

Stochastic Calculus for Pathwise Observables of Markov-Jump Processes: Unification of Diffusion and Jump Dynamics

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Pathwise observables—functionals of stochastic trajectories—are at the heart of time-averaged statistical mechanics and are central to thermodynamic inequalities such as uncertainty relations, speed limits, and correlation bounds. They provide a means of thermodynamic inference in the typical situation, when not all dissipative degrees of freedom in a system are experimentally accessible. So far, theories focusing on pathwise observables have been developing in two major directions, diffusion processes and Markov-jump dynamics, in a virtually disjoint manner. Moreover, even the respective results for diffusion and jump dynamics were derived with a patchwork of different approaches that are predominantly indirect. Stochastic calculus was recently shown to provide a direct approach to pathwise observables of diffusion processes, while a corresponding framework for jump dynamics remained elusive. In our work, we develop, in an exact parallelism with continuous-space diffusion, a complete stochastic calculus for pathwise observables of Markov-jump processes. We formulate a “Langevin equation” for jump processes, define general pathwise observables, and establish their covariation structure, whereby we fully account for transients and time-inhomogeneous dynamics. We prove the known kinds of thermodynamic inequalities in their most general form and discuss saturation conditions. We determine the response of pathwise observables to general (including thermal) perturbations and introduce a corresponding response-function formalism. We carry out the continuum limit to achieve the complete unification of diffusion and jump dynamics. In addition, we connect the framework to quantum unraveling and the Belavkin equation for open quantum systems, associating quantum and classical descriptions of thermal systems. Our results open avenues in the direction of discrete-state analogs of generative diffusion models and the learning of stochastic thermodynamics from fluctuating trajectories.

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I. INTRODUCTION

A large variety of systems in and out of equilibrium with nominally discrete-state spaces, or with continuous-state spaces but well-defined metastable states, can be accurately and thermodynamically consistently described by Markov-jump dynamics [1–19]. Intense research over the past few decades has led to quite a deep understanding of the (stochastic) thermodynamics [3,5,6,7,9,20–25] and

kinetics [24,26–35] of Markov dynamics under so-called local detailed balance [6,11,36,37], including fluctuation theorems [5,38–43], speed limits [44–51], thermodynamic uncertainty relations (TURs) [9,52–61], anomalous relaxation phenomena [32,62–64], nonequilibrium response relations [4,18,65–71], and, recently, descriptions within the framework of information geometry [21,30,30,31,64,72].

From a practical perspective, state-of-the-art experiments, in particular, single-particle tracking [73,74] and single-molecule spectroscopy [75–79] probe stochastic time series. Single-molecule techniques invariably track low, predominantly one-dimensional projections of high-dimensional dynamics (e.g., Förster resonance energy transfer efficiencies reporting on the instantaneous distance between fluorescent dyes [80–84], molecular extensions [77–79,84–88], or on the instantaneous distance between plasmonic particles [89,90] attached to the molecule). These projected time series are typically analyzed by averaging along individual realizations, thus giving rise to “pathwise

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observables” (i.e., functionals of stochastic paths) and leading naturally to the field of time-averaged statistical mechanics [73,91–95].

Currently, the quantity of central interest is typically the thermodynamic cost—the total entropy production—of nonequilibrium processes that may be considered as the nonequilibrium “counterpart” of free energy. However, one almost never has experimental access to all dissipative degrees of freedom and therefore probes only coarse observables (i.e., projections) of Markov-jump dynamics. Diverse approaches have meanwhile been developed for thermodynamic inference from coarse observations [9,19,96–104]. Thermodynamic inequalities, that is, diverse speed limits [44–51] and uncertainty relations [9,52–61,105–109], in particular, attracted much attention, as they provide a general means to infer a lower bound on dissipation of the entire system from a measured observable. These “thermodynamical inequalities” in various forms (and valid under different conditions) provide important insight into how dissipation bounds fluctuations [52–61], transport [45,46,51,110], and correlations [111–114] and, in turn, allow for efficient thermodynamic inference based on (generally coarse) observables. In addition to these three major classes of thermodynamic inequalities, alternative inference methods have been developed as well, based on the kinetic uncertainty relation [54], statistics of waiting times [97,115], first-passage times [26,53,55,116], via the so-called variance-sum rule [117,118], from the statistics of coarsely observed trajectories [100,104,119], and others.

However, despite the general consensus about their importance and applicability, there is no unified approach to deriving and proving the above results. For example, there are strategies involving the Cramér-Rao inequality [54,57,120–122], a variational approach [113], the scaled cumulant-generating function [59], large-deviation theory [123,124], and the master fluctuation theorem [56], to name a few. Because the above methods are generally indirect, not much is known about the sharpness and conditions required to saturate the various inequalities.

In the case of diffusion processes, a direct method based on stochastic calculus was recently introduced [51,61,71,114,125,126], which allows for a direct and unified approach. While the mathematical intricacies in correctly handling nowhere differentiable functions still seem to pose a barrier to the proliferation of the above ideas into the physics literature, the underlying concept of Itô calculus is well established.

In contrast, Markov-jump processes enjoy a much greater popularity in physics and, in particular, in stochastic thermodynamics [6,8,9,23,127]. Here, master-equation approaches [3,29,128] (and corresponding “quantum Hamiltonian” analogy [129]) and Feynman-Kac “tilting” [95,130], as well as approaches relying on path measures [6,20,22,131] are widely adopted in the community. Nevertheless, as far as proving thermodynamic

inequalities is concerned, these methods are not direct and do not provide insight about the sharpness and saturation conditions. A stochastic-calculus approach in the spirit of Refs. [51,61,71,114,125,126] is therefore desired to provide a unification of results for diffusion and Markov-jump dynamics and, specifically, of different approaches to Markov-jump dynamics.

The first steps in this direction, instigated in the appendix of Ref. [61], have indeed already been made in the context of TURs [60] and linear response [70]. However, the full battery of results, which is required for a true unification and for the approach to be able to compete with existing methods, remains to be developed.

Here, we carry out the complete program. We develop, in exact parallelism with the continuous diffusion counterpart, the stochastic equations of motion—a Langevin equation for Markov-jump processes with a central noise-time correlation lemma—and define general pathwise observables (i.e., densities and currents). The results are throughout presented in direct analogy with the continuous-space framework. We allow for time-inhomogeneous dynamics (e.g., time-dependent driving). Equivalent to diffusions [96], Stratonovich increments emerge that govern current-type observables and allow for a direct proof of the complete covariations (including in transients) of general density and current observables that take the form of (generalized) Green-Kubo relations. We use the developed stochastic calculus to prove directly the known thermodynamic inequalities (TUR, correlation TUR, transport bounds, bounds on correlations, etc.) in their most general form, assess their sharpness, and establish the respective saturation conditions. Moreover, fully within the continuous-space stochastic-calculus approach [71], we derive the response of an observable to general (including thermal) perturbations for Markov-jump dynamics. Finally, we carry out the continuum limit to achieve the unification of diffusion and jump dynamics. We conclude with an outlook on open questions and future directions.

The manuscript is structured as follows. In Sec. II, we first provide a summary of our main results. Next, in Sec. III, we develop the stochastic calculus for jump processes, formalize general pathwise observables and establish their complete covariation structure. In Sec. IV, we use the stochastic calculus to prove the (quite complete) list of thermodynamic inequalities in their most general form and apply them to thermodynamic inference on a selection of biophysical model systems. Following this, we show in Sec. V how the stochastic calculus can be applied to derive results for the response to general perturbations for discrete-state systems, establish the corresponding response-function formalism, and show how this relates to the fluctuation-dissipation theorem in equilibrium. In Sec. VI, we take the continuum limit to show the equivalence of stochastic calculi for continuous- and discrete-state systems and, in Sec. VII, we extend the results to time-inhomogeneous dynamics. Subsequently, in Sec. VIII, we discuss how the classical

stochastic-calculus approach is connected to quantum unraveling and the (discrete) Belavkin equation and state its classical analog. We conclude in Sec. IX with an outlook. The mathematical proofs of the noise-time correlation lemma and increment correlations, and other technical details, are given in the Appendix.

II. SUMMARY OF MAIN RESULTS

We aim to bridge the gap between continuous-space dynamics and Markov jump processes (MJPs) using stochastic calculus. Throughout, we will develop the results for MJPs in analogy with those of diffusions; all results will therefore be shown in parallel to make the analogy as clear and natural as possible. The central results of the stochastic calculus for continuous-space diffusion and Markov-jump processes are highlighted in Fig. 1.

In the context of continuous-space dynamics, we will focus on overdamped Langevin dynamics in d dimensions governed by [6,61,132,133]

$$d\mathbf{x}_\tau = \mathbf{F}(\mathbf{x}_\tau)d\tau + \boldsymbol{\sigma}d\mathbf{W}_\tau, \quad (1)$$

for the d -dimensional position $\mathbf{x}_\tau$ in a drift field $\mathbf{F}(\mathbf{x}_\tau)$ subject to thermal noise $\boldsymbol{\sigma}d\mathbf{W}_\tau$, where $d\mathbf{W}_\tau$ are increments of the d -dimensional Wiener process (i.e., d -dimensional “white noise”), with $\langle d\mathbf{W}_\tau \rangle = 0$ and $\langle (d\mathbf{W}_\tau)_i (d\mathbf{W}_{\tau'})_j \rangle = \delta_{ij}\delta(\tau - \tau')d\tau d\tau'$, and $\boldsymbol{\sigma}$ is the noise amplitude assumed to have full rank (nonzero determinant). In Sec. VII, we will also allow for time-inhomogeneous (temporally driven) dynamics, while, for clarity, we will develop the results within the time-homogeneous setting.

We will prove in Sec. III that trajectories x_τ of MJPs follow the matrix stochastic differential equation (i.e., a “discrete-space Langevin equation”)

$$d\mathbf{n}(\tau) = \mathbf{R}(\mathbf{x}_\tau, \tau)d\tau + d\boldsymbol{\varepsilon}(\tau), \quad (2)$$

where the displacements have elements $[d\mathbf{n}(\tau)]_{xy} = d\mathbf{n}_{xy}(\tau)$ describing jumps from state x to y in $[\tau, \tau + d\tau]$. The matrix $[\mathbf{R}(\mathbf{x}_\tau, \tau)]_{xy}d\tau = \delta_{x,x'}r_{xy}d\tau$ encodes the expected (average) drift in $[\tau, \tau + d\tau]$ with time-independent transition rate r_{xy} [following from the corresponding master

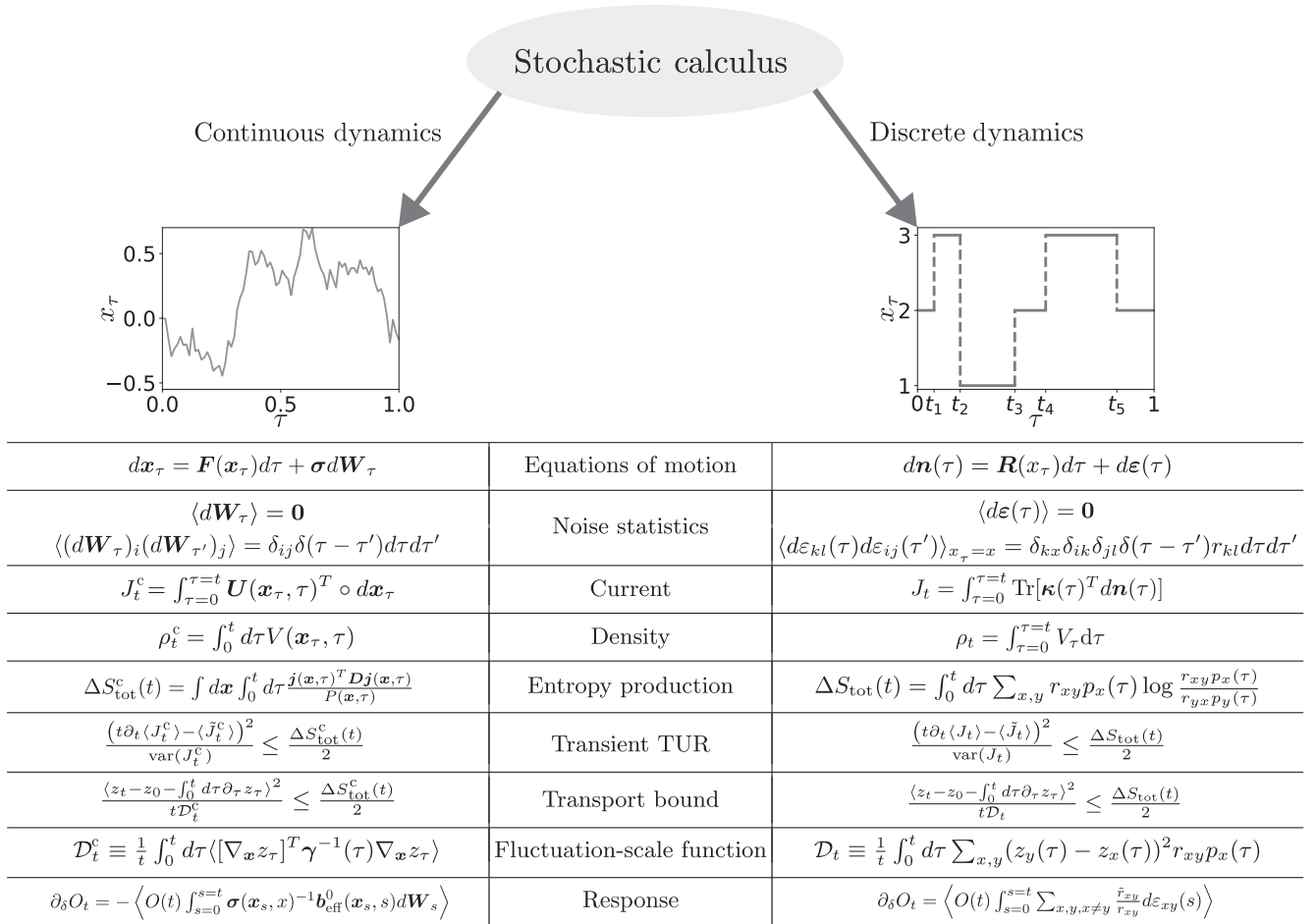


FIG. 1. Comparison of key quantities in continuous and discrete space, namely, the equations of motion, noise statistics, fundamental path observables, thermodynamic bounds, fluctuation-scale function, and response to perturbations (including temperature changes).

equation with generator $(L)_{xy} = -\delta_{xy} \sum_{y \neq x} r_{xy} + (1 - \delta_{xy})r_{yx}$, and the noise is encoded in the time-inhomogeneous shifted Poisson process $[d\mathbf{e}(\tau)]_{xy} = d\mathbf{e}_{xy}(\tau)$ [10,60,61,134]. This noise has zero mean $\langle d\mathbf{e}_{xy}(\tau) \rangle = 0$ and the white noise property $\langle d\mathbf{e}_{xy}(\tau) d\mathbf{e}_{ij}(\tau') \rangle_{x_\tau=k} = \delta_{ix} \delta_{jy} \delta_{ik} \delta(\tau - \tau') r_{ij} d\tau d\tau'$, where the expectation is conditioned on $x_\tau = k$. The Kronecker δ 's show that the noise increments on different edges are independent and only diagonal elements survive, e.g., $\langle d\mathbf{e}_{ij}(\tau) d\mathbf{e}_{ij}(\tau') \rangle_{x_\tau=k} = \delta_{ik} \delta(\tau - \tau') r_{ij} d\tau d\tau'$. Moreover, since $|d\mathbf{e}_{ij}| \sim \sqrt{d\tau}$, higher moments scale as $|d\mathbf{e}_{ij}|^n \sim (d\tau)^{n/2}$, so that all higher moments and cumulants with $n \geq 3$ vanish for small $d\tau$. Note that the Langevin Eq. (2) has already been introduced in Ref. [60].

We prove the central time-noise correlation lemma with $d\tau_i(\tau) = \delta_{x_i} d\tau$,

$$\frac{\langle d\mathbf{e}_{kl}(\tau) d\tau_i(\tau') \rangle_{x_\tau=x}}{d\tau d\tau'} = \delta_{xk} \mathbb{1}_{\tau < \tau'} [P(i, \tau' | l, \tau) - P(i, \tau' | k, \tau)] r_{kl} + \mathcal{O}(d\tau), \quad (3)$$

which gives access to nontrivial correlations between differentials in Eq. (2)

$$\begin{aligned} \langle dn_{xy}(\tau') d\tau_i(\tau) \rangle_{x_\tau=i}^{x_{\tau'}=x} &= r_{xy} P(x, \tau' | i, \tau) p_i(\tau) d\tau d\tau', \\ \langle dn_{xy}(\tau) d\tau_i(\tau') \rangle_{x_\tau=x}^{x_{\tau'}=i} &= r_{xy} P(i, \tau' | y, \tau) p_x(\tau) d\tau d\tau', \\ \langle dn_{xy}(\tau) dn_{ij}(\tau') \rangle_{x_\tau=x}^{x_{\tau'}=i} &= r_{ij} r_{xy} P(i, \tau' | y, \tau) p_x(\tau) d\tau d\tau', \end{aligned} \quad (4)$$

where $P(x, \tau' | i, \tau)$ is the transition probability (i.e., the “propagator”) from state i at τ to state x at $\tau' \geq \tau$ and $p_i(\tau)$ is the probability to find the system in state i at time τ . Note that the averages are “pinned,” e.g., $\langle \cdot \rangle_{x_\tau=i}^{x_{\tau'}=x}$ is the average conditioned on $x_\tau = i$ and $x_{\tau'} = x$ at times $\tau \leq \tau'$. The above correlations were shown in Ref. [60] using a different approach.

These correlations are required for the covariation structure of observables, such as currents and densities. Specifically, time-integrated currents are defined as [61]

$$\begin{aligned} J_t^c &= \int_{\tau=0}^t \mathbf{U}(\mathbf{x}_\tau, \tau)^T \circ d\mathbf{x}_\tau, & (\text{Stratonovich}) \\ J_t &= \int_{\tau=0}^t \text{Tr}[\boldsymbol{\kappa}(\tau)^T d\mathbf{n}(\tau)], \end{aligned} \quad (5)$$

for continuous-space and MJPs, respectively, where the former is a Stratonovich integral over some vector-valued $\mathbf{U}(\mathbf{x}_\tau, \tau)$ and the T denotes the transpose. Recall that the Stratonovich integral is a Riemann-Stieltjes-type integral defined as the limit of functions evaluated at midpoints, e.g., $\mathbf{f}(\mathbf{x}_\tau)^T \circ d\mathbf{x}_\tau = \mathbf{f}[(\mathbf{x}_{\tau+d\tau} + \mathbf{x}_\tau)/2]^T (\mathbf{x}_{\tau+d\tau} - \mathbf{x}_\tau)$. To give an intuition for $\mathbf{U}$, consider the example $[\mathbf{U}(\mathbf{x}_\tau, \tau)]_i = \mathbb{1}_{\mathbf{x}_\tau \in \{-h/2, h/2\}^d}$ the indicator-valued vector being nonzero if

$\mathbf{x}_\tau$ is in the hypercube with side length h , then the current “counts up” the displacement of the trajectory $\{\mathbf{x}_\tau\}_{0 \leq \tau \leq t}$ in that hypercube. Note the superscript “c” throughout this manuscript refers to continuous-space quantities, and we write superscript (c) as a placeholder when the corresponding relation is valid in both continuous- and discrete-space systems. For MJPs, the transitions are weighted by a time-dependent antisymmetric transition weight $\boldsymbol{\kappa}(\tau) = -\boldsymbol{\kappa}(\tau)$, which ensures a sign change in the current when reversing time [6]. Hence, we identify “Stratonovich integrals for MJPs” as integrals over traces of a two-point function and the jump increments. The above currents naturally decompose into a stochastic and “usual” integral [61], $J_t^{(c)} = J_t^{(c),I} + J_t^{(c),II}$, where the stochastic part is

$$\begin{aligned} J_t^{(c),I} &= \int_{\tau=0}^t \mathbf{U}(\mathbf{x}_\tau, \tau)^T \boldsymbol{\sigma} d\mathbf{W}_\tau & (\text{It\^o}) \\ J_t^I &= \int_{\tau=0}^t \text{Tr}[\boldsymbol{\kappa}(\tau)^T d\mathbf{e}(\tau)], \end{aligned} \quad (6)$$

respectively, while the usual part reads $J_t^{(c),II} = \int_0^t \mathcal{U}_\tau^{(c)} d\tau$, where $\mathcal{U}_\tau^c \equiv \mathbf{U}(\mathbf{x}_\tau, \tau)^T \mathbf{F}(\mathbf{x}_\tau) + \nabla \cdot [\mathbf{D}\mathbf{U}(\mathbf{x}_\tau, \tau)]$, $\mathbf{D} = \boldsymbol{\sigma}\boldsymbol{\sigma}^T/2$ is the diffusion matrix, and $\mathcal{U}_\tau \equiv \text{Tr}[\boldsymbol{\kappa}(\tau)^T \mathbf{R}(\mathbf{x}_\tau)]$. Thus, we identify in the second line of Eq. (6) the It\^o-type integral for observables of MJPs by analogy to diffusions.

Similarly, time-integrated densities are defined as [61]

$$\begin{aligned} \rho_t^c &= \int_0^t d\tau V(\mathbf{x}_\tau, \tau), \\ \rho_t &= \int_{\tau=0}^t V_\tau d\tau, \end{aligned} \quad (7)$$

for continuous and discrete dynamics, respectively, where $V(\mathbf{x}_\tau, \tau)$ and $V_\tau \equiv V(\mathbf{x}_\tau, \tau) = \sum_k \delta_{x_\tau, k} V_k(\tau)$ are scalar-valued functions.

(Co)variances of stationary densities and currents can be expressed in terms of integral operators [96,133]

$$\begin{aligned} \hat{\mathcal{X}}_{M,N}^{t,c}[\cdot] &= \int_0^t d\tau \int_\tau^t d\tau' \int d\mathbf{z} \int d\mathbf{z}' M(\mathbf{z})^T [\cdot] N(\mathbf{z}'), \\ \hat{I}_{G^\alpha, G^\beta}^t[\cdot] &= \int_0^t d\tau \int_\tau^t d\tau' \sum_{x,y} G_{xy}^\alpha \sum_{i,j} G_{ij}^\beta [\cdot], \end{aligned} \quad (8)$$

for continuous and discrete dynamics, respectively. The operator in the first line of Eq. (8) is already known [96,125]. For $X_t^{(c)} \in \{J_{t,k}^{(c)}, \rho_{t,k}^{(c)}\}$ and $Y_t^{(c)} \in \{J_{t,l}^{(c)}, \rho_{t,l}^{(c)}\}$, $k, l \in \{1, 2\}$, we find

$$\begin{aligned} \text{cov}(X_t^c, Y_t^c) &= \hat{\mathcal{X}}_{X,Y}^{t,c}[\Xi_m^{zz}] - \langle X_t^c \rangle \langle Y_t^c \rangle, \\ \text{cov}(X_t, Y_t) &= \hat{I}_{G^X, G^Y}^t[\Xi_{ij,xy}^m] - \langle X_t \rangle \langle Y_t \rangle, \end{aligned} \quad (9)$$

where $X_t^{(c)}, Y_t^{(c)}$ are the appropriate pathwise observables and G^X, G^Y functions that define them (e.g., κ in the case of currents for MJPs). Moreover, $m \in \{1, 2, 3\}$ indicates density-density ($m = 1$), current-density ($m = 2$), and current-current ($m = 3$) covariances. For the density covariance ($m = 1$), $X_t^{(c)} = \rho_{t,k}^{(c)}$ and $Y_t^{(c)} = \rho_{t,l}^{(c)}$, we get

$$\Xi_1^{zz'} = \langle 1 \rangle_{x_t=z}^{x_{t'}=z'} + \langle 1 \rangle_{x_t=z'}^{x_{t'}=z},$$

$$\Xi_{ijxy}^1 = \frac{\langle d\tau_x(\tau) d\tau_i(\tau') \rangle_{x_t=x}^{x_{t'}=i}}{d\tau d\tau'} + \frac{\langle d\tau_i(\tau) d\tau_x(\tau') \rangle_{x_t=i}^{x_{t'}=x}}{d\tau d\tau'}, \quad (10)$$

for current-density covariances ($m = 2$), we recover

$$\Xi_2^{zz'} = \frac{\langle \circ d\mathbf{x}_\tau \rangle_{x_t=z}^{x_{t'}=z'}}{d\tau} + \frac{\langle \circ d\mathbf{x}_{\tau'} \rangle_{x_t=z'}^{x_{t'}=z}}{d\tau'},$$

$$\Xi_{ijxy}^2 = \frac{\langle dn_{xy}(\tau) d\tau_i(\tau') \rangle_{x_t=x}^{x_{t'}=i}}{d\tau d\tau'} + \frac{\langle dn_{xy}(\tau') d\tau_i(\tau) \rangle_{x_t=i}^{x_{t'}=x}}{d\tau d\tau'}, \quad (11)$$

and for the current-current covariance ($m = 3$), we find

$$\Xi_3^{zz'} = \frac{\langle \circ d\mathbf{x}_\tau \circ d\mathbf{x}_{\tau'}^T \rangle_{x_t=z}^{x_{t'}=z'}}{d\tau d\tau'} + \frac{\langle \circ d\mathbf{x}_{\tau'} \circ d\mathbf{x}_\tau^T \rangle_{x_t=z'}^{x_{t'}=z}}{d\tau d\tau'}$$

$$\Xi_{ijxy}^3 = \frac{\langle dn_{xy}(\tau) dn_{ij}(\tau') \rangle_{x_t=x}^{x_{t'}=i}}{d\tau d\tau'} + \frac{\langle dn_{xy}(\tau') dn_{ij}(\tau) \rangle_{x_t=i}^{x_{t'}=x}}{d\tau d\tau'}. \quad (12)$$

These above correlations can all be evaluated explicitly. For MJPs, we find, using $\int_0^t d\tau \int_0^t d\tau' \rightarrow \int_0^t d\tau' (t - \tau')$ [96], that

$$\text{cov}(\rho_{t,k}, \rho_{t,l}) = \hat{I}_{V^k, V^l \delta}^t [P_s(x, \tau; i, \tau') + P_s(x, \tau'; i, \tau) - p_x^s p_i^s],$$

$$\text{cov}(J_{t,k}, \rho_{t,l}) = \hat{I}_{\kappa^k, V^l \delta}^t [\hat{J}_{xy} P(x, t' | i) p_i^s + \hat{J}_{yx}^\dagger P(i, t' | y) p_y^s - J_{xy}^s p_i^s],$$

$$\text{cov}(J_{t,k}, J_{t,l}) = t \sum_{x,y} \kappa_{xy}^k \kappa_{xy}^l r_{xy} p_x^s + \hat{I}_{\kappa^k, \kappa^l}^t [\hat{J}_{xy} \hat{J}_{ji}^\dagger P(x, t' | j) p_j^s + \hat{J}_{ij} \hat{J}_{yx}^\dagger P(i, t' | y) p_y^s - J_{xy}^s J_{ij}^s], \quad (13)$$

where $V^{\alpha/\beta} \delta$ is a shorthand notation for $V_i^{\alpha/\beta} \delta_{ij}$, J_{xy}^s is the local steady-state current between x and y , and $\hat{J}_{xy}^\dagger$ is the so-called dual-reverse current operator (reversed steady-state current) [96,125,133], which for MJPs reads $\hat{J}_{xy} = r_{xy} \rightarrow \hat{J}_{xy}^\dagger = r_{yx} p_y^s / p_x^s$ [6]. In Eq. (13), the joint stationary probabilities for state x at τ and i at τ' are denoted $P_s(x, \tau; i, \tau')$, while the marginal stationary distribution to be in a state x is p_x^s . Additionally, we use the fact that the propagator for time-homogeneous systems is time-translation invariant $P(i, \tau' | x, \tau) = P(i, \tau' - \tau | x)$. The results for continuous-space diffusion are given in Refs. [96,125]. For stationary initial conditions and with time-independent state function and transition weights, Eq. (13) have the form of generalized Green-Kubo-like relations, in the sense

that they relate (co)variances of observables to time integrals of (generalized) correlation functions of density and current observables (see Refs. [96,133] for a discussion of diffusion processes). Notably, Eq. (13) have a striking similarity to the continuous-space expressions [96,133]. Later, we show how to generalize Eq. (13) to include time-dependent transition weights and state functions, as well as transient dynamics.

A. Thermodynamic inequalities

Since we now have a stochastic calculus for MJPs at our disposal (including fluctuation and correlation relations), we can employ the same strategy as in Ref. [61] and derive thermodynamic inequalities from the Cauchy-Schwarz inequality by appropriately choosing an auxiliary functional. The first family of inequalities we prove in Sec. IV are generalized (including transient) correlation TURs [57,61],

$$\frac{\left(t \partial_t \langle J_t^{(c)} \rangle - \langle \tilde{J}_t^{(c)} \rangle - c(t) \left\{ [t \partial_t - 1] \langle \rho_t^{(c)} \rangle - \langle \tilde{\rho}_t^{(c)} \rangle \right\} \right)^2}{\text{var} \left(J_t^{(c)} - c(t) \rho_t^{(c)} \right)} \leq \frac{\Delta S_{\text{tot}}^{(c)}(t)}{2}, \quad (14)$$

where $c(t) : \mathbb{R} \rightarrow \mathbb{R}$ is a deterministic weight function for the density and $\Delta S_{\text{tot}}^{(c)}$ is the discrete (continuous) space entropy production [5]

$$\Delta S_{\text{tot}}^c(t) = \int_0^t d\tau \int d\mathbf{x} \frac{\mathbf{j}(\mathbf{x}, \tau)^T \mathbf{D}^{-1} \mathbf{j}(\mathbf{x}, \tau)}{P(\mathbf{x}, \tau)}, \quad (15)$$

$$\Delta S_{\text{tot}}(t) = \int_0^t d\tau \sum_{i,j} r_{ij} p_i(\tau) \log \frac{r_{ij} p_i(\tau)}{r_{ji} p_j(\tau)}. \quad (16)$$

Here, $\mathbf{j}(\mathbf{x}, \tau) = [\mathbf{F}(\mathbf{x}) - \mathbf{D} \nabla] P(\mathbf{x}, \tau)$ is the probability current entering the Fokker-Planck equation. In analogy with Ref. [61], we introduced the discrete-space modified time-integrated density and current $\tilde{\rho}_t = \int_{\tau=0}^t \tau \partial_\tau V_\tau d\tau$ and $\tilde{J}_t = \int_{\tau=0}^t \tau \text{Tr}[[\partial_\tau \kappa(\tau)]^T d\mathbf{n}(\tau)]$ that account for the dependence of $V_i(\tau)$ and $\kappa(\tau)$ on τ . To compare, the continuous-space modified current and density read $\tilde{J}_t^c = \int_{\tau=0}^t \tau \partial_\tau \mathbf{U}(\mathbf{x}_\tau, \tau)^T \circ d\mathbf{x}_\tau$ and $\tilde{\rho}_t^c = \int_0^t \tau \partial_\tau V(\mathbf{x}_\tau, \tau) d\tau$, respectively. The transient correlation TUR for MJPs in Eq. (14) has not yet been proven in this generality since previous results were restricted to steady states [57] or did not consider correlations [135].

Setting $c(t) = 0$, we recover the transient TUR. The correlation TUR (CTUR) (in contrast to the TUR) allows one to turn the Cauchy-Schwarz inequality into an equality for all times, given a suitable choice of V_τ and $\kappa(\tau)$. This choice, however, requires explicit and detailed information about the system and is therefore not applicable in most

realistic applications. We can, nevertheless, optimize Eq. (14) with respect to $c(t)$ for given V_τ and $\kappa(\tau)$ to find

$$c^*(t) = \frac{a(t)\text{cov}(\rho_t, J_t) - b(t)\text{var}(J_t)}{a(t)\text{var}(\rho_t) - b(t)\text{cov}(\rho_t, J_t)}, \quad (17)$$

where $a(t) = t\partial_t \langle J_t^{(c)} \rangle - \langle \tilde{J}_t^{(c)} \rangle$ and $b(t) = [t\partial_t - 1] \langle \rho_t^{(c)} \rangle - \langle \tilde{\rho}_t^{(c)} \rangle$. Note that this optimal CTUR contains only operationally accessible quantities and affords an improved thermodynamic inference compared to using currents or densities alone. Interestingly, in contrast to the steady-state result [57], choosing an arbitrary $c(t)$ may even deteriorate the inference compared to the bare current or density TURs.

The second thermodynamic inequality we prove is the thermodynamic bound on the transport of any scalar observable $z_\tau \equiv z(x_\tau, \tau)$ [51],

$$\frac{\langle z_t - z_0 - \int_0^t d\tau \partial_\tau z_\tau \rangle^2}{t\mathcal{D}_t^{(c)}} \leq \frac{\Delta S_{\text{tot}}^{(c)}}{2}, \quad (18)$$

where in continuous space it was shown [51,113] that

$$\mathcal{D}_t^{(c)} = \frac{1}{t} \int_0^t d\tau \left\langle [\nabla_x z_\tau]^T \boldsymbol{\gamma}^{-1}(\tau) \nabla_x z_\tau \right\rangle, \quad (19)$$

while for MJPs we find

$$\mathcal{D}_t \equiv \frac{1}{t} \int_0^t d\tau \sum_{x,y} [z_y(\tau) - z_x(\tau)]^2 r_{xy} p_x(\tau). \quad (20)$$

Here, $\mathcal{D}_t^{(c)}$ is the so-called “fluctuation-scale function” accounting for how much the observation stretches microscopic coordinates. For example, note that stretching $z_\tau \mapsto az_\tau$ for some constant $a \in \mathbb{R}$ does not alter Eq. (18), as the stretch in the nominator is canceled by the change in $\mathcal{D}_t^{(c)}$. In Eq. (20), $z_x(\tau)$ is the specific value of the function z_τ if $x_\tau = x$, i.e., $z_\tau \equiv z(x_\tau, \tau) = \sum_k \delta_{x,k} z_k(\tau)$. The fluctuation-scale function for both continuous- and discrete-space dynamics is operationally accessible by considering increments $dz(\tau) = z(x_{\tau+d\tau}, \tau + d\tau) - z(x_\tau, \tau)$ along a trajectory and recognizing (as in continuous space [51,113]) that

$$\mathcal{D}_t^{(c)} = \frac{1}{t} \int_{\tau=0}^{\tau=t} \text{var}[dz(\tau)]. \quad (21)$$

Contrary to the CTUR, the transport bound cannot be saturated, in general. We provide a counterexample to illustrate how an attempt to saturate Eq. (17), in general, fails.

The last family of thermodynamic bounds we prove are thermodynamic bounds on observable correlations (or, in short, “correlation bounds”) as a generalization of the bounds in Ref. [113]. It involves correlations of time-independent observables $V_\tau \equiv V(x_\tau) = \sum_k \delta_{x,k} V_k$ and

$z_\tau \equiv z(x_\tau) = \sum_k \delta_{x,k} z_k$ and their time average along a trajectory, e.g., $\bar{V}_t = t^{-1} \int_0^t V_\tau d\tau$, resulting in a lower bound of the integrated entropy production rate $\dot{S}_{\text{tot}}(\tau)$ weighted by a “pseudovariance” $\text{pvar}_{\text{ps}}^F(z_\tau) = \sum_{x,y} p_{xy}^{\text{ps}}(\tau) [z_x + z_y - 2F(\tau)]^2$ [114],

$$\frac{[2\text{cov}(V_t, \bar{z}_t) - \frac{2}{t} \int_0^t d\tau \text{cov}(V_\tau, z_\tau)]^2}{t\text{var}(\bar{V}_t)} - \mathcal{D}_t + \frac{2}{t} [\text{var}(z_t) - \text{var}(z_0)] \leq \frac{1}{t} \int_0^t d\tau \dot{S}_{\text{tot}}(\tau) \text{pvar}_{\text{ps}}^F(z_\tau), \quad (22)$$

where $F(\tau)$ may be any time-(in)dependent function. The tilted two-point probability,

$$p_{xy}^{\text{ps}}(\tau) = \frac{p_x(\tau) r_{xy} Z_{xy}(\tau)^2}{\Sigma_{\text{ps}}}, \quad (23)$$

where $Z_{xy}(s) = [r_{xy} p_x(\tau) - r_{yx} p_y(\tau)] / [r_{xy} p_x(\tau) + r_{yx} p_y(\tau)]$ and $\Sigma_{\text{ps}} = \sum_{x,y} p_x(\tau) r_{xy} Z_{xy}(\tau)^2$, requires knowledge about transition rates, hence the pseudovariance is not operationally accessible. However, it can be controlled by choosing bounded observables. From the expression Eq. (23), we can see that $p_{xy}^{\text{ps}}(\tau)$ tilts the probability weight onto dissipating transitions. Hence, the pseudovariance projects the observable onto dissipating transitions. Further, we emphasize that the pseudovariance is a mathematical construct, which needs to be bounded further, hence the physical interpretation is not relevant. In nonequilibrium steady states (NESS), Eq. (22) reads

$$\frac{4[\text{cov}(V_t, \bar{z}_t) - \text{cov}_s(V, z)]^2}{t\text{var}(\bar{V}_t)} - \mathcal{D}_t \leq \frac{\Delta S_{\text{tot}}(t)}{2t} \text{pvar}_{\text{ps}}^F(z). \quad (24)$$

In Sec. IV, we provide an example to showcase how the correlation bound can be applied to systems where both the CTUR and transport bound fail to infer a nonzero entropy production.

B. Time-inhomogeneous dynamics

The generalization of the above results to systems exposed to time-dependent driving with constant protocol speed v [altering the generator as $\mathbf{L} \rightarrow \mathbf{L}(v\tau)$] is in most cases straightforward. Indeed, the covariation results Eq. (9), the CTUR Eq. (14), and the transport bound Eq. (18) generalize immediately. While the results for the covariation and the transport bound remain unaltered (up to the obvious change in the expectation operation $\langle \cdot \rangle$), the CTUR becomes altered with the differential operator $\hat{\Lambda} \equiv t\partial_t - v\partial_v$ and reads

$$\frac{(\hat{\Lambda} \langle J_t \rangle - c(t) \{ [\hat{\Lambda} - 1] \langle \rho_t \rangle \})^2}{\text{var}[J_t - c(t) \rho_t]} \leq \frac{\Delta S_{\text{tot}}}{2}. \quad (25)$$

Conversely, the correlation bound does not easily generalize to include time-dependent driving.

C. Response to external perturbations

The response of a single-time observable $O(t)$ of a continuous-space diffusion to a perturbation in the noise amplitude, which effectively is a temperature perturbation [136], $\sigma \rightarrow \sigma + \delta\tilde{\sigma}$ with perturbation noise amplitude $\tilde{\sigma}$ was recently derived using stochastic calculus and reads [137]

$$\partial_\delta O_t \equiv \lim_{\delta \rightarrow 0} \frac{1}{\delta} (\langle O(t) \rangle_\delta - \langle O(t) \rangle) \quad (26)$$

$$= - \left\langle O(t) \int_{s=0}^{s=t} \sigma(x_s, s)^{-1} b_{\text{eff}}^0(x_s, s) dW_s \right\rangle, \quad (27)$$

where $\langle \cdot \rangle$ is the average with respect to the unperturbed process in Eq. (1) [now with multiplicative noise $\sigma(x, \tau)$] and $\langle \cdot \rangle_\delta$ is the average with respect to the perturbed process

$$d\mathbf{x}_\tau^\delta = F(\mathbf{x}_\tau^\delta) d\tau + [\sigma(\mathbf{x}_\tau^\delta, \tau) + \delta\tilde{\sigma}(\mathbf{x}_\tau^\delta, \tau)] dW_\tau. \quad (28)$$

The effective drift $[b_{\text{eff}}^0(\mathbf{x}, s)]_i = \frac{1}{2} [\Sigma(\mathbf{x}, s) s^0(\mathbf{x}, s)]_i + \frac{1}{2} \sum_j \partial_{x_j} \Sigma_{ij}(\mathbf{x}, s)$ can be written in terms of the score function $s^0(\mathbf{x}, t) = \nabla_{\mathbf{x}} \log p(\mathbf{x}, t)$ of the instantaneous probability distribution of $\mathbf{x}_\tau$ in Eq. (1) and $\Sigma = \sigma\sigma^T + \tilde{\sigma}\tilde{\sigma}^T$ [137].

We derive the equivalent results for MJPs perturbing a general control parameter $\chi \rightarrow \chi + \delta$, where we find that Eq. (26) takes the form

$$\partial_\delta O_t = \left\langle O(t) \int_{s=0}^{s=t} \sum_{x,y \neq x} \frac{\tilde{r}_{xy}}{r_{xy}} d\epsilon_{xy}(s) \right\rangle, \quad (29)$$

where the unperturbed system evolves according to Eq. (2), whereas the perturbed system obeys

$$d\mathbf{n}^\delta(\tau) = \mathbf{R}^\delta(\mathbf{x}_\tau^\delta) d\tau + d\epsilon^\delta(\tau), \quad (30)$$

with rates r_{xy}^δ perturbed as

$$r_{xy}^\delta = r_{xy} + \delta\tilde{r}_{xy} + \mathcal{O}(\delta^2). \quad (31)$$

Note that similar results have recently been obtained with a martingale approach [138].

For equilibrium systems where

$$r_{xy} = D e^{(\lambda E_x - (1-\lambda) E_y)/T}, \quad (32)$$

with mixing parameter $\lambda \in [0, 1]$ and free energies E_x of state x , we find that Eq. (29) for temperature perturbations $T \rightarrow T + \delta$ equals the equilibrium correlation function of O and free energy E ,

$$\partial_\delta O_t = \frac{1}{T^2} (\langle OE \rangle_{\text{eq}} - \langle O(t) E(0) \rangle_{\text{eq}}) \equiv \frac{1}{T^2} C_{OE}(t). \quad (33)$$

The result in Eq. (29) relates the response to an observable O to a general small perturbation of the dynamics to correlation functions of the unperturbed dynamics (which, notably, for both MJPs and diffusions are not necessarily operationally accessible). In the case of equilibrium dynamics, Eq. (29) reduces to the fluctuation-dissipation theorem (FDT) in Eq. (33). Therefore, Eq. (29) can in some sense be seen as a (mathematical) extension of the FDT to irreversible and transient systems.

We further generalize the response in Eq. (29) to perturbations of pathwise observables of MJPs (see Appendix A 8). Without loss of generality, we set

$$O_1(t) = \int_{s=0}^{s=t} \text{Tr}[\mathbf{b}(s)^T d\epsilon(s)],$$

$$O_2(t) = \int_0^t g_s ds,$$

for some time-dependent hollow matrix $\mathbf{b}(s)$ and state function $g_s \equiv \sum_x \delta_{x,s} g_x(s)$. For a perturbation strength $h(s)$, i.e., $r_{xy} \rightarrow r_{xy} + h(s) \tilde{r}_{xy}$, the result Eq. (29) for $O_p(t) = O_1(t) + O_2(t)$ and its pathwise extension in Sec. V C 3 can be recast into the familiar response-function formalism

$$\begin{aligned} \Delta O_p(t) &\equiv \langle O_p(t) \rangle_h - \langle O_p(t) \rangle \\ &= \int_0^t ds h(s) \chi_{O_p}(t, s) + \mathcal{O}(h^2), \end{aligned} \quad (34)$$

with response function $\chi_{O_p}(t, s)$,

$$\begin{aligned} \chi_{O_p}(t, s) &= \chi_{O_1}(t, s) + \chi_{O_2}(t, s) \\ &= \mathbb{1}_{s < t} \sum_{x,y \neq x} b_{xy}(s) \tilde{r}_{xy} p_x(s) \\ &\quad + \int_0^t d\mathbb{1}_{z > s} \langle g_z R(s) \rangle, \end{aligned} \quad (35)$$

with $R_x(s) = \sum_y \tilde{r}_{yx} p_y(s) / p_x(s)$.

The results in Eqs. (27) and (29) may be useful in the context of computer simulations of high-dimensional systems, where knowing the drift, diffusivity, and dW_s (and their discrete-state counterparts) allows one to evaluate perturbations without the need to solve the high-dimensional Fokker-Planck (or master) equation of the perturbed system. In this context, Eq. (29) is expected to be useful, e.g., when the diagonalization of the transition matrix becomes computationally too demanding.

D. Stochastic calculus and open quantum systems

Open discrete quantum systems coupled to a thermal bath are described by the Belavkin equation [139]

$$d\rho_s^u = \mathcal{B}(\rho_s^u)ds + \sum_i \left(\frac{\mathcal{J}_i(\rho_s^u)}{\text{Tr}[\mathcal{J}_i(\rho_s^u)]} - \rho_s^u \right) d\tilde{n}_{is}, \quad (36)$$

where the pure state ρ_s^u is a rank-one matrix and $\mathcal{J}_i(\rho_s^u) = \hat{J}_i \rho_s^u \hat{J}_i^\dagger$ with jump operator $\hat{J}_i$ for the i th quantum jump. The deterministic drift in Eq. (36) has the form

$$\begin{aligned} \mathcal{B}(\rho_s^u) = & -i\hat{H}_{\text{eff}}\rho_s^u + \rho_s^u\hat{H}_{\text{eff}}^\dagger \\ & - \rho_s^u \text{Tr}(-i\hat{H}_{\text{eff}}\rho_s^u + \rho_s^u\hat{H}_{\text{eff}}^\dagger), \end{aligned} \quad (37)$$

where the effective Hamiltonian $\hat{H}_{\text{eff}} = \hat{H} - (i/2) \sum_j \hat{J}_j^\dagger \hat{J}_j$ includes the Hamiltonian $\hat{H}$ and $d\tilde{n}_{is}$ is a stochastic differential that takes values of 1 if the i th transition occurs in $[s, s + ds]$ and 0 otherwise. The statistical properties of the noise are $\langle d\tilde{n}_{is} \rangle = \text{Tr}[\mathcal{J}_i(\rho_s)]$ and $d\tilde{n}_{is}d\tilde{n}_{js} = \delta_{ij}d\tilde{n}_{is}$.

We show that the classical analog to Eq. (36) reads

$$\begin{aligned} d\delta_{x_s x} = & \sum_{y \neq x} (r_{yx}\delta_{x_s y}ds - \langle dn_{yx} \rangle - r_{xy}\delta_{x_s x}ds + \langle dn_{xy} \rangle) \\ & + \sum_{y \neq x} (d\epsilon_{yx} + \langle dn_{yx} \rangle - d\epsilon_{xy} - \langle dn_{xy} \rangle). \end{aligned} \quad (38)$$

Taking the average over all noise histories in Eqs. (36) and (38) recovers the Lindblad and master equation, respectively. Hence, Eqs. (36) and (38) are the stochastic evolution of states in the system. These, as well as other functionals of stochastic increments, we can study, as we know the underlying equations of motion, e.g., Eq. (2).

In the following section, we provide detailed definitions and derivations of the above results and present applications. Technical steps and lemmas are deferred to the Appendix.

III. THEORY

A. Stochastic equations of motion

To facilitate the comparison between discrete- and continuous-state spaces, we briefly summarize the basics of overdamped (for simplicity, additive-noise) diffusions.

Let $(x_\tau)_{0 \leq \tau \leq t}$ be a trajectory of $x_\tau \in \mathbb{R}^d$ evolving according to overdamped Langevin dynamics [6,132,137],

$$dx_\tau = F(x_\tau)d\tau + \sigma dW_\tau, \quad (39)$$

where dW_τ is the d -dimensional Wiener process with $\langle dW_\tau \rangle = 0$ and $\langle (dW_\tau)_i (dW_{\tau'})_j \rangle = \delta_{ij} \delta(\tau - \tau') d\tau d\tau'$, F is a drift field, and σ is the noise amplitude yielding the diffusion matrix $D = \sigma\sigma^T/2$. While some bounds for continuous trajectories presented in the next section also apply to underdamped trajectories, we here limit the

discussion to overdamped systems. This restriction allows for consistent comparisons with jump dynamics, since these descriptions are valid for negligible and marginalized momenta [1,132], respectively. The evolution of the probability density $P(x, \tau)$ of x_τ is governed by the Fokker-Planck equation [140] $\partial_\tau P(x, \tau) = -\nabla \cdot \mathbf{j}(x, \tau)$, written as a continuity equation with probability current $\mathbf{j}(x, \tau) = [F(x) - D\nabla]P(x, \tau)$.

Consider now a discrete-state space $\mathcal{N} \subseteq \mathbb{N}$ which, without loss of generality, we can enumerate as $\mathcal{N} = \{1, 2, \dots, N\}$. Focusing for the time being on time-homogeneous systems (i.e., time-independent transition rates r_{ij} between states i and j), the state probability vector $p_i(\tau)$ evolves according to the master equation [8,14]

$$\frac{d}{d\tau} p_i(\tau) = \sum_{j \neq i} [r_{ji}p_j(\tau) - r_{ij}p_i(\tau)], \quad (40)$$

where the summation is over only j . In terms in the incoming and outgoing fluxes $J_{xy}(\tau) = r_{xy}p_x(\tau)$, we have as $[d/(\tau)]p_i(\tau) = \sum_{j \neq i} [J_{ij}(\tau) - J_{ji}(\tau)]$, and in vector notation $[d/(\tau)]\mathbf{p}(\tau) = \mathbf{L}\mathbf{p}(\tau)$ with generator $\mathbf{L}$ having entries $L_{ij} = \delta_{ij}r_{ii} + (1 - \delta_{ij})r_{ji}$ and exit rate $r_{ii} = -\sum_{j \neq i} r_{ij}$. The transition probability (or propagator) is therefore given by $P(i, \tau' - \tau | j) = P(i, \tau' | j, \tau) = (\exp(\tau' - \tau)\mathbf{L})_{ij}$.

A path is fully determined by the sequence of states (x_i) and transition times t_i , $(x_\tau)_{0 \leq \tau \leq t} = (x_0, t_0 = 0; x_1, t_1; \dots)$. The normalized probability of such a trajectory is then [6,36,95,141,142]

$$\mathbb{P}[(x_\tau)_{0 \leq \tau \leq t}] = p_{x_0}(0) e^{\sum_k \tau_k(t) r_{kk}} \prod_{i,j} (r_{ij})^{n_{ij}(t)}, \quad (41)$$

where $p_{x_0}(0)$ is the probability of the initial state x_0 and $n_{ij}(t)$ and $\tau_k(t)$ are the number of transitions $i \rightarrow j$ and the total time spent in state k along the trajectory of length t , respectively, and can be formulated as [61]

$$\begin{aligned} n_{ij}(t) &= \int_{\tau=0}^{\tau=t} dn_{ij}(\tau), \\ \tau_i(t) &= \int_{\tau=0}^{\tau=t} d\tau_i(\tau). \end{aligned} \quad (42)$$

Suppose $x_\tau = i \neq j$, then $dn_{ij}(\tau) \sim \text{Poi}(r_{ij}d\tau)$ is Poisson distributed and describes the number of transitions i to j that occur in the time interval $[\tau, \tau + d\tau]$. In particular [10,60,61,134],

$$\begin{aligned} dn_{ij}(\tau) & \xrightarrow{d\tau \rightarrow 0} \begin{cases} 1, & x_\tau = i \text{ and transition } i \rightarrow j \text{ occurs in } [\tau, \tau + d\tau], \\ 0, & \text{else.} \end{cases} \end{aligned} \quad (43)$$

Note that $n_{ij}(\tau)$ is not continuous (and therefore not differentiable). Similarly, the differential describing the time spent in a state is [10,60,61,134]

$$d\tau_i(\tau) = \begin{cases} d\tau, & x_\tau = i, \\ 0, & \text{else.} \end{cases} \quad (44)$$

For any state i along the trajectory, the probability to transition to another state j in the $d\tau$ is given by $r_{ij}d\tau$. Therefore, it is natural to define a noise [10,60,61,70]

$$d\epsilon_{ij}(\tau) \equiv dn_{ij}(\tau) - r_{ij}d\tau_i(\tau), \quad (45)$$

by subtracting the expected number of jumps $r_{ij}d\tau_i(\tau)$ from the actual jumps $dn_{ij}(\tau)$. This noise has also been studied in the context of martingales [10].

Rearranging Eq. (45) yields the consistent stochastic equation of motion for $x \neq y$ for MJPs,

$$\underbrace{dn_{xy}(\tau)}_{\text{displacement}} = \underbrace{r_{xy}\delta_{x,\tau}d\tau}_{\text{drift}} + \underbrace{d\epsilon_{xy}(\tau)}_{\text{noise}}. \quad (46)$$

Defining the matrix $[\mathbf{R}(x_\tau)]_{ij} \equiv (1 - \delta_{ij})r_{ij}\delta_{x_\tau,i}$, we can write Eq. (46) as a stochastic matrix equation

$$d\mathbf{n}(\tau) = \mathbf{R}(x_\tau)d\tau + d\boldsymbol{\epsilon}(\tau). \quad (47)$$

The differential matrices have entries $[d\mathbf{n}(\tau)]_{ij} = dn_{ij}(\tau)$ and $[d\boldsymbol{\epsilon}(\tau)]_{ij} = d\epsilon_{ij}(\tau)$, where

$$\langle d\epsilon_{kl}(\tau)d\epsilon_{ij}(\tau') \rangle_{x_\tau=x} = \delta_{kx}\delta_{lx}\delta_{ij}\delta(\tau - \tau')r_{kl}d\tau d\tau', \quad (48)$$

in complete analogy with the Wiener process $dW_\tau \propto \sqrt{d\tau}$. Equation (47) is a matrix evolution equation, while the continuous evolution, Eq. (39), is vectorial. However, it has the same structure as the Langevin equation, as it consists of a “displacement,” “deterministic drift,” and “noise,” see Eq. (46). We highlight the comparison in Table I. It should be stressed that the diagonal terms in Eq. (47) are to be neglected, as they do not have any physically relevant meaning.

Note that $d\boldsymbol{\epsilon}(\tau)$ is not Gaussian noise, but rather a shifted [due to the $\mathbf{R}(x_\tau)d\tau$ term] time-inhomogeneous Poisson process. Explicitly, because for $x_\tau = x$ and $y \neq x$ the differential $dn_{xy}(\tau) \sim \text{Poi}(r_{xy}d\tau)$ is Poisson, the values $d\epsilon_{xy}(\tau)$ can take for any x_τ are $d\epsilon_{xy}(\tau) \in \{0, -r_{xy}d\tau,$

$1 - r_{xy}d\tau, 2 - r_{xy}d\tau, 3 - r_{xy}d\tau, \dots\}$, where $d\epsilon_{xy}(\tau) = 0$ happens if $x_\tau \neq x$. In case $x_\tau = x$, one can identify $P[d\epsilon_{xy}(\tau) = k - r_{xy}d\tau | x_\tau = x] = \text{Poi}_{r_{xy}d\tau}(k)$ for any $k \in \mathbb{N}_{\geq 0}$, where $\text{Poi}_\lambda(k) = \lambda^k e^{-\lambda}/k!$ is the Poisson distribution function. In the limit of small $d\tau$, to linear order in $d\tau$, the noise therefore takes values $d\epsilon_{xy}(\tau) \in \{0, -r_{xy}d\tau, 1 - r_{xy}d\tau\}$ with probabilities $1 - p_x(\tau), (1 - r_{xy}d\tau)p_x(\tau), r_{xy}d\tau p_x(\tau)$, respectively. The probability for any $k \geq 2$ is $\mathcal{O}(d\tau^k)$ and can therefore be neglected.

Additionally, the scaling of the noise $d\boldsymbol{\epsilon}(\tau) \sim \sqrt{d\tau}$ [see Eq. (48)] implies that $|d\boldsymbol{\epsilon}(\tau)/d\tau| \sim 1/\sqrt{d\tau}$ and, therefore, $|d\mathbf{n}(\tau)/d\tau| \sim 1/\sqrt{d\tau}$. The limit $d\tau \rightarrow 0$ does not exist. This scaling is similar to the well-known (and often ignored) issue with writing the Langevin equation in the “physicist’s” way using $\dot{\mathbf{x}}_\tau$.

Further similarities in the equations of motion become obvious, e.g., in Fig. 2. Any trajectory is fully characterized by $d\mathbf{n}(\tau)$ or $d\mathbf{x}_\tau$ (see Fig. 2). Moreover, as shown in Appendix A 3, the master equation follows from Eq. (47) in the same manner as the Fokker-Planck equation follows from Eq. (39).

We further require the statistical properties of the above stochastic differentials. Conditioning the expectation on being in a specific state, e.g., $x_\tau = x$, we recover for $\tau \leq \tau'$,

$$\begin{aligned} \langle dn_{ij}(\tau) \rangle_{x_\tau=x} &= \delta_{ix}r_{ij}d\tau, \\ \langle d\tau_i(\tau) \rangle_{x_\tau=x} &= \delta_{ix}d\tau, \\ \langle d\epsilon_{ij}(\tau) \rangle_{x_\tau=x} &= 0, \\ \langle d\tau_i(\tau)d\tau_j(\tau') \rangle_{x_\tau=x} &= \delta_{ix}P(j, \tau' | i, \tau)d\tau d\tau'. \end{aligned} \quad (49)$$

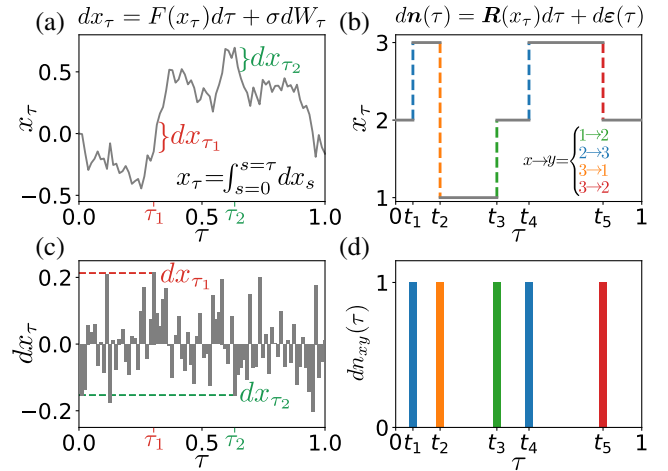


FIG. 2. Schematic comparison of discrete and continuous trajectories. (a) A continuous trajectory is shown. (b) A discrete trajectory in a three-state MJP. The transitions $2 \rightarrow 3$ (blue), $3 \rightarrow 1$ (orange), $1 \rightarrow 2$ (green), and $3 \rightarrow 2$ (red) are marked with the respective colors. The displacement and jump increments dx_τ and $dn_{xy}(\tau)$ are presented in (c) and (d) for the continuous and discrete trajectories. The colors in (d) correspond to the different transitions in (b).

TABLE I. Overview of quantities entering the stochastic equations of motion in continuous and discrete space.

Meaning	Continuous	Discrete
Displacement	$d\mathbf{x}_\tau$	$d\mathbf{n}(\tau)$
Deterministic drift	$\mathbf{F}(x_\tau)d\tau$	$\mathbf{R}(x_\tau)d\tau$
Noise	σdW_τ	$d\boldsymbol{\epsilon}(\tau)$

We are also required to evaluate cross-correlations between the noise and the time spent in a state, which follows from the noise-time correlation lemma

$$\begin{aligned} & \frac{\langle d\epsilon_{kl}(\tau) d\tau_i(\tau') \rangle_{x_\tau=x}}{d\tau d\tau'} \\ &= \delta_{xk} \mathbb{1}_{\tau < \tau'} [P(i, \tau' | l, \tau) - P(i, \tau' | k, \tau)] r_{kl} + \mathcal{O}(d\tau). \end{aligned} \quad (50)$$

The above lemma has been shown before [60]; in Appendix A 1 we provide a new alternative proof. Note that, due to the Markovianity of the system, we do not need to restrict on $\tau \leq \tau'$ in evaluating the expectation, as $\tau > \tau'$ vanishes.

The above correlators allow, for example, one to evaluate the covariance between the number of jumps at different space-time points along the trajectory, i.e., for $\tau \leq \tau'$ [60],

$$\begin{aligned} & \langle dn_{kl}(\tau) dn_{ij}(\tau') \rangle_{x_\tau=x} \\ &= d\tau d\tau' \delta_{kx} r_{kl} [\delta(\tau - \tau') \delta_{ik} \delta_{jl} + \mathbb{1}_{\tau=\tau'} \delta_{ik} r_{ij} \\ &+ \mathbb{1}_{\tau < \tau'} r_{ij} P(i, \tau' | l, \tau)]. \end{aligned} \quad (51)$$

The middle term can be neglected when integrating over τ and τ' as it has measure zero. The first term accounts for jumps occurring at $\tau = \tau'$, while the last term accounts for the jumps $k \rightarrow l$ at time τ that result in $i \rightarrow j$ at some later time $\tau' > \tau$.

We may rewrite the path measure Eq. (41) with the stochastic differentials discussed above as

$$\begin{aligned} \mathbb{P}[(x_\tau)_{0 \leq \tau \leq t}] &= p_{x_0}(0) \exp \left[\int_{s=0}^{s=t} \sum_x r_{xx} d\tau_x(s) \right. \\ &\quad \left. + \int_{s=0}^{s=t} \sum_{x,y \neq x} \log r_{xy} dn_{xy}(s) \right], \end{aligned} \quad (52)$$

where the second sum is taken over both x and $y \neq x$. The advantage of writing the path measure as in Eq. (52) instead of Eq. (41) is that it allows for possible time dependencies of the rates.

B. Pathwise observables: Currents and densities

We now introduce pathwise observables, i.e., time-integrated densities and currents that were recently analyzed extensively in the context of diffusions [61,96,125,133]. As before, we start with the continuous-space setting, where a time-integrated current is defined as [61]

$$J_t^c = \int_{\tau=0}^{\tau=t} U(\mathbf{x}_\tau, \tau)^T \circ d\mathbf{x}_\tau, \quad (53)$$

as a Stratonovich integral over some (square-integrable) vector-valued window function $U(\mathbf{x}_\tau, \tau)$, and a time-integrated density is defined as [61]

$$\rho_t^c = \int_0^t d\tau V(\mathbf{x}_\tau, \tau), \quad (54)$$

where $V(\mathbf{x}_\tau, \tau)$ is some (square-integrable) scalar-valued function.

In the context of MJPs, the time-integrated currents weigh the transitions occurring along a trajectory with a fully antisymmetric, possibly time-dependent weight $\kappa(\tau)$, i.e., $\kappa_{ij}(\tau) = -\kappa_{ji}(\tau)$. The current defined this way is manifestly antisymmetric such that the current changes sign upon time reversal. Note that $\kappa(\tau)$ describes experimentally accessible transitions. We therefore define a (scalar) time-integrated current as [61]

$$J_t \equiv \int_{\tau=0}^{\tau=t} \text{Tr}[\kappa(\tau)^T d\mathbf{n}(\tau)]. \quad (55)$$

A comparison of Eqs. (53) and (55) highlights the fact that integrating over time and tracing over $d\mathbf{n}(\tau)$ is the MJP correspondence to the Stratonovich integral Eq. (53). The stochastic integral Eq. (55) is time antisymmetric in analogy to the current defined for diffusion processes in the form of a Stratonovich integral Eq. (53). The current in Eq. (55) naturally decomposes (as for diffusions [61]) into a “usual time integral” J_t^I and the stochastic integral $J_t = J_t^I + J_t^{\text{II}}$, where

$$J_t^I = \int_{\tau=0}^{\tau=t} \text{Tr}[\kappa(\tau)^T d\epsilon(\tau)], \quad (56a)$$

$$J_t^{\text{II}} = \int_0^t \text{Tr}[\kappa(\tau)^T R(x_\tau)] d\tau, \quad (56b)$$

i.e., integrals with traces over $d\epsilon(\tau)$ are not necessarily time antisymmetric and therefore may be identified (per analogy) as Itô integrals due to the correspondence to the stochastic part of Eq. (53) [61]. This analogy (i) allows us to distinguish more easily between the integrals over noise or jump increments and (ii) is fully consistent with observables of continuous-space diffusion. By means of the latter, we will later demonstrate how continuous-space Itô integrals emerge from the corresponding integrals of MJPs with traces over $d\epsilon(\tau)$ in the continuum limit. This approach will later provide a unified description of MJPs and overdamped diffusions within the framework of stochastic calculus.

Similarly, a density assigns each state i a weight $V_i(\tau)$ and then integrates these along the trajectory. These weights can be combined into the state function $V_\tau \equiv V(x_\tau, \tau) = \sum_k \delta_{x_\tau k} V_k(\tau)$. With V_τ , we define the density [61]

$$\rho_t = \int_{\tau=0}^{\tau=t} V_\tau d\tau. \quad (57)$$

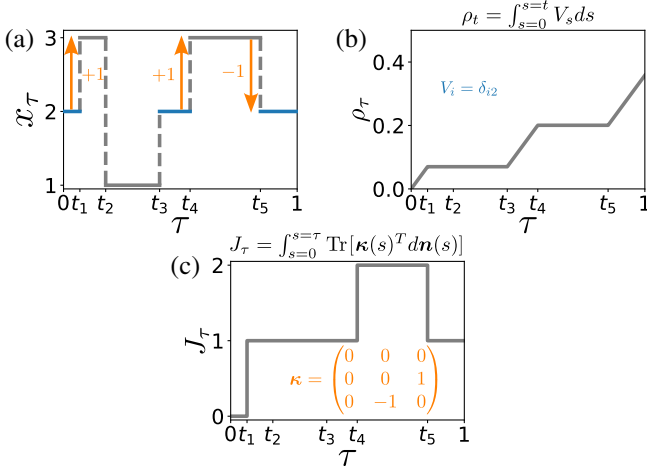


FIG. 3. Example trajectory and examples of an arising current and density. The part of the trajectory in (a) that contributes to the density ρ_τ with state function, $V_i(\tau) = \delta_{i2}$, is marked in blue. Similarly, the transitions contributing to the current J_τ with transition weights, $\kappa_{ij} = \delta_{i2}\delta_{j3} - \delta_{i3}\delta_{j2}$, are marked by orange arrows with numbers representing the weight of the transition. The resulting density and current can be seen in (b) and (c), respectively.

An exemplary trajectory with corresponding time-integrated density and current is shown in Fig. 3 to visualize Eqs. (55) and (57).

C. From Stratonovich increments to observable correlations

In the case of diffusion processes, correlations of pathwise observables were shown to provide deep information about the passage of pinned trajectories through the respective window in terms of generalized Green-Kubo-like relations [96]. They are furthermore relevant in the context of thermodynamic inequalities, e.g., TURs [61,126] and thermodynamic correlation bounds (CBs) [113,114]. Following Refs. [96,125,133], we now show how the steady-state correlations of stochastic differentials relate to covariances of pathwise observables of MJPs. In particular, we emphasize how these compare to the corresponding continuous-space results.

In order to express (co)variances of continuous and discrete currents, Eqs. (53) and (55), and densities, Eqs. (54) and (57), in a compact unifying form [96,125,133], we define the integration operators

$$\hat{J}_{M,N}^{t,c}[\cdot] = \int_0^t d\tau \int_\tau^t d\tau' \int dz \int dz' M(z)^\top [\cdot] N(z'), \quad (58a)$$

$$\hat{I}_{G^\alpha, G^\beta}^t[\cdot] = \int_0^t d\tau \int_\tau^t d\tau' \sum_{x,y} G_{xy}^\alpha \sum_{i,j} G_{ij}^\beta [\cdot], \quad (58b)$$

where $[\cdot]$ denotes functions that depend on z, z', τ , and τ' . Similarly, the functions entering $\hat{I}_{G^\alpha, G^\beta}^t[\cdot]$ depend on x, y, i ,

j, τ , and τ' . The functions $M(z)$ and $N(z)$ may be scalar- or vector-valued functions, while G^α and G^β are two-point quantities, e.g., κ . Equation (58b) corresponds to Eq. (58a), where each continuous spatial integral has been changed to a discrete double sum. While one may expect the integrals to be substituted by a single sum, the double sum is indeed required to include nonlocal quantities, e.g., currents.

We will now consider two observables $X_t^{(c)} \in \{J_{t,k}^{(c)}, \rho_{t,k}^{(c)}\}$ and $Y_t^{(c)} \in \{J_{t,l}^{(c)}, \rho_{t,l}^{(c)}\}$, where the superscript (c) is used to distinguish discrete (no superscript) from the continuous (superscript c) setting, and $k, l \in \{1, 2\}$ is the index for currents $J_{t,1}^{(c)}, J_{t,2}^{(c)}$ and densities $\rho_{t,1}^{(c)}, \rho_{t,2}^{(c)}$. These currents and densities may have different current- and density-defining functions, which we take into consideration here.

As shown in Refs. [96,125,133], the continuous (co)variances can be written compactly in terms of Eq. (58), together with fundamental increment correlations. We show here that the same structure appears for the discrete case. In fact, the covariances can be written as

$$\begin{aligned} \text{cov}(X_t^c, Y_t^c) &= \hat{J}_{X,Y}^{t,c}[\Xi_m^{zz'}] - \langle X_t^c \rangle \langle Y_t^c \rangle, \\ \text{cov}(X_t, Y_t) &= \hat{I}_{UX,UY}^t[\Xi_{ij}^{xy}] - \langle X_t \rangle \langle Y_t \rangle, \end{aligned} \quad (59)$$

where the Ξ matrices are defined through increment correlations, see Eqs. (60), (62), and (67). The index m we use to distinguish between different observable correlations: $m = 1$ for $X_t^{(c)} = \rho_{t,k}^{(c)}$ and $Y_t^{(c)} = \rho_{t,l}^{(c)}$, without loss of generality $m = 2$ for $X_t^{(c)} = J_{t,k}^{(c)}$ and $Y_t^{(c)} = \rho_{t,l}^{(c)}$, and $m = 3$ for $X_t^{(c)} = J_{t,k}^{(c)}$ and $Y_t^{(c)} = J_{t,l}^{(c)}$. For density-density covariance ($m = 1$), the increment correlations read [96]

$$\begin{aligned} \Xi_1^{zz'} &= \langle 1 \rangle_{x_t=z}^{x_{t'}=z'} + \langle 1 \rangle_{x_t=z'}^{x_{t'}=z}, \\ \Xi_{ij}^{xy} &= \frac{\langle d\tau_x(\tau) d\tau_i(\tau') \rangle_{x_t=x}^{x_{t'}=i}}{d\tau d\tau'} + \frac{\langle d\tau_x(\tau') d\tau_i(\tau) \rangle_{x_t=i}^{x_{t'}=x}}{d\tau d\tau'}. \end{aligned} \quad (60)$$

Here, $\langle \cdot \rangle_{x_t=z}^{x_{t'}=z'}$ is expectation conditioned on $x_t = z$ and $x_{t'} = z'$ with $t \leq t'$ and analogously for the discrete case. Evaluating these correlations yields the stationary covariances [96,125]

$$\begin{aligned} \text{cov}(\rho_{t,k}^c, \rho_{t,l}^c) &= \hat{J}_{V^k, V^l}^{t,c} [P_s(z, \tau; z', \tau') + P_s(z', \tau; z, \tau') \\ &\quad - p_s(z) p_s(z')], \\ \text{cov}(\rho_{t,k}, \rho_{t,l}) &= \hat{I}_{V^k \delta, V^l \delta}^t [P_s(x, \tau; i, \tau') \\ &\quad + P_s(x, \tau'; i, \tau) - p_x^s p_i^s]. \end{aligned} \quad (61)$$

The two-point function $V^k \delta$ stands for the (effectively one-point) quantity $V_i^k \delta_{ij}$ [143] and $P_s(\cdot; \cdot)$ denotes the joint probability for stationary systems, i.e., $P_s(x, \tau; i, \tau') = P(i, \tau' | x, \tau) p_x^s$.

Similarly, for current-density covariances ($m = 2$), we need the following increment correlations [96]:

$$\Xi_{22}^{zz'} = \frac{\langle \circ d\mathbf{x}_\tau \rangle_{x_\tau=z}^{x_{\tau'}=z'}}{d\tau} + \frac{\langle \circ d\mathbf{x}_{\tau'} \rangle_{x_{\tau'}=z'}^{x_\tau=z}}{d\tau'},$$

$$\Xi_{ijxy}^2 = \frac{\langle dn_{xy}(\tau) d\tau_i(\tau') \rangle_{x_\tau=x}^{x_{\tau'}=i}}{d\tau d\tau'} + \frac{\langle dn_{xy}(\tau') d\tau_i(\tau) \rangle_{x_{\tau'}=i}^{x_\tau=x}}{d\tau d\tau'}, \quad (62)$$

which include correlations of a Stratonovich increment $\circ d\mathbf{x}_\tau$ and $dn_{xy}(\tau)$ with a future event. The evaluation of such correlations is possible by means of the generalized time-reversal symmetry, i.e., dual-reversal symmetry [96,125,133,144]. In both cases, the dual system (denoted by $\ddagger$) has the same steady-state probability, whereas the irreversible drift $\mathbf{j}_s(\mathbf{x})$ has the opposite sign $\mathbf{j}_s^\ddagger(\mathbf{x}) = -\mathbf{j}_s(\mathbf{x})$. It is useful to define current and dual current operators; in the continuous-space setting, these are [96,125,133] $\hat{\mathbf{j}}_x = p_s(\mathbf{x})^{-1} \mathbf{j}_s(\mathbf{x}) - p_s(\mathbf{x}) \mathbf{D} \nabla_x [p_s(\mathbf{x})^{-1}]$ and $\hat{\mathbf{j}}_x^\ddagger = p_s(\mathbf{x})^{-1} \mathbf{j}_s(\mathbf{x}) + p_s(\mathbf{x}) \mathbf{D} \nabla_x [p_s(\mathbf{x})^{-1}]$. The corresponding operators for discrete-state systems are much simpler and read $\hat{j}_{xy} = r_{xy}$ and $\hat{j}_{xy}^\ddagger = r_{yx} p_y^s / p_x^s$, respectively. The latter is the dual current operator reversing the steady-state currents [6]. When these current operators act on p_x^s , they result in the probability flux and dual probability flux on edge $x \rightarrow y$, i.e., $\hat{j}_{xy} p_x^s = r_{xy} p_x^s = J_{xy}^s$ and $\hat{j}_{xy}^\ddagger p_x^s = r_{yx} p_y^s = J_{yx}^s$. By means of the flux operators, it can be shown that

$$\langle dn_{xy}(\tau') d\tau_i(\tau) \rangle_{x_\tau=i}^{x_{\tau'}=x} = \hat{j}_{xy} P(x, \tau' - \tau | i) p_i^s d\tau d\tau'$$

$$= r_{xy} P(x, \tau' - \tau | i) p_i^s d\tau d\tau', \quad (63)$$

which is the current on edge $x \rightarrow y$ at time $\tau' > \tau$ in addition to $x_\tau = i$. With an approach analogous to Ref. [96], we use the dual current operator to express the correlation of an initial transition with future events. To be precise, we find that (see Appendix A 2 a)

$$\langle dn_{xy}(\tau) d\tau_i(\tau') \rangle_{x_\tau=x}^{x_{\tau'}=i} = \hat{j}_{yx}^\ddagger P(i, \tau' - \tau | y) p_y^s d\tau d\tau'$$

$$= r_{yx} P(i, \tau' - \tau | y) p_y^s d\tau d\tau', \quad (64)$$

as well as (see Appendix A 2 b)

$$\langle dn_{xy}(\tau) dn_{ij}(\tau') \rangle_{x_\tau=x}^{x_{\tau'}=i} = \hat{j}_{ij} \hat{j}_{yx}^\ddagger P(i, \tau' - \tau | y) p_y^s d\tau d\tau'$$

$$= r_{ij} r_{yx} P(i, \tau' - \tau | y) p_x^s d\tau d\tau'. \quad (65)$$

Equations (64) and (65) enable the calculation of (co) variances of n_{ij} and thus provide valuable insight about, e.g., how noisy transitions are in a given system [for an explicit example, see Figs. 5(a) and 5(b) on the statistics of transitions and dwell time, respectively, in a model of secondary active transport (SAT) in Sec. IV]. Moreover, we can rewrite the current-density covariances compactly and in a unified form as [96,125]

$$\text{cov}(J_{t,k}^c, \rho_{t,l}^c) = \hat{\mathcal{I}}_{U^k, V^l}^{t,c} \left[\hat{\mathbf{j}}_{z'} P(z', t' | z) p_s(z) + \hat{\mathbf{j}}_z^\ddagger P(z', t' | z) p_s(z) - \mathbf{j}_s(z) p_s(z') \right],$$

$$\text{cov}(J_{t,k}, \rho_{t,l}) = \hat{\mathcal{I}}_{\kappa^k, V^l \delta}^t \left[\hat{j}_{xy} P(x, t' | i) p_i^s + \hat{j}_{yx}^\ddagger P(i, t' | y) p_y^s - J_{xy}^s p_i^s \right]. \quad (66)$$

The only time dependence in the integrands in Eq. (66) is the time-translation invariant propagators $P(i, t | y)$; that is, the integrands depend on only the time difference t . Hence, the time integrals in Eqs. (58a) and (58b) may be simplified to $\int_0^t d\tau \int_0^\tau d\tau' \rightarrow \int_0^t dt' (t - t')$ [96].

It remains to consider current-current covariances, which require the correlations of Stratonovich increments [in case of MJPs, Stratonovich differentials $dn_{xy}(\tau)$ are defined by analogy; see Eq. (55)] at different times [96]

$$\Xi_{33}^{zz'} = \frac{\langle \circ d\mathbf{x}_\tau \circ d\mathbf{x}_{\tau'}^T \rangle_{x_\tau=z}^{x_{\tau'}=z'}}{d\tau d\tau'} + \frac{\langle \circ d\mathbf{x}_{\tau'} \circ d\mathbf{x}_\tau^T \rangle_{x_{\tau'}=z'}^{x_\tau=z}}{d\tau d\tau'},$$

$$\Xi_{ijxy}^3 = \frac{\langle dn_{xy}(\tau) dn_{ij}(\tau') \rangle_{x_\tau=x}^{x_{\tau'}=i}}{d\tau d\tau'} + \frac{\langle dn_{xy}(\tau') dn_{ij}(\tau) \rangle_{x_{\tau'}=i}^{x_\tau=x}}{d\tau d\tau'}. \quad (67)$$

Using again the generalized time-reversal symmetry, we can evaluate these correlations to obtain

$$\text{cov}(J_{t,k}^c, J_{t,l}^c) = 2t \int d\mathbf{z} [U^k(\mathbf{z})]^T \mathbf{D} U^l(\mathbf{z}) p_s(\mathbf{z}) + \hat{\mathcal{I}}_{U^k, U^l}^{t,c} \left[\hat{\mathbf{j}}_z \left(\hat{\mathbf{j}}_{z'}^\ddagger \right)^T P(z, t' | z') p_s(z') + \hat{\mathbf{j}}_z^\ddagger \hat{\mathbf{j}}_{z'}^T P(z', t' | z) p_s(z) - \mathbf{j}_s(z) \mathbf{j}_s(z')^T \right]$$

$$\text{cov}(J_{t,k}, J_{t,l}) = t \sum_{x,y} \kappa_{xy}^k \kappa_{xy}^l r_{xy} p_x^s + \hat{\mathcal{I}}_{\kappa^k, \kappa^l}^t \left[\hat{j}_{xy} \hat{j}_{ji}^\ddagger P(x, t' | j) p_j^s + \hat{j}_{ij} \hat{j}_{yx}^\ddagger P(i, t' | y) p_y^s - J_{xy}^s J_{ij}^s \right], \quad (68)$$

where the analogy between continuous- and discrete-state spaces is evident. Note that one can derive the results for covariances in different, less direct, ways, e.g., using Feynman-Kac and (spectral) perturbation theory (see Refs. [95,145] and references therein).

Equations (61), (66), and (68) have the form of generalized Green-Kubo relations, connecting (co)variances of pathwise

observables to generalized (auto)correlation functions, which in the continuous-space setting have been discussed in Ref. [96]. Here we highlight the similarities and differences between discrete space and continuous space.

The mathematical structure of the results is (up to the analogy) the same, which should not come as a surprise, at least (but not only) in the sense that the MJP process can

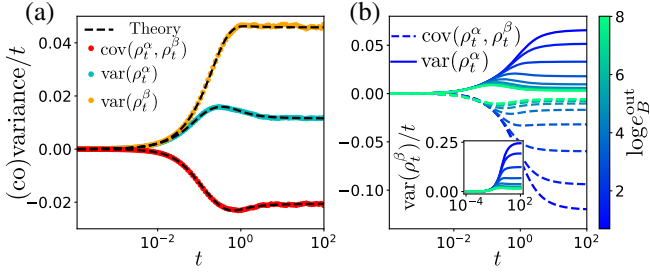


FIG. 4. Two densities, ρ_t^α and ρ_t^β , are used to visualize density (co)variances in the SAT model, see Sec. IV A 1. These correspond to the state functions $V_i^\alpha = \delta_{i1} + \delta_{i2}$ and $V_i^\beta = \delta_{i5} + \delta_{i6}$ measuring if molecules of type *A* and *B* are in the channel, respectively. (a) The (scaled) variances $\text{var}(\rho_t^{\alpha/\beta})/t$ are shown together with the (scaled) covariance between them $\text{cov}(\rho_t^\alpha, \rho_t^\beta)/t$ from numerical simulations (colored) and analytical solutions, Eq. (61) (dashed lines). The analytical variance of ρ_t^α (solid lines) and covariance (black dashed lines), both modulated by $1/t$, are shown in (b) for various values of e_B^{out} . The inset shows $\text{var}(\rho_t^\beta)/t$. The numerics in (a) are evaluated using $N = 10^4$ trajectories sampled using the celebrated Gillespie algorithm [146,147]. The initial condition is $p_i = (\delta_{i1} + \delta_{i3} + \delta_{i5})/3$ and the values of the parameters can be found in Table IV. (b) $e_B^{\text{out}} = 40$ is used.

[under appropriate conditions on the drift $\mathbf{F}$ in Eq. (1), i.e., that the reversible contribution stems from a generalized potential with deep minima separated by high barriers [1–3,11,16]] be seen as the long-time coarse-grained limit of the continuous system.

The continuous-space correlations in Eqs. (60), (62), and (67) are valid for all $t \geq 0$ and similar for systems with nominally discrete degrees of freedom (such as spin systems). Conversely, if the MJP is meant as an approximate, long-time effective description of a system with continuous degrees of freedom, Eqs. (60), (62), and (67) describe covariances of pathwise observables at sufficiently long times.

A nonzero $\text{cov}(J_t^c, \rho_t^c)$ necessarily indicates that detailed balance is broken [96]. The same observation can be made in the discrete case, as the equilibrium dual operator $\hat{J}_{xy}^{\ddagger, \text{eq}} = \hat{J}_{xy}^{\text{eq}}$ together with $\kappa = \kappa(\tau) = -\kappa^T$ yields $\text{cov}_{\text{eq}}(J_t, \rho_t) = 0$.

To provide preliminary intuition, density (co)variances (scaled by t^{-1}) are shown in Fig. 4 for the SAT model, which will be discussed in more detail in Sec. IV. In addition, in Fig. 5(c), we show the mean current J_t arising in the stationary SAT model with the magnitude of the typical fluctuations using the standard deviation, $\sqrt{\text{var}(J_t)}$,

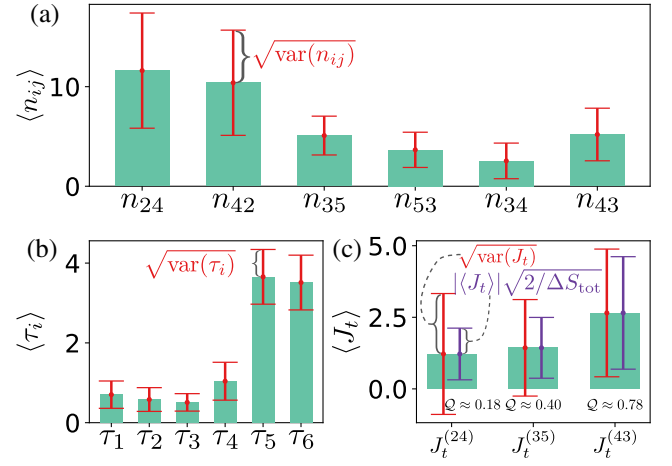


FIG. 5. Statistics of transitions and waiting times in the stationary SAT model. The average number of transitions $\langle n_{ij} \rangle$ are shown in (a) for a selection of edges. (b) The average time spent $\langle \tau_i \rangle$ in each state is presented. The steady-state currents resulting from the transitions in (a) are presented in (c). The red error bars are the respective standard deviations $\sqrt{\text{var}(J_t)}$. (c) The lower bound $|\langle J_t \rangle| \sqrt{2/\Delta S_{\text{tot}}} \leq \sqrt{\text{var}(J_t)}$ resulting from the steady-state TUR is added as purple error bars. We use $t = 10$ in every panel.

and how these can be bounded from below using the stationary TUR.

D. Transient covariances

The generalizations of Eqs. (61), (66), and (68) to transient dynamics have been performed in Ref. [133] for continuous-space dynamics. We give a brief overview of the generalization for MJPs in this section. The first difference arises in the integration operator Eq. (58b)

$$\hat{I}_{G^\alpha, G^\beta}^t[\cdot] = \int_0^t d\tau \int_0^\tau d\tau' \sum_{x,y} G_{xy}^\alpha(\tau) \sum_{i,j} G_{ij}^\beta(\tau')[\cdot], \quad (69)$$

where U^α and U^β are explicitly time dependent. Note also that the integration limits differ, as the explicit time dependence of the U 's and probabilities requires the full range of both temporal integrals. It is, at this point, easier to consider the covariances not in terms of probability flux operators, but rather in terms of transition rates. The discrete covariances in Eqs. (61), (66), and (68) generalize to

$$\begin{aligned} \text{cov}(\rho_{t,k}, \rho_{t,l}) &= \hat{I}_{V^k, V^l}^t[P(x, \tau; i, \tau') - p_x(\tau)p_i(\tau')], \\ \text{cov}(J_{t,k}, \rho_{t,l}) &= \hat{I}_{\kappa^k, V^l}^t[\mathbb{1}_{\tau > \tau'} r_{xy} P(x, \tau | i, \tau') p_i(\tau') + \mathbb{1}_{\tau < \tau'} r_{yx} P(i, \tau' | y, \tau) p_y(\tau) - r_{xy} p_x(\tau) p_i(\tau')], \\ \text{cov}(J_{t,k}, J_{t,l}) &= \int_0^t d\tau \sum_{x,y} \kappa_{xy}^k(\tau) \kappa_{xy}^l(\tau) r_{xy} p_x(\tau) + \hat{I}_{\kappa^k, \kappa^l}^t[\mathbb{1}_{\tau > \tau'} r_{xy} r_{ij} P(x, \tau | j, \tau') p_i(\tau') \\ &\quad + \mathbb{1}_{\tau < \tau'} r_{ij} r_{xy} P(i, \tau' | y, \tau) p_y(\tau) - r_{xy} p_x(\tau) r_{ij} p_i(\tau')], \end{aligned} \quad (70)$$

For a generalization to time-dependent rates, see Sec. VII, and for time-inhomogeneous diffusion, see Ref. [133].

IV. APPLICATION OF STOCHASTIC CALCULUS TO THERMODYNAMIC BOUNDS

A. Model systems

While discussing various applications of the developed stochastic calculus for MJPs, we will throughout allude to biophysically relevant model systems shown in Fig. 6. Thereby, we aim mostly at illustrating how to apply the theoretical results rather than to discuss the respective biological implications. The three models we introduce in the following sections are the secondary active transport across cell membranes (and an extension of this model), the calmodulin folding dynamics, and a four-state toy model in various settings.

1. Secondary active transport

We first consider a Markov model of SAT of molecule A through a protein funnel facilitated by

molecule B [148–150]. The model, shown in Fig. 6(a) and listed in Table II, consists of six states: three [i.e., (1, 3, 5)] corresponding to the funnel being open toward the exterior of the cell and another three [i.e., (2, 4, 6)] open toward the interior of cell. Hence, the state space is $\mathcal{N} = \{1, 2, 3, 4, 5, 6\}$. In the absence of A or B bound, the funnel changes conformation with rate γ . Conversely, the crossing via A - or B -filled states occurs with γx for a dimensionless speedup factor x . A and B leave or enter the funnel inside and outside the cell with rates $l_{A/B}$ and $e_{A/B}^{\text{out/in}}$, respectively. The adopted parametrization is listed in Table IV in Appendix A 11.

We further consider a periodic extension of coupled SAT models to describe the total transport of molecules A through the membrane [Fig. 6(b)]. We leave the rates in the system unchanged, whereas the state space is extended to $\mathcal{N} \times \mathbb{Z}$, with the additional degree of freedom accounting for the total number of A molecules outside the cell.

The transport can be split into two categories: symporters and antiporters. These refer to molecule A being

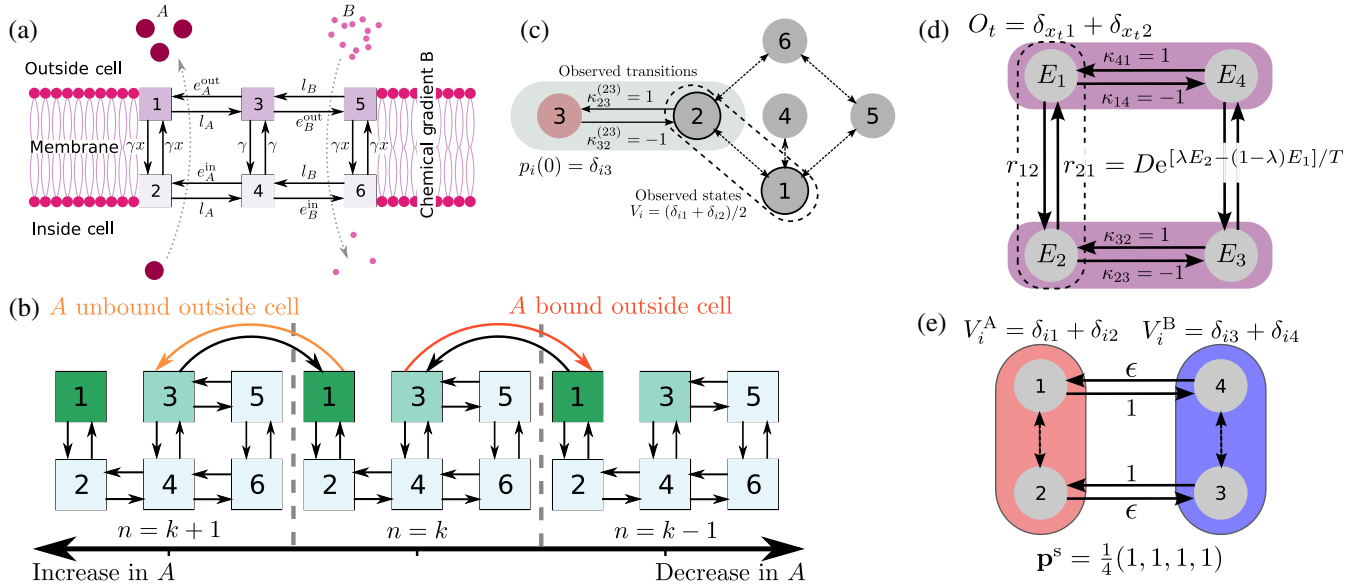


FIG. 6. Overview of models used to visualize the results: (a) Markov model for SAT; the states (1, 3, 5) correspond to the protein funnel being open toward the cell exterior, while states (2, 4, 6) describe the funnel being open toward the cell interior (see Table II). The transition rate for the conversion of the opening from the interior to the exterior (and vice versa) is γ , which in the presence of ligands A or B is scaled by a dimensionless factor x . A and B leave the funnel with rate $l_{A/B}$ and enter it with rate $e_{A/B}^{\text{out/in}}$ outside (inside) the cell. Of particular interest in the (extended) SAT model is the impact of e_B^{out} , i.e., the concentration of the helper molecule. (b) Schematic of how the SAT model in (a) may be extended to a “train” of SAT models to capture the number of A molecules n transported through the cell membrane. (c) Schematic of the Markov model for calmodulin folding. We focus on the inference of dissipation by observing a current with weights $\kappa_{ij}^{(23)} = \delta_{i2}\delta_{j3} - \delta_{j2}\delta_{i3}$ and/or density with weight $V_i = (\delta_{i1} + \delta_{i2})/2$. (d) Four-state ring model with equilibrium transition rates parametrized by free energies E_i for state i , local diffusion coefficient D , temperature T , and mixing parameter λ [see Eq. (71)], and upon constant driving, respectively. We are interested in the response to temperature perturbations and investigate the effect on a single-time observable $A_t = \delta_{x,1} + \delta_{x,2}$ and a current with transition weights $\kappa_{ij} = \delta_{i4}\delta_{j1} - \delta_{i1}\delta_{j4} + \delta_{i3}\delta_{j2} - \delta_{i2}\delta_{j3}$. (e) Four-state ring model with constant driving having rates 1 in the clockwise and ϵ in counterclockwise direction; the stationary distribution is independent of ϵ . The model is used for a comparison of the quality of thermodynamic bounds in situations where only the mesostates A and B , corresponding to states (1, 2) and (3, 4), respectively, are observed without the ability to distinguish the respective transition pathways between them.

TABLE II. Overview of states in SAT model.

State	Meaning
1	Funnel outside with A bound
2	Funnel inside with A bound
3	Funnel outside with nothing bound
4	Funnel inside with nothing bound
5	Funnel outside with B bound
6	Funnel inside with B bound

transported parallel or antiparallel to molecule B , respectively. We are interested in the fraction of the total steady-state entropy production that we can estimate via the thermodynamic bounds for various values of transition rates e_B^{out} . These transition rates are assumed proportional to the concentration of B outside the cell [148], allowing us to “control” the value of e_B^{out} , leaving it as a free parameter we can tune.

2. Calmodulin folding dynamics

Being a Ca^{2+} receptor, calmodulin plays an important role in physiological signaling processes [151]. The Markov model for the calmodulin folding pathway [88] is commonly used as a paradigmatic example in, e.g., the study of first-passage times [152] and stochastic thermodynamics [59,153]. The respective states represent different conformations of the protein and the transitions are changes of conformation [88]. Here we adopt the transition rates from Ref. [152], summarized in Table III in Appendix A 11, while the topology of the folding network is shown in Fig. 6(c). The calmodulin example will be used to gauge the quality of thermodynamic inference via the derived thermodynamic inequalities.

3. Four-state ring toy model

Here we consider, as a minimal example, a four-state model with states $\{1, 2, 3, 4\}$ on a ring to visualize results. We will choose two different parametrizations of the model, visualized in Figs. 6(d) and 6(e).

In the equilibrium (detailed-balance) setting, we assign to each state a free energy E_i , $i \in \{1, 2, 3, 4\}$, such that the stationary probability is $p_i^{\text{eq}} \propto e^{-E_i/T}$ (note that we explicitly include the temperature here). For any $\lambda \in [0, 1]$, the following transition rates obey detailed balance [20]:

$$r_{xy} = D e^{[\lambda E_x - (1-\lambda) E_y]/T}. \quad (71)$$

We use the free energies listed in Table V in Appendix A 11.

In the constant driving setting, we set the clockwise rates to unity, whereas the counterclockwise rates are controlled by the parameter ϵ . This way the steady-state distribution $p_i^s = p = 1/4$ is independent of ϵ .

B. Thermodynamic inequalities and inference

To highlight the power of the developed stochastic calculus for observables of MJPs, we now apply it to directly prove a broad selection of thermodynamic inequalities. Throughout, we draw comparisons to continuous-space results and highlight some fundamental differences between the two. We immediately gauge the quality of the bounds by means of model examples and discuss the respective saturation conditions. The section thus entails a brief discussion of the crucial steps in the proofs of the thermodynamic bounds for diffusions.

1. Entropy and pseudoentropy production

The central object of interest for thermodynamic inference is the mean total entropy production, which consist of the entropy change in the system as well as the surrounding medium. For continuous systems, the total entropy production (EP) is [5,6,142]

$$\Delta S_{\text{tot}}^c(t) = \int_0^t d\tau \int d\mathbf{x} \frac{\mathbf{j}(\mathbf{x}, \tau)^T \mathbf{D}(\mathbf{x}) \mathbf{j}(\mathbf{x}, \tau)}{P(\mathbf{x}, \tau)}. \quad (72)$$

In the direct proofs in Refs. [51,61], the stochastic integral

$$A_t^c \equiv \int_{\tau=0}^{\tau=t} \frac{\mathbf{j}(\mathbf{x}_\tau, \tau)^T}{P(\mathbf{x}_\tau, \tau)} [2\mathbf{D}(\mathbf{x}_\tau)]^{-1} \boldsymbol{\sigma}(\mathbf{x}_\tau) d\mathbf{W}_\tau \quad (73)$$

is a central object, chosen to immediately yield $\langle (A_t^c)^2 \rangle = \Delta S_{\text{tot}}^c(t)/2$, which allows for crucial simplifications in the proofs.

Conversely, in discrete-state systems, the total entropy production reads [5,7,142]

$$\Delta S_{\text{tot}}(t) = \frac{1}{2} \int_0^t d\tau \sum_{i,j} [r_{ij} p_i(\tau) - r_{ji} p_j(\tau)] \log \frac{r_{ij} p_i(\tau)}{r_{ji} p_j(\tau)}. \quad (74)$$

As a key quantity in the various proofs of thermodynamic bounds, we introduce the auxiliary integral

$$A_t = \int_{\tau=0}^{\tau=t} \text{Tr}[\mathbf{Z}(\tau)^T d\boldsymbol{\epsilon}(\tau)], \quad (75)$$

where

$$[\mathbf{Z}(\tau)]_{ij} = \frac{r_{ij} p_i(\tau) - r_{ji} p_j(\tau)}{r_{ij} p_i(\tau) + r_{ji} p_j(\tau)}. \quad (76)$$

Using Eq. (49), the mean is $\langle A_t \rangle = 0$ and the variance can be identified as a “pseudoentropy production” [45,122]

$$\langle A_t^2 \rangle = \frac{1}{2} \int_0^t d\tau \sum_{i,j} \frac{[r_{ij} p_i(\tau) - r_{ji} p_j(\tau)]^2}{r_{ij} p_i(\tau) + r_{ji} p_j(\tau)}. \quad (77)$$

Applying the logarithmic inequality $(a-b)^2/(a+b) \leq (a+b) \log(a/b)/2 \forall a, b > 0$, the total entropy production Eq. (74) can be bounded from below using Eq. (77), i.e., $\langle A_t^2 \rangle \leq \Delta S_{\text{tot}}(t)/2$. The logarithmic inequality is saturated only for $a = b$ where the right-hand side vanishes, and therefore (for discrete-state spaces) $\langle A_t^2 \rangle = \Delta S_{\text{tot}}(t)/2$ only at equilibrium where $\Delta S_{\text{tot}}(t) = 0$.

Note that the inability to saturate $\langle A_t^2 \rangle \leq \Delta S_{\text{tot}}(t)/2$ outside of equilibrium is the first fundamental difference between discrete and continuous systems. In the former the pseudoentropy production (which, in turn, bounds the total entropy production) is bound and in the latter the total entropy production is directly bound. As a consequence, when discussing the saturation of bounds in discrete space, we refer to lower bounds on the pseudoentropy production, not the total entropy production. However, we will show in Sec. VI, if the continuum limit exists, the discrete pseudoentropy production in Eqs. (77) and (74) converges to continuous entropy production in Eq. (72), which may be saturated far from equilibrium [61].

2. General TUR and correlation TUR

In the direct proof of the TUR in Refs. [60,61], the time-integrated current is split as $J_t^c = J_t^{c,I} + J_t^{c,II}$, with

$$\begin{aligned} J_t^{c,I} &= \int_{\tau=0}^{\tau=t} U(\mathbf{x}_\tau, \tau)^T \sigma d\mathbf{W}_\tau, \\ J_t^{c,II} &= \int_0^t U(\mathbf{x}_\tau, \tau) d\tau, \end{aligned} \quad (78)$$

where $U(\mathbf{x}_\tau, \tau) = \mathbf{U}(\mathbf{x}_\tau, \tau)^T \mathbf{F}(\mathbf{x}_\tau) + \nabla \cdot [\mathbf{D}\mathbf{U}(\mathbf{x}_\tau, \tau)]$.

The proof of the transient TUR for MJPs, which can be found, e.g., in Ref. [60], is analogous to the continuous case [61]. We will reiterate the proof here, focusing on the use of stochastic calculus, as well as including densities to obtain the CTUR.

We start from Eq. (47) and split the current in Eq. (55) as

$$J_t = J_t^I + J_t^{II}, \quad (79)$$

where

$$\begin{aligned} J_t^I &= \int_{\tau=0}^{\tau=t} \text{Tr}[\boldsymbol{\kappa}(\tau)^T d\boldsymbol{\varepsilon}(\tau)], \\ J_t^{II} &= \int_0^t \text{Tr}[\boldsymbol{\kappa}(\tau)^T \mathbf{R}(\mathbf{x}_\tau)] d\tau, \end{aligned} \quad (80)$$

which are a stochastic and a usual integral, respectively. Moreover, we have $\langle J_t^I \rangle = 0$ and

$$\langle J_t^{II} \rangle = \langle J_t \rangle = \int_0^t d\tau \sum_{x,y} \kappa_{xy}(\tau) r_{xy} p_x(\tau). \quad (81)$$

To prove the TUR, we use the Cauchy-Schwarz inequality

$$\langle A_t(J_t - \langle J_t \rangle) \rangle^2 \equiv \langle A_t \Delta J_t \rangle^2 \leq \text{var}(J_t) \langle A_t^2 \rangle. \quad (82)$$

One can easily show that $\langle A_t J_t^I \rangle = \langle J_t \rangle$. Evaluating

$$\begin{aligned} \langle A_t J_t^{II} \rangle &= \int_0^t d\tau' \int_0^t d\tau \sum_{i,j} \kappa_{ij}(\tau') r_{ij} \mathbb{1}_{\tau < \tau'} \\ &\times \sum_{x,y} [P(i, \tau' | y, \tau) - P(i, \tau' | x, \tau)] p_x(\tau) r_{xy} Z_{xy}(\tau) \end{aligned} \quad (83)$$

requires Eq. (50) and two integrations by part (for details, see Appendix A 4), which yield

$$\langle A_t J_t^{II} \rangle = (t\partial_t - 1) \langle J_t \rangle - \langle \tilde{J}_t \rangle, \quad (84)$$

where we introduced the modified current

$$\tilde{J}_t \equiv \int_{\tau=0}^{\tau=t} \tau \text{Tr}[(\partial_\tau \boldsymbol{\kappa}(\tau)^T) d\mathbf{n}(\tau)], \quad (85)$$

that accounts for the change of $\boldsymbol{\kappa}(\tau)$ in time τ . We thus proved the transient TUR

$$\frac{[t\partial_t \langle J_t \rangle - \langle \tilde{J}_t \rangle]^2}{\text{var}(J_t)} \leq \langle A_t^2 \rangle \leq \frac{\Delta S_{\text{tot}}(t)}{2}. \quad (86)$$

As in the continuous case [61], the modified current is necessary for the validity of Eq. (86).

With slight modifications, Eq. (86) also holds for time-dependent driving as proven in Ref. [59] using scaled cumulant-generating functions. In Ref. [60], the same TUR was proven using a stochastic-calculus approach. Note that Eq. (86) is a special case of the results in Refs. [59,60] for systems with constant rates and $\boldsymbol{\kappa}(v\tau)$ with $v = 1$ as the protocol velocity. In other words, the modified current in Eq. (85) corresponds to $v\partial_v J_t|_{v=1}$ where the generator is constant in time.

As shown in Ref. [61], one needs to include a density to saturate Eq. (86). By means of a calculation that is analogous to the evaluation of density-current correlations in Sec. III D, we here further show that

$$\begin{aligned} \langle A_t \rho_t \rangle &= (t\partial_t - 1) \langle \rho_t \rangle - \langle \tilde{\rho}_t \rangle, \\ \tilde{\rho}_t &\equiv \int_{\tau=0}^{\tau=t} \tau \partial_\tau V_\tau d\tau. \end{aligned} \quad (87)$$

By shifting the current $\Delta J_t \rightarrow \Delta J_t - c(t) \Delta \rho_t$ with some $c: \mathbb{R} \rightarrow \mathbb{R}$ in Eq. (82) already yields the transient CTUR

$$\frac{[t\partial_t \langle J_t \rangle - \langle \tilde{J}_t \rangle - c(t)((t\partial_t - 1) \langle \rho_t \rangle - \langle \tilde{\rho}_t \rangle)]^2}{\text{var}[J_t - c(t) \rho_t]} \leq \frac{\Delta S_{\text{tot}}(t)}{2}. \quad (88)$$

This route to proving thermodynamic bounds may thus legitimately be referred to as “direct” and allows us to discuss saturation in a straightforward manner, as we show next.

The lhs of Eq. (88) corresponds to the estimated total entropy production $\Sigma_{\text{est}}(t)$. To effectively visualize how much of the total entropy produced is recovered in the estimate, we use the quality factor

$$\mathcal{Q} = \frac{\Sigma_{\text{est}}(t)}{\Delta S_{\text{tot}}(t)}. \quad (89)$$

For the TUR, CTUR, and transport bound (TB), the quality factor is bounded by $0 \leq \mathcal{Q} \leq 1$. We will later show that for the correlation bound the quality factor is only trivially bounded from above $\mathcal{Q}^{\text{CB}} \leq 1$.

3. Optimization of TUR and CTUR

There are two ways to optimize Eq. (88), either by saturating Eq. (82) or by choosing the optimal $c(t)$ for fixed J_t and ρ_t . The former requires $\Delta J_t - c(t)\Delta\rho_t \propto A_t$. Since $c(t) \neq 0$, we see that the saturation is achieved when $V_i(\tau) = \hat{e}_i^T \kappa(\tau) \mathbf{L} \hat{e}_i / c(t) = \sum_j \kappa_{ij}(\tau) r_{ij} / c(t)$ and $\kappa = c' \mathbf{Z}$ for any $c' \in \mathbb{R}$. Here, $\hat{e}_i$ is the i th unit vector. However, these choices do not saturate Eq. (88), but only the estimate for the pseudoentropy production [see first inequality in Eq. (86)]. In other words, the “saturated” CTUR quality factor reads

$$\mathcal{Q}_{\text{sat}}^{\text{CTUR}} = \frac{2\langle A_t^2 \rangle}{\Delta S_{\text{tot}}(t)} \leq 1. \quad (90)$$

We again highlight that $\mathcal{Q}_{\text{sat}}^{\text{CTUR}} = 1$ in equilibrium or (as we show below) in the continuum limit (if said limit exists). Moreover, the optimization requires the rates and transient probability distribution to be known, which makes the saturated bound superfluous. Namely, knowing the rates and the transient probability distribution allows the EP to be determined exactly.

The saturation approach shown here is analogous to the approach for continuous-space dynamics [61] as it involves choosing $V(\mathbf{x}_\tau, \tau)$ such that $c(t)\rho_t^c = J_t^{\text{c,II}}$. Then, the vector-valued function $\mathbf{U}(\mathbf{x}_\tau, \tau)$ needs to be chosen proportional to the integrand in A_t^c .

Hence, it seems to be more practical to optimize the bound with respect to $c(t)$ for a given J_t and ρ_t . The lhs of Eq. (88), which we denote $h(t)$, has two extrema in $c(t)$,

$$\begin{aligned} c^{\min}(t) &= \frac{a(t)}{b(t)}, \\ c^{\text{opt}}(t) &= \frac{a(t)\text{cov}(\rho_t, J_t) - b(t)\text{var}(J_t)}{a(t)\text{var}(\rho_t) - b(t)\text{cov}(\rho_t, J_t)}, \end{aligned} \quad (91)$$

where $a(t) \equiv t\partial_t \langle J_t \rangle - \langle \tilde{J}_t \rangle$ and $b(t) \equiv (t\partial_t - 1)\langle \rho_t \rangle - \langle \tilde{\rho}_t \rangle$. All quantities entering Eq. (91) are accessible from J_t and

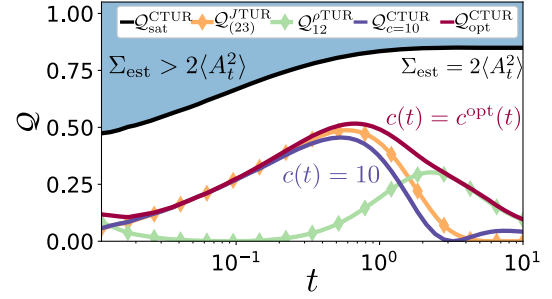


FIG. 7. Saturation of CTUR in the transient calmodulin folding dynamics [see Fig. 6(c)]. We present the various CTUR quality factors $\mathcal{Q}$ arising from various combinations of density ρ_t and current J_t as a function of time. The black line denotes the saturation of the TUR, i.e., when $\kappa(\tau) = \mathbf{Z}(\tau)$ and $c(t)\rho_t = J_t^{\text{II}}$, corresponding to the estimated entropy production being the pseudoentropy production $\Sigma_{\text{est}} = 2\langle A_t^2 \rangle$. Above the black line is the region $\Sigma_{\text{est}} > 2\langle A_t^2 \rangle$, which is not accessible using the (C)TUR. The remaining quality factors shown use the current ($\mathcal{Q}_{(23)}^{\text{TUR}}$), density ($\mathcal{Q}_{12}^{\text{TUR}}$), or a combination of these ($\mathcal{Q}_{c=10}^{\text{CTUR}}$ and $\mathcal{Q}_{\text{opt}}^{\text{CTUR}}$) in orange, green, purple, and red, respectively. For the CTURs, the proportionality $c(t) = 10$ (purple) and $c(t) = c^{\text{opt}}(t)$ (red) are chosen, the latter optimizing the quality factor for given J_t and ρ_t . The rates can be found in Table III.

ρ_t , making the optimization practically feasible. Note that $c^{\min}(t)$ and $c^{\text{opt}}(t)$ correspond to the minimum and maximum of $h(t)$, respectively, as

$$\begin{aligned} \frac{\partial^2}{\partial c^2} h(c, t)|_{c(t)=c^{\min}(t)} &= \frac{4b(t)^2}{\text{var}\left(J_t - \frac{a(t)}{b(t)}\rho_t\right)} \geq 0, \\ \frac{\partial^2}{\partial c^2} h(c, t)|_{c(t)=c^{\text{opt}}(t)} &= \frac{-4b(t)^2 \text{var}\left(J_t - \frac{a(t)}{b(t)}\rho_t\right)}{[\text{var}(J_t - c^{\text{opt}}(t)\rho_t)]^2} \leq 0. \end{aligned} \quad (92)$$

Moreover, one can immediately see that using $c^{\min}(t)$ one recovers the second law of thermodynamics, as $t\partial_t \langle J_t \rangle - \langle \tilde{J}_t \rangle - c^{\min}(t)[(t\partial_t - 1)\langle \rho_t \rangle - \langle \tilde{\rho}_t \rangle] = 0$. The optimal quality factor therefore reads

$$\begin{aligned} \mathcal{Q}_{\text{opt}}^{\text{CTUR}} &= \frac{2[a(t)^2 \text{var}(\rho_t) - 2a(t)b(t)\text{cov}(J_t, \rho_t) + b(t)^2 \text{var}(J_t)]}{[\text{var}(J_t)\text{var}(\rho_t) - \text{cov}(J_t, \rho_t)^2] \Delta S_{\text{tot}}(t)}. \end{aligned} \quad (93)$$

The saturated quality factor $\mathcal{Q}_{\text{sat}}^{\text{CTUR}}$ in Eq. (90) is shown in Fig. 7 together with the optimal $\mathcal{Q}_{\text{opt}}^{\text{CTUR}}$ and the quality factors of the current TUR $\mathcal{Q}_{(23)}^{\text{TUR}}$, density TUR $\mathcal{Q}_{12}^{\text{TUR}}$, and a CTUR $\mathcal{Q}_{c=10}^{\text{CTUR}}$ with $c(t) = 10$ for the calmodulin system [see Fig. 6(c)]. We consider the transition weights $\kappa_{ij}^{(23)} = \delta_{i2}\delta_{j3} - \delta_{i3}\delta_{j2}$ and state function $V_i = (\delta_{i1} + \delta_{i2})/2$. Only the saturated quality factor remains finite for

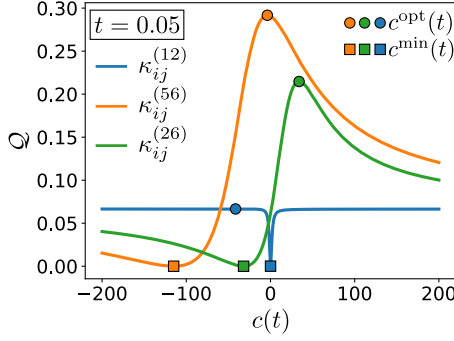


FIG. 8. Quality factor as a function of density weighting function $c(t)$ in the calmodulin system at a fixed $t = 0.05$. The colors correspond to different transition weights $\kappa_{ij}^{(kl)} = \delta_{ik}\delta_{jl} - \delta_{il}\delta_{jk}$ between two states, i.e., $\kappa_{ij}^{(12)}$ (blue), $\kappa_{ij}^{(56)}$ (orange), and $\kappa_{ij}^{(26)}$ (green). The state function entering the density is $V_i(\tau) = \delta_{i3}$ and the initial condition is $p_i(0) = \delta_{i6}$. The circles are the quality factors for most optimal $c(t) = c^{\text{opt}}(t)$, while the squares denote the least optimal $c(t) = c^{\text{min}}(t)$.

$t \rightarrow \infty$. As expected, the optimal $\mathcal{Q}_{\text{opt}}^{\text{CTUR}}$ gives the best inferred entropy production when $\kappa(\tau)$ and V_τ do not saturate the TUR, whereas $\mathcal{Q}_{c=10}^{\text{CTUR}} \leq \mathcal{Q}_{(23)}^{\text{JTUR}}$ for $t \leq 3$. Hence, simply using an arbitrary $c(t)$ in the CTUR may, in fact, lead to a worse estimate for the entropy production compared to the current TUR. The nontrivial behavior of $c(t)$ is also highlighted in Fig. 8. The expressions of $c^{\text{opt}}(t)$ and $c^{\text{min}}(t)$, Eq. (91), can be both positive and negative. Furthermore, they are in no particular relation to another; i.e., one cannot easily say if and when $c^{\text{opt}}(t) < c^{\text{min}}(t)$ and vice versa. A more detailed discussion is given in Appendix A 10.

C. Thermodynamic transport bound

The thermodynamic bound on the transport (or short “transport bound”) of a scalar observable $z_\tau = z(\mathbf{x}_\tau, \tau)$ in continuous space was derived in Refs. [51,154] and reads

$$\frac{\langle z_t - z_0 - \int_0^t d\tau \partial_\tau z_\tau \rangle^2}{t \mathcal{D}_t^c} \leq \frac{\Delta S_{\text{tot}}^c(t)}{2}, \quad (94)$$

where $\mathcal{D}_t^c$ is the continuous-space fluctuation-scale function

$$\mathcal{D}_t^c \equiv \frac{1}{t} \int_0^t d\tau \langle [\nabla_{\mathbf{x}} z_\tau]^T \boldsymbol{\gamma}^{-1}(\tau) \nabla_{\mathbf{x}} z_\tau \rangle, \quad (95)$$

which accounts for how much $z(\mathbf{x}_\tau, \tau)$ “stretches” microscopic coordinates $\mathbf{x}_\tau$ [51]. Here, $\boldsymbol{\gamma}$ is a positive-definite and symmetric friction matrix that is allowed to depend on time and the averages $\langle \cdot \rangle$ in Eqs. (94) and (95) are taken over transient trajectories. In Refs. [51,113], it was further shown how $\mathcal{D}_t^c$ relates to the short-time fluctuations $dz_\tau = z_{\tau+d\tau} - z_\tau$, i.e.,

$$\mathcal{D}_t^c = \int_0^t d\tau \frac{\text{var}(dz_\tau)}{2d\tau}. \quad (96)$$

To prove the discrete-space transport bound, we use Eq. (75) and the stochastic integral

$$B_t = \int_{\tau=0}^t \text{Tr}[\mathbf{H}(\tau) d\boldsymbol{\epsilon}(\tau)], \quad (97)$$

where $[\mathbf{H}(\tau)]_{ij} = z_i(\tau) - z_j(\tau)$ is the difference of some observable state function $z_\tau \equiv z(\mathbf{x}_\tau, \tau) = \sum_k \delta_{x,k} z_k(\tau)$. The mean of B_t vanishes, while the second moment reads

$$\langle B_t^2 \rangle = \int_0^t d\tau \sum_{i,j} [z_i(\tau) - z_j(\tau)]^2 r_{ij} p_i(\tau), \quad (98)$$

which we can identify with the short-time fluctuation function $\mathcal{D}_t = \langle B_t^2 \rangle / t$. Namely, consider the infinitesimal difference $dz(\tau) = z_{\tau+d\tau} - z_\tau$ along the trajectory. Then, for any $n \in \mathbb{N}_{>0}$, we then get $\langle [dz(\tau)]^n \rangle = \sum_{x,y} (z_y - z_x)^n r_{xy} p_x(\tau) d\tau + \mathcal{O}(d\tau^2)$. Thus, $\text{var}[dz(\tau)] = \sum_{x,y} (z_y - z_x)^2 r_{xy} p_x(\tau) d\tau + \mathcal{O}(d\tau^2)$ and

$$\mathcal{D}_t = \frac{1}{t} \int_0^t \text{var}[dz(\tau)]. \quad (99)$$

After performing an integration by parts, the cross-correlation between A_t [given in Eq. (75)] and B_t is

$$\begin{aligned} \langle A_t B_t \rangle &= \sum_i \left[z_i(t) p_i(t) - z_i(0) p_i(0) - \int_0^t d\tau \partial_\tau z_i(\tau) p_i(\tau) \right] \\ &= \langle z_t - z_0 - \int_0^t d\tau \partial_\tau z_\tau \rangle. \end{aligned} \quad (100)$$

The average of z_t is given by $\langle z_t \rangle = \sum_k \sum_l \delta_{kl} z_k(\tau) p_l(t)$. By combining the various averages entering the Cauchy-Schwarz inequality $\langle A_t B_t \rangle \leq \langle A_t^2 \rangle \langle B_t^2 \rangle$, we obtain the transport bound for MJPs

$$\frac{\langle z_t - z_0 - \int_0^t d\tau \partial_\tau z_\tau \rangle^2}{t \mathcal{D}_t} \leq \frac{\Delta S_{\text{tot}}(t)}{2}. \quad (101)$$

Upon identifying the dynamical activity $\int_0^t d\tau \sum_{x,y \neq x} r_{xy} p_x(\tau)$ [111,112], the fluctuation-scale function $\mathcal{D}_t$ can be seen as a $[z_y(\tau) - z_x(\tau)]^2$ -weighted dynamical activity, which justifies referring to $\mathcal{D}_t$ as the diffusion constant of z_τ on a graph.

1. Saturation of the transport bound

While the continuous TB in Eq. (94) can be saturated, however not uniquely, with $\nabla_{\mathbf{x}} z_\tau = c \boldsymbol{\gamma} \mathbf{j}(\mathbf{x}, \tau) / P(\mathbf{x}, \tau)$ (see Ref. [51] for details), there is no general way to saturate the discrete TB. We provide a simple counterexample to show

why this is the case. Consider some $a, b, c > 0$ and let

$$\mathbf{L} = \begin{pmatrix} -1-a & b & 1 \\ 1 & -1-b & c \\ a & 1 & -1-c \end{pmatrix} \quad (102)$$

be the generator for a fully connected three-state MJP with states $\{1, 2, 3\}$. Saturation of Eq. (101) entails choosing z_τ such that $\mathbf{H}(\tau)^T \propto \mathbf{Z}(\tau)$ to saturate the Cauchy-Schwarz inequality. Explicitly, for all τ ,

$$\begin{aligned} z_2(\tau) - z_1(\tau) &\stackrel{!}{=} Z_{12}(\tau) = \frac{p_1(\tau) - bp_2(\tau)}{p_1(\tau) + bp_2(\tau)}, \\ z_3(\tau) - z_1(\tau) &\stackrel{!}{=} Z_{13}(\tau) = \frac{ap_1(\tau) - p_3(\tau)}{ap_1(\tau) + p_3(\tau)}, \\ z_3(\tau) - z_2(\tau) &\stackrel{!}{=} Z_{23}(\tau) = \frac{p_2(\tau) - cp_3(\tau)}{p_2(\tau) + cp_3(\tau)}. \end{aligned} \quad (103)$$

A solution of Eq. (103) involves $Z_{23}(\tau) = Z_{13}(\tau) - Z_{12}(\tau)$, i.e.,

$$\frac{p_2(\tau) - cp_3(\tau)}{p_2(\tau) + cp_3(\tau)} = \frac{2p_1(\tau)[ap_2(\tau) - p_3(\tau)]}{[ap_1(\tau) + p_3(\tau)][p_1(\tau) + bp_2(\tau)]}. \quad (104)$$

Even for $abc = 1$, which corresponds to a system relaxing toward equilibrium, we can always choose an initial condition $\mathbf{p}(\tau = 0)$ such that the equality in Eq. (104) is not achieved. For example, let $a = b = c = 2$ and $p_2(0) = p_3(0) = 1/2$. The lhs of Eq. (104) yields $-1/3$, while the rhs is 0, hence the equality is not achieved and the set of equations in Eq. (103) has no solution. Thus, there is no state function z_τ that saturates the TB.

2. Unification of (C)TUR and TB

It turns out that the TB is a special case of the CTUR. Starting from the transient CTUR Eq. (88), we now choose ρ_t such that $J_t - c(t)\rho_t = J_t^I$, i.e., $V_i(\tau) = \sum_j \kappa_{ij}(\tau)r_{ij}/c(t)$. Then,

$$\begin{aligned} t\partial_t \langle \rho_t \rangle &= t \sum_i V_i(t) p_i(t) \\ &= t \sum_{i,j \neq i} \frac{\kappa_{ij}(\tau)r_{ij}}{c(t)} p_i(t) \\ &= \frac{1}{c(t)} t\partial_t \langle J_t \rangle, \end{aligned} \quad (105)$$

and similarly,

$$\begin{aligned} \langle \tilde{\rho}_t \rangle &= \int_0^t d\tau \sum_i \tau \partial_\tau V_i(\tau) p_i(\tau) \\ &= \int_0^t d\tau \sum_{i,j \neq i} \frac{\tau \partial_\tau \kappa_{ij}(\tau) r_{ij}}{c(t)} p_i(\tau) \\ &= \frac{1}{c(t)} \int_0^t d\tau \sum_{i,j \neq i} \tau \partial_\tau \kappa_{ij}(\tau) r_{ij} p_i(\tau) \\ &= \frac{1}{c(t)} \langle \tilde{J}_t \rangle. \end{aligned} \quad (106)$$

An analogous calculation reveals $\langle \rho_t \rangle = \langle J_t \rangle / c(t)$ and hence using this choice of ρ_t in Eq. (88) yields the following form of the transient CTUR:

$$\frac{\langle J_t \rangle^2}{\text{var}[J_t - c(t)\rho_t]} = \frac{\langle J_t \rangle^2}{\text{var}(J_t^I)} \leq \frac{\Delta S_{\text{tot}}(t)}{2}. \quad (107)$$

We call Eq. (107) the generalized TB (gTB) because the choice $\kappa_{ij}(\tau) = z_j(\tau) - z_i(\tau)$ yields the transport bound. Explicitly, the mean current is

$$\begin{aligned} \langle J_t \rangle &= \int_0^t ds \sum_{i,j \neq i} [z_j(s) - z_i(s)] r_{ij} p_i(s) \\ &= \int_0^t ds \sum_i z_i(s) \underbrace{\sum_{j \neq i} [r_{ji} p_j(s) - r_{ij} p_i(s)]}_{=\partial_s p_i(s)} \\ &= \sum_i \left(z_i(t) p_i(t) - z_i(0) p_i(0) - \int_0^t ds [\partial_s z_i(s)] p_i(s) \right), \end{aligned} \quad (108)$$

and the variance of the dissipative current reads

$$\begin{aligned} \text{var}(J_t^I) &= \langle (J_t^I)^2 \rangle - \underbrace{\langle J_t^I \rangle^2}_{=0} \\ &= \int_0^t ds \sum_{i,j \neq i} [z_j(s) - z_i(s)]^2 r_{ij} p_i(s) \\ &= t\mathcal{D}_t. \end{aligned} \quad (109)$$

With the specific choice $\kappa_{ij}(\tau) = z_j(\tau) - z_i(\tau)$, i.e., using Eqs. (108) and (109), Eq. (107) becomes the TB

$$\frac{\langle z_t - z_0 - \int_0^t d\tau \partial_\tau z_\tau \rangle^2}{t\mathcal{D}_t} \leq \frac{\Delta S_{\text{tot}}(t)}{2}. \quad (110)$$

Equation (107) therefore naturally relates the TB to the CTUR as a special case. Indeed, the gTB is efficient, i.e., yields a nonzero bound in both transient and stationary systems, while the TB yields only nontrivial bounds in transient systems. A similar connection can be made in continuous space, where a recent TUR for underdamped

Langevin dynamics [126] can be seen as a generalization of the continuous TB [51]. It should be noted that, while the TB, in general, cannot be saturated, the gTB can be saturated with the choice of weight $\kappa(\tau) \propto Z(\tau)$. Moreover, in some cases, the transient TB of one system may be identical to the stationary gTB of another system. The following example, an extension of the SAT model [see Fig. 6(b)], shows how the TB may give rise to the gTB in a special case.

To make reasonable comparisons in the SAT model, we either have to consider symporter or antiporter systems. We are going to focus on the latter. We first vary e_B^{out} to assess which values of transition rates give rise to antiporter behavior before addressing thermodynamic inference.

We start with the cycle affinities of the model. The six-state SAT model consist of three cycles: $C_1 = \{1 \rightarrow 2, 2 \rightarrow 4, 4 \rightarrow 3, 3 \rightarrow 1\}$, $C_2 = \{3 \rightarrow 4, 4 \rightarrow 6, 6 \rightarrow 5, 5 \rightarrow 3\}$, and $C_3 = \{1 \rightarrow 2, 2 \rightarrow 4, 4 \rightarrow 6, 6 \rightarrow 5, 5 \rightarrow 3, 3 \rightarrow 1\}$. The corresponding cycle affinities are $\mathcal{A}_{C_1} = \log(e_A^{\text{out}}/e_A^{\text{in}})$, $\mathcal{A}_{C_2} = \log(e_B^{\text{in}}/e_B^{\text{out}})$, and $\mathcal{A}_{C_3} = \mathcal{A}_{C_1} + \mathcal{A}_{C_2} = \log(e_A^{\text{out}}e_B^{\text{in}}/e_A^{\text{in}}e_B^{\text{out}})$. Since the transport of molecule *A* with help of *B* is of interest, one could naively assume that the transport relates to $\mathcal{A}_{C_3}$. However, $\mathcal{A}_{C_3}$ does not quantify the direction of transport, as $\mathcal{A}_{C_3}$ does not give any information on the transport of type *A* alone. One can also convince oneself that $\mathcal{A}_{C_1}$ is insufficient as well, due to the cycle affinity being independent of e_B^{out} .

However, the current (entering the stationary TUR) in the six-state model gives the insight we require. The relevant transition weight is $\kappa_{ij}^{\text{SAT}} = \delta_{i1}\delta_{j3} - \delta_{i3}\delta_{j1}$, effectively counting the total number of molecules *A* being transported toward the exterior of the cell. The mean current is $\langle J_t^{\text{SAT}} \rangle_s = \sum_{x,y} \kappa_{xy}^{\text{SAT}} r_{xy} p_x^s$. If $\langle J_t^{\text{SAT}} \rangle_s > 0$, the average total number of molecules *A* transported toward the outside of the cell is positive, corresponding to an average transport of *A* from the inside to the outside of the cell. Thus, the condition for an antiporter behavior is $l_A/e_A^{\text{out}} > p_3^s/p_1^s$,

which depends on e_B^{out} via the steady-state distribution. With the parameters we use, see Table IV, we need $p_3^s/p_1^s < 2/3$. The value $2/3$ is marked as a black line in the inset of Fig. 9(a), where the green line corresponds to the value of p_3^s/p_1^s as a function of e_B^{out} . The dashed red line marks the value of e_B^{out} such that $\mathcal{A}_{C_3} = 0$, while the dashed orange line is where $p_3^s/p_1^s = 2/3$. The same can be readily seen in Fig. 9(b), where the mean current is presented for various values of e_B^{out} . Clearly, the condition $\mathcal{A}_{C_3} = 0$ is not sufficient for a positive current.

Additionally, we can consider the transient extended model and apply the TB. For the extended model, consider $p_{x,n}(\tau)$, the probability of being in state *x* in system *n* at time τ , where $n \in \mathbb{Z}$ corresponds to the number of *A* molecules transported through the membrane. When marginalizing over $\mathbb{Z}$, we recover the steady-state probability $p_x^s = \sum_{n \in \mathbb{Z}} p_{x,n}(\tau)$. As a state function, we choose the number of *A* molecules $z_\tau = n$, such that

$$\langle z_\tau \rangle = \sum_{n \in \mathbb{Z}} n \sum_{x=1}^6 p_{x,n}(\tau) = \sum_{n \in \mathbb{Z}} n \tilde{p}_n(\tau), \quad (111)$$

where $\tilde{p}_n(\tau)$ is the probability distribution marginalized over $\mathcal{N}$. Without loss of generality, we use $\langle z_0 \rangle = 0$. Equation (111) therefore describes the average number of net transitions $\langle n_{13} - n_{31} \rangle$ between states 1 and 3 in the original system until time τ , with z_τ the net number of transitions. Hence, one can immediately recognize that $\langle z_\tau \rangle = \langle J_t^{\text{SAT}} \rangle_s$, which can be readily seen in Fig. 9(a).

The fluctuation-scale function is recognized to be

$$\begin{aligned} \mathcal{D}_t^{\text{ext}} = & \frac{1}{t} \sum_{n \in \mathbb{Z}} \sum_{x,y \in \mathcal{N}} \int_0^t d\tau [(z_{y,n} - z_{x,n})^2 \delta_{x \rightarrow y,n} \\ & + (z_{y,n+1} - z_{x,n})^2 \delta_{x \rightarrow y,n \rightarrow n+1} \\ & + (z_{y,n-1} - z_{x,n})^2 \delta_{x \rightarrow y,n \rightarrow n-1}] r_{xy} p_{x,n}(\tau). \end{aligned} \quad (112)$$

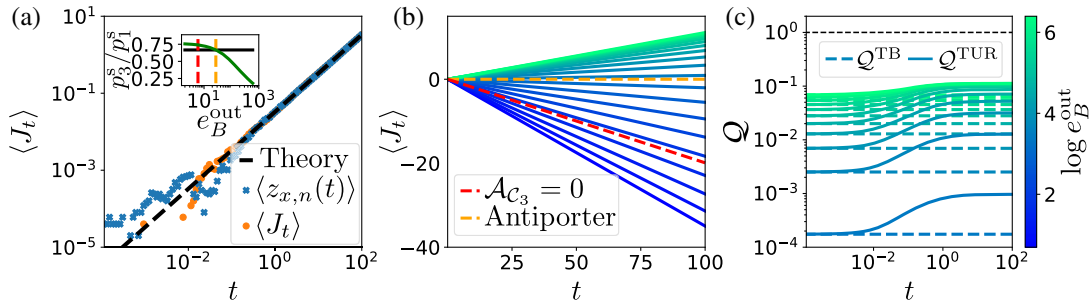


FIG. 9. Comparison of TUR and transport bound with the periodic extension of the SAT model in Fig. 6(b). The mean of J_t (orange) and $z_{x,n}$ (blue) from $N = 50\,000$ trajectories sampled with the Gillespie algorithm is shown in (a) as a function of t , compared to the analytic $\langle J_t \rangle$ [see Eq. (81)], for $e_B^{\text{out}} \approx 40$. The inset shows the fraction p_3^s/p_1^s for different values of e_B^{out} . The dashed orange and red lines indicate the values of e_B^{out} where the antiporter regime begins ($e_B^{\text{out}} \approx 27$) and where $\mathcal{A}_{C_3} = 0$ ($e_B^{\text{out}} = 6$), respectively, while the black line is the upper limit p_3^s/p_1^s can have so that the system is an antiporter. The mean current is shown in (b) for various values of e_B^{out} . The steady-state quality factors for TUR (solid) and TB (dashed) are shown in (c) as a function of t for various values of e_B^{out} in the antiporter regime. The parameters are listed in Table IV.

Note that $\delta_{x \rightarrow y, n \rightarrow n+1}$ is 1 if the transition $x \rightarrow y$ is observed while the system goes from n to $n+1$ and 0 otherwise. We can simplify Eq. (112) to find

$$\mathcal{D}_t^{\text{ext}} = \frac{1}{t} \sum_{n \in \mathbb{Z}} \int_0^t d\tau [r_{13} p_{1,n}(\tau) + r_{31} p_{3,n}(\tau)], \quad (113)$$

because $z_{x,n} - z_{y,n} = 0$ and $z_{x,n} - z_{y,n \pm 1} = \pm 1$. Marginalizing over n finally gives

$$\mathcal{D}_t^{\text{ext}} = [r_{13} p_1^s + r_{31} p_3^s] = \sum_{x,y \in \mathcal{N}} (\kappa_{xy}^{\text{SAT}})^2 r_{xy} p_x^s. \quad (114)$$

Upon comparing Eq. (114) to Eq. (68), it becomes apparent that $\mathcal{D}_t^{\text{ext}} = \lim_{t \rightarrow 0} \text{var}_s(J_t^{\text{SAT}})/t$. Furthermore, using the TB on the transient extended SAT model yields the stationary gTB of the original six-state SAT model, as the TB reduces to Eq. (107).

The quality factors of the TUR $\mathcal{Q}^{\text{TUR}}$ and TB $\mathcal{Q}^{\text{TB}}$ are shown in Fig. 9(c) (solid and dashed line, respectively) for e_B^{out} in the antiporter regime. Because $t\mathcal{D}_t^{\text{ext}} > \text{var}_s(J_t^{\text{SAT}})$ for all $t > 0$, the TUR infers a higher fraction of the entropy production, i.e., $\mathcal{Q}^{\text{TUR}} \geq \mathcal{Q}^{\text{TB}}$. Additionally, one may show that taking $e_B^{\text{out}} \rightarrow \infty$ leads to the quality factors converging to a finite value [12,155]. Hence, there is no improvement in the inference of dissipation at higher concentrations of B outside the cell beyond a certain point.

D. Thermodynamic correlation bound

Thermodynamic bounds on correlation times were studied in the context of Langevin dynamics in Ref. [113] in stationary systems at large times. Recently, such thermodynamic correlation inequalities were extended to finite times and transients [114]. Following the latter stochastic-calculus approach, we here develop analogous results for time-homogeneous MJPs, in the general transient setting and for arbitrary times. That such results are possible was already anticipated in Ref. [113].

The proof of the correlation bound starts from the auxiliary stochastic integral

$$B_t = \frac{1}{\sqrt{t}} \int_0^{\tau=t} \text{Tr} \left[\left(\mathbf{H}(\tau) - \tilde{\mathbf{Z}}(\tau)^T \right) d\mathbf{e}(\tau) \right], \quad (115)$$

where $\tilde{\mathbf{Z}}_{xy}(\tau) = Z_{xy}(\tau)[z_x(\tau) + z_y(\tau) - 2F(\tau)]$ for some time-dependent function $F(\tau)$, Z_{xy} is given by Eq. (76), and $\mathbf{H}$ is the same matrix also entering Eq. (97). The second key ingredient is the shifted and rescaled density observable

$$C_t = \frac{1}{\sqrt{t}} \int_0^{\tau=t} [V_\tau - \langle V_\tau \rangle] d\tau, \quad (116)$$

where $\langle V_\tau \rangle = \sum_i V_i p_i(\tau)$. While the TUR and TB allow the state functions z_τ and V_τ to be explicitly time dependent, the correlation bound requires these to be strictly time independent. Furthermore, we write, e.g., $\langle z_\tau \rangle = \sum_i z_i p_i(\tau)$ to explicitly highlight that the average depends on time through $p_i(\tau)$. Additionally, we need to introduce the reweighted two-point probability

$$p_{xy}^{\text{ps}}(\tau) = \frac{p_x(\tau) r_{xy} Z_{xy}(\tau)^2}{\Sigma_{\text{ps}}}, \quad (117)$$

with the renormalization constant $\Sigma_{\text{ps}} = \sum_{x,y} p_x(\tau) \times r_{xy} Z_{xy}(\tau)^2$ which is the pseudoentropy production rate (pseudo-EPR). Expectation values with respect to $p_{xy}^{\text{ps}}(\tau)$ will be denoted by $\langle \cdot \rangle_{\text{ps}}$. We will also introduce the pseudovariance $\text{pvar}_{\text{ps}}^F(z_\tau) = \sum_{x,y} [z_x + z_y - 2F(\tau)]^2 p_{xy}^{\text{ps}}(\tau)$, which is the “true” variance for only $F(\tau) = \langle z_\tau \rangle_{\text{ps}}/2 = \sum_{x,y} (z_x + z_y) p_{xy}^{\text{ps}}(\tau)/2$ and some other positive time-dependent quantity otherwise.

We immediately see that

$$\langle C_t^2 \rangle = \frac{1}{t} \int_0^t d\tau \int_0^t d\tau' \text{cov}(V_\tau, V_{\tau'}), \quad (118)$$

where $V_\tau \equiv V(x_\tau) = \sum_k \delta_{k,x_\tau} V_k$, and introducing the time-averaged density

$$\begin{aligned} \bar{V}_t &\equiv \frac{1}{t} \int_{\tau=0}^{\tau=t} V_\tau d\tau, \\ \bar{z}_t &\equiv \frac{1}{t} \int_{\tau=0}^{\tau=t} z_\tau d\tau, \end{aligned} \quad (119)$$

Eq. (118) can be identified as

$$t\text{var}(\bar{V}_t) = \langle C_t^2 \rangle. \quad (120)$$

With the shorthand notations $V_x^\Delta(\tau) = V_x - \langle V_\tau \rangle$ and $z_\tau^F = z_\tau - \langle F(\tau) \rangle$, the cross term is computed to be

$$\begin{aligned} t\langle B_t C_t \rangle &= \int_0^t d\tau' \int_0^t d\tau \sum_{x,y,i} \mathbb{1}_{\tau < \tau'} V_i^\Delta(\tau') (H_{yx} - Z_{xy}(\tau)) \\ &\quad \times [z_x^F(\tau) + z_y^F(\tau)] r_{xy} p_x(\tau) \\ &\quad \times [P(i, \tau' | y, \tau) - P(i, \tau' | x, \tau)], \end{aligned} \quad (121)$$

where the sum over x, y can be simplified because of symmetries (we suppress the time indices here) to get

$$\begin{aligned} &\sum_{x,y} H_{yx} r_{xy} p_x [P(i|y) - P(i|x)] \\ &= - \sum_{x,y} z_x^F (r_{xy} p_x + r_{yx} p_y) [P(i|y) - P(i|x)], \end{aligned} \quad (122)$$

and

$$\sum_{x,y} Z_{xy}(z_x^F + z_y^F) r_{xy} p_x [P(i|y) - P(i|x)] \\ = \sum_{x,y} z_x^F (r_{xy} p_x - r_{yx} p_y) [P(i|y) - P(i|x)]. \quad (123)$$

Using time homogeneity of the semigroup $\mathbf{P}(\tau'|\tau) = \mathbf{P}(\tau' - \tau) \equiv e^{\mathbf{L}(\tau' - \tau)}$, which obeys the master equation Eq. (40), i.e., $\partial_\tau \mathbf{P}(\tau) = \mathbf{L} \mathbf{P}(\tau) = \mathbf{P}(\tau) \mathbf{L}$, and $\partial_{\tau'} \mathbf{P}(\tau' - \tau) = -\partial_{\tau'} \mathbf{P}(\tau' - \tau)$, the integrand in Eq. (121) simplifies to $2 \sum_{x,i} \mathbb{1}_{\tau < \tau'} V_i^\Delta(\tau') z_x^F(\tau) p_x(\tau) \partial_{\tau'} P(i, \tau' | x, \tau)$. Since

$$\sum_{x,i} [\partial_{\tau'} V_i^\Delta(\tau')] z_x^F(\tau) p_x(\tau) P(i, \tau' | x, \tau) \\ = -\partial_{\tau'} \langle V_{\tau'} \rangle \sum_x z_x^F(\tau) p_x(\tau) \underbrace{\sum_i P(i, \tau' | x, \tau)}_{=1} \\ \underbrace{= \langle z_{\tau'} \rangle - F(\tau)}_{=1} \quad (124)$$

the particular choice $F(\tau) = \langle z_{\tau} \rangle$ yields

$$t \langle B_t C_t \rangle = 2 \int_0^t d\tau' \int_0^{\tau'} d\tau \mathbb{1}_{\tau < \tau'} \partial_{\tau'} \text{cov}(V_{\tau'}, z_{\tau}). \quad (125)$$

An integration by parts in τ' with $\partial_{\tau'} \mathbb{1}_{\tau < \tau'} = \delta(\tau' - \tau)$ further yields

$$\langle B_t C_t \rangle = 2 \text{cov}[V_t, \bar{z}_t] - \frac{2}{t} \int_0^t d\tau \text{cov}[V_{\tau}, z_{\tau}]. \quad (126)$$

Finally, the second moment of B_t reads

$$\langle B_t^2 \rangle = \mathcal{D}_t + \frac{1}{t} \int_0^t d\tau \Sigma^{\text{ps}}(\tau) \text{pvar}_{\text{ps}}^F(z_{\tau}) \\ - \frac{2}{t} \int_0^t d\tau \sum_{x,y} \left([z_y - F(\tau)]^2 - [z_x - F(\tau)]^2 \right) \\ \times Z_{xy}(\tau) r_{xy} p_x(\tau). \quad (127)$$

The integrand of the last term in Eq. (127) reduces to

$$\sum_{x,y} \left([z_y - F(\tau)]^2 - [z_x - F(\tau)]^2 \right) Z_{xy}(\tau) r_{xy} p_x(\tau) \\ = \sum_y [z_y - F(\tau)]^2 \partial_\tau p_y(\tau). \quad (128)$$

Choosing $F(\tau) = \langle z_{\tau} \rangle$ again simplifies Eq. (127) to

$$\langle B_t^2 \rangle = \mathcal{D}_t + \frac{1}{t} \int_0^t d\tau \Sigma^{\text{ps}}(\tau) \text{pvar}_{\text{ps}}^F(z_{\tau}) \\ - \frac{2}{t} [\text{var}(z_t) - \text{var}(z_0)]. \quad (129)$$

Combining Eqs. (120), (126), and (129) yields the transient finite-time correlation bound

$$\frac{\left[2 \text{cov}(V_t, \bar{z}_t) - \frac{2}{t} \int_0^t d\tau \text{cov}(V_{\tau}, z_{\tau}) \right]^2}{t \text{var}(\bar{V}_t)} - \mathcal{D}_t \\ + \frac{2}{t} [\text{var}(z_t) - \text{var}(z_0)] \leq \frac{1}{t} \int_0^t d\tau \Sigma^{\text{ps}}(\tau) \text{pvar}_{\text{ps}}^F(z_{\tau}). \quad (130)$$

In NESS, Eq. (130) simplifies to [we suppress time indices for stationary single-time (pseudo and/or co)variances]

$$\frac{4 [\text{cov}(V_t, \bar{z}_t) - \text{cov}_s(V, z)]^2}{t \text{var}(\bar{V}_t)} - \mathcal{D}_t \\ \leq \frac{\langle A_t^2 \rangle_s}{t} \text{pvar}_{\text{ps}}^F(z) \leq \frac{\Delta S_{\text{tot}}(t)}{2t} \text{pvar}_{\text{ps}}^F(z). \quad (131)$$

The two-point probability density $p_{xy}(\tau)$ is not accessible, since it requires knowing $\mathbf{L}$; hence, the pseudovariance in Eqs. (130) and (131) needs to be further bounded. In the former case, it was assumed that $F(\tau) = \langle z_{\tau} \rangle$, while in the stationary case the choice of $F(\tau) = F$ is free. Since we consider bounded z_{τ} on finite-state spaces, there exist bounds $z_{\text{max}}/z_{\text{min}}$ such that for all $x \neq y$ [156] the function entering the pseudovariance satisfies $z_{\text{min}} \leq z_x + z_y \leq z_{\text{max}}$. In steady state with $F = \langle z_{\tau} \rangle_{\text{ps}}/2$, $\text{pvar}_{\text{ps}}^F(z) = \text{var}_{\text{ps}}(z) \leq (z_{\text{max}} - z_{\text{min}})^2/4$, where we used the Popoviciu's inequality.

It should also be clear from Eqs. (130) and (131) that the quality factor for the CB $\mathcal{Q}^{\text{CB}}$ can become negative (and hence the bound is uninformative). To be precise, let

$$G(t) \equiv \frac{\left[2 \text{cov}(V_t, \bar{z}_t) - \frac{2}{t} \int_0^t d\tau \text{cov}(V_{\tau}, z_{\tau}) \right]^2}{t \text{var}(\bar{V}_t)}, \quad (132)$$

then clearly $G(t), \mathcal{D}_t, \text{var}(z_t) \geq 0$ for all $t \geq 0$. Therefore, if $G(t) - \mathcal{D}_t + (2/t)[\text{var}(z_t) - \text{var}(z_0)] < 0$, the inferred entropy production is negative. The fact that the quality factor may become negative, giving a lower bound on the total entropy production that is worse than the second law of thermodynamics, is not particularly appealing. However, the CB can be applied in situations where many established methods fail to infer entropy production. In the following, we provide a simple four-state example where CB can be applied successfully, but other methods fail.

1. Example II: Four-state toy model

Consider a four-state model $\{1, 2, 3, 4\}$ on a ring, see Fig. 6(e). The rates clockwise are unity and the counter-clockwise rates are controlled by the parameter ϵ . The steady-state distribution $p_i^s = p = 1/4$ is independent of ϵ . Suppose that we can only distinguish between a pair of mesostates A and B, i.e., it can only distinguish whether the system is in either states 1 and 2 (mesostate A) or states 3 and 4 (mesostate B).

and 4 (mesostate B). These we refer to mesostates A (containing $\{1, 2\}$) and B (containing $\{3, 4\}$), see Fig. 6(e).

Inferring the total steady-state entropy production $\Delta S_{\text{tot}}(t) = t(\epsilon - 1) \log \epsilon$ by only observing transitions between states A and B is a challenge where surprisingly few bounds provide nontrivial estimates. For example, the TUR gives (only) the second law, as

$$\langle J_t \rangle = p \left(\underbrace{\epsilon \kappa_{AB}}_{2 \rightarrow 3} + \underbrace{\kappa_{BA}}_{3 \rightarrow 2} + \underbrace{\epsilon \kappa_{BA}}_{4 \rightarrow 1} + \underbrace{\kappa_{AB}}_{1 \rightarrow 4} \right) = 0. \quad (133)$$

Including a density, i.e., using the CTUR Eq. (88), yields the same bound, because the density contributes only in transient dynamics. Similarly, the TB is only nontrivial for transient systems. Using the gTB is not profitable either, due to Eq. (133).

However, the CB can be applied to yield a positive bound on the EP for sufficiently large t and ϵ . The fluctuation-scale function is $\mathcal{D}_t = (1 + \epsilon)/2$ and for $\mathbf{X} = \mathbf{A}, \mathbf{B}$ the steady-state (co)variance is $\text{cov}_s(V^A, V^X) = (\delta_{X,A} - \delta_{X,B})/4$. If λ_k , $k \in \{1, 2, 3, 4\}$, are the eigenvalues of the generator

$$\begin{aligned} \lambda_1 &= 0, \\ \lambda_2 &= -2(\epsilon + 1), \\ \lambda_{3/4} &= -1 - \epsilon \pm (\epsilon - 1)i, \end{aligned} \quad (134)$$

then for times $t \gg \max_{k \in \{2,3,4\}} (-1/\text{Re}(\lambda_k)) = 1/(1 + \epsilon)$, we can use

$$\text{tvar}(\bar{V}_t^A) = 2 \int_0^t d\tau \text{cov}(V_\tau^A, V_0^A) + \mathcal{O}(t^{-1}), \quad (135)$$

and is therefore similar to

$$\begin{aligned} \text{cov}(V_t^A, \bar{V}_t^B) &= -\frac{1}{t} \int_0^t d\tau \text{cov}(V_\tau^A, V_\tau^A) \\ &= -\frac{1}{t} \int_0^t d\tau \text{cov}(V_\tau^A, V_0^A). \end{aligned} \quad (136)$$

Thus, the lhs of Eq. (131) for $t \gg 1/(1 + \epsilon)$ reads

$$\begin{aligned} &\frac{4[\text{cov}(V_t, \bar{z}_t) - \text{cov}_s(V, z)]^2}{\text{tvar}(\bar{V}_t)} - \mathcal{D}_t \\ &= \frac{1}{8 \int_0^t d\tau \text{cov}(V_\tau^A, V_0^A)} - \frac{1 + \epsilon}{2} + \mathcal{O}(t^{-1}). \end{aligned} \quad (137)$$

The first term can be simplified further to be $(\epsilon^2 + 1)/(\epsilon + 1)$ (see Appendix A 6), so that the large- t quality factor becomes

$$\begin{aligned} \mathcal{Q} &\xrightarrow{t \rightarrow \infty} \frac{1}{\log \epsilon} \left[\frac{(\epsilon + 1)^2 + (\epsilon - 1)^2}{(\epsilon^2 - 1)} - \frac{\epsilon + 1}{\epsilon - 1} \right] \frac{1}{\text{pvar}_{\text{ps}}^F(V^A)} \\ &= \frac{(\epsilon - 1)}{(\epsilon + 1) \log \epsilon} \frac{1}{\text{pvar}_{\text{ps}}^F(V^A)}. \end{aligned} \quad (138)$$

Recall that the choice of $F(\tau)$ is free for stationary systems, hence we can choose $F(\tau) = \langle V_x^A + V_y^A \rangle_{\text{ps}}/2$ such that $\text{pvar}_{\text{ps}}^F(V^A) = \text{var}_{\text{ps}}(V^A)$. Using Popoviciu's inequality, the pseudovariance (i.e., variance) with the choice $F(\tau) = \langle V_x^A + V_y^A \rangle_{\text{ps}}/2$ (i.e., the two-point variance of $V_x^A + V_y^A$) can be bounded by $\text{var}_{\text{ps}}^F(V^A) = 1/2 \leq 1$ (see Appendix A 6). Thus, the estimated entropy production using Popoviciu's inequality is half of that estimated with the exact pseudovariance, resulting in $2\mathcal{Q}^{\text{Pop}} = \mathcal{Q}$, which is shown in Fig. 10(a), where the exact EPR is shown together with the long-time limit of estimated EPR with and without Popoviciu's inequality. The inset in Fig. 10(a) shows the corresponding quality factors, Eq. (138), in the limit $t \rightarrow \infty$. As a sanity check, theoretical and simulation results obtained with the celebrated Gillespie algorithm [146,147] of $G(t) - \mathcal{D}_t$ are compared in Fig. 10(b), where a good agreement is found. In addition, the leading-order correction is shown in Fig. 10(c) by considering

$$\delta[G(t) - \mathcal{D}_t] = G(t) - \mathcal{D}_t - \frac{(\epsilon - 1)^2}{2(\epsilon + 1)}, \quad (139)$$

i.e., subtracting the $t \rightarrow \infty$ limit. As expected, the leading-order correction decays as t^{-1} .

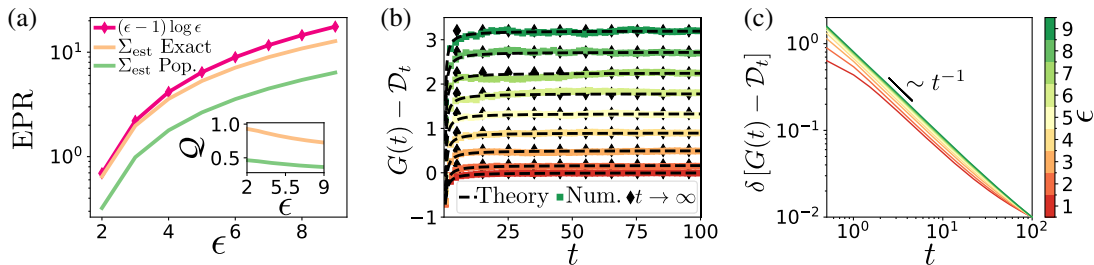


FIG. 10. Correlation bound applied to the driven ring, see Fig. 6(e). (a) The exact EPR and long-time estimated EPR with and without bounding the (pseudo)variance are shown in dependence of ϵ . Specifically, the choice $F(\tau) = \langle V_x^A + V_y^A \rangle_{\text{ps}}/2$ is used. The inset shows the resulting quality factors. The lhs of the stationary CB, $G(t) - \mathcal{D}_t$, is shown in (b) evaluated analytically and with simulations. Additionally, the long-time limit is included. The deviation from the long-time limit $\delta[G(t) - \mathcal{D}_t]$ is presented in (c) correctly displaying the $\mathcal{O}(t^{-1})$ decay. The simulations are performed with the Gillespie algorithm using $N = 50000$ trajectories.

V. RESPONSE TO GENERAL PERTURBATION

Numerous works addressed the response of Markovian dynamics to perturbations by means of various methods in the setting of equilibrium systems [157–159] and nonequilibrium steady states [18,69,160–163], as well as general perturbations of single-time observables [4], which was recently generalized to path observables of diffusions [137]. Here we develop the counterpart of Ref. [137] for MJPs using the developed stochastic calculus.

A. Derivation of response formula for MJPs

We are interested in the response of a (generally pathwise) observable $O(t) = O[(x_\tau)_{0 \leq \tau \leq t}]$ to a perturbation of a control parameter $\chi \rightarrow \chi + \delta$ (e.g., a temperature change $T \rightarrow T + \delta$). We seek an exact result for

$$\partial_\delta O_t = \lim_{\delta \rightarrow 0} \frac{1}{\delta} (\langle O(t) \rangle_\delta - \langle O(t) \rangle), \quad (140)$$

where $\langle O(t) \rangle$ is the expectation with respect to the unperturbed process in Eq. (47), while $\langle O(t) \rangle_\delta$ is the average with respect to the perturbed process evolving according to

$$d\mathbf{n}^\delta(\tau) = \mathbf{R}^\delta(x_\tau^\delta) d\tau + d\mathbf{e}^\delta(\tau). \quad (141)$$

Depending on the observable, the averages $\langle O(t) \rangle$ and $\langle O(t) \rangle_\delta$ can either be understood as single-time or pathwise averages. For example, if $O(t)$ measures some instantaneous quantity at time t , e.g., the instantaneous internal energy of the system, the averages are to be understood as $\langle O(t) \rangle_{(\delta)} = \sum_x O_x(t) p_x^{(\delta)}(t)$, where $p_x^{(\delta)}(t)$ is the single-time probability evolving according to the master equation of the (perturbed) system. Conversely, if $O(t) = O[(x_\tau)_{0 \leq \tau \leq t}]$ is a pathwise observable depending on the entire trajectory, e.g., a time-integrated current J_t , the average $\langle \cdot \rangle$ is over all paths evolving according to Eq. (47) [and $\langle \cdot \rangle_{(\delta)}$ over all paths evolving according to Eq. (141)],

$$\langle O(t) \rangle_{(\delta)} = \sum_{(x_\tau)_{0 \leq \tau \leq t}} O[(x_\tau)_{0 \leq \tau \leq t}] \mathbb{P}^{(\delta)}[(x_\tau)_{0 \leq \tau \leq t}]. \quad (142)$$

The path measures Eq. (41) of processes in Eqs. (47) and (141) can be conveniently written in terms of the stochastic differentials as

$$\mathbb{P}^\delta[(x_\tau)_{0 \leq \tau \leq t}] = p_{x_0}(0) \exp \left[\int_{s=0}^{s=t} \sum_x r_{xx}^\delta d\tau_x(s) + \int_{s=0}^{s=t} \sum_{x,y \neq x} \log r_{xy}^\delta dn_{xy}(s) \right], \quad (143)$$

where $p_{x_0}(0)$ is the distribution of the initial state $x_{\tau=0} = x_0$. Note that a given path realization defines a unique sequence of transitions and hence $d\tau_x(s)$ and $dn_{xy}(s)$, which, in turn, enter equally $\mathbb{P}$ in Eq. (41) and $\mathbb{P}^\delta$ in Eq. (143). However, because of the different rates (r_{xy}^δ versus r_{xy}), the measure of the same path is generally different under $\mathbb{P}$ and $\mathbb{P}^\delta$. Moreover, writing the path measure in terms of stochastic differentials as in Eq. (143) further has the advantage of allowing for time-dependent rates.

Consider the perturbed rates

$$r_{xy}^\delta = r_{xy}(\chi + \delta) = r_{xy}(\chi) + \delta \tilde{r}_{xy}(\chi) + \mathcal{O}(\delta^2). \quad (144)$$

Note that we assume that the rates $r_{xy} = r_{xy}(\chi)$ and r_{xy}^δ are functions of χ and $\chi + \delta$, respectively (χ is a placeholder for the perturbed quantity, e.g., temperature T), and that the function is analytic at $\delta = 0$, i.e., that it has a well-defined Taylor expansion at that point. Therefore, $\mathbb{P}^\delta$ is absolutely continuous with respect to $\mathbb{P}$ for sufficiently small δ [164] and the perturbed average $\langle O(t) \rangle_\delta$ can be written in terms of the unperturbed process in Eq. (47) using the Cameron-Martin-Girsanov theorem with the Radon-Nikodym derivative [165]

$$\langle O(t) \rangle_\delta = \left\langle O(t) \frac{d\mathbb{P}^\delta}{d\mathbb{P}} \right\rangle, \quad (145)$$

where we assumed that the processes start from the same initial distribution. The Radon-Nikodym derivative reads

$$\begin{aligned} \frac{d\mathbb{P}^\delta}{d\mathbb{P}}[(x_\tau)_{0 \leq \tau \leq t}] &= \exp \left[\int_{s=0}^{s=t} \sum_x (r_{xx}^\delta - r_{xx}) d\tau_x(s) + \int_{s=0}^{s=t} \sum_{x,y \neq x} \log \frac{r_{xy}^\delta}{r_{xy}} dn_{xy}(s) \right] \\ &= \exp \left[-\delta \int_{s=0}^{s=t} \sum_{x,y \neq x} \tilde{r}_{xy} d\tau_x(s) + \delta \int_{s=0}^{s=t} \sum_{x,y \neq x} \frac{\tilde{r}_{xy}}{r_{xy}} dn_{xy}(s) + \mathcal{O}(\delta^2) \right] \\ &= 1 - \delta \int_{s=0}^{s=t} \sum_{x,y \neq x} \frac{\tilde{r}_{xy}}{r_{xy}} [r_{xy} d\tau_x(s) - dn_{xy}(s)] + \mathcal{O}(\delta^2) \\ &= 1 + \delta \int_{s=0}^{s=t} \sum_{x,y \neq x} \frac{\tilde{r}_{xy}}{r_{xy}} d\mathbf{e}_{xy}(s) + \mathcal{O}(\delta^2). \end{aligned} \quad (146)$$

The response to a perturbation in χ (e.g., the temperature) is therefore evaluated to be

$$\partial_\delta O_t = \left\langle O(t) \int_{s=0}^{s=t} \sum_{x,y \neq x} \frac{\tilde{r}_{xy}}{r_{xy}} d\epsilon_{xy}(s) \right\rangle. \quad (147)$$

Note that we did not use any particular property of $O(t)$ that would distinguish between single-time and pathwise observables. Nevertheless, for the sake of completeness, we provide in Appendix A 8 an explicit derivation of pathwise observables.

While elegant, Eq. (147) (similar to the continuous-space result [137]) cannot generally be applied to experimental data. This restriction is due to the integration over noise (which is never known in experiments) and the effective drift, including what defines the rates, which renders Eq. (147) operationally inaccessible. However, Eq. (147) may be useful in simulations of high-dimensional systems, where the rates and noise are known but the generator $\mathbf{L}$ cannot be easily diagonalized. Note that $d\epsilon_{xy}(s)$ depends on $p_x(s)$ through Eq. (48).

The stochastic-analysis route to Eq. (147) can be seen as an alternative way of evaluating responses to perturbations of observables complementing well established existing methods [4]. The limit in Eq. (140) can, in fact, be evaluated directly using a type of Dyson identity [4] (see Appendix A 8 for details). However, Eq. (147) allows for the same result to be obtained using correlations of stochastic differentials without invoking perturbative calculations.

B. Equilibrium response to temperature perturbations

For MJPs in equilibrium, we have $p_i^{\text{eq}} \propto e^{-E_i/T}$ in terms of free energies E_i . In addition, we have detailed balance, which, however, does not uniquely specify the rates. We choose the rates to be

$$r_{xy} = D e^{(\lambda E_x - (1-\lambda)E_y)/T} \quad (148)$$

for any $\lambda \in [0, 1]$ (commonly used are $\lambda = 1$ and $\lambda = 1/2$) and D may scale with T ($D = \tilde{D}T$ with $\tilde{D} = \text{const.}$). The rates in Eq. (148) satisfy detailed balance.

The aim here is to relate the response in Eq. (147) of a single-time observable $O(t)$ to the equilibrium correlation function,

$$C_{OE}(t) = (\langle OE \rangle_{\text{eq}} - \langle O(t)E(0) \rangle_{\text{eq}}). \quad (149)$$

We start from Eq. (147) and use the noise-time lemma in Eq. (50) to get

$$\begin{aligned} & \left\langle O(t) \int_{s=0}^{s=t} \sum_{x,y \neq x} \frac{\tilde{r}_{xy}}{r_{xy}} d\epsilon_{xy}(s) \right\rangle_{\text{eq}} \\ &= \frac{1}{T^2} \int_0^t ds \sum_i \sum_{x,y \neq x} O_i [P(i, t|y, s) - P(i, t|x, s)] \\ & \quad \times r_{xy} p_x^{\text{eq}} (-\lambda E_x + (1-\lambda)E_y + T), \end{aligned} \quad (150)$$

since

$$\begin{aligned} \frac{\tilde{r}_{xy}}{r_{xy}} &= \frac{\partial_\delta \tilde{D}(T + \delta) e^{(\lambda E_x - (1-\lambda)E_y)/(T+\delta)}|_{\delta=0}}{\tilde{D}T e^{(\lambda E_x - (1-\lambda)E_y)/T}} \\ &= \frac{\tilde{D}(1 - \frac{\lambda E_x - (1-\lambda)E_y}{T}) e^{(\lambda E_x - (1-\lambda)E_y)/T}}{\tilde{D}T e^{(\lambda E_x - (1-\lambda)E_y)/T}} \\ &= \frac{T - \lambda E_x + (1-\lambda)E_y}{T^2}. \end{aligned} \quad (151)$$

The last term in Eq. (150) including T vanishes because

$$\begin{aligned} & \sum_{x,y \neq x} [P(i, t|y, s) - P(i, t|x, s)] r_{xy} p_x^{\text{eq}} \\ &= \sum_{x,y \neq x} P(i, t|x, s) r_{yx} p_y^{\text{eq}} - \sum_{x,y \neq x} P(i, t|x, s) r_{xy} p_x^{\text{eq}} \\ &= \sum_{x,y \neq x} P(i, t|x, s) r_{xy} p_x^{\text{eq}} - \sum_{x,y \neq x} P(i, t|x, s) r_{xy} p_x^{\text{eq}} \\ &= 0, \end{aligned} \quad (152)$$

where we use detailed balance in the third line. Similarly, the first terms in Eq. (150) simplify to

$$\begin{aligned} & \sum_{x,y \neq x} [P(i, t|y, s) - P(i, t|x, s)] r_{xy} p_x^{\text{eq}} (-\lambda E_x + (1-\lambda)E_y) \\ &= \sum_{x,y \neq x} P(i, t|x, s) r_{xy} p_x^{\text{eq}} \\ & \quad \times \underbrace{(-\lambda E_y + (1-\lambda)E_x + \lambda E_x - (1-\lambda)E_y)}_{=E_x - E_y} \\ &= -\sum_x p_x^{\text{eq}} E_x \sum_{y \neq x} [P(i, t|y, s) - P(i, t|x, s)] r_{xy} \\ & \quad \underbrace{= \sum_{y \neq x} P(i, t|y, s) r_{xy} + P(i, t|x, s) r_{xx}}_{= \sum_{y \neq x} P(i, t|y, s) r_{xy} + P(i, t|x, s) r_{xx}} \\ &= -\sum_x p_x^{\text{eq}} E_x \sum_y \underbrace{P(i, t|y, s) L_{yx}}_{=-\partial_s P(i, t|x, s)}. \end{aligned} \quad (153)$$

Plugging Eqs. (152) and (153) into Eq. (150), we finally get

$$\begin{aligned}
\left\langle O(t) \int_{s=0}^{s=t} \sum_{x,y \neq x} \frac{\tilde{r}_{xy}}{r_{xy}} d\epsilon_{xy}(s) \right\rangle_{\text{eq}} &= \frac{1}{T^2} \int_0^t ds \sum_i \sum_x O_i E_x p_x^{\text{eq}} \partial_s P(i, t|x, s) \\
&= \frac{1}{T^2} \left(\sum_i \sum_x O_i E_x p_x^{\text{eq}} \underbrace{P(i, t|x, t)}_{\delta_{ix}} - \sum_i \sum_x O_i E_x p_x^{\text{eq}} P(i, t|x, 0) \right) \\
&= \frac{1}{T^2} (\langle OE \rangle_{\text{eq}} - \langle O(t)E(0) \rangle). \tag{154}
\end{aligned}$$

Note that Eq. (154) does not explicitly depend on λ , only implicitly through the propagator, i.e., it holds for every parametrization of the rates in Eq. (71). Equation (154) is the linear response of an equilibrium MJPs to a temperature perturbation.

C. Connection to response-function formalism

In this section, we connect the results derived in the previous sections to the well-established “response-function formalism,” which is often used to describe the fluctuation-dissipation theorem. While the results of response functions for MJPs have been previously derived in, e.g., Refs. [4,68,70,166,167], we show how these may be extracted from our results to bridge the “gap” to the literature.

1. Equilibrium response

For a first-order perturbation theory of a single-time observable $B(t)$ in an equilibrium system with perturbation $h(s)$, $0 \leq s \leq t$, conjugate to some observable $R(s)$, the response reads [4,166]

$$\Delta B(t) \equiv \langle B(t) \rangle_h - \langle B \rangle_{\text{eq}} = \int_0^t ds h(s) \chi(t-s). \tag{155}$$

Here, $\chi(s)$ is the response function (recall that $k_B = 1$ throughout the manuscript) [4]

$$\chi(s) = -\frac{1}{T} \frac{d}{ds} \langle R(0)B(s) \rangle_{\text{eq}}. \tag{156}$$

To connect this to the result we derived in the previous section, we first consider the case a constant perturbation to an equilibrium system, i.e., $h(s) = h$. Comparing Eq. (154) to Eq. (155) (with $\delta \rightarrow h$), we see that to first order in h ,

$$\begin{aligned}
\Delta O(t) &= \frac{h}{T^2} (\langle OE \rangle_{\text{eq}} - \langle O(t)E(0) \rangle_{\text{eq}}) \\
&= \frac{1}{T^2} \int_0^t ds \frac{d}{ds} \langle O(t)E(s) \rangle_{\text{eq}} h. \tag{157}
\end{aligned}$$

Since the equilibrium correlation is time-translation invariant, we can rewrite the above response of Eq. (157) as

$$\Delta O(t) = \int_0^t ds \chi(t-s) h + \mathcal{O}(h^2), \tag{158}$$

with $\chi(t-s) \equiv (1/T^2)[d/(ds)]\langle O(t)E(s) \rangle_{\text{eq}} = -(1/T^2) \times [d/(dt)]\langle O(t-s)E(0) \rangle_{\text{eq}}$ consistent with Eq. (156) with $R = T^{-1}E$.

For time-dependent $h(s)$, we get to first order

$$\Delta O(t) = \left\langle O(t) \int_{s=0}^{s=t} h(s) \sum_{x \neq y} \frac{\tilde{r}_{xy}}{r_{xy}} d\epsilon_{xy}(s) \right\rangle. \tag{159}$$

The simplifications performed in Eqs. (151)–(153) can still be made, as these are independent of the perturbation $h(s)$,

$$\begin{aligned}
\Delta O(t) &= \frac{1}{T^2} \int_0^t h(s) \sum_i \sum_x O_i E_x \partial_s P(i, t|x, s) p_x^{\text{eq}} ds \\
&= \frac{1}{T^2} \int_0^t h(s) \partial_s \langle O(t)E(s) \rangle_{\text{eq}} ds \\
&= \int_0^t h(s) \chi(t-s), \tag{160}
\end{aligned}$$

again with

$$\begin{aligned}
\chi(t-s) &= \frac{1}{T^2} \frac{d}{ds} \langle O(t)E(s) \rangle_{\text{eq}} \\
&= -\frac{1}{T^2} \frac{d}{dt} \langle O(t-s)E(0) \rangle_{\text{eq}}. \tag{161}
\end{aligned}$$

The extension of these results, e.g., in case of nonstationary systems, has already been discussed in Ref. [4].

2. Response of a stationary system

To further connect our result to responses of (non-equilibrium) steady states, we realize that the perturbation rates $\tilde{r}_{xy}$ are the elements of the perturbation generator L^1 , i.e., $L = L_0 + hL^1$ with $L_{xy} = r_{yx}$ and $L_{xy}^1 = \tilde{r}_{yx}$. Using the correlation lemma, Eq. (50), the response of a single-time observable in steady state reads to first order in h ,

$$\begin{aligned}\Delta_s O(t) &\equiv \langle O(t) \rangle_h - \langle O(t) \rangle_s \\ &= \int_0^t ds h(s) \sum_i O_i \sum_{x,y \neq x} \frac{\tilde{r}_{xy}}{r_{xy}} \\ &\quad \times [P(i, t|y, s) - P(i, t|x, s)] r_{xy} p_x^s. \quad (162)\end{aligned}$$

The last double-sum simplifies as follows:

$$\begin{aligned}\sum_{y,x \neq y} \tilde{r}_{xy} [P(i, t|y, s) - P(i, t|x, s)] p_x^s \\ = \sum_{y,x \neq y} \tilde{r}_{yx} P(i, t|x, s) p_y^s - \underbrace{\sum_{y,x \neq y} \tilde{r}_{xy} P(i, t|x, s)}_{\tilde{r}_{xx}} p_x^s \\ = \sum_{y,x} \tilde{r}_{yx} P(i, t|x, s) p_y^s, \quad (163)\end{aligned}$$

where we split the sum and relabel $x \leftrightarrow y$ in the first line, and then use the definition of the diagonal elements to simplify the expression. As a consequence, we can now write the conjugate observable $R_x^s \equiv \sum_y L_{xy}^1 p_y^s / p_x^s$ and identify that inserting Eq. (163) into Eq. (162) yields to first order

$$\begin{aligned}\Delta_s O(t) &= \int_0^t ds h(s) \sum_i O_i \sum_{y,x} \underbrace{\tilde{r}_{yx}}_{L_{xy}^1} P(i, t|x, s) p_y^s \\ &= \int_0^t ds h(s) \sum_i O_i \sum_x P(i, t|x, s) \underbrace{\sum_y L_{xy}^1 \frac{p_y^s}{p_x^s}}_{R_x^s} p_x^s \\ &= \int_0^t ds h(s) \sum_{i,x} O_i P(i, t|x, s) R_x^s p_x^s. \quad (164)\end{aligned}$$

Here, we can identify the stationary response function

$$\begin{aligned}\chi_s(t-s) &\equiv \mathbb{1}_{s < t} \langle O(t) R^s(s) \rangle_s \\ &= \mathbb{1}_{s < t} \langle O(t-s) R^s(0) \rangle_s, \quad (165)\end{aligned}$$

so that Eq. (164) can be written as

$$\Delta_s O(t) = \int_0^t ds h(s) \chi_s(t-s) + \mathcal{O}(h^2). \quad (166)$$

This result is consistent with the results from Ref. [167].

3. Response of pathwise observables

Finally, we consider the response of, possibly transient, pathwise observables. Specifically, consider the observables

$$O_1(t) = \int_0^t \sum_{x,y \neq x} b_{xy}(s) d\epsilon_{xy}(s), \quad (167)$$

$$O_2(t) = \int_0^t g_s ds. \quad (168)$$

Using Eq. (48), the response of Eq. (167) can be stated directly to first order

$$\begin{aligned}\Delta O_1(t) &\equiv \langle O_1(t) \rangle_h - \langle O_1(t) \rangle \\ &= \int_0^t dz \sum_{x,y \neq x} b_{xy}(z) \int_0^t ds h(s) \sum_{i,j \neq i} \frac{\tilde{r}_{ij}}{r_{ij}} \\ &\quad \times \delta_{ix} \delta_{jy} \delta(s-z) r_{ij} p_i(s) \\ &= \int_0^t dz \sum_{x,y \neq x} b_{xy}(z) h(z) \tilde{r}_{xy} p_x(z). \quad (169)\end{aligned}$$

Similarly, using Eq. (50), the response of $O_2(t)$ becomes to first order (note that this result is compared to the approach used in Ref. [4] in Appendix A 8)

$$\begin{aligned}\Delta O_2(t) &\equiv \langle O_2(t) \rangle_h - \langle O_2(t) \rangle \\ &= \int_0^t dz \int_0^t ds \mathbb{1}_{s < z} h(s) \sum_{i,x,y \neq x} \\ &\quad \times g_i(z) \tilde{r}_{xy} p_x(s) [P(i, z|y, s) - P(i, z|x, s)]. \quad (170)\end{aligned}$$

The sum over x, y can again be simplified using Eq. (163), so that

$$\begin{aligned}\Delta O_2(t) &= \int_0^t dz \int_0^t ds \mathbb{1}_{s < z} h(s) \sum_{i,x,y} g_i(z) \tilde{r}_{yx} p_y(s) P(i, z|x, s) \\ &\quad + \mathcal{O}(h^2). \quad (171)\end{aligned}$$

Defining $R_x(s) = \sum_y \tilde{r}_{yx} p_y(s) / p_x(s) = \sum_y L_{xy}^1 p_y(s) / p_x(s)$, the response functions for $O_1(t)$ and $O_2(t)$ become

$$\chi_{O_1}(t, s) = \mathbb{1}_{t > s} \sum_{x,y \neq x} b_{xy}(s) \tilde{r}_{xy} p_x(s), \quad (172)$$

$$\chi_{O_2}(t, s) = \int_0^t dz \mathbb{1}_{z > s} \langle g_z R(s) \rangle, \quad (173)$$

so that the response to any additive functional $O_p(t) = O_1(t) + O_2(t)$ becomes

$$\begin{aligned}\Delta O_p(t) &\equiv \langle O_p(t) \rangle_h - \langle O_p(t) \rangle \\ &= \int_0^t ds h(s) \chi_{O_p}(t, s) + \mathcal{O}(h^2), \\ \chi_{O_p}(t, s) &= \chi_{O_1}(t, s) + \chi_{O_2}(t, s). \quad (174)\end{aligned}$$

Note that observables of integrals over $d\mathbf{n}(s)$ are a special case where $g_x(s)$ and $b_{xy}(s)$ have been chosen appropriately to satisfy Eq. (46).

D. Examples

To visualize the results in Eqs. (147) and (154), we consider the response of a single-time observable $O(t) = (1, 1, 0, 0)$ of a four-state ring in an equilibrium system [see Fig. 11(a)] and in a transient system with constant driving [see Fig. 11(b)], as well as of a current J_t with weight $\kappa_{ij} = \delta_{i4}\delta_{j1} - \delta_{i1}\delta_{j4} + \delta_{i3}\delta_{j2} - \delta_{i2}\delta_{j3}$ in transient systems with equilibrium [see Fig. 11(c)] rates and constant driving [see Fig. 11(d)].

For simplicity, we set $D = T$ in Eq. (148). In Figs. 11(a) and 11(c), we use Eq. (71) with the free energies listed in Table V. In Fig. 11(a), we compare $\lambda = 0.3$ and $\lambda = 0.9$,

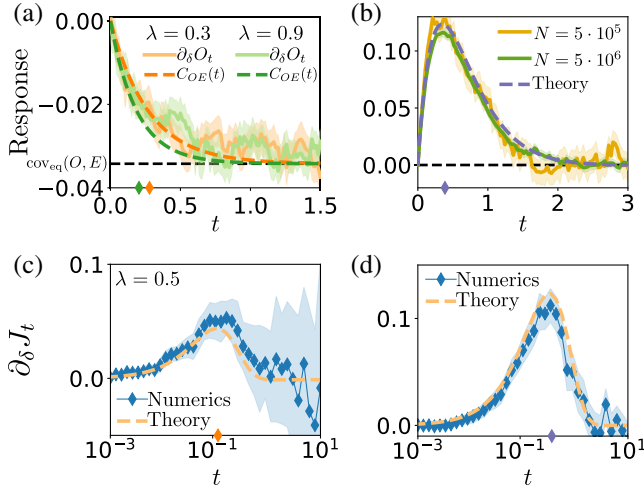


FIG. 11. Perturbations of the equilibrium and driven rings. Analytical and numerical response curves of $O = (1, 1, 0, 0)$ for equilibrium (a) and transient (b) dynamics on a four-state ring. (a) We compare the numerical simulations (solid lines) with theoretical prediction Eq. (154) (dashed lines) for $\lambda = 0.3$ (orange) and $\lambda = 0.9$ (green). The remaining parameters are $T = 1$, $\delta = 0.1$, $N = 5 \times 10^6$, and $\tilde{D}_{xy} = 1$. (b) The initial distribution is $p^{\text{init}} = (0, 0, 1, 0)$ and the rates are $r_{12} = r_{23} = r_{34} = r_{41} = Te^{-\log \epsilon/T}$ and $r_{21} = r_{32} = r_{43} = r_{14} = Te^{-\log \alpha/T}$ with $\epsilon = 3$ and $\alpha = 2$, respectively. The theoretical result Eq. (A40) (dashed purple line) is compared with numerical simulations using $N = 5 \times 10^5$ (solid yellow line) and $N = 5 \times 10^6$ (solid green line) trajectories, respectively. The remaining parameters are $T = 2$, $\delta = 0.1$, and $\tilde{D}_{xy} = 1$. (a), (b) Markers denote the largest relaxation timescales in the systems. The dashed black lines are the expected $t \rightarrow \infty$ values $\text{cov}_{\text{eq}}(A, E)$ in (a) and 0 in (b). (c) The response to a current with weight $\kappa_{ij} = \delta_{i4}\delta_{j1} - \delta_{i1}\delta_{j4} + \delta_{i3}\delta_{j2} - \delta_{i2}\delta_{j3}$ for the aforementioned equilibrium rates with $T = 2$, $\delta = 0.05$, $N = 2 \times 10^6$, $\lambda = 0.5$, and initial condition as in (b). (d) The same parameters as in (c) are used, with the same rates as in (b). The dashed orange lines in (c), (d) are the theoretically predicted values, while the blue markers are values extracted from numerical simulations. (a)–(d) The uncertainty bands are extrapolated from bootstrapping the trajectories into 20 samples with 30% of the respective N 's. The free energies E_i used in (a), (c) are listed in Table V. The simulations are performed with the celebrated Gillespie algorithm.

while in Fig. 11(c) we use $\lambda = 0.5$. The rates used in Figs. 11(b) and 11(d) are $r_{12} = r_{23} = r_{34} = r_{41} = Te^{-\log \epsilon/T}$ in one direction and $r_{21} = r_{32} = r_{43} = r_{14} = Te^{-\log \alpha/T}$ in the opposite direction with $\epsilon = 3$ and $\alpha = 2$, respectively. The temperature is set to $T = 1$ and equilibrium initial conditions $p_i^{\text{init}} = p_i^{\text{eq}} \propto e^{-E_i/T}$ are assumed in Fig. 11(a), while $T = 2$ and initial condition $p^{\text{init}} = (0, 0, 1, 0)$ are used in Figs. 11(b)–11(d). The diamonds on the horizontal axis denote the largest relaxation time of the respective generators.

As a visual aid, the value of the equilibrium covariance between O and E , $\text{cov}_{\text{eq}}(O, E) = \langle OE \rangle_{\text{eq}} - \langle O \rangle_{\text{eq}} \langle E \rangle_{\text{eq}}$, is included in Fig. 11(a) to show how, independent of λ , the response $\partial_\delta O_t \rightarrow \text{cov}_{\text{eq}}(O, E)$ for $t \rightarrow \infty$.

VI. CONTINUUM LIMIT

While we treated continuous-space (Langevin) and discrete-state MJP dynamics separately so far, it is well known that the two descriptions should agree in a particular limit. Namely, a d -dimensional continuous description can be approximated by a jump process on a d -dimensional grid (here, we assume a hypercubic lattice) with grid spacing Δx , where the MJP description reproduces the dynamics as $\Delta x \rightarrow 0$ or for observations on scales much larger than Δx (see, e.g., Ref. [168]). For thermodynamic consistency, we here show that both the entropy Eq. (74) and pseudoentropy Eq. (77) approach the continuous-space expression Eq. (72) as $\Delta x \rightarrow 0$ for any jump dynamics on a grid approaching the continuous-space dynamics in this limit. In particular, this implies that the pseudoentropy Eq. (77) and entropy Eq. (74) agree in this limit (as they do for continuous dynamics). This agreement, in turn, implies that the bounds for jump processes can also become saturated in this continuum limit, exactly as they can be saturated for continuous-space dynamics.

We now introduce jump rates for a given d -dimensional continuous dynamics $d\mathbf{x}_\tau = \mathbf{F}(\mathbf{x}_\tau)d\tau + \sqrt{2D}d\mathbf{W}_\tau$ and given Δx . For simplicity, we first consider dynamics settling into an equilibrium for long times, i.e., $\mathbf{F}(\mathbf{x}) = -D\nabla U(\mathbf{x})$ for some sufficiently confining potential $U(\mathbf{x})$ (in principle, the approach equally works for irreversible—i.e., $D^{-1}\mathbf{F}$ not a potential field—and even nonergodic dynamics). Following Ref. [168], the rate from $\mathbf{x}$ to a neighboring state $\mathbf{x}' = \mathbf{x} + \Delta \mathbf{x}$ can be written for small Δx as

$$\begin{aligned} r_{\mathbf{x}\mathbf{x}'} &= \frac{D}{\Delta x^2} \exp \left[-\frac{U(\mathbf{x}') - U(\mathbf{x})}{2} \right] \\ &\approx \frac{D}{\Delta x^2} \exp \left[-\frac{\nabla U(\mathbf{x}) \cdot \Delta \mathbf{x}}{2} \right]. \end{aligned} \quad (175)$$

Note that there are other possible choices that give rise to the correct continuum limit, which all give the same result in the following calculations, since they have to agree up to

second order for $\Delta x \rightarrow 0$ [168]. Given a continuous-space probability density $p(\mathbf{x}, \tau)$, the consistent discretization is $p_{\mathbf{x}}(\tau) \approx p(\mathbf{x}, \tau) \Delta x^d$. To address the thermodynamic entropy production defined in Eq. (74), note that (in the following, the approximate symbol denotes equality for $\Delta x \rightarrow 0$)

$$\begin{aligned} \ln\left(\frac{p_{\mathbf{x}}(\tau)}{p_{\mathbf{x}'}(\tau)}\right) &\approx \ln[p(\mathbf{x}, \tau)] - \ln[p(\mathbf{x}, \tau) + \nabla p(\mathbf{x}, \tau) \cdot \Delta \mathbf{x}] \\ &\approx -\nabla \ln[p(\mathbf{x}, \tau)] \cdot \Delta \mathbf{x}, \\ \ln\left(\frac{r_{\mathbf{x}\mathbf{x}'}(\tau)}{r_{\mathbf{x}'\mathbf{x}}(\tau)}\right) &\stackrel{\text{Eq. (175)}}{=} -\nabla U(\mathbf{x}) \cdot \Delta \mathbf{x}/2 + \nabla U(\mathbf{x}') \cdot \Delta \mathbf{x}/2 \\ &= -\nabla U(\mathbf{x}) \cdot \Delta \mathbf{x}, \\ \ln\left(\frac{p_{\mathbf{x}}(\tau)r_{\mathbf{x}\mathbf{x}'}(\tau)}{p_{\mathbf{x}'}(\tau)r_{\mathbf{x}'\mathbf{x}}(\tau)}\right) &= [-\nabla U(\mathbf{x}) - \nabla \ln[p(\mathbf{x}, \tau)]] \cdot \Delta \mathbf{x} \\ &= \frac{\mathbf{j}(\mathbf{x}, \tau)}{Dp(\mathbf{x}, \tau)} \cdot \Delta \mathbf{x}. \end{aligned} \quad (176)$$

Similarly, we obtain

$$\begin{aligned} p_{\mathbf{x}}(\tau)r_{\mathbf{x}\mathbf{x}'} - p_{\mathbf{x}'}(\tau)r_{\mathbf{x}'\mathbf{x}} &\approx \Delta x^d p(\mathbf{x}, \tau)r_{\mathbf{x}\mathbf{x}'} - \Delta x^d [p(\mathbf{x}, \tau) + \nabla p(\mathbf{x}, \tau) \cdot \Delta \mathbf{x}]r_{\mathbf{x}'\mathbf{x}} \\ &\approx \Delta x^d p(\mathbf{x}, \tau)(r_{\mathbf{x}\mathbf{x}'} - r_{\mathbf{x}'\mathbf{x}} - \nabla \ln[p(\mathbf{x}, \tau)] \cdot \Delta \mathbf{x}) \\ &\approx \Delta x^{d-2} Dp(\mathbf{x}, \tau)(-\nabla U(\mathbf{x}) - \nabla \ln[p(\mathbf{x}, \tau)]) \cdot \Delta \mathbf{x} \\ &= \Delta x^{d-2} \mathbf{j}(\mathbf{x}, \tau) \cdot \Delta \mathbf{x}, \end{aligned} \quad (177)$$

and

$$\begin{aligned} p_{\mathbf{x}}(\tau)r_{\mathbf{x}\mathbf{x}'} + p_{\mathbf{x}'}(\tau)r_{\mathbf{x}'\mathbf{x}} &\approx \Delta x^d p(\mathbf{x}, \tau)r_{\mathbf{x}\mathbf{x}'} + [p(\mathbf{x}, \tau) + \nabla p(\mathbf{x}, \tau) \cdot \Delta \mathbf{x}]r_{\mathbf{x}'\mathbf{x}} \\ &\approx \Delta x^{d-2} 2Dp(\mathbf{x}, \tau). \end{aligned} \quad (178)$$

For the simple hypercubic lattice, the increment vectors $\Delta \mathbf{x}$ to neighboring states are $\Delta \mathbf{x} = \pm \Delta x \mathbf{e}_i$. Here, $\mathbf{e}_i$ with $i \in \{1, 2, \dots, d\}$ is a unit vector in the i th coordinate, projecting onto individual components as $\mathbf{j} \cdot \Delta \mathbf{x} = \pm j_i \Delta x$. The relevant terms from the definitions in Eqs. (77) and (74) for the pseudoentropy and entropy turn out to be

$$\begin{aligned} \frac{1}{2} [p_{\mathbf{x}}(\tau)r_{\mathbf{x}\mathbf{x}'} - p_{\mathbf{x}'}(\tau)r_{\mathbf{x}'\mathbf{x}}] \ln \left[\frac{p_{\mathbf{x}}(\tau)r_{\mathbf{x}\mathbf{x}'}}{p_{\mathbf{x}'}(\tau)r_{\mathbf{x}'\mathbf{x}}} \right] \\ \approx \Delta x^d \frac{j_i(\mathbf{x}, \tau)^2}{2Dp(\mathbf{x}, \tau)}, \end{aligned} \quad (179)$$

$$\frac{[p_{\mathbf{x}}(\tau)r_{\mathbf{x}\mathbf{x}'} - p_{\mathbf{x}'}(\tau)r_{\mathbf{x}'\mathbf{x}}]^2}{p_{\mathbf{x}}(\tau)r_{\mathbf{x}\mathbf{x}'} + p_{\mathbf{x}'}(\tau)r_{\mathbf{x}'\mathbf{x}}} \approx \Delta x^d \frac{j_i(\mathbf{x}, \tau)^2}{2Dp(\mathbf{x}, \tau)}. \quad (180)$$

A summation over i yields $\sum_{i=1}^d j_i(\mathbf{x}, \tau)^2 = \mathbf{j}(\mathbf{x}, \tau)^2$. Upon summation over $\mathbf{x}, \mathbf{x}'$ as done in Eqs. (77) and (74) for the pseudoentropy and entropy production, respectively, we find that both quantities approach the continuous-space formula for the entropy production in Eq. (72). Following Ref. [168], one can directly extend the argument to nonisotropic diffusion and nonconservative dynamics by using different “pseudopotentials” for each entry of the vector $\mathbf{F}(\mathbf{x})$ and thus the above statements about the limit generalize.

In particular, this implies that the inequality pseudoentropy $\leq$ entropy for jump processes becomes saturated in the continuous limit (even far from equilibrium).

VII. TIME-DEPENDENT DRIVING

We now show how most of the results shown so far generalize to systems with time-dependent driving (i.e., time-inhomogeneous systems), i.e., where the generator is explicitly time-dependent $\mathbf{L}(v\tau)$ with some (constant) protocol velocity v . Notably, this means that the propagator is no longer time-translation invariant, $P(i, \tau'|x, \tau; v) \neq P(i, \tau' - \tau|x, 0; v)$, as it reads [4,60]

$$P(i, \tau'|x, \tau; v) = \left[\mathcal{T} \exp \left\{ \int_{\tau}^{\tau'} ds \mathbf{L}(vs) \right\} \right]_{ix}, \quad (181)$$

where $\mathcal{T}$ is the time-ordering operator. A straightforward calculation reveals that the expressions for increment correlations, Eqs. (60), (62), and (67), observable covariances Eq. (70), and transport bound Eq. (101) remain unchanged apart from additional arguments for v . For instance, the observable covariances become

$$\begin{aligned} \text{cov}(\rho_i^k, \rho_i^l) &= \hat{I}_{V^k \delta, V^l \delta}^t [P(x, \tau; i, \tau'; v) - p_x(\tau; v) p_i(\tau'; v)], \\ \text{cov}(J_i^k, \rho_i^l) &= \hat{I}_{\kappa^k, V^l \delta}^t [\mathbb{1}_{\tau > \tau'} r_{xy}(v\tau) P(x, \tau|i, \tau'; v) p_i(\tau'; v) + \mathbb{1}_{\tau < \tau'} r_{yx}(v\tau) P(i, \tau'|y, \tau; v) p_y(\tau; v) - r_{xy}(v\tau) p_x(\tau; v) p_i(\tau'; v)], \\ \text{cov}(J_i^k, J_i^l) &= \int_0^t d\tau \sum_{x,y} \kappa_{xy}^k(v\tau) \kappa_{xy}^l(v\tau) r_{xy}(v\tau) p_x(\tau; v) \\ &\quad + \hat{I}_{\kappa^k, \kappa^l}^t [\mathbb{1}_{\tau > \tau'} r_{xy}(v\tau) r_{ji}(v\tau') P(x, \tau|j, \tau'; v) p_i(\tau'; v) + \mathbb{1}_{\tau < \tau'} r_{ij}(v\tau') r_{yx}(v\tau) P(i, \tau'|y, \tau; v) p_y(\tau; v) \\ &\quad - r_{xy}(v\tau) p_x(\tau; v) r_{ij}(v\tau') p_i(\tau'; v)], \end{aligned} \quad (182)$$

where the functions $V^{l/k}(v\tau)\delta$ and $\kappa^{l/k}(v\tau)$ inside the integration operator $\hat{I}_t$ are time dependent as well.

However, this does not hold for the CTUR, as shown in Refs. [59,60], since the TUR with time-dependent driving reads [59,60]

$$\frac{[(t\partial_t - v\partial_v)\langle J_t \rangle]^2}{\text{var}(J_t)} \leq \frac{\Delta S_{\text{tot}}(t)}{2}, \quad (183)$$

and thus requires some special care. The observable current and entropy production entering Eq. (183) read

$$\begin{aligned} \Delta S_{\text{tot}}(t) &= \int_0^t d\tau \sum_{x,y \neq x} r_{xy}(v\tau) p_x(\tau; v) \log \frac{r_{xy}(v\tau) p_x(\tau; v)}{r_{yx}(v\tau) p_y(\tau; v)}, \\ J_t &= \int_{\tau=0}^{\tau=t} \text{Tr}[\kappa(v\tau)^T d\mathbf{n}(\tau)]. \end{aligned} \quad (184)$$

Note that, although we write $d\mathbf{n}(\tau)$, the differential is not independent of v . The dependence can be seen, e.g., in the

statistical properties, such as the mean $\langle d\mathbf{n}_{xy}(\tau) \rangle_{x_t=i} = \delta_{ix} r_{xy}(v\tau) d\tau$. However, as the differential $d\mathbf{n}(\tau)$ is “observed” at time τ , regardless of v , we choose to suppress the v argument. Central to the proof of the TUR for driven systems is the identity [60]

$$\begin{aligned} \int_0^{\tau'} d\tau \sum_x [\partial_\tau P(i, \tau' | x, \tau; v)] p_x(\tau; v) \\ = -(\tau' \partial_{\tau'} - v \partial_v) p_i(\tau'; v). \end{aligned} \quad (185)$$

With this identity, we can extend the time-dependent TUR in Eq. (183) to also include densities,

$$\rho_t = \int_{\tau=0}^{\tau=t} V_{v\tau} d\tau, \quad (186)$$

as well. To do so, we require $\langle A_t \rho_t \rangle$, which after some simplification using Eq. (50) reads

$$\langle A_t \rho_t \rangle = \int_0^t d\tau' \int_0^{\tau'} d\tau \sum_i V_i(v\tau') \mathbb{1}_{\tau < \tau'} \sum_{x,y} [P(i, \tau' | y, \tau; v) - P(i, \tau' | x, \tau; v)] p_x(\tau; v) r_{xy}(v\tau) Z_{xy}(v\tau). \quad (187)$$

Rearranging the inner sum (x, y), we find that Eq. (187) simplifies to

$$\langle A_t \rho_t \rangle \int_0^t d\tau' \int_0^{\tau'} d\tau \sum_{i,x} V_i(v\tau') P(i, \tau' | x, \tau; v) \partial_\tau p_x(\tau; v) = - \int_0^t d\tau' \int_0^{\tau'} d\tau \sum_{i,x} V_i(v\tau') [\partial_\tau P(i, \tau' | x, \tau; v)] p_x(\tau; v),$$

where we performed a partial integration over τ to obtain the result in the third line. The boundary term vanishes because $\sum_x P(i, \tau' | x, \tau'; v) p_x(\tau'; v) = \sum_x P(i, \tau' | x, 0; v) p_x(0; v)$. Using Eq. (185), the integral over τ and sum over x vanish, such that

$$\langle A_t \rho_t \rangle = \int_0^t d\tau' \sum_i V_i(v\tau') (\tau' \partial_{\tau'} - v \partial_v) p_i(\tau'; v). \quad (188)$$

Another integration by parts and recognizing $\tau' \partial_{\tau'} V_i(v\tau') = v \partial_v V_i(v\tau')$ finally yields

$$\langle A_t \rho_t \rangle = (t\partial_t - v\partial_v - 1) \langle \rho_t \rangle. \quad (189)$$

Hence, the Cauchy-Schwarz inequality delivers (for the first time) the CTUR for time-dependent driving

$$\frac{(\hat{\Lambda} \langle J_t \rangle - c(t) \{ [\hat{\Lambda} - 1] \langle \rho_t \rangle \})^2}{\text{var}[J_t - c(t) \rho_t]} \leq \frac{\Delta S_{\text{tot}}}{2}, \quad (190)$$

with differential operator $\hat{\Lambda} \equiv t\partial_t - v\partial_v$. Notably, we are still able to saturate the Cauchy-Schwarz inequality, although the practical inaccessibility of the required transition weights and

state function remains. However, one may again optimize the CTUR Eq. (190) with respect to $c(t)$. The results are again given by Eq. (91), albeit with $a(t) = \hat{\Lambda} \langle J_t \rangle$ and $b(t) = (\hat{\Lambda} - 1) \langle \rho_t \rangle$.

Conversely, the correlation bound is not easily generalizable to systems with time-dependent driving. Specifically, since $z_x^{F(\tau)}$ explicitly depends on time τ through $F(\tau)$, Eq. (185) cannot be applied to shift the time derivative of the propagator. Hence, the expectation $\langle B_t C_t \rangle$ [see Eq. (121)] does not reduce to an accessible quantity.

VIII. CONNECTION TO QUANTUM UNRAVELING

Stochastic calculus has also found traction in the theory of open quantum systems [139,169–172], i.e., in the context of quantum unraveling. In the following, we provide some insight into how the classical stochastic-calculus approach presented here is connected to quantum unraveling. Before doing so, we introduce some basic notation and theory. Subsequently, we highlight the relation to our work.

Let ρ_s^u be a rank-one matrix denoting a pure state in a discrete-state open quantum system at time s . It evolves according to the Belavkin equation [139]

$$d\rho_s^u = \mathcal{B}(\rho_s^u)ds + \sum_i \left(\frac{\mathcal{J}_i(\rho_s^u)}{\text{Tr}[\mathcal{J}_i(\rho_s^u)]} - \rho_s^u \right) d\tilde{n}_{is}, \quad (191)$$

where $\mathcal{J}_i(\rho_s^u) = \hat{J}_i \rho_s^u \hat{J}_i^\dagger$ with jump operator $\hat{J}_i$ for the i th quantum jump. The first term in Eq. (191) has the form

$$\mathcal{B}(\rho_s^u) = -i\hat{H}_{\text{eff}}\rho_s^u + \rho_s^u\hat{H}_{\text{eff}}^\dagger - \rho_s^u\text{Tr}(-i\hat{H}_{\text{eff}}\rho_s^u + \rho_s^u\hat{H}_{\text{eff}}^\dagger), \quad (192)$$

where the Hamiltonian $\hat{H}$ of the system enters through the effective Hamiltonian $\hat{H}_{\text{eff}} = \hat{H} - (i/2) \sum_j \hat{J}_j^\dagger \hat{J}_j$. Finally, $d\tilde{n}_{is}$ is a stochastic differential (i.e., a sequence of step functions) that takes values 1 if the i th transition occurs in $[s, s + ds]$ and 0 otherwise. Since the probability of more than one transition in the interval ds vanishes faster than ds [173], we have $d\tilde{n}_{is}d\tilde{n}_{js} = \delta_{ij}d\tilde{n}_{is}$ and $d\tilde{n}_{is}ds = 0$. Furthermore, we have $\langle d\tilde{n}_{is} \rangle = \text{Tr}[\mathcal{J}_i(\rho_s)]$. Taking the average over noise histories in Eq. (191), the resulting density matrix $\rho_s = \langle \rho_s^u \rangle$ evolves according to the Lindblad equation, often referred to as “quantum master equation”.

With this short insight into quantum stochastic differential equations (SDEs), we now turn to the question of how these concepts are related to the work we present in this article. Since classical stochastic dynamics should correspond to a special case of quantum open-system evolutions [174], one may at first think that Eq. (46) describes the classical counterpart to Eq. (191); they both aim to describe a trajectory (the former a classical sequence of discrete states and the latter the evolution of pure states in a Hilbert space) and both include Poissonian noise $d\mathbf{n}$ and $d\tilde{\mathbf{n}}$, respectively.

However, Eq. (46) is not the classical counterpart to Eq. (191), which can be seen from two observations: (i) Eq. (46) is an SDE describing the evolution of transitions and (ii) Eq. (191) is a “functional” of the transitions describing the evolution of the states. Moreover, Eq. (46) allows us to consider the (stochastic) evolution of transitions occurring in a discrete system and further enables us to form and study additive functionals of the dynamics. Hence, using (i) enables us to study functionals such as (ii). To be precise on this last point, we can construct a classical functional of the transitions, which is the classical counterpart to Eq. (191). It turns out that this functional is simply $d\delta_{x,x} \equiv [d/(d\tau)]\delta_{x,x}d\tau$, see Eq. (A17). Explicitly, using Eq. (46) in Eq. (A17) yields

$$\begin{aligned} d\delta_{x,x} &= \sum_{y \neq x} (dn_{yx} - dn_{xy}) \\ &= \sum_{y \neq x} (r_{yx}\delta_{x,y}ds - r_{xy}\delta_{x,x}ds) \\ &\quad + \sum_{y \neq x} (d\epsilon_{yx} - d\epsilon_{xy}). \end{aligned} \quad (193)$$

The first sum is the deterministic evolution of the state, i.e., the master operator acting on the “population vector” $\delta_{x,x}$

and the second sum is the zero-mean stochastic noise in the system. Shifting the mean of the noise increments by adding and subtracting $\sum_{y \neq x} (\langle dn_{yx} \rangle - \langle dn_{xy} \rangle)$ [this corresponds to the trace terms in Eq. (191)], we recover the classical analog of Eq. (191),

$$\begin{aligned} d\delta_{x,x} &= \sum_{y \neq x} (r_{yx}\delta_{x,y}ds - \langle dn_{yx} \rangle - r_{xy}\delta_{x,x}ds + \langle dn_{xy} \rangle) \\ &\quad + \sum_{y \neq x} (d\epsilon_{yx} + \langle dn_{yx} \rangle - d\epsilon_{xy} - \langle dn_{xy} \rangle). \end{aligned} \quad (194)$$

Indeed, taking the average of Eq. (193) with respect to the noise history recovers the master equation, i.e., the classical analog of the Lindblad equation, further showing the correspondence between Eqs. (191) and (193).

For completeness, it should be mentioned that the quantum analog of Eq. (46) has already been identified in Ref. [60] as

$$d\tilde{n}_{it} = \text{Tr}[\mathcal{J}_i(\rho_t)]dt + d\tilde{\epsilon}_{it}, \quad (195)$$

where the noise $d\tilde{\epsilon}_{it}$ corresponds to Eq. (45) and the statistical properties can be evaluated in a similar fashion; $\langle d\tilde{\epsilon}_{it} \rangle = 0$ and $\langle d\tilde{\epsilon}_{it}d\tilde{\epsilon}_{jt'} \rangle = \delta_{ij}\delta(t-t')\text{Tr}[\mathcal{J}_i(\rho_t)]dt dt'$. While the connection to the unraveling of the Lindblad equation and, thus, the Belavkin equation is therefore established, the question of how this, in turn, relates to the classical counterpart remains elusive, further motivating our discussion here.

IX. OUTLOOK

We developed a stochastic calculus for pathwise observables (i.e., functionals) of Markov-jump processes that unifies the different approaches to Markov-jump dynamics, as well as the descriptions of diffusion and jump dynamics. We presented the approach as an exact parallelism with the continuous-space diffusion counterpart, starting from a Langevin equation for Markov-jump processes together with a central noise-time correlation lemma, defined general pathwise observables and determined their complete (co)variation structure, and identified (generalized) Green-Kubo relations. The approach includes general transients and time-inhomogeneous dynamics (e.g., time-dependent driving). We used the stochastic calculus to prove directly the known thermodynamic inequalities (TUR, correlation TUR, transport bounds, bounds on correlations, etc.) in their most general form and, afforded by the directness of the approach, discussed their saturation conditions. We showed that these inequalities follow directly from the equations of motion, which establishes them as an inherent property of stochastic (Markov-jump) equations of motion.

We further derived the response of any (generally pathwise) observable to a general (including thermal) perturbation and constructed a corresponding response-function formalism for single-time as well as pathwise observables.

Subsequently, we established the continuum limit to achieve the complete unification of diffusion and jump dynamics. Finally, we derived the classical analog of the Belavkin equation and commented on the analogy with open quantum systems. Our results ultimately place functionals of diffusion and jump processes on an equal footing on the level of individual stochastic realizations and hence achieve a “contraction” of two, until now, disjoint frameworks in time-averaged statistical mechanics. Our newly developed framework has recently already been applied in Ref. [175].

The results enable, and are expected to inspire, new directions of research. In particular, one may extend the jump-dynamics results to account for dynamics in phase space (i.e., momentum exchange) in the spirit of Ref. [176] (see Chap. 11 therein) on the discrete-state side. Conversely, one may also deepen the results on underdamped dynamics (i.e., unify the transport bound and the TUR derived in Ref. [126]). Moreover, we expect our results to inspire research in the direction of discrete-state analogs of generative diffusion models as in Refs. [71,177] and the learning of stochastic thermodynamics from fluctuating discrete-state trajectories as recently carried out for diffusions in Ref. [178]. There the power of stochastic calculus unfolds in a very prominent manner.

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DATA AVAILABILITY

The data that support the findings of this article are openly available [179].

APPENDIX: PROOFS AND DERIVATIONS

In this appendix, we provide some technical results that are required to understand the detailed derivations, but are not critical for a conceptual understanding of the results.

1. Proof of noise-time correlation lemma

To prove how the noise in Eq. (45) and time spent in a state in Eq. (44) correlate, i.e., $\langle d\epsilon_{xy}(\tau)d\tau_i(\tau') \rangle$, we consider

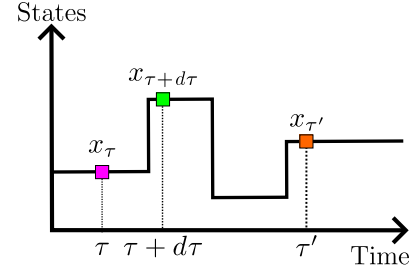


FIG. 12. Visualization of the intermediate point considered in the proof of the noise-time correlation lemma. The general idea to evaluate the noise in x_τ at τ and being in state $x_{\tau'}$ at time $\tau' > \tau$ is to include the intermediate point $x_{\tau+d\tau}$.

three cases: The transition from x to y happens (i) before τ' , (ii) at τ' , or (iii) after τ' , corresponding to $\tau < \tau'$, $\tau = \tau'$, and $\tau > \tau'$, respectively. Specifically, we can write

$$\langle d\epsilon_{xy}(\tau)d\tau_i(\tau') \rangle = \mathbb{1}_{\tau \geq \tau'} \langle d\epsilon_{xy}(\tau)d\tau_i(\tau') \rangle + \mathbb{1}_{\tau < \tau'} \langle d\epsilon_{xy}(\tau)d\tau_i(\tau') \rangle, \quad (\text{A1})$$

where the first term can be written as

$$\mathbb{1}_{\tau \geq \tau'} \langle d\epsilon_{xy}(\tau)d\tau_i(\tau') \rangle = \underbrace{\sum_{d\epsilon_{xy}} d\epsilon_{xy} p(d\epsilon_{xy}) P(x, \tau | i, \tau') p_i(\tau')}_{=0}. \quad (\text{A2})$$

Since the system is Markovian, (ii) and (iii) do not contribute. Hence, without loss of generality, we can write

$$\langle d\epsilon_{xy}(\tau)d\tau_i(\tau') \rangle = \mathbb{1}_{\tau < \tau'} \langle d\epsilon_{xy}(\tau)d\tau_i(\tau') \rangle. \quad (\text{A3})$$

For small $d\tau \rightarrow 0$, the noise increment can take only two values,

$$d\epsilon_{xy}(\tau) = \delta_{x,x}(\tau) \begin{cases} 1 - r_{xy}d\tau & \text{transition,} \\ -r_{xy}d\tau & \text{no transition.} \end{cases} \quad (\text{A4})$$

These values occur with probability $r_{xy}d\tau$ and $1 - r_{xy}d\tau$, respectively. Defining the state function

$$\gamma[d\epsilon_{xy}(\tau)] = \begin{cases} y & \text{transition,} \\ x & \text{no transition,} \end{cases} \quad (\text{A5})$$

allows us to explicitly evaluate Eq. (A3) by introducing an intermediate point (see Fig. 12), such that to leading order

$$\begin{aligned} \langle d\epsilon_{xy}(\tau)d\tau_i(\tau') \rangle &= \mathbb{1}_{\tau < \tau'} d\tau' \sum_{d\epsilon_{xy}(\tau)} p[d\epsilon_{xy}(\tau)] d\epsilon_{xy}(\tau) P(i, \tau' | \gamma[d\epsilon_{xy}(\tau)], \tau + d\tau) p_x(\tau) \\ &= \mathbb{1}_{\tau < \tau'} d\tau' p_x(\tau) r_{xy}d\tau (1 - r_{xy}d\tau) [P(i, \tau' | y, \tau + d\tau) - P(i, \tau' | x, \tau + d\tau)] \\ &= \mathbb{1}_{\tau < \tau'} d\tau' [P(i, \tau' | y, \tau) - P(i, \tau' | x, \tau)] p_x(\tau) r_{xy}d\tau. \end{aligned} \quad (\text{A6})$$

2. Derivation of increment correlations

a. Jump-time correlations

We seek for an explicit expression for $\langle dn_{xy}(\tau)d\tau_i(\tau') \rangle$. We can decompose this expectation using Eq. (46) as

$$\langle dn_{xy}(\tau)d\tau_i(\tau') \rangle = \langle d\epsilon_{xy}(\tau)d\tau_i(\tau') \rangle + r_{xy}\langle d\tau_x(\tau)\tau_i(\tau') \rangle. \quad (\text{A7})$$

Using the last two equations in Eq. (49), we get

$$\frac{\langle dn_{xy}(\tau)d\tau_i(\tau') \rangle}{r_{xy}d\tau d\tau'} = \mathbb{1}_{\tau < \tau'} P(i, \tau' | y, \tau) p_x(\tau) + \mathbb{1}_{\tau \geq \tau'} P(x, \tau | i, \tau') p_i(\tau'). \quad (\text{A8})$$

b. Jump-jump correlations

Similar to the jump-time correlation, we again decompose the jump-jump correlation as

$$\begin{aligned} \langle dn_{xy}(\tau)dn_{ij}(\tau') \rangle &= \langle d\epsilon_{xy}(\tau)d\epsilon_{ij}(\tau') \rangle \\ &\quad + r_{xy}\langle d\tau_x(\tau)d\epsilon_{ij}(\tau') \rangle \\ &\quad + r_{ij}\langle d\epsilon_{xy}(\tau)d\tau_i(\tau') \rangle \\ &\quad + r_{xy}r_{ij}\langle d\tau_x(\tau)\tau_i(\tau') \rangle. \end{aligned} \quad (\text{A9})$$

Using Eq. (49) therefore yields

$$\begin{aligned} \frac{\langle dn_{xy}(\tau)dn_{ij}(\tau') \rangle}{r_{xy}r_{ij}d\tau d\tau'} &= r_{ij}\delta_{ix}\delta_{jy}\delta(\tau - \tau')p_x(\tau) \\ &\quad + \mathbb{1}_{\tau < \tau'} P(i, \tau' | y, \tau) p_x(\tau) \\ &\quad + \mathbb{1}_{\tau \geq \tau'} P(x, \tau | j, \tau') p_i(\tau'). \end{aligned} \quad (\text{A10})$$

3. From equations of motion to ensemble description

a. Continuous space: Langevin to Fokker-Planck equations

To highlight the analogy between continuous- and discrete-space dynamics, we first recapitulate how the Fokker-Planck equation follows directly from the Langevin equation in Eq. (39). The calculation is well known (see, e.g., Ref. [132]). Let $K(x)$ be an arbitrary test function that is sufficiently smooth and obeys the boundary conditions. Considering the expectation $\langle K[\mathbf{x}(t)] \rangle = \int d\mathbf{x} K(\mathbf{x}) P(\mathbf{x}, t)$ for the dummy function at some time t , the temporal derivative can be evaluated using Itô's lemma [132]

$$\begin{aligned} \frac{d}{dt} \langle K[\mathbf{x}(t)] \rangle &= \langle \mathbf{F}(\mathbf{x}) \cdot \nabla K(\mathbf{x}) + \nabla \cdot \mathbf{D} \nabla K(\mathbf{x}) \rangle \\ &= \int d\mathbf{x} P(\mathbf{x}, t) [\mathbf{F}(\mathbf{x}) \cdot \nabla K(\mathbf{x}) + \nabla \cdot \mathbf{D} \nabla K(\mathbf{x})]. \end{aligned} \quad (\text{A11})$$

Equivalently, the derivative can be written as

$$\frac{d}{dt} \langle K[\mathbf{x}(t)] \rangle = \int d\mathbf{x} K(\mathbf{x}) \frac{\partial}{\partial t} P(\mathbf{x}, t). \quad (\text{A12})$$

By equating Eqs. (A11) and (A12), we find

$$\begin{aligned} &\int d\mathbf{x} K(\mathbf{x}) \frac{\partial}{\partial t} P(\mathbf{x}, t) \\ &= \int d\mathbf{x} P(\mathbf{x}, t) [\mathbf{F}(\mathbf{x}) \cdot \nabla K(\mathbf{x}) + \nabla \cdot \mathbf{D} \nabla K(\mathbf{x})] \\ &= \int d\mathbf{x} K(\mathbf{x}) [-\nabla \cdot \mathbf{F}(\mathbf{x}) P(\mathbf{x}, t) + \nabla \cdot \mathbf{D} \nabla P(\mathbf{x}, t)], \end{aligned} \quad (\text{A13})$$

where we performed a partial integration to obtain the last line [the boundary terms vanish by the properties assumed on $K(\mathbf{x})$]. Since the above equation holds for any test function $K(\mathbf{x})$, we derived the Fokker-Planck equation

$$\partial_t P(\mathbf{x}, t) = [\nabla \cdot \mathbf{D} \nabla - \nabla \cdot \mathbf{F}(\mathbf{x})] P(\mathbf{x}, t). \quad (\text{A14})$$

b. Discrete space: Jumps to master equation

To show how the master equation emerges from the stochastic equations of motion in Eq. (46), we first need to consider the indicator function $\delta_{x_\tau x}$ of being in state x at time τ . Consider $\delta_{x_{\tau+d\tau} x} = \delta_{x_\tau x} + [d/(d\tau)] \delta_{x_\tau x} d\tau + \mathcal{O}(d\tau^2)$, where the derivative should be understood as

$$\frac{d}{d\tau} \delta_{x_\tau x} = \lim_{d\tau \rightarrow 0^+} \frac{\delta_{x_{\tau+d\tau} x} - \delta_{x_\tau x}}{d\tau}. \quad (\text{A15})$$

By the nonexplosive property of MJPs [180], a finite number of jumps occur in any finite time interval with probability 1. Therefore, we do not need to consider any higher-order correction, as the probability of a second transition occurring in an infinitesimal increment vanishes. The term $[d/(d\tau)] \delta_{x_\tau x} d\tau$ can therefore take on values

$$\frac{d}{d\tau} \delta_{x_\tau x} d\tau = \begin{cases} 0 & \text{no transition in } [\tau, \tau + d\tau], \\ 1 & x_\tau = y \neq x, y \rightarrow x \text{ in } [\tau, \tau + d\tau], \\ -1 & x_\tau = x, x \rightarrow y \neq x \text{ in } [\tau, \tau + d\tau]. \end{cases} \quad (\text{A16})$$

As a consequence, we can write

$$\frac{d}{d\tau} \delta_{x_\tau x} d\tau = \sum_{y \neq x} [dn_{yx}(\tau) - dn_{xy}(\tau)], \quad (\text{A17})$$

because, at most, one jump differential will be nonzero as $d\tau \rightarrow 0$. The probability of being in a state x at time τ is $p_x(\tau) = \langle \delta_{x_\tau x} \rangle$. Therefore,

$$\begin{aligned}
p_x(\tau + d\tau) - p_x(\tau) &= \langle \delta_{x\tau+d\tau x} - \delta_{x\tau x} \rangle \\
&= \left\langle \frac{d}{d\tau} \delta_{x\tau x} d\tau \right\rangle \\
&= \left\langle \sum_{y \neq x} [dn_{yx}(\tau) - dn_{xy}(\tau)] \right\rangle \\
&= d\tau \sum_{y \neq x} [r_{yx} p_y(\tau) - r_{xy} p_x(\tau)]. \quad (\text{A18})
\end{aligned}$$

Rearranging Eq. (A18) and taking the limit $d\tau \rightarrow 0$ yields the master equation (40) in a way equivalent to the Fokker-Planck equation (A14).

4. Derivation of Eq. (84)

Starting from Eq. (83), we can simplify the sum over x, y by using the symmetry of $Z_{xy}(\tau)[P(i, \tau'|y, \tau) - P(i, \tau'|x, \tau)]$ to get

$$\begin{aligned}
\langle A_t J_t^{\text{II}} \rangle &= \frac{1}{2} \int_0^t d\tau' \int_0^t d\tau \sum_{i,j} \kappa_{ij}(\tau') r_{ij} \mathbb{1}_{\tau < \tau'} \\
&\quad \times \sum_{x,y} [P(i, \tau'|y, \tau) - P(i, \tau'|x, \tau)] [p_x(\tau) r_{xy} - p_y(\tau) r_{yx}] \\
&= - \int_0^t d\tau' \int_0^t d\tau \sum_{i,j} \kappa_{ij}(\tau') r_{ij} \mathbb{1}_{\tau < \tau'} \\
&\quad \times \sum_x P(i, \tau'|x, \tau) \sum_{y, y \neq x} [p_x(\tau) r_{xy} - p_y(\tau) r_{yx}]. \quad (\text{A19})
\end{aligned}$$

With Eq. (40) and an integration by parts, Eq. (A19) reduces to

$$\begin{aligned}
\langle A_t J_t^{\text{II}} \rangle &= \int_0^t d\tau' \sum_{i,j} \kappa_{ij}(\tau') r_{ij} \left[- \sum_x P(i, \tau'|x, 0) p_x(0) \right. \\
&\quad \left. - \int_0^t d\tau \sum_x p_x(\tau) \partial_\tau \{ P(i, \tau'|x, \tau) \mathbb{1}_{\tau < \tau'} \} \right] \\
&= -\langle J_t \rangle + \int_0^t d\tau' \sum_{i,j} \kappa_{ij}(\tau') r_{ij} \partial_{\tau'} [\tau' p_i(\tau')], \quad (\text{A20})
\end{aligned}$$

where we use that $\partial_\tau P(i, \tau'|x, \tau) = -\partial_{\tau'} P(i, \tau'|x, \tau)$, $\partial_\tau \mathbb{1}_{\tau < \tau'} = -\partial_{\tau'} \mathbb{1}_{\tau < \tau'}$, and $\int_0^{\tau'} d\tau \mathbb{1}_{\tau < \tau'} = \tau'$. With another integration by parts, the correlator finally becomes

$$\begin{aligned}
\langle A_t J_t^{\text{II}} \rangle &= -\langle J_t \rangle + t \underbrace{\sum_{i,j} \kappa_{ij} r_{ij} p_i(t)}_{= i \partial_t \langle J_t \rangle} \\
&\quad - \int_0^t d\tau' \sum_{i,j} \partial_{\tau'} [\kappa_{ij}(\tau')] r_{ij} \partial_{\tau'} \tau' p_i(\tau'). \quad (\text{A21})
\end{aligned}$$

5. Indispensability of the modified current

Consider a three-state system with generator

$$L = \begin{pmatrix} -4 & 2 & 1 \\ 1 & -3 & 1 \\ 3 & 1 & -2 \end{pmatrix}, \quad (\text{A22})$$

with eigenvalues 0, -4, -5. Let the current-defining transition weights be $\kappa_{ij}(\tau) = e^{4\tau}(\delta_{i1}\delta_{j2} - \delta_{i2}\delta_{j1})$. Figure 13 shows various quality factors of the transient system with initial distribution $p_i(0) = (\delta_{i1} + 2\delta_{i2})/3$; explicitly, the generalized transport bound in Eq. (107), nonequilibrium steady-state TUR, and the transient TUR in Eq. (86) with and without modified current $\tilde{J}_t$, see Eq. (85). As can be seen in Fig. 13, one needs $\tilde{J}_t$ in order to ensure that the bound $\mathcal{Q} \leq 1$ is not violated. To leading order $t \partial_t \langle J_t \rangle \sim te^{4t}$ for large t , while $t \partial_t \langle J_t \rangle - \langle \tilde{J}_t \rangle \sim e^{4t}$. Additionally, $\text{var}(J_t) \Delta S_{\text{tot}}(t) \sim te^{8t}$ for large t , so that

$$\begin{aligned}
\frac{2(t \partial_t \langle J_t \rangle)^2}{\text{var}(J_t) \Delta S_{\text{tot}}(t)} &\sim t, \\
\frac{2(t \partial_t \langle J_t \rangle - \langle \tilde{J}_t \rangle)^2}{\text{var}(J_t) \Delta S_{\text{tot}}(t)} &\sim \frac{1}{t}. \quad (\text{A23})
\end{aligned}$$

Hence, the inclusion of the modified current is indeed necessary for the quality factor to remain bounded, as it

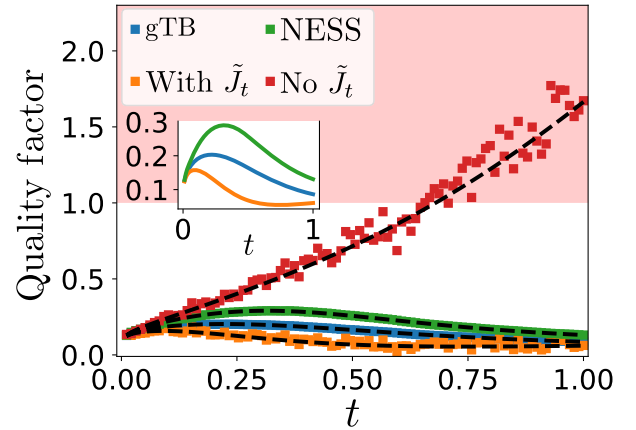


FIG. 13. Validity and comparison of generalized transport bound and various TUR quality factors. A three-state system with generator Eq. (A22) and initial condition $p_i(0) = (\delta_{i1} + 2\delta_{i2})/3$. The transition weights is $\kappa_{ij}(\tau) = e^{4\tau}(\delta_{i1}\delta_{j2} - \delta_{i2}\delta_{j1})$. The black dashed lines are the theoretical predictions to the corresponding numerical quality factors of generalized transport bound Eq. (107) (blue), nonequilibrium steady-state TUR (green), transient TUR with $\tilde{J}_t$ (orange), and transient TUR without $\tilde{J}_t$ (red). A clear violation (shaded red region) of $\mathcal{Q} \leq 1$ is seen for the transient TUR without $\tilde{J}_t$. The inset shows the theory of the former three quality factors to better visualize their values. The numerical values are extracted from $N = 5 \times 10^5$ trajectories using the Gillespie algorithm.

otherwise diverges for $t \rightarrow \infty$, which obviously is a violation of the upper bound of the quality factor. Note that t in Fig. 13 is not large enough to observe the t^{-1} decay.

6. Long-time limit of driven ring

a. Integrated covariance

Here we present details on the large- t limit of the stationary correlation bound in Eq. (131) applied to the driven ring of Sec. IV A with the assumption that $\epsilon > 1$. We start by realizing that $V_\tau^\Delta = V_\tau - \langle V_\tau \rangle = \boldsymbol{\delta}(\tau)^T \Delta \mathbf{V}$ with $\boldsymbol{\delta}(\tau)^T = (\delta_{x_\tau 1}, \delta_{x_\tau 2}, \delta_{x_\tau 3}, \delta_{x_\tau 4})$ and $\Delta \mathbf{V} \equiv \mathbf{V}^A - \langle \mathbf{V}^A \rangle \mathbf{1} = \frac{1}{2}(1, 1, -1, -1)^T$. Hence, we can write

$$\int_0^t d\tau \text{cov}_s[V_\tau^A, V_0^A] = \frac{1}{4} \int_0^t d\tau \Delta \mathbf{V}^T \mathbf{P}(\tau) \Delta \mathbf{V}, \quad (\text{A24})$$

because $p_i^s = 1/4$. Writing the propagator as

$$\mathbf{P}(\tau) = \begin{pmatrix} \mathbf{P}_1(\tau) & \mathbf{P}_2(\tau) \\ \mathbf{P}_3(\tau) & \mathbf{P}_4(\tau) \end{pmatrix}, \quad (\text{A25})$$

with $\mathbf{P}_i(\tau)$ are 2×2 matrices. Equation (A24) therefore reads

$$\begin{aligned} \int_0^t d\tau \text{cov}_s[V_\tau^A, V_0^A] \\ = \frac{1}{16} \int_0^t d\tau \mathbf{1}^T [\mathbf{P}_1(\tau) + \mathbf{P}_4(\tau) - \mathbf{P}_2(\tau) - \mathbf{P}_3(\tau)] \mathbf{1}. \end{aligned} \quad (\text{A26})$$

All that remains is to evaluate the matrices $\mathbf{P}_i(\tau)$ and solve the integral. Consider the generator

$$\mathbf{L} = \begin{pmatrix} -1-\epsilon & 1 & 0 & \epsilon \\ \epsilon & -1-\epsilon & 1 & 0 \\ 0 & \epsilon & -1-\epsilon & 1 \\ 1 & 0 & \epsilon & -1-\epsilon \end{pmatrix}, \quad (\text{A27})$$

which can be written as $\mathbf{L} = \mathbf{U} \mathbf{E} \mathbf{U}^{-1}$ with matrices

$$\mathbf{U} = \begin{pmatrix} 1 & i & -i & -1 \\ 1 & -1 & -1 & 1 \\ 1 & -i & i & -1 \\ 1 & 1 & 1 & 1 \end{pmatrix}, \quad (\text{A28})$$

$$\mathbf{E} = \text{diag}(0, \lambda_4, \lambda_3, \lambda_2), \quad (\text{A29})$$

$$\mathbf{U}^{-1} = \frac{1}{4} \begin{pmatrix} 1 & 1 & 1 & 1 \\ -i & -1 & i & 1 \\ i & -1 & -i & 1 \\ 1 & 1 & -1 & 1 \end{pmatrix}. \quad (\text{A30})$$

The eigenvalues of $\mathbf{L}$ are listed in Eq. (134). Hence, the propagator is simply $\mathbf{P}(\tau) = \mathbf{U} \exp\{\mathbf{E}\tau\} \mathbf{U}^{-1}$ and Eq. (A26) can explicitly be evaluated to be

$$\begin{aligned} \int_0^t d\tau \text{cov}_s[V_\tau^A, V_0^A] &= \frac{4}{16} \int_0^t d\tau e^{-\tau(1+\epsilon)} \cos[\tau(\epsilon-1)] \\ &= \frac{1}{4} \frac{e^{-\tau(1+\epsilon)}((1+\epsilon)e^{\tau(1+\epsilon)} - (1+\epsilon)\cos[(\epsilon-1)t] + (\epsilon-1)\sin[(\epsilon-1)t])}{2(1+\epsilon^2)} \\ &= \frac{1}{8} \frac{1+\epsilon}{1+\epsilon^2} + \mathcal{O}(e^{-(1+\epsilon)t}). \end{aligned} \quad (\text{A31})$$

b. (Pseudo)variance

Consider $\text{pvar}_{\text{ps}}^F(V^A)$ with the choice $F(\tau) = \langle V_x^A + V_y^A \rangle_{\text{ps}}/2$, i.e., the variance $\text{var}_{\text{ps}}(V^A)$, for the stationary driven four-state ring. The two-point probability is

$$p^{\text{ps}} = \frac{1}{4(\epsilon+1)} \begin{pmatrix} 0 & \epsilon & 0 & 1 \\ 1 & 0 & \epsilon & 0 \\ 0 & 1 & 0 & \epsilon \\ \epsilon & 0 & 1 & 0 \end{pmatrix}, \quad (\text{A32})$$

since $\Sigma_{\text{ps}} = (\epsilon-1)^2/(\epsilon+1)$, $p_x^s = 1/4$, and, for $x \neq y$, $Z_{xy}^2 = (\epsilon-1)^2/(\epsilon+1)^2$. Hence,

$$\begin{aligned} 2F &= \frac{1}{4(1+\epsilon)} \left(\underbrace{2\epsilon}_{x=1,y=2} + \underbrace{1}_{x=1,y=4} + \underbrace{2}_{x=2,y=1} \right. \\ &\quad \left. + \underbrace{\epsilon}_{x=2,y=3} + \underbrace{1}_{x=3,y=2} + \underbrace{\epsilon}_{x=4,y=1} \right) \\ &= 1, \end{aligned} \quad (\text{A33})$$

and similarly,

$$\begin{aligned} \langle (V_x^A + V_y^A)^2 \rangle_{\text{ps}} &= \frac{1}{4(1+\epsilon)} \left(\underbrace{4\epsilon}_{x=1,y=2} + \underbrace{1}_{x=1,y=4} + \underbrace{4}_{x=2,y=1} \right. \\ &\quad \left. + \underbrace{\epsilon}_{x=2,y=3} + \underbrace{1}_{x=3,y=2} + \underbrace{\epsilon}_{x=4,y=1} \right) \\ &= 1.5, \end{aligned} \quad (\text{A34})$$

so that

$$\text{var}_{\text{ps}}(V^A) = \left\langle (V_x^A + V_y^A)^2 \right\rangle_{\text{ps}} - 4F^2 = 0.5. \quad (\text{A35})$$

We may immediately recognize that $0 \leq V_x^A + V_y^A \leq 2$, the former inequality saturates when $x, y \in \{3, 4\}$ and the latter inequality saturates when $x, y \in \{1, 2\}$. Thus, Popoviciu's inequality yields

$$\text{var}_{\text{ps}}(V^A) \leq \frac{(2-0)^2}{4} = 1. \quad (\text{A36})$$

7. Physically motivated rates: Pseudopotential form

We specifically assume the transition rates to be of the form [168]

$$r_{xy} = D_{xy} e^{-V_{xy}/T} = \tilde{D}_{xy} T e^{-V_{xy}/T}, \quad (\text{A37})$$

where D_{xy} is an edge-specific “diffusion coefficient” and V_{xy} is a pseudopotential on the edge. This pseudopotential allows for general nonequilibrium systems to be implemented and therefore allows, under given conditions, for taking the continuum limit. Temperature perturbations enter the rates as

$$r_{xy}^\delta = \tilde{D}_{xy}(T + \delta) e^{-V_{xy}/(T+\delta)}. \quad (\text{A38})$$

By expanding Eq. (A38) around $\delta = 0$, we get

$$r_{xy}^\delta = r_{xy} + \tilde{D}_{xy}^{\text{eff}} e^{-V_{xy}/T} \delta + \mathcal{O}(\delta^2), \quad (\text{A39})$$

where $\tilde{D}_{xy}^{\text{eff}} \equiv \tilde{D}_{xy}(1 + V_{xy}/T)$, so that $r_{xy}^\delta - r_{xy} = \tilde{D}_{xy}^{\text{eff}} e^{-V_{xy}/T} \delta + \mathcal{O}(\delta^2)$. We can plug everything into Eq. (147) to obtain

$$\begin{aligned} \partial_\delta O_t &= \lim_{\delta \rightarrow 0} \frac{1}{\delta} \left(\left\langle O(t) \frac{d\mathbb{P}^\delta}{d\mathbb{P}} \right\rangle - \langle O(t) \rangle \right) \\ &= \frac{1}{T^2} \left\langle O(t) \int_{s=0}^t \sum_{x,y \neq x} (V_{xy} + T) d\epsilon_{xy}(s) \right\rangle. \end{aligned} \quad (\text{A40})$$

Note that we can remove the T in the bracket in the last line if we assume the D_{xy} not to scale with temperature, i.e.,

only a perturbation in the exponential in Eq. (A38). By identifying the effective drift $-(V_{xy} + T)$, the result Eq. (A40) corresponds to the result from Ref. [137].

8. Perturbations of path observables

We already stated that Eq. (A40) is valid for both single-time and path observables. The latter, however, perhaps need some clarification in the context of evaluating expectations over path ensembles. To clarify this, consider some hollow matrix $\mathbf{b}$,

$$O(t) = \int_{s=0}^{s=t} \text{Tr}[\mathbf{b}^T d\epsilon(s)]. \quad (\text{A41})$$

In this case, Eq. (147) simplifies to

$$\partial_\delta O_t = \int_0^t ds \sum_{x,y \neq x} b_{xy} \tilde{r}_{xy} p_x(s), \quad (\text{A42})$$

which, in general, is nonzero. However, the definition of the derivative in Eq. (140) contains averages of Eq. (A41). One may, falsely, assume both averages to vanish [recall that $\langle d\epsilon_{xy}(t) \rangle = 0$ for all $x \neq y$ and $t \geq 0$]. Only $\langle O(t) \rangle = 0$, while $\langle O(t) \rangle_\delta \neq 0$, in general. To further understand this, we can decompose Eq. (A41) into jump- and dwell-time integrals using Eq. (47),

$$\begin{aligned} O(t) &= \int_{s=0}^{s=t} \sum_{x,y \neq x} b_{xy} dn_{xy}(s) \\ &\quad - \int_{s=0}^{s=t} \sum_{x,y \neq x} b_{xy} r_{xy} d\tau_x(s). \end{aligned} \quad (\text{A43})$$

Taking the average with respect to the perturbed system, it can be recognized that

$$\begin{aligned} \langle O(t) \rangle_\delta &= \left\langle \int_{s=0}^{s=t} \sum_{x,y \neq x} b_{xy} dn_{xy}(s) \right\rangle_\delta \\ &\quad - \left\langle \int_{s=0}^{s=t} \sum_{x,y \neq x} b_{xy} r_{xy} d\tau_x(s) \right\rangle_\delta \\ &= \int_0^t ds \sum_{x,y \neq x} b_{xy} r_{xy}^\delta p_x^\delta(s) - \int_0^t ds \sum_{x,y \neq x} b_{xy} r_{xy} p_x^\delta(s) \\ &= \int_0^t ds \sum_{x,y \neq x} b_{xy} \underbrace{(r_{xy}^\delta - r_{xy})}_{\delta \tilde{r}_{xy}} p_x^\delta(s) \\ &= \delta \int_0^t ds \sum_{x,y \neq x} b_{xy} \tilde{r}_{xy} p_x(s) + \mathcal{O}(\delta^2), \end{aligned} \quad (\text{A44})$$

where $p_x^\delta(s)$ is the probability of $x_s^\delta = x$ in the perturbed system. The discrepancy of probabilities $\Delta p_x(s) = p_x^\delta(s) - p_x(s)$ in any state x at time s is $\mathcal{O}(\delta)$ [137], so that $p_x^\delta(s) = p_x(s) + \Delta p_x(s) = p_x(s) + \mathcal{O}(\delta)$.

Dividing Eq. (A44) by δ and taking the limit $\delta \rightarrow 0$ delivers Eq. (A42). In other words, it is important to account for the perturbation in the stochastic differentials only, since the observable is nominally independent of the perturbation; i.e., b_{xy} and $b_{xy}r_{xy}$ in the first and second term of Eq. (A43), respectively, are invariant under perturbations (even though the unperturbed rates enter the latter term).

Now let the observable $O(t)$ be a dwell-time integral

$$O(t) = \int_{s=0}^{s=t} g_s ds, \quad (\text{A45})$$

with some state function $g_\tau \equiv \sum_k \delta_{x_\tau k} g_k$. The response is

$$\partial_\delta O_t = \lim_{\delta \rightarrow 0} \frac{1}{\delta} \int_0^t ds \sum_x g_x \left[p_x^\delta(s) - p_x(s) \right]. \quad (\text{A46})$$

Using the Dyson identity for the perturbed generator $\mathbf{L}^\delta = \mathbf{L} + \delta \tilde{\mathbf{L}} + \mathcal{O}(\delta^2)$ with $(\tilde{\mathbf{L}})_{ij} = \tilde{r}_{ji}$ [4] yields

$$\mathbf{e}^{\mathbf{L}^\delta t} = \mathbf{e}^{\mathbf{L}t} + \delta \int ds \mathbf{e}^{\mathbf{L}(t-s)} \tilde{\mathbf{L}} \mathbf{e}^{\mathbf{L}s} + \mathcal{O}(\delta^2). \quad (\text{A47})$$

To linear order in δ , the probability is [4]

$$\begin{aligned} p_x^\delta(t) &= p_x(t) + \delta \sum_{i,j,n} \int_0^t ds P(x, t|i, s) \tilde{r}_{ji} P(j, s|n, 0) p_n(0) \\ &= p_x(t) + \delta \sum_{i,j} \int_0^t ds P(x, t|i, s) \tilde{r}_{ji} p_j(s). \end{aligned} \quad (\text{A48})$$

Hence, the limit in Eq. (A46) reduces to

$$\lim_{\delta \rightarrow 0} \frac{1}{\delta} \left[p_x^\delta(s) - p_x(s) \right] = \sum_{i,j} \int_0^s dz P(x, s|i, z) \tilde{r}_{ji} p_j(z), \quad (\text{A49})$$

so that Eq. (A46) becomes

$$\begin{aligned} \partial_\delta O_t &= \int_0^t ds \sum_x g_x \sum_{i,j} \int_0^s dz P(x, s|i, z) \tilde{r}_{ji} p_j(z) \\ &= \int_0^t ds \sum_x g_x \int_0^s dz \left[\sum_{i,j \neq i} P(x, s|i, z) \tilde{r}_{ji} p_j(z) + \sum_i P(x, s|i, z) \tilde{r}_{ii} p_i(z) \right] \\ &= \int_0^t ds \sum_x g_x \int_0^s dz \sum_{i,j \neq i} [P(x, s|i, z) \tilde{r}_{ji} p_j(z) - P(x, s|i, z) \tilde{r}_{ij} p_i(z)] \\ &= \int_0^t ds \sum_x g_x \int_0^s dz \sum_{i,j \neq i} [P(x, s|j, z) - P(x, s|i, z)] \tilde{r}_{ij} p_i(z). \end{aligned} \quad (\text{A50})$$

Conversely, employing Eqs. (147) and (50) yields

$$\begin{aligned} \partial_\delta O_t &= \sum_{i,x,y \neq x} \int_0^t d\tau \int_0^t ds \mathbb{1}_{s < \tau} g_i \tilde{r}_{xy} p_x(s) \\ &\quad \times [P(i, \tau|y, s) - P(i, \tau|x, s)], \end{aligned} \quad (\text{A51})$$

which agrees with Eq. (A50).

Since the jump increments $d\mathbf{n}$ are a linear combination of the dwell-time and noise increments, it follows immediately that Eq. (147) applies for jump-integrated observables, e.g., currents, as well.

Finally, although not explicitly written, the matrix $\mathbf{b}$ and functions g_k may also depend on time. Equations (A42) and (A50) are written to readily accommodate for this.

9. Time-dependent rates

The result in Eq. (147) easily allows for time-dependent rates to be included. In fact, the Radon-Nikodym derivative

in Eq. (146) is already written in a form that allows one to accommodate time-inhomogeneous dynamics. If $\tilde{r}_{xy}(t)$ depends on t , then it may even be seen as a time-dependent perturbation.

10. Optimization of CTUR

In Fig. 14, we further elaborate on the influence of $c(t)$ in the CTUR. The quality factor $\mathcal{Q}$ for the calmodulin system (see Fig. 6) for currents with $\kappa^{(12)}$, $\kappa^{(56)}$, and $\kappa^{(26)}$ (recall the notation $\kappa_{ij}^{(kl)} = \delta_{ik}\delta_{jl} - \delta_{il}\delta_{jk}$) and density with $V_i(\tau) = \delta_{i3}$ is shown in Figs. 14(a)–14(c). Various values of $c(t)$ are used, including $c(t) = 0$, $c^{\text{opt}}(t)$, and $c^{\text{min}}(t)$. The absolute values of the considered $c(t)$ are shown in Figs. 14(d)–14(f). As can be easily seen, the behavior of $c^{\text{opt}}(t)$ and $c^{\text{min}}(t)$ is highly nontrivial and changes greatly in magnitude.

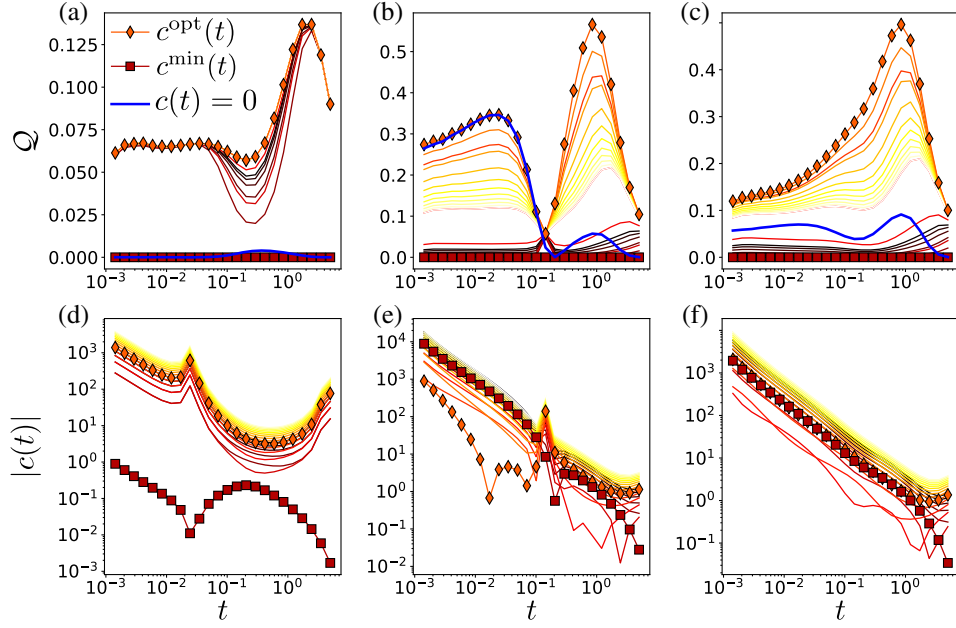


FIG. 14. Quality factor of the CTUR in (a)–(c) using values of $c(t)$ shown in (d)–(f) in the calmodulin model. The values of $c(t) = c^{\text{opt}}(t) + (\gamma/5)[c^{\text{opt}}(t) - c^{\text{min}}(t)]$ are shown for values $-10 \leq \gamma \leq 10$, where $\gamma = -10$ is black and $\gamma = 10$ is yellow. The initial condition is $p_i(0) = \delta_{i6}$ and the density uses $V_i(\tau) = \delta_{i3}$ in each panel. The transition weights are $\kappa^{(12)}$ in (a), (d); $\kappa^{(56)}$ in (b), (e); and $\kappa^{(26)}$ in (c), (f). The most optimal $c(t) = c^{\text{opt}}(t)$ is marked by diamonds and the least optimal $c(t) = c^{\text{min}}(t)$ is marked by squares. In (a)–(c), the Q for $c = 0$ is included as a blue line.

11. Simulation parameters

TABLE III. Transition rates used in the calmodulin example from Ref. [152], which are adapted from Ref. [88].

Transition $i \rightarrow j$	Rate r_{ij}
$1 \rightarrow 2$	5.997
$2 \rightarrow 1$	0.774
$1 \rightarrow 4$	13.439
$4 \rightarrow 1$	127.968
$1 \rightarrow 5$	15.330
$5 \rightarrow 1$	0.121
$5 \rightarrow 6$	3.749
$6 \rightarrow 5$	13.326
$2 \rightarrow 3$	1514.820
$3 \rightarrow 2$	53.0661
$2 \rightarrow 6$	13.441
$6 \rightarrow 2$	2.922

TABLE IV. Values of fixed parameters in SAT simulations, which are adapted from Ref. [149].

Symbol	Value
γ	5
x	2
l_A	20
l_B	1
e_A^{out}	30
e_A^{in}	10
e_B^{in}	2

TABLE V. Overview of free energies for the four-state ring with equilibrium rates.

State	E_i
1	0.1
2	0.3
3	0.5
4	0.2

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