Controlling Uncertainty of Empirical First-Passage Times in the Small-Sample Regime

Rick Bebon◉ and Aljaž Godec◉*

Mathematical bioPhysics Group, Max Planck Institute for Multidisciplinary Sciences, 37077 Göttingen, Germany

We derive general bounds on the probability that the *empirical* first-passage time $\bar{\tau}_n \equiv \sum_{i=1}^{n} \tau_i/n$ of a reversible ergodic Markov process inferred from a sample of n independent realizations deviates from the true mean first-passage time by more than any given amount in either direction. We construct nonasymptotic confidence intervals that hold in the elusive small-sample regime and thus fill the gap between asymptotic methods and the Bayesian approach that is known to be sensitive to prior belief and tends to underestimate uncertainty in the small-sample setting. We prove sharp bounds on extreme first-passage times that control uncertainty even in cases where the mean alone does not sufficiently characterize the statistics. Our concentration-of-measure-based results allow for model-free error control and reliable error estimation in kinetic inference, and are thus important for the analysis of experimental and simulation data in the presence of limited sampling.

Introduction.—The first-passage time τ denotes the time a random process reaches a threshold a, referred to as "target," for the first time. First-passage phenomena [1–4] are ubiquitous; they quantify the kinetics of physical, chemical, and biological [5–31] processes from the low-copy [32–41] to the "fastest encounter" [42–50] limit, characterize persistence properties [51–57], search processes [58–65], and fluctuations of path observables in stochastic thermodynamics [66–73]. First-passage ideas are tied to the statistics of extremes [74–77], and were extended to quantum systems [78,79], additive functionals [80–85], intermittent targets [86–89], active particles [90–92], non-Markovian dynamics [93–96], and resetting processes [97–106].

Whereas theoretical studies focus on predicting first-passage statistics, practical applications typically aim at inferring kinetic rates—inverse mean first-passage times—from experiments [17,107–111] or simulations [16,112–118]. The inference of *empirical first-passage times* $\bar{\tau}_n \equiv \sum_{i=1}^{n} \tau_i/n$ from data is, however, challenging because usually only a small number of realizations n (typically 1–10 [118–123], sometimes up to 100 [124]) are available, which gives rise to large uncertainties and non-Gaussian errors. Subsampling issues are especially detrimental in the case of broadly distributed [16,125,126] and high-dimensional data [111]. Moreover, first-passage times are generically *not*

exponentially distributed [9,10,38,40,44,45,127–132], which further complicates quantification of uncertainty. A systematic understanding of statistical deviations of the empirical from the true mean first-passage time [see Fig. 1(a)], especially in the small-sample $n \lesssim 100$ regime, remains elusive.

Computer simulations often especially suffer from insufficient sampling, which leads to substantial errors in
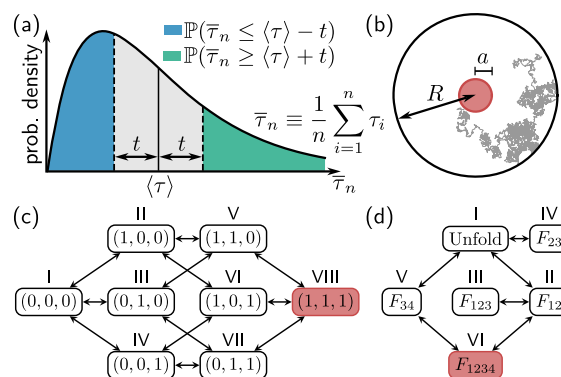

FIG. 1. Deviations of empirical first-passage times from the true mean and model systems. (a) Schematic probability density of empirical first-passage time $\bar{\tau}_n$ inferred from a sample of n realizations of an ergodic reversible Markov process. The tail probability that the estimate $\bar{\tau}_n$ deviates from the true mean $\langle \tau \rangle$ by more or equal than t upwards $\mathbb{P}(\bar{\tau}_n \geq \langle \tau \rangle + t)$ or downwards $\mathbb{P}(\bar{\tau}_n \leq \langle \tau \rangle - t)$ is shown in green and blue, respectively. (b) Brownian molecular search process in a d-dimensional domain (here $d = 2$) with outer radius R and target radius a. Discrete-state Markov jump models of protein folding for (c) a toy protein and (d) experimentally inferred model of calmodulin [129]. Transitions between states obey detailed balance and absorbing targets are colored red.

inferred rates [133–136] and, in the worst case, erroneous conclusions (see discussion in [118,137]). Even extensive computing resources may result in only a few independent estimates spread over many orders of magnitude, rendering uncertainty quantification challenging and *not* amenable to standard error analysis [121].

Constructing *reliable* confidence intervals is a fundamental challenge in statistical inference, and many prevalent methods only hold when $n \to \infty$. The applicability of such asymptotic results in a finite-sample setting is, by definition, problematic. In particular, Central-Limit- and bootstrapping-based methods [138] may easily underestimate the uncertainty for small n and fail to guarantee coverage of the confidence level [121,139–144].

Conversely, Bayesian methods (e.g. [145]), despite not relying on asymptotic arguments, must be treated with care, as estimates and their uncertainties are sensitive to, dependent on, and potentially biased by, the specification of the prior distribution, *especially* in the small-sample setting [120,146] (see Refs. [128,134,147–149] for kinetic inference). Moreover, prior-dependent uncertainty estimates seem to remain, even in the asymptotic limit, an elusive problem (see extended discussion in [150]).

There is thus a pressing need for understanding fluctuations of inferred empirical first-passage times, a rigorous error control, and reliable *nonasymptotic* error estimation in the small-sample regime. These are fundamental unsolved problems of statistical kinetics and are essential for the analysis of experimental and simulation data.

Here, we present general bounds on fluctuations of *empirical first-passage times* that allow a rigorous uncertainty quantification (e.g. using confidence intervals with guaranteed coverage probabilities for all sample sizes) under minimal assumptions. We prove nonasymptotic lower ($\mathcal{L}$) and upper ($\mathcal{U}$) bounds on the deviation probability $\mathbb{P}(\bar{\tau}_n \geq \langle\tau\rangle + t)$ and $\mathbb{P}(\bar{\tau}_n \leq \langle\tau\rangle - t)$ [see Fig. 1(a)], i.e., the probability that the empirical first-passage time inferred from a sample of $n \geq 1$ realizations of an ergodic reversible Markov process, $\bar{\tau}_n$, deviates from the true mean $\langle\tau\rangle$ by more than t in either direction,

$$\mathcal{L}_n^{\pm}(t) \leq \mathbb{P}(\pm[\bar{\tau}_n - \langle\tau\rangle] \geq t) \leq \mathcal{U}_n^{\pm}(t) \quad \forall \; t \geq 0, \quad (1)$$

the upper bounds $\mathcal{U}_n^{\pm}(t)$ corresponding to so-called *concentration inequalities* [187]. The most conservative version of the derived upper bounds is *independent of any details about the underlying dynamics*. We use the bounds $\mathcal{U}_n^{\pm}(t)$ to quantify the uncertainty of the inferred sample mean $\bar{\tau}_n$ *in a general setting and under minimal assumptions*, for all $n \geq 1$. We further derive general lower ($\underline{\mathcal{M}}$) and upper ($\overline{\mathcal{M}}$) bounds on the expected minimum $\tau_n^- = \min_{i \in [1,n]} \tau_i$ and maximum $\tau_n^+ = \max_{i \in [1,n]} \tau_i$ of n realizations, i.e.

$$\underline{\mathcal{M}}_n^{\pm} \leq \langle\tau_n^{\pm} - \langle\tau\rangle\rangle \leq \overline{\mathcal{M}}_n^{\pm} \quad \forall \; n \geq 1, \quad (2)$$

controlling the uncertainty of first-passage times even when multiple timescales are involved, rendering $\langle\tau\rangle$ an *a priori* insufficient statistic. The validity and sharpness of bounds are demonstrated by means of spatially confined Brownian search processes in dimensions 1 and 3 [Fig. 1(b)], and discrete-state Markov jump models of protein folding for a toy protein [45,134,188,189] [Fig. 1(c)] and the experimentally inferred model of calmodulin [129] [Fig. 1(d)]. We conclude with a discussion of the practical implications of the results and further research directions.

Setup.—We consider time-homogeneous Markov processes x_t on a continuous or discrete state-space Ω with generator $\hat{L}$ corresponding to a Markov rate matrix or an effectively one-dimensional Fokker-Planck operator. Let the transition probability density of x_t at x at time t given that it evolved from x_0 be $p_t(x|x_0) \equiv e^{\hat{L}t}\delta_{x_0}(x)$ where $\delta_{x_0}(x)$ denotes the Dirac or Kronecker delta for continuous and discrete state spaces, respectively. We assume the process to be ergodic $\lim_{t\to\infty} p_t(x|x_0) = p_{eq}(x)$, where $p_{eq}(x) \equiv e^{-\varphi(x)}$ denotes the equilibrium probability density and $\varphi(x)$ the generalized potential in units of thermal energy $k_B T$ [190]. We assume that $\hat{L}$ obeys detailed balance [191] and is either (i) bounded, (ii) Ω is finite with reflecting boundary $\partial\Omega$, or (iii) Ω is infinite but $\varphi(x)$ sufficiently confining (see Ref. [192]). Each of the conditions (i)–(iii) ensures that the spectrum of $\hat{L}$ is discrete [193].

We are interested in the first-passage time to a target a when $x_{t=0}$ is drawn from a density $p_0(x)$

$$\tau = \inf_t[t|x_t = a, p_0(x_0)], \quad (3)$$

and focus on the setting $p_0(x) = \tilde{p}_{eq}(x)$, since x_0 usually cannot be controlled experimentally (see e.g., [38,39,61,62,65,134,194,195]), and the tilde denotes that the absorbing state is excluded (see Appendix A for details). For completeness we also provide results for general initial conditions $p_0(x)$ in Appendix B and [150] that require more precise conditions on $\varphi(x)$. The probability density of τ for such processes has the generic form [44,45]

$$\wp_a(t|x_0) = \sum_{k>0} \mu_k w_k^{x_0} e^{-\mu_k t}, \quad (4)$$

with first-passage rates $\mu_k > 0$ and (not necessarily positive) spectral weights $w_k^{x_0}$ normalized according to $\sum_{k>0} w_k^{x_0} = 1$ and $w_1^{x_0} > 0$. The mth moment of τ is given by $\langle\tau^m\rangle = m! \sum_{k>0} w_k^{x_0}/\mu_k^m$ and the *survival probability* reads $\mathbb{P}(\tau > t) \equiv S_a(t|x_0) = \sum_{k>0} w_k^{x_0} e^{-\mu_k t}$. If x_0 is drawn from the equilibrium density, $\tilde{p}_{eq}(x)$, we have $\wp_a(t|\tilde{p}_{eq}) \equiv \int_{\Omega\backslash a} \wp_a(t|x_0)\tilde{p}_{eq}(x_0)dx_0$ [196] which renders all weights
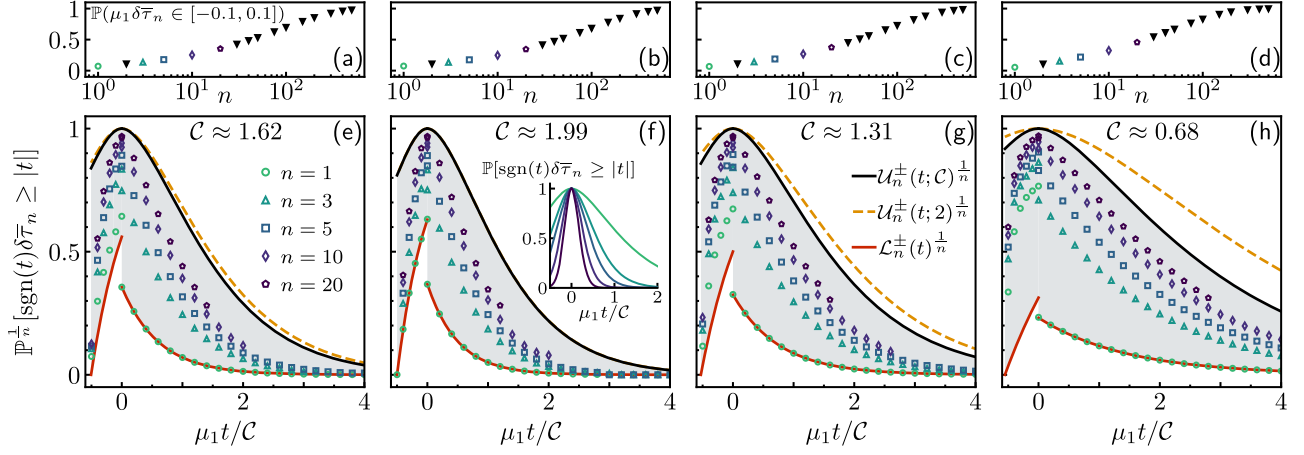
FIG. 2. Deviation probabilities and corresponding bounds for a spatially confined Brownian search process in (a),(e) $d = 1$ and (b),(f) $d = 3$ dimensions, and Markov-jump models of protein folding for (c),(g) the experimentally inferred model of calmodulin and (d),(h) the toy protein. (a)–(d) Probability that $\delta\bar{\tau}_n = \bar{\tau}_n - \langle\tau\rangle$ lies within a range of $\pm 10\%$ of the longest timescale $1/\mu_1$, $\mathbb{P}(\mu_1\delta\bar{\tau}_n \in [-0.1, 0.1])$, as a function of n determined from the statistics of $\bar{\tau}_n$ for different fixed n for all model systems. (e)–(h) Scaled probabilities $\mathbb{P}^{1/n}[\mathrm{sgn}(t)\delta\bar{\tau}_n \geq |t|]$ that the sample mean $\bar{\tau}_n$ inferred from n realizations deviates from $\langle\tau\rangle$ by more than t in either direction. Right tail areas are shown for $t > 0$ and left for $t < 0$, respectively. Lower $\mathcal{L}_n^\pm(t)^{1/n}$ and upper $\mathcal{U}_n^\pm(t;\mathcal{C})^{1/n}$ bounds are depicted as red and black lines, respectively, and the model-free upper bound $\mathcal{U}_n^\pm(t;2)^{1/n}$ as the dashed yellow line. Symbols denote corresponding scaled empirical deviation probabilities as a function of t and are sampled for different n.

non-negative, $w_k \equiv \int_{\Omega\backslash a} w_k^{x_0} \tilde{p}_{\mathrm{eq}} dx_0 \geq 0$ (see proof in [150]). We henceforth abbreviate $S_a(t|\tilde{p}_{\mathrm{eq}}) \equiv S_a(t)$.

To exemplify the need for uncertainty bounds in Eq. (1) we show in Figs. 2(a)–2(d) that the probability that $\bar{\tau}_n - \langle\tau\rangle$ lies within a desired range of say $\pm 10\%$ of the *longest* first-passage time scale μ_1^{-1}, $\mathbb{P}(\mu_1[\bar{\tau}_n - \langle\tau\rangle] \in [-0.1, 0.1])$ is low even for $n \approx 50$ for all models in Figs. 1(b)–1(d). This inherent *intrinsic noise floor* of the inferred observable $\bar{\tau}_n$ for any n is embodied in, and can be explicitly demonstrated by, the existence of lower bounds $\mathcal{L}_n^\pm$ (see Appendix C).

Cramér-Chernoff bounds.—To tackle this issue we now prove upper bounds using the Cramér-Chernoff approach. Let $\delta\bar{\tau}_n \equiv |\bar{\tau}_n - \langle\tau\rangle|$ and $\lambda \in \mathbb{R}^+$. We start with the inequality $e^{\lambda t} \mathbb{1}_{\delta\bar{\tau}_n \geq t} \leq e^{\lambda\delta\bar{\tau}_n}$, where $\mathbb{1}_b$ is the indicator function of the set b. Taking the expectation yields $\mathbb{P}(\delta\bar{\tau}_n \geq t) \leq e^{-\lambda t}\langle e^{\lambda\delta\bar{\tau}_n}\rangle \equiv e^{-\lambda t + \psi_{\delta\bar{\tau}_n}(\lambda)}$, where we defined the cumulant generating function of $\delta\bar{\tau}_n$ as $\psi_{\delta\bar{\tau}_n}(\lambda) \equiv \ln\langle e^{\lambda\delta\bar{\tau}_n}\rangle$. Note that τ_i are statistically independent. The bound can be optimized [197] to find Chernoff's inequality $\mathbb{P}(\delta\bar{\tau}_n \geq t) \leq e^{-n\psi_{\delta\tau}^*(t)}$ where $\psi_{\delta\tau}^*(t)$ is the Cramér transform of $\psi_{\delta\tau}(\lambda)$ [187],

$$\psi_{\delta\tau}^*(t) \equiv \sup_\lambda[\lambda t - \psi_{\delta\tau}(\lambda)], \qquad (5)$$

with $\delta\tau \equiv \delta\bar{\tau}_1$. On the interval $\lambda \in [0, \mu_1)$ we have the following bounds on $\psi_{\delta\tau}(\lambda)$ (see proof in [150]):

$$\psi_{\delta\tau}(\lambda) \leq \phi_{\delta\tau}(\lambda;\mathcal{C}) \equiv \begin{cases} \frac{\lambda^2}{2\mu_1^2}\frac{\mathcal{C}}{1-\lambda/\mu_1} & \tau \geq \langle\tau\rangle \\ \frac{\lambda^2}{2\mu_1^2}\frac{\mathcal{C}}{1-(\lambda/\mu_1)^2} & \tau < \langle\tau\rangle, \end{cases} \qquad (6)$$

which are non-negative, convex, and increasing on $\lambda \in [0, \mu_1)$, and we introduced $\mathcal{C} \equiv \mu_1^2\langle\tau^2\rangle$. Note that general initial conditions $p_0(x_0)$ are accounted for by simply replacing $\langle\tau^2\rangle$ in $\mathcal{C}$ (see Appendix B and [150] for details). The bound (6) further implies $\psi_{\delta\tau}^*(t) \geq \phi_{\delta\tau}^*(t;\mathcal{C})$, $\forall\ t \geq 0$, and may thus be optimized [197] to obtain the inequalities announced in Eq. (1) via Chernoff's inequality:

$$\mathcal{U}_n^+(t;\mathcal{C}) = \exp[-n\mathcal{C}h_+(\mu_1 t/\mathcal{C})] \qquad 0 \leq t \leq \infty,$$
$$\mathcal{U}_n^-(t;\mathcal{C}) = \exp[-n\mathcal{C}h_-(\mu_1 t/\mathcal{C})] \qquad 0 \leq t \leq \langle\tau\rangle, \qquad (7)$$

where we defined the functions

$$h_+(u) \equiv 1 + u - \sqrt{1 + 2u}, \qquad (8)$$

$$h_-(u) \equiv \Lambda(u)u - \frac{1}{2}\frac{\Lambda(u)^2}{1 - \Lambda(u)^2}, \qquad (9)$$

with $\Lambda(u) \equiv \frac{1}{2}\left[g(u) - \sqrt{4 + 2/g(u)u - g(u)^2}\right]$, and

$$g(u) \equiv \frac{2}{\sqrt{3}}\left\{1 + 2\cosh\left[\frac{1}{3}\mathrm{arcosh}\left(1 + \frac{3^3}{2^7 u^2}\right)\right]\right\}^{1/2}. \qquad (10)$$

These results control the deviations of the inferred $\bar{\tau}_n$ from $\langle\tau\rangle$ for all n. Note that in general whenever $\mu_1\langle\tau\rangle \not\approx 1$ (e.g. in "compact" search processes [38,39]), $\langle\tau\rangle$ is not necessarily representative due to the multiple relevant timescales [63–65]. However, as we show below, $\langle\tau\rangle$ sharply bounds extreme first-passage times. Thus, inferring $\bar{\tau}_n$ provides

insight about first-passage statistics even when $\langle \tau \rangle$ is *a priori* not a sufficient statistic.

Concerning practical applications, deviations are readily expressed relative to the *longest natural* timescale $1/\mu_1$ that does *not* need to be known. That is, errors in units of $1/\mu_1$, $\mu_1(\bar{\tau}_n - \langle \tau \rangle)$, are naturally parametrized by the *dimensionless* variable $\mu_1 t$. Remarkably, details about the underlying dynamics then only enter the bounds (7) via a system-dependent constant $\mathcal{C}$ that, however, can be bounded. In particular, for equilibrium initial conditions we have $0 \leq 2w_1 \leq \mathcal{C} \leq 2$ (see Ref. [150]). Since $\phi_{\delta\tau}$ is monotonically increasing with $\mathcal{C} \in (0,2]$, we have $\phi_{\delta\tau}(\lambda;\mathcal{C}) \leq \phi_{\delta\tau}(\lambda;2)$ which implies $\phi^*_{\delta\tau}(t;\mathcal{C}) \geq \phi^*_{\delta\tau}(t;2)$. Thus, we find the *model-free* bounds by setting $\mathcal{C} \equiv 2$,

$$\mathcal{U}^{\pm}_n(t;\mathcal{C}) \leq \mathcal{U}^{\pm}_n(t;2) \equiv \mathcal{U}^{\pm}_n(t), \qquad (11)$$

requiring no information about the system. The *nonasymptotic* bounds on deviation probabilities of $\bar{\tau}_n$ in Eqs. (7) and (11) are our first main result. Their most general and conservative version states that for all sample-sizes n, the probability of observing a relative error larger than a specified value $\mu_1 t$ (e.g., $\mu_1 t = 0.1$ or 10%), $\mathbb{P}(\mu_1[\bar{\tau}_n - \langle \tau \rangle] \geq \mu_1 t)$, is lower than the corresponding upper bound $\mathcal{U}^{\pm}_n(\mu_1 t)$, which solely depends on $\mu_1 t$.

Lastly, as $n \to \infty$, $\mathcal{U}^{\pm}_n$ is substantial only for $\mu_1 t/\mathcal{C} \ll 1$ and the tails become symmetric and sub-Gaussian [187], $h_+(u) = u^2/2 - \mathcal{O}(u^3)$ and $h_-(u) = u^2/2 - \mathcal{O}(u^4)$ (see Ref. [150]). Notably, concentration inequalities were recently derived for time averages of "classical" [198–200] (see Ref. [201]), and quantum [202] Markov processes, as well as inverse thermodynamic uncertainty relations [203].

Illustration of deviation bounds.—The upper $\mathcal{U}^{\pm}_n(t)$ and lower $\mathcal{L}^{\pm}_n(t)$ bounds on $\mathbb{P}(\pm[\bar{\tau}_n - \langle \tau \rangle] \geq t)$ in Eqs. (7) and (C1), respectively, are exemplified in Figs. 2(e)–2(h) (see black and red lines) for the model systems shown in Figs. 1(b)–1(d). Note that to illustrate all bounds we formally let $t \to -t$ for the left tails $\mathcal{L}^-_n(t)$ and $\mathcal{U}^-_n(t)$, such that their support is on $[-\langle \tau \rangle, \infty)$. Deviation probabilities are in turn expressed as $\mathbb{P}(\text{sgn}(t)\delta\bar{\tau}_n \geq |t|)$ where $\text{sgn}(x)$ denotes the signum function and $\delta\bar{\tau}_n = \bar{\tau}_n - \langle \tau \rangle$.

To assess the quality of our bounds we scale probabilities $\mathbb{P}^{1/n}$ such that $\mathcal{L}^{\pm}_n(t)^{1/n}$ and $\mathcal{U}^{\pm}_n(t)^{1/n}$ collapse onto a master curve for all n [see inset Fig. 2(f)]. Symbols denote empirical deviation probabilities obtained by sampling $\bar{\tau}_n$ for different n (see Ref. [150] for details), which approach the upper bound as n increases. For $n = 1$ right-tail deviations are close to $\mathcal{L}^+_1(t)$ even for $w_1 \leq 1$ [204]. As expected the model-free bound $\mathcal{U}^{\pm}_n(t;2)$ (yellow) holds universally but is generally more conservative. Notably, it remains remarkably good even for $\mathcal{C} \gtrsim 1.3$ [Figs. 2(e)–2(g)].

Uncertainty quantification.—The bounds (7) and (11) provide the elusive systematic framework to *rigorously quantify the uncertainty* of the estimate $\bar{\tau}_n$ for any, and

especially for small, sample sizes. In particular, they allow the construction of "with high probability" guarantees such as confidence intervals, which—unlike traditional confidence intervals in statistics—are *not only* asymptotically correct but hold for any n. Concentration-based guarantees do further *not* require specifying a prior belief as in the Bayesian context. Setting $\mathcal{U}^{\pm}_n(t^{\pm}_{\alpha_{\pm}};\mathcal{C}) = \alpha_{\pm}$ for chosen acceptable left- and right-tail error probabilities $\alpha_{\pm}$ (with $\alpha_+ + \alpha_- < 1$), we get an implicit definition of the confidence interval $[-t^-_{\alpha_-}, t^+_{\alpha_+}]$ at confidence level (or "coverage probability") $1 - (\alpha_- + \alpha_+)$ in the form

$$\mathbb{P}(-t^-_{\alpha_-} \leq \delta\bar{\tau}_n \leq t^+_{\alpha_+}) \geq 1 - \alpha_- - \alpha_+ \equiv 1 - \alpha, \qquad (12)$$

stating that with probability of *at least* $1 - \alpha$ the sample mean $\bar{\tau}_n$ lies within $[\langle \tau \rangle - t^-_{\alpha_-}, \langle \tau \rangle + t^+_{\alpha_+}]$. Confidence intervals are closely related to, and can be used for, statistical significance tests [205,206], and beyond that provide quantitative bounds on statistical uncertainty. Two-sided central confidence intervals for $\delta\bar{\tau}_n$ as a function of n for a confidence level of $\alpha = 0.1$ and models systems in Figs. 1(b)–1(d) are shown (rescaled to a master scaling) in Fig. 3(a) (for a detailed discussion see Ref. [150]).

In particular, we may now also answer the practical question: How many realizations are required to achieve a desired accuracy with a specified probability? To ensure with probability of at least $1 - \alpha$ that $\delta\bar{\tau}_{n^*} \in [-t^-_{\alpha_-}, t^+_{\alpha_+}]$ one needs a minimal sample size n^* defined via

$$\mathcal{U}^+_{n^*}(t^+_{\alpha_+};\mathcal{C}) + \mathcal{U}^-_{n^*}(t^-_{\alpha_-};\mathcal{C}) = \alpha. \qquad (13)$$

The number of samples n^* required to *guarantee* that $\bar{\tau}_{n^*}$ falls within a symmetric interval of length $\Delta t = 0.2/\mu_1$, (i.e. $\bar{\tau}_{n^*} \in [\langle \tau \rangle - 0.1/\mu_1, \langle \tau \rangle + 0.1/\mu_1]$) with probability of *at least* $1 - \alpha$ is shown in Fig. 3(b) for several values of $\mathcal{C}$ (intersections with the dashed line yield n^* guaranteeing a coverage of *at least* 90%). Figure 3(c) depicts the complementary symmetric interval Δt covering the range of $\delta\bar{\tau}_n$ for a given n with probability of *at least* 90%. Note that hundreds to thousands of samples may be required to ensure an accuracy of $\pm 0.1/\mu_1$ with a 90% confidence, which is seemingly not met in experiments [118–124].

Equations (12) and (13) can be solved for $t^{\pm}_{\alpha_{\pm}}$ and n^*, respectively, using standard root-finding methods (see Ref. [150]) and constitute our second main result. They allow for rigorous error control in kinetic inference in the small-n regime. Using Eq. (11) we can further construct system-independent but more conservative *universal confidence intervals* [see yellow line in Figs. 3(b) and 3(c)]. Interestingly, even when $\mathcal{C} \approx 1$ the universal bound remains reasonably tight, only for $\mathcal{C} \ll 1$ differences become substantial.

Bounding extreme deviations.—Finally, we show that $\langle \tau \rangle$ controls the range of inferred τ_i in any sample of n independent realizations, i.e., it *sharply* bounds the average
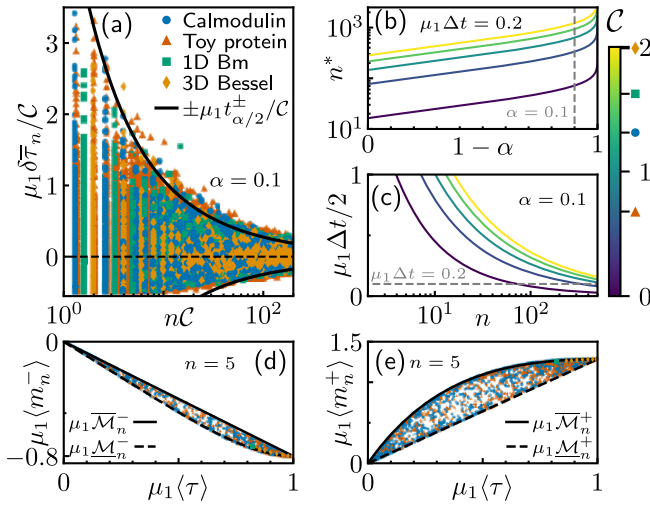
FIG. 3. Nonasymptotic uncertainty quantification of the sample mean $\bar{\tau}_n$ and extreme deviations from $\langle\tau\rangle$. (a) Relative error $\mu_1\delta\bar{\tau}_n = \mu_1(\bar{\tau}_n - \langle\tau\rangle)$ (symbols) obtained from sampling of $\bar{\tau}_n$ for different n and model systems. The central confidence interval $[-\mu_1 t_{\alpha/2}^-, \mu_1 t_{\alpha/2}^+]$ with $\alpha = 0.1$ in black. (b) Number of samples n^* to ensure that the error $\mu_1\delta\bar{\tau}_{n^*}$ falls in the interval $[-0.1, 0.1]$ of length $\Delta t = 0.2/\mu_1$ with probability of at least $1 - \alpha$ for several values of $\mathcal{C}$. (c) Symmetric confidence interval $[-\mu_1\Delta t/2, \mu_1\Delta t/2]$ (upper limit shown) for $\alpha = 0.1$ as a function of n for different $\mathcal{C}$. Average extreme deviation from the mean $\langle m_n^\pm\rangle \equiv \langle\tau_n^\pm - \langle\tau\rangle\rangle$ (symbols) and bounds (lines) for the minimum (d) and maximum (e) of $n = 5$ realizations for different models and values of $\mu_1\langle\tau\rangle$.

minimum τ_n^- and maximum τ_n^+ deviations from the mean $m_n^\pm \equiv \tau_n^\pm - \langle\tau\rangle$. As our third main results we prove (see sketch of proof and saturation conditions in Appendix D and [150] for details) two-sided bounds $\underline{\mathcal{M}}_n^\pm \leq \langle m_n^\pm\rangle \leq \overline{\mathcal{M}}_n^\pm$, where

$$\underline{\mathcal{M}}_n^+ \equiv \langle\tau\rangle\sum_{k=2}^{n}\frac{1}{k}, \quad \overline{\mathcal{M}}_n^+ \equiv \sum_{k=1}^{n}\binom{n}{k}(-1)^{k+1}\frac{(\mu_1\langle\tau\rangle)^k}{\mu_1 k} - \langle\tau\rangle,$$

$$\underline{\mathcal{M}}_n^- \equiv \langle\tau\rangle[n^{-1}(\mu_1\langle\tau\rangle)^{n-1} - 1], \quad \overline{\mathcal{M}}_n^- \equiv \langle\tau\rangle[n^{-1} - 1].$$

$$(14)$$

Remarkably, the tight bounds on $\mu_1\langle m_n^\pm\rangle$ are completely specified by the dimensionless parameter $\mu_1\langle\tau\rangle$. This motivates the inference of $\bar{\tau}_n$ in a general setting, even when $\langle\tau\rangle$ is a priori not representative, since via the bounds (14) [shown in Figs. 3(d) and 3(e)] $\langle\tau\rangle$ controls the range of estimates. The bounds (14) provide insight about the slowest and fastest out of n first-passage times, and are thus relevant in the "few encounter" limit [44,46,47,207].

Conclusion.—Leveraging spectral analysis and the framework of concentration inequalities we derived general upper and lower bounds on the probability that the empirical first-passage time $\bar{\tau}_n$ inferred from n independent realizations deviates from the true mean $\langle\tau\rangle$ by any given

amount. Using these bounds we constructed nonasymptotic confidence intervals that hold in the elusive small-sample regime and thus go beyond Central-Limit- and bootstrapping-based methods which fail for small n. The results require minimal input and in particular do not require any prior belief as in the Bayesian approach that is known to be problematic and likely underestimates the uncertainty in subsampling settings. Our concentration-based results and bounds on extreme deviations allow for rigorous, model-free error control and reliable error estimation, which is essential for the analysis of experimental and simulation data. They may further be extended to nonergodic and irreversible dynamics.

Appendix A: Equilibrium initial conditions.—We mainly consider that the initial value x_0 of the first-passage process is drawn from a "quasistationary" equilibrium density $\tilde{p}_{\text{eq}}(x)$. However, compared to standard relaxation processes with "true" stationary density $p_{\text{eq}}(x)$, an appropriate definition of $\tilde{p}_{\text{eq}}(x)$ for absorption (i.e., first-passage) processes is more subtle as the absorbing target a has to be accounted for. In discrete state-space we have $\tilde{p}_{\text{eq}}(x_{k\neq a}) \equiv p_{\text{eq}}(x_k)/\sum_{k\neq a}p_{\text{eq}}(x_k)$, i.e., the quasistationary density $\tilde{p}_{\text{eq}}(x)$ is obtained via renormalization of $p_{\text{eq}}(x)$ by excluding the target a. On the contrary, in the continuous state-space setting, the absorbing state a has nominally zero measure such that trivially $\tilde{p}_{\text{eq}}(x) = p_{\text{eq}}(x)$ remains unchanged.

Appendix B: Arbitrary initial conditions.—Unless the state-space Ω is both discrete and finite, an extension to arbitrary initial conditions, where x_0 is drawn from a general density $p_0(x)$, requires some additional assumptions about the generalized potential $\varphi(x)$. In particular, when $p_0(x) \neq \tilde{p}_{\text{eq}}(x)$, $\varphi(x)$ must be sufficiently confining to ensure a "nice" asymptotic growth of eigenvalues ν_k of $\hat{L}$ of the relaxation dynamics [193], i.e., $\lim_{k\to\infty}\nu_k = bk^\beta$ with $\beta > 1/2$ and $0 < b < \infty$. The latter condition is automatically satisfied when Ω is finite, since regular Sturm-Liouville problems display Weyl asymptotics with $\beta = 2$ [208]. The condition is in fact satisfied by most physically relevant processes with discrete spectra, including the (Sturm-Liouville irregular) Ornstein-Uhlenbeck or Rayleigh process [209] with $\beta = 1$.

Manifestations of general initial conditions $p_0(x_0) \neq \tilde{p}_{\text{eq}}(x_0)$ are then fully accounted for by simply replacing $\langle\tau^2\rangle$ with $2\sum_i w_i \mathbb{1}_{w_i>0}/\mu_i^2 < \infty$ in the presented results, i.e., $\mathcal{C} \to 2\sum_i w_i \mathbb{1}_{w_i>0}(\mu_1/\mu_i)^2$. Additional details, such as

a proof of convergence of the sum $\sum_i w_i \mathbb{1}_{w_i > 0}/\mu_i^2$, are given in [150].

Appendix C: Lower bounds on deviation probabilities.—There exists a "noise floor" in the estimate $\bar{\tau}_n$ for any n. Since $\mu_k \leq \mu_{k+1}$ and the weights are non-negative $w_k \geq 0$ [150] and normalized [44,45], the survival probability obeys the bound $w_1 e^{-\mu_1 t} \leq S_a(t) \leq e^{-\mu_1 t}$. Using that $\bar{\tau}_n \geq \tau_n^-$ and $\bar{\tau}_n \leq \tau_n^+$ it follows immediately that $\mathbb{P}(\tau_n^- \geq t) \leq \mathbb{P}(\bar{\tau}_n \geq t) \leq \mathbb{P}(\tau_n^+ \geq t)$. Furthermore, we have $\mathbb{P}(\tau_n^- \geq t) = S_a(t)^n$ as well as $\mathbb{P}(\tau_n^+ \leq t) = (1 - S_a(t))^n$ such that we arrive at the lower bounds

$$\mathbb{P}(\bar{\tau}_n - \langle \tau \rangle \geq t) \geq \left(w_1 e^{-\mu_1(\langle \tau \rangle + t)}\right)^n \equiv \mathcal{L}_n^+(t),$$

$$\mathbb{P}(\bar{\tau}_n - \langle \tau \rangle \leq -t) \geq \left(1 - e^{-\mu_1(\langle \tau \rangle - t)}\right)^n \equiv \mathcal{L}_n^-(t). \quad \text{(C1)}$$

We remark that analogous results are also obtained for upper bounds (see Ref. [150]) which, however, are weaker than those derived above in Eqs. (7) and (11) with the Cramér-Chernoff approach and concurrently require more information about the dynamics.

Appendix D: Sketch of proof of extreme-deviation bounds and their saturation.—In essence, the proofs of "squeeze" bounds $\underline{\mathcal{M}}_n^\pm \leq \langle m_n^\pm \rangle \leq \overline{\mathcal{M}}_n^\pm$ rely on bounding the average value of the minimum $\tau_n^- \equiv \min_{i \in [1,n]} \tau_i$ or maximum $\tau_n^+ \equiv \max_{i \in [1,n]} \tau_i$ out of n first-passage times. As a first step recall that τ_i's are independent identically distributed, such that we may write $\langle \tau_n^\pm \rangle = \int_0^\infty \mathbb{P}(\tau_n^\pm > t) dt$ solely in terms of the survival probability $S_a(t)$, that is,

$$\langle \tau_n^+ \rangle = \int_0^\infty \{1 - [1 - S_a(t)]^n\} dt,$$

$$\langle \tau_n^- \rangle = \int_0^\infty S_a(t)^n dt. \quad \text{(D1)}$$

This enables us to fully exploit the mathematical structure of the spectral decomposition of $S_a(t)$, allowing us to ultimately arrive at Eq. (14) by bounding the respective integrands in Eq. (D1).

To briefly outline the key ideas, bounds $\underline{\mathcal{M}}_n^-$ and $\overline{\mathcal{M}}_n^+$ follow by recognizing [since $\wp_a(t|\tilde{p}_{eq})$ is monotonic in t] that $\langle \tau_n^+ \rangle$ is maximal and $\langle \tau_n^- \rangle$ is minimal, respectively, whenever the contribution w_1/μ_1 of the longest first-passage timescale is maximal. For any fixed value of $\mu_1 \langle \tau \rangle \in (0, 1]$, this condition is generally met in the presence of a spectral gap $\mu_1/\mu_k \to 0$, $\forall\, k > 1$, for which one may utilize in Eq. (D1) the ansatz

$$S_a(t) = \lim_{\varepsilon \to 0} (1 - \mu_1 \langle \tau \rangle) e^{-t/\varepsilon} + \mu_1 \langle \tau \rangle e^{-\mu_1 t}. \quad \text{(D2)}$$

The announced bounds are consequently obtained after some straightforward calculations and become saturated (i.e. the inequality becomes an equality) in systems with the above stated spectral gap [150].

The main idea behind proving the bound $\underline{\mathcal{M}}_n^+$ relies on the inequality $S_a(t) \geq w_{k_+} e^{-\mu_{k_+} t}$, where $k_+ \equiv \operatorname{argmin}_k w_k > 0$ denotes the smallest k for which the corresponding weight w_k is strictly positive. Saturation occurs when $w_{k_+} \to 1$.

The remaining bound $\overline{\mathcal{M}}_n^-$ follows directly from upper bounding the convex function x^n, $\forall\, n \geq 1$, $x \geq 0$, by means of Jensen's inequality and is saturated when $w_k \to 1$ for some k and for degenerate systems with identical first-passage eigenvalues $\mu_i = \mu$, $\forall\, i$ for some $\mu > 0$.

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*agodec@mpinat.mpg.de

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