Inference in gated first-passage processes

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The first-passage time of a stochastic process provides invaluable insight into its fundamental properties. However, imperfect observation conditions, which is a form of gating, often renders the process intermittently observable, such that the exact first-passage instance might be missed. In such cases, the measured detection times differ from the first-passage times of interest, as e.g., happens in imperfect chemical reactions and when tracking photoblinking particles. Motivated by the inference challenge posed by these real-life situations we develop a universal scheme for the inference of first-passage times from the detection times of gated first-passage processes. We further provide a way to infer underlying model-based parameters (e.g., the diffusion coefficient in the case of diffusion), and even the gating rates themselves via the hitherto overlooked short-time regime of the gated detection times. The power of our approach is illustrated with examples.

Introduction.—The importance of first-passage processes is recognized universally across scientific disciplines, owing to its 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 [21–29].

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 [30–34]. 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. However, intermittent detection of the time-series can lead to a gross mischaracterization of the statistics of such extreme-events [35–37]. In such cases, the relevant quantity is the first detection time, which denotes the first time the time-series is observed above the threshold [37].

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 [38–47]. Other reasons for such gating can be the intermittent loss of focus on a moving particle in 3-dimensions [48] or slow frame acquisition rate [49]; (b) A gated chemical reaction

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. For such processes, we show how the first-passage time distribution and further relevant observables can be inferred from the detection time distributions.
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 signalling driven by narrow escape [50, 51] and among fluorescent probes [52].

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 from gated observations, which can e.g., be used for the inference of 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 on a discrete set of states. 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 $\alpha$, and from $I$ to $A$ at $\beta$. For $\sigma_0, \sigma \in \{A, I\}$, we define $p_t(\sigma|\sigma_0)$ to be the probability that the gate is in state $\sigma$ at time $t$, given that it was in state $\sigma_0$ initially (see SI for an explicit formula [53]). 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 $T_I(m|n_0)$, 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 $Q$, 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 1-dimensional intermittent time-series with nearest-neighbor transitions, where $Q$ denotes all states above a certain threshold $m$ and $T_d(n_0, \sigma_0)$ is the first time when $X_{n_0}(t) \geq m$ while the gate is open ($A$), and (ii) gated reactions or target search on any arbitrary network, where $Q$ is typically a single target state $m$, 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.

**First-passage times from gated observations.**—We begin our analysis by noting that for $n_0 \not\in Q$ we have

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

(1)

where the probability for a detection event occurring at time $t$ has two contributions: (i) the first detection time coinciding with the first-passage time, and (ii) the gate being closed during the first-passage event, and detection happening strictly after this event. The Laplace transform of Eq. (1), can be expressed in compact form as [53]

$$\tilde{D}_s(n_0, \sigma_0) = \left[\pi_A + \pi_I \tilde{D}_s(m, I)\right] \tilde{F}_s(m|n_0)$$

$$+ \mathbb{1}(\sigma_0)(1 - \pi_{\sigma_0}) \left[1 - \tilde{D}_s(m, I)\right] \tilde{F}_{s+\lambda}(m|n_0),$$

(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 $\tilde{F}_{s+\lambda}(m|n_0)$ from the equations, we arrive at [53]

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

(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. However, inference of the first-passage time density $F_t(m|n_0)$, requires the detection statistics with initial conditions $\{n_0, A\}, \{n_0, I\}, \{m, I\}$ and the equilibrium probabilities $\pi_A$ and $\pi_I$. 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 $\pi_A$ and $\pi_I$ may also be unknown.

In such situations, the most practically realizable initial condition is the equilibrium state $\sigma_0 \equiv E$, where the system is in the active state $A$ with probability $\pi_A$, and in the inactive state $I$ with probability $\pi_I$. Note that this initial condition is naturally achieved if the system is simply allowed to equilibrate. Interestingly, the first 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):

$$\tilde{F}_s(m|n_0) = \frac{\tilde{D}_s(n_0, E)}{D_s(m, E)},$$

(4)
Strikingly, Eq. (4) asserts that the first-passage time density can be inferred from the detection statistics, even without the explicit knowledge of \( \pi_A \) and \( \pi_I \), or control over the initial state of the gate. Furthermore, Eq. (4) is reminiscent of the seminal renewal formula 

\[
\tilde{F}_s(m|n_0) = \tilde{P}_s(m|n_0) \quad \text{which relates, in Laplace space, the first-passage time density and the probability density } P_s(n_i|n_j) \text{ of finding the underlying process in state } n_i \text{ at time } t, \text{ given its initial state } n_j [1]. \]

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 [53]

\[
\frac{\tilde{D}_s(n_0, E)}{\tilde{D}_s(n'_0, E)} = \frac{\tilde{P}_s(m|n_0)}{\tilde{P}_s(m|n'_0)}, \tag{5}
\]

suggesting that the ratio in Laplace space of the detection time densities, starting from any two initial states \( n_0 \) and \( n'_0 \) is counter-intuitively independent of \( \alpha \) and \( \beta \).

We remark that Eq. (5) holds in both settings: when \( D_s(n_0, E) \) corresponds to gated target search or detection of threshold crossing events under intermittent sensing.

To illustrate our results, we consider a Markovian birth-death process \( X_{n_0}(t) \), with \( W_+(j) = (N-j)k_+ \) and \( W_-(j) = jk_- \) denoting the transition rates from state \( j \) to \( j+1 \) and \( j-1 \) respectively, where \( j \in \{0, 1, \ldots, N\} \). These rates were previously used to model threshold activated processes [54] in the context of triggering of biochemical reactions [55–57], and the dynamics of chemical reactions on catalysts [58, 59]. Furthermore, this choice of rates confer features to the birth-death process that we expect to see in several practical time-series data, where \( X_{n_0}(t) \) is less likely to take very low or high values.

Figure 2 demonstrates the validity of Eq. (4), using the birth-death process defined above.

**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. For example, the mean first-passage time is given by

\[
\langle T_I(m|n_0) \rangle = \langle T_d(n_0, E) \rangle - \langle T_d(m, E) \rangle. \tag{6}
\]

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 [60], the mean first-passage time can also shed light on fundamental properties of the system at hand [61, 62].

**Inferring the diffusion coefficient.**—While Eq. (4), and thus subsequently Eq. (6), were derived for Markov processes in discrete space, the discreteness of the state space was not used explicitly, and starting from Eq. (1) it is easy to see that these equations also hold for continuous space Markov processes. A paramount example of such a process is simple diffusion, where one is often interested in inferring the diffusion coefficient \( D \).

We now illustrate how one can utilize our framework to infer underlying model-based parameters like \( D \). 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 \( x_0 \), and an unknown (equilibrated) internal state (\( \sigma_0 = E \)). Let us further assume that we have a model for its motion in the medium. For ease of illustration, we assume that the particle is freely diffusing inside an effectively one-dimensional box \([0, L] \) with reflecting boundaries and a gated target located at \( x_0 < m < L \). Utilizing Eq. (6) we find that for this model [53]

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

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 have simulated the aforementioned scenario and tested 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 \( L = 5 \mu m \). For each value of \( D \), the corresponding
mean detection times were estimated from averages of
$N = 10^2$ and $10^3$ simulations, and the diffusion coeffi-
cient was calculated via Eq. (7). To estimate the error,
the procedure was repeated $10^2$ times. 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 $\alpha$ and $\beta$ 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 internal dynamics of
the process.

In the short-time limit, the dominant contribution to
$D_t(n_0, E)$ comes from trajectories where the detec-
tion 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 underlying process leaves the
target or falls below the threshold.

These limiting representations of the probabilities $\pi_A$
and $\pi_I$, along with their normalization, allows us to ob-
tain the gating rates as follows

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

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

Equations (8) and (9) are corroborated in Fig. 4, for the
birth-death process with parameters described earlier in
the text. In the SI, we show that these relations hold
even for an arbitrary (non-equilibrium) initial condition of
the gate. We then derive simpler inference relations for
the gating rates, which are obtained at the cost of per-
fect control over $\sigma_0$ [53]. Finally, we discuss the widely
applicable case of simple diffusion in the SI [53] and de-
rive inference relations for $\alpha$ and $\beta$, which only differ by
a factor of 2 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 intermit-
tent measurements, and using these quantities, key fea-
tures 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, includ-
ing sparsely sampled time-series or missing data prob-
lem. On the other hand, the asymptotic results pre-
sented in this Letter suggest a systematic approach to
obtaining the gating rates which, depending on the access-
able timescales of the problem, can be improved upon by
considering higher-order corrections to the asymptotics.

While we worked in the setting of Markov processes
for simplicity, we note that all our results even when the
underlying process is a general renewal process with ar-
bitrary (non-exponential) inter-event times. This can be
seen directly by noticing that Eq. (2) holds true for re-
newal processes [53], and the dominant mechanisms gov-
erning the short-time asymptotics also remain exactly the
same.

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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 $\alpha$ and $\beta$. (v) Models used for simulations presented in main text.

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Supplemental Material for “Inference in gated first-passage processes”

This Supplemental Material provides further discussion and derivations which support our findings reported in the Letter, and provides details of the models and simulations used to validate our results.

**DYNAMICS OF THE GATE: EXPLICIT FORMULA FOR** \( p_t(\sigma|\sigma_0) \)

The gate is modeled as a two-state Markov process, which switches from state \( A \) to \( I \) at rate \( \alpha \), and from \( I \) to \( A \) at rate \( \beta \). For \( \sigma_0, \sigma \in \{A, I\} \), we define \( p_t(\sigma|\sigma_0) \) to be the probability that the gate is in state \( \sigma \) at time \( t \), given that it was in state \( \sigma_0 \) initially, and 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 internal dynamics propagator \( p_t(A|A) \) is thus governed by the following differential equation

\[
\frac{dp_t(A|A)}{dt} = -\alpha p_t(A|A) + \beta (1 - p_t(A|A)), \tag{S1}
\]

and from normalization we have \( p_t(I|A) = 1 - p_t(A|A) \). Similarly,

\[
\frac{dp_t(A|I)}{dt} = -\alpha p_t(A|I) + \beta (1 - p_t(A|I)), \tag{S2}
\]

and \( p_t(I|I) = 1 - p_t(A|I) \). The solutions for these differential equations, that also follow the above equilibrium occupancies for \( t \gg \lambda^{-1} \), are

\[
\begin{align*}
    p_t(A | I) &= \pi_A(1 - e^{-\lambda t}), \\
    p_t(I | I) &= \pi_I + \pi_Ae^{-\lambda t}, \\
    p_t(A | A) &= \pi_A + \pi_Ie^{-\lambda t}, \\
    p_t(I | A) &= \pi_I(1 - e^{-\lambda t}).
\end{align*} \tag{S3}
\]

**FIRST-PASSAGE TIMES FROM GATED MEASUREMENTS: DERIVATION OF EQS. (2-4) OF THE MAIN TEXT**

We recall that Eq. (1) of the main text states

\[
D_t(n_0, \sigma_0) = F_t(m|n_0)p_t(A|\sigma_0) + \int_0^t F_{t'}(m|n_0)p_{t'}(I|\sigma_0)D_{t-t'}(m, I)dt', \tag{S4}
\]

where \( n_0 \) denotes the initial state of the underlying process, and \( m \) denotes the target state (in the context of gated target search), or a threshold (in the context of gated threshold crossing). It is to be noted that Eq. (S4) is valid when \( n_0 \neq m \) in gated target search, and \( n_0 < m \) for the threshold crossing problem. Setting \( \sigma_0 = A \) we plug in Eq. (S4) the relevant expressions from Eq. (S3). Then, moving to Laplace space, the Laplace transform of the first term on the right-hand side reads

\[
\mathcal{L}\{F_t(m|n_0)p_t(A|A)\} = \int_0^\infty F_t(m|n_0) (\pi_A + \pi_Ie^{-\lambda t}) e^{-st}dt = \pi_A \tilde{F}_s(m|n_0) + \pi_I \tilde{F}_{s+\lambda}(m|n_0), \tag{S5}
\]

and the second term, which is a convolution (denoted by \( * \) for brevity), reads

\[
\mathcal{L}\{[F_t(m|n_0)\pi_I(1 - e^{-\lambda t})] * D_t(m, I)\} = \mathcal{L}\{F_t(m|n_0)\pi_I(1 - e^{-\lambda t})\}\mathcal{L}\{D_t(m, I)\} = \pi_I \left( \tilde{F}_s(m|n_0) - \tilde{F}_{s+\lambda}(m|n_0) \right) \tilde{D}_s(m, I). \tag{S6}
\]

Put together, we have

\[
\tilde{D}_s(n_0, A) = \pi_A \tilde{F}_s(m|n_0) + \pi_I \tilde{F}_{s+\lambda}(m|n_0) + \pi_I \left( \tilde{F}_s(m|n_0) - \tilde{F}_{s+\lambda}(m|n_0) \right) \tilde{D}_s(m, I), \tag{S7}
\]
or
\[
\tilde{D}_s(n_0, A) = \left( \pi_A + \pi_I \tilde{D}_s(m, I) \right) \tilde{F}_s(m|n_0) + \pi_I \left( 1 - \tilde{D}_s(m, I) \right) \tilde{F}_{s+\lambda}(m|n_0).
\]  
(S8)

Similarly, the corresponding equation for \( \sigma_0 = I \) reads
\[
\tilde{D}_s(n_0, I) = \left( \pi_A + \pi_I \tilde{D}_s(m, I) \right) \tilde{F}_s(m|n_0) - \pi_A \left( 1 - \tilde{D}_s(m, I) \right) \tilde{F}_{s+\lambda}(m|n_0).
\]  
(S9)

It is easy to see that Eqs. (S8) and (S9) can be written in compact form as
\[
\tilde{D}_s(n_0, \sigma_0) = \left[ \pi_A + \pi_I \tilde{D}_s(m, I) \right] \tilde{F}_s(m|n_0) + \mathbb{1}(\sigma_0)(1 - \pi_{\sigma_0}) \left[ 1 - \tilde{D}_s(m, I) \right] \tilde{F}_{s+\lambda}(m|n_0),
\]
where \( \mathbb{1}(\sigma_0) \) takes values +1 or −1 when \( \sigma_0 = A \) or \( I \), respectively, yielding Eq. (2) of the main text. Furthermore, the term containing \( \tilde{F}_{s+\lambda}(m|n_0) \) can be eliminated from Eqs. (S8) and (S9) by multiplying them by \( \pi_A \) and \( \pi_I \) respectively, and adding the two resulting equations. This allows us to write
\[
\tilde{F}_s(m|n_0) = \frac{\pi_A \tilde{D}_s(n_0, A) + \pi_I \tilde{D}_s(n_0, I)}{\pi_A + \pi_I \tilde{D}_s(m, I)}
\]
(S11)

which identifies with Eq. (3) in the main text and completes our proof that the first-passage time density \( F_i(m|n_0) \) can be expressed in terms of the gated detection time densities, and the gate steady-state probabilities \( \pi_A \) and \( \pi_I \).

**Extension to renewal processes**

In our Letter, we derived our results assuming that the underlying process is modelled as a continuous-time Markov process. However, this modelling assumption can be relaxed, and our results can be shown to be valid even when the underlying process is modelled as a renewal process.

To see this, we use as a starting point the following renewal structure \([1]\)
\[
T_d(n_0, \sigma_0) = T_f(m|n_0) + \begin{cases} 0, & \text{if } \sigma_{T_f(m|n_0)} = A \\ T_d(m, I), & \text{otherwise}, \end{cases}
\]
(S12)

where \( T_d(n_0, \sigma_0) \), \( T_d(m, I) \), and \( T_f(m|n_0) \) denote random variables whose densities have been denoted by \( D_d(n_0, \sigma_0) \), \( D_d(m, I) \), and \( F_i(m|n_0) \) in the main text. By \( \sigma_{T_f(m|n_0)} = A \) in the above equation, we mean that the random variable denoting the state of the gate takes value \( A \) at time \( T_f(m|n_0) \), given that its state initially was \( \sigma_0 \). Equation (S12) is valid even when the underlying process is an arbitrary renewal process \([1]\) and thus allows us to relax our Markovian assumption.

Taking a Laplace transform of Eq. (S12), and rearranging, we get
\[
\tilde{D}_s(n_0, \sigma_0) = \left[ \pi_A + \pi_I \tilde{D}_s(m, I) \right] \tilde{F}_s(m|n_0) + \mathbb{1}(\sigma_0)(1 - \pi_{\sigma_0}) \left[ 1 - \tilde{D}_s(m, I) \right] \tilde{F}_{s+\lambda}(m|n_0),
\]
(S13)

which is the same as Eq. (2) in the main text. Hence, Eq. (3) in the main text follows for renewal processes as well, using the exact same procedure.

**THE CONNECTION BETWEEN THE DETECTION TIMES AND PROPAGATORS: DERIVATION OF EQ. (5) IN THE MAIN TEXT**

Equation (4) in the main text reads
\[
\tilde{F}_s(m|n_0) = \frac{\tilde{D}_s(n_0, E)}{D_s(m, E)}
\]
(S14)

asserting that the first-passage time density can be inferred from the detection statistics, even without the explicit knowledge of \( \pi_A \) and \( \pi_I \), or control over the initial state of the gate. Moreover, Eq. (S14) is reminiscent of the seminal renewal formula
\[
\tilde{F}_s(m|n_0) = \frac{\tilde{P}_s(m|n_0)}{P_s(m|m)},
\]
(S15)
which relates, in Laplace space, the first-passage time density and the propagator $P_l(n_i|n_j)$ denoting the probability of finding the underlying process in state $n_i$ at time $t$, given its initial state $n_j$. By equating the two expressions we obtain

$$
\frac{\tilde{D}_s(n_0, E)}{D_s(m, E)} = \frac{\bar{P}_s(m|n_0)}{P_s(m|m)},
$$

(S16)

which remarkably holds for both settings: when $D_t(n_0, E)$ corresponds to gated target search or detection of threshold crossing events under intermittent sensing.

To explore further, consider the first detection time densities, starting from two arbitrary initial conditions $n_0$ and $n_0'$. From (S16), we have the two equations,

$$
\frac{\tilde{D}_s(n_0, E)}{D_s(n_0', E)} = \frac{\bar{P}_s(m|n_0)}{P_s(m|n_0')},
$$

(S17)

whose ratio is simply given by

$$
\frac{\tilde{D}_s(n_0, E)}{\tilde{D}_s(n_0', E)} = \frac{\bar{P}_s(m|n_0)}{\bar{P}_s(m|n_0')},
$$

(S18)

which is Eq. (5) in the main text.

In fact, this equality can be easily extended to give

$$
\frac{\tilde{D}_s(n_0, E)}{\tilde{D}_s(n_0', E)} = \frac{\bar{P}_s(m|n_0)}{\bar{P}_s(m|n_0')}.
$$

(S19)

**INFERRING THE GATING RATES $\alpha$ AND $\beta$**

Derivation of Eqs. (8-9)

In this section, we provide a detailed derivation and discussion of our short-time asymptotic calculations, which allow us to infer $\alpha$ and $\beta$ from the detection time densities in the form of Eqs. (8) and (9) in the main text.

For $\sigma_0 = E$, we have the relation,

$$
D_t(n_0, E) = \pi_A F_l(m|n_0) + \pi_I \int_0^t F_{l'}(m|n_0)D_{l-l'}(m,I)dt',
$$

(S20)

which can be obtained from Eq. (S4), by noting that $D_t(n_0, E) = \pi_A D_t(n_0, A) + \pi_I D_t(n_0, I)$. Furthermore, we have $D_t(m, E) = \pi_A \delta(t) + \pi_I D_t(m, I)$. Evidently, the short-time behaviour of $D_t(m, E)$ is governed by that of $D_t(m, I)$, which can in turn be expressed as

$$
D_t(m, I) \approx \beta(1 - \Delta(t))
$$

(S21)

where $\Delta(t) \to 0$ in the $t \to 0$ limit. For example, in the case of gated chemical reactions where $m$ denotes a target state, the short-time expression for $D_t(m, I)$ is

$$
D_t(m, I) \approx \beta e^{-\beta t} e^{-\gamma_m t}
$$

(S22)

where $\gamma_m$ denotes the rate at which the reactant escapes the target state $m$. Equation (S22) expresses the fact that the dominant contribution to reaction events in the short-time limit comes from the events where the gate opens before the reactant leaves the target state $m$. Using the approximation $e^{-\lambda t} \approx 1 - \lambda t$, it is easy to see that $\Delta(t) = (\beta + \gamma_m)t + o(t)$, and in the $t \to 0$ limit, we have

$$
\lim_{t \to 0} D_t(m, I) = \beta.
$$

(S23)

Equation (S23) asserts that $D_t(m, I)$ tends to a constant ($\beta$) in the short-time limit. Similarly, the second term of the right-hand side in Eq. (S20) can be safely ignored in the short-time limit, yielding

$$
D_t(n_0, E) \approx \pi_A F_l(m|n_0).
$$

(S24)
From here, we have

\[ \pi_A = \lim_{t \to 0} \frac{D_t(n_0, E)}{F_t(m|n_0)}, \tag{S25} \]

which appeared in the main text. In a similar vein, the short-time asymptotics of \( D_t(m, E) \) can be expressed as

\[ D_t(m, E) \simeq \pi_I D_t(m, I). \tag{S26} \]

Using Eq. (S23), we arrive at

\[ \pi_I = \lim_{t \to 0} \frac{1}{\beta} D_t(m, E), \tag{S27} \]

which appeared in the main text.

We are now in the position to derive relations for the inference of \( \alpha \) and \( \beta \) from Eqs. (S25) and (S27). To obtain these relations, we will use two identities: (i) \( \pi_A + \pi_I = 1 \), and (ii) \( \pi_A \alpha = \pi_I \beta \). While the first identity is trivially the normalization of occupancy probabilities, the latter can be seen as a statement of detailed balance for the two-state Markov process which models our gate.

Writing Eq. (S27) as \( \pi_I \beta = \lim_{t \to 0} D_t(m, E) \), and using \( \pi_A \alpha = \pi_I \beta \), we have

\[ \pi_A \alpha = \lim_{t \to 0} D_t(m, E), \tag{S28} \]

where, \( \pi_A \) can be further substituted from Eq. (S25), to obtain Eq. (8) in the main text

\[ \alpha = \lim_{t \to 0} \frac{D_t(m, E) F_t(m|n_0)}{D_t(n_0, E)}. \tag{S29} \]

To obtain the corresponding inference relation for \( \beta \), we note that Eq. (S27) gives

\[ \beta = \frac{1}{\pi_I} \lim_{t \to 0} D_t(m, E), \tag{S30} \]

where \( \pi_I = \frac{\alpha}{\alpha + \beta} \). This gives us

\[ \beta = \frac{\alpha + \beta}{\alpha} \lim_{t \to 0} D_t(m, E), \tag{S31} \]

which can be further simplified to obtain

\[ \beta = \left(1 + \frac{\beta}{\alpha}\right) \lim_{t \to 0} D_t(m, E). \tag{S32} \]

Substituting for \( \alpha \) in the above equation from Eq. (S29), we get

\[ \beta = \lim_{t \to 0} \frac{D_t(m, E) F_t(m|n_0)}{F_t(m|n_0) - D_t(n_0, E)}, \tag{S33} \]

which is Eq. (9) from the main text.

**Inference for arbitrary initial condition of the gate**

In this subsection, we demonstrate that Eqs. (S29) and (S33) hold more generally, and we can relax the condition that the gate is initially equilibrated.

Consider a situation where we do not have information about the initial conditions of the gate. Let us denote by \( p_A \) and \( p_I \) the unknown probabilities for the gate to be initially active \( A \) and inactive \( I \) respectively, for \( p_A \in (0, 1) \) and \( p_I = 1 - p_A \). Note that we do not assume that \( p_A = \pi_A \) and \( p_I = \pi_I \). Following the intuition developed for Eq. (S25) and Eq. (S27), we have the following short-time asymptotic relations,

\[ p_A = \lim_{t \to 0} \frac{D_t(n_0)}{F_t(m|n_0)}. \tag{S34} \]
FIG. S1. Inference of the gating rates $\alpha$ and $\beta$ from short-time asymptotics for the birth-death process (defined in the main text and Sec. S5.A) with $k_+ = 0.1$, $k_1 = 1$, and $N = 10$. (a) A plot demonstrating that early deviations of the detection time distribution from the first-passage time distribution, as captured by Eq. (S39), can be used to infer the numerical value of $\alpha$. (b) Inference of $\beta$ through the short-time asymptotic behaviour of $D_t(m, I)$ given by Eq. (S40). It is clear that the short-time asymptotics of the detection time distributions can be leveraged to infer the gating rates in gated first-passage processes.

and

\[ p_t = \frac{1}{\beta} \lim_{t \to 0} D_t(m), \quad (S35) \]

where we have dropped the notation for gate initialization ($D_t(n_0)$ denotes the detection time density given that the initial state of the underlying process is $n_0$, and the initial preparation of the gate is unknown). The normalization of probabilities dictates that $p_A + p_I = 1$. So, adding up the above two equations, we get,

\[ 1 = \lim_{t \to 0} \left( \frac{1}{\beta} D_t(m) + \frac{D_t(n_0)}{F_t(m|n_0)} \right) \]

yielding:

\[ \beta = \frac{F_t(m|n_0) D_t(m)}{F_t(m|n_0) + D_t(n_0)} \quad (S37) \]

which is the same as Eq. (9) from the main text. Similarly, Eq. (8) can be derived in this even more general setting.

**Inference in the presence of control over gate initialization**

In this subsection, we discuss the possibility of inferring $\alpha$ and $\beta$ in the case where we can control the initial state of the gate $\sigma_0$. Using the fact that $p_t(A|A) = \pi_A + \pi_I e^{-\lambda t}$ and $p_t(I|A) = \pi_I - \pi_I e^{-\lambda t}$, we have

\[ D_t(n_0, A) = F_t(m|n_0)(\pi_A + \pi_I e^{-\lambda t}) + \int_0^t F_t(m|n_0) \left( \pi_I (1 - e^{-\lambda t'}) \right) D_{t-t'}(m, I)dt'. \]

In the limit of short-time ($t \to 0$), we can write $e^{-\lambda t} \simeq 1 - \lambda t$, which gives us

\[ D_t(n_0, A) \simeq F_t(m|n_0) - \pi_I \lambda t F_t(m|n_0), \quad (S38) \]

where we neglect the second term. It is a matter of simple algebra to see that

\[ \alpha = \lim_{t \to 0} \frac{F_t(m|n_0) - D_t(n_0, A)}{t \cdot F_t(m|n_0)} \quad (S39) \]

Equation (S39) asserts that the early deviations of $D_t(n_0, A)$ from $F_t(m|n_0)$ can be leveraged to obtain the gating rate $\alpha$ corresponding to deactivation of the gate. On the other hand, Eq. (S23) is sufficient to infer $\beta$ as

\[ \beta = \lim_{t \to 0} D_t(m, I). \quad (S40) \]

In Fig. S1, we corroborate the validity of Eqs. (S39) and (S40) using the birth-death process described in Sec. of this SI (also used in the main text).
Inference in the case of diffusion

An important quantity in the inference of $\alpha$ and $\beta$ from the detection time distributions is the short-time asymptotics of $D_t(m, I)$. This quantity was derived in Eq. (S23) using the fact that, at short-times, the dominant contribution to detection events comes from trajectories where the gate opens before the underlying process escapes the target-region (i.e., for detection of threshold crossing events, it means that the time-series has not dropped below the threshold, and for gated chemical reactions, it corresponds to the particle not escaping the target site before the opening of the gate). However, in continuous-space Markov processes this underlying assumption does not hold, since the process can leave and return to the target region multiple times during an infinitesimally small time interval. This means that the second term on the right-hand side of Eq. (S20) can no longer be ignored.

Let us consider the example of a freely diffusing particle in 1-dimension, whose position at time $t$ we denote by $X_m(t)$ given that it starts from position $n_0$. We define $T_d(n_0, I)$ to be the time taken for the particle to be detected in a location $X_m(t) \geq m$, given that initially, the gate is in state $\sigma_0 = I$. While Eq. (S25) is valid even in this setting, Eq. (S27) is not. Thus, in order infer $\alpha$ and $\beta$, our goal is to compute the short-time asymptotics of the probability density $D_t(m, I)$ of the random variable $T_d(m, I)$.

We note that the dominant contribution to $D_t(m, I)$ at short-times comes from the events where detection happens as soon as the gate opens. Note that, in this time, owing to the continuous nature of the process, $X_m(t)$ could have dropped below the threshold $m$ and crossed it subsequently several times. Thus, instead of looking at the first time when it drops below the threshold, the more meaningful question to ask in this setting is: what is the probability that $X_m(t) \geq m$ when the gate opens? Owing to the symmetry of the free diffusion problem, the answer is clearly $\frac{1}{2}$. This observation allows us to write

$$\lim_{t \to 0} D_t(m, I) = \frac{\beta}{2}, \quad (S41)$$

and thus

$$\lim_{t \to 0} D_t(m, E) = \pi_I \lim_{t \to 0} D_t(m, I) = \pi_I \frac{\beta}{2}. \quad (S42)$$

Rearranging, we get the analogue of Eq. (S27) for continuous processes as

$$\pi_I = \frac{2}{\beta} \lim_{t \to 0} D_t(m, E), \quad (S43)$$

where we remark that the right-hand side of Eq. (S43) differs from the right-hand side of Eq. (S27) only by a factor of 2. This relation can be utilized along with Eq. (S25) to obtain

$$\beta = \lim_{t \to 0} \frac{2}{\pi_I} \frac{D_t(m, E) F_t(m|n_0)}{F_t(m|n_0) - D_t(n_0, E)}, \quad (S44)$$

and following the same steps as in the previous sections, we get

$$\alpha = \lim_{t \to 0} \frac{2}{\pi_I} \frac{D_t(m, E) F_t(m|n_0)}{D_t(n_0, E)}. \quad (S45)$$

This completes our derivation of the inference relations for $\alpha$ and $\beta$ for the case of continuous Markov processes. It is to be noted that though Eq. (S41) was derived for the detection of $X_m(t)$ above $m$, we expect it to be valid at short-times for detection in any finite sized interval $[m, m + \Delta]$ as well. The reason is that at short times the probability that the process $X_m(t)$ crosses above $m + \Delta$ is negligible. Thus, finite-size effects do not play a role at this level. Clearly, the threshold crossing problem is recovered in the $\Delta \to \infty$ limit.

MODELS USED FOR SIMULATIONS PRESENTED IN MAIN TEXT

The birth-death process

In this section of the Supplemental Material, we describe the birth-death process (BDP) used in the main text of our paper to produce Figs. 2 and 3.
We considered a BDP on a state space \( S \in \{0, 1, 2, \cdots, N\} \), with transition rates
\[
\begin{align*}
W_+(j) &= k_+(N - j), \\
W_-(j) &= k_-(j),
\end{align*}
\] (S46)  
which govern the rate of transitioning from state \( j \) to states \( j + 1 \) and \( j - 1 \) respectively, with \( j \in \{0, 1, 2, \cdots, N\} \). Clearly, states 0 and \( N \) act as reflecting boundaries, as \( W_-(0) = W_+(N) = 0 \).

Let us define \( F_t(m|n_0) \) to be the probability distribution of the time the BDP reaches state \( m \) for the first time, starting from state \( n_0 \). \( F_t(m|n_0) \) is called the first-passage time density, and it is known that \( F_t(m|n_0) \) obeys a Phase-type distribution \([2, 3]\), whose Laplace transform is easy to compute.

More explicitly, taking the example of \( n_0 = 0 \), we note that \( F_t(m|0) \) can be simply expressed as
\[
F_t(m|0) = k_+(N - m + 1) [\exp(\mathbb{W}(m)t)]_{m,1}.
\] (S48)
where \( \mathbb{W}(m) \) is the \( m \times m \) matrix obtained by retaining only the first \( m \) columns and \( m \) rows of the \( N + 1 \times N + 1 \) transition matrix \( \mathbb{W} \) containing all zeros, except where
\[
\mathbb{w}_{i+1,i} = k_+(N + 1 - i) \quad \text{and} \quad \mathbb{w}_{i,i+1} = k_- i,
\]
for \( i \in \{1, 2, \ldots, N\} \), and \( \mathbb{w}_{i,i} \) are chosen so that the columns of \( \mathbb{W} \) add up to zero.

Alternatively, one can also use the renewal method to determine the Laplace transformed first-passage distribution as
\[
\tilde{F}_t(m|n_0) = \frac{\tilde{P}_t(m|n_0)}{\tilde{P}_t(m|m)},
\] (S49)
where \( \tilde{P}_t(i|j) \) is the Laplace transform of the propagator \( P_t(i|j) \), which denotes the probability of finding the BDP in state \( i \in S \) at time \( t \), given that the system started from state \( j \in S \) initially. The propagator \( \tilde{P}_t(i|j) \) can be obtained for any BDP (see Eq. (2.4) in Ref.[4]).

**Diffusing particle in a closed interval with one reflective boundary and one absorbing boundary**

We start by computing the Green’s function \( C(x, t \mid x_0) \), namely, the conditional probability density function to find the particle at position \( x \) at time \( t \), given that the initial position is \( x_0 \), and given a reflective boundary at 0 and an absorbing boundary at \( m \). The initial condition is \( C(x, t = 0 \mid x_0) = \delta(x - x_0) \) by definition, and the boundary conditions we require are a Neumann boundary condition \( \frac{\partial C(x,t|x_0)}{\partial x}|_{x=0} = 0 \) and a Dirichlet boundary condition \( C(x = m, t|x_0) = 0 \).

Laplace transforming the diffusion equation, we obtain
\[
s\tilde{C}(x, s|x_0) = D\frac{d^2\tilde{C}(x, s|x_0)}{dx^2},
\] (S50)
which is a second-order, linear, homogeneous differential equation. It has a general solution
\[
\tilde{C}(x, s|x_0) = \begin{cases} 
\tilde{C}_-(x, s|x_0) = c_1(s)e^{x\sqrt{s}} + c_2(s)e^{-x\sqrt{s}}, & x < x_0 \\
\tilde{C}_+(x, s|x_0) = c_3(s)e^{x\sqrt{s}} + c_4(s)e^{-x\sqrt{s}}. & x > x_0
\end{cases}
\] (S51)

Similarly, Laplace transforming the boundary conditions we obtain
\[
\frac{d\tilde{C}(x, s|x_0)}{dx}|_{x=0} = 0,
\] (S52)
and
\[
\tilde{C}(m, s|x_0) = 0.
\] (S53)

Finally, the initial condition is translated to two matching conditions at the initial position of the particle, one for the continuity of the Laplace transform of the probability density
\[
\tilde{C}_+(x_0, s|x_0) = \tilde{C}_-(x_0, s|x_0),
\] (S54)
and one for the Laplace transform of the fluxes

$$-1 = D \left[ \frac{d\tilde{C}_+(x, s|x_0)}{dx} \Big|_{x=x_0} - \frac{d\tilde{C}_-(x, s|x_0)}{dx} \Big|_{x=x_0} \right], \quad (S55)$$

which is obtained by integrating both sides of the Laplace transformed diffusion equation (Eq. (S50)) over an infinitesimally small interval surrounding the initial position. Note that the 1 on the left-hand side comes from the Laplace transform of the delta function initial condition.

Imposing the above conditions produces a system of four equations with four unknowns, from which we can obtain $c_i(s)$ ($1 \leq i \leq 4$)

$$\begin{align*}
    c_1(s) &= \frac{\operatorname{sech}(m\sqrt{s}) \sinh(\sqrt{s}(m-x_0))}{2\sqrt{D}} \\
    c_2(s) &= \frac{\operatorname{sech}(m\sqrt{s}) \sinh(\sqrt{s}(m-x_0))}{2\sqrt{D}} \\
    c_3(s) &= \frac{\tanh(m\sqrt{s})-1 \cosh(x_0\sqrt{s})}{2\sqrt{D}} \\
    c_4(s) &= \frac{e^{-\frac{m\sqrt{s}}{2}}} {2\sqrt{D}} \operatorname{sech}(m\sqrt{s}) \cosh(x_0\sqrt{s}) \\
\end{align*} \quad (S56)$$

The Laplace transform of the first-passage probability density function is given by

$$\tilde{T}_f(m, s) = -D \frac{d\tilde{C}_+(x, s|x_0)}{dx} \Big|_{x=m} = \frac{m^2 - x_0^2}{2D} \quad (S57)$$

The Laplace transform is a moment generating function, and so the mean first-passage time is given by

$$\langle T_f \rangle = -\frac{d\tilde{T}_f(m, s)}{ds} \Big|_{s=0} = \frac{m^2 - x_0^2}{2D} \quad (S58)$$

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