SEARCH TIME FOR A SMALL RIBBON AND APPLICATION TO VESICULAR RELEASE AT NEURONAL SYNAPSES∗

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Abstract. The arrival of a Brownian particle at a narrow cusp located underneath a ball is a model of vesicular release at neuronal synapses, triggered by calcium ions. The asymptotic computation of the arrival time presents several difficulties that can be overcome using conformal mappings and asymptotic analysis of the model equations. Using a regular expansion of the solution of the Laplace equation in the mapped domain, we compute the solution involving both small and large spatial scales. We derive novel asymptotic formulas for Brownian escape through cusps in both two and three dimensions. The range of validity of the asymptotic formulas is challenged by stochastic simulations. Finally, we apply the analysis to estimate the vesicular release probability at presynaptic terminals and, in particular, we suggest that vesicular organization imposes a severe constraint on calcium channel localization: diffusing calcium ions can trigger vesicular release only in a specific range of positions that we provide.

Key words. first passage time, narrow escape, conformal mapping, multiscale asymptotics, Laplace equation, stochastic simulations, neuronal synapses, calcium diffusion, vesicular release, presynaptic terminal

AMS subject classifications. 35Q92, 35B40

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1. Introduction. The search time by a Brownian particle, for a small target hidden inside a narrow cusp, is usually much longer than for a freely accessible target located on a smooth surface. This difference in time is quantified by the mean first passage times [8, 9, 10]. Asymptotic expressions are difficult to obtain due to geometrical difficulties that cannot be resolved by classical methods [3, 10, 16, 20]. This situation is, however, ubiquitous in cell biology: it can represent the search for an active site located inside a complex protein, or for an ensemble of interacting proteins located between circumvoluted membranes. For example, a key step in synaptic transmission between neurons is the release of a vesicle from the presynaptic terminal [5, 13, 17, 19, 28]. This event is triggered by calcium ions entering through voltage-gated channels [13]. Although the detailed mechanism of this process remains unclear, a key molecular step is the binding of the diffusing calcium ions to specific proteins such as synaptotagmin, located between the membranes of the docked vesicle and the synaptic terminal. Vesicular release has also been investigated using stochastic numerical simulations [4, 17, 18, 24, 6].

Interestingly, the probability of vesicular release varies over six orders of magnitude for some synapses [15, 21], the exact mechanism of which remains elusive. To investigate the possible mechanism underlying this large range of modulation, we build here a diffusion model to estimate the time for diffusing particles (calcium ions) to find hidden small targets (proteins). We study the effect of several parameters on the search time, such as the initial position of the channels, the size, and the position

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of the activating molecules. A random particle searching for a small target is a dire
strait time (DST) problem, as described in [7, 8, 9, 10]. The principle of computing
the DST relies on solving a mixed boundary value problem for the Laplace equation
with a geometrical cusp at the boundary. The present method combines asymptotic
expansion of the solution and conformal mapping to resolve the cusp singularity. Once
the cusp singularity is desingularized, we compute the solution by a regular matching
asymptotic expansion for the inner (inside the cusp) and outer solutions. Using
symmetries in dimension three, the analysis can be reduced to two dimensions, al-
lowing again the use of conformal maps. We apply this procedure several times and
derive asymptotic expansions for the search time in two and three dimensions. The
parameter getting asymptotically smaller here is the size of the small target (size of
the binding molecule). One of the most striking results we obtained here is formula
(2.39). This formula gives the DST of a Brownian particle to a small ribbon that
connects a ball and its tangent plane (Figure 1A):

\[ \langle \tau \rangle = \frac{|\bar{\Omega}|}{4\pi D\varepsilon}, \]  

(1.1)

where $|\bar{\Omega}|$ is the volume of the domain and $D$ is the diffusion coefficient. $\varepsilon$ is the
height of the ribbon whose surface is $S_{rib} = 2\pi \sqrt{2R\varepsilon^{3/2}}$, where $R$ is the radius of ball.

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**Fig. 1.** Search in a cusp. **A:** A Brownian trajectory is reflected on the boundary of two tangent
spheres (blue and green) until it finds a small ribbon target (red). The ribbon is a small cylinder that
connects the two tangent spheres. **B:** Two-dimensional projection of the ribbon target; the domain
$\Omega'$ is obtained by projecting the three-dimensional domain $\bar{\Omega}$ in a plane containing the $\Delta$-axis. **C, D:**
Conformal mapping of the domain $\bar{\Omega}$ into $\tilde{\Omega}$. The map is $\omega = f(\xi) = 1/\xi$. Circles of radius $a$
centered in $(0, a)$ are mapped into straight lines of ordinate $t = -1/2a$; the gray dashed circle in C
is transformed into a line in D. (Color available in electronic version.)
This formula is valid for a general domain, as long as the cusp geometry is preserved.

The manuscript is organized as follows: In section 2, we compute the escape time when the target is a narrow absorbing band at a cusp located between a plane and a sphere. We solve the Laplace equation with Dirichlet boundary conditions at the cusp and reflecting conditions otherwise. We use a Möbius transformation to map the domain into a rectangle and derive formulas in dimensions two and three. The range of validity of the asymptotic formulas is investigated using Brownian simulations. In the third and final section, we apply the asymptotic method to estimate the spread of calcium ions near vesicles in the presynaptic terminal. We relate the probability of vesicular release to the distance of calcium channels in a model of square lattice vesicle organization. We also estimate the rate of arrival for calcium ions to small protein sites, involved in triggering vesicular release. Finally, we discuss consequences of clustering channels near vesicles. In the appendix, we compute the Brownian escape time when the target is at the end of a three-dimensional cusp in a funnel-shaped domain. The Möbius transformation maps the domain into a banana-shaped domain. The final asymptotic formula corrects by a factor of 2 the previous one, derived in [8].

2. Search for a small two-dimensional cusp located between two tangent spheres. A Brownian particle is described by the stochastic equation

\[ \dot{X} = \sqrt{2D}\dot{w}, \]

where \( D \) is the diffusion coefficient and \( \dot{w} \) is white noise.

The Brownian search for a small target, located between an almost flat line and a circle membrane, corresponds to an escape through a narrow cusp in a two-dimensional bounded domain \( \Omega' \); see Figure 1B. The domain \( \Omega' \) lies between two tangent disks of radii \( R_1 \) and \( R_2 \) \((R_1 \ll R_2)\). The target is the two segments of length \( \varepsilon \) \((\varepsilon \ll R_1)\) joining the two disks \((\partial\Omega'_a \text{ (red)}\) in Figure 1B). The axial symmetry along \( \Delta \) (Figure 1B) allows us to reduce the domain \( \Omega' \) to the half-domain \( \Omega \) (Figure 1C).

To estimate the escape time in the two-dimensional domain \( \Omega \), we solve the boundary value problem

\[ D\Delta u(x) = -1 \text{ for } x \in \Omega, \]
\[ \frac{\partial u}{\partial n}(x) = 0 \text{ for } x \in \partial\Omega \setminus \partial\Omega_a, \]
\[ u(x) = 0 \text{ for } x \in \partial\Omega_a \]

using the conformal mapping

\[ f(\xi) = \frac{1}{\xi} = \omega, \]

which maps the cusp region into a rectangular domain. The coordinate \( \xi = r + iz \) is transformed into \( \omega = s + it \), while the domain \( \Omega \) is mapped into \( \bar{\Omega} \) (Figure 1D). The boundary of \( \bar{\Omega} \) is mapped as follows: The green and blue half-circles are mapped onto horizontal lines (same colors in Figure 1C–D) located at \( t_1 = -1/(2R_1) \) and \( t_2 = -1/(2R_2) \), respectively. The \( z \)-axis is mapped onto itself (black). The absorbing boundary is parameterized by

\[ \partial\Omega_a = \{(r_a, z) | r_a = \sqrt{2R\varepsilon (1 + o(1))} \text{ and } z_1 \leq z \leq z_2\}, \]
A regular expansion of map the boundary value problem (2.2), we set
\begin{align}
(2.10) & \quad z_1 = \frac{R_2}{R_2 - R_1} \varepsilon (1 + o(1)), \\
(2.12) & \quad z_2 = \frac{R_1}{R_2 - R_1} \varepsilon (1 + o(1)).
\end{align}

The points $P_1 = (r_a, z_1)$ and $P_2 = (r_a, z_2)$ are mapped into
\begin{align}
(2.7) & \quad f(r_a + iz_1) = \frac{1}{\sqrt{2R\varepsilon}} (1 + o(\sqrt{\varepsilon})) - i\frac{1}{2R_1}, \\
(2.8) & \quad f(r_a + iz_2) = \frac{1}{\sqrt{2R\varepsilon}} (1 + o(\sqrt{\varepsilon})) - i\frac{1}{2R_2}.
\end{align}

Hence, the absorbing boundary is mapped at the first order on a straight vertical line located at
\begin{align}
(2.9) & \quad s_a = \frac{1}{\sqrt{2R\varepsilon}} = \frac{1}{\sqrt{\varepsilon}}.
\end{align}

2.1. Asymptotic computation of the mean time in two dimensions. To map the boundary value problem (2.2), we set $u(\xi) = v(\omega)$, and we have $\Delta u(\xi) = |f'(\xi)|^2 \Delta v(\omega)$. Because $f'(\xi) = -\frac{1}{\varepsilon}$, and $|f'(f^{-1}(\omega))|^2 = |\omega|^4$, (2.2) is transformed into
\begin{align}
(2.10) & \quad |\omega|^4 \Delta v(\omega) = -\frac{1}{D} \quad \text{for } \omega \in \tilde{\Omega}, \\
& \quad \frac{\partial v}{\partial n}(\omega) = 0 \quad \text{for } \omega \in \partial \tilde{\Omega} \setminus \partial \tilde{\Omega}_a, \\
& \quad v(\omega) = 0 \quad \text{for } \omega \in \partial \tilde{\Omega}_a.
\end{align}

To determine the solution, we scale the variable $\zeta = \frac{s}{\varepsilon} = s\sqrt{2R\varepsilon}$ and derive an equation for $Y(\zeta, t) = v(\omega)$ for which (2.10) becomes
\begin{align}
(2.11) & \quad \left(\frac{\zeta^2}{\varepsilon} + t^2\right)^2 \left(\frac{\partial^2 Y}{\partial \xi^2}(\zeta, t) + \frac{\partial^2 Y}{\partial t^2}(\zeta, t)\right) + \frac{1}{D} \quad \text{for } (\zeta, t) \in [0, 1] \times \left[-\frac{1}{2R_2}, -\frac{1}{2R_1}\right], \\
& \quad \frac{\partial Y}{\partial t} \left(\zeta, -\frac{1}{2R_1}\right) = \frac{\partial Y}{\partial t} \left(\zeta, -\frac{1}{2R_2}\right) = \frac{\partial Y}{\partial \xi}(0, t) = 0, \\
& \quad Y(1, t) = 0.
\end{align}

A regular expansion of $Y$ in power of $\xi = 2\varepsilon$ is
\begin{align}
(2.12) & \quad Y(\zeta, t) = Y_0(\zeta, t) + \varepsilon Y_1(\zeta, t) + \varepsilon^2 Y_2(\zeta, t) + \cdots
\end{align}
and gives in (2.11)
\begin{align}
& \quad \left(\frac{\zeta^2}{\varepsilon} + t^2\right)^2 \left(\zeta^4 \frac{\partial^2 Y_0}{\partial \xi^2}(\zeta, t) + \frac{1}{\varepsilon} \left(\zeta^4 \frac{\partial^2 Y_1}{\partial \xi^2}(\zeta, t) + \zeta^4 \frac{\partial^2 Y_0}{\partial \xi^2}(\zeta, t) + 2\zeta^2 t \frac{\partial^2 Y_0}{\partial \xi \partial t}(\zeta, t)\right) + \left(\zeta^4 \frac{\partial^2 Y_1}{\partial \xi^2}(\zeta, t) + t^2 \frac{\partial^2 Y_0}{\partial t^2}(\zeta, t) + \zeta^4 \frac{\partial^2 Y_0}{\partial \xi \partial t}(\zeta, t) + 2\zeta^2 t \frac{\partial^2 Y_1}{\partial \xi \partial t}(\zeta, t) + \frac{1}{D}\right)
\right. \\
& \quad \left. = O(\varepsilon).\right)
\end{align}
The leading order $O(\varepsilon^{-2})$ is
\begin{equation}
(2.13) \quad \frac{\partial^2 Y_0}{\partial t^2}(\zeta, t) = 0.
\end{equation}

Hence, using the boundary conditions in (2.12), we obtain that $Y_0$ is independent of $t$. The second order term $O(\varepsilon^{-1})$ gives the equation
\begin{equation}
(2.14) \quad \zeta^4 \frac{\partial^2 Y_1}{\partial t^2}(\zeta, t) + \zeta^4 \frac{\partial^2 Y_0}{\partial \zeta^2}(\zeta) = 0.
\end{equation}

Integrating this equation over $t$ between $-\frac{1}{2R\varepsilon}$ and $-\frac{1}{R\varepsilon}$ and using the boundary condition in (2.12), we obtain
\begin{equation}
(2.15) \quad \frac{\partial^2 Y_0}{\partial \zeta^2}(\zeta) = 0,
\end{equation}

and thus $Y_0(\zeta) = A\zeta + B$, where $A$ and $B$ are two constants. Using the absorbing boundary condition in (2.12), $Y_0(\zeta) = A(\zeta - 1)$ and finally
\begin{equation}
(2.16) \quad v(s, t) = A \left(1 - s \sqrt{2R\varepsilon}\right).
\end{equation}

To determine the constant $A$, we use the compatibility condition obtained by integrating (2.2):
\begin{equation}
(2.17) \quad -\frac{|\Omega|}{D} = \int_\Omega \Delta u(x) dx = \int_{\partial \Omega_a} \frac{\partial u(y)}{\partial n} dS_y.
\end{equation}

The normal derivative is
\[\frac{\partial u}{\partial n} \bigg|_{\partial \Omega_a} = \frac{\partial u}{\partial r} \bigg|_{\partial \Omega_a} = -\frac{A \sqrt{2R\varepsilon}}{2R\varepsilon} (1 + O(\varepsilon)) = -\frac{A}{\sqrt{2R\varepsilon}} (1 + O(\varepsilon)).\]

Thus with (2.17), we get
\begin{equation}
(2.18) \quad \frac{|\Omega|}{D} = \int_{\partial \Omega_a} \frac{A}{\sqrt{2R\varepsilon}} dS = \varepsilon \frac{A}{\sqrt{2R\varepsilon}},
\end{equation}

which gives
\begin{equation}
(2.19) \quad A = \sqrt{2R|\Omega|} D \varepsilon^{-1},
\end{equation}

and finally
\begin{equation}
(2.20) \quad v(s, t) = \frac{\sqrt{2R|\Omega|}}{D \varepsilon} \left(1 - s \sqrt{2R\varepsilon}\right).
\end{equation}

We conclude that the escape time is
\begin{equation}
(2.21) \quad u(r, z) = \frac{\sqrt{2R|\Omega|}}{D \varepsilon} \left(1 - \frac{r}{r^2 + z^2} \sqrt{2R\varepsilon}\right),
\end{equation}

where the leading order term is
\begin{equation}
(2.22) \quad \langle \tau \rangle = \frac{\sqrt{2R|\Omega|}}{2D \varepsilon} (1 + o(1)) = \frac{\sqrt{2R|\Omega|}}{2D \varepsilon} (1 + o(1)).
\end{equation}

This analytical result is valid in a large range, as shown using Brownian simulations (Figure 2A–B): the analytical curve (blue) is compared to Brownian simulation results (red) and a fitted approximation ($f(x) = \frac{x}{\sqrt{2}}$) (magenta).
2.2. A three-dimensional escape to a narrow ribbon. In three dimensions, the domain $\Omega$ is obtained by rotating $\Omega'$ around the axis $\Delta$ (Figure 1A–B). We solve (2.2) in domain $\Omega$, where the absorbing boundary is the ribbon of height $\varepsilon$, located between the two spheres. In cylindrical coordinates $(r, \theta, z)$, the domain $\Omega$ is invariant in $\theta$. Integrating (2.2) according to $\theta$ reduces the problem to a two-dimensional one in $\Omega$:

\[
\begin{align*}
\frac{\partial^2 u}{\partial r^2}(r, z) + \frac{1}{r} \frac{\partial u}{\partial r}(r, z) + \frac{\partial^2 u}{\partial z^2}(r, z) &= -\frac{1}{D} \quad \text{for} \quad (r, z) \in \Omega, \\
\frac{\partial u}{\partial n}(r, z) &= 0 \quad \text{for} \quad (r, z) \in \partial \Omega \setminus \partial \Omega_\alpha, \\
u(r, z) &= 0 \quad \text{for} \quad (r, z) \in \partial \Omega_\alpha.
\end{align*}
\]
The inversion $\omega = f(\xi) = 1/\xi$ sends the coordinate system $\xi = (r, z)$ into $\omega = (s, t)$, where

$$r = \frac{s}{s^2 + t^2}, \quad z = -\frac{t}{s^2 + t^2}$$

and

$$\frac{\partial s}{\partial r}(s, t) = t^2 - s^2 \quad \text{and} \quad \frac{\partial t}{\partial r}(s, t) = 2st.$$

In $\tilde{\Omega}$, we set $u(\xi) = v(\omega)$ and (2.23) becomes

$$\frac{(s^2 + t^2)^2}{2s} \Delta v(s, t) + \frac{s^2 + t^2}{s} \left( \frac{\partial s}{\partial r} \frac{\partial v}{\partial s}(s, t) + \frac{\partial t}{\partial r} \frac{\partial v}{\partial t}(s, t) \right)$$

$$= -\frac{1}{D} \quad \text{for } (s, t) \in \tilde{\Omega},$$

$$\frac{\partial v}{\partial n}(s, t) = 0 \quad \text{for } (s, t) \in \partial \tilde{\Omega} \setminus \partial \tilde{\Omega}_a,$$

$$v(s, t) = 0 \quad \text{for } (s, t) \in \partial \tilde{\Omega}_a.$$

The structure of the solution is similar to the one of section 2.1: it is composed of an inner layer near the absorbing boundary $s = s_a$ and an outer solution far away. The scaling variable $\zeta = \frac{s}{s_a}$, $s_a = \frac{1}{\sqrt{2}\tilde{\xi}t}$, and $Y(\zeta, t) = v(s, t) = v(\frac{s}{\sqrt{2}\tilde{\xi}t}, t)$ can be used in the entire domain. The scaled equation becomes

$$\left( \frac{\zeta^2}{\tilde{\xi}} + t^2 \right)^2 \left( \tilde{\xi} \frac{\partial Y}{\partial \zeta}(\zeta, t) + \frac{\partial^2 Y}{\partial t^2}(\zeta, t) \right)$$

$$+ \frac{\zeta^2}{\tilde{\xi}} \left( (t^2 - \frac{\zeta^2}{\tilde{\xi}}) \tilde{\xi} \frac{\partial Y}{\partial \zeta}(\zeta, t) + 2\zeta \frac{\partial Y}{\partial t}(\zeta, t) \right) = -\frac{1}{D}.$$

We look for a solution using a regular expansion

$$Y(\zeta, t) = Y_0(\zeta, t) + \tilde{\xi}Y_1(\zeta, t) + \tilde{\xi}^2Y_2(\zeta, t) + \cdots,$$

which transforms (2.27) into

$$\frac{1}{\tilde{\xi}^2} \left[ \zeta^4 \frac{\partial^2 Y_0}{\partial t^2} \right] + \frac{1}{\tilde{\xi}^2} \left[ \zeta^4 \frac{\partial^2 Y_1}{\partial t^2} + \zeta^4 \frac{\partial^2 Y_2}{\partial \zeta^2} \right] + 2\zeta^2 t^2 \frac{\partial^2 Y_0}{\partial t^2} - \zeta^3 \frac{\partial Y_0}{\partial \zeta} + 2\zeta^2 \frac{\partial Y_0}{\partial t} = O(1).$$

The first order in $O(\tilde{\xi}^{-2})$ is

$$\zeta^4 \frac{\partial^2 Y_0}{\partial t^2} = 0,$$

and using the boundary conditions in (2.26), we find that $Y_0$ is independent of $t$. At order $O(\tilde{\xi}^{-1})$, we get

$$\zeta^4 \frac{\partial^2 Y_1(\zeta, t)}{\partial t^2} + \zeta^4 \frac{\partial^2 Y_0(\zeta)}{\partial \zeta^2} - \zeta^3 \frac{\partial Y_0(\zeta)}{\partial \zeta} = 0.$$
Integrating over $t$ and using the boundary conditions in (2.26), we obtain

$$\zeta^4 \frac{\partial^2 Y_0}{\partial \zeta^2} - \zeta^3 \frac{\partial Y_0}{\partial \zeta} = 0.$$  \hfill (2.32)

It follows that $Y_0(\zeta) = A\zeta^2 + B$, where $A$ and $B$ are two constants. Using the absorbing boundary condition in (2.26), we get $Y_0(\zeta) = A(1 - \zeta^2)$. To conclude, the leading order approximation depends on the $s$-variable only and

$$v(s) = A(1 - 2R\varepsilon s^2).$$  \hfill (2.33)

To compute the remaining constant $A$, we compute

$$\frac{\partial u}{\partial n} \bigg|_{\partial \Omega_a} = -\left[ - (s^2 - t^2) \frac{\partial v}{\partial r} \right]_{r=1/\sqrt{2R\varepsilon}} = \left[ \left( \frac{1}{2R\varepsilon} - t^2 \right) \frac{4R\varepsilon A}{\sqrt{2R\varepsilon}} \right] \approx \frac{2A}{\sqrt{2R\varepsilon}}(1 + O(\varepsilon))$$

and

$$\int_{\partial \Omega_a} \frac{\partial u}{\partial n} dS = 2\pi \sqrt{2R\varepsilon} \int_0^{\varepsilon} \frac{\partial u}{\partial r} dz = 4\pi A \varepsilon,$$  \hfill (2.34)

and, using the compatibility condition,

$$-\frac{\bar{\Omega}}{D} = \int_{\Omega} \Delta u(x) dx = \int_{\partial \Omega_a} \frac{\partial u(y)}{\partial n} dS_y.$$  \hfill (2.35)

Thus

$$A = -\frac{\bar{\Omega}}{4\pi D \varepsilon},$$  \hfill (2.36)

and the solution $v$ is

$$v(s) = \frac{\bar{\Omega}}{4\pi D \varepsilon} \left( 1 - 2R\varepsilon s^2 \right).$$  \hfill (2.37)

In the initial variable (Figure 2C),

$$u(r, z) = \frac{\bar{\Omega}}{4\pi D \varepsilon} \left( 1 - 2R\varepsilon \left( \frac{r}{r^2 + z^2} \right)^2 \right).$$  \hfill (2.38)

The mean time to the ribbon is obtained by setting $s = 0$ in (2.37):

$$\langle \tau \rangle = \frac{\bar{\Omega}}{4\pi D \varepsilon}.$$  \hfill (2.39)

The range of validity of this formula is examined using Brownian simulations in Figure 2D. The search time to a narrow ribbon is surprisingly different from that for a funnel cusp ([8]; see also the appendix), as it does not depend on the curvature at the cusp and it diverges to infinity with $\frac{1}{\varepsilon}$, as $\varepsilon$ tends to zero. This divergence is the same as in the narrow escape for a small hole [8, 9, 10]. We note, however, that the surface of the ribbon is $S_{rib} = 2\pi \sqrt{2R\varepsilon}^{3/2}$, which increases with a power law different from that for a regular circular small hole of radius $\varepsilon$. Formula (2.39) is valid for a general domain, not only the geometry between two spheres, as long as the cusp geometry is preserved. It would be interesting to extend formula (2.39) to higher order cusp

$$z = A \left( \frac{r}{l} \right)^{\nu} + o(r^\nu),$$  \hfill (2.40)

where $\nu > 2$ and $A, l$ are two characteristic lengths.
3. Diffusion to proteins located underneath a presynaptic vesicle.

3.1. Modeling calcium diffusion near a vesicle. We now apply the analytical results derived in the previous sections to estimate the probability that diffusing calcium ions find a small region located underneath a vesicle, when they are initially located at a given distance on the surface membrane (Figure 3). This scenario models a key step in synaptic transmission: When calcium ions are flowing across voltage-gated calcium channels, in the presynaptic terminal, a certain fraction of them make their way underneath a docked vesicle. Here, they can bind to fundamental molecules or calcium-dependent proteins such as synaptotagmin, a family of proteins (SNARE complex) located between the vesicle and the presynaptic membrane (Figure 3A), leading ultimately to vesicular fusion. Although the exact number of calcium ions needed for this process is small, from 4 to 8, it is still an open question to understand how these ions find such small molecular sites and how the mean time and release probability depend on the local geometry and calcium channel location. Because the distance of the calcium channels to the center of the vesicle can vary, the goal of the present computation is to base the release probability on key parameters of calcium diffusion in the nanodomain between docked vesicles. We shall also explore here how...
the distribution of vesicles in clusters or uniformly distributed in the active zone (AZ) modulates the release probability.

The model to compute the probability of vesicular release is the following: When several ions hit the narrow ribbon underneath a vesicle, this event triggers the release. As we shall see, this event depends on the relative position of the calcium channels with respect to the vesicles, their organization, and the initial number of calcium ions. Exocytosis cannot be triggered by calcium ions diffusing far away from the vesicles. For example, in a presynaptic terminal of volume \( 1 \mu m^3 \) [27], one diffusing calcium ion located in the presynaptic bulk will enter the region underneath the vesicle in approximately 4 sec, as computed from (2.39) with an effective diffusing coefficient that accounts for crowding \( D = 20 \mu m^2 \cdot s^{-1} \) [2], and \( \varepsilon = 10^{-3} \mu m \). If the terminal contains 7 docked vesicles, the ion reaches any vesicle in approximately 570 ms. This estimate of 570 ms is two orders of magnitude higher than the time scale of exocytosis, which occurs in less than a millisecond following calcium entry into the presynaptic terminal [28]. This dimensional analysis reveals that exocytosis is triggered mainly by calcium ions located in the neighborhood of a vesicle. We conclude that when calcium ions exit the neighborhood of the docked vesicles, they should no longer contribute to the vesicular release probability.

### 3.2. Splitting probability of a Brownian ion to hit a vesicular ribbon versus entering the presynaptic bulk

The splitting probability here is the probability for a Brownian ion to hit the small ribbon below the vesicle before it reaches a distance \( 2R \) away from the membrane, where it is considered to be lost inside the presynaptic bulk. To compute this probability, we shall account for the geometry of the AZ at the presynaptic terminal: It is approximated as a flat three-dimensional domain, containing vesicles regularly distributed on the membrane surface, spaced apart at a distance \( 2H \) (Figure 3B–C). The activation site for vesicular release is the small two-dimensional ribbon of height \( \varepsilon \ll R \), as already mentioned in section 2.2 (Figure 4A (red)). The AZ is divided into elementary squares \( \Omega_p \) (see Figure 4A). Ions are absorbed at the cusp (Figure 4A (red)) and at the upper part of the domain (Figure 4A (orange)), and are reflected otherwise. The probability \( p_{3D}(x) \) for a Brownian ion starting at position \( x = (x,y,z) \) to reach the ribbon before the upper part of the three-dimensional domain \( \Omega_P \) (Figure 4A) satisfies the mixed boundary value Laplace equation [14, 23, 26]

\[
\begin{align*}
\Delta p_{3D}(x) &= 0 \text{ for } x \in \bar{\Omega}_P, \\
p_{3D}(x) &= 1 \text{ for } x \in \partial \bar{\Omega}_{P,a}, \\
p_{3D}(x) &= 0 \text{ for } x \in \partial \bar{\Omega}_{P,out}, \\
\frac{\partial p_{3D}}{\partial n}(x) &= 0 \text{ for } x \in \partial \bar{\Omega}_P \setminus (\partial \bar{\Omega}_{P,a} \cup \partial \bar{\Omega}_{P,out}).
\end{align*}
\]

The domain, composed of vesicles centered on a square lattice, is not invariant by rotation around any axis. Nevertheless, the results of the previous sections motivate the restriction of our analysis to the fundamental square domain \( \Omega_P \) (Figure 4B). In
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We neglect the change in the geometry along the angle \( \theta \), which should give a term of order \( O(1) \). Using the conformal mapping \( f(\zeta) = \frac{1}{\zeta} \), we map the domain \( \Omega_P \) into \( \tilde{\Omega}_P \) (see (2.3) and Figure 4C). The mapping \( \omega = (s, t) = f(\zeta) \), where \( \zeta = r + iz \), transforms horizontal lines \( r = \alpha \), \( \alpha \in \mathbb{R} \) (resp., vertical lines \( z = \beta \), \( \beta \in \mathbb{R} \)) into circles of radius \( \frac{1}{2s} \) and centered at \( (s, t) = (\frac{1}{2\alpha}, 0) \) (resp., \( \frac{1}{2\beta} \) and \( (s, t) = (0, \frac{1}{2\beta}) \)). In particular, the interval at the cusp \( (r = \sqrt{2r\varepsilon}) \) is mapped into a portion of a circle of radius \( \frac{1}{2\sqrt{2r\varepsilon}} \) centered at \( (\frac{1}{2\sqrt{2r\varepsilon}}, 0) \). The first order approximation is a segment \( s = s_a = \frac{1}{\sqrt{2r\varepsilon}}, \ t \in [0, -\frac{1}{2R}] \). We set \( p_{3D}(r, z) = v_{3D, in}(s, t) \). In the scaling variable \( \xi = \frac{s}{s_a} \), the regular expansion of the solution

\[
Y_{3D, in}(\xi, t) = v_{3D, in}(s, t)
\]
is
\begin{equation}
Y_{3D,\text{in}}(\xi, t) = Y_{3D,\text{in}}^0(\xi, t) + \varepsilon Y_{3D,\text{in}}^1(\xi, t) + \cdots,
\end{equation}
where the small parameter is $\varepsilon = 2R\varepsilon$. $Y_{3D,\text{in}}^0(\xi, t)$ is the solution of (2.29), and at first order in $O(\varepsilon^{-2})$ with the boundary conditions in (3.2), we obtain that the leading order term $Y_0$ is independent of $t$. At order $O(\varepsilon^{-1})$, the equation for $Y_{3D,\text{in}}^0$ becomes
\begin{equation}
\xi^4 \frac{\partial^2 Y_{3D,\text{in}}^0}{\partial \xi^2} - \xi^3 \frac{\partial Y_{3D,\text{in}}^0}{\partial \xi} = 0,
\end{equation}
and hence $Y_{3D,\text{in}}^0(\xi) = A\xi^2 + B$, where $A$ and $B$ are two constants. Thus, the solution $v_{3D,\text{in}}$ is
\begin{equation}
v_{3D,\text{in}}(s) = As^2 + B.
\end{equation}
We are left with the constants $A$ and $B$ to be determined. We shall compute here the probability $p_{3D}(r, 0)$, where the initial starting point is located on the surface $z = 0$. The splitting probability $p_{3D}$ has the general form
\begin{equation}
p_{3D}(r, z) = A \frac{r^2}{(z^2 + r^2)^2} + B
\end{equation}
and
\begin{equation}
p_{3D}(r, 0) = \frac{A}{r^2} + B.
\end{equation}
We now use the boundary conditions and some approximation to determine these constants $A$ and $B$. First, the absorbing boundary condition at the cusp in (3.2) gives that
\begin{equation}
p_{3D}(r, 0) = 1 - A \left(1 - \frac{2R\varepsilon}{r^2}\right),
\end{equation}
and the constant $A$ depends on the refined geometry of the domain and the distances $H$, $R$, and $\varepsilon$.

To determine $A$, we first assume that the value $p_{3D}(H, 0)$ is known and express the splitting probability as a function of $p_{3D}(H, 0) = p(\varepsilon, R, H)$ in (3.9). We obtain
\begin{equation}
p_{3D}(r, 0) = 1 - \frac{1 - p(\varepsilon, R, H)}{1 - \frac{2R\varepsilon}{H^2}} \left(1 - \frac{2R\varepsilon}{r^2}\right),
\end{equation}
We now determine numerically $p(\varepsilon, R, H)$ when $H$, $R$, and $\varepsilon$ are changing. We start by changing $H$ for fixed values $R$ and $\varepsilon$. We ran stochastic simulations and obtain with a best fit procedure the following interpolation:
\begin{equation}
p(\varepsilon, R, H) \approx \frac{a(R, \varepsilon)}{H^3},
\end{equation}
where the function $a(R, \varepsilon)$ depends on $\varepsilon$ and $R$ (see Figure 5A). Similarly, we obtain by varying $\varepsilon$ and fixing $H$ and $R$ the following estimation (Figure 5B):
\begin{equation}
p(\varepsilon, R, H) \approx b(R, H)\varepsilon.
\end{equation}
Finally, the dependency in the radius $R$ can be obtained by rescaling the domain. Combining (3.11) and (3.12), we propose that

\begin{equation}
    p_3D(\varepsilon, R, H) = \alpha \frac{R^2 \varepsilon}{H^3},
\end{equation}

where the constant $\alpha$ is fitted numerically using MATLAB. We obtain $\alpha \approx 9.8$. Thus, the splitting probability $p_{3D}(r, 0)$ to reach the absorbing window before the upper part of the thin layer $z = 2R$ is approximated by

\begin{equation}
    p_{3D}^{\text{approx}}(r, 0) = 1 - \frac{1 - 9.8 \frac{R^2 \varepsilon}{H^3}}{1 - \frac{2R \varepsilon}{H^2}} \left(1 - \frac{2R \varepsilon}{r^2}\right).
\end{equation}

The range of validity of this formula is investigated in Figure 5C–D, showing the nice agreement between the asymptotic formula and Brownian simulations for different values of $H$ and $\varepsilon$. 

Fig. 5. Approximation of the splitting probability $p_{3D}(r, 0)$. A, B: The splitting probability $p_{3D}(H, 0)$ function of the domain size $H$ for $R$ and $\varepsilon$ fixed (A), then for varying $\varepsilon$ and fixed $H$ and $R$ (B). The fittings are obtained using MATLAB, $a = 3767$ (A) and $b = 0.1485$ (B). C, D: Comparison of the splitting probability computed from Brownian simulations (blue) and the numerical approximation (magenta; see (3.14)) (red in Figure 4A). We vary the distance to the absorbing (red) boundary. The radius of a vesicle is $R = 20$ nm, and the diffusion coefficient for calcium is $D = 200 \mu m^2 \cdot s^{-1}$. The initial position of the Brownian particle $r$ goes from $\sqrt{2}R \varepsilon$ to $\sqrt{2}H$ and $H$ takes the following values (C, $H = 25, 30, 40, 90$), $\varepsilon = 1$. We also show $p_{3D}(r, 0)$ for different values of $\varepsilon$ (D, $\varepsilon = 0.5, 0.7, 1$, $H = 30$). We use 2000 runs per simulation. (Color available in electronic version.)
Fig. 6. Consequences on the release probability of calcium channel location and vesicular crowding at the AZ. A, B: Probability of finding three, four, or five calcium ions (resp., full, dashed, and dotted lines) underneath a vesicle in the case of sparse vesicular distribution: $H = 100$ nm (A); and in the case of crowding of vesicles at the AZ: $H = 35$ nm (B). The relation depends on the initial number of calcium ions. The diameter of the presynaptic vesicles is fixed at $R = 40$ nm (gray dashed circle), and the diffusion coefficient for free calcium ions is $D_{Ca} = 200 \mu m^2 s^{-1}$. The height of the absorbing boundary is $\epsilon = 1$ nm (red dashed line). C, D: Maximal channels distance $r_{max, p_{act}}(N)$ to activate a vesicle with a probability $p_{act} \geq 0.8$ (blue) and 0.2 (green) when there are $N$ initial ions for $H = 100$ nm (C) and $H = 35$ nm (D). We fix the threshold to 3, 4, or 5 calcium ions. The gray dashed line represents the maximal distance to the vesicle in the elementary domain: $\sqrt{2H}$. (Color available in electronic version.)

4. Discussion: Estimation of the vesicular release probability. In this final section, we apply the result obtained in section 3.2 about the splitting probability to estimate the variability of the vesicular release process. Indeed, we can now compute the probability

$$p_{act}(r, N) = \mathbb{P}(T \text{ ions have reached the synaptotagmin}|N \text{ ions, distance } r)$$

that a finite number $T$ of calcium ions (we consider $T = 3, 4, \text{ and } 5$ ions) bind a molecule such as synaptotagmin when $N$ calcium ions have entered through a channel. The synaptotagmin molecules are positioned between a vesicle and the synaptic membrane and calcium channels are at a distance $r$ from the center of the closest vesicle.

If we neglect the dynamics of calcium ion unbinding events, the probability $p_{act}(r, N)$ is thus the one of finding at least $T$ ions inside the ribbon. Because the probability of finding exactly $k$ ions out of $N$ follows the Binomial distribution
We obtain that
\[
\begin{align*}
    p_{\text{act}}(r, N) &= \sum_{k \geq T} \binom{N}{k} p_{3D}(r)^k (1 - p_{3D}(r))^{N-k} \\
    &= 1 - \sum_{k=0}^{T-1} \binom{N}{k} p_{3D}(r)^k (1 - p_{3D}(r))^{N-k}.
\end{align*}
\]

Using approximation (3.14), we obtain an explicit expression for the probability of activation \(p_{\text{act}}(r, N)\) after a single channel opens. The probability \(p_{\text{act}}\) depends on the channel locations, decreasing from one to almost zero in only a few nanometers (Figure 6A–B). This result can explain the large variability in the release probability as the calcium channel position can vary over time.

Moreover, the organization of vesicles in the AZ determines the release probability. Indeed, when vesicles are sparsely distributed (Figure 6A, \(H = 100\) nm) and 100 ions have entered, then to obtain a 80% release probability (\(p_{\text{act}} = 0.8\)), the distance between the vesicle and the channels must be smaller than 24 nm, which has to be compared to the 20 nm radius of the vesicle. This result shows that the colocalization of channels with a vesicle is a key feature determining a high release probability. However, for high vesicular crowding (Figure 6B, described by choosing the distance \(H = 35\) nm) in which 100 ions have entered, then the probability \(p_{\text{act}}\) is higher than 0.9, regardless of the initial position of the channels, suggesting that vesicles are certainly released. We predict that a high crowding of vesicles should be associated with a high release probability.

Channels can be organized in cluster or uniformly distributed, and this is also a major determinant governing release probability. Indeed, channels clustering in our model is accounted for by an increase in the number of entering ions. When vesicles are sparsely distributed, the 24 nm distance required to obtain a release probability \(p_{\text{act}} = 0.8\) when 100 ions are entering through one channel is increased to 61 nm for 500 ions. This effect results from the local geometry of the ribbon underneath the vesicle. When the number of ions is low, this maximal distance to guarantee \(p_{\text{act}} = 0.8\) does not vary much when the activation threshold \(T\) increases from 3 to 5; however, for 500 ions, this distance changes significantly over 15 nm.

To better understand how the maximal distance \(r_{\text{max,act}}(N)\) between channels and vesicles varied with the number \(N\) of entering ions, for a fixed probability \(p_{\text{act}}\), we plotted \(r_{\text{max,act}}(N)\) in Figure 6C–D. For a sparse distribution of vesicles, characterized by the distance \(H = 100\) nm, a vesicle is activated with a probability \(p_{\text{act}} = 0.8\) (resp., \(p_{\text{act}} = 0.2\)) when 1200 ions are entering at a distance 100 nm (resp., 450 ions), and 340 ions at a distance 50 nm (resp., 125 ions). This result has to be compared to the 200–500 nm diameter of the AZ [25]. Consequently, a sparse distribution of vesicles at the AZ requires a high number of entering ions in order to trigger fusion, which can be achieved when channels are clustered. However, when channels are colocalized with vesicles, the activation probability \(p_{\text{act}}\) is significantly increased: indeed 450 ions are necessary for activation for \(p_{\text{act}} = 0.2\) at a distance 100 nm. When the probability increases to 0.8, the distance reduces to 58 nm. Thus, a synapse with high release probability requires a nanometer precision of the channel location. However, this high requirement can be compensated for by increasing the number of initial ions: with 2000 ions, the maximum distance is relaxed to 140 nm. On the contrary, in a presynaptic terminal crowded at its surface with vesicles (characterized by \(H = 35\) nm), very few initial ions are needed for an efficient release. Indeed, 50 ions are enough to
activate a vesicle with probability 0.8, wherever the channels are located in AZ (Figure 6D). The number of calcium ions estimated for reliable release could be affected by calcium buffers located within the nanometer layer of the AZ, but not in the bulk as discussed above.

5. Conclusion. To conclude, the present asymptotic analysis of the model equations and their corresponding stochastic simulations provide a robust tool to study diffusion in cellular nanodomains and in particular in the presynaptic terminal of neuronal synapses. We reported here that channel positioning, the number of entering ions, and the organization of the AZ are key factors governing the search by diffusing ions to relevant proteins that trigger vesicular release. Channel clustering provides a way to increase the initial number of calcium ions at a specific location. According to the present results, we found that vesicles located near channel clusters will be reliably activated at distances of tens of nanometers. We speculate that releasing a sequence of vesicles at the same location might be an unrealistic scenario due to relocalization of the channels following vesicular fusion [21, 22]. The present approach complements previous numerical studies by specifically addressing the role of the three-dimensional geometry between a vesicle and the synaptic membrane for diffusing calcium ions to trigger vesicular release [4, 17, 18].

Finally, we reported here that a uniform distribution of calcium channels is associated with a low release probability. For vesicles positioned near a small amount of calcium channels, a train of stimulations will most likely activate several vesicles. Thus changing the AZ organization, or the colocalization of calcium channels with respect to vesicles, can modify the synaptic response. After several stimulations this redistribution of channels can influence short-term synaptic plasticity, the mechanism of which could be further investigated using the present modeling approach.

Appendix. Revisiting the dire strait search in a three-dimensional cusp located at the end of a funnel. In this appendix, we compute the time for a Brownian particle to escape through a narrow cusp located at the end of a funnel.
in a three dimensional bounded domain ($\bar{\Sigma}_R$; see Figure 7A). The mean first passage time $\tilde{u}(x)$ starting at position $x$ is a solution of

\begin{align}
D \Delta \tilde{u}(x) &= -1 \quad \text{for } x \in \bar{\Sigma}_R, \\
\frac{\partial \tilde{u}}{\partial n}(x) &= 0 \quad \text{for } x \in \partial \bar{\Sigma}_R \setminus \partial \bar{\Sigma}_{R,a}, \\
\tilde{u}(x) &= 0 \quad \text{for } x \in \partial \bar{\Sigma}_{R,a},
\end{align}

where $D$ is the diffusion coefficient and $\partial \bar{\Sigma}_R$ (resp., $\partial \bar{\Sigma}_{R,a}$) is the boundary (resp., the absorbing part of the boundary). We compute asymptotically the solution $u(x)$ for problem (A.1) using the conformal mapping method. The geometry of the domain $\bar{\Sigma}_R$ is the following: It contains a small absorbing window $\partial \Sigma_{R,a}$ of diameter $E$ located at the end of the funnel connected smoothly to a three-dimensional ball. The domain $\bar{\Sigma}_R$ can be as large as desired. The radius of curvature $R$ at the boundary shapes the funnel, as shown in Figure 7A. The symmetric cusp can be parameterized in the cylindrical coordinates $(\rho, \psi, z)$ ($\rho$ is the distance to the $z$-axis) by

$$\rho(z) = \frac{1}{2R} z^2 + \frac{\xi}{2}$$

for $z$ small. In dimensionless variables $x' = Rx$ and $\tilde{u}(x') = u(x)$, the equation is written as

\begin{align}
D \Delta u(x) &= -1 \quad \text{for } x \in \bar{\Sigma}_1, \\
\frac{\partial u}{\partial n}(x) &= 0 \quad \text{for } x \in \partial \bar{\Sigma}_1 \setminus \partial \bar{\Sigma}_{1,a}, \\
u(x) &= 0 \quad \text{for } x \in \partial \bar{\Sigma}_{1,a}.
\end{align}

The domain $\bar{\Sigma}_R$ is mapped on its image $\bar{\Sigma}_1$, $|\Sigma_R| = R^2 |\Sigma_1|$, $E = R \varepsilon$, $L = R l$, and $D = R^2 D$. Due to the rotational invariance, in cylindrical coordinates $(\rho, \psi, z)$, the solution of the two-dimensional problem in the domain $\{\psi = 0\}$ (see Figure 7B) satisfies

\begin{align}
\frac{\partial^2 u}{\partial \rho^2}(\rho, z) + \frac{1}{\rho} \frac{\partial u}{\partial \rho}(\rho, z) + \frac{\partial^2 u}{\partial z^2}(\rho, z) &= -\frac{1}{D} \quad \text{for } (\rho, z) \in \Sigma, \\
\frac{\partial u}{\partial n}(\rho, z) &= 0 \quad \text{for } (\rho, z) \in \partial \Sigma \setminus \partial \Sigma_a, \\
u(\rho, z) &= 0 \quad \text{for } (\rho, z) \in \partial \Sigma_a.
\end{align}

**A.1. Mapping the cusp domain with a M"obius transformation into a narrow banana.** The key step to the asymptotic computation is the M"obius transformation that maps domain $\bar{\Sigma}_1$ into a narrow domain, where the mapped equation reduces to a single variable,

$$f(\xi) = \frac{\xi - \alpha}{\xi - \beta},$$

where $\xi = \rho + iz$ is the variable in the original domain, which maps the domain $\Sigma$ into two concentric circles. The pair $(\alpha, \beta)$ lies symmetric on the real axis $\text{Re}(z) = 0$. We obtain their values using the conditions $\alpha = -\beta$ and $(1 + \varepsilon/2 - \alpha) (1 + \varepsilon/2 - \beta) = 1$. Finally, we obtain

\begin{align}
\alpha_\varepsilon &= \sqrt{\varepsilon (1 + \varepsilon/4)} = \sqrt{\varepsilon} \left(1 + \frac{1}{8} \varepsilon + o(\varepsilon)\right), \\
f(\xi) &= \frac{\xi - \alpha_\varepsilon}{\xi + \alpha_\varepsilon}.
\end{align}
The domain \( \Sigma \) (Figure 7B) is mapped into \( \Gamma \) (Figure 7C), and the boundary parts \( \partial \Sigma_a \) is mapped on the segment \( \partial \Gamma_a = [-1, -1 + \sqrt{\epsilon}] \) of length \( \sqrt{\epsilon} \). The cusp is mapped on the narrow hot-dog-shaped domain, and the other external part of the domain is mapped on the small green region (Figure 7C), concentrated at an angle \( \theta \) of order \( \sqrt{\epsilon} \). To map (A.4) into the new domain, we use \( \omega = re^{i \theta} = f(\xi) \) and \( u(\xi) = v_c(\omega) \). The conformal map changes the Laplace equation into

\[
\Delta u(\xi) = |f'(\xi)|^2 \Delta v(\omega),
\]

(A.8)

\[
f'(\xi) = \frac{2\alpha_\varepsilon}{(\xi + \alpha_\varepsilon)^2} = \frac{(1 - \omega)^2}{2\alpha_\varepsilon}.
\]

The first order derivative is

\[
\frac{\partial u}{\partial \rho} = \frac{\partial v_\varepsilon}{\partial \rho} \frac{\partial r}{\partial \rho} + \frac{\partial v_\varepsilon}{\partial \theta} \frac{\partial \theta}{\partial \rho} = \frac{1 - r^2}{2\alpha_\varepsilon} \cos(\theta) + \frac{r}{\alpha_\varepsilon} (r \cos(\theta) - 1) \frac{\partial v_\varepsilon}{\partial r} + \frac{r^2 - 1}{2\alpha_\varepsilon r} \sin(\theta) \frac{\partial v_\varepsilon}{\partial \theta},
\]

(A.10)

and the variable \( \rho \) is now expressed by

\[
\rho = \alpha_\varepsilon \text{Re} \left( \frac{\omega + 1}{1 - \omega} \right) = \alpha_\varepsilon \frac{1 - |\omega|^2}{1 - |\omega|^2} = \alpha_\varepsilon \frac{r^2 - 1}{2r \cos(\theta) - 1 - r^2}.
\]

(A.11)

Equation (A.4) is mapped into

\[
\frac{|1 - \omega|^4}{4\alpha_\varepsilon^2} \Delta v_\varepsilon + \frac{|1 - \omega|^2}{\alpha_\varepsilon (1 - |\omega|^2)} \left[ \frac{\partial v_\varepsilon}{\partial r} \frac{\partial r}{\partial \rho} + \frac{\partial v_\varepsilon}{\partial \theta} \frac{\partial \theta}{\partial \rho} \right] = -\frac{1}{D} \text{ for } (r, \theta) \in \Gamma,
\]

\[
\frac{\partial v_\varepsilon}{\partial n}(r, \theta) = 0 \text{ for } (r, \theta) \in \partial \Gamma \setminus \partial \Gamma_a,
\]

\[
v_\varepsilon(r, \theta) = 0 \text{ for } (r, \theta) \in \partial \Gamma_a.
\]

To solve asymptotically (A.12) in \( \Gamma \), we neglect the variation in the \( r \)-variable because \( r = 1 + O(\sqrt{\epsilon}) \) and thus \( v_\varepsilon(r, \theta) \approx v_\varepsilon(\theta) \) with absorbing boundary condition at \( \pi \) \( (v_\varepsilon(\pi) = 0) \) and reflection inside the upper part \( (v_\varepsilon(c\sqrt{\epsilon}) = 0) \), where the constant \( c = O(1) \). Equation (A.12) reduces to

\[
v_\varepsilon''(\theta) + \frac{\sin(\theta)}{\cos(\theta) - 1} v_\varepsilon'(\theta) = -\frac{\alpha_\varepsilon^2}{D(\cos(\theta) - 1)^2},
\]

(A.13)

the general solutions of which has the form

\[
v_\varepsilon(\theta) = A (\sin(\theta) - \theta) + B + \frac{\alpha_\varepsilon^2}{15D} \left[ 2 \ln (1 - \cos(\theta)) - 2 \cos(\theta) + \frac{3}{\cos(\theta) - 1} \right],
\]

(A.14)

where the two constants \( A \) and \( B \) are found from the boundary conditions. From \( v_\varepsilon(\pi) = 0 \), we get

\[
v_\varepsilon(\theta) = A (\sin(\theta) + \pi - \theta) + \frac{\alpha_\varepsilon^2}{15D} \left[ 2 \ln \left( \frac{1 - \cos(\theta)}{2} \right) - 2 (1 + \cos(\theta)) + \frac{3}{\cos(\theta) - 1} + \frac{3}{2} \right].
\]

(A.15)
To estimate the other constant, $A$, we use the compatibility condition [8] obtained by integrating equation (A.3) over the initial domain

(A.16) \[ \frac{|\Sigma_1|}{D} = \int_{\Sigma_1} \Delta u(x) dx = \int_{\partial \Sigma_1} \frac{\partial u}{\partial n}(y) dS. \]

Using expression (A.15) for the solution $v_\varepsilon$, we get

\[
\frac{\partial u}{\partial n} \bigg|_{\Sigma_1} = -\frac{\partial u}{\partial z} \bigg|_{\Sigma_1} = -\frac{\partial u}{\partial \Sigma_a} \bigg|_{\partial u/\partial n}(y) \bigg|_{\theta=\pi, r\in[-1;1]} = -\frac{2}{\alpha} (1 + O(\sqrt{\varepsilon})).
\]

Thus,

\[
\int_{\partial \Sigma_1} \frac{\partial u}{\partial n}(\rho, z) dS = -2\pi \frac{4A}{\alpha} \int_0^{\varepsilon/2} \rho d\rho = -2\pi \frac{4A \varepsilon^2}{\alpha} = -A\pi \varepsilon \varepsilon = -A\pi \varepsilon \sqrt{\varepsilon} (1 + O(\sqrt{\varepsilon})).
\]

Using the compatibility condition (A.16), we get

(A.17) \[ A_\varepsilon = \frac{|\Sigma_1|}{D\pi \varepsilon \sqrt{\varepsilon}} \]

and

(A.18) \[ v_\varepsilon(\theta) = \frac{|\Sigma_1|}{D\pi \varepsilon \sqrt{\varepsilon}} (\sin(\theta) + \pi - \theta)
+ \frac{\alpha^2}{15D} \left[ 2 \ln \left( \frac{1 - \cos(\theta)}{2} \right) - 2 \left( 1 + \cos(\theta) \right) + \frac{3}{\cos(\theta) - 1} + \frac{3}{2} \right]. \]

The solution and the extension of the boundary layer [1] are represented in Figure 8A.

The mean first passage time $\langle \tau \rangle$ from the domain is computed for trajectories starting outside the cusp, located in the mapped domain by the starting angle $\theta = c\sqrt{\varepsilon}$:

(A.19) \[ \langle \tau \rangle = \frac{|\Sigma_1|}{D\varepsilon \sqrt{\varepsilon}} + O(1). \]

In dimensional units, we obtain

(A.20) \[ \langle \tau \rangle = \frac{|\Sigma_R|\sqrt{R}}{D\varepsilon \sqrt{\varepsilon}} + O(1), \]

where $R$ is the curvature at the cusp, $D$ the diffusion coefficient, and $|\Sigma_R|$ the total volume of the domain. This formula corrects by a factor of 2 the asymptotic expansion.
Fig. 8. Profile of the solution $v_\epsilon$ for escape in the three-dimensional funnel-shaped cusp. A: Solution $v_\epsilon$ in the mapped domain for $\epsilon = 10^{-2}$ (top) and $2 \cdot 10^{-2}$ (bottom), with $R = 1$, $D = 0.2$, and $|\Sigma_1| = \frac{3}{2} \pi 5^2$. There are two regions: the boundary layer and the outer region. B: Analytical formula (blue) for the DST (eq. (A.20)) versus Brownian simulations (red). We used 2000 runs for values of $\epsilon$ in the range 0.01 to 0.1. The parameters are described in A. The optimal fit using MATLAB (magenta) gives $a = 2650$ is comparable with the estimation from the analytical formula $a = 2618$. (Color available in electronic version.)

for the DST derived in [8, 9, 10, 11]. The asymptotic formula (A.20) seems to be valid in a large range of the absorbing radius $\mathcal{E}$ as shown in Figure 8B, where the analytical formula is directly compared to Brownian simulations.

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