Published in final edited form as:

J Phys Chem B. 2019 May 02; 123(17): 3786–3796. doi:10.1021/acs.jpcc.9b01616.

Exact Solutions for Distributions of First-Passage, Direct-Transit, and Looping Times in Symmetric Cusp Potential Barriers and Wells

Alexander M. Berezhkovskii^{†,‡}, Leonardo Dagdug[§], Sergey M. Bezrukov^{*,†}

[†]Section on Molecular Transport, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland 20892, United States

[‡]Mathematical and Statistical Computing Laboratory, Office of Intramural Research, Center for Information Technology, National Institutes of Health, Bethesda, Maryland 20892, United States

[§]Departamento de Física, Universidad Autonoma Metropolitana-Iztapalapa, 09340 Mexico City, Mexico

Abstract

For a particle diffusing in one dimension, the distribution of its first-passage time from point a to point b is determined by the durations of the particle trajectories that start from point a and are terminated as soon as they touch point b for the first time. Any such trajectory consists of looping and direct-transit segments. The latter is the final part of the trajectory that leaves point a and goes to point b without returning to point a . The rest of the trajectory is the looping segment that makes numerous loops which begin and end at the same point a without touching point b . In this article we discuss general relations between the first-passage time distribution and those for the durations of the two segments. These general relations allow us to find exact solutions for the Laplace transforms of the distributions of the first-passage, direct-transit, and looping times for transitions between two points separated by a symmetric cusp potential barrier or well of arbitrary height and depth, respectively. The obtained Laplace transforms are inverted numerically, leading to nontrivial dependences of the resulting distributions on the barrier height and the well depth.

Graphical Abstract

*Corresponding Author: bezrukos@mail.nih.gov.

The authors declare no competing financial interest.

INTRODUCTION

Consider a particle diffusing in a one-dimensional constraining potential, $U(x)$, which does not allow the particle to escape to infinity, $U(x)|_{x \rightarrow \pm\infty} \rightarrow \infty$. The time evolution of the particle spatial distribution is governed by the Smoluchowski equation. Our focus is on trajectories making transitions from point a to point b , $a < b$, i.e., they start from point a and are terminated as soon as they touch point b for the first time. Any such trajectory can be decomposed into direct-transit and looping parts (segments).^{1–3} The former is the final part of the trajectory, when it leaves point a and goes to point b without touching point a . The rest of the trajectory is its looping part which starts and ends at point a . The two segments are illustrated in Figure 1. Note, that the direct-transit time is frequently referred to as the transition path time in the literature on the barrier crossing problem.

Let $t_{a \rightarrow b}^{\text{FP}}$, $t_{a \rightarrow b}^{\text{dtr}}$, and $t_a^1(b)$ be the durations of a first-passage (FP) a -to- b trajectory and its direct-transit (dtr) and looping (1) segments, respectively, where the notation $t_a^1(b)$ means looping time around point a without touching point b . The duration of the first-passage trajectory is the sum of the durations of its parts (see Figure 1)

$$t_{a \rightarrow b}^{\text{FP}} = t_{a \rightarrow b}^{\text{dtr}} + t_a^1(b) \quad (1.1)$$

Averaging eq 1.1 over realizations of the first-passage trajectory, one finds that the mean first-passage time $\bar{t}_{a \rightarrow b}^{\text{FP}}$ is the sum of the mean direct-transit and looping times, $\bar{t}_{a \rightarrow b}^{\text{dtr}}$ and $\bar{t}_a^1(b)$

$$\bar{t}_{a \rightarrow b}^{\text{FP}} = \bar{t}_{a \rightarrow b}^{\text{dtr}} + \bar{t}_a^1(b) \quad (1.2)$$

There are exact quadrature expressions for $\bar{t}_{a \rightarrow b}^{\text{FP}}$ ^{4,5}

$$\bar{t}_{a \rightarrow b}^{\text{FP}} = \int_a^b (e^{\beta U(y)} / D(y)) dy \int_{-\infty}^y e^{-\beta U(x)} dx \quad (1.3)$$

(one can find early work citations in ref 5) and for $\bar{t}_{a \rightarrow b}^{\text{dtr}}$ ⁶⁻⁸

$$\bar{t}_{a \rightarrow b}^{\text{dtr}} = \frac{\int_a^b \left(\int_a^x (e^{\beta U(y)} / D(y)) dy \right) \left(\int_x^b (e^{\beta U(y)} / D(y)) dy \right) e^{-\beta U(x)} dx}{\int_a^b (e^{\beta U(y)} / D(y)) dy} \quad (1.4)$$

Here, $D(x)$ is the particle position-dependent diffusivity, and $\beta = 1/(k_B T)$, where k_B and T are the Boltzmann constant and the absolute temperature. Using these expressions and eq 1.2, one can find the mean looping time, $\bar{t}_a^1(b)$

$$\bar{t}_a^1(b) = \bar{t}_{a \rightarrow b}^{\text{FP}} - \bar{t}_{a \rightarrow b}^{\text{dtr}} \quad (1.5)$$

Although the above expressions for the mean values of the three times are exact for any choice of points a and b and for an arbitrary constraining potential, $U(x)$, analytical solutions for their distributions, $\varphi_{a \rightarrow b}^{\text{FP}}(t)$, $\varphi_{a \rightarrow b}^{\text{dtr}}(t)$, and $\varphi_a^1(t|b)$, are unknown. The only exception is the direct-transit (transition path) time distribution between two points symmetrically located with respect to the top of a high parabolic barrier separating these points. This distribution has been studied theoretically for various stochastic dynamics governing the trajectory using the free boundary conditions at the end points.⁹⁻¹⁷ In this approximate approach, no constraints are imposed on the particle motion at points a and b . The approach takes advantage of the fact that one can find an exact solution for the Green's function when the motion occurs in a quadratic potential in the absence of any boundary conditions. This Green's function can be used to calculate the probability flux passing through point b located on the opposite side of the barrier top, as a function of time. The direct-transit time distribution is then determined by dividing this flux by the time integral of the flux from zero to infinity. One might expect that this ratio provides a reasonable estimate of the direct-transit time distribution when points a and b are located sufficiently far from the barrier top.

Here, we derive exact solutions for the Laplace transforms of the three distributions for the symmetric cusp potential barrier and well (see Figure 2) of arbitrary height and depth, assuming that the particle diffusivity is position independent, $D(x) = D = \text{const}$. The looping time distributions are discussed when looping occurs (i) near the left reflecting wall and (ii) near the barrier top and the well bottom of the corresponding potential, without touching either the reflecting wall or the absorbing end of the interval. All the Laplace transforms are given by simple expressions, which can be easily inverted numerically. The key step in our approach is decomposition of the trajectories into simple segments. This allows us to find

the Laplace transforms of the distributions of interest using the results obtained in ref 3, which were verified by Brownian dynamics simulations.

The outline of this paper is as follows. In the following First-Passage Time Distributions, Direct-Transit Time Distributions, and Looping Time Distributions sections, we derive exact solutions for the Laplace transforms of the time distributions mentioned above. Then, in the Discussion section, we numerically invert these Laplace transforms and discuss the obtained time dependencies, focusing on how they vary with the change in the barrier height and well depth. The obtained results are summarized in the final Concluding Remarks section, where we also consider a decomposition of the looping segment.

Our interest to the questions discussed in this article was stimulated by single-molecule experiments on large solute dynamics in single membrane channels. Entering the channel, a large solute molecule blocks the small ion current flowing through the channel. If the solute stays in the channel long enough, individual blockage events can be detected in high-time-resolution single-channel current measurements. Typical examples of single-channel records of the current through VDAC (voltage-dependent anionic channel of the outer mitochondrial membrane) in the presence of a polymeric blocker, the alpha-synuclein polypeptide chain, are shown in Figure 3.

Alpha-synuclein can be thought of as a diblock copolymer composed of two parts with different charge distributions, as shown in Figure 3. While the N-terminal part of the protein is mostly neutral, its C-terminal part is highly negatively charged. The process starts with the trapping of the C-terminus by the VDAC nanopore and then proceeds with either whole protein translocation to the other side of the membrane or the terminus retraction. The drastic difference in charge between the two parts of the chain allows to experimentally discriminate between the two possibilities.¹⁸

Thus, channel-facilitated solute transitions between two reservoirs, separated by a membrane, share a lot of similarities with transitions between two deep wells of a double-well potential. The latter may describe isomerization reactions like folding of proteins and nucleic acids, in which individual folding–unfolding transitions can be detected in single-molecule experiments with sufficient time resolution to observe individual transitions.^{7,20–34} System dynamics in a double-well potential involves long fluctuations near the bottoms of the two wells, interrupted by fast interwell transitions, when the system traverses the barrier (saddle point) region separating the wells. The same is true for solute dynamics in two reservoirs separated by the membrane. Here the reservoirs and membrane channel play the roles of the potential wells and barrier region, respectively.

Entering the channel, a solute molecule either returns to the reservoir from which it entered, or traverses the channel and exits the second reservoir, thus making a direct transition from one reservoir to the other (Figure 3). Similarly, in isomerization reactions, the system entering the barrier region either returns to the initial well or traverses this region and enters the second well, performing a direct interwell transition. One of the characteristics of the system dynamics in the barrier region is the duration of the direct transition. The direct-

transit (transition path) time is a random variable which is characterized by the direct-transit time distribution. This distribution is the focus of the present work.

FIRST-PASSAGE TIME DISTRIBUTIONS

General Relations.

Let point c be located between points a and b , $a < c < b$. Then, any a -to- b trajectory passes through point c . Coming to this point, the trajectory either returns to point a or goes to point b . Therefore, the probability density $\varphi_{a \rightarrow b}^{\text{FP}}(t)$ satisfies

$$\begin{aligned} \varphi_{a \rightarrow b}^{\text{FP}}(t) = & \int_0^t dt_1 \varphi_{a \rightarrow c}^{\text{FP}}(t_1) \int_0^{t-t_1} dt_2 \varphi_c^l(t_2|a, b) \\ & [P_{c \rightarrow b} \varphi_{c \rightarrow b}^{\text{dtr}}(t-t_1-t_2) + P_{c \rightarrow a} \int_0^{t-t_1-t_2} dt_3 \varphi_{c \rightarrow a}^{\text{dtr}}(t_3) \varphi_{a \rightarrow b}^{\text{FP}}(t-t_1-t_2-t_3)] \end{aligned} \quad (2.1)$$

Here, $\varphi_{a \rightarrow c}^{\text{FP}}(t)$ is the first-passage time distribution for transitions from point a to point c , $\varphi_c^l(t|a, b)$ is the distribution of looping time around point c without touching either point a or point b , $P_{c \rightarrow a}$ and $P_{c \rightarrow b}$ are the splitting probabilities for transitions from point c to points a and b , $P_{c \rightarrow a} + P_{c \rightarrow b} = 1$, $\varphi_{c \rightarrow a}^{\text{dtr}}(t)$ and $\varphi_{c \rightarrow b}^{\text{dtr}}(t)$ are direct-transit time distributions for these transitions. The right-hand side of eq 2.1 is the sum of two terms. The first one, proportional to $P_{c \rightarrow b}$, is due to such trajectory realizations which come to point c and then, after some looping time, t_2 , around this point, make a direct transition to point b . The second term, proportional to $P_{c \rightarrow a}$, is due to such realizations which return from point c to point a .

After the Laplace transformation, eq 2.1 takes the form

$$\hat{\varphi}_{a \rightarrow b}^{\text{FP}}(s) = \hat{\varphi}_{a \rightarrow c}^{\text{FP}}(s) \hat{\varphi}_c^l(s|a, b) [P_{c \rightarrow b} \hat{\varphi}_{c \rightarrow b}^{\text{dtr}}(s) + P_{c \rightarrow a} \hat{\varphi}_{c \rightarrow a}^{\text{dtr}}(s) \hat{\varphi}_{a \rightarrow b}^{\text{FP}}(s)] \quad (2.2)$$

where s is the Laplace parameter, and $\hat{f}(s)$ denotes the Laplace transform of function $f(t)$, $\hat{f}(s) = \int_0^\infty e^{-st} f(t) dt$. We find the Laplace transform of the first-passage time distribution, $\varphi_{a \rightarrow b}^{\text{FP}}(t)$, by solving eq 2.2. The result is

$$\hat{\varphi}_{a \rightarrow b}^{\text{FP}}(s) = \frac{P_{c \rightarrow b} \hat{\varphi}_{a \rightarrow c}^{\text{FP}}(s) \hat{\varphi}_c^l(s|a, b) \hat{\varphi}_{c \rightarrow b}^{\text{dtr}}(s)}{1 - P_{c \rightarrow a} \hat{\varphi}_{a \rightarrow c}^{\text{FP}}(s) \hat{\varphi}_c^l(s|a, b) \hat{\varphi}_{c \rightarrow a}^{\text{dtr}}(s)} \quad (2.3)$$

When point c is in the center of the (a, b) -interval, $c - a = b - c$, and the potential $U(x)$ is symmetric about point c in this interval, $U(x - c) = U(c - x)$, $a < x < b$, we have

$$P_{c \rightarrow a} = P_{c \rightarrow b} = 1/2, \varphi_{c \rightarrow a}^{\text{dtr}}(t) = \varphi_{c \rightarrow b}^{\text{dtr}}(t) \quad (2.4)$$

and

$$\varphi_c^1(t|a, b) = \varphi_c^1(t|a|R) = \varphi_c^1(t|b|R) \quad (2.5)$$

Here, $\varphi_c^1(t|a|R)$ and $\varphi_c^1(t|b|R)$ are the distributions of looping times around point c , located on the imaginary reflecting (R) wall in the center of the (a, b) -interval, without touching points a and b , respectively. Note, that the distributions of the first passage times from the imaginary reflecting wall, located at point c , to points a and b are identical. These distributions, denoted by $\varphi_{c \rightarrow a(b)}^{\text{FP}}(t|R)$, are convolutions of the corresponding distributions of the looping times around point c and the direct-transit times from point c to points a and b

$$\varphi_{c \rightarrow a}^{\text{FP}}(t|R) = \varphi_{c \rightarrow b}^{\text{FP}}(t|R) = \int_0^t \varphi_c^1(t'|a, b) \varphi_{c \rightarrow a(b)}^{\text{dtr}}(t - t') dt' \quad (2.6)$$

After the Laplace transformation, this equation reduces to

$$\hat{\varphi}_{c \rightarrow a}^{\text{FP}}(s|R) = \hat{\varphi}_{c \rightarrow b}^{\text{FP}}(s|R) = \hat{\varphi}_c^1(s|a, b) \hat{\varphi}_{c \rightarrow a(b)}^{\text{dtr}}(s) \quad (2.7)$$

Using this, we can simplify eq 2.3 and write the Laplace transform of the first-passage time distribution for a -to- b transitions in terms of the Laplace transforms of such distributions for a -to- c and c -to- b transitions as

$$\hat{\varphi}_{a \rightarrow b}^{\text{FP}}(s) = \frac{\hat{\varphi}_{a \rightarrow c}^{\text{FP}}(s) \hat{\varphi}_{c \rightarrow b}^{\text{FP}}(s|R)}{2 - \hat{\varphi}_{a \rightarrow c}^{\text{FP}}(s) \hat{\varphi}_{c \rightarrow b}^{\text{FP}}(s|R)} \quad (2.8)$$

This is used in the next subsection to obtain analytical expressions for the Laplace transforms of the first-passage time distributions in the case of symmetric cusp potential barriers and wells.

Symmetric Cusp Potential Barrier and Well.

Symmetric cusp potential barrier (b) and well (w) shown in Figure 2 are defined by

$$U_b(x) = \begin{cases} -F|x|, & |x| < L \\ \infty, & |x| = L \end{cases}, F > 0 \quad (2.9a)$$

$$U_w(x) = \begin{cases} -F|x|, & |x| < L \\ \infty, & |x| = L \end{cases}, F > 0 \quad (2.9b)$$

where F is the absolute value of the force acting on the diffusing particle. Although these potentials look different, the first-passage time distributions, $\varphi_{-L \rightarrow L}^{\text{FP}}(t|R)$, for transitions from the reflecting wall, located at $x = -L$, to point L in both potentials are equal. This may be seen as a consequence of the fact that if the cusp potential barrier and well shown in Figure 2 are repeated periodically, the resulting periodic potentials are indistinguishable.

To find the Laplace transform of the distribution $\varphi_{-L \rightarrow L}^{\text{FP}}(t|R)$, we take advantage of the expression in eq 2.8, which in this case takes the form

$$\hat{\varphi}_{-L \rightarrow L}^{\text{FP}}(s|R) = \frac{\hat{\varphi}_{-L \rightarrow 0}^{\text{FP}}(s|R)\hat{\varphi}_{0 \rightarrow L}^{\text{FP}}(s|R)}{2 - \hat{\varphi}_{-L \rightarrow 0}^{\text{FP}}(s|R)\hat{\varphi}_{0 \rightarrow L}^{\text{FP}}(s|R)} \quad (2.10)$$

It is important, that the Laplace transforms of the first-passage time distributions $\varphi_{-L \rightarrow L}^{\text{FP}}(t|R)$ and $\varphi_{0 \rightarrow L}^{\text{FP}}(t|R)$ entering the above equation are known. According to eq 7 from ref 3, they are given by

$$\hat{\varphi}_{-L \rightarrow 0}^{\text{FP}}(s|R) = \frac{ze^{-\tilde{F}/2}}{z \cosh(z) - (\tilde{F}/2) \sinh(z)} \quad (2.11a)$$

$$\hat{\varphi}_{0 \rightarrow L}^{\text{FP}}(s|R) = \frac{ze^{\tilde{F}/2}}{z \cosh(z) + (\tilde{F}/2) \sinh(z)} \quad (2.11b)$$

Where z and $\tilde{F}$ are

$$z = \sqrt{sL^2/D + (\tilde{F}/2)^2}, \tilde{F} = \beta FL \quad (2.12)$$

The above expressions, with positive $\tilde{F}$, are derived for the case of a linear uphill potential. Corresponding expressions for the case of a linear downhill potential can be obtained by replacing in eqs 2.11a and 2.11b $\tilde{F}$ by $-\tilde{F}$. However, the sign of $\tilde{F}$ is not important, since eq 2.10 contains the product of the Laplace transforms, $\hat{\varphi}_{-L \rightarrow 0}^{\text{FP}}(s|R)\hat{\varphi}_{0 \rightarrow L}^{\text{FP}}(s|R)$, which depends on $\tilde{F}^2$. Note, that $\tilde{F} > 0$ has different meanings in the potential barrier and well cases, where it is the dimensionless barrier height and well depth, respectively.

Using the relations in eqs 2.11a, 2.11b, and 2.12, we can write $\hat{\varphi}_{-L \rightarrow L}^{\text{FP}}(s|R)$ in eq 2.10 as

$$\hat{\varphi}_{-L \rightarrow L}^{\text{FP}}(s|R) = \frac{sL^2/D + (\tilde{F}/2)^2}{(sL^2/D)\cosh(2z) + (\tilde{F}/2)^2} \quad (2.13)$$

This is an exact expression for the Laplace transform of the distribution of the first-passage time from a reflecting wall, located at $x = -L$ to point L , when the two end points are separated by a symmetric cusp potential barrier or well. This expression is one of the main results of this work. One can find the mean first-passage time between points $-L$ and L , $\bar{t}_{-L \rightarrow L}^{\text{FP}}(R)$, using the relation $\bar{t}_{-L \rightarrow L}^{\text{FP}}(R) = -d\hat{\varphi}_{-L \rightarrow L}^{\text{FP}}(s|R)/ds|_{s=0}$. This leads to the recovery of the result for $\bar{t}_{-L \rightarrow L}^{\text{FP}}(R)$ given in eq 9 of ref 1

$$\bar{t}_{-L \rightarrow L}^{\text{FP}}(R) = \frac{2L^2}{D} \left[\frac{2}{\tilde{F}} \sinh\left(\frac{\tilde{F}}{2}\right) \right]^2 \quad (2.14)$$

When $F=0$, eqs 2.13 and 2.14 give the Laplace transform of the distribution and the mean value of the first-passage time for $-L$ -to- L transitions in the case of free diffusion

$$\hat{\varphi}_{-L \rightarrow L}^{\text{FP}}(s|R)|_{F=0} = \frac{1}{\cosh(2L\sqrt{s/D})}, \quad \bar{t}_{-L \rightarrow L}^{\text{FP}}(R)|_{F=0} = 2L^2/D \quad (2.15)$$

DIRECT-TRANSIT TIME DISTRIBUTIONS

General Relations.

Consider direct a -to- b transitions, when a trajectory starting from point a goes to point b without returning to the starting point. Such trajectories are direct-transit segments of the first-passage a -to- b trajectories. Introducing point c , located between points a and b , $a < c < b$, we can decompose any direct-transit segment into three parts, direct transition from point a to point c , looping around point c without touching either point a or point b , and direct transition from point c to point b . With this in mind, we can now write an integral equation for the direct-transit time distribution, $\varphi_{a \rightarrow b}^{\text{dtr}}(t)$

$$\varphi_{a \rightarrow b}^{\text{dtr}}(t) = \int_0^t dt_1 \varphi_{a \rightarrow c}^{\text{dtr}}(t_1) \int_0^{t-t_1} dt_2 \varphi_c^1(t_2|a, b) \varphi_{c \rightarrow b}^{\text{dtr}}(t-t_1-t_2) \quad (3.1)$$

This equation simplifies when point c is in the center of the (a, b) -interval, that is $c-a = b-c$, and the potential $U(x)$ is symmetric about point c in this interval, $U(x-c) = U(c-x)$, $a < x < b$. In this case, we can use the relations in eqs 2.5 and 2.6 and write eq 3.1 as

$$\varphi_{a \rightarrow b}^{\text{dtr}}(t) = \int_0^t \varphi_{a \rightarrow c}^{\text{dtr}}(t_1) \varphi_{c \rightarrow b}^{\text{FP}}(t - t_1 | R) dt_1 \quad (3.2)$$

The Laplace transform of this equation is

$$\hat{\varphi}_{a \rightarrow b}^{\text{dtr}}(s) = \hat{\varphi}_{a \rightarrow c}^{\text{dtr}}(s) \hat{\varphi}_{c \rightarrow b}^{\text{FP}}(s | R) \quad (3.3)$$

In the two following subsections, we use this relation to find the Laplace transforms of the direct-transit time distribution for the symmetric cusp potential barrier and well shown in Figure 2.

Symmetric Cusp Potential Barrier.

For the symmetric cusp potential barrier, eq 2.9a and Figure 2A, eq 3.3 reduces to

$$\hat{\varphi}_{-L \rightarrow L}^{\text{dtr}}(s) = \hat{\varphi}_{-L \rightarrow 0}^{\text{dtr}}(s) \hat{\varphi}_{0 \rightarrow L}^{\text{FP}}(s | R) \quad (3.4)$$

The Laplace transform of the direct-transit time distribution for the $-L$ -to-0 transitions, $\tilde{t}_{-L \rightarrow L}^{\text{dtr}}(s)$, has been derived in ref 3. According to eq 3 from ref 3, the Laplace transform is given by

$$\hat{\varphi}_{-L \rightarrow 0}^{\text{dtr}}(s) = \frac{z \sinh(\tilde{F}/2)}{(\tilde{F}/2) \sinh(z)} \quad (3.5)$$

The Laplace transform of the first-passage time distribution for downhill transitions from the reflecting wall at the origin to point L , $\hat{\varphi}_{0 \rightarrow L}^{\text{FP}}(s | R)$, is given by eq 2.11b. Substituting the expressions for the two Laplace transforms into eq 3.4, we arrive at the final expression for the Laplace transform of the direct-transit time distribution for $-L$ -to- L transitions over the symmetric cusp potential barrier of the dimensionless height $\tilde{F}$

$$\hat{\varphi}_{-L \rightarrow L}^{\text{dtr}}(s) = \frac{z^2 (e^{\tilde{F}} - 1)}{\tilde{F} \sinh(z) [z \cosh(z) + (\tilde{F}/2) \sinh(z)]} \quad (3.6)$$

This is another main result of this work. We can find the mean direct-transit time, $\tilde{t}_{-L \rightarrow L}^{\text{dtr}}$, using the relation $\tilde{t}_{-L \rightarrow L}^{\text{dtr}} = -d\hat{\varphi}_{-L \rightarrow L}^{\text{dtr}}(s)/ds|_{s=0}$. This leads to the recovery of the expression for $\tilde{t}_{-L \rightarrow L}^{\text{dtr}}$ given in eq 7 of ref 2

$$\bar{t}_{-L \rightarrow L}^{\text{dtr}} = \frac{L^2(2\tilde{F} - 3 + 4e^{-F} - e^{-2\tilde{F}})}{D\tilde{F}^2(1 - e^{-\tilde{F}})} \quad (3.7)$$

Symmetric Cusp Potential Well.

To find the Laplace transform of the direct-transit time distribution, $\hat{\varphi}_{-L \rightarrow L}^{\text{dtr}}(s)$, in the case of the cusp potential well, eq 2.9b and Figure 2B, we again use eq 3.4 with $\hat{\varphi}_{-L \rightarrow 0}^{\text{dtr}}(s)$ given in eq 3.5, because this time distribution is independent of whether the transition occurs in the uphill or downhill direction, $\varphi_{-L \rightarrow 0}^{\text{dtr}}(t) = \varphi_{0 \rightarrow -L}^{\text{dtr}}(t)$.^{6,35–37} The difference between the cusp potential barrier and well manifests itself in the second factor on the right-hand side of eq 3.4; while in the case of the potential barrier we used $\hat{\varphi}_{0 \rightarrow L}^{\text{FP}}(s|R)$ for downhill transitions in eq 2.11b, here, we use $\hat{\varphi}_{0 \rightarrow L}^{\text{FP}}(s|R)$ for uphill transitions in eq 2.11a. Substituting $\hat{\varphi}_{-L \rightarrow 0}^{\text{dtr}}(s)$ and $\hat{\varphi}_{0 \rightarrow L}^{\text{FP}}(s|R)$, given in eqs 3.5 and 2.11a, into eq 3.4, we arrive at one more main result of this work, an exact expression for the Laplace transform of the direct-transit time distribution for $-L$ -to- L transitions when the end points $-L$ and L are separated by the symmetric cusp potential well of the dimensionless depth $\tilde{F}$

$$\hat{\varphi}_{-L \rightarrow L}^{\text{dtr}}(s) = \frac{z^2(1 - e^{-\tilde{F}})}{\tilde{F} \sinh(z)[z \cosh(z) - (\tilde{F}/2) \sinh(z)]} \quad (3.8)$$

Using the relation $\bar{t}_{-L \rightarrow L}^{\text{dtr}} = -d\hat{\varphi}_{-L \rightarrow L}^{\text{dtr}}(s)/ds|_{s=0}$, we recover the expression for the mean direct-transit time, $\bar{t}_{-L \rightarrow L}^{\text{dtr}}$, given in eq 19 of ref 1

$$\bar{t}_{-L \rightarrow L}^{\text{dtr}} = \frac{L^2(e^{2\tilde{F}} - 4e^{\tilde{F}} + 3 + 2\tilde{F})}{D\tilde{F}^2(e^{\tilde{F}} - 1)} \quad (3.9)$$

One can see that the expressions in eqs 3.8 and 3.9 can be obtained from their counterparts for the case of the symmetric cusp potential barrier, eqs 3.6 and 3.7, by replacing $\tilde{F}$ by $-\tilde{F}$ in the latter expressions.

In the case of free diffusion in the interval $(-L, L)$, expressions for the Laplace transforms of the direct-transit time distributions, eqs 3.6 and 3.8, and the mean direct-transit times, eqs 3.7 and 3.9, simplify and reduce to

$$\hat{\varphi}_{-L \rightarrow L}^{\text{dtr}}(s)|_{F=0} = \frac{2L\sqrt{s/D}}{\sinh(2L\sqrt{s/D})}, \quad \bar{t}_{-L \rightarrow L}^{\text{dtr}}|_{F=0} = \frac{2L^2}{3D} \quad (3.10)$$

LOOPING TIME DISTRIBUTIONS

General Relations.

As mentioned earlier, any a -to- b trajectory can be decomposed into direct-transit and looping segments. Therefore, the first-passage time distribution, $\varphi_{a \rightarrow b}^{\text{FP}}(t)$, is a convolution of the distributions of the direct-transit and looping times

$$\varphi_{a \rightarrow b}^{\text{FP}}(t) = \int_0^t \varphi_{a \rightarrow b}^{\text{dtr}}(t-t') \varphi_a^1(t'|b) dt' \quad (4.1)$$

After the Laplace transformation, this relation reduces to

$$\hat{\varphi}_{a \rightarrow b}^{\text{FP}}(s) = \hat{\varphi}_{a \rightarrow b}^{\text{dtr}}(s) \hat{\varphi}_a^1(s|b) \quad (4.2)$$

Then, the Laplace transform of the looping time distribution can be written as the ratio of the Laplace transforms of the first-passage and direct-transit time distributions

$$\hat{\varphi}_a^1(s|b) = \frac{\hat{\varphi}_{a \rightarrow b}^{\text{FP}}(s)}{\hat{\varphi}_{a \rightarrow b}^{\text{dtr}}(s)} \quad (4.3)$$

The distribution $\varphi_a^1(t|b)$ is that of the duration of the segment looping around point a , on condition that it does not touch point b . This is a one-side constraint on this segment. In discussing the first-passage and direct-transit time distributions, we introduced looping segments constrained from two sides. When looping occurs around point c located between points a and b , $a < c < b$, and it is required that the looping segment does not touch either point a or point b , the looping time distribution was denoted by $\varphi_c^l(t|a, b)$ (see eqs 2.1 and 3.1). To find the Laplace transform of this distribution, we use eq 3.1 that, after the Laplace transformation, reduces to

$$\hat{\varphi}_{a \rightarrow b}^{\text{dtr}}(s) = \hat{\varphi}_{a \rightarrow c}^{\text{dtr}}(s) \hat{\varphi}_c^1(s|a, b) \hat{\varphi}_{c \rightarrow b}^{\text{dtr}}(s) \quad (4.4)$$

Then the desired expression for the Laplace transform of $\varphi_c^1(t|a, b)$ is

$$\hat{\varphi}_c^1(s|a, b) = \frac{\hat{\varphi}_{a \rightarrow b}^{\text{dtr}}(s)}{\hat{\varphi}_{a \rightarrow c}^{\text{dtr}}(s) \hat{\varphi}_{c \rightarrow b}^{\text{dtr}}(s)} \quad (4.5)$$

Thus, the Laplace transform of the time distribution for the looping segment constrained on one side, $\hat{\varphi}_a^1(s|b)$, is expressed in terms of $\hat{\varphi}_{a \rightarrow b}^{\text{FP}}(s)$ and $\hat{\varphi}_{a \rightarrow b}^{\text{dtr}}(s)$, eq 4.3, whereas its counterpart for looping segments constrained on both sides, $\hat{\varphi}_c^1(s|a, b)$, is expressed in terms of $\hat{\varphi}_{a \rightarrow b}^{\text{dtr}}(s)$, $\hat{\varphi}_{a \rightarrow c}^{\text{dtr}}(s)$, and $\hat{\varphi}_{c \rightarrow b}^{\text{dtr}}(s)$, eq 4.5.

Symmetric Cusp Potential Barrier.

In the case of the symmetric cusp potential barrier, eq 2.9a, shown in Figure 2a, the Laplace transform in eq 4.3 takes the form

$$\hat{\varphi}_{-L}^1(s|L|R) = \frac{\hat{\varphi}_{-L \rightarrow L}^{\text{FP}}(s|R)}{\hat{\varphi}_{-L \rightarrow L}^{\text{dtr}}(s)} \quad (4.6)$$

Substituting, here, $\hat{\varphi}_{-L \rightarrow L}^{\text{FP}}(s|R)$ and $\hat{\varphi}_{-L \rightarrow L}^{\text{dtr}}(s)$ given in eqs 2.13 and 3.6, we arrive at

$$\hat{\varphi}_{-L}^1(s|L|R) = \frac{\tilde{F} \sinh(z) [z \cosh(z) + (\tilde{F}/2) \sinh(z)]}{(e^{\tilde{F}} - 1) [(sL^2/D) \cosh(2z) + (\tilde{F}/2)^2]} \quad (4.7)$$

This is one more main result of this work. The mean looping time near the reflecting wall, located at $x = -L$, denoted by $\bar{t}_{-L}^1(L|R)$, can be obtained using the relation

$\bar{t}_{-L}^1(L|R) = -d\hat{\varphi}_{-L}^1(s|L|R)/ds|_{s=0}$, which leads to

$$\bar{t}_{-L}^1(L|R) = \bar{t}_{-L \rightarrow L}^{\text{FP}}(R) - \bar{t}_{-L \rightarrow L}^{\text{dtr}} = \frac{L^2 (2e^{\tilde{F}} - 2\tilde{F} - 3 + 2e^{-\tilde{F}} - e^{-2\tilde{F}})}{D\tilde{F}^2 (1 - e^{-\tilde{F}})} \quad (4.8)$$

This has been published in ref 1 in eq 14.

When looping occurs near the top of the barrier, i.e., point c is located at $x = 0$ (see Figure 2a), eq 4.5 takes the form

$$\hat{\varphi}_0^1(s|-L, L) = \frac{\hat{\varphi}_{-L \rightarrow L}^{\text{dtr}}(s)}{(\hat{\varphi}_{-L \rightarrow 0}^{\text{dtr}}(s))^2} \quad (4.9)$$

Substituting, here, $\hat{\varphi}_{-L \rightarrow 0}^{\text{dtr}}(s)$ and $\hat{\varphi}_{-L \rightarrow L}^{\text{dtr}}(s)$, given in eqs 3.5 and 3.6, we arrive at the following expression for the Laplace transform of the looping time distribution

$$\hat{\varphi}_0^1(s|-L, L) = \frac{\tilde{F} \sinh(z)}{(1 - e^{-\tilde{F}})[z \cosh(z) + (\tilde{F}/2) \sinh(z)]} \quad (4.10)$$

Because of the symmetry of the cusp potential barrier, this expression is identical to the expression for the Laplace transform of the looping time distribution, $\hat{\varphi}_0^1(s|L|R)$, when looping occurs in the interval $(0, L)$ near the reflecting wall, located at $x = 0$, in the presence of a downhill linear potential characterized by the force $F > 0$ or, equivalently, by the dimensionless force $\tilde{F}$ given in eq 2.12. The expression for $\hat{\varphi}_0^1(s|L|R)$ is derived in ref 3 (see eq 8). The mean looping time, $\bar{t}_0^1(-L, L)$, can be obtained using the relation $\bar{t}_0^1(-L, L) = -d\hat{\varphi}_0^1(s|-L, L)/ds|_{s=0}$, which leads to

$$\bar{t}_0^1(-L, L) = \frac{L^2}{D\tilde{F}^2} \left[1 + e^{-\tilde{F}} + \tilde{F}(1 - \coth(\tilde{F}/2)) \right] \quad (4.11)$$

As might be expected, alternatively, this can be obtained using the relation $\bar{t}_0^1(-L, L) = \bar{t}_{-L \rightarrow L}^{\text{dtr}} - 2\bar{t}_{-L \rightarrow 0}^{\text{dtr}}$. The above expression for the mean looping time is identical to that for the mean looping time near the reflecting wall, $\bar{t}_0^1(L|R)$, that has been derived in ref 2 (see eq 9).

Symmetric Cusp Potential Well.

In this subsection, we find the Laplace transform of the looping time distribution, $\varphi_{-L}^1(t|L|R)$, when looping occurs near the reflecting wall, located at $x = -L$, and the points $-L$ and L are separated by the symmetric cusp potential well, eq 2.9b, as shown in Figure 2b. To do this, we use eq 4.6 with $\hat{\varphi}_{-L \rightarrow L}^{\text{FP}}(s|R)$ and $\hat{\varphi}_{-L \rightarrow L}^{\text{dtr}}(s)$ given in eqs 2.13 and 3.8. Substituting these expressions into eq 4.6, we arrive at

$$\hat{\varphi}_{-L}^1(s|L|R) = \frac{\tilde{F} \sinh(z)[z \cosh(z) - (\tilde{F}/2) \sinh(z)]}{(1 - e^{-\tilde{F}})[(sL^2/D) \cosh(2z) + (\tilde{F}/2)^2]} \quad (4.12)$$

This is also one of the main results of this work. The mean looping time, $\bar{t}_{-L}^1(L|R)$, when points $-L$ and L are separated by the symmetric cusp potential well, can be obtained using the relation $\bar{t}_{-L}^1(L|R) = -d\hat{\varphi}_{-L}^1(s|L|R)/ds|_{s=0}$. The result is

$$\bar{t}_{-L}^1(L|R) = \bar{t}_{-L \rightarrow L}^{\text{FP}}(R) - \bar{t}_{-L \rightarrow L}^{\text{dtr}} = \frac{L^2(e^{2\tilde{F}} - 2e^{\tilde{F}} + 3 - 2\tilde{F} - 2e^{-\tilde{F}})}{D\tilde{F}^2(e^{\tilde{F}} - 1)} \quad (4.13)$$

This expression for the mean looping time has been obtained in ref 1 (see eq 20).

The Laplace transform of the looping time near the well bottom is given by eq 4.9 with $\hat{\varphi}_{-L \rightarrow 0}^{\text{dtr}}(s)$ in eq 3.5 and $\hat{\varphi}_{-L \rightarrow L}^{\text{dtr}}(s)$ given by eq 3.8. Substituting these expressions into eq 4.9, we recover the expression earlier obtained in ref 2 (see eq 8)

$$\hat{\varphi}_0^1(s|-L, L) = \frac{\tilde{F} \sinh(z)}{(e^{\tilde{F}} - 1)[z \cosh(z) - (\tilde{F}/2) \sinh(z)]} \quad (4.14)$$

The mean looping time near the well bottom, $\bar{t}_0^1(-L, L)$ again can be obtained using the relation $\bar{t}_0^1(-L, L) = -d\hat{\varphi}_0^1(s|-L, L)/ds|_{s=0}$. The result is

$$\bar{t}_0^1(-L, L) = \frac{L^2}{D\tilde{F}^2} \left[1 + e^{\tilde{F}} - \tilde{F}(1 + \coth(\tilde{F}/2)) \right] \quad (4.15)$$

One can check that $\bar{t}_0^1(-L, L)$ is equal to the difference $\bar{t}_{-L \rightarrow L}^{\text{dtr}} - 2\bar{t}_{-L \rightarrow 0}^{\text{dtr}}$, as it must be.

Because of the symmetry of the potential, the expression for the mean looping time in eq 4.15 is identical to that for the mean looping time near the reflecting wall, $\bar{t}_0^1(L|R)$, that has been derived in ref 3 (see eq 9).

The above results for the symmetric cusp potential well, eqs 4.12–4.15, and their counterparts in eqs 4.7, 4.8, 4.10, and 4.11 for the cusp potential barrier are not independent. The former can be obtained from the latter by replacing $\tilde{F}$ by $-\tilde{F}$. When $F=0$, the above results reduce to those for free diffusion

$$\hat{\varphi}_{-L}^1(s|L|R)|_{F=0} = \frac{\tanh(2L\sqrt{s/D})}{2L\sqrt{s/D}}, \bar{t}_{-L}^1(L|R)|_{F=0} = \frac{4L^2}{3D} \quad (4.16)$$

and

$$\hat{\varphi}_0^1(s|-L, L)|_{F=0} = \frac{\tanh(L\sqrt{s/D})}{L\sqrt{s/D}}, \bar{t}_0^1(-L, L)|_{F=0} = \frac{L^2}{3D} \quad (4.17)$$

DISCUSSION

In this section, we discuss the time dependencies of the distributions $\varphi_{-L \rightarrow L}^{\text{FP}}(t|R)$, $\varphi_{-L}^1(t|L|R)$, $\varphi_0^1(t|-L, L)$, and $\varphi_{-L \rightarrow L}^{\text{dtr}}(t)$ obtained by numerically inverting their Laplace transforms derived in the First-Passage Time Distributions, Direct-Transit Time Distributions, and Looping Time Distributions sections. The focus is on how these distributions change with $\tilde{F}$, which is the dimensionless barrier height and well depth in the cases of the cusp potential barrier and well, respectively.

First-Passage Time Distribution.

The first-passage time distributions, $\varphi_{-L \rightarrow L}^{\text{FP}}(t|R)$, for the symmetric cusp potential barrier and well, eqs 2.9a and 2.9b and Figure 2, are identical. We obtain $\varphi_{-L \rightarrow L}^{\text{FP}}(t|R)$ by numerically inverting its Laplace transform, $\hat{\varphi}_{-L \rightarrow L}^{\text{FP}}(s|R)$, given in eq 2.13. The first-passage time distributions for $\tilde{F} = 0$ (free diffusion), 3, and 5 are shown in Figure 4. One can see that the distributions are bell-shaped functions. As $\tilde{F}$ increases, the process slows down, as might be expected. This results in broadening of the distributions.

The asymptotic large $\tilde{F}$ behavior of the Laplace transform $\hat{\varphi}_{-L \rightarrow L}^{\text{FP}}(s|R)$ can be obtained from eq 2.13. As $\tilde{F} \rightarrow \infty$, this Laplace transform reduces to

$$\hat{\varphi}_{-L \rightarrow L}^{\text{FP}}(s|R) = \frac{k}{s+k} \quad (5.1)$$

where the rate constant k given by

$$k = \frac{D\tilde{F}^2}{2L^2} e^{-\tilde{F}} \quad (5.2)$$

This expression for rate constant can be obtained using the Kramers theory. One can see, that the rate constant vanishes, as $\tilde{F}$ tends to infinity. Inverting the Laplace transform in eq 5.1, one arrives at

$$\varphi_{-L \rightarrow L}^{\text{FP}}(t|R) = k e^{-kt} \quad (5.3)$$

which is the large $\tilde{F}$ asymptotic behavior of the first-passage time distribution, $\varphi_{-L \rightarrow L}^{\text{FP}}(t|R)$.

Distributions of Looping Time Near Reflecting Wall.

The distributions of the looping time near the reflecting wall, located at $x = -L$, $\varphi_{-L}^1(t|L|R)$, in the presence of the symmetric cusp potential barrier and well (see Figure 2), are obtained

by numerically inverting the Laplace transforms, $\hat{\varphi}_{-L}^1(s|L|R)$, given in eqs 4.7 and 4.12, respectively. These distributions are shown in Figure 5 for $\tilde{F} = 0$ (free diffusion), 3, and 5. In contrast to the bell-shaped first-passage time distributions, $\varphi_{-L \rightarrow L}^{\text{FP}}(t|R)$, shown in Figure 4, the looping time distributions monotonically decay with time, diverging at short times as $1/\sqrt{t}$. One can see this from the large s asymptotic behavior of the Laplace transforms in eqs 4.7 and 4.12, which approach zero as $1/\sqrt{s}$, as $s \rightarrow \infty$.

While the mean looping time, $\bar{t}_{-L}^1(L|R)$, increases with $\tilde{F}$ for both potential barrier and well, the $\tilde{F}$ -effect on the distribution shape for the two potentials is quite different. As $\tilde{F}$ increases, the looping time distribution flattens for the cusp potential barrier and sharpens for the cusp potential well.

Distributions of Looping Time Near Barrier Top and Well Bottom.

As mentioned above, effects of the cusp potential barrier and well on the mean looping time near the reflecting wall, $\bar{t}_{-L}^1(L|R)$, are qualitatively similar; the mean looping time increases with the barrier height and well depth. This is not the case when looping occurs near the barrier top and the well bottom. The mean looping time near the barrier top, $\bar{t}_0^1(-L, L)$, decreases with the barrier height as $1/\tilde{F}^2$, while its counterpart near the well bottom increases with the well depth as $e^{\tilde{F}}/\tilde{F}^2$. One can see this from eqs 4.11 and 4.15. The difference between the two potentials also manifests itself in the looping time distributions, $\varphi_0^1(t|-L, L)$, which are obtained by numerically inverting the Laplace transforms, $\hat{\varphi}_0^1(s|-L, L)$, given in eqs 4.10 and 4.14. In Figure 6, these distributions are shown for $\tilde{F} = 0$ (free diffusion), 3, and 5.

The distributions of looping time near both the barrier top and well bottom are monotonically decreasing functions of time, diverging at short times as $1/\sqrt{t}$. Again, this can be seen from the large s asymptotic behavior of their Laplace transforms, eqs 4.10 and 4.14, which tend to zero as $1/\sqrt{s}$, as $s \rightarrow \infty$. In spite of the shape similarity of the distributions in the two cases, their dependencies on $\tilde{F}$ are quite different. As shown in Figure 6A, the distribution of the looping time near the barrier top sharpens, as $\tilde{F}$ (barrier height) increases. In contrast, the distribution of the looping time near the well bottom flattens, as $\tilde{F}$ (well depth) increases. Such a behavior of the distributions might be expected based on common sense arguments. The difference between the two distributions can also be seen from the large $\tilde{F}$ asymptotic behavior of the Laplace transforms in eqs 4.10 and 4.14, corresponding to the cases of the symmetric cusp potential barrier and well, respectively. As $\tilde{F} \rightarrow \infty$, both Laplace transforms take the same asymptotic form

$$\hat{\varphi}_0^1(s|-L, L)|_{\tilde{F} \rightarrow \infty} = \frac{k}{s+k} \quad (5.4)$$

which implies single exponential distribution of the looping time

$$\varphi_0^1(t| -L, L)|_{\tilde{F} \rightarrow \infty} = ke^{-kt} \quad (5.5)$$

The difference between the two distributions manifests itself in the $\tilde{F}$ dependence of the rate constants, obtained when deriving the asymptotic behavior in eq 5.4 from the Laplace transforms in eqs 4.10 and 4.14. These rate constants for the barrier (b) and well (w) cases are given by

$$k_b = \frac{D\tilde{F}^2}{L^2}, k_w = \frac{D\tilde{F}^2}{L^2}e^{-\tilde{F}} \quad (5.6)$$

Thus, as the barrier height and the well depth tend to infinity ($\tilde{F} \rightarrow \infty$), the rate constant k_b diverges, while its counterpart k_w vanishes.

Direct-Transit Time Distribution.

Direct-transit time distributions, $\varphi_{-L \rightarrow L}^{\text{dtr}}(t)$, for the cases of the potential barrier and well are shown in Figure 7. These distributions are obtained by numerically inverting the Laplace transforms $\hat{\varphi}_{-L \rightarrow L}^{\text{dtr}}(s)$, given in eqs 3.6 and 3.8, with $\tilde{F} = 0$ (free diffusion), 3, and 5.

Although both distributions are bell-shaped functions, their dependences on $\tilde{F}$ are qualitatively different. As $\tilde{F}$ increases, the cusp potential barrier becomes higher and sharper. As a consequence, the direct transition over the barrier “accelerates”, its mean duration decreases, and the direct-transit time distribution sharpens (see Figure 7A). This is not the case when the direct transition occurs via the potential well. Here, as the well depth, $\tilde{F}$, increases, the direct transition slows down, its mean duration increases, and the direct-transit time distribution flattens (see Figure 7B).

As follows from eq 4.9, the Laplace transform of the direct-transit time distribution is given by

$$\hat{\varphi}_{-L \rightarrow L}^{\text{dtr}}(s) = \hat{\varphi}_0^1(s| -L, L) \left(\hat{\varphi}_{-L \rightarrow 0}^{\text{dtr}}(s) \right)^2 \quad (5.7)$$

The direct-transit time distributions for uphill and downhill transitions, $\hat{\varphi}_{-L \rightarrow 0}^{\text{dtr}}(s)$, are identical (see eq 3.5). Therefore, the difference in the distributions of the direct-transit time over the potential barrier and through the potential well is a consequence of the difference in the looping time distributions, $\hat{\varphi}_0^1(s| -L, L)$, in the two cases, discussed above.

CONCLUDING REMARKS

In this article, we study distributions of the first-passage, direct-transit (transition path), and looping times for a particle diffusing in the symmetric cusp potential barriers and wells (see

Figure 2). Our main results are simple expressions for the exact solutions for the Laplace transforms of these distributions given in eqs 2.13, 3.5, 3.8, 4.7, 4.10, 4.12, and 4.14. Illustrative plots of these time distributions obtained by numerically inverting their Laplace transforms are shown in Figures 4–7. Note, that we study these distributions at a fixed distance, $2L$, between the end points, varying the barrier height and the well depth by changing the absolute value of the force F . Alternatively, these distributions can be studied at a constant value of F , varying the barrier height and well depth by changing the distance $2L$. The time distributions shown in Figures 4–7 would then look different, because the change in this distance results in variation of the time distribution even in the absence of the potential. It is also worth noting, that, in reality, potentials near both the well bottom and the barrier top are quadratic rather than cusped. The latter is a simplified version of the former that has an important advantage, it allows to find exact solutions for the Laplace transforms of the distributions of interest, which cannot be obtained for quadratic potentials. It seems to be interesting to compare the results reported above with their counterparts for quadratic potential barriers and wells, which can be found numerically.

The key step of our approach to the problem is decomposition of the diffusion trajectory into direct-transit and looping segments. The approach has been used above to study the distributions in the case of cusp potential barriers and wells. In the rest of this section, we discuss decomposition of the looping segment constrained on one side in general.

Consider looping segments when looping occurs around point a , and it is constrained by the requirement that the trajectory does not touch point b , $a < b$. The looping time distribution, in this case, was denoted by $\varphi_a^1(t|b)$. Its Laplace transform, $\hat{\varphi}_a^1(s|b)$, is given in eq 4.3. The looping trajectory starts and ends at point a . It spends some time at $x < a$ and some time at $x > a$, between points a and b . Let $t_{a-}^1(b)$ and $t_{a+}^1(b)$ be the durations of the “negative” ($x < a$) and “positive” ($a < x < b$) parts of the looping trajectory. The sum of these times is the total trajectory duration, $t_a^1(b)$

$$t_a^1(b) = t_{a-}^1(b) + t_{a+}^1(b) \quad (6.1)$$

Denoting the time distributions of the two parts by $\varphi_{a-}^1(t|b)$ and $\varphi_{a+}^1(t|b)$, we can write $\varphi_a^1(t|b)$ as

$$\varphi_a^1(t|b) = \int_0^t \varphi_{a-}^1(t'|b) \varphi_{a+}^1(t-t'|b) dt' \quad (6.2)$$

After the Laplace transformation, this reduces to

$$\hat{\varphi}_a^1(s|b) = \hat{\varphi}_{a-}^1(s|b) \hat{\varphi}_{a+}^1(s|b) \quad (6.3)$$

Because the diffusion trajectory has no memory, looping at $a < x < b$ occurs as if there is a reflecting wall at point a . Therefore, the looping time distribution, $\varphi_{a+}^1(t|b)$, and its counterpart, when looping occurs near the reflecting wall located at point a , $\varphi_a^1(t|b|R)$, are equal, $\varphi_{a+}^1(t|b) = \varphi_a^1(t|b|R)$. Then, we can use eq 6.3 to find the Laplace transform of the distribution $\varphi_{a-}^l(t|b)$

$$\hat{\varphi}_{a-}^1(s|b) = \frac{\hat{\varphi}_a^1(s|b)}{\hat{\varphi}_a^1(s|b|R)} \quad (6.4)$$

The Laplace transform $\hat{\varphi}_a^1(s|b)$ is given in eq 4.3. The Laplace transform of its counterpart, $\hat{\varphi}_a^1(s|b|R)$, is

$$\hat{\varphi}_a^1(s|b|R) = \frac{\hat{\varphi}_{a \rightarrow b}^{\text{FP}}(s|R)}{\hat{\varphi}_{a \rightarrow b}^{\text{dtr}}(s)} \quad (6.5)$$

Substituting the two expressions for the Laplace transforms into eq 6.4, we obtain an expression for the Laplace transform $\varphi_{a-}^1(s|b)$ in terms of the Laplace transforms of the first-passage time distributions $\hat{\varphi}_{a \rightarrow b}^{\text{FP}}(s)$ and $\hat{\varphi}_{a \rightarrow b}^{\text{FP}}(s|R)$

$$\hat{\varphi}_{a-}^1(s|b) = \frac{\hat{\varphi}_{a \rightarrow b}^{\text{FP}}(s)}{\hat{\varphi}_{a \rightarrow b}^{\text{FP}}(s|R)} \quad (6.6)$$

To find the mean looping time $\bar{t}_{a-}^1(b)$, we average eq 6.1 over trajectory realizations. This leads to

$$\bar{t}_a^1(b) = \bar{t}_{a-}^1(b) + \bar{t}_{a+}^1(b) = \bar{t}_{a-}^1(b) + \bar{t}_a^1(b|R) \quad (6.7)$$

Here, we have taken advantage of the fact that $\bar{t}_{a+}^1(b) = \bar{t}_a^1(b|R)$, where $\bar{t}_a^1(b|R)$ is the mean looping time around point a located on the reflecting wall and constrained by the requirement that the trajectory does not touch point b . According to eq 6.7, the mean looping time $\bar{t}_{a-}^1(b)$ is

$$\bar{t}_{a-}^1(b) = \bar{t}_a^1(b) - \bar{t}_a^1(b|R) \quad (6.8)$$

The two mean looping times on the right-hand side of the above equation are

$$\bar{t}_a^1(b) = \bar{t}_{a \rightarrow b}^{\text{FP}} - \bar{t}_{a \rightarrow b}^{\text{dtr}} \quad (6.9)$$

and

$$\bar{t}_a^1(b|R) = \bar{t}_{a \rightarrow b}^{\text{FPP}}(R) - \bar{t}_{a \rightarrow b}^{\text{dtr}} \quad (6.10)$$

where $\bar{t}_{a \rightarrow b}^{\text{FP}}(R)$ is the mean first-passage time from the reflecting wall, located at point a , to point b . Substituting the mean looping times in eqs 6.9 and 6.10 into eq 6.8, we find that the mean looping time $\bar{t}_{a-}^1(b)$ is the difference between the mean first-passage times $\bar{t}_{a \rightarrow b}^{\text{FP}}$ and $\bar{t}_{a \rightarrow b}^{\text{FPP}}(R)$

$$\bar{t}_{a-}^1(b) = \bar{t}_{a \rightarrow b}^{\text{FP}} - \bar{t}_{a \rightarrow b}^{\text{FPP}}(R) \quad (6.11)$$

Alternatively, this expression for $\bar{t}_{a-}^1(b)$ can be obtained using the relation

$$\bar{t}_{a-}^1(b) = -d\hat{\varphi}_{a-}^1(s|b)/ds|_{s=0}, \text{ with } \bar{t}_{a-}^1(s|b) \text{ given in eq 6.6.}$$

The mean first-passage time $\bar{t}_{a \rightarrow b}^{\text{FP}}$ is given in eq 1.3. Its counterpart $\bar{t}_{a \rightarrow b}^{\text{FPP}}(R)$, when point a is located on the reflecting wall, is

$$\bar{t}_{a \rightarrow b}^{\text{FPP}}(R) = \int_a^b (e^{\beta U(y)}/D(y)) dy \int_a^y e^{-\beta U(x)} dx \quad (6.12)$$

The difference between the mean first-passage times $\bar{t}_{a \rightarrow b}^{\text{FP}}$ and $\bar{t}_{a \rightarrow b}^{\text{FPP}}(R)$, which is the mean looping time $\bar{t}_{a-}^1(b)$, is given by

$$\bar{t}_{a-}^1(b) = \left(\int_a^b (e^{\beta U(y)}/D(y)) dy \right) \left(\int_{-\infty}^a e^{-\beta U(x)} dx \right) \quad (6.13)$$

Thus, we have derived a quadrature formula for the mean looping time $\bar{t}_{a-}^1(b)$.

ACKNOWLEDGMENTS

We are grateful to Dima Makarov for helpful comments on the manuscript. This study was partially supported by the Intramural Research Program of the NIH, Center for Information Technology, and Eunice Kennedy Shriver National Institute of Child Health and Human Development.

REFERENCES

- (1). Berezhkovskii AM; Dagdug L; Bezrukov SM Mean Direct-Transit and Looping Times as Functions of the Potential Shape. *J. Phys. Chem. B* 2017, 121, 5455–5460. [PubMed: 28475835]
- (2). Berezhkovskii AM; Dagdug L; Bezrukov SM First Passage, Looping, and Direct Transition in Expanding and Narrowing Tubes: Effects of the Entropy Potential. *J. Chem. Phys* 2017, 147, 104103. [PubMed: 28915752]
- (3). Berezhkovskii AM; Dagdug L; Bezrukov SM A New Insight into Diffusional Escape from a Biased Cylindrical Trap. *J. Chem. Phys* 2017, 147, 104103. [PubMed: 28915752]
- (4). Redner S A Guide to First-Passage Processes, 1 ed.; Cambridge University Press: Boston, 2007.
- (5). Hanggi P; Talkner P; Borkovec M Reaction-Rate Theory - 50 Years after Kramers. *Rev. Mod. Phys* 1990, 62, 251–341.
- (6). Berezhkovskii AM; Pustovoit MA; Bezrukov SM Channel-Facilitated Membrane Transport: Average Lifetimes in the Channel. *J. Chem. Phys* 2003, 119, 3943–3951.
- (7). Chung HS; Gopich IV Fast Single-Molecule Fret Spectroscopy: Theory and Experiment. *Phys. Chem. Chem. Phys* 2014, 16, 18644–18657. [PubMed: 25088495]
- (8). Hummer G From Transition Paths to Transition States and Rate Coefficients. *J. Chem. Phys* 2004, 120, 516–523. [PubMed: 15267886]
- (9). Chaudhury S; Makarov DE A Harmonic Transition State Approximation for the Duration of Reactive Events in Complex Molecular Rearrangements. *J. Chem. Phys* 2010, 133, No. 034118. [PubMed: 20649319]
- (10). Pollak E Transition Path Time Distribution and the Transition Path Free Energy Barrier. *Phys. Chem. Chem. Phys* 2016, 18, 28872–28882. [PubMed: 27722352]
- (11). Zhang BW; Jasnow D; Zuckerman DM Transition-Event Durations in One-Dimensional Activated Processes. *J. Chem. Phys* 2007, 126, No. 074504. [PubMed: 17328617]
- (12). Caraglio M; Put S; Carlon E; Vanderzande C The Influence of Absorbing Boundary Conditions on the Transition Path Time Statistics. *Phys. Chem. Chem. Phys.* 2018, 20, 25676–25682. [PubMed: 30211419]
- (13). Carlon E; Orland H; Sakaue T; Vanderzande C Effect of Memory and Active Forces on Transition Path Time Distributions. *J. Phys. Chem. B* 2018, 122, 11186–11194. [PubMed: 30102039]
- (14). Janakiraman D Transition Path Time Distributions for Levy Flights. *J. Phys. A: Math. Theor* 2018, 51, 285001.
- (15). Laleman M; Carlon E; Orland H Transition Path Time Distributions. *J. Chem. Phys* 2017, 147, 214103. [PubMed: 29221402]
- (16). Medina E; Satija R; Makarov DE Transition Path Times in Non-Markovian Activated Rate Processes. *J. Phys. Chem. B* 2018, 122, 11400–11413. [PubMed: 30179506]
- (17). Satija R; Das A; Makarov DE Transition Path Times Reveal Memory Effects and Anomalous Diffusion in the Dynamics of Protein Folding. *J. Chem. Phys* 2017, 147, 152707. [PubMed: 29055292]
- (18). Hoogerheide DP; Gurnev PA; Rostovtseva TK; Bezrukov SM Real-Time Nanopore-Based Recognition of Protein Translocation Success. *Biophys. J* 2018, 114, 772–776. [PubMed: 29338842]
- (19). Comer J Chasing a Protein's Tail: Detection of Polypeptide Translocation through Nanopores. *Biophys. J* 2018, 114, 759–760. [PubMed: 29490238]
- (20). Chung HS; Eaton WA Single-Molecule Fluorescence Probes Dynamics of Barrier Crossing. *Nature* 2013, 502, 685–688. [PubMed: 24153185]
- (21). Chung HS; Eaton WA Protein Folding Transition Path Times from Single Molecule Fret. *Curr. Opin. Struct. Biol* 2018, 48, 30–39. [PubMed: 29080467]
- (22). Chung HS; McHale K; Louis JM; Eaton WA Single-Molecule Fluorescence Experiments Determine Protein Folding Transition Path Times. *Science* 2012, 335, 981–984. [PubMed: 22363011]

- (23). Chung HS; Piana-Agostinetti S; Shaw DE; Eaton WA Structural Origin of Slow Diffusion in Protein Folding. *Science* 2015, 349, 1504–1510. [PubMed: 26404828]
- (24). Manuel AP; Lambert J; Woodside MT Reconstructing Folding Energy Landscapes from Splitting Probability Analysis of Single-Molecule Trajectories. *Proc. Natl. Acad. Sci. U. S. A* 2015, 112, 7183–7188. [PubMed: 26039984]
- (25). Neupane K; Foster DAN; Dee DR; Yu H; Wang F; Woodside MT Direct Observation of Transition Paths During the Folding of Proteins and Nucleic Acids. *Science* 2016, 352, 239–242. [PubMed: 27124461]
- (26). Neupane K; Hoffer NQ; Woodside MT Testing Kinetic Identities Involving Transition-Path Properties Using Single-Molecule Folding Trajectories. *J. Phys. Chem. B* 2018, 122, 11095–11099. [PubMed: 30004229]
- (27). Neupane K; Manuel AP; Lambert J; Woodside MT Transition-Path Probability as a Test of Reaction-Coordinate Quality Reveals DNA Hairpin Folding Is a One-Dimensional Diffusive Process. *J. Phys. Chem. Lett* 2015, 6, 1005–1010. [PubMed: 26262860]
- (28). Neupane K; Manuel AP; Woodside MT Protein Folding Trajectories Can Be Described Quantitatively by One-Dimensional Diffusion over Measured Energy Landscapes. *Nat. Phys* 2016, 12, 700–703.
- (29). Neupane K; Ritchie DB; Yu H; Foster DAN; Wang F; Woodside MT Transition Path Times for Nucleic Acid Folding Determined from Energy-Landscape Analysis of Single-Molecule Trajectories. *Phys. Rev. Lett* 2012, 109, No. 068102. [PubMed: 23006308]
- (30). Ritchie DB; Woodside MT Probing the Structural Dynamics of Proteins and Nucleic Acids with Optical Tweezers. *Curr. Opin. Struct. Biol* 2015, 34, 43–51. [PubMed: 26189090]
- (31). Truex K; Chung HS; Louis JM; Eaton WA Testing Landscape Theory for Biomolecular Processes with Single Molecule Fluorescence Spectroscopy. *Phys. Rev. Lett* 2015, 115, No. 018101. [PubMed: 26182121]
- (32). Yu H; Gupta AN; Liu X; Neupane K; Brigley AM; Sosova I; Woodside MT Energy Landscape Analysis of Native Folding of the Prion Protein Yields the Diffusion Constant, Transition Path Time, and Rates. *Proc. Natl. Acad. Sci. U. S. A* 2012, 109, 14452–14457. [PubMed: 22908253]
- (33). Kim JY; Meng FJ; Yoo J; Chung HS Diffusion-Limited Association of Disordered Protein by Non-Native Electrostatic Interactions. *Nat. Commun* 2018, 9, 4707. [PubMed: 30413699]
- (34). Sturzenegger F; Zosel F; Holmstrom ED; Buholzer KJ; Makarov DE; Nettels D; Schuler B Transition Path Times of Coupled Folding and Binding Reveal the Formation of an Encounter Complex. *Nat. Commun* 2018, 9, 4708. [PubMed: 30413694]
- (35). Alvarez J; Hajek B Equivalence of Trans Paths in Ion Channels. *Phys. Rev. E* 2006, 73, 046126.
- (36). Berezhkovskii AM; Bezrukov SM Site Model for Channel-Facilitated Membrane Transport: Invariance of the Translocation Time Distribution with Respect to Direction of Passage. *J. Phys.: Condens. Matter* 2007, 19, 065148.
- (37). Berezhkovskii AM; Hummer G; Bezrukov SM Identity of Distributions of Direct Uphill and Downhill Translocation Times for Particles Traversing Membrane Channels. *Phys. Rev. Lett* 2006, 97, No. 020601. [PubMed: 16907424]

Figure 1.

Looping and direct-transit segments of a trajectory that starts at point a and is terminated when it comes to point b for the first time. The latter is the final part of the trajectory that leaves point a and goes to point b without returning to point a . The rest of the trajectory is the looping segment that makes numerous loops that begin and end at the same point a without touching point b . The durations of the two segments are denoted by $t_{a \rightarrow b}^{dtr}$ and $t_a^l(b)$, respectively. Their sum is the trajectory duration, $t_{a \rightarrow b}^{FP}$.

Figure 2. Symmetric cusp potential barrier (A) and well (B) of the height and depth FL , $F > 0$, respectively, separating the points $x = -L$ and $x = L$.

Figure 3. Time-resolved records of ionic current through a single VDAC nanopore in the presence of a trapped alpha-synuclein molecule. Adapted with permission from refs 18 and 19. Copyright 2018 Cell Press.

Figure 4.

First-passage time distributions, $\phi_{-L \rightarrow L}^{FP}(t|R)$, for transitions from a reflecting wall located at $x = -L$ to point $x = L$ separated from the wall by a symmetric cusp potential barrier or well of the dimensionless height and depth $\tilde{F} = \beta FL$, respectively, are identical. The distributions are obtained by numerically inverting the Laplace transform in eq 2.13 with $\tilde{F} = 0, 3$, and 5. The values of $\tilde{F}$ are given in the frames near the curves. $\tilde{F} = 0$ corresponds to the case of free diffusion. One can see, that, though the maxima of the distributions slightly shift to shorter times as the height and depth increase, the mean first-passage time, eq 2.14, increases (see the plot in Figure 3 of ref 1) due to the significant flattening of the distributions.

Figure 5.

Distributions $\varphi_{-L}^1(t|L|R)$ of the looping time near the reflecting wall located at the $x = -L$ conditional on that the loops do not touch point $x = L$, which is separated from the wall by a symmetric cusp potential barrier (A) or well (B) of the dimensionless height and depth $\tilde{F} = \beta FL$, respectively. The distributions are obtained by numerically inverting the Laplace transforms in eqs 4.7 and 4.12 with $\tilde{F} = 0, 3$, and 5 . The values of $\tilde{F}$ are given in the frames near the curves. In both panels, the curves with $\tilde{F} = 0$, corresponding to the case of free diffusion, are identical. One can see that the distributions flatten, as $\tilde{F}$ increases, in the case of the cusp potential barrier (A). In contrast, in the case of the cusp potential well, the distributions sharpen as $\tilde{F}$ increases (B).

Figure 6.

Distributions $\phi_0^1(t|L, L)$ of the looping time near the origin, $x = 0$, conditional on that the loops do not touch points $x = -L$ and $x = L$, which are separated by a symmetric cusp potential barrier (A) or well (B) of dimensionless height and depth $\tilde{F} = \beta FL$, respectively. The distributions are obtained by numerically inverting the Laplace transforms in eqs 4.10 and 4.14 with $\tilde{F} = 0, 3$, and 5 . The values of $\tilde{F}$ are given in the frames near the curves. In both panels, the curves with $\tilde{F} = 0$, corresponding to the case of free diffusion, are identical. One can see that, as $\tilde{F}$ increases, the distributions sharpen in the case of the cusp potential barrier A) and flatten in the case of the cusp potential well (B). This is in sharp contrast to the $\tilde{F}$ -dependencies of the looping time distributions, when looping occurs near the reflecting wall, shown in Figure 5.

Figure 7.

Distributions $\varphi_{-L \rightarrow L}^{dir}(t)$ of the direct-transit time from point $x = -L$ to point $x = L$, which are separated by a cusp potential barrier (A) or well (B) of the dimensionless height and depth $\tilde{F} = \beta FL$, respectively. The distributions are obtained by numerically inverting the Laplace transforms in eqs 3.6 and 3.8 with $\tilde{F} = 0, 3$, and 5. The values of $\tilde{F}$ are given in the frames near the curves. In both panels, the curves with $\tilde{F} = 0$, corresponding to the case of free diffusion, are identical. The insert in panel A shows the short-time behavior of the distributions at higher resolution. As might be expected, both distributions are bell-shaped functions. However, their $\tilde{F}$ -dependences are qualitatively different. As $\tilde{F}$ increases, the direct transitions over the cusp potential barrier accelerate, while the direct transitions via the cusp potential well slowdown. As a consequence, the direct-transit time distributions sharpen in the former case (A) and flatten in the latter one (B).