Letter

Inference from gated first-passage times

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First-passage times provide invaluable insight into fundamental properties of stochastic processes. Yet, various forms of *gating* mask first-passage times and differentiate them from actual *detection times*. For instance, imperfect conditions may intermittently gate our ability to observe a system of interest, such that exact first-passage instances might be missed. In other cases, e.g., certain chemical reactions, direct observation of the molecules involved is virtually impossible, but the reaction event itself can be detected. However, this instance need not coincide with the first collision time since some molecular encounters are infertile and hence, gated. Motivated by the challenge posed by such real-life situations we develop a universal—model free—framework for the inference of first-passage times from the detection times of gated first-passage processes. In addition, when the underlying laws of motions are known, our framework also provides a way to infer physically meaningful parameters, e.g., diffusion coefficients. Finally, we show how to infer the gating rates themselves via the hitherto overlooked short-time regime of the measured detection times. The robustness of our approach and its insensitivity to underlying details are illustrated in several settings of physical relevance.

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Introduction. The importance of first-passage processes is recognized universally across scientific disciplines, owing to their ubiquity and wide-ranging applications [1–7]. How long does it take for a chemical reaction to be triggered? Or what is the time taken for an order to be executed in the stock market? These disparate examples fall under the purview of first-passage processes, where the first-passage time is now established as an indispensable tool to quantify the time taken for a given task to be completed.

In several practically relevant scenarios, however, the completion of a task also relies on additional constraints. For example, for a chemical reaction to be triggered, two reactants must collide. Additionally, the collision must be fertile, i.e., the reactants must be in a reactive internal state during collision. This internal state acts like a "gate": a reaction can only happen when the gate is "open," i.e., the molecules are in their reactive internal state. The macroscopic kinetics of these so called gated reactions has a history spanning over four decades now [8–20], and more recently, the study of single-particle gated reactions has gained interest [21–31].

While the terminology of "gating" is unique to reaction kinetics, numerous examples fall under the wide umbrella of gated processes. An important one is that of intermittently observed stochastic time series, where the underlying cause for intermittent observations can include energy costs of continuous observations, imperfect detection conditions, or simply a faulty sensor [32–36]. Irrespective of the reasons behind such intermittent observations, an important consequence is that key features of the time series can be missed. In particular, in the increasingly relevant field of extreme and record statistics of time series, a crucial quantity is the time taken to cross a specific threshold for the first time. However, intermittent detection of the time series can lead to a gross mischaracterization of the statistics of such events [37–41]. In such cases, the relevant quantity is the *first detection time*, which denotes the first time the time series is *observed* above the threshold [39].

Figure 1 exemplifies two instances where gating arises naturally: (a) Single particle tracking of an intermittently observed particle, which transitions between a visible state and an invisible state. For example, a wide class of fluorophores undergo photoblinking [42–51]. Other reasons for such gating can be the intermittent loss of focus on a moving particle in three dimensions [52] or slow frame acquisition rate [53]; (b) A gated chemical reaction or target search, where tracking of the particle is not possible, and the reaction time is the only measurable quantity. Such instances may arise in cellular signaling driven by narrow escape [54,55] and among fluorescent probes [56].

In both examples illustrated in Fig. 1, the first-passage time statistics carry invaluable information, but are inaccessible to direct measurement. In such scenarios, a crucial challenge is to reliably infer these statistics and other fundamental properties of interest.

In this Letter, we address this challenge and solve it. First, we show how the first-passage time density can be inferred

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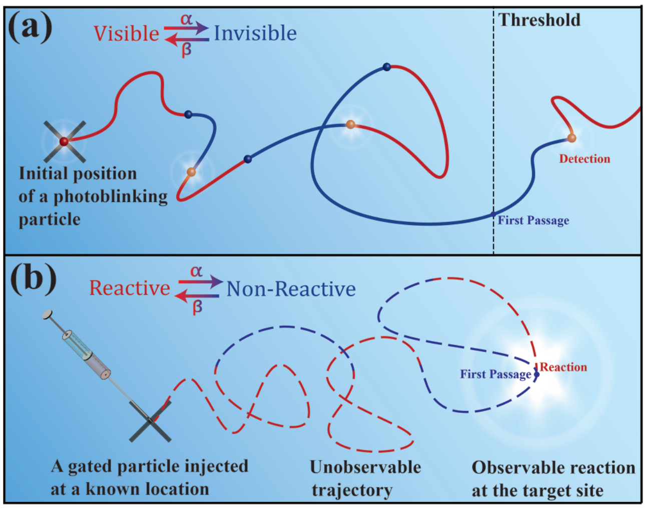

FIG. 1. Instances highlighting the need for inference in gated first-passage processes. (a) Detection of threshold crossing under intermittent sensing. Consider single particle tracking of a photoblinking particle. The first-passage properties of the particle can be mischaracterized as the particle can cross the threshold while being in its invisible state. (b) Gated chemical reaction or target search. Imagine a situation where tracking of the particle is not possible, and the only observable is the reaction time. In such settings, the important task is to infer the first-passage time distribution, and other observables of interest, from the observed detection/reaction times. In this Letter, we present a general framework that addresses this challenge and solves it.

from gated observations via a model-free formalism, which upon specification of the underlying laws of motions can be further used to infer physically meaningful parameters (e.g., the diffusion coefficient). Second, using the joint knowledge of the gated (observed) and ungated (inferred) first-passage time densities, we establish that the overlooked short-time regime of the gated detection time distribution can be leveraged to obtain the gating rates.

Modeling gated processes. We start by modeling a gated process consisting of two independent components. First, an underlying process $X_{n_0}(t)$, initially at n_0, modeled as a continuous-time Markov process. Second, a gate modeled by a two-state continuous-time Markov process, that intermittently switches between an "open" active (A) state and a "closed" inactive (I) state. This gate accounts for the additional constraint that needs to be satisfied for the task of interest to be completed. The gate switches from state A to I at rate α, and from I to A at β. For $\sigma_0, \sigma \in \{A, I\}$, we define $p_t(\sigma|\sigma_0)$ to be the probability that the gate is in state σ at time t, given that it was in state σ_0 initially (see the SM for an explicit formula [57]). Also, let $\pi_A = \beta/\lambda$ and $\pi_I = \alpha/\lambda$ denote the equilibrium occupancy probabilities of states A and I, respectively, where $\lambda = \alpha + \beta$ is the relaxation rate to equilibrium.

The central quantity of interest in our Letter is the first-passage time $T_f(m|n_0)$, which is the time taken for $X_{n_0}(t)$ to reach state m for the first time, and we denote its probability density by $F_t(m|n_0)$. In many scenarios the first-passage time is not directly measurable, and instead we can only measure the detection time $T_d(n_0, \sigma_0)$, of a reaction or threshold crossing event. We denote by $D_t(n_0, \sigma_0)$ the probability density of $T_d(n_0, \sigma_0)$, which is the first time the underlying process is detected in some target-set $\mathcal{Q}$, given that the initial state of the composite process (underlying + gate) is initially at $\{n_0, \sigma_0\}$.

In this work, we focus on two widely applicable settings: (i) the detection of threshold crossing events of a one-dimensional intermittent time series with nearest-neighbor transitions, where $\mathcal{Q}$ denotes all states above a certain threshold m, and $T_d(n_0, \sigma_0)$ is the first time when $X_{n_0}(t) \geqslant m$ while the detector is active (A); and (ii) gated reactions or target search on an arbitrary network in discrete space or in arbitrary dimension in continuous space. Here, $\mathcal{Q}$ is typically a single target state/point m, and $T_d(n_0, \sigma_0)$ denotes the first time the underlying process $X_{n_0}(t)$ is at m, while the gate is open (A).

First-passage times from gated observations. We begin our analysis by noting that for $n_0 \notin \mathcal{Q}$ we have

$$D_t(n_0, \sigma_0) = F_t(m|n_0)p_t(A|\sigma_0) + \int_0^t F_{t'}(m|n_0)p_{t'}(I|\sigma_0)D_{t-t'}(m, I)\,dt', \quad (1)$$

where the probability for a detection event occurring at time t has two contributions: (i) the detection time coinciding with the first-passage time; and (ii) the gate being closed during the first-passage event (I), and detection happening strictly after this moment in time. The Laplace transform of Eq. (1), can be expressed in compact form as [57]

$$\widetilde{D}_s(n_0, \sigma_0) = [\pi_A + \pi_I \widetilde{D}_s(m, I)]\widetilde{F}_s(m|n_0) + \mathbb{1}(\sigma_0)(1 - \pi_{\sigma_0})[1 - \widetilde{D}_s(m, I)]\widetilde{F}_{s+\lambda}(m|n_0), \quad (2)$$

where $\lambda = \alpha + \beta$, and $\mathbb{1}(\sigma_0)$ takes values $+1$ or -1 when $\sigma_0 = A$ or I, respectively. By explicitly writing down the equations for $\sigma_0 = A$ and I, and further eliminating $\widetilde{F}_{s+\lambda}(m|n_0)$ from the equations, we arrive at [57]

$$\widetilde{F}_s(m|n_0) = \frac{\pi_A \widetilde{D}_s(n_0, A) + \pi_I \widetilde{D}_s(n_0, I)}{\pi_A + \pi_I \widetilde{D}_s(m, I)}, \quad (3)$$

which is our first result. Equation (3) asserts that the first-passage density can be obtained exactly in terms of detection time densities and the gating rates. In [57], we further show that Eq. (3) holds even when the underlying process in not Markovian, and instead is a renewal process. Yet, inference of the first-passage time density $F_t(m|n_0)$ using Eq. (3) requires the detection statistics with initial conditions $\{n_0, A\}$, $\{n_0, I\}$, and $\{m, I\}$, and the equilibrium probabilities π_A and π_I. Such information may not be accessible in experimentally realizable scenarios where, e.g., it may not be possible to initialize a gated molecule in a specific internal state $\sigma_0 = A$ or I, and the values of π_A and π_I may also be unknown.

In such situations, the most practically realizable initial condition is the equilibrium $\sigma_0 \equiv E$, where the gate is in the active state A with probability π_A, and in the inactive state I with probability π_I. Note that this initial condition is naturally achieved if the system is simply allowed to equilibrate. Interestingly, the detection time density starting from the initial condition (n_0, E) is given by $D_t(n_0, E) = \pi_A \cdot D_t(n_0, A) + \pi_I \cdot D_t(n_0, I)$, whose Laplace transform is the numerator standing on the right-hand side of Eq. (3). Further noting that the Laplace transform of $D_t(m, E) = \pi_A \cdot \delta(t) + \pi_I \cdot D_t(m, I)$ gives the denominator on the right-hand side, we obtain an elegant reinterpretation of Eq. (3):

$$\widetilde{F}_s(m|n_0) = \frac{\widetilde{D}_s(n_0, E)}{\widetilde{D}_s(m, E)}. \tag{4}$$

Strikingly, Eq. (4) asserts that the first-passage time density can be inferred from the detection statistics, even without the explicit knowledge of π_A and π_I, or control over the initial state of the gate.

The usefulness and validity of Eq. (4) is demonstrated in Fig. 2, with the help of three case studies of wide interest and applicability. First, a Markovian birth-death process which has been extensively used to model threshold activated reactions [58–61] and the dynamics of chemical reactions on catalysts [62,63]. Second, the paradigmatic continuous-space diffusion in a 1D confinement. Third, a gated chemical reaction/target search modeled by a non-Markovian continuous-time random walk (CTRW) [64,65] on a network [66], which is, e.g., used to model the motion of reactants, cells, or organisms in complex environments [30,66–72]. In all of these settings, we show that the first-passage time distributions inferred from Eq. (4) using a procedure described in [57] (circles) are in excellent agreement with the true first-passage time distributions. We stress that this inference was performed solely using detection time histograms obtained from gated simulations of 10^6 detection events, without assuming knowledge of the analytical expressions of their probability densities or model specific details (e.g., the network structure and the waiting time distribution in the CTRW example). We note that numerical errors start to appear in the tail region when estimating very small probabilities [57]. These errors can potentially be addressed through parametric inference methods which use domain-specific knowledge (e.g., exponential tail of first-passage time distributions in confined systems) to perform the inference. Moreover, when analytical expressions are available, like in the case of the birth-death process [39], one can directly perform the inference through Laplace inversion of Eq. (4) [57].

Before moving forward, we note that Eq. (4) is reminiscent of the seminal renewal formula $\widetilde{F}_s(m|n_0) = \frac{\widetilde{P}_s(m|n_0)}{\widetilde{P}_s(m|m)}$ which relates, in Laplace space, the first-passage time density and the probability density $P_t(n_i|n_j)$ of finding the underlying process in state n_i at time t, given its initial state n_j [1]. Clearly, the right-hand side of this formula and that of Eq. (4) are equal. In fact, we can obtain an even more general relation—considering two different initial states n_0 and n_0', and after some algebra, we uncover the fundamental relation [57]

$$\frac{\widetilde{D}_s(n_0, E)}{\widetilde{D}_s(n_0', E)} = \frac{\widetilde{P}_s(m|n_0)}{\widetilde{P}_s(m|n_0')}, \tag{5}$$

asserting that the ratio of the detection time densities (in Laplace space), starting from any two initial states n_0 and n_0', is independent of the gating rates α and β. Note that this is true despite the fact that the detection time densities themselves depend on the gating rates. We remark that Eq. (5) holds in both settings: when $D_t(n_0, E)$ corresponds to gated target

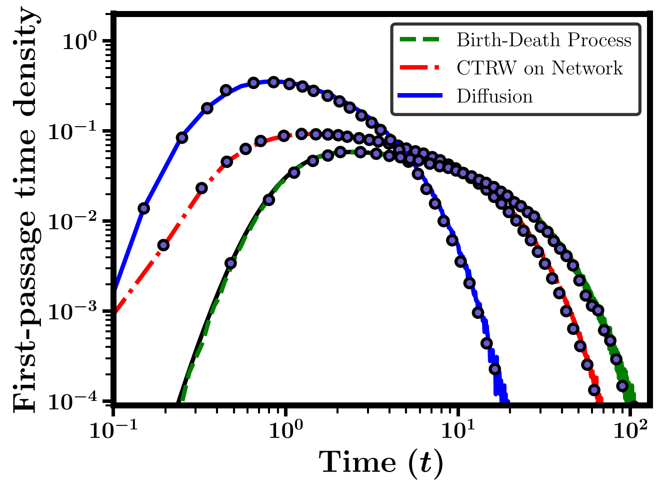

FIG. 2. Inference of first-passage time distributions from gated observations. We plot the first-passage time distributions of a Markovian birth-death process (green), CTRW on a network (red), and a continuous space diffusion (blue) using numerical simulations. Details of the models and their parameters are given in Ref. [57]. Circles denote the values of the first-passage time distributions inferred using Eq. (4) from histograms of 10^6 simulated gated detection times. The inferred distributions are in excellent agreement with first-passage time distributions that are computed directly by simulation. In addition, the analytical first-passage time distribution (solid black line) is also plotted for the birth-death process to show the overall consistency of our results.

search and to the detection of threshold crossing events under intermittent sensing.

Inferring the mean first-passage time. The Laplace transform in Eq. (4) allows us to obtain all moments of the first-passage time in terms of moments of the detection time. Equation (4) further implies that all cumulants of the first-passage time can be expressed as differences between cumulants of detection times. For example, the mean first-passage time is given by

$$\langle T_f(m|n_0)\rangle = \langle T_d(n_0, E)\rangle - \langle T_d(m, E)\rangle. \tag{6}$$

While simple, Eq. (6) carries utmost importance in practical scenarios, where reliably estimating the full probability distribution is not a viable option, and only the mean can be accurately measured. Apart from setting an important time scale for a wide class of chemical reactions in confinement, where the mean reaction time can be used to infer full reaction time statistics [73], the mean first-passage time can also shed light on fundamental properties of the system at hand [74,75].

Inferring the diffusion coefficient. We now illustrate how one can utilize our framework to infer physically meaningful parameters like the diffusion coefficient $\mathcal{D}$. Importantly, we show that this can be done even when the actual motion of the particle cannot be tracked. Imagine a scenario like that depicted in Fig. 1(b), namely we inject an unobservable particle—whose detection is possible only upon reaction—at a known location x_0. Assume that the internal state of the particle is initially equilibrated ($\sigma_0 = E$), and further assume that it is freely diffusing inside an effectively one-dimensional box $[0, L]$ with reflecting boundaries and a gated target located at

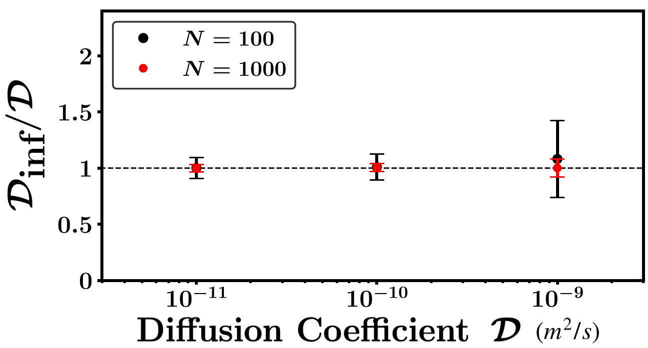

FIG. 3. Inference of the diffusion coefficient. Equation (7) is used to infer the diffusion coefficient of an unobservable particle that is injected at a known location $x_0 = 0$ into a box [0, 5μm] with reflecting boundaries. The initial internal state is equilibrated $\sigma_0 = E$, and a gated point target is located at $m = 4$ μm, with gating rates $\alpha = \beta = 10^2$ s^{-1}.

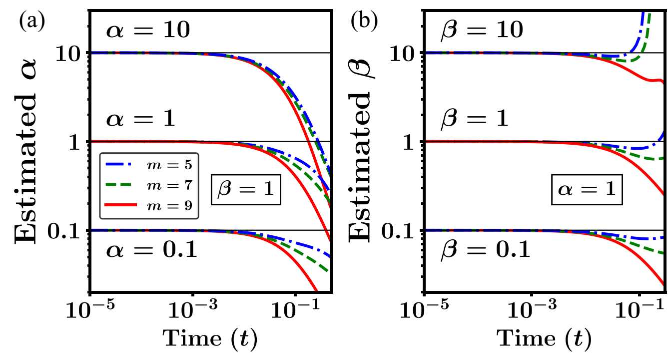

FIG. 4. Inference of the gating rates α [panel (a)] and β [panel (b)] from the short-time asymptotics of Eqs. (8) and (9), respectively. Results are for the birth-death model used in Fig. 2, and various values of α and β. Details of the model and parameter values are given in [57].

$x_0 < m < L$. Utilizing Eq. (6) we find that [57]

$$\mathcal{D} = \frac{1}{2}\frac{m^2 - x_0^2}{\langle T_d(x_0, E)\rangle - \langle T_d(m, E)\rangle}. \tag{7}$$

Equation (7) asserts that the diffusion coefficient can be inferred from the difference in the measurable detection times $\langle T_d(x_0, E)\rangle$ and $\langle T_d(m, E)\rangle$.

To corroborate this finding, we simulate the aforementioned scenario and test it for a wide range of possible diffusion coefficients (Fig. 3). As implied by Eq. (6), the difference in the detection times is independent of the transition rates, the box size L, and the target size (the same equation will hold for threshold crossing). It is thus up to the experimentalist to tune these parameters such that the detection times can be measured with sufficient accuracy. Here we set $\alpha = \beta = 10^2$ s^{-1} and $L = 5$ μm. For each value of $\mathcal{D}$, the corresponding mean detection times were estimated from averages of $N = 10^2$ and 10^3 simulations, and the diffusion coefficient was inferred via Eq. (7). The error bars were estimated by repeating this procedure 10^2 times and noting the standard deviation. In Fig. 3 we plot the ratio between the inferred values and the actual ones. We find this estimation procedure robust, even when the number of measurements is relatively small ($N = 10^2$). For the parameters used here, the estimation is especially accurate for smaller diffusion coefficients, where mean detection times are longer.

Inferring the gating rates. Equation (4) states that the first-passage time density can be inferred from its gated counterparts, even without any prior knowledge of the gating rates α and β or control over the initial internal condition. We will now illustrate how the inferred first-passage time distribution can be used together with the observed detection time distribution to infer the gating rates, thus providing insight into the dynamics of the gating process.

To proceed, we shift our focus to short-time asymptotics analysis which, despite several recent applications in stochastic thermodynamics [76–78] and chemical kinetics [79,80], has not yet been used to further our knowledge on gated processes. In the short-time limit, the dominant contribution to $D_t(n_0, E)$ comes from trajectories where the detection occurs upon first arrival. This insight translates to the limiting equation $\pi_A = \lim_{t\to 0} D_t(n_0, E)/F_t(m|n_0)$. Similarly, the short-time asymptotics of $D_t(m, E)$ is given by $\pi_I = \beta^{-1}\lim_{t\to 0} D_t(m, E)$, owing to the fact that when the underlying process starts on m, the dominant contribution to detection comes from events where the gate opens before the particle leaves the target or falls below the threshold.

These limiting representations of the probabilities π_A and π_I, along with their normalization, allow us to obtain the gating rates as follows:

$$\alpha = \lim_{t\to 0}\frac{D_t(m, E)F_t(m|n_0)}{D_t(n_0, E)}, \tag{8}$$

$$\beta = \lim_{t\to 0}\frac{D_t(m, E)F_t(m|n_0)}{F_t(m|n_0) - D_t(n_0, E)}. \tag{9}$$

Equations (8) and (9) are corroborated in Fig. 4 for the birth-death process with parameters described in [57]. Furthermore, in [57] we also show that these relations hold even for an arbitrary (nonequilibrium) initial condition of the gate. We then derive simpler inference relations for the gating rates, which are obtained at the cost of perfect control over σ_0. Finally, we discuss the widely applicable case of simple diffusion and derive inference relations for α and β, which only differ by a factor of two from Eqs. (8) and (9).

Discussion. Using the unified framework of gated first-passage processes, we demonstrated how the first-passage time distribution can be inferred from gated measurements, and using these quantities, key features of the process can be extracted. The exact results obtained in this Letter can help inform statistical inference frameworks designed to deal with situations pertaining to imperfect observation conditions, including sparsely sampled time series or missing data problems. The asymptotic results presented in this Letter moreover provide a systematic approach to the inference of gating rates which, depending on the accessible timescales of the problem, can be improved upon by considering higher-order corrections to the asymptotics.

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[1] S. Redner, *A Guide to First-Passage Processes* (Cambridge University Press, Cambridge, United Kingdom, 2001).

[2] D. S. Grebenkov, D. Holcman, and R. Metzler, Preface: new trends in first-passage methods and applications in the life sciences and engineering, J. Phys. A: Math. Theor. **53**, 190301 (2020).

[3] R. Metzler, G. Oshanin, and S. Redner, *First-passage Phenomena and Their Applications* (World Scientific, Singapore, 2014).

[4] G. H. Weiss, First passage time problems in chemical physics, Adv. Chem. Phys. **13**, 1 (1967).

[5] R. Chicheportiche and J.-P. Bouchaud, Some applications of first-passage ideas to finance, in *First-passage Phenomena And Their Applications*, edited by R. Metzler, G. Oshanin, and S. Redner (World Scientific, Singapore, 2014), pp. 447–476.

[6] S. Iyer-Biswas and A. Zilman, First-Passage Processes in Cellular Biology, Adv. Chem. Phys. **160**, 261 (2016).

[7] Y. Zhang and O. K. Dudko, First-Passage Processes in the Genome, Annu. Rev. Biophys. **45**, 117 (2016).

[8] J. A. McCammon and S. H. Northrup, Gated binding of ligands to proteins, Nature (London) **293**, 316 (1981).

[9] A. Szabo, K. Schulten, and Z. Schulten, First passage time approach to diffusion controlled reactions, J. Chem. Phys. **72**, 4350 (1980).

[10] A. Szabo, D. Shoup, S. H. Northrup, and J. A. McCammon, Stochastically gated diffusion-influenced reactions, J. Chem. Phys. **77**, 4484 (1982).

[11] S. H. Northrup, F. Zarrin, and J. A. McCammon, Rate theory for gated diffusion-influenced ligand binding to proteins, J. Phys. Chem. **86**, 2314 (1982).

[12] G. H. Weiss, Overview of theoretical models for reaction rates, J. Stat. Phys. **42**, 3 (1986).

[13] G. A. Whitmore, First-passage-time models for duration data: Regression structures and competing risks, J. R. Stat. Soc. Ser. D (The Statistician) **35**, 207 (1986).

[14] H.-X. Zhou and A. Szabo, Theory and simulation of stochastically-gated diffusion-influenced reactions, J. Phys. Chem. **100**, 2597 (1996).

[15] A. M. Berezhkovskii, D.-Y. Yang, S. H. Lin, Y. A. Makhnovskii, and S.-Y. Sheu, Smoluchowski-type theory of stochastically gated diffusion-influenced reactions, J. Chem. Phys. **106**, 6985 (1997).

[16] Y. A. Makhnovskii, A. M. Berezhkovskii, S.-Y. Sheu, D.-Y. Yang, J. Kuo, and S. H. Lin, Stochastic gating influence on the kinetics of diffusion-limited reactions, J. Chem. Phys. **108**, 971 (1998).

[17] O. Bénichou, M. Moreau, and G. Oshanin, Kinetics of stochastically gated diffusion-limited reactions and geometry of random walk trajectories, Phys. Rev. E **61**, 3388 (2000).

[18] T. Bandyopadhyay, K. Seki, and M. Tachiya, Theoretical analysis of the influence of stochastic gating on the transient effect in fluorescence quenching by electron transfer, J. Chem. Phys. **112**, 2849 (2000).

[19] P. C. Bressloff and S. D. Lawley, Stochastically gated diffusion-limited reactions for a small target in a bounded domain, Phys. Rev. E **92**, 062117 (2015).

[20] I. V. Gopich and A. Szabo, Reversible stochastically gated diffusion-influenced reactions, J. Phys. Chem. B **120**, 8080 (2016).

[21] C. E. Budde, M. O. Cáceres, and M. A. Ré, Transient behaviour in the absorption probability distribution in the presence of a non-markovian dynamic trap, Europhys. Lett. **32**, 205 (1995).

[22] J. L. Spouge, A. Szabo, and G. H. Weiss, Single-particle survival in gated trapping, Phys. Rev. E **54**, 2248 (1996).

[23] P. C. Bressloff and S. D. Lawley, Escape from a potential well with a randomly switching boundary, J. Phys. A: Math. Theor. **48**, 225001 (2015).

[24] P. C. Bressloff and S. D. Lawley, Escape from subcellular domains with randomly switching boundaries, Multiscale Model. Simul. **13**, 1420 (2015).

[25] A. Godec and R. Metzler, First passage time statistics for two-channel diffusion, J. Phys. A: Math. Theor. **50**, 084001 (2017).

[26] G. Mercado-Vásquez and D. Boyer, First hitting times between a run-and-tumble particle and a stochastically gated target, Phys. Rev. E **103**, 042139 (2021).

[27] P. C. Bressloff, Diffusive search for a stochastically-gated target with resetting, J. Phys. A: Math. Theor. **53**, 425001 (2020).

[28] S. Toste and D. Holcman, Arrival time for the fastest among n switching stochastic particles, Eur. Phys. J. B **95**, 113 (2022).

[29] G. Mercado-Vásquez and D. Boyer, First Hitting Times to Intermittent Targets, Phys. Rev. Lett. **123**, 250603 (2019).

[30] Y. Scher and S. Reuveni, Unified Approach to Gated Reactions on Networks, Phys. Rev. Lett. **127**, 018301 (2021).

[31] Y. Scher and S. Reuveni, Gated reactions in discrete time and space, J. Chem. Phys. **155**, 234112 (2021).

[32] M. S. Obaidat and S. Misra, *Principles of Wireless Sensor Networks* (Cambridge University Press, Cambridge, United Kingdom, 2014).

[33] W. Dargie and C. Poellabauer, *Fundamentals of Wireless Sensor Networks: Theory and Practice* (John Wiley & Sons, Hoboken, New Jersey, United States, 2010).

[34] H. Inaltekin, C. R. Tavoularis, and S. B. Wicker, Event detection time for mobile sensor networks using first passage processes, in *IEEE GLOBECOM 2007 - IEEE Global Telecommunications Conference* (IEEE, Piscataway, New Jersey, United States, 2007), pp. 1174–1179.

[35] C. Hsin and M. Liu, Randomly duty-cycled wireless sensor networks: Dynamics of coverage, IEEE Trans. Wireless Commun. **5**, 3182 (2006).

[36] D. Song, C. Kim, and J. Yi, On the time to search for an intermittent signal source under a limited sensing range, IEEE Trans. Robotics **27**, 313 (2011).

[37] L. Zarfaty, E. Barkai, and D. A. Kessler, Discrete sampling of correlated random variables modifies the long-time behavior of their extreme value statistics, arXiv:2108.06778 (2021).

[38] L. Zarfaty, E. Barkai, and D. A. Kessler, Discrete Sampling of Extreme Events Modifies Their Statistics, Phys. Rev. Lett. **129**, 094101 (2022).

[39] A. Kumar, A. Zodage, and M. S. Santhanam, First detection of threshold crossing events under intermittent sensing, Phys. Rev. E **104**, L052103 (2021).

[40] D. E Makarov, A. Berezhkovskii, G. Haran, and E. Pollak, The effect of time resolution on apparent transition path times observed in single-molecule studies of biomolecules, J. Phys. Chem. B **126**, 7966 (2022).

[41] K. Song, D. E. Makarov, and E. Vouga, The effect of time resolution on the observed first passage times in diffusive dynamics, J. Chem. Phys. **158**, 111101 (2023).

[42] T. Ha, T. Enderle, D. S. Chemla, P. R. Selvin, and S. Weiss, Quantum jumps of single molecules at room temperature, Chem. Phys. Lett. **271**, 1 (1997).

[43] H. P. Lu and X. S. Xie, Single-molecule spectral fluctuations at room temperature, Nature (London) **385**, 143 (1997).

[44] R. M. Dickson, A. B. Cubitt, R. Y. Tsien, and W. E. Moerner, On/off blinking and switching behaviour of single molecules of green fluorescent protein, Nature (London) **388**, 355 (1997).

[45] E. J. G. Peterman, S. Brasselet, and W. E. Moerner, The fluorescence dynamics of single molecules of green fluorescent protein, J. Phys. Chem. A **103**, 10553 (1999).

[46] D. A. V. Bout, W.-T. Yip, D. Hu, D.-K. Fu, T. M. Swager, and P. F. Barbara, Discrete intensity jumps and intramolecular electronic energy transfer in the spectroscopy of single conjugated polymer molecules, Science **277**, 1074 (1997).

[47] M. Nirmal, B. O. Dabbousi, M. G. Bawendi, J. J. Macklin, J. K. Trautman, T. D. Harris, and L. E. Brus, Fluorescence intermittency in single cadmium selenide nanocrystals, Nature (London) **383**, 802 (1996).

[48] M. Kuno, D. P. Fromm, H. F. Hamann, A. Gallagher, and D. J. Nesbitt, "on"/"off" fluorescence intermittency of single semiconductor quantum dots, J. Chem. Phys. **115**, 1028 (2001).

[49] J. Schuster, F. Cichos, and C. Von Borczyskowski, Blinking of single molecules in various environments, Opt. Spectrosc. **98**, 712 (2005).

[50] K. Claytor, S. Khatua, J. M. Guerrero, A. Tcherniak, J. M. Tour, and S. Link, Accurately determining single molecule trajectories of molecular motion on surfaces, J. Chem. Phys. **130**, 164710 (2009).

[51] S. Khatua, J. M. Guerrero, K. Claytor, G. Vives, A. B. Kolomeisky, J. M. Tour, and S. Link, Micrometer-scale translation and monitoring of individual nanocars on glass, ACS Nano **3**, 351 (2009).

[52] A. S. Hansen, M. Woringer, J. B. Grimm, L. D. Lavis, R. Tjian, and X. Darzacq, Robust model-based analysis of single-particle tracking experiments with spot-on, Elife **7**, e33125 (2018).

[53] T. Kues and U. Kubitscheck, Single molecule motion perpendicular to the focal plane of a microscope: application to splicing factor dynamics within the cell nucleus, Single Mol. **3**, 218 (2002).

[54] J. Reingruber and D. Holcman, Gated Narrow Escape Time for Molecular Signaling, Phys. Rev. Lett. **103**, 148102 (2009).

[55] J. Reingruber and D. Holcman, Narrow escape for a stochastically gated brownian ligand, J. Phys.: Condens. Matter **22**, 065103 (2010).

[56] B. N. G. Giepmans, S. R. Adams, M. H. Ellisman, and R. Y. Tsien, The fluorescent toolbox for assessing protein location and function, Science **312**, 217 (2006).

[57] See Supplemental Material at http://link.aps.org/supplemental/10.1103/PhysRevResearch.5.L032043 for (i) Dynamics of the gate: explicit formula for $p_t(\sigma|\sigma_0)$. (ii) First-passage times from gated measurements: derivation of Eqs. (2) and (3) of the main text. (iii) The connection between the detection times and propagators: derivation of Eq. (5) of the main text. (iv) Inferring the gating rates α and β. (v) Models used for simulations presented in main text.

[58] S. D. Lawley and J. B. Madrid, First passage time distribution of multiple impatient particles with reversible binding, J. Chem. Phys. **150**, 214113 (2019).

[59] D. S. Grebenkov, First passage times for multiple particles with reversible target-binding kinetics, J. Chem. Phys. **147**, 134112 (2017).

[60] D. S. Grebenkov and A. Kumar, Reversible target-binding kinetics of multiple impatient particles, J. Chem. Phys. **156**, 084107 (2022).

[61] D. S. Grebenkov and A. Kumar, First-passage times of multiple diffusing particles with reversible target-binding kinetics, J. Phys. A: Math. Theor. **55**, 325002 (2022).

[62] S. Chaudhury, D. Singh, and A. B. Kolomeisky, Theoretical investigations of the dynamics of chemical reactions on nanocatalysts with multiple active sites, J. Phys. Chem. Lett. **11**, 2330 (2020).

[63] B. Punia, S. Chaudhury, and A. B. Kolomeisky, Understanding the Reaction Dynamics on Heterogeneous Catalysts Using a Simple Stochastic Approach, J. Phys. Chem. Lett. **12**, 11802 (2021).

[64] E. W. Montroll and G. H. Weiss, Random walks on lattices. ii, J. Math. Phys. **6**, 167 (1965).

[65] J. Klafter and I. M. Sokolov, *First Steps in Random Walks: From Tools to Applications* (OUP Oxford, 2011).

[66] N. Masuda, M. A. Porter, and R. Lambiotte, Random walks and diffusion on networks, Phys. Rep. **716-717**, 1 (2017).

[67] R. Metzler and J. Klafter, The random walk's guide to anomalous diffusion: a fractional dynamics approach, Phys. Rep. **339**, 1 (2000).

[68] P. K. Kang, M. Dentz, T. Le Borgne, and R. Juanes, Spatial Markov Model of Anomalous Transport Through Random Lattice Networks, Phys. Rev. Lett. **107**, 180602 (2011).

[69] F. Höfling and T. Franosch, Anomalous transport in the crowded world of biological cells, Rep. Prog. Phys. **76**, 046602 (2013).

[70] D. S. Grebenkov and L. Tupikina, Heterogeneous continuous-time random walks, Phys. Rev. E **97**, 012148 (2018).

[71] B. Berkowitz and H. Scher, Anomalous Transport in Random Fracture Networks, Phys. Rev. Lett. **79**, 4038 (1997).

[72] B. Berkowitz and H. Scher, Theory of anomalous chemical transport in random fracture networks, Phys. Rev. E **57**, 5858 (1998).

[73] T. Guérin, M. Dolgushev, O. Bénichou, and R. Voituriez, Universal kinetics of imperfect reactions in confinement, Commun. Chem. **4**, 157 (2021).

[74] R. Belousov, M. N. Qaisrani, A. Hassanali, and E. Roldan, First-passage fingerprints of water diffusion near glutamine surfaces, Soft Matter **16**, 9202 (2020).

[75] R. Belousov, A. Hassanali, and É. Roldán, Statistical physics of inhomogeneous transport: Unification of diffusion laws and inference from first-passage statistics, Phys. Rev. E **106**, 014103 (2022).

[76] B. Das, S. K. Manikandan, and A. Banerjee, Inferring entropy production in anharmonic brownian gyrators, Phys. Rev. Res. **4**, 043080 (2022).

[77] S. K. Manikandan, S. Ghosh, A. Kundu, B. Das, V. Agrawal, D. Mitra, A. Banerjee, and S. Krishnamurthy, Quantitative analysis of nonequilibrium systems from short-time experimental data, Commun. Phys. **4**, 258 (2021).

[78] J. van der Meer, B. Ertel, and U. Seifert, Thermodynamic Inference in Partially Accessible Markov Networks: A Unifying Perspective from Transition-Based Waiting Time Distributions, Phys. Rev. X **12**, 031025 (2022).

[79] A. L. Thorneywork, J. Gladrow, Y. Qing, M. Rico-Pasto, F. Ritort, H. Bayley, A. B. Kolomeisky, and U. F. Keyser, Direct detection of molecular intermediates from first-passage times, Sci. Adv. **6**, eaaz4642 (2020).

[80] X. Li and A. B. Kolomeisky, Mechanisms and topology determination of complex chemical and biological network systems from first-passage theoretical approach, J. Chem. Phys. **139**, 144106 (2013).