

Direct experimental measurement of relative path probabilities and stochastic actions

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For diffusive stochastic dynamics, the probability to observe any individual trajectory is vanishingly small, making it unclear how to experimentally validate theoretical results for ratios of path probabilities. We provide the missing link between theory and experiment, by establishing a protocol to extract ratios of path probabilities from measured time series without fitting a model. For experiments on a single colloidal particle in a microchannel, we extract both ratios of path probabilities, and the most probable path for a barrier crossing. While we find excellent agreement with independently calculated predictions based on the Onsager-Machlup stochastic action, our experimental results are inconsistent with the Freidlin-Wentzell stochastic action. The direct experimental measurement of relative path probabilities presented here paves the way for experimental investigation of any theoretical result related to individual stochastic trajectories.

Introduction. Stochastic effects are of fundamental relevance for statistical physics and beyond [1–9]. For example, diffusion processes are used to model colloidal particles [4, 10, 11], polymer dynamics [12–15], or active particles such as driven colloidal systems, cells, or bacteria [8, 10]. Any continuous stochastic dynamics is fully characterized by its path probabilities, which are also highly relevant in applications; examples are irreversibility in stochastic thermodynamics, which is expressed in terms of ratios of path probabilities [10, 16], or transition pathways between metastable states, as relevant e.g. for conformational transitions in biomolecules [17–19].

For diffusive dynamics, the probability of any path is zero; however ratios of path probabilities can be described theoretically by stochastic actions [20–34]. The literature contains several proposals for stochastic actions, the prominent ones being associated with the names of Onsager and Machlup (OM) [20–23], as well as Freidlin and Wentzell (FW) [35–37]. Since it is not straightforward to measure experimentally the ratio of two vanishingly small quantities, hitherto it was not clear how to experimentally determine which action describes the actual path probabilities observed in experiments.

We here overcome this difficulty, by establishing an experimental protocol to determine ratios of path probabilities from observed data, without fitting a model. We achieve this by considering the probability for a stochastic trajectory to remain within a tube of small but finite radius R around a reference path, called the sojourn probability [21, 23, 35]. We directly measure the sojourn probability for two reference paths for a colloid in a microchannel subject to a double-well potential, and subsequently extrapolate the ratio of sojourn probabilities to the limit $R \rightarrow 0$. We find that this experimentally observed ratio of path probabilities is well-described by the difference in OM Lagrangians along the two reference paths [20–23], thereby transforming the OM action from

a purely mathematical construct into a physical observable. We furthermore observe that our results for relative path probabilities are markedly different from the predictions of the FW Lagrangian [35–37]. Considering the most probable path, or instanton, as zero-radius limit of the most probable tube, we furthermore determine the instanton for experimental barrier-crossing paths in a double-well potential, which is again well-described by the OM Lagrangian, and different from the FW prediction. We finally discuss quantitatively for which system parameters the FW Lagrangian [35] is expected to describe the physical most probable path. Our results remove any ambiguity as to which stochastic action is a measure for physically observed relative path probabilities, and show that these are in fact described by the OM stochastic action.

Sojourn probability and stochastic action. For a smooth reference path $\varphi(t)$, we write the sojourn probability, i.e. the probability that a continuous stochastic dynamics $X_t \equiv X(t)$ stays within a ball of radius R around φ up to time t , as $P_R^\varphi(t)$ [21, 23]; The relative likelihood for two given reference paths $\varphi(t)$, $\psi(t)$, can be quantified by introducing a stochastic action S , defined via [38] [21–27]

$$\frac{e^{-S[\varphi]}}{e^{-S[\psi]}} \equiv \lim_{R \rightarrow 0} \frac{P_R^\varphi(t_f)}{P_R^\psi(t_f)}, \quad (1)$$

where t_i, t_f are the initial and final time considered. For Markovian dynamics, the action is the integral over a Lagrangian [23, 27],

$$S[\varphi] = \int_{t_i}^{t_f} ds \mathcal{L}^\varphi(s), \quad (2)$$

and inserting this expression into the logarithm of Eq. (1), differentiating the result with respect to t_f , and subsequently renaming t_f to t , leads to

$$\mathcal{L}^\varphi(t) - \mathcal{L}^\psi(t) = \lim_{R \rightarrow 0} \left(\alpha_R^\varphi(t) - \alpha_R^\psi(t) \right), \quad (3)$$

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where the instantaneous exit rate at which stochastic trajectories first leave the ball of radius R around φ is given by $\alpha_R^\varphi(t) \equiv -\dot{P}_R^\varphi(t)/P_R^\varphi(t)$, where a dot denotes a derivative with respect to time t . For a finite radius R the right-hand side of Eq. (3) can be measured directly experimentally, via the ratio of recorded trajectories which stay within the threshold distance R to φ as a function of time. Thus, Eq. (3) yields an experimental route to action Lagrangian differences, via extrapolating exit-rate differences measured at finite radius to the limit $R \rightarrow 0$.

Experimental setup. In our experiments, we observe the motion of a colloidal particle confined to a microchannel. Our experimental setup, illustrated in Fig. 1, consists of a holographic optical tweezer, which can autonomously capture colloidal particles and position them inside a microchannel filled with aqueous salt solution. Due to the strong confinement created by the channel, the motion of the center point of the colloidal particle can be considered effectively one-dimensional. A spatial light modulator is used to form an optical landscape which gives rise to a potential energy landscape that the colloid experiences inside the channel; we tune the modulator to create an approximate double-well potential, shown in Fig. 1 (c). The position of the colloidal particle is recorded at 1000 frames per second, in total we record and analyze approximately 104 minutes of experimental measurements, partitioned into short trajectories of variable length ranging from 10 to 60 seconds. The experimental setup is discussed in more detail in Refs. [39, 40].

Relative path likelihoods from experiment. We now compare the experimentally measured right-hand side of Eq. (3) to the corresponding difference in theoretical stochastic action Lagrangians. From recorded experimental time series of a colloidal particle in a microchannel, as illustrated in Fig. 1, we evaluate

$$\Delta\alpha_R(t) \equiv \alpha_R^\varphi(t) - \alpha_R^\psi(t), \quad (4)$$

for several finite values of R . Since the sojourn probabilities for the paths and radii we consider are so small that not a single recorded trajectory remains within the tube until the final time, we introduce an algorithm to obtain the experimental exit rate based on concatenating short recorded trajectories, see Fig. 2 for an illustration and Appendix B for further details. For φ we consider a path which moves from the left minimum of the experimental potential energy to the right minimum of the potential energy in $\Delta t = 20$ s, as illustrated in Fig. 3 (a). For ψ we consider a constant path, which rests at the right minimum for the duration $\Delta t = 20$ s, shown as the upper horizontal dashed line in Fig. 3 (a). In Fig. 3 (b) we show the exit rate differences Eq. (4) for the paths φ, ψ for several finite values of R . We extrapolate to $R = 0$ as follows. Since the exit rate is invariant under a parity transformation around the instantaneous tube center $\varphi(t)$, for small radius the difference in exit rates scales as $\Delta\alpha_R(t) = \Delta\alpha^{(0)}(t) + R^2\Delta\alpha^{(2)}(t) + \mathcal{O}(R^4)$. For every time t , we therefore fit a quadratic function $f(t, R) = a(t) + R^2b(t)$ to the data shown in Fig. 3 (b), and ex-

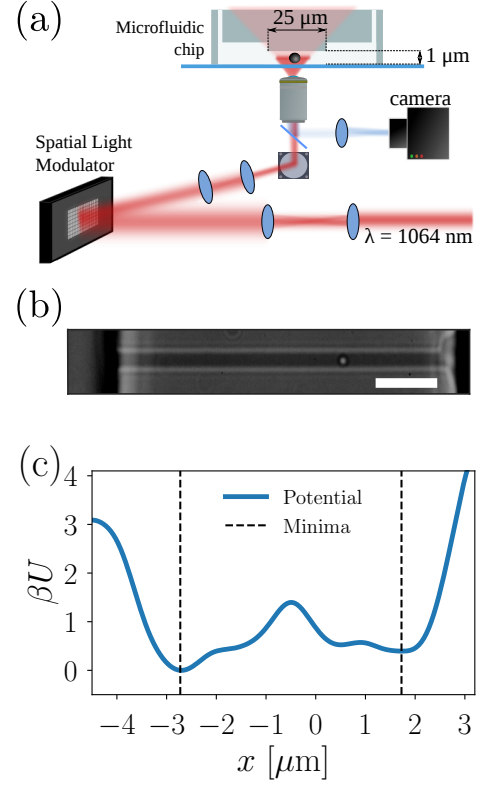


Figure 1. (a) *Experimental setup.* In our experiments, following the general setup of Ref. [40], we observe the motion of a colloidal particle inside a microchannel. (b) *Image of colloidal particle in microchannel.* The motion of the colloidal particle can be considered effectively one-dimensional. The horizontal scale bar in the lower right corner is 5 μm in length, the colloidal particle has a diameter of 500 nm. Subfigures (a) and (b) are adapted from Ref. [40]. (c) *Potential energy extracted from experimental time series.* The blue solid line depicts the potential energy, obtained from evaluating the first two Kramer-Moyal coefficients based on experimental data, and subsequent smoothing as explained in Appendix A. The vertical dashed lines denote two local minima of the potential energy landscape, located at $x_0^{\min} \approx -2.7 \mu\text{m}$, $x_1^{\min} \approx 1.7 \mu\text{m}$.

trapolate to vanishing radius as $\lim_{R \rightarrow 0} \Delta\alpha_R(t) \equiv a(t)$. Figure 3 (c) compares the result with the theoretical difference in OM Lagrangians [20–23],

$$\mathcal{L}^\varphi(t) = \frac{1}{4D} [\dot{\varphi}(t) - D\beta F(\varphi(t))]^2 + \frac{1}{2} D\beta(\partial_x F)(\varphi(t)), \quad (5)$$

where $D \approx 0.23 (\mu\text{m})^2/\text{s}$ is the diffusivity, $\beta^{-1} = k_B T$ the thermal energy with k_B the Boltzmann constant and T the absolute temperature, and $F(x) = -\nabla U$ the force corresponding to the potential shown in Fig. 1; for details on the parametrization of $D, U(x)$, see Appendix A. While in Fig. 3 (c) there are some minor differences between theory and experimental extrapolation, the overall agreement is very good. This shows both that our protocol for extracting ratios of path probabilities from experiments yields meaningful results, and that relative

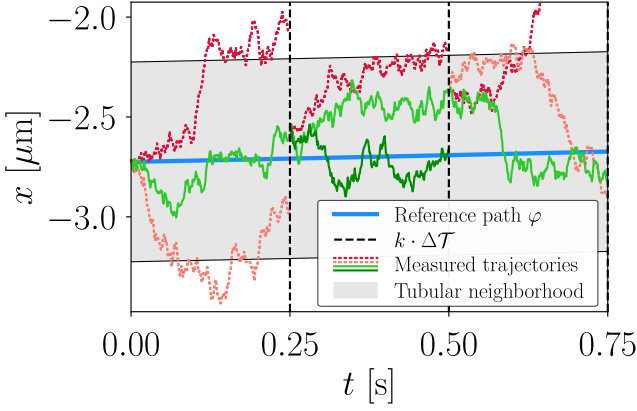


Figure 2. Illustration of our algorithm for obtaining sojourn probabilities from measured time series. The solid blue line represents a reference path φ , around which a tube of radius $R = 0.5 \mu\text{m}$ is shown as grey shaded area. We randomly select $M = 3$ measured trajectories which start in a small interval around $x_0^{\min} \approx -2.7 \mu\text{m}$, and follow them for a duration $\Delta\mathcal{T} = 0.25 \text{ s}$ (vertical dashed lines). Trajectories which leave the tube (red dotted lines) are discarded, the final positions of those trajectories that stay (green solid lines) are collected. We then again randomly select $M = 3$ measured trajectories, which start in a small interval around any of the collected final positions, and repeat the process. The exit rate $\alpha_R^\varphi(t)$ which appears in Eq. (4) is the rate at which the red sample trajectories leave the tube for the first time. The small value $M = 3$ is chosen here for illustration; to calculate exit rates from experimental data, we use values of the order 10^4 , which are chosen dynamically, see Appendix B for details. To demonstrate that concatenating measured trajectories at multiples of $\Delta\mathcal{T}$ does not artificially alter the dynamics, we in Appendix B compare exit rates obtained using this algorithm for $\Delta\mathcal{T} = 0.1, 0.25, 0.5 \text{ s}$, leading to identical results. All trajectories shown here are actual experimental data, the reference path φ is the same as in Fig. 3 (a).

path probabilities are indeed quantified by the OM Lagrangian. On the other hand, the difference in FW Lagrangians [35], given by

$$\mathcal{L}_{\text{FW}}^\varphi(t) = \frac{1}{4D} [\dot{\varphi}(t) - D\beta F(\varphi(t))]^2, \quad (6)$$

and also shown in Fig. 3 (c), disagrees considerably with both the experimental data and the OM prediction.

Most probable path from experiment. The most probable path φ^* , also called instanton, connecting an initial point $\varphi^*(t_i) = x_i$ and a final point $\varphi^*(t_f) = x_f$, is given by

$$\varphi^* \equiv \lim_{R \rightarrow 0} \left[\operatorname{argmin}_{\varphi} \int_{t_i}^{t_f} dt \alpha_R^\varphi(t) \right], \quad (7)$$

where we minimize over all continuous paths with given endpoints $\varphi(t_i) = x_i$, $\varphi(t_f) = x_f$. This equation follows from maximizing the right-hand side of Eq. (1) with respect to φ for any fixed ψ , and states that the most probable path is the one where the exit rate diverges slowest as $R \rightarrow 0$.

As in Fig. 3 we use $t_i = 0$, $t_f = 20 \text{ s}$, and for x_i, x_f , consider the two minima of the experimental potential energy, c.f. Fig. 1. Using our experimental time series, we minimize the right-hand side of Eq. (7), but without the limit, to obtain the most probable tube for several finite values of R . To obtain the most probable path, we subsequently extrapolate the result to the limit $R \rightarrow 0$, for details see Appendix C. In Fig. 4 (a) we compare the resulting experimental instanton, to the directly minimized OM action, obtained by integrating Eq. (5) along a path. As the figure shows, the extrapolated most probable path agrees very well with the OM instanton, demonstrating that the most probable path can be extracted directly from experimental data without fitting a model. The FW instanton, obtained from minimizing the temporal integral over the Lagrangian Eq. (6), is also shown in Fig. 4 (a), and disagrees significantly with the experimental data. We conclude that the OM Lagrangian is the correct action to describe physically observed most probable paths, as was conjectured before [33].

Range of validity of FW Lagrangian. To understand for which parameters the FW Lagrangian Eq. (6) yields the physical most probable path, we investigate for which parameters the two Lagrangians Eqs. (5), (6), predict the same instanton. In Fig. 4 (b) we show the numerically evaluated average difference between FW and OM instanton,

$$\|\varphi_{\text{FW}}^* - \varphi_{\text{OM}}^*\| \equiv \frac{1}{\Delta t \cdot L} \int_{t_i}^{t_f} dt |\varphi_{\text{FW}}^*(t) - \varphi_{\text{OM}}^*(t)|, \quad (8)$$

as a function of the total duration $\Delta t = t_f - t_i$, and temperature $\beta T / (\beta T_0)$, with the experimental temperature $T_0 = 294 \text{ K}$ indicated in the plot by a red vertical dotted line. For the typical length scale in Eq. (8) we use $L = 1 \mu\text{m}$. As can be seen the FW Lagrangian predicts the correct instanton if the total duration Δt is short, or if the temperature $\beta T / (\beta T_0)$ is low. In view of the latter result we remark that sometimes [35], but not always [32, 33], the FW Lagrangian is associated with a low-temperature approximation.

A quantitative estimate for the range of applicability of the FW action is obtained by investigating for which parameters the second term in Eq. (5) is negligible as compared to the first term. For this, we distinguish between the two limiting cases. If the total duration Δt is short, the precise meaning of which will be quantified in the following, then the trajectory needs a large velocity to reach the given final position $x_f = x_i + \Delta x$. For this scenario we estimate the typical velocity as $\dot{\varphi} \approx \Delta x / \Delta t$, so that $\dot{\varphi}^2 / (4D)$ dominates the first term in Eq. (5) if the total time is much smaller than a crossover time

$$\Delta t \ll \Delta t_c \equiv \frac{\gamma \Delta x}{\langle |F| \rangle}, \quad (9)$$

where the brackets $\langle \rangle$ denote a spatial average between x_i and x_f . Using the experimentally inferred values for γ, F , Eq. (9) yields $\Delta t_c \approx 34 \text{ s}$, which is shown in Fig. 4

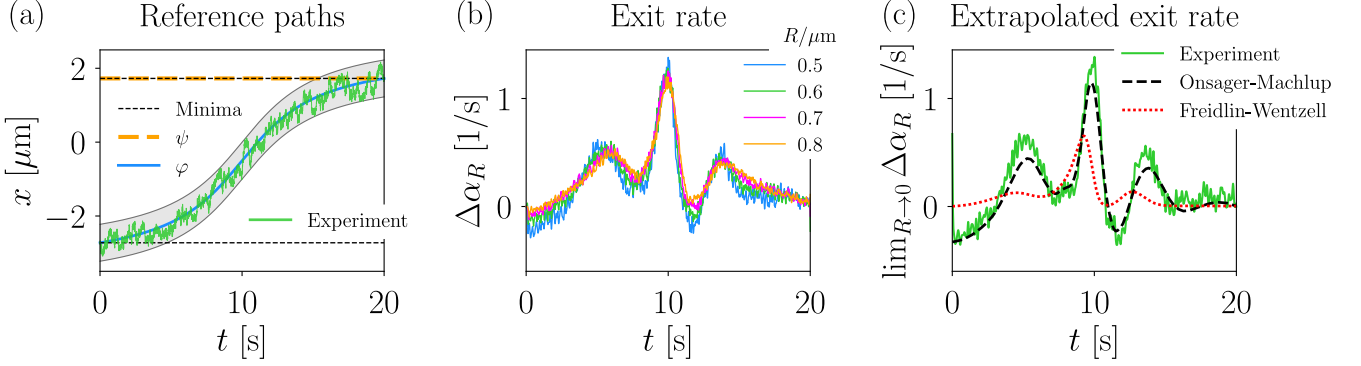


Figure 3. (a) Reference paths used to extract relative path probabilities. The thin horizontal dashed lines denote the minima in the experimental potential energy landscape, c.f. Fig. 1; the upper dashed line additionally denotes the constant path ψ , as indicated by a thick orange dashed line. The blue solid line denotes a path φ which moves from the left potential-energy minimum to the right minimum in 20 seconds. The gray shaded region around the path φ indicates a tube of radius $R = 0.5 \mu\text{m}$; the green solid line depicts concatenated experimental time series, obtained using the algorithm from Fig. 2. (b) Exit rate differences for finite radius R . Colored solid lines denote the exit rate difference Eq. (4), extracted directly from experimental time series for various values of the radius R , as indicated in the legend. The used reference paths φ , ψ , are shown in subplot (a), the shown exit rates are smoothed using a Hann window of width 0.101 s. (c) Extrapolation of exit rate differences to radius $R = 0$. The green solid line denotes the extrapolation to $R = 0$ of (the pre-smoothing versions of) the finite-radius exit rate differences shown in subplot (b). The shown extrapolated exit rate is smoothed using a Hann window of width 0.011 s. The black dashed line and the red dotted line denote the difference in the OM and FW Lagrangians for the paths φ , ψ , calculated using Eqs. (5), (6), and the diffusivity and force estimated from the experimental data, c.f. Fig. 1.

(b) as horizontal dashed line. For a fast transition, $\Delta t \ll \Delta t_c$, the second term in the OM Lagrangian Eq. (5) is negligible as compared to the first term if and only if

$$\Delta t \ll \frac{1}{\sqrt{\beta T / (\beta T_0)}} \frac{\Delta x}{D_0 \sqrt{\beta_0 \langle |\partial_x F| \rangle}}, \quad (10)$$

where we write $\beta^{-1} = k_B T = k_B T_0 \cdot T / T_0 \equiv \beta_0^{-1} \cdot T / T_0$, as well as $D = k_B T / \gamma = T / T_0 \cdot k_B T_0 / \gamma \equiv T / T_0 \cdot D_0$. For our experimental system, $\Delta x / (D_0 \sqrt{\beta_0 \langle |\partial_x F| \rangle}) \approx 14 \text{ s}$. The right-hand side of Eq. (10) is shown in Fig. 4 (b) as diagonal black dashed line, and indeed in the lower left corner of the plot, where both Eqs. (9), (10), are fulfilled, the FW action predicts the correct instanton. Surprisingly, the FW action in fact predicts correct instantons even at $\beta T / (\beta T_0) = 1$ if the transition is fast enough, as illustrated with an example in Appendix E. For long total duration, $\Delta t \gg \Delta t_c$, the first term in the OM Lagrangian Eq. (5) is expected to be of order $D |\beta F|^2 / 4$, so that the second term is negligible if the temperature is much smaller than a crossover temperature T_c , defined by

$$\frac{\beta T}{\beta T_0} \ll \frac{\beta T_c}{\beta T_0} \equiv \frac{1}{2} \frac{\langle |\beta_0 F|^2 \rangle}{\langle |\beta_0 \partial_x F| \rangle}. \quad (11)$$

For our system, $T_c / T_0 \approx 0.08$, which is shown as vertical dashed line in Fig. 4 (b); as can be seen, in the parameter regime where both $\Delta t \gg \Delta t_c$ and Eq. (11) are fulfilled, i.e. in the upper left corner of the plot, the FW action again predicts the correct instanton. In summary, Fig. 4 (b) shows that Eqs. (9), (10), (11), allow to globally estimate the parameter regions where the FW Lagrangian

describes the physical instanton, given by the OM Lagrangian.

Conclusions. In this work, we establish a protocol to determine ratios of path probabilities from measured time series, without fitting a model to the data. Applying this protocol to time series of a colloidal particle in a microchannel, we find that the Onsager-Machlup action Lagrangian [20–23] describes both ratios of path probabilities and the most probable path extracted from our experimental data. The Freidlin-Wentzell action [35–37] disagrees with our experimental results, and we quantify for which parameters it is expected to predict the physical instanton.

Our results constitute a direct experimental measurement of relative likelihoods of stochastic trajectories, and demonstrate that from a physical point of view there is no ambiguity as to which stochastic action describes observed path probabilities.

More generally, our framework enables experimentally testing any theoretical result on individual stochastic trajectories; this is particularly important for the field of stochastic thermodynamics, which extensively employs the concept of single trajectories [4, 10]. For example, considering measured ratios of probabilities for forward- and backward tubes will allow to directly characterize the irreversibility along individual paths.

With Eq. (3) we provide a model-free and experimentally accessible definition of the stochastic action Lagrangian. Based on this relation between observable exit rates and path probabilities, physically relevant and experimentally accessible stochastic actions can be defined for any kind of stochastic dynamics [41].

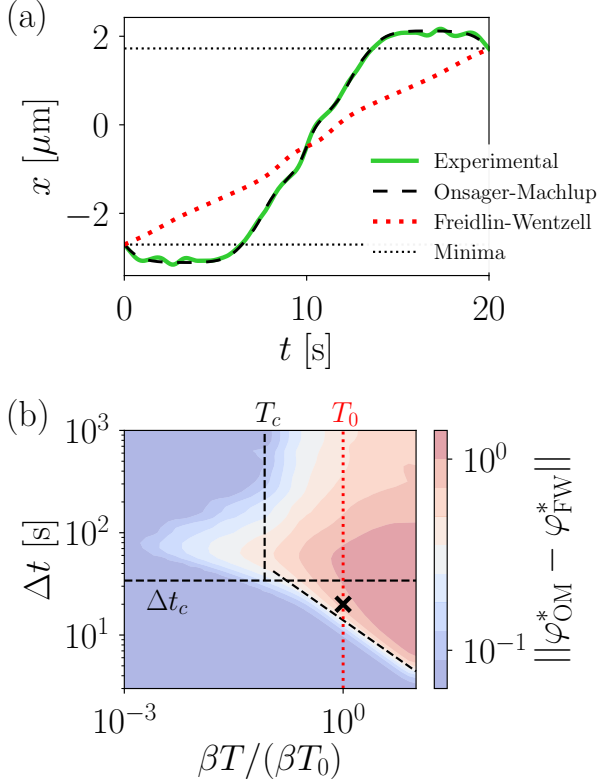


Figure 4. (a) *Most probable paths for barrier crossing.* The green solid line denotes the most probable path extracted directly from experimental data, see Appendix C for details. The black dashed line is obtained by minimizing the integrated OM Lagrangian Eq. (5), the red dotted line is obtained by minimizing the integrated FW Lagrangian Eq. (6). (b) *Mean difference between OM and FW instanton.* The actions corresponding to the Lagrangians Eq. (5), (6) are minimized for various values of temperature $\beta T / (\beta T_0)$ and total transition time Δt . The plot shows the mean difference between the resulting instantons, as defined in Eq. (8); for technical details see Appendix D. The horizontal and diagonal black dashed lines denote the crossover time $\Delta t_c \approx 34$ s defined in Eq. (9), and the right-hand side of Eq. (10). The black vertical dashed line denotes the crossover temperature $\beta T / (\beta T_0) \approx 0.08$ defined in Eq. (11); the red vertical dotted line denotes the reference temperature $T_0 = 294$ K. The cross denotes the parameters $(\beta T / (\beta T_0), \Delta t)$ used for subplot (a).

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Appendix A: Parametrizing the overdamped Langevin equation

We consider the overdamped one-dimensional Langevin equation

$$\dot{X}_t = D\beta F(X_t) + \sqrt{2D}\eta_t, \quad (\text{A1})$$

with D the diffusivity, $\beta^{-1} = k_B T$ the thermal energy with k_B the Boltzmann constant and T the absolute temperature, $F(x) = -\nabla U$ an external force with a potential U , and η Gaussian white noise with zero mean and unit variance. As we explain in the following, we parametrize Eq. (A1) by locally calculating the first two Kramers-Moyal coefficients based on the experimental time series. While this parameterization allows for a position-dependent diffusivity $D(x)$, we will see below that for our experimental system the diffusivity is well-approximated by a spatially constant diffusivity. This in particular implies that, while we use the Ito interpretation for Eq. (A1), the choice of stochastic integral does not lead to any ambiguity in our results, because for constant diffusivity D the Ito- and Stratonovich interpretation of Eq. (A1) are equivalent.

From 104 minutes of experimental measurements we obtain $N = 230$ uncorrelated discrete time series

$$X_i(t_j) \equiv X_i(j \cdot \Delta t) \equiv X_{ij}, \quad (\text{A2})$$

where $i \in I = \{1, \dots, N\}$ labels the time series, and the maximal time index $j \in \{0, \dots, J_i\}$ for each time series depends on i , meaning the recorded time series are of variable length. All time series have identical time step $\Delta t = 0.001$ s, lengths of time series range from 10 to 60 s. We divide space into bins of width $\Delta x = 0.05 \mu\text{m}$, with the k -th bin

$$B_k = [\hat{x}_L + k \cdot \Delta x, \hat{x}_L + (k+1) \cdot \Delta x], \quad (\text{A3})$$

where for the left boundary $\hat{x}_L = -4.8 \mu\text{m}$, and $k \in \{0, \dots, K\}$ with $K = 192$, so that $\hat{x}_R \equiv \hat{x}_L + K \cdot \Delta x = 4.8 \mu\text{m}$. The center of the k -th bin, denoted by x_k , is located at $x_k \equiv \hat{x}_L + (k + 1/2) \cdot \Delta x$. The positions \hat{x}_L, \hat{x}_R are still well within the experimental microchannel, meaning that a colloid starting at \hat{x}_L, \hat{x}_R is very unlikely to leave the tube within one second. For every bin B_k we create a list of all the experimentally recorded tuples (i, j) such that $X_{ij} \in B_k$, i.e. we for every k construct the set

$$\mathcal{B}_k = \{(i, j) \mid X_{ij} \in B_k\}. \quad (\text{A4})$$

We denote the total number of data points in bin B_k by

$$N_k \equiv |\{(i, j) \mid X_{ij} \in B_k\}| \equiv |\mathcal{B}_k|, \quad (\text{A5})$$

and show a plot of N_k as a function of the bin center x_k in Fig. 5.

To parametrize the overdamped Langevin Eq. (A1), we locally estimate both the diffusivity and the force via

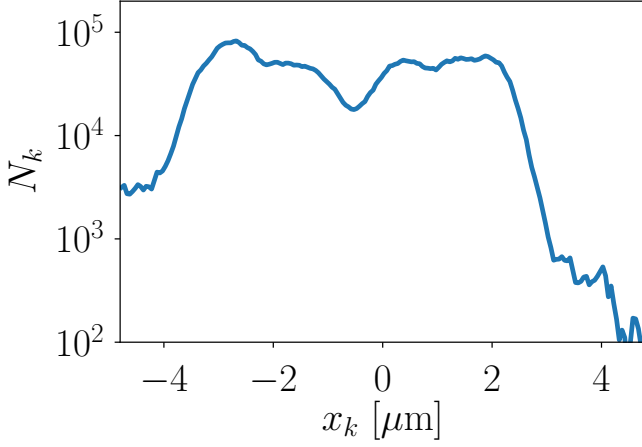


Figure 5. Number of experimental data points per discretization bin. The solid line denotes the number of experimental data points per bin, as defined in Eq. (A5). The bin center x_k is the center of the bin B_k , defined in Eq. (A3).

discretized Kramers-Moyal coefficients [1]. At the bin centered around x_k we obtain

$$D(x_k) = \frac{1}{2 \cdot N_k \cdot \Delta t^*} [\langle \Delta X^2(\Delta t^*) \rangle_k - \langle \Delta X(\Delta t^*) \rangle_k^2 / N], \quad (\text{A6})$$

$$\beta F(x_k) = \frac{\langle \Delta X(\Delta t^*) \rangle_k}{D(x_k) \cdot N_k \cdot \Delta t^*}, \quad (\text{A7})$$

where the average $\langle \bullet \rangle_k$ means that we average over all N_k experimental time series which start in the bin B_k . In the evaluation of Eqs. (A6), (A7), we furthermore use the lagtime $\Delta t^* = 15\Delta t = 0.015$ s, a discussion of the dependence of our results on lagtime is given further below. From the force a potential is obtained as

$$\beta U(x_k) = - \int_{x_L}^{x_k} dx' \beta F(x'), \quad (\text{A8})$$

where we use the trapezoidal rule to perform the integral on the right-hand side numerically; the result of this integration is furthermore smoothed using a Hann-window that at each x_k incorporates the 20 closest datapoints. The smoothed potential is then interpolated using polynomial splines of degree 3; this polynomial interpolation is used in evaluations of the stochastic action to calculate the force F and its derivative $\partial_x F$.

The diffusivity and potential energy profiles obtained from Eqs. (A6), (A7) are shown in Fig. 6. The potential energy in subplot (a) shows two local minima at $x_0^{\min} \approx -2.725 \mu\text{m}$, $x_1^{\min} \approx 1.725 \mu\text{m}$, separated by a barrier at $x \approx -0.5 \mu\text{m}$. Note that in the main text a constant is added to the potential, such that the potential vanishes at x_0^{\min} . From Fig. 6 (b) we conclude that the diffusivity is almost independent of position within the interval $[x_0^{\min} - 1 \mu\text{m}, x_1^{\min} + 1 \mu\text{m}]$, with an average value

$$\langle D \rangle \approx 0.232 \frac{(\mu\text{m})^2}{\text{s}}. \quad (\text{A9})$$

The dependence of the inferred potential and diffusivity, Eqs. (A6), (A7), on the lagtime Δt^* is shown in Fig. 7. Subplots (a), (b) show that both the potential and the diffusivity for the two lagtimes $\Delta t^* = 0.015, 0.025$ s, agree with each other. Figure 7 (c) shows the average diffusivity $\langle D \rangle$ as a function of the lagtime Δt^* . For short lagtimes $\Delta t^* \lesssim 0.01$ s, the mean diffusivity slightly depends on the lagtime (note the scaling on the y -axis), which we attribute to inaccuracies of the centroid algorithm which we use to estimate colloidal positions. For lagtimes $\Delta t^* \gtrsim 0.01$ s, the mean diffusivity is independent of the lagtime, which justifies our choice $\Delta t^* = 0.015$ s.

Appendix B: Extracting sojourn probabilities from experimental time series

Algorithm. We now explain how we extract sojourn probabilities and exit rates from experimental time series. We assume as given several uncorrelated time series, a reference path $\varphi(t)$, and a radius R . In essence, the algorithm concatenates randomly sampled short recorded trajectories.

We assume that the dynamics is time-homogeneous, that the time series are Markovian, and that the time series have been indexed as described in the beginning of App. A.

At the initial time t_i , we choose an initial probability density inside the tube. In the discretization of space described in App. A, this probability density is represented by a normalized histogram that is only nonzero in the approximately $2R/\Delta x$ bins which intersect with the tube at time t_i , which is given by the interval $[\varphi(t_i) - R, \varphi(t_i) + R]$. To estimate the sojourn probability for a short time interval $\Delta \mathcal{T}$, we proceed as follows.

1. From the histogram representing the initial condition, we draw M sample bins (with replacement) $\{B_{k_1}, B_{k_2}, \dots, B_{k_M}\}$; for the definition of a bin see Eq. (A3). Each sample bin represents an initial condition for a sample trajectory starting inside the tube.
2. For each sample bin B_{k_i} , we draw one of the N_{k_i} measured data points inside this bin (with replacement, and using a uniform distribution on the set of all measured data points inside the bin), where N_i is defined in Eq. (A5). If the bin B_{k_i} only partly intersects the tube interior, and the drawn data point lies outside the tube, a new datapoint is drawn. The drawn datapoint belongs to a recorded time series, and we assume that this time series extends at least until time $t_{k_i} + \Delta \mathcal{T}$ (this requirement can always be ensured by reducing the maximal index J_i corresponding to the trajectory X_i , and removing trajectories X_i that are shorter than $\Delta \mathcal{T}$).
3. We follow each of the M randomly drawn time series from step 2 for the time $\Delta \mathcal{T}$, and discard each

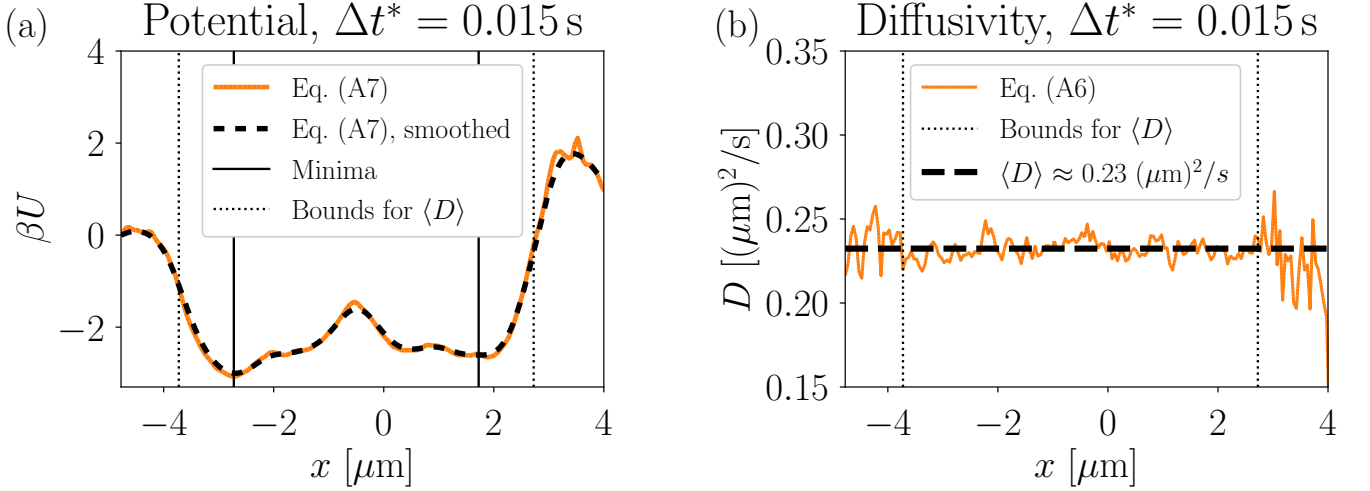


Figure 6. *Local potential and diffusivity extracted from experimental time series.* (a) The orange solid line depicts the potential energy as obtained from Eqs. (A7), (A8), for $\Delta t^* = 0.015$ s. The black dashed solid line is a smoothed version of the orange line, obtained via a Hann window average using 20 datapoints at each point x_k . The vertical solid lines denote local minima $x_0^{\min} \approx -2.725 \mu\text{m}$, $x_1^{\min} \approx 1.725 \mu\text{m}$, of the smoothed potential energy. The vertical dashed lines indicate the bounds of the interval $[x_0^{\min} - 1 \mu\text{m}, x_1^{\min} + 1 \mu\text{m}]$ over which the average diffusivity $\langle D \rangle$ is calculated in subplot (b). (b) The orange line shows the local diffusivity as obtained from Eq. (A6). The horizontal dashed line depicts the average over the diffusivity inside the interval $[x_0^{\min} - 1 \mu\text{m}, x_1^{\min} + 1 \mu\text{m}]$, as indicated by the two vertical lines, c.f. subplot (a).

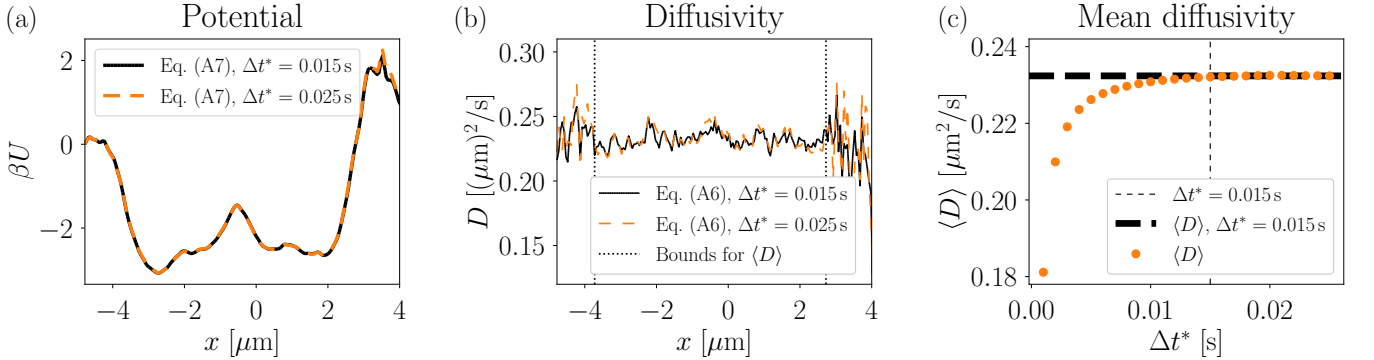


Figure 7. *Lagtime dependence of potential and diffusivity extracted from experiments.* (a) The potential energy as obtained from Eqs. (A7), (A8), is shown for $\Delta t^* = 0.015$ s as black solid line, and for $\Delta t^* = 0.025$ s as orange dashed line. (b) The diffusivity as obtained from Eq. (A6) is shown for $\Delta t^* = 0.015$ s as black solid line, and for $\Delta t^* = 0.025$ s as orange dashed line. The vertical dashed lines depict the boundary of the interval $[x_0^{\min} - 1 \mu\text{m}, x_1^{\min} + 1 \mu\text{m}]$, where $x_0^{\min} \approx -2.725 \mu\text{m}$, $x_1^{\min} \approx 1.725 \mu\text{m}$ are two local minima of the potential energy, c.f. Fig. 6. (c) Mean diffusivity $\langle D \rangle$, averaged over $[x_0^{\min} - 1 \mu\text{m}, x_1^{\min} + 1 \mu\text{m}]$, as function of lagtime Δt^* used in Eq. (A6). The horizontal thick dashed line denotes the value $\langle D \rangle$ for $\Delta t^* = 0.015$ s, as indicated by the vertical dashed line.

trajectory as soon as it first leaves the tube. The number of trajectories left in the tube at each time step, denoted by M_j , yields an estimate for the sojourn probability via $P_R^p(j \cdot \Delta t) \equiv P_j \equiv M_j/M$, subject to the given initial condition, and for a duration $\Delta \mathcal{T}$.

4. By creating a histogram from the final positions of those trajectories that stay inside the tube until time $\Delta \mathcal{T}$, a new initial distribution is obtained, and the algorithm can be repeated from step 1 for another time interval $\Delta \mathcal{T}$.

Figure 2 illustrates the algorithm for an initial distribution $P(x) = \delta(x - \varphi(0))$, $\Delta \mathcal{T} = 0.25$ s, $M = 3$ (to obtain a reliable estimate for the sojourn probability, of course much larger values for M need to be used). For the analysis of the experimental data we use $\Delta x = 0.05 \mu\text{m}$, $\Delta \mathcal{T} = 0.25$ s; at the end of the present section we show that results of this algorithm are independent of our particular choice for $\Delta \mathcal{T}$.

From the discrete time series P_j for the sojourn prob-

ability, the exit rate α_R^φ is obtained by discretizing

$$\alpha_R^\varphi = -\frac{\dot{P}_R^\varphi(t)}{P_R^\varphi(t)}. \quad (\text{B1})$$

For the first iteration of steps 1-3 of the algorithm outline above, we choose $M = 10^5$ and as initial condition a smeared-out delta peak at the tube center, consisting of a uniform distribution on the 3 bins closest to the tube center. For each subsequent iteration of steps 1-3, we estimate the number of trajectories M , based on the recent trend of the exit rate. More explicitly, assuming we are at the k -th repetition of steps 1-3 (where $k > 1$), we fit a linear function

$$\alpha_{\text{fit}}(t) = a \cdot (t - k \cdot \Delta\mathcal{T}) + b, \quad (\text{B2})$$

to the exit rate in the time interval $[k \cdot \Delta\mathcal{T} - \Delta t_{\text{fit}}, k \cdot \Delta\mathcal{T}]$, where $\Delta t_{\text{fit}} = \min\{0.4 \text{ s}, \Delta\mathcal{T}\}$. Using the fitted Eq. (B2), we estimate the number M such that the expected number of trajectories inside the tube at the final time of the k -th iteration step is approximately N_{final} , which yields

$$N_{\text{final}} = M \exp \left[- \int_{k \cdot \Delta\mathcal{T}}^{(k+1) \cdot \Delta\mathcal{T}} ds \alpha_{\text{fit}}(s) \right], \quad (\text{B3})$$

$$\iff M = N_{\text{final}} \exp \left[a \frac{\Delta\mathcal{T}^2}{2} + b \Delta\mathcal{T} \right]. \quad (\text{B4})$$

For all exit rates shown in this paper, we use $N_{\text{final}} = 10^5$; for the minimization leading to the most probable path we also use smaller values for N_{final} , as described in detail in App. C.

Relative path likelihoods for several barrier crossing paths. Using the algorithm described just above, we extract from experimental data the exit rate around a reference path

$$\varphi(t) = \frac{x_f - x_i}{2 \arctan(\kappa/2)} \arctan \left[\frac{\kappa}{\Delta t} (t - \Delta t/2) \right] + \frac{x_f + x_i}{2}, \quad (\text{B5})$$

where we use $\Delta t = 20 \text{ s}$, $x_i \equiv x_0^{\text{min}} \approx -2.725 \mu\text{m}$, $x_f \equiv x_1^{\text{min}} = 1.725 \mu\text{m}$ are two minima of the potential energy, and we consider $\kappa = 1, 5, 10, 20$; in the main text, only the results for $\kappa = 5$ are shown. As illustrated in Fig. 8, the path Eq. (B5) describes a barrier crossing starting at time $t = 0$ at the left minimum and arriving at the right minimum at time $t = 20 \text{ s}$, with the parameter κ controlling the maximal path velocity during barrier crossing. For each value of κ , we calculate the exit rate α_R^φ for tube radii $R = 0.5, 0.55, 0.6, 0.65, 0.7, 0.75, 0.8 \mu\text{m}$ using the algorithm introduced above. For each R , we furthermore extract the exit rate α_R^ψ for a path ψ that rests at the minimum x_1^{min} .

Figure 9 shows the resulting exit rate difference,

$$\Delta\alpha_R(t) \equiv \alpha_R^\varphi(t) - \alpha_R^\psi(t), \quad (\text{B6})$$

for several values of R . For each value of κ , we extrapolate the finite-radius exit rate difference to $R = 0$

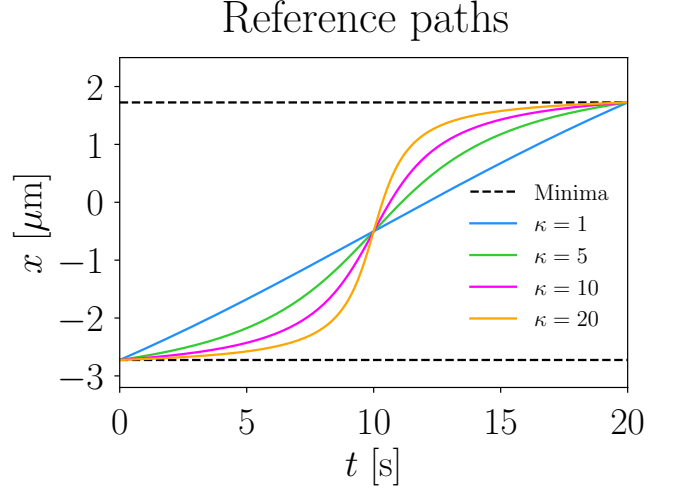


Figure 8. *Reference paths considered in the main text and App. B.* The horizontal dashed lines denote the minima $x_0^{\text{min}} \approx -2.725 \mu\text{m}$, $x_1^{\text{min}} \approx 1.725 \mu\text{m}$, of the experimental potential energy landscape, c.f. Fig. 6; the upper dashed line additionally denotes the constant path ψ . The colored solid lines denote several paths φ , defined in Eq. (B5), which move from x_0^{min} to x_1^{min} in $\Delta t = 20 \text{ s}$. In the main text, the path corresponding to $\kappa = 5$ is considered.

as described in the main text; the result is shown in Fig. 10. As the figure shows, the extrapolated difference in exit rates is quantitatively described by the OM Lagrangian, Eq. (5), and deviates significantly from the FW Lagrangian, Eq. (6).

Invariance of algorithm under variation of $\Delta\mathcal{T}$. To show that exit rates calculated using the algorithm presented above are independent of the particular choice of the parameter $\Delta\mathcal{T}$, we now consider the exit rate difference of the barrier-crossing path φ defined in Eq. (B5), with $\kappa = 5$, and a path ψ resting at the right potential energy minimum $x_1^{\text{min}} \approx 1.725 \mu\text{m}$, for radii $R = 0.5, 0.8 \mu\text{m}$. In Fig. 11 we compare exit rate differences obtained for $\Delta\mathcal{T} = 0.1, 0.5 \text{ s}$, to results obtained using $\Delta\mathcal{T} = 0.25 \text{ s}$. All curves show excellent agreement, so that we conclude that our results are independent of $\Delta\mathcal{T}$, and in particular that our algorithm does not create any unwanted correlations/decorrelations in the time series.

Appendix C: Calculating the most probable path from experimental data

To extract the most probable path from experimental data, we minimize the functional

$$\varphi_R^* \equiv \underset{\varphi}{\operatorname{argmin}} \int_{t_i}^{t_f} dt \alpha_R^\varphi(t), \quad (\text{C1})$$

for the finite values $R = 0.5, 0.55, 0.6, 0.65, 0.7, 0.75, 0.8 \mu\text{m}$, and then extrapolate to $R = 0$.

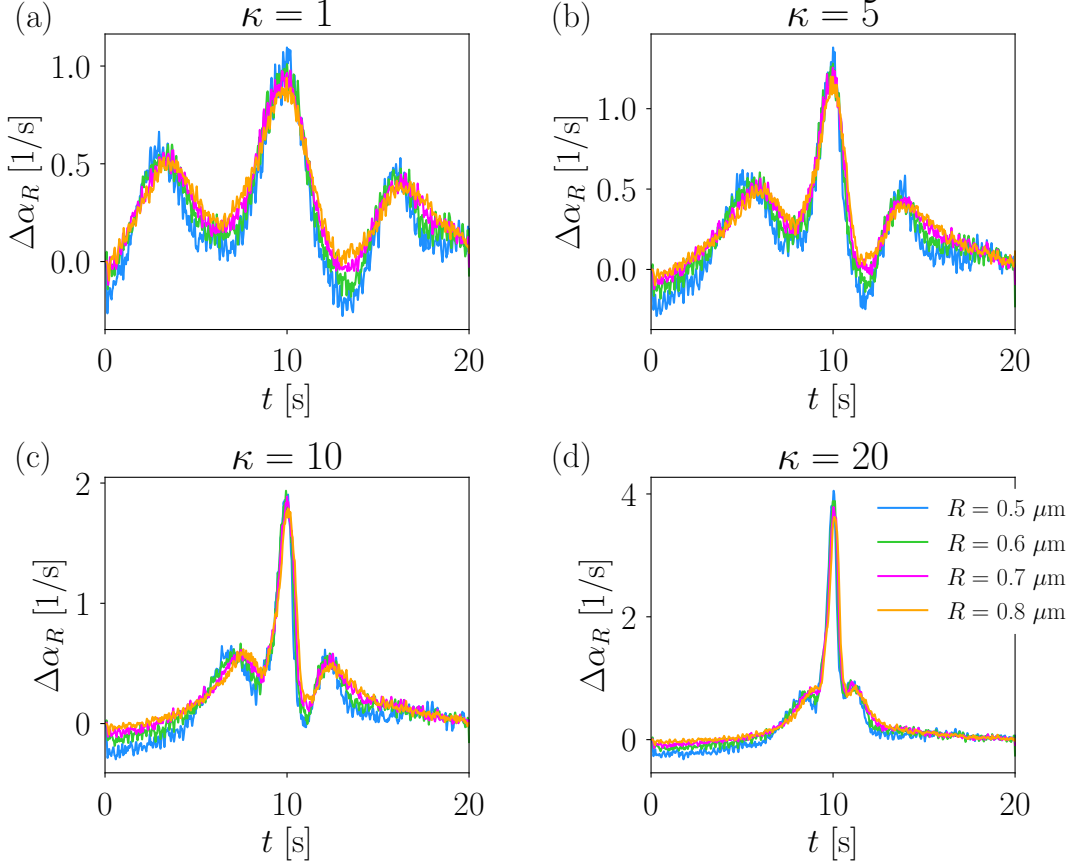


Figure 9. *Exit rate differences for finite radius R .* The legend in the lower right plot is valid for all subplots. Colored solid lines denote the exit rate difference Eq. (B6) as extracted directly from experimental time series for various values of the radius R , as indicated in the legend. The four subplots correspond to the four reference paths φ shown in Fig. 8, with crossing speeds (a) $\kappa = 1$, (b) $\kappa = 5$, (c) $\kappa = 10$, and (d) $\kappa = 20$, respectively. For ψ a path that rests at the right minimum $x_1^{\min} \approx 1.725 \mu\text{m}$ of the potential energy is used throughout. Each exit rate shown in smoothed using a Hann window with 101 datapoints, corresponding to a temporal window width of $\Delta T_{\text{smooth}} = 0.101 \text{ s}$.

For each R , the minimization in Eq. (C1) is over all continuous paths with given endpoints $\varphi(t_i) = x_i$, $\varphi(t_f) = x_f$, so that the minimization is over an infinite-dimensional space of functions. To approximate this space by a finite-dimensional space of dimension N , we parametrize φ as

$$\varphi(t) = x_i + \frac{t - t_i}{t_f - t_i} (x_f - x_i) + \sum_{n=1}^N \frac{a_n}{n^2} \sin \left[2\pi n \frac{t - t_i}{t_f - t_i} \right]. \quad (\text{C2})$$

Note that for any given set of coefficients $(a_1, \dots, a_N) \in \mathbb{R}^N$, Eq. (C2) fulfills the boundary conditions $\varphi(t_i) = x_i$, $\varphi(t_f) = x_f$. Employing this approximate parametrization, the minimization in Eq. (C1) is, for given R , over \mathbb{R}^N . Based on our experimental data, we minimize the right-hand side of Eq. (C1), for $N = 20$ and $R = 0.5, 0.55, 0.6, 0.65, 0.7, 0.75, 0.8 \mu\text{m}$ using a standard minimization algorithm [42]. For each evaluation of the sojourn probability we employ the algorithm detailed in App. B. Since the algorithm presented there is based on stochastic sampling of recorded stochastic trajectories,

the sojourn probability obtained using it is also stochastic. Using a larger value for N_{final} decreases the variance of the inferred exit rate, but increases the computational time necessary to evaluate the exit rate for a given reference path.

For computational efficiency, we proceed in several steps to minimize Eq. (C1) for each given R . First, we perform a minimization using $N_{\text{final}} = 1000$, an initial condition $a_n = 0$ for $n = 1, \dots, 20$, and a starting variance $\sigma_0 = 0.5$ for the minimization algorithm. Using the result of this minimization as new initial condition, we minimize again using $N_{\text{final}} = 10^4$, and a starting variance $\sigma_0 = 0.1$. This procedure is repeated 3 times for each radius R . Then, for each R the sojourn probabilities for the three minima are evaluated again using $N_{\text{final}} = 10^5$, and the path with the largest sojourn probability is chosen as φ_R^* .

Having obtained the most probable tube for several finite values of R , we subsequently extrapolate the corresponding modes $a_n(R)$, to $R = 0$ by fitting a function $f_n(R) = A_n + R^2 B_n$ to the finite-radius minimization

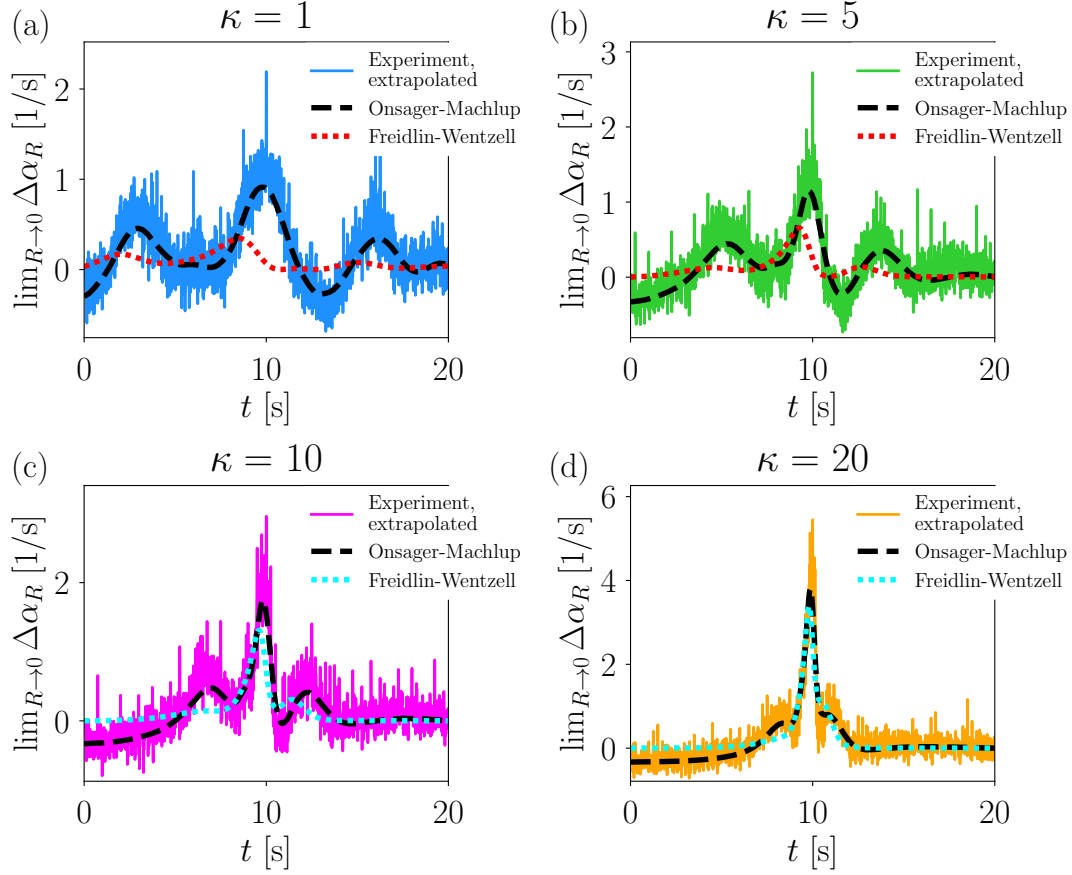


Figure 10. *Exit rate differences extrapolated to radius $R = 0$.* Colored solid lines denote the extrapolation to $R = 0$ of the (pre-smoothing versions of the) finite-radius exit rate differences shown in Fig. 9. The four subplots correspond to the four reference paths φ shown in Fig. 8, with crossing speeds (a) $\kappa = 1$, (b) $\kappa = 5$, (c) $\kappa = 10$, and (d) $\kappa = 20$, respectively. For ψ a path that rests at the minimum at $x_1^{\min} \approx 1.725 \mu\text{m}$ of the potential energy is used throughout. The black dashed line and the colored dotted line denote the difference in the OM and FW Lagrangians for the paths φ , ψ , calculated using Eqs. (5), (6), and the diffusivity and force inferred in App. A.

results, and defining the corresponding expansion coefficients of the most probable path φ^* as

$$a_n^* \equiv \lim_{R \rightarrow 0} f_n(R) = A_n. \quad (\text{C3})$$

To minimize the OM and FW actions, obtained by integrating Eqs. (5), (6) along a path, we also use the parametrization Eq. (C2), with $N = 40$; the resulting instantons are shown in Fig. 4. Since the OM instanton agrees very well with the experimental extrapolation, for which we use $N = 20$, we conclude that $N = 20$ modes are indeed sufficient to characterize the most probable path for the transition considered.

Appendix D: Protocol for calculation of Fig. 4 (b)

A contour plot of Eq. (8) is shown in Fig. 4 (b) as a function of $\beta T/(\beta T_0)$ and Δt . For this, the actions corresponding to the OM and FW Lagrangians, defined in

Eqs. (5), (6), are minimized using the experimental diffusivity and force from App. A, and a path parametrized via Eq. (C2) using $N = 40$. Finding the most probable path for each action is then a minimization problem in \mathbb{R}^N . For this minimization we use a standard algorithm [42], and to further ensure we find the global minimum for each parameter combination $(\beta T/(\beta T_0), \Delta t)$, we minimize each action in total 10 times. For every odd-numbered of these 10 minimizations, we start from an initial condition $a_n = 0$, $n = 1, \dots, 40$, with a variance $\sigma_0 = 1$ for the minimization algorithm; for every even-numbered of these 10 minimizations, we use the most probable OM/FW path from the previous minimizations as initial condition for the respective other action, with a variance $\sigma_0 = 0.1$ for the minimization algorithm. To obtain the instanton, the action is evaluated on all 10 paths, and the path with the smallest action is used in Eq. (8). For Fig. 4 (b), the resulting 2D array of data is subsequently smoothed using a Gaussian filter.

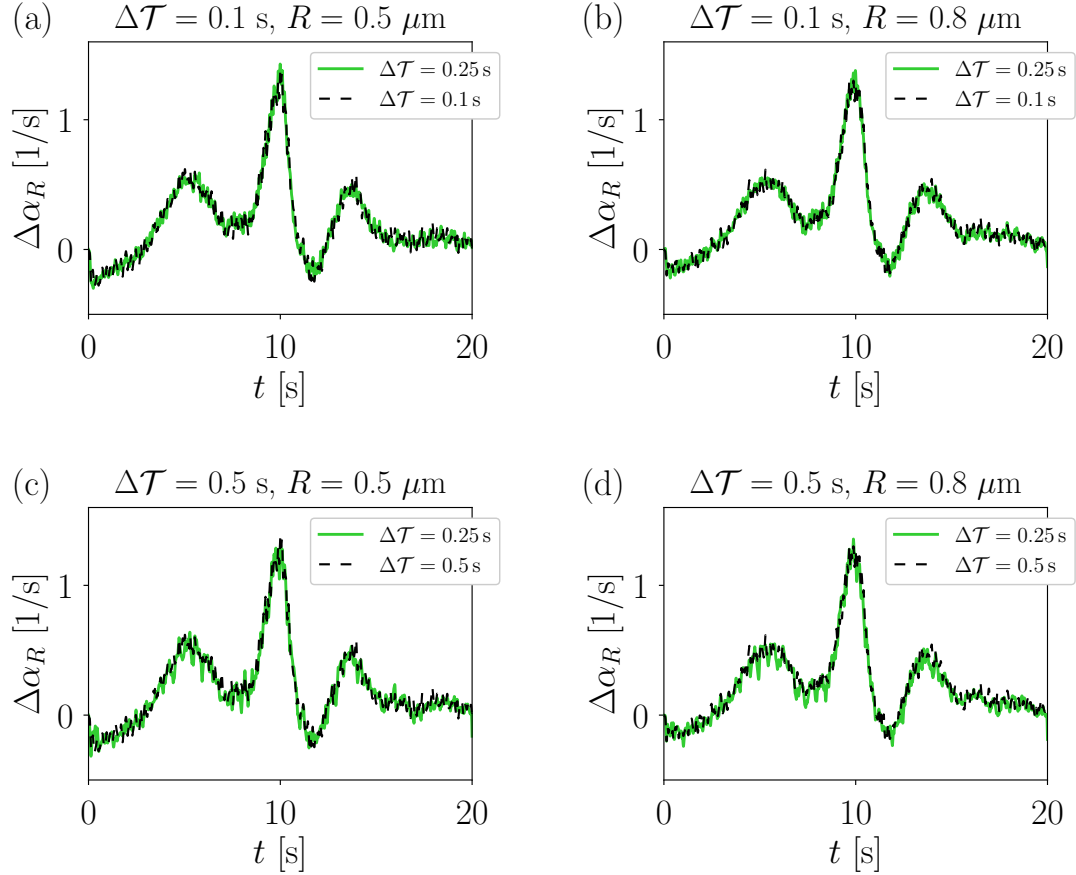


Figure 11. *Exit rate differences for various values of $\Delta\mathcal{T}$.* All lines denote the exit rate difference for a reference path φ , defined in Eq. (B5) with $\kappa = 5$, and shown in Fig. 8, and a reference path ψ that rests at the right minimum $x_1^{\min} \approx 1.725 \mu\text{m}$ of the potential energy. For all data shown, the algorithm presented in App. B is used; while for the green solid lines, we use $\Delta\mathcal{T} = 0.25 \text{ s}$, for the black dashed lines we use (a), (b) $\Delta\mathcal{T} = 0.1 \text{ s}$, and (c), (d) $\Delta\mathcal{T} = 0.5 \text{ s}$. Subplots (a), (c) show results for radius $R = 0.5 \mu\text{m}$, the data shown in subplots (b), (d) is obtained for $R = 0.8 \mu\text{m}$. All data is smoothed using a Hann-window average with an averaging window of width 0.101 s .

Appendix E: Experimental instanton for $\Delta t = 5 \text{ s}$

According to Fig. 4 (b) of the main text, even at the experimental temperature $\beta T = \beta T_0$ there is a regime where the FW Lagrangian predicts the correct instan-

ton, namely if the total duration of the transition is sufficiently short. To illustrate this, we compare in Fig. 12 the experimentally extracted most probable path and the FW as well as OM instanton. As can be seen, all three curves agree very well, showing that the FW action predicts the physical instanton not only for low temperature, but also for fast transitions.

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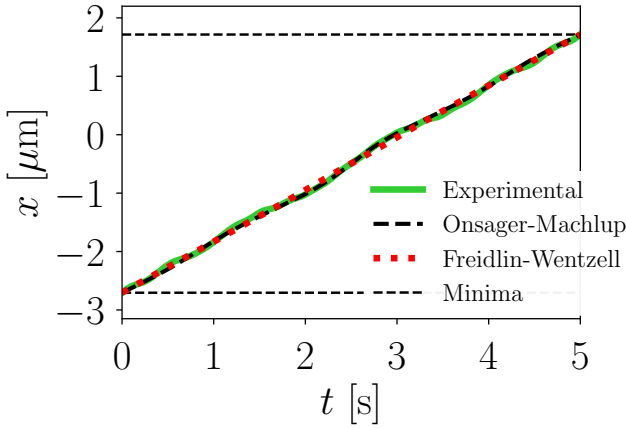


Figure 12. *Most probable paths for barrier crossing with total duration $\Delta t = 5$ s.* The blue dashed line denotes the most probable path extracted from experimental data using Eq. (C3). The green solid line is obtained by minimizing the integrated OM Lagrangian Eq. (5), the magenta dotted line is obtained by minimizing the integrated FW Lagrangian Eq. (6). For evaluation of the OM and FW Lagrangian, diffusivity and force inferred in App. A are used. The horizontal dashed lines denote the local minima $x_0^{\min} \approx -2.725 \mu\text{m}$, $x_1^{\min} \approx 1.725 \mu\text{m}$, of the inferred potential.

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