First passage, looping, and direct transition in expanding and narrowing tubes: Effects of the entropy potential

Alexander M. Berezhkovskii,^{1,2} Leonardo Dagdug,^{1,2,a)} and Sergey M. Bezrukov¹

¹*Section on Molecular Transport, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland 20892, USA*

²*Mathematical and Statistical Computing Laboratory, Division of Computational Bioscience, Center for Information Technology, National Institutes of Health, Bethesda, Maryland 20892, USA*

(Received 27 June 2017; accepted 14 September 2017; published online 3 October 2017)

We study transitions of diffusing particles between the left and right ends of expanding and narrowing conical tubes. In an expanding tube, such transitions occur faster than in the narrowing tube of the same length and radius variation rate. This happens because the entropy potential pushes the particle towards the wide tube end, thus accelerating the transitions in the expanding tube and slowing them down in the narrowing tube. To gain deeper insight into how the transitions occur, we divide each trajectory into the direct-transit and looping segments. The former is the final part of the trajectory, where the particle starting from the left tube end goes to the right end without returning to the left one. The rest of the trajectory is the looping segment, where the particle, starting from the left tube end, returns to this end again and again until the direct transition happens. Our focus is on the durations of the two segments and their sum, which is the duration of the particle first passage between the left and right ends of the tube. We approach the problem using the one-dimensional description of the particle diffusion along the tube axis in terms of the modified Fick-Jacobs equation. This allows us to derive analytical expressions for the Laplace transforms of the probability densities of the first-passage, direct-transit, and looping times, which we use to find the mean values of these random variables. Our results show that the direct transits are independent of the entropy potential and occur as in free diffusion. However, this “free diffusion” occurs with the effective diffusivity entering the modified Fick-Jacobs equation, which is smaller than the particle diffusivity in a cylindrical tube. This is the only way how the varying tube geometry manifests itself in the direct transits. Since direct-transit times are direction-independent, the difference in the first-passage times in the tubes of the two types is due to the difference in the durations of the looping segments in the expanding and narrowing tubes. Obtained analytical results are supported by three-dimensional Brownian dynamics simulations. *Published by AIP Publishing.* <https://doi.org/10.1063/1.4993129>

I. INTRODUCTION

Transitions between two deep wells over high energy or entropy barriers underlie single-exponential kinetics of various processes, ranging from isomerization reactions to channel-facilitated transport of solutes. In the last years, the barrier crossing dynamics has attracted attention of many researchers,^{1–44} who frequently model the dynamics as one-dimensional diffusion in a potential of mean force. The quantity of interest in such studies is the time required for the system to traverse the barrier region. This time, called the transition path or direct-transit time, is a random variable, characterized by the probability density and mean value.

When the effective particle, representing the system, enters the barrier region, it either returns to the initial (reactant) well or traverses the region and enters the other (product) well. By cutting out all pieces of the initial trajectory outside the barrier region, one can form a new trajectory that describes

diffusion of the particle in the barrier region, assuming that this region is terminated by reflecting endpoints. Such a truncated trajectory contains all the information about the particle dynamics in the barrier region. Of course, this can be done not only for the barrier region but for any interval visited by the particle. It is worth noting that this procedure is applicable only for diffusion trajectories, i.e., when the inertial effects can be neglected.

In a recent paper,⁴⁷ we proposed a new approach to the analysis of the particle transitions between the two ends of a one-dimensional interval. The key step of our approach is to split a trajectory starting at one end of the interval and eventually coming to the other end into two segments: a looping segment, when the particle starting from the initial end returns to this end without touching the opposite end of the interval, and a direct-transit segment, when the particle starting from the initial end traverses the interval without returning to the starting point. The sum of the durations of these segments is the first-passage time from one end of the interval to the other. Analysis of the segment durations provides additional information about the particle transitions between the two ends. In Ref. 47, we use the approach to analyze end-to-end transitions

^{a)}Permanent address: Physics Department, Universidad Autonoma Metropolitana-Iztapalapa, 09340 Mexico City, Mexico.

FIG. 1. Schematic illustration of the expanding, (a), and narrowing, (b), tubes with a constant radius variation rate, $|dr(x)/dx| = \text{const} = \lambda$. In both cases, particles starting from the left reflecting boundary are trapped by the right absorbing boundary.

when the two ends of the interval are separated by a potential barrier of well. One might also find interesting to see the discussion in Ref. 32.

The present paper focuses on the wide-to-narrow and narrow-to-wide transitions between the two ends of a tube of linearly varying radius, shown in Fig. 1. First, we map the three-dimensional description of the particle dynamics in the tube onto one-dimensional description in terms of the modified Fick-Jacobs equation. As a result, transitions between the two tube ends reduce to those between the ends of a one-dimensional interval in the presence of an entropy potential. Solving the one-dimensional problem, we derive, for the first time, exact analytical solutions for the Laplace transforms of the probability densities of the first-passage, direct-transit, and looping times for transitions in the tubes of the two types, Eqs. (2.11), (2.12), (2.18), and (2.20)–(2.22). These solutions are used to find the mean values of these random variables, Eqs. (2.14), (2.15), (2.19), and (2.23). While the distributions of the first-passage and looping times depend on the entropy potential and hence varying tube radius, surprisingly, the distribution of the direct-transit time turns out to be independent of the entropy potential. This distribution is identical to that for a freely diffusing particle. The variation of the tube radius manifests itself only through the effective diffusivity which differs from the free-particle diffusivity D_0 and depends on the radius variation rate.

We compare our analytical results derived in the framework of the one-dimensional description with the results obtained from three-dimensional Brownian dynamics simulations. The comparison shows good agreement between the two when the radius variation rate λ does not exceed unity. It is interesting that the predicted independence of the mean direct-transit time of the entropy potential holds not only when $\lambda \leq 1$ but also at $\lambda = 1, 1.5, 2.0$, and 2.5 , where the one-dimensional description undoubtedly fails.

The outline of this paper is as follows. Theory based on the one-dimensional description is developed in Sec. II. Comparison of its predictions with the simulation results is presented

and discussed in Sec. III. Some concluding remarks are made in Sec. IV.

II. THEORY

Consider a particle diffusing in an expanding tube of length L shown in Fig. 1(a). The tube radius $r(x)$ increases in the axial direction with a constant rate $\lambda > 0$, $r(x) = a + \lambda x$, $0 \leq x \leq L$, where the x -coordinate is measured along the tube axis, and a is the tube radius at $x = 0$. The particle starts from the reflecting boundary located at $x = 0$ and is trapped by the absorbing boundary at $x = L$, as soon as it touches this boundary for the first time. The particle starting point is assumed to be uniformly distributed over the surface of the reflecting boundary.

To describe the particle propagation along the tube axis, we take advantage of the one-dimensional description of diffusion in a tube of varying cross sections in terms of the modified Fick-Jacobs equation.^{48,49} Let $G(x, t)$ be the particle propagator in the axial direction, which is the probability density of finding the particle at distance x from the reflecting boundary at time t , conditional on that the particle started from this boundary, located at $x = 0$, at $t = 0$. This propagator satisfies the modified Fick-Jacobs equation^{48,49}

$$\frac{\partial G}{\partial t} = \frac{\partial}{\partial x} \left\{ D(x) r^2(x) \frac{\partial}{\partial x} \left[\frac{1}{r^2(x)} G \right] \right\}, \quad (2.1)$$

where $D(x)$ is a position-dependent effective diffusivity, subject to the initial and boundary conditions

$$G(x, 0) = \delta(x), \quad \left. \frac{\partial G}{\partial x} \right|_{x=0} = G|_{x=L} = 0. \quad (2.2)$$

Introducing the entropy potential of mean force,

$$\begin{aligned} \beta U_{ent}(x) &= -\ln(A(x)/A(0)) = -2 \ln(r(x)/a) \\ &= -2 \ln(1 + \lambda x/a), \end{aligned} \quad (2.3)$$

where $\beta = 1/(k_B T)$ with k_B and T denoting the Boltzmann constant and absolute temperature, and $A(x) = \pi r^2(x)$ is the tube cross section area at a given value of x , one can write Eq. (2.1) in terms of the entropy potential as the Smoluchowski equation

$$\frac{\partial G}{\partial t} = \frac{\partial}{\partial x} \left\{ D(x) e^{-\beta U_{ent}(x)} \frac{\partial}{\partial x} \left[e^{\beta U_{ent}(x)} G \right] \right\}. \quad (2.4)$$

The position-dependent effective diffusivity, $D(x)$, is a function of the radius variation rate, $|dr(x)/dx|$. In our case, this rate is constant, $|dr(x)/dx| = \lambda$, and, consequently, the effective diffusivity is a position-independent function of λ . Denoting this diffusivity by D_λ , Eq. (2.1) can be written as

$$\frac{\partial G}{\partial t} = D_\lambda \frac{\partial}{\partial x} \left\{ r^2(x) \frac{\partial}{\partial x} \left[\frac{1}{r^2(x)} G \right] \right\}. \quad (2.5)$$

To find the probability densities of the first-passage and direct-transit times, we consider an auxiliary problem, where the boundary at $x = 0$ is partially absorbing. Therefore, the reflecting boundary condition at $x = 0$ is replaced by the radiation one

$$a^2 D_\lambda \partial [G_\kappa / r^2(x)] / \partial x|_{x=0} = \kappa G_\kappa|_{x=0}, \quad (2.6)$$

where the subscript κ near the propagator indicates the boundary trapping rate; $\kappa=0$ and ∞ correspond to reflecting and absorbing boundaries at $x=0$, respectively. Having in hand the propagator $G_\kappa(x, t)$, one can find the probability flux $f_\kappa(t)$ entering the absorbing boundary at $x=L$ at time t ,

$$f_\kappa(t) = -D_\lambda \partial G_\kappa / \partial x|_{x=L}. \quad (2.7)$$

The integral of this flux over time from zero to infinity, $\int_0^\infty f_\kappa(t)dt$, is the probability that the particle is trapped by the absorbing boundary located at $x=L$, in the presence of a partially absorbing boundary at $x=0$.

The ratio of $f_\kappa(t)$ to this trapping probability is the lifetime probability density $\varphi_\kappa(t)$ of the particle, on condition that it is trapped by the right boundary of the interval,

$$\varphi_\kappa(t) = f_\kappa(t) / \int_0^\infty f_\kappa(t')dt'. \quad (2.8)$$

As $\kappa \rightarrow 0$, the boundary at $x=0$ becomes reflecting, the trapping probability in the denominator of Eq. (2.8) approaches unity, and the conditional probability density $\varphi_\kappa(t)$ reduces to the probability density of the first-passage (FP) time, $\varphi_{FP}(t)$,

$$\varphi_{FP}(t) = \lim_{\kappa \rightarrow 0} \varphi_\kappa(t). \quad (2.9)$$

In the opposite limiting case, $\kappa \rightarrow \infty$, the left boundary of the interval becomes absorbing, and both the flux $f_\kappa(t)$ and the trapping probability $\int_0^\infty f_\kappa(t)dt$ tend to zero, but their ratio remains finite. This ratio, by definition, is the probability density of the direct-transit (dtr) time, $\varphi_{dtr}(t)$,

$$\varphi_{dtr}(t) = \lim_{\kappa \rightarrow \infty} \varphi_\kappa(t). \quad (2.10)$$

We find the Laplace transforms of the probability densities $\varphi_{FP}(t)$ and $\varphi_{dtr}(t)$ using the Laplace transform of $\varphi_\kappa(t)$ derived in Appendix. The Laplace transform of a function $f(t)$, denoted by $\hat{f}(s)$, is defined in the standard way as $\hat{f}(s) = \int_0^\infty e^{-st}f(t)dt$, where s is the Laplace parameter. We indicate that the expressions below refer to transitions between the narrow and wide ends of the expanding tube (see Fig. 1) by introducing the superscript “ $n \rightarrow w$.” Using this notation, we can write our results for the Laplace transforms of the two probability densities as

$$\begin{aligned} \hat{\varphi}_{FP}^{n \rightarrow w}(s) &= \hat{\varphi}_{\kappa \rightarrow 0}^{n \rightarrow w}(s) \\ &= \frac{(a + \lambda L) \sqrt{s D_\lambda}}{a \sqrt{s D_\lambda} \cosh(L \sqrt{s/D_\lambda}) + \lambda D_\lambda \sinh(L \sqrt{s/D_\lambda})} \end{aligned} \quad (2.11)$$

and

$$\hat{\varphi}_{dtr}^{n \rightarrow w}(s) = \hat{\varphi}_{\kappa \rightarrow \infty}^{n \rightarrow w}(s) = \frac{L \sqrt{s/D_\lambda}}{\sinh(L \sqrt{s/D_\lambda})}. \quad (2.12)$$

The latter expression shows that the distribution of the direct transit time is the same as that for a particle freely diffusing on an interval of length L with the effective diffusivity

D_λ .⁴⁷ It depends on the varying tube radius only through the λ -dependence of the effective diffusivity.

We use the Laplace transforms $\hat{\varphi}_{FP}^{n \rightarrow w}(s)$ and $\hat{\varphi}_{dtr}^{n \rightarrow w}(s)$ to find the mean first-passage and direct-transit times, $\bar{t}_{FP}^{n \rightarrow w}$ and $\bar{t}_{dtr}^{n \rightarrow w}$, by taking advantage of the relation between the Laplace transform of the lifetime probability density, $\varphi(t)$, and the mean lifetime, $\bar{t}$,

$$\bar{t} = \int_0^\infty t \varphi(t) dt = -d\hat{\varphi}(s)/ds|_{s=0}. \quad (2.13)$$

The results are

$$\bar{t}_{FP}^{n \rightarrow w} = \frac{L^2}{6D_\lambda} \frac{3a + \lambda L}{a + \lambda L} \quad (2.14)$$

and

$$\bar{t}_{dtr}^{n \rightarrow w} = \frac{L^2}{6D_\lambda}. \quad (2.15)$$

Since for each trajectory the first-passage time is the sum of the looping (l) and direct-transit times, the probability densities $\varphi_{FP}^{n \rightarrow w}(t)$, $\varphi_{dtr}^{n \rightarrow w}(t)$, and $\varphi_l^{n \rightarrow w}(t)$ satisfy

$$\varphi_{FP}^{n \rightarrow w}(t) = \int_0^t \varphi_{dtr}^{n \rightarrow w}(t - t') \varphi_l^{n \rightarrow w}(t') dt'. \quad (2.16)$$

The Laplace transformation of the above relation leads to

$$\hat{\varphi}_{FP}^{n \rightarrow w}(s) = \hat{\varphi}_{dtr}^{n \rightarrow w}(s) \hat{\varphi}_l^{n \rightarrow w}(s). \quad (2.17)$$

We use this and Eqs. (2.11) and (2.12) to find the Laplace transform of the probability density of the looping time

$$\begin{aligned} \hat{\varphi}_l^{n \rightarrow w}(s) &= \frac{\hat{\varphi}_{FP}^{n \rightarrow w}(s)}{\hat{\varphi}_{dtr}^{n \rightarrow w}(s)} \\ &= \frac{(a + \lambda L) D_\lambda \sinh(L \sqrt{s/D_\lambda})}{L [a \sqrt{s D_\lambda} \cosh(L \sqrt{s/D_\lambda}) + \lambda D_\lambda \sinh(L \sqrt{s/D_\lambda})]}. \end{aligned} \quad (2.18)$$

Next, we find the mean looping time, $\bar{t}_l^{n \rightarrow w}$, using the relation in Eq. (2.13),

$$\bar{t}_l^{n \rightarrow w} = - \left. \frac{d\hat{\varphi}_l^{n \rightarrow w}(s)}{ds} \right|_{s=0} = \frac{L^2}{3D_\lambda} \frac{a}{a + \lambda L} = \frac{L^2}{3D_\lambda} \frac{r(0)}{r(L)}, \quad (2.19)$$

where the x -dependence of the tube radius, $r(x) = a + \lambda x$, has been used. This mean time is the difference between the mean first-passage and direct transit times given in Eqs. (2.14) and (2.15), respectively.

One can repeat the above derivation for a narrowing tube of length L shown in Fig. 1(b), where the x -dependence of the tube radius has the form $r(x) = a + \lambda(L - x)$, $0 \leq x \leq L$, $\lambda > 0$. Assuming that the wide end of the tube at $x=0$ is reflecting and its narrow end at $x=L$ is absorbing, one can find the Laplace transforms of the probability densities and the mean values of the first-passage, direct-transit, and looping times for wide-to-narrow ($w \rightarrow n$) transitions. The final results are

$$\hat{\varphi}_{FP}^{w \rightarrow n}(s) = \frac{a \sqrt{s D_\lambda}}{(a + \lambda L) \sqrt{s D_\lambda} \cosh(L \sqrt{s/D_\lambda}) - \lambda D_\lambda \sinh(L \sqrt{s/D_\lambda})}, \quad (2.20)$$

$$\hat{\varphi}_{dtr}^{w \rightarrow n}(s) = \hat{\varphi}_{dtr}^{n \rightarrow w}(s) = \frac{L\sqrt{sD_\lambda}}{\sinh(L\sqrt{s/D_\lambda})}, \quad (2.21)$$

$$\hat{\varphi}_l^{w \rightarrow n}(s) = \frac{aD_\lambda \sinh(L\sqrt{s/D_\lambda})}{L \left[(a + \lambda L) \sqrt{sD_\lambda} \cosh(L\sqrt{s/D_\lambda}) - \lambda D_\lambda \sinh(L\sqrt{s/D_\lambda}) \right]}, \quad (2.22)$$

$$\bar{t}_{FP}^{w \rightarrow n} = \frac{L^2}{6D_\lambda} \left(3 + 2\lambda \frac{L}{a} \right), \quad \bar{t}_{dtr}^{w \rightarrow n} = \bar{t}_{dtr}^{n \rightarrow w} = \frac{L^2}{6D_\lambda}, \quad \bar{t}_l^{w \rightarrow n} = \frac{L^2}{3D_\lambda} \left(1 + \lambda \frac{L}{a} \right). \quad (2.23)$$

The identity of the probability densities and, consequently, the mean values of the direct-transit times for the narrow-to-wide and wide-to-narrow transitions is a particular case of the general relations between the time distributions for the forward and backward transitions.^{3,8} What is interesting is that the probability densities in Eq. (2.21) are identical to that for a free particle diffusing on an interval of length L with diffusivity D_λ , which performs direct transitions between the ends of the interval.⁴⁷

To summarize, expressions in Eqs. (2.11), (2.12), (2.14), (2.15), and (2.18)–(2.23) giving the Laplace transforms of the probability densities of the first-passage, direct-transit, and looping times for particles diffusing in expanding and narrowing tubes, as well as the mean values of these times are main analytical results of this paper.

III. COMPARISON WITH SIMULATION RESULTS

In this section, we compare our analytical predictions with the results obtained from three-dimensional Brownian dynamics simulations.

A. L -dependences of the mean times

We begin with the L -dependences of the mean times given in Eqs. (2.14), (2.15), (2.19), and (2.23). For the sake of comparison, it is convenient to normalize these mean times to the mean direct-transit time of a free particle in the cylindrical ($\lambda = 0$) tube, $L^2/(6D_0)$.⁴⁷ As a result, we obtain

$$\frac{6D_0 \bar{t}_{FP}^{n \rightarrow w}}{L^2} = \frac{D_0}{D_\lambda} \frac{3 + \lambda L/a}{1 + \lambda L/a}, \quad \frac{6D_0 \bar{t}_l^{n \rightarrow w}}{L^2} = \frac{D_0}{D_\lambda} \frac{2}{1 + \lambda L/a}, \quad (3.1)$$

$$\frac{6D_0 \bar{t}_{FP}^{w \rightarrow n}}{L^2} = \frac{D_0}{D_\lambda} \left(3 + 2\lambda \frac{L}{a} \right), \quad \frac{6D_0 \bar{t}_l^{w \rightarrow n}}{L^2} = \frac{2D_0}{D_\lambda} \left(1 + \lambda \frac{L}{a} \right), \quad (3.2)$$

$$\frac{6D_0 \bar{t}_{dtr}^{n \rightarrow w}}{L^2} = \frac{6D_0 \bar{t}_{dtr}^{w \rightarrow n}}{L^2} = \frac{D_0}{D_\lambda}. \quad (3.3)$$

In Fig. 2, the theoretically predicted dimensionless mean times are shown as functions of the dimensionless argument $\lambda L/a$ (lines) at the radius variation rate $\lambda = 0.6$. The predicted L -dependences are compared with the values of the dimensionless mean times obtained from the Brownian dynamics simulations (symbols) in tubes with the following values of the L/a ratio, $L/a = 2, 6, 10, 14, 18$. One can see excellent agreement between the theoretical predictions and simulation results.

As shown in Fig. 2, the normalized mean first-passage and looping times decrease with L for $n \rightarrow w$ transitions and increase with L for transitions in the opposite direction. This direction dependence can be rationalized using the entropy potential, which drives the particles to the absorbing boundary in the case of $n \rightarrow w$ transitions (downhill scenario) and pushes them back towards the reflecting boundary (uphill scenario) in the case of $w \rightarrow n$ transitions. This is in contrast with the behavior of the normalized mean direct-transit time which is

FIG. 2. L -dependences of the mean times for expanding (left panel) and narrowing (right panel) tubes at $\lambda = 0.6$. Theoretical predictions (lines) are compared with the values of the mean times obtained from Brownian dynamics simulations (symbols) performed in tubes with the following values of the L/a ratio, $L/a = 2, 6, 10, 14, 18$. Mean first-passage times are shown by blue lines and symbols (Δ), mean looping times are shown by yellow lines and symbols (∇), and mean direct-transit times are shown by green lines and symbols ($\circ$).

independent of L . Surprisingly, particles performing direct transitions are “unaware” of the entropy potential.

B. Probability densities

Next, we compare the probability densities predicted theoretically and obtained from the three-dimensional Brownian dynamics simulations. It is convenient to do this using the dimensionless time $\tilde{t} = D_\lambda t / L^2$. The relation between the probability densities $\tilde{\varphi}(\tilde{t})$ and $\varphi(t)$ is given by $\tilde{\varphi}(\tilde{t}) = \varphi(t) D_\lambda / L^2$. The Laplace transform $\hat{\varphi}(s)$ of the probability density $\varphi(t)$ is identical to the Laplace transform $\hat{\tilde{\varphi}}(\sigma)$ of the probability density $\tilde{\varphi}(\tilde{t})$, $\hat{\tilde{\varphi}}(\sigma) = \int_0^\infty e^{-\sigma \tilde{t}} \tilde{\varphi}(\tilde{t}) d\tilde{t}$, where σ is the dimensionless Laplace parameter, $\sigma = s L^2 / D_\lambda$.

Using the fact that $\hat{\tilde{\varphi}}(\sigma) = \hat{\varphi}(s)$, we can write the probability densities in Eqs. (2.11), (2.12), (2.18), (2.20), and (2.22) as

$$\hat{\varphi}_{FP}^{n \rightarrow w}(\sigma) = \frac{(1 + \lambda L/a) \sqrt{\sigma}}{\sqrt{\sigma} \cosh(\sqrt{\sigma}) + (\lambda L/a) \sinh(\sqrt{\sigma})}, \quad (3.4)$$

$$\hat{\varphi}_l^{n \rightarrow w}(\sigma) = \frac{(1 + \lambda L/a) \sinh(\sqrt{\sigma})}{\sqrt{\sigma} \cosh(\sqrt{\sigma}) + (\lambda L/a) \sinh(\sqrt{\sigma})}, \quad (3.5)$$

$$\hat{\varphi}_{FP}^{w \rightarrow n}(\sigma) = \frac{\sqrt{\sigma}}{(1 + \lambda L/a) \cosh(\sqrt{\sigma}) - (\lambda L/a) \sinh(\sqrt{\sigma})}, \quad (3.6)$$

$$\hat{\varphi}_l^{w \rightarrow n}(\sigma) = \frac{\sinh(\sqrt{\sigma})}{(1 + \lambda L/a) \cosh(\sqrt{\sigma}) - (\lambda L/a) \sinh(\sqrt{\sigma})}, \quad (3.7)$$

$$\hat{\varphi}_{dir}^{n \rightarrow w}(\sigma) = \hat{\varphi}_{dir}^{w \rightarrow n}(\sigma) = \frac{\sqrt{\sigma}}{\sinh(\sqrt{\sigma})}. \quad (3.8)$$

Theoretically predicted probability densities obtained by numerically inverting the Laplace transforms in Eqs. (3.4)–(3.8) are shown in Fig. 3 by lines. This is done for tubes with $\lambda = 0.6$ and $L/a = 10$, using $D_\lambda / D_0 = 0.887$ inferred from the simulation results (see the discussion below). The bars show the probability densities obtained from the Brownian dynamics simulations. Again, one can see excellent agreement between the theoretical predictions and simulation results. One can also see that while the time scales of the first-passage and looping times in the $n \rightarrow w$ and $w \rightarrow n$ directions differ by orders of magnitude, the probability densities of the direct-transit

FIG. 3. Probability densities of the first-passage, looping, and direct-transit times (top to bottom) predicted by the theory (lines) and obtained from the simulations (bars) for expanding, (a), and narrowing, (b), tubes. The tube parameters are $\lambda = 0.6$ and $L/a = 10$.

times in the two directions are identical. The latter probability densities are equal to that of the direct-transit time of a free particle diffusing in an interval of length L with diffusivity D_λ .

C. Range of applicability of the effective one-dimensional description

The modified Fick-Jacobs equation, Eq. (2.1), provides an effective one-dimensional description of diffusive transport in a three-dimensional tube of varying radii. Zwanzig⁴⁸ derived this equation assuming that the radius variation rate is much smaller than unity, $|dr(x)/dx| = 1$. As the rate increases, the effective one-dimensional description becomes less accurate. However, as has been demonstrated above (see also Ref. 50), this description works well not only when the radius variation rate is very low but also at moderate values of the rate.

We studied the range of applicability of the one-dimensional description in Ref. 50. Our analysis was based on the comparison of the effective diffusivities D_λ obtained from the mean first-passage times $\bar{t}_{FP}^{n \rightarrow w}$ and $\bar{t}_{FP}^{w \rightarrow n}$ found in Brownian dynamics simulations by using Eqs. (2.14) and (2.23). As a criterion of the applicability, we used the requirement that the ratio of the diffusivities must be close to unity. In tubes with $L/a = 20$, we found that the ratio $D_\lambda(n \rightarrow w)/D_\lambda(w \rightarrow n)$ grew with λ and reached the value 1.1 at $\lambda = 1$. Based on this, we proposed to consider the inequality $\lambda \leq 1$ as the condition determining the range of applicability of the one-dimensional description.

Now, when we have six mean times for a conical tube fully determined by the values of two parameters, L/a and λ , we can find six effective diffusivities and compare their values. The one-dimensional description is applicable when all six D_λ at a fixed value of λ are close. Six values of the ratio D_λ/D_0 determined from the six dimensionless mean times obtained from the simulations in conical tubes with $\lambda = 0.6, 1, 1.5, 2, 2.5$ and $L/a = 6, 10, 14, 18$ by means of Eqs. (3.1)–(3.3) are collected in Table I. Inspection of the diffusivity ratios presented in these tables (i) supports our earlier evaluation of the range of applicability of the one-dimensional description, $\lambda \leq 1$, and (ii) shows the correctness of the predicted free-diffusion behavior of the mean direct-transit time at all λ , i.e., far beyond the range of applicability of the one-dimensional description.

D. Reguera-Rubi formula for the effective diffusivity D_λ

The effective diffusivity $D(x)$ entering Eq. (2.1) depends on x through its dependence on the local radius variation rate, $D(x) = D(|dr(x)/dx|)$. Reguera and Rubi (RR) proposed a simple formula for the effective diffusivity,⁵¹

$$D_{RR}(x) = \frac{D_0}{\sqrt{1 + [dr(x)/dx]^2}}. \quad (3.9)$$

In our case, when $|dr(x)/dx| = \text{const} = \lambda$, the Reguera-Rubi formula reduces to

$$D_{RR}(\lambda) = \frac{D_0}{\sqrt{1 + \lambda^2}}. \quad (3.10)$$

TABLE I. Diffusivity ratios, D_λ/D_0 , at $\lambda = 0.6, 1.0, 1.5, 2.0, 2.5$. For each λ , the diffusivity ratio is given at $L/a = 6, 10, 14, 18$ with the goal to demonstrate (i) the failure of the one-dimensional description at $\lambda > 1$ and (ii) the correctness of the predicted free-diffusion behavior of the direct-transit time at all λ , i.e., far beyond the range of applicability of the one-dimensional description. $D_{RR}(\lambda)$ are the values of the diffusivity ratio given by the Reguera-Rubi formula (see below).

$\lambda = 0.6 \quad D_{RR}(\lambda = 0.6)/D_0 = 0.857$						
L/a	$n \rightarrow w$			$w \rightarrow n$		
	FP	l	dtr	FP	l	dtr
6	0.886	0.866	0.895	0.884	0.882	0.894
10	0.882	0.854	0.891	0.872	0.886	0.871
14	0.884	0.875	0.886	0.866	0.886	0.865
18	0.878	0.879	0.868	0.871	0.882	0.870
$\lambda = 1 \quad D_{RR}(\lambda = 1)/D_0 = 0.707$						
L/a	$n \rightarrow w$			$w \rightarrow n$		
	FP	l	dtr	FP	l	dtr
6	0.774	0.722	0.791	0.747	0.744	0.794
10	0.774	0.708	0.788	0.741	0.738	0.789
14	0.769	0.722	0.776	0.732	0.730	0.778
18	0.772	0.702	0.780	0.736	0.735	0.778
$\lambda = 1.5 \quad D_{RR}(\lambda = 1.5)/D_0 = 0.554$						
L/a	$n \rightarrow w$			$w \rightarrow n$		
	FP	l	dtr	FP	l	dtr
6	0.674	0.585	0.696	0.628	0.625	0.702
10	0.668	0.561	0.684	0.600	0.598	0.690
14	0.665	0.568	0.675	0.602	0.601	0.679
18	0.668	0.575	0.676	0.601	0.600	0.680
$\lambda = 2 \quad D_{RR}(\lambda = 2)/D_0 = 0.447$						
L/a	$n \rightarrow w$			$w \rightarrow n$		
	FP	l	dtr	FP	l	dtr
6	0.605	0.466	0.634	0.524	0.520	0.642
10	0.605	0.460	0.624	0.503	0.500	0.624
14	0.599	0.428	0.616	0.508	0.506	0.617
18	0.596	0.383	0.615	0.499	0.498	0.615
$\lambda = 2.5 \quad D_{RR}(\lambda = 2.5)/D_0 = 0.371$						
L/a	$n \rightarrow w$			$w \rightarrow n$		
	FP	l	dtr	FP	l	dtr
6	0.555	0.394	0.584	0.455	0.451	0.600
10	0.553	0.383	0.573	0.435	0.433	0.581
14	0.551	0.378	0.565	0.429	0.427	0.572
18	0.551	0.365	0.564	0.431	0.430	0.571

To check the accuracy of this formula, we compare its predictions with the values of D_λ determined from the direct-transit times $\bar{t}_{dtr}^{n \rightarrow w}$ and $\bar{t}_{dtr}^{w \rightarrow n}$ obtained from the simulations in tubes with $L/a = 10$ at different values of λ . The λ -dependence of the ratio $D_{RR}(\lambda)/D_0$ and the values of the diffusivities D_λ obtained from the simulation results and normalized to D_0 are shown in Fig. 4. One can see that when the radius variation rate falls within the range of the

FIG. 4. Diffusivity ratio D_λ/D_0 given by the Reguera-Rubi (RR) formula, Eq. (3.10) (line), and the values of this ratio obtained using the mean direct-transit time found in simulations at $L/a = 10$ (symbols). Two overlapping symbols are the values of the diffusivity ratio obtained from the mean direct-transit times in the $n \rightarrow w$ and $w \rightarrow n$ directions.

applicability of the one-dimensional description, $\lambda \leq 1$, the Reguera-Rubi formula predicts the effective diffusivity reasonably well. The deviation of its predictions from the values of the ratio D_λ/D_0 obtained from the simulation data increases with λ . The relative error of the prediction at $\lambda = 1$ is about 10%.

IV. DISCUSSION AND CONCLUDING REMARKS

We have studied escape of a diffusing particle from the conical tubes of linearly varying radii shown in Fig. 1. As might be expected, the particle takes more time to escape from the narrowing tube [Fig. 1(b)] than from the expanding one [Fig. 1(a)]. The reason is that in the narrowing tube the access to the exit is hindered by the entropy potential, whereas in the expanding tube the potential drives the particle towards the exit. The mean first-passage times are monotonic functions of the radius variation rate λ . As λ increases, at a fixed tube length, the mean first-passage time increases/decreases in the narrowing/expanding tube. Introducing separation of the particle trajectory into the looping and direct-transit segments, we were able to analyze the “fine structure” of the escape trajectories. It turns out that the difference in the mean first-passage times for the narrowing and expanding tubes is due to the difference in the mean looping times, corresponding to the trajectory segment in which the particle returns to the reflecting tube end at the origin without touching the absorbing boundary at the opposite end of the tube.

In the limiting case of an expanding tube with large λ , particle diffusion is mostly unperturbed by the tube walls. This

statement is supported by Fig. 5 which shows spatial distributions of the particle first-passage points to the absorbing end of the tube. It is seen that for a quickly expanding tube of $\lambda = 2.5$, most of the arrival points are grouped around the center suggesting that the particle diffuses nearly freely. This result was obtained with a uniform distribution of the particle starting points over the reflecting tube boundary at the origin shown in the figure by the dashed lines. We would like to draw the reader’s attention to the fact that when running simulations in the opposite case of a narrowing tube, we used a uniform distribution of the starting points over the area of the reflecting wide end of the tube. In this case, as follows from the time reversibility of diffusion trajectories, the distributions shown in Fig. 5 would represent the distributions of the starting points of the direct-transit segments only.

At the same time, the mean direct-transit time is not sensitive to whether the tube is narrowing or expanding. Quite surprisingly, not only the mean values (Fig. 2) but also the distributions of this time (Fig. 3, bottom panels) in the narrowing and expanding tubes are identical to that for a freely diffusing particle. Moreover, this is true even at $\lambda = 2.5$, where the one-dimensional description obviously fails. Similar results were reported by Cheng and Makarov²⁰ who studied polymer cyclization. Using simulations, they showed that direct transitions in the loop closure in a long Rouse chain were insensitive to the chain length, i.e., the entropy potential, and reasonably well described by “a model where the chain ends diffuse freely.” Their main conclusion is that the one-dimensional description in terms of the Smoluchowski equation with the entropy potential of mean force fails to describe the mean direct-transit times observed in simulations. In a recent paper,⁴⁴ Makarov came to the same inference about the potential failure to predict the mean direct-transit time and its distribution on the basis of the Smoluchowski equation when the potential of mean force contains “a significant entropic part.”

In contrast, we derive the free-diffusion behavior of the direct-transit time starting with the modified Fick-Jacobs equation, Eq. (2.1), which is the Smoluchowski equation, Eq. (2.4), with the entropy potential of mean force, Eq. (2.3). We hope that our results will be of importance for the conceptual understanding and quantitative interpretation of time-resolved single molecule dynamics observed in experiments on pulling of proteins and nucleic acids, fluorescence spectroscopy investigations of protein folding, and studies of polymer capture by single nanopores.

FIG. 5. Distribution of particle arrival points to the absorbing wide end of the expanding tube of length $L/a = 10$ at different values of the radius variation rate λ . The images are scaled to facilitate the comparison. The reflecting tube end at the origin (of the same radius a , see Fig. 1), from which the particle starts, is shown by the dashed lines in the image centers.

ACKNOWLEDGMENTS

This study was 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.

APPENDIX: LAPLACE TRANSFORM OF THE CONDITIONAL PROBABILITY DENSITY $\varphi_\kappa(t)$

Let $\hat{G}_\kappa(x, s)$ be the Laplace transform of the propagator $G_\kappa(x, t)$. Applying the Laplace transformation to equation (2.5) and the boundary conditions at $x = L$, Eq. (2.2), and at $x = 0$, Eq. (2.6), we arrive at

$$s\hat{G}_\kappa - \delta(x) = D_\lambda \frac{d}{dx} \left\{ r^2(x) \frac{d}{dx} \left[\frac{1}{r^2(x)} \hat{G}_\kappa \right] \right\}, \quad (\text{A1})$$

$$a^2 D_\lambda \frac{d}{dx} \left[\frac{1}{r^2(x)} \hat{G}_\kappa \right] \Big|_{x=0} = \kappa \hat{G}_\kappa \Big|_{x=0}, \quad \hat{G}_\kappa \Big|_{x=L} = 0. \quad (\text{A2})$$

By writing the Laplace transform of the propagator in the form

$$\hat{G}_\kappa(x, s) = r(x)F(x, s), \quad (\text{A3})$$

and substituting this into Eqs. (A1) and (A2), we find that function $F(x, s)$ satisfies the equation

$$\frac{1}{a} \delta(x) = D_\lambda \frac{d^2 F}{dx^2} - sF \quad (\text{A4})$$

subject to the boundary conditions

$$D_\lambda \frac{dF}{dx} \Big|_{x=0} = \left(\kappa + \frac{\lambda D}{a} \right) F \Big|_{x=0}, \quad F \Big|_{x=L} = 0. \quad (\text{A5})$$

We find function $F(x, s)$ by solving this equation. The result is

$$F(x, s) = A(s) \sinh \left((L-x) \sqrt{s/D_\lambda} \right), \quad (\text{A6})$$

where $A(s)$ is given by

$$A(s) = \frac{1}{a\sqrt{sD_\lambda} \cosh \left(L\sqrt{s/D_\lambda} \right) + (\kappa a + \lambda D_\lambda) \sinh \left(L\sqrt{s/D_\lambda} \right)}. \quad (\text{A7})$$

As follows from Eq. (2.7), the Laplace transform of the flux $f_\kappa(t)$ is

$$\begin{aligned} \hat{f}_\kappa(s) &= -D_\lambda \frac{d\hat{G}_\kappa}{dx} \Big|_{x=L} = -D_\lambda (a + \lambda L) \frac{dF}{dx} \Big|_{x=L} \\ &= \sqrt{sD_\lambda} (a + \lambda L) A(s). \end{aligned} \quad (\text{A8})$$

We use this to find the Laplace transform of the conditional probability density $\varphi_\kappa(t)$ defined in Eq. (2.8), where the integral in the denominator is $\hat{f}_\kappa(s=0)$. Eventually we obtain

$$\begin{aligned} \hat{\varphi}_\kappa(s) &= \frac{\hat{f}_\kappa(s)}{\hat{f}_\kappa(0)} \\ &= \frac{\sqrt{sD_\lambda} [D_\lambda (a + \lambda L) + \kappa a L]}{a\sqrt{sD_\lambda} \cosh \left(L\sqrt{s/D_\lambda} \right) + (\kappa a + \lambda D_\lambda) \sinh \left(L\sqrt{s/D_\lambda} \right)}. \end{aligned} \quad (\text{A9})$$

This result is used in the main text to find the Laplace transforms of the probability densities of the first-passage

($\kappa \rightarrow 0$) and direct-transit ($\kappa \rightarrow \infty$) times given in Eqs. (2.11) and (2.12).

- ¹A. M. Berezhevskii, M. A. Pustovoit, and S. M. Bezrukov, *J. Chem. Phys.* **116**, 9952 (2002).
- ²D. M. Zuckerman and T. B. Woolf, *J. Chem. Phys.* **116**, 2586 (2002).
- ³A. M. Berezhevskii, M. A. Pustovoit, and S. M. Bezrukov, *J. Chem. Phys.* **119**, 3943 (2003).
- ⁴S. M. Bezrukov, O. V. Krasilnikov, L. N. Yuldasheva, A. M. Berezhevskii, and C. G. Rodrigues, *Biophys. J.* **87**, 3162 (2004).
- ⁵G. Hummer, *J. Chem. Phys.* **120**, 516 (2004).
- ⁶E. Rhoades, M. Cohen, B. Schuler, and G. Haran, *J. Am. Chem. Soc.* **126**, 14686 (2004).
- ⁷R. B. Best and G. Hummer, *Proc. Natl. Acad. Sci. U. S. A.* **102**, 6732 (2005).
- ⁸A. M. Berezhevskii, G. Hummer, and S. M. Bezrukov, *Phys. Rev. Lett.* **97**, 020601 (2006).
- ⁹W. E and E. Vanden-Eijnden, *J. Stat. Phys.* **123**, 503 (2006).
- ¹⁰P. Metzner, C. Schutte, and E. Vanden-Eijnden, *J. Chem. Phys.* **125**, 084110 (2006).
- ¹¹E. Vanden-Eijnden, in *Computer Simulations in Condensed Matter: From Materials to Chemical Biology*, edited by M. M. Ferrario, G. Ciccotti, and K. Binder (Springer, Berlin, 2006).
- ¹²T. H. Lee, L. J. Lapidus, W. Zhao, K. J. Travers, D. Herschlag, and S. Chu, *Biophys. J.* **92**, 3275 (2007).
- ¹³M. Sega, P. Faccioli, F. Pederiva, G. Garberoglio, and H. Orland, *Phys. Rev. Lett.* **99**, 118102 (2007).
- ¹⁴B. W. Zhang, D. Jasnow, and D. M. Zuckerman, *J. Chem. Phys.* **126**, 074504 (2007).
- ¹⁵H. S. Chung, J. M. Louis, and W. A. Eaton, *Proc. Natl. Acad. Sci. U. S. A.* **106**, 11837 (2009).
- ¹⁶S. Chaudhury and D. E. Makarov, *J. Chem. Phys.* **133**, 034118 (2010).
- ¹⁷P. Faccioli, A. Lonardi, and H. Orland, *J. Chem. Phys.* **133**, 045104 (2010).
- ¹⁸S. V. Malinin and V. Y. Chernyak, *J. Chem. Phys.* **132**, 014504 (2010).
- ¹⁹S. A. Beccara, P. Faccioli, M. Sega, F. Pederiva, G. Garberoglio, and H. Orland, *J. Chem. Phys.* **134**, 024501 (2011).
- ²⁰R. R. Cheng and D. E. Makarov, *J. Chem. Phys.* **134**, 085104 (2011).
- ²¹H. Orland, *J. Chem. Phys.* **134**, 174114 (2011).
- ²²M. Pirchi, G. Ziv, I. Riven, S. S. Cohen, N. Zohar, Y. Barak, and G. Haran, *Nat. Commun.* **2**, 493 (2011).
- ²³H. S. Chung, K. McHale, J. M. Louis, and W. A. Eaton, *Science* **335**, 981 (2012).
- ²⁴K. Neupane, D. B. Ritchie, H. Yu, D. A. N. Foster, F. Wang, and M. T. Woodside, *Phys. Rev. Lett.* **109**, 068102 (2012).
- ²⁵S. Piana, K. Lindorff-Larsen, and D. E. Shaw, *Proc. Natl. Acad. Sci. U. S. A.* **109**, 17845 (2012).
- ²⁶Z. Q. Zhang and H. S. Chan, *Proc. Natl. Acad. Sci. U. S. A.* **109**, 20919 (2012).
- ²⁷H. S. Chung and W. A. Eaton, *Nature* **502**, 685 (2013).
- ²⁸H. S. Chung and I. V. Gopich, *Phys. Chem. Chem. Phys.* **16**, 18644 (2014).
- ²⁹R. Frederickx, T. in't Veld, and E. Carlon, *Phys. Rev. Lett.* **112**, 198102 (2014).
- ³⁰P. A. Gurnev, T. L. Yap, C. M. Pfefferkorn, T. K. Rostovtseva, A. M. Berezhevskii, J. C. Lee, V. A. Parsegian, and S. M. Bezrukov, *Biophys. J.* **106**, 556 (2014).
- ³¹H. S. Chung, S. Piana-Agostinetti, D. E. Shaw, and W. A. Eaton, *Science* **349**, 1504 (2015).
- ³²W. K. Kim and R. R. Netz, *J. Chem. Phys.* **143**, 224108 (2015).
- ³³D. E. Makarov, in *Single Molecule Science: Physical Principles and Models* (CRC Press, Taylor & Francis Group, Boca Raton, 2015).
- ³⁴D. E. Makarov, *J. Chem. Phys.* **143**, 194103 (2015).
- ³⁵K. Truex, H. S. Chung, J. M. Louis, and W. A. Eaton, *Phys. Rev. Lett.* **115**, 018101 (2015).
- ³⁶R. B. Best and G. Hummer, *Proc. Natl. Acad. Sci. U. S. A.* **113**, 3263 (2016).
- ³⁷J. O. Daldrop, W. K. Kim, and R. R. Netz, *Europhys. Lett.* **113**, 18004 (2016).
- ³⁸D. E. Makarov, *J. Chem. Phys.* **144**, 030901 (2016).
- ³⁹T. Mori and S. Saito, *J. Phys. Chem. B* **120**, 11683 (2016).
- ⁴⁰K. Neupane, D. A. N. Foster, D. R. Dee, H. Yu, F. Wang, and M. T. Woodside, *Science* **352**, 239 (2016).

- ⁴¹K. Neupane, A. P. Manuel, and M. T. Woodside, *Nat. Phys.* **12**, 700 (2016).
- ⁴²E. Pollak, *Phys. Chem. Chem. Phys.* **18**, 28872 (2016).
- ⁴³D. P. Hoogerheide, P. A. Gurnev, T. K. Rostovtseva, and S. M. Bezrukov, *Nanoscale* **9**, 183 (2017).
- ⁴⁴D. E. Makarov, *J. Chem. Phys.* **146**, 071101 (2017).
- ⁴⁵E. Pollak, *Phys. Rev. Lett.* **118**, 070401 (2017).
- ⁴⁶E. Pollak, *J. Phys. Chem. Lett.* **8**, 352 (2017).
- ⁴⁷A. M. Berezhkovskii, L. Dagdug, and S. M. Bezrukov, *J. Phys. Chem. B* **121**, 5455–5460 (2017).
- ⁴⁸R. Zwanzig, *J. Phys. Chem.* **96**, 3926 (1992).
- ⁴⁹A. M. Berezhkovskii and A. Szabo, *J. Chem. Phys.* **135**, 074108 (2011).
- ⁵⁰A. M. Berezhkovskii, M. A. Pustovoi, and S. M. Bezrukov, *J. Chem. Phys.* **126**, 134706 (2007).
- ⁵¹D. Reguera and J. M. Rubi, *Phys. Rev. E* **64**, 061106 (2001).