left( \frac{y_1 + at}{\sqrt{4Dt}} \right) + e^{\frac{y_1}{D}} \text{erfc} \left( \frac{y_2 + at}{\sqrt{4Dt}} \right) \right).
\]

The asymptotics for the short-time is given by

\[
S(t) \sim 1 - \frac{D\sqrt{Dt}}{a(y_2 - y_1)\sqrt{\pi}} \left[ \exp \left\{ -\frac{(y_1 - at)^2}{4Dt} \right\} - \exp \left\{ -\frac{(y_2 - at)^2}{4Dt} \right\} \right]
+ \exp \left\{ \frac{a(y_2 - D)}{y_2} \exp \left\{ -\frac{(y_2 + at)^2}{4Dt} \right\} \right\} - \exp \left\{ \frac{a(y_1 - D)}{y_1} \exp \left\{ -\frac{(y_1 + at)^2}{4Dt} \right\} \right\}
\]

(38)

We shall consider the case where \( y_2 = y_1(1 + \varepsilon) \) in (38), and \( \varepsilon \) tends to zero, thus

\[
S(t) \sim S_0(t) + S_1(t)\varepsilon + S_2(t)\frac{\varepsilon^2}{2} + ...
\]

(39)

where

\[
S_0(t) = 1 - \frac{\sqrt{Dt}}{y_1\sqrt{\pi}} \exp \left\{ -\frac{y_1^2}{4Dt} \right\} \left( 1 + e^{\frac{y_1}{D}} \right)
\]

\[
S_1(t) = \frac{3}{\sqrt{4Dt}} \exp \left\{ -\frac{(y_1 - at)^2}{4Dt} \right\} - \frac{a}{2D} e^{\frac{y_1}{D}} \text{erfc} \left( \frac{y_1 + at}{\sqrt{4Dt}} \right)
+ \frac{D(y_1 - at)}{2aDt\sqrt{4Dt}} \exp \left\{ -\frac{(y_1 - at)^2}{4Dt} \right\} \left( 1 - e^{\frac{y_1}{D}} \right)
\]

When \( \varepsilon \to 0 \) (that is \( y_2 \to y_1 \)), we recover in equation (39), the survival probability of the Dirac delta function \( \delta(x - y_1) \), but we cannot get the MFAT due to the exponentially small terms that appear canceling with each other when \( \varepsilon \) and \( \frac{\varepsilon}{t} \) are small. Thus, to leading order, we have

\[
N^* \sim \frac{y_1^2}{4D \log \left( \frac{N(1 + \exp \left\{ \frac{y_1}{D} \right\})}{2\sqrt{\pi}} \right)}
\]

(40)
6. DISCUSSION AND CONCLUDING REMARKS

In summary, we have obtained several asymptotic formulas for the mean time of the fastest Brownian particles to reach a target. These formulas crucially depend on the initial distribution toward the isolate target: we found algebraic vs $1/\log N$ decay depending on the different initial density profile. In the context of extreme value statistics, the distribution of the first arrival time $\tau_1(N)$ is the minimum among the random variables

$$
\tau_1(N) = \min (t_1, t_2, \cdots, t_N) \geq 0,
$$

and thus the limiting distribution of $\tau_1(N)$ is given by the Weibull distribution (because of the lower bound of the support which is positive). This is the case when the target site located at the origin is included in the support of the initial distribution of the particles. Indeed, in that case, the pdf of the $t_i$ behaves as a power law near zero. The Weibull expression implies the algebraic dependence of $\tau_1(N)$ with $N$. However, if the origin is not part of the initial density profile, the pdf of the $t_i$’s has an essential singularity at small argument (see above equation 10). Consequently, the limiting form is not a Weibull distribution but instead a Gumbel law, which in turn implies a decay in the form of $1/\log N$, as discussed in the review [11].

In general, the renewal interest of extreme statistics [9, 11, 21] is due to recent direct applications in cell biology [5, 22–24] which appears as a frame to explain fast molecular activation. The frame of extreme statistics can be used to compute how the molecular activation time depends on the main parameters, involving the geometrical organization and the dynamics (diffusion or other stochastic processes). The fastest molecules to activate a target site uses the shortest path, thus showing that the redundancy property can overcome the hindrance of a crowded environment.

This redundancy principle is ubiquitous in cell biology: One class of example is calcium signalling that can be amplified by activating the calcium-induced-calcium released pathway [3]. This amplification does not require the transport of all ions but only the first ones to arrive to a specific targets made of few clustered receptors. The amplification occurs in few milliseconds instead of hundreds of milliseconds as would be predicted by the time scale of the classical diffusion and the narrow escape theory [22] at synapse of neuronal cells [24].

Interestingly the arrival time of the fastest among $N$ decays with $\delta^2/\log N$, when the source and the target are well separated by a distance $\delta$. However, there are several situations where choosing the Dirac delta function might not be the best model, as we discussed here. For example, when the particle injection could take a certain time, an extended initial distribution can build up, that could be approximated by a Gaussian or any other related distribution with an algebraic decay, especially when the motion can be modeled as anomalous diffusion (see relation (11)).

Another transduction applications concerns the activation of secondary messengers such as IP$_3$ receptors involved in the genesis of calcium wave in astrocytes [31] or the fast activation of TRP channels in fly photo-receptor, which are located very close to the source of the photoconversion.

In addition, we obtained here a novel formula when the dynamics contains a local constant flow added to the Brownian component. A local flow could accelerate the transport of the fastest molecules, which could be the case for the delivery occurring inside the endoplasmic reticulum network [31]. This network is indeed composed of thin tubules well approximated as dimension one segment intersecting at nodes.

Finally, it would be interesting to extend the present analysis to the case of exiting from a basin of attraction and study the mean arrival time of the fastest. The case of an OU process is already delicate as there is no exact closed formula for the survival probability with a zero absorbing boundary condition at a given threshold. Indeed for an OU process $dx = -\theta x dt + \sqrt{2D} dw$ centered at the origin with an absorbing boundary at $x = 0$ and initial point at $x = y$ and $\theta \geq 0$, the arrival time for the fastest is given at leading order by
the same formula as if there was only diffusion and no drift. Indeed in this very particular case, the solution has the form

\[ p(x, t) = \sqrt{\frac{\theta}{2\pi D(1 - e^{-2\theta t})}} \left[ \exp \left\{ -\frac{\theta}{2D} \frac{(x - ye^{-\theta t})^2}{1 - e^{-2\theta t}} \right\} - \exp \left\{ -\frac{\theta}{2D} \frac{(x + ye^{-\theta t})^2}{1 - e^{-2\theta t}} \right\} \right] \] (42)

and the survival probability is

\[ Pr\{t_1 > t\} = 1 - \text{erfc} \left( \frac{\sqrt{\theta ye^{-\theta t}}}{\sqrt{2D(1 - e^{-2\theta t})}} \right). \] (43)

Then, for \( t \) small, we have

\[ \tau_N \sim \frac{y^2}{4D \log \left( \frac{N}{\sqrt{\pi}} \right)}. \] (44)

However for other cases in which the absorbing boundary is not at the maximum point of the parabola, a general approximated formula \cite{32} has been proposed, correcting erroneous expression found in the literature. At this stage, we could not use their complex formula to estimate the time of the fastest. We speculate that the formula for the mean arrival time for the fastest should be associated not with the Euclidean distance but with the control problem for the Wencell-Freidlin functional in the Large-Deviation theory, a project for a future investigation.

7. APPENDIX: ALGORITHM TO SIMULATE STOCHASTIC TRAJECTORIES OF THE FASTEST WHEN THE INITIAL DISTRIBUTION CAN INTERSECT WITH THE TARGET

To simulate the arrival of the fastest particle to an absorbing boundary, we use the classical Euler’s scheme \cite{33}. When the source is well separated from the absorbing boundary, we follow each Brownian particle and estimated the time for the first one to arrive. When particles are initially positioned with a distribution that could intersect with the absorbing boundary, the simulation scheme requires more attention, because in principle, particles can be found as close as we wish to the absorbing boundary, and thus the discretization time step could influence the time of the fastest. We thus design the following algorithm:

1. We generated \( N \) initial positions uniformly distributed: \( \chi_1, \cdots, \chi_N \in [0, y_0] \), where 0 and \( a \) are the absorbing boundaries and \( y_0 < a \).

2. The time step \( \Delta t \) of the Euler’s scheme depends on the shortest distance

\[ \delta_N = \min_N \{|\chi_1|, \cdots, |\chi_N|\}, \] (45)

so that the mean square jump is smaller that the shortest distance:

\[ \Delta t \leq p \frac{\delta_N^2}{2D}, \] (46)

where \( D \) is the diffusion coefficient, \( p < 1 \) is a security parameter. In practice, we choose \( p = 0.2 \).
3. For each realization \( \omega \), we generated a simulation following step 1 and 2 and computed the first arrival time of the fastest:

\[
\tau_{\omega,j}^N = \inf_{i=1}^{N} t_{i,j},
\]

where \( j = \inf_k \{ X(k\Delta t) \leq 0 | X((k-1)\Delta t) > 0 \text{ or } X(k\Delta t) \geq a | X((k-1)\Delta t) < a \} \).

4. We approximate the mean fastest arrival time by the empirical sums:

\[
\bar{\tau}^N_m = \frac{1}{m} \sum_{j=1}^{m} \tau_{\omega,j}^N, \text{ with } \bar{\tau}^N = \lim_{m \to +\infty} \bar{\tau}^N_m.
\]

[1] W. K. Purves, D. E. Sadava, G. H. Orians, and H. C. Heller, *Life: The Science of Biology Seventh Edition 7th Edition*. Sinauer Associates and W. H. Freeman, 2004.

[2] K. Basnayake, E. Korkotian, and D. Holcman, “Fast calcium transients in neuronal spines driven by extreme statistics,” bioRxiv, p. 290734, 2018.

[3] G. L. Fain, *Sensory transduction*. Oxford University Press, 2019.

[4] D. Holcman and Z. Schuss, *Asymptotics of Elliptic and Parabolic PDEs: and their Applications in Statistical Physics, Computational Neuroscience, and Biophysics*, vol. 199. Springer, 2018.

[5] D. Coombs, “First among equals: Comment on “redundancy principle and the role of extreme statistics in molecular and cellular biology” by Z. Schuss, K. Basnayake and D. Holcman,” *Physics of life reviews*, 2019.

[6] S. Redner and B. Meerson, “Redundancy, extreme statistics and geometrical optics of brownian motion: Comment on” redundancy principle and the role of extreme statistics in molecular and cellular biology” by z. schuss et al.,” *Physics of life reviews*, 2019.

[7] R. Metzler and J. Klafter, “The random walk’s guide to anomalous diffusion: a fractional dynamics approach,” *Physics reports*, vol. 339, no. 1, pp. 1–77, 2000.

[8] B. E. Herring and R. A. Nicoll, “Long-term potentiation: from camkii to ampa receptor trafficking,” *Annual review of physiology*, vol. 78, pp. 351–365, 2016.

[9] G. H. Weiss, K. E. Shuler, and K. Lindenberg, “Order statistics for first passage times in diffusion processes,” *Journal of Statistical Physics*, vol. 31, no. 2, pp. 255–278, 1983.

[10] G. Schehr and S. N. Majumdar, “Exact record and order statistics of random walks via first-passage ideas,” in *First-Passage Phenomena and Their Applications*, pp. 226–251, World Scientific, 2014.

[11] S. N. Majumdar, A. Pal, and G. Schehr, “Extreme value statistics of correlated random variables: a pedagogical review,” *Physics Reports*, vol. 840, pp. 1–32, 2020.

[12] S. Redner, *A guide to first-passage processes*. Cambridge University Press, 2001.

[13] K. Basnayake and D. Holcman, “Fastest among equals: a novel paradigm in biology. reply to comments: Redundancy principle and the role of extreme statistics in molecular and cellular biology,” *PhLRv*, vol. 28, pp. 96–99, 2019.

[14] D. Grebenkov, R. Metzler, and G. Oshanin, “From single-particle stochastic kinetics to macroscopic reaction rates: fastest first-passage time of n random walkers,” *New Journal of Physics*, 2020.

[15] J. Yang, I. Kupka, Z. Schuss, and D. Holcman, “Search for a small egg by spermatozoa in restricted geometries,” *Journal of mathematical biology*, vol. 73, no. 2, pp. 423–446, 2016.

[16] B. Alberts, D. Bray, K. Hopkin, A. D. Johnson, J. Lewis, M. Raff, K. Roberts, and P. Walter, *Essential cell biology*. Garland Science, 2015.

[17] T. Riedl and J.-M. Egly, “Phosphorylation in transcription: the ctd and more,” *Gene Expression The Journal of Liver Research*, vol. 9, no. 1-2, pp. 3–13, 2001.

[18] K. Basnayake, Z. Schuss, and D. Holcman, “Asymptotic formulas for extreme statistics of escape times in 1, 2 and 3-dimensions,” *Journal of Nonlinear Science*, Sep 2018.

[19] K. Basnayake, A. Hubl, Z. Schuss, and D. Holcman, “Extreme narrow escape: Shortest paths for the first particles among n to reach a target window,” *Physics Letters A*, vol. 382, no. 48, pp. 3449–3454, 2018.
[20] K. Basnayake and D. Holcman, “Extreme escape from a cusp: When does geometry matter for the fastest brownian particles moving in crowded cellular environments?,” The Journal of Chemical Physics, vol. 152, no. 13, p. 134104, 2020.

[21] S. N. Majumdar, S. Sabhapandit, and G. Schehr, “Exact distributions of cover times for n independent random walkers in one dimension,” Physical Review E, vol. 94, no. 6, p. 062131, 2016.

[22] K. Basnayake and D. Holcman, “Fastest among equals: a novel paradigm in biology. reply to comments: Redundancy principle and the role of extreme statistics in molecular and cellular biology,” Physics of life reviews, vol. 28, pp. 96–99, 2019.

[23] I. M. Sokolov, “Extreme fluctuation dominance in biology: On the usefulness of wastefulness: Comment on “redundancy principle and the role of extreme statistics in molecular and cellular biology” by Z. Schuss, K. Basnayake and D. Holcman,” Physics of life reviews, 2019.

[24] D. A. Rasakov and L. P. Savtchenko, “Extreme statistics may govern avalanche-type biological reactions: Comment on “redundancy principle and the role of extreme statistics in molecular and cellular biology” by z. schuss, k. basnayakey, d. holcman,” Physics of life reviews, 2019.

[25] D. Holcman and Z. Schuss, Stochastic Narrow Escape in Molecular and Cellular Biology: Analysis and Applications. Springer, 2015.

[26] E. Korkotian, E. Oni-Biton, and M. Segal, “The role of the store-operated calcium entry channel orai1 in cultured rat hippocampal synapse formation and plasticity,” The Journal of physiology, vol. 595, no. 1, pp. 125–140, 2017.

[27] E. Korkotian, M. Frotscher, and M. Segal, “Synaptopodin regulates spine plasticity: mediation by calcium stores,” Journal of Neuroscience, vol. 34, no. 35, pp. 11641–11651, 2014.

[28] E. Korkotian and M. Segal, “Release of calcium from stores alters the morphology of dendritic spines in cultured hippocampal neurons,” Proceedings of the National Academy of Sciences, vol. 96, no. 21, pp. 12068–12072, 1999.

[29] K. Basnayake, D. Mazaud, A. Bemelmans, N. Rouach, E. Korkotian, and D. Holcman, “Fast calcium transients in dendritic spines driven by extreme statistics,” PLoS biology, vol. 17, no. 6, p. e2006202, 2019.

[30] N. Rouach, J. Glowinski, and C. Giame, “Activity-dependent neuronal control of gap-junctional communication in astrocytes,” The Journal of cell biology, vol. 149, no. 7, pp. 1513–1526, 2000.

[31] M. Dora and D. Holcman, “Active unidirectional network flow generates a packet molecular transport in cells,” arXiv preprint arXiv:1810.07272, 2018.

[32] R. Martin, M. Kearney, and R. Craster, “Long-and short-time asymptotics of the first-passage time of the orstein–uhlenbeck and other mean-reverting processes,” Journal of Physics A: Mathematical and Theoretical, vol. 52, no. 13, p. 134001, 2019.

[33] Z. Schuss, Brownian dynamics at boundaries and interfaces. Springer, 2015.