

Temporal disorder and fluctuation theorem in chemical reactions

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We report the analytical study of a class of chemical reactions described as birth-and-death stochastic processes ruled by a master equation compatible with the mass action law of chemical kinetics. We solve analytically this master equation to find the generating functions of the fluctuating fluxes and of the Lebowitz-Spohn action functional. These generating functions are explicitly shown to obey fluctuation theorems. In the case of fluxes, we derive relations for the nonlinear response coefficients, extending Onsager's reciprocity relations. Moreover, symmetry relations reminiscent of the fluctuation theorem are obtained for the finite-time probability distributions of the fluxes. The temporal disorder of the stochastic process is also characterized and related to the thermodynamic entropy production.

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I. INTRODUCTION

Chemical reactions are dynamical processes evolving on several scales. At the microscopic level, a reacting system is composed of molecules of different species involved in inelastic collisions. During such collisions, the reactant molecules meet and form a transition complex, which thereafter dissociates into the product molecules. Each reactive event is ruled by the reversible Hamiltonian motion of the nuclei on the Born-Oppenheimer potential energy surface of a given electronic state. Since these surfaces control both the vibrational and reactional motions of the molecules, the scales of a reactive event are of the same order as for the vibrational motion, i.e., they take place over distances of 1–10 Å in 10–100 fs depending on the masses of the nuclei. Some reactions may require longer time scales if they proceed, for instance, by quantum tunneling, but typical reactive events can be supposed to happen quasi-instantaneously with respect to the mesoscopic time scale over which the numbers of reactive molecules evolve.

At the mesoscopic or macroscopic levels, chemical reactions are described in terms of the numbers of molecules involved in the reaction. These numbers undergo random jumps each time a reactive event occurs somewhere in the system. The jumps take integer values determined by the changes in the numbers of molecules which are consumed or produced during each reactive event (the so-called stoichiometric coefficients) [1–3]. Although the time scale of each reactive event is typically very short of the order of 10–100 fs, the intervals between successive reactive events may extend over much longer time scales of the order of milliseconds, seconds, or else, depending on the reaction constant, the concentrations of the reactants, and the volume of the system.

Because of the important separation of scales both in time and in space, the reactive events happen randomly in time, here or there in the whole volume of the reactional system. Contrary to the thermal fluctuations which affect the mechanical properties, the randomness of chemical reactions concerns the numbers of molecules themselves. In this regard, chemical reactions are special and their study requires

appropriate extensions of the basic methods of statistical thermodynamics. At the mesoscopic level, the random jumps can be described as Markovian birth-and-death processes. The master equation ruling these stochastic processes should reduce to the rate equations of chemical kinetics for the molecular concentrations at the macroscopic level. Such a master equation was proposed by Nicolis and co-workers who showed that the transition rates can be fixed by the mass action law of chemical kinetics [4–9]. This master equation applies to chemical reactions evolving far as well as close to thermodynamic equilibrium.

Recently, much interest has been devoted to the so-called fluctuation theorems, most of which concern mechanical nonequilibrium systems [10–16,18–23]. Fluctuation theorems have also been proved for chemical stochastic processes [24–28]. These fluctuation theorems concern either dissipation or the fluxes of matter from reactants to products. Each fluctuation theorem characterizes the breaking of detailed balance as the system is driven out of equilibrium [14–17]. This breaking manifests itself in the positivity of entropy production or in the nonvanishing of the fluxes from reactants to products. At equilibrium, detailed balance is recovered implying that the reactive events proceeding in one direction are balanced by the reversed reactions. Out of equilibrium, the balance is broken because of the net transformations of reactants into products. The fluctuation theorem shows that the probabilities of the reversed reactive events are smaller than the probabilities of the forward reactive events by a factor increasing exponentially with the magnitudes of the fluctuations and of the external nonequilibrium drives. These latter are the so-called De Donder affinities given by the free enthalpy changes in the reactions [1–3]. The fluctuation theorem remarkably explains that unidirectional fluxes tend to dominate the fluctuations as the system is driven away from equilibrium. If the chemical reactions are pushed far away from equilibrium, the reversed reactive events can be so rare that their probabilities vanish. In this case, the chemical reaction is said to be fully irreversible because its entropy production can be supposed to be infinite. We notice that such situations are not uncommon if the products of the reaction are rapidly evacuated. Furthermore, the fluctuation theorem has been extended to chemical sys-

tems with time-dependent external control [26] and applied to enzymes and mechanochemical systems such as molecular motors [27,28].

A considerable advance has been performed in Refs. [25,29–31], where a fluctuation theorem was derived for the several independent fluxes which may cross a nonequilibrium system. Indeed, if a chemical reactor is connected to several reservoirs of reactants as it is the case for continuously stirred tank reactors, several independent fluxes may flow from the different reactants to their products. Contrary to mechanical systems where these different fluxes are driven by mechanical forces directly acting on the molecules, the chemical fluxes are driven by affinities which are defined after cycles containing several successive states are completed. It is by properly dealing with these cycles thanks to the graph theory of Hill, Schnakenberg, and others [32–34], that the fluctuation theorem for currents was proved in Ref. [30]. Thanks to this fluctuation theorem, it is possible to obtain relationships among the nonlinear response coefficients beyond the Onsager reciprocity relations for the linear response coefficients [35]. These important results concern general nonequilibrium systems. Among them, the nonequilibrium chemical reactions are important because of the broad diversity of their applications in chemistry, biology, and mineralogy. Moreover, advances in single-molecule techniques and chemical sensors are such that the fluctuations of chemical reactions may soon be experimentally observable.

The purpose of this paper is to report on the theoretical study of a class of chemical reactions for which the master equation can be solved analytically to obtain the generating function of the fluctuating fluxes, not only on average in the steady state but also over a finite-time interval. For these chemical reactions, an analytical expression is thus given for the generating function of the independent fluctuating fluxes, which is shown to obey the symmetry of the fluctuation theorem. This allows us to get not only the linear but also the nonlinear response coefficients and to verify symmetry relationships extending Onsager's reciprocity relations. Furthermore, the dynamical randomness or temporal disorder of the chemical stochastic process is characterized in terms of its τ entropy per unit time [36]. Its difference with respect to the time-reversed τ entropy per unit time [37] is shown to be equal to the thermodynamic entropy production of the reactions. Accordingly, this latter appears to result from a time asymmetry in the nonequilibrium fluctuations of the chemical reactions.

The paper is organized as follows. In Sec. II, we present the theoretical results which are applied to a class of chemical reactions in Sec. III. Section IV is devoted to the finite-time characterization of the fluctuations. Conclusions are drawn in Sec. V.

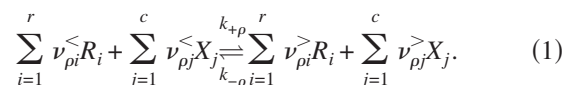
II. GENERALITIES

In this section, we summarize the main theoretical results that will be used in the following sections. First of all, we define the framework by introducing the chemical master equation ruling the birth-and-death stochastic processes,

which describe nonequilibrium chemical reactions at the mesoscopic level. In this framework, we present the fluctuation theorem for the independent fluxes proved in Refs. [25,30] and its implications for the nonlinear response coefficients [31]. In the last section, the temporal disorder of the stochastic processes is characterized in terms of their τ entropies per unit time and the relationship to the thermodynamic entropy production is stated.

A. Master equation

Chemical reactions can be driven out of equilibrium by pumping reactants into a reactor and allowing the outflow of products. If the reactor is continuously stirred and maintained at constant temperature, the system is homogeneous and isothermal. Under such conditions, the reacting system can be described by the randomly fluctuating numbers of molecules of the intermediate species $\{X_j\}_{j=1}^c$. On the other hand, the reactants and products are denoted by $\{R_i\}_{i=1}^r$. The possible reactive events form the following network of the reactions $\rho=1, 2, \dots, p$:



During each reactive event of the reaction ρ , the number of molecules X_j changes by an integer value given by the stoichiometric coefficient as follows:

$$\nu_{\rho j} \equiv \nu_{\rho j}^> - \nu_{\rho j}^< = -\nu_{-\rho j} \quad (2)$$

since $\nu_{-\rho j}^< = \nu_{\rho j}^>$.

The reactive events occur randomly with transition rates given by the mass action law as follows:

$$W_{\rho}(X|X + \nu_{\rho}) = \Omega k_{\rho} \prod_{i=1}^r [R_i]^{\nu_{\rho i}^<} \prod_{j=1}^c \frac{X_j X_j - 1}{\Omega} \frac{X_j - 2}{\Omega} \dots \frac{X_j - \nu_{\rho j}^< + 1}{\Omega}, \quad (3)$$

where Ω is an extensivity parameter such as the volume of the reactor, k_{ρ} is the reaction constant, and the brackets denote the concentrations [4–9,33,38]. The probability $P(X;t)$ that the reactor contains X molecules at time t is thus ruled by the master equation

$$\frac{d}{dt} P(X;t) = \sum_{\rho=\pm 1}^{\pm r} [P(X - \nu_{\rho}; t) W_{\rho}(X - \nu_{\rho}|X) - P(X;t) W_{-\rho}(X|X - \nu_{\rho})]. \quad (4)$$

The birth-and-death stochastic process corresponding to this master equation can be simulated numerically by an algorithm proposed by Gillespie [39,40]. The chemical master equation (4) obeys a H theorem, allowing us to identify the mean entropy production in terms of the probability distribution $P(X;t)$ [9,24,25,33].

In this framework, the macroscopic description is recovered by defining the chemical concentrations of the intermediate species in terms of the statistical averages of the numbers of molecules as

$$[X_j] = \frac{1}{\Omega} \sum_{\mathbf{X}} P(\mathbf{X}; t) X_j = \frac{\langle X_j \rangle}{\Omega}. \quad (5)$$

These concentrations can be shown to obey the rates equations of chemical kinetics in the large-system limit $\Omega \rightarrow \infty$.

We assume that the Markovian process is ergodic so that the statistical averages can be performed by time averaging in the equilibrium or nonequilibrium steady states. These steady states are described by the probability distribution given by the stationary solution of the master equation (4) such that $(d/dt)P_{\text{st}}(\mathbf{X})=0$.

B. Fluctuation theorem for the independent fluxes

Out of equilibrium, the reactor is crossed by fluxes of molecules flowing from the reservoirs of reactants to the pipe evacuating the products and the excess of reactants. In this flow, the molecules are transformed by the chemical reactions. In this regard, the currents in this nonequilibrium system correspond to the fluxes from reactants to products. These fluxes are driven by the affinities (also called the thermodynamic forces) given by the differences of free enthalpies between products and reactants if the reaction proceeds under constant pressure and temperature. The free enthalpies are given in terms of the chemical potentials and they are therefore fixed by the concentrations $[R_i]$ of the reactants and products. The equilibrium state is reached if all these concentrations are in their equilibrium ratios satisfying the detailed balance conditions. The system is out of equilibrium if the concentrations do not satisfy these conditions. *A priori*, the nonequilibrium states depend on r possible parameters which are the concentrations $\{[R_i]\}_{i=1}^r$. However, the equilibrium states form a manifold in this r -dimensional space. This manifold is determined not only by the detailed balance conditions, but also by the ergodic properties of the master equation (4). A method to identify all the independent affinities is to use the graph theory of Hill, Schnakenberg, and others [32–34].

A graph G is associated with the Markovian stochastic process ruled by the master equation (4). The vertices of this graph are the states defined by the vectors $\mathbf{X} \in \mathbb{N}^c$ of molecular numbers. The vertices are connected by directed edges $e \equiv \mathbf{X} \xrightarrow{\rho} \mathbf{X}' = \mathbf{X} + \boldsymbol{\nu}_\rho$ corresponding to each nonvanishing transition rate $W_\rho(\mathbf{X}|\mathbf{X}')$. Among all the possible subgraphs of the graph G , a very special role is played by the cycles. The concept of maximal tree allows us to identify a fundamental set of cycles $\{C_l\}$, which provides a decomposition $T(G)$ of the graph G [33]. We notice that there exist, in general, several maximal trees which can be defined by linear combinations of $T(G)$ with its cycles.

Remarkably, the ratio of the products of the transition rates along the two possible orientations of a cycle C_l is independent of the instantaneous numbers of molecules and only depends on the chemical concentrations in the external reservoirs fixing the nonequilibrium constraints. Indeed, according to Eq. (3), we observe with Schnakenberg [33] that the ratio

$$\prod_{\rho \in C_l} \frac{W_\rho(\mathbf{X}|\mathbf{X} + \boldsymbol{\nu}_\rho)}{W_{-\rho}(\mathbf{X} + \boldsymbol{\nu}_\rho|\mathbf{X})} = \prod_{\rho \in C_l} \frac{k_\rho \prod_{i=1}^r [R_i]^{v_{\rho i}^<}}{k_{-\rho} \prod_{i=1}^r [R_i]^{v_{\rho i}^>}} = e^{\mathcal{A}_l/k_B T} \equiv e^{\mathcal{A}_l} \quad (6)$$

only depends on the chemical concentrations of reactants and products and defines the affinity corresponding to the cycle C_l . In Eq. (6), T denotes the temperature and k_B Boltzmann's constant. The concept of affinity was introduced by De Donder [1] as the free enthalpy change in a reaction. For the cycle we here consider, the original definition of affinity would give $\mathcal{A}_l = -\sum_{i,\rho \in C_l} \mu_i v_{\rho i}$ in terms of the chemical potentials $\mu_i = \mu_i^0 + k_B T \ln([R_i]/c^0)$, where μ_i^0 are the reference values for the concentration c^0 of one mole per liter. In the following, we use the affinities $A_l \equiv \mathcal{A}_l/(k_B T)$ expressed in units of the thermal energy $k_B T$ following the convention of Callen [41]. We emphasize that the affinities A_l are defined for the cycles C_l of the graph G . Several cycles C_l may correspond to the same macroscopic reaction γ , whereupon the affinities A_l of these cycles correspond to the same macroscopic affinity A_γ . In this way, all the independent affinities $\{A_\gamma\}$ of the nonequilibrium process can be identified.

According to the stochastic process, the time evolution of the system is a sequence of random jumps due to the reactive events occurring at the successive times $0 < t_1 < t_2 < \dots < t_n < t$. A *path* or *history* of the process can thus be represented as

$$\mathcal{X}(t) = \mathbf{X}_0 \xrightarrow{\rho_1} \mathbf{X}_1 \xrightarrow{\rho_2} \mathbf{X}_2 \xrightarrow{\rho_3} \dots \xrightarrow{\rho_n} \mathbf{X}_n. \quad (7)$$

The random reactive events contribute to the independent currents or fluxes from reactants to products. These fluxes are given by random Dirac delta peaks each time a cycle contributing to a given macroscopic reaction γ is closed. We can suppose that the cycle C_l closes at the instant t_n a transition e_n occurs on its chord l . Accordingly, the instantaneous current or flux associated with the macroscopic reaction γ is defined by

$$j_\gamma(t) \equiv \sum_{l \in \gamma} \sum_{n=-\infty}^{+\infty} S_l(e_n) \delta(t - t_n), \quad (8)$$

where $S_l(e_n) = \pm 1$ whether the transition e_n occurring at time t_n is parallel or antiparallel to the chord l of the cycle C_l contributing to the reaction γ [30]. The so-called Helfand moment [42] associated with the flux (8) is defined as the cumulated flux

$$G_\gamma(t) \equiv \int_0^t dt' j_\gamma(t'). \quad (9)$$

For each path (7), this Helfand moment depicts a piecewise constant function of time taking positive or negative integer values and giving the number of reactive events contributing to the macroscopic reaction of independent affinity A_γ since the initial time $t=0$.

The fluctuation theorem for the independent currents or fluxes can now be enunciated as [30].

Fluctuation theorem for the fluxes. In a nonequilibrium steady state of macroscopic affinities $\mathbf{A}=\{A_\gamma\}$ defined by the conditions (6), the generating function of the fluctuating cumulated fluxes $\mathbf{G}(t)=\{G_\gamma(t)\}$,

$$Q(\boldsymbol{\lambda};\mathbf{A}) \equiv \lim_{t \rightarrow \infty} -\frac{1}{t} \ln \langle e^{-\boldsymbol{\lambda} \cdot \mathbf{G}(t)} \rangle, \quad (10)$$

obeys the symmetry

$$Q(\boldsymbol{\lambda};\mathbf{A}) = Q(\mathbf{A} - \boldsymbol{\lambda};\mathbf{A}). \quad (11)$$

Taking the Legendre transform of the generating function, we obtain the fluctuation theorem in the form

$$\frac{\text{Prob} \left[\frac{1}{t} \int_0^t dt' j(t') \in (\boldsymbol{\xi}, \boldsymbol{\xi} + d\boldsymbol{\xi}) \right]}{\text{Prob} \left[\frac{1}{t} \int_0^t dt' j(t') \in (-\boldsymbol{\xi}, -\boldsymbol{\xi} + d\boldsymbol{\xi}) \right]} \approx \exp \boldsymbol{\xi} \cdot \mathbf{A} t \quad (t \rightarrow \infty), \quad (12)$$

showing that, in the long-time limit, the probabilities of the reversed fluxes $-\boldsymbol{\xi}$ are exponentially suppressed by a factor growing at the rate given by the sum of the affinities \mathbf{A} with the magnitudes $\boldsymbol{\xi}$ of the random fluxes averaged over the finite time interval t . This rate is precisely the rate of entropy production

$$\left. \frac{d_i S}{dt} \right|_{\text{st}} = \mathbf{J} \cdot \mathbf{A} \geq 0, \quad (13)$$

if the random fluxes take their mean values

$$\mathbf{J} = \langle \boldsymbol{\xi} \rangle = \lim_{t \rightarrow \infty} \frac{1}{t} \int_0^t dt' \langle \mathbf{j}(t') \rangle = \lim_{t \rightarrow \infty} \frac{1}{t} \langle \mathbf{G}(t) \rangle = \frac{\partial Q}{\partial \boldsymbol{\lambda}}(0; \mathbf{A}), \quad (14)$$

in some steady state of affinities \mathbf{A} . It should be emphasized that these mean fluxes are nothing else but the reaction rates of macroscopic chemical kinetics. Indeed, the mean flux J_γ is the mean frequency of the reactive events of the macroscopic reaction γ . Each one of these reactive events contributes to increasing the entropy by the associated affinity A_γ in agreement with Eq. (13).

We notice that, in a steady state, the entropy production can also be obtained in terms of a further fluctuating quantity introduced by Lebowitz and Spohn [15],

$$Z(t) = \int_0^t dt' \sum_{n=-\infty}^{+\infty} \delta(t' - t_n) \ln \frac{W_{\rho_n}(\mathbf{X}_{n-1} | \mathbf{X}_n)}{W_{-\rho_n}(\mathbf{X}_n | \mathbf{X}_{n-1})}, \quad (15)$$

which measures the breaking of detailed balance along a random path (7). The fluctuations of this quantity are characterized by its generating function

$$q(\eta) \equiv \lim_{t \rightarrow \infty} -\frac{1}{t} \ln \langle e^{-\eta Z(t)} \rangle, \quad (16)$$

which obeys the fluctuation theorem [15]

$$q(\eta) = q(1 - \eta). \quad (17)$$

The entropy production (13) is equivalently given by

$$\left. \frac{d_i S}{dt} \right|_{\text{st}} = \frac{dq}{d\eta}(0) = \lim_{t \rightarrow \infty} \frac{1}{t} \langle Z(t) \rangle \geq 0, \quad (18)$$

as discussed in Refs. [15,24].

C. Symmetries for the response coefficients

The macroscopic fluxes (14) can be expanded around the state of thermodynamic equilibrium where all the affinities vanish $\{A_\epsilon=0\}$ as follows:

$$J_\alpha = \sum_\beta L_{\alpha\beta} A_\beta + \frac{1}{2!} \sum_{\beta,\gamma} M_{\alpha\beta\gamma} A_\beta A_\gamma + \frac{1}{3!} \sum_{\beta,\gamma,\delta} N_{\alpha\beta\gamma\delta} A_\beta A_\gamma A_\delta + \dots \quad (19)$$

For small perturbations in the affinities $\{A_\epsilon\}$, these expansions give the values of the fluxes close to equilibrium. The linear response of the system is characterized by the Onsager coefficients $L_{\alpha\beta}$, and the nonlinear response by the higher-order coefficients $M_{\alpha\beta\gamma}$, $N_{\alpha\beta\gamma\delta}$, ... These coefficients are defined in terms of the generating function (10) according to

$$L_{\alpha\beta} = \frac{\partial^2 Q}{\partial \lambda_\alpha \partial A_\beta}(0;0), \quad (20)$$

$$M_{\alpha\beta\gamma} = \frac{\partial^3 Q}{\partial \lambda_\alpha \partial A_\beta \partial A_\gamma}(0;0), \quad (21)$$

$$N_{\alpha\beta\gamma\delta} = \frac{\partial^4 Q}{\partial \lambda_\alpha \partial A_\beta \partial A_\gamma \partial A_\delta}(0;0), \quad (22)$$

...

Since the response coefficients are obtained by differentiating the generating function with respect to its arguments, symmetry relations can be deduced for them as the consequence of the fluctuation theorem (11). In this way, the Onsager reciprocity relations $L_{\alpha\beta}=L_{\beta\alpha}$ could be rederived in Ref. [13] for thermostated systems, and in Ref. [15] for mechanical stochastic systems. In Refs. [25,31], it has been shown that new relationships can also be deduced this time for the nonlinear response coefficients. In particular, the second-order response coefficients (21) are given by the highly nontrivial formula [31]

$$M_{\alpha\beta\gamma} = \frac{\partial D_{\alpha\beta}}{\partial A_\gamma}(0) + \frac{\partial D_{\alpha\gamma}}{\partial A_\beta}(0), \quad (23)$$

in terms of the matrix of diffusivities in the *nonequilibrium* steady state

$$D_{\alpha\beta}(\mathbf{A}) \equiv -\frac{1}{2} \frac{\partial^2 Q}{\partial \lambda_\alpha \partial \lambda_\beta}(0; \mathbf{A}) = \lim_{t \rightarrow \infty} \frac{1}{2t} \langle \Delta G_\alpha(t) \Delta G_\beta(t) \rangle, \quad (24)$$

where the statistical averages are taken with respect to the nonequilibrium steady state and $\Delta G_\alpha(t) = G_\alpha(t) - \langle G_\alpha(t) \rangle$.

Equation (23) gives the second-order response coefficients (21) in terms of the diffusivities (24), which characterize the nonequilibrium fluctuations. Although the diffusivities reduce to the linear response coefficients at equilibrium $D_{\alpha\beta}(0)=L_{\alpha\beta}$, it is their derivatives which connect to the nonlinear response coefficients in Eq. (23). The formula (23) is highly nontrivial because the second-order response coefficients (21) are defined by two derivatives with respect to \mathbf{A} , while only one remains in the right-hand side of Eq. (23). Symmetry relations similar to Eq. (23) have been obtained in Ref. [31] for all the nonlinear response coefficients. Each response coefficient is thus related to a fluctuation property, at arbitrary orders in the response [31].

D. Temporal disorder and entropy production

The dynamical randomness or temporal disorder of a continuous-jump stochastic process can be characterized in terms of its τ entropy per unit time [36]. An analogy here exists with the thermodynamic entropy per spin of a one-dimensional spin chain. This thermodynamic entropy characterizes the spatial disorder of the instantaneous statistical state of the spin chain. This characterization is here applied to the random paths (7) of the stochastic process seen along the time axis instead of the space axis. From this viewpoint, the τ entropy per unit time gives us the amount of temporal disorder in the random paths of the process.

The birth-and-death stochastic processes are continuous in time since the waiting times between the jumps are exponentially distributed random variables. Therefore, the paths (7) have to be sampled with a sampling time τ before defining an entropy per unit time. The τ entropy per unit time is thus defined as the mean decay rate of the so-sampled path probabilities [36]. Applying this definition to the stochastic process of the chemical master equation (4), the τ entropy per unit time is given by

$$h(\tau) = \sum_{\rho, X} P_{\text{st}}(\mathbf{X} - \mathbf{v}_\rho) W_\rho(\mathbf{X} - \mathbf{v}_\rho | \mathbf{X}) \ln \frac{e}{\tau W_\rho(\mathbf{X} - \mathbf{v}_\rho | \mathbf{X})} + O(\tau). \quad (25)$$

Similarly, the time-reversed τ entropy per unit time is obtained as [37,43–45]

$$h^R(\tau) = \sum_{\rho, X} P_{\text{st}}(\mathbf{X} - \mathbf{v}_\rho) W_\rho(\mathbf{X} - \mathbf{v}_\rho | \mathbf{X}) \ln \frac{e}{\tau W_{-\rho}(\mathbf{X} | \mathbf{X} - \mathbf{v}_\rho)} + O(\tau). \quad (26)$$

We notice that these dynamical entropies increase as the sampling time decreases, $\tau \rightarrow 0$. The reason is that the stochastic process is continuous in time so that it generates dynamical randomness on an arbitrarily short time interval. This feature is due to the approximation of the microscopic dynamics by the stochastic process. Indeed, the deterministic character of the microscopic Hamiltonian dynamics would be revealed if the process was sampled on the short time scale τ_c of the collisions. For sampling times shorter than the collision time, $\tau \ll \tau_c$, the dynamical entropies would tend to saturate because of the deterministic microscopic dynamics.

On this microscopic time scale, the stochastic model would thus overestimate the actual dynamical randomness of the process [36].

A fundamental result is that the difference between the time-reversed and the forward τ entropies per unit time is equal to the thermodynamic entropy production [37,43–46]. Indeed, we get from Eqs. (25) and (26) that

$$\begin{aligned} h^R(\tau) - h(\tau) &= \frac{1}{2} \sum_{\rho, X} [P_{\text{st}}(\mathbf{X} - \mathbf{v}_\rho) W_\rho(\mathbf{X} - \mathbf{v}_\rho | \mathbf{X}) \\ &\quad - P_{\text{st}}(\mathbf{X}) W_{-\rho}(\mathbf{X} | \mathbf{X} - \mathbf{v}_\rho)] \\ &\quad \times \ln \frac{P_{\text{st}}(\mathbf{X} - \mathbf{v}_\rho) W_\rho(\mathbf{X} - \mathbf{v}_\rho | \mathbf{X})}{P_{\text{st}}(\mathbf{X}) W_{-\rho}(\mathbf{X} | \mathbf{X} - \mathbf{v}_\rho)} + O(\tau), \end{aligned} \quad (27)$$

which is the known expression for the thermodynamic entropy production involved in the H theorem of the master equation (4) [9,33] and equivalent to Eqs. (13) and (18) as shown explicitly in Refs. [24,25,37]. We thus find that the thermodynamic entropy production arises from the time asymmetry in the temporal disorder if the stochastic process is driven out of equilibrium [37,43–46]

$$\left. \frac{d_i S}{dt} \right|_{\text{st}} = \lim_{\tau \rightarrow 0} [h^R(\tau) - h(\tau)] \geq 0. \quad (28)$$

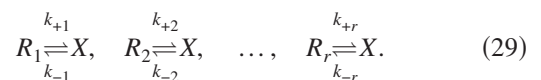
At equilibrium where detailed balance is satisfied, the time-reversal symmetry $h^R=h$ is recovered and the thermodynamic entropy production vanishes. Out of equilibrium, the time asymmetry manifests itself in the temporal disorder, leading to a phenomenon of temporal ordering [46].

III. SOLVABLE MODELS OF CHEMICAL REACTIONS

Our purpose in this section is to show that the generating function of the fluxes can be obtained analytically for a class of chemical reactions, allowing the direct verification of the fluctuation theorem and of the symmetry relations among the nonlinear response coefficients.

A. Reaction network, master equation, and nonequilibrium steady state

We consider the reaction network



The molecules of the species X enter into the system from r different reservoirs $\{R_\rho\}_{\rho=1}^r$. Equivalently, the molecules of the species X are produced by r different reactions from so many reactants. $k_{\pm\rho}$ denote the reaction constants. According to the mass action law [4–9,24,25,33,38], the transition rates of these reactions are proportional to the concentrations and are given by

$$W_{+\rho}(X|X+1) = k_{+\rho} \langle R_\rho \rangle, \quad (30)$$

$$W_{-\rho}(X|X-1) = k_{-\rho}X, \tag{31}$$

with $\langle R_\rho \rangle = \Omega [R_\rho]$ and $\rho = 1, 2, \dots, r$. The chemical reactions are linear in the sense that the transition rates are constant or linear in the molecular number X .

The master equation ruling the time evolution of the probability $P(X, t)$ that the system contains X molecules of the species X at the time t takes the form

$$\begin{aligned} \frac{d}{dt}P(X, t) = & \sum_{\rho=1}^r P(X-1, t)k_{+\rho}\langle R_\rho \rangle + \sum_{\rho=1}^r P(X+1, t)k_{-\rho}(X+1) \\ & - \sum_{\rho=1}^r P(X, t)[k_{+\rho}\langle R_\rho \rangle + k_{-\rho}X]. \end{aligned} \tag{32}$$

The concentration (5) of the species X thus evolves in time according to the following rate equation of macroscopic chemical kinetics:

$$\frac{d[X]}{dt} = \sum_{\rho=1}^r k_{+\rho}[R_\rho] - \sum_{\rho=1}^r k_{-\rho}[X], \tag{33}$$

with $[X] = \langle X \rangle / \Omega$. This equation is linear as a consequence of the linearity of the transition rates. For the same reason, any statistical moment $\langle X^m \rangle$ obeys the same linear equation. Therefore, the concentration and all the moments converge exponentially to their stationary value at the rate $\sum_{\rho=1}^r k_{-\rho}$.

The stationary state of the master equation (32) is given by the Poisson distribution

$$P_{st}(X) = e^{-\langle X \rangle} \frac{\langle X \rangle^X}{X!}, \tag{34}$$

with the mean value

$$\langle X \rangle = \frac{\sum_{\rho=1}^r k_{+\rho}\langle R_\rho \rangle}{\sum_{\rho=1}^r k_{-\rho}}. \tag{35}$$

The fact that the steady state is described by a Poisson distribution finds its origin in the linearity of the chemical reactions. We notice that, typically, the stationary distributions of nonlinear chemical reactions are not Poissonian [4–9, 33, 38].

B. Graph analysis and affinities

We emphasize that the macroscopic affinities are not apparent in the master equation contrary to the systems where the affinities are given in terms of mechanical forces. In order to identify the affinities, we use graph theory [33]. The graph of this stochastic process is depicted in Fig. 1.

Using the cycle which starts from the state X in Fig. 1 going to the state $X+1$ by some edge $\rho = \alpha$ and returning to the state X by the edge $-\rho$, the corresponding macroscopic affinity is defined by Eq. (6) as

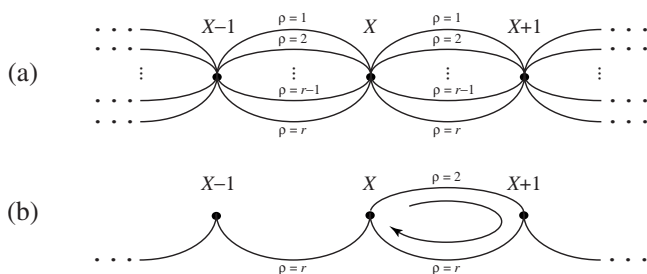


FIG. 1. (a) Graph G associated with the reaction network (29). (b) Subgraph $T(G)+l$ composed of the maximal tree $T(G)$ formed by all the edges of the reaction $\rho=r$ and the chord $l=X \rightarrow X+1$, forming the cycle used to define the macroscopic affinity (36) with $\alpha = \rho = 2$.

$$A_\alpha \equiv \ln \frac{W_{+\alpha}(X|X+1)W_{-r}(X+1|X)}{W_{-\alpha}(X+1|X)W_{+r}(X|X+1)} = \ln \frac{k_{-r}k_{+\alpha}\langle R_\alpha \rangle}{k_{-\alpha}k_{+r}\langle R_r \rangle}, \tag{36}$$

for $\alpha = 1, 2, \dots, r-1$. There are therefore $r-1$ independent affinities in this chemical reaction network. These affinities only depend on the concentrations of the external reservoirs.

The state of thermodynamic equilibrium is reached if all these affinities vanish, i.e., if the following detailed balance conditions are satisfied,

$$\frac{k_{+1}\langle R_1 \rangle}{k_{-1}} = \frac{k_{+2}\langle R_2 \rangle}{k_{-2}} = \dots = \frac{k_{+r}\langle R_r \rangle}{k_{-r}} = \langle X \rangle_{eq}. \tag{37}$$

These conditions fix the concentrations of $r-1$ reservoirs in terms of the last reservoir R_r . The equilibrium states thus depend on the last concentration $[R_r] = \langle R_r \rangle / \Omega$ and form a hyperplane of codimension one in the r -dimensional space of the concentrations. The distance with respect to this equilibrium hyperplane is controlled by the $r-1$ affinities (36).

C. Generating function of the fluxes and the fluctuation theorem

In order to treat the r reactions on the same footing, we introduce the quantities

$$B_\rho \equiv \ln \frac{k_{+\rho}\langle R_\rho \rangle}{k_{-\rho}\langle X \rangle}, \tag{38}$$

with $\rho = 1, 2, \dots, r$. The affinities (36) are related to them by $A_\alpha = B_\alpha - B_r$.

The instantaneous flux of the reaction ρ is defined according to

$$j_\rho(t) \equiv \sum_{X=-\infty}^{+\infty} \sum_{n=-\infty}^{+\infty} S_{\rho, X}(e_n) \delta(t - t_n), \tag{39}$$

where $S_{\rho, X}(e_n) = \pm 1$ whether the transition e_n occurring at time t_n is parallel or antiparallel to the edge ρ between the vertices X and $X+1$ in Fig. 1(a). The corresponding cumulated flux is defined as

$$G_\rho(t) \equiv \int_0^t dt' j_\rho(t'). \quad (40)$$

We can introduce the generating function of the statistical moments of the cumulated fluxes multiplied by their associated quantities (38) as

$$\Phi(\eta_1, \dots, \eta_r) \equiv \lim_{t \rightarrow \infty} -\frac{1}{t} \ln \left\langle \exp \left[- \sum_{\rho=1}^r \eta_\rho B_\rho G_\rho(t) \right] \right\rangle. \quad (41)$$

This function can be obtained from the eigenvalue problem of the following equation:

$$\begin{aligned} \frac{d}{dt} F(X, t) = & \sum_{\rho=1}^r F(X-1, t) (k_{+\rho} \langle R_\rho \rangle)^{\eta_\rho} (k_{-\rho} \langle X \rangle)^{1-\eta_\rho} \\ & + \sum_{\rho=1}^r F(X+1, t) (k_{+\rho} \langle R_\rho \rangle)^{1-\eta_\rho} (k_{-\rho} \langle X \rangle)^{\eta_\rho} \frac{X+1}{\langle X \rangle} \\ & - \sum_{\rho=1}^r F(X, t) [k_{+\rho} \langle R_\rho \rangle + k_{-\rho} X] \end{aligned} \quad (42)$$

for the mean value

$$F(X, t) \equiv \left\langle \exp \left[- \sum_{\rho=1}^r \eta_\rho B_\rho G_\rho(t) \right] \right\rangle_X, \quad (43)$$

defined under the condition that the system is in the state X at the initial time $t=0$. We notice that Eq. (42) reduces to the master equation (32) if $\eta_\rho=1$ for $\rho=1, 2, \dots, r$. The solution of Eq. (42) can be written as

$$F(X, t) = \frac{C}{X!} \Gamma^X \exp(-\Phi t), \quad (44)$$

where Φ is the eigenvalue, Γ is a parameter to be determined, and C is a normalization constant. Replacing this solution in Eq. (42), we find that the parameter should be taken as

$$\Gamma(\eta_1, \dots, \eta_r) = \frac{1}{\sum_{\rho=1}^r k_{-\rho} \langle X \rangle^{\rho-1}} \sum_{\rho=1}^r (k_{+\rho} \langle R_\rho \rangle)^{\eta_\rho} (k_{-\rho} \langle X \rangle)^{1-\eta_\rho}, \quad (45)$$

and the eigenvalue as

$$\begin{aligned} \Phi(\eta_1, \dots, \eta_r) = & \left(\sum_{\rho=1}^r k_{+\rho} \langle R_\rho \rangle \right) [1 - \Gamma(\eta_1, \dots, \eta_r)] \\ & \times \Gamma(1 - \eta_1, \dots, 1 - \eta_r). \end{aligned} \quad (46)$$

We notice that this function already has the symmetry

$$\Phi(\eta_1, \dots, \eta_r) = \Phi(1 - \eta_1, \dots, 1 - \eta_r) \quad (47)$$

of the fluctuation theorem.

If we define $\lambda_\rho \equiv \eta_\rho B_\rho$, we obtain the generating function of the fluxes as

$$\begin{aligned} \Psi(\lambda_1, \dots, \lambda_r) \\ \equiv \lim_{t \rightarrow \infty} -\frac{1}{t} \ln \left\langle \exp \left[- \sum_{\rho=1}^r \lambda_\rho G_\rho(t) \right] \right\rangle \end{aligned} \quad (48)$$

$$= \left(\sum_{\rho=1}^r k_{+\rho} \langle R_\rho \rangle \right) \left(1 - \frac{\sum_{\rho=1}^r k_{-\rho} e^{\lambda_\rho} \sum_{\rho=1}^r k_{-\rho} e^{B_\rho - \lambda_\rho}}{\sum_{\rho=1}^r k_{-\rho} \sum_{\rho=1}^r k_{-\rho} e^{B_\rho}} \right), \quad (49)$$

which has the symmetry

$$\Psi(\lambda_1, \dots, \lambda_r) = \Psi(B_1 - \lambda_1, \dots, B_r - \lambda_r). \quad (50)$$

Now, the generating function for the independent fluxes is defined as

$$Q(\lambda_1, \dots, \lambda_{r-1}) \equiv \Psi(\lambda_1, \dots, \lambda_{r-1}, \lambda_r = 0) \quad (51)$$

$$\begin{aligned} & = \frac{k_{+r} \langle R_r \rangle}{k_{-r}} \left[\sum_{\rho=1}^{r-1} k_{-\rho} (e^{\lambda_\rho} - 1) (e^{A_\rho - \lambda_\rho} - 1) \right. \\ & \quad \left. - \frac{\sum_{\rho=1}^{r-1} k_{-\rho} (e^{\lambda_\rho} - 1) \sum_{\rho=1}^{r-1} k_{-\rho} (e^{A_\rho - \lambda_\rho} - 1)}{\sum_{\rho=1}^r k_{-\rho}} \right], \end{aligned} \quad (52)$$

which thus satisfies the fluctuation theorem (11)

$$Q(\lambda_1, \dots, \lambda_{r-1}) = Q(A_1 - \lambda_1, \dots, A_{r-1} - \lambda_{r-1}) \quad (53)$$

in terms of the macroscopic affinities (36) associated with the independent macroscopic fluxes.

D. Response coefficients and their symmetry

From the generating function (52), we can derive the mean fluxes as

$$\begin{aligned} J_\alpha = & \left. \frac{\partial Q}{\partial \lambda_\alpha} \right|_{\lambda=0} \\ = & \frac{k_{+r} \langle R_r \rangle}{k_{-r}} k_{-\alpha} \left[e^{A_\alpha} - 1 - \frac{1}{\sum_{\rho=1}^{r-1} k_{-\rho}} \sum_{\rho=1}^{r-1} k_{-\rho} (e^{A_\rho} - 1) \right] \end{aligned} \quad (54)$$

$$\begin{aligned}
 &= \frac{k_{+r}\langle R_r \rangle}{k_{-r}} k_{-\alpha} \left[A_\alpha + \frac{1}{2!} A_\alpha^2 + \frac{1}{3!} A_\alpha^3 + \cdots - \frac{1}{\sum_{\rho=1}^r k_{-\rho}} \right. \\
 &\quad \left. \times \sum_{\rho=1}^{r-1} k_{-\rho} \left(A_\rho + \frac{1}{2!} A_\rho^2 + \frac{1}{3!} A_\rho^3 + \cdots \right) \right]. \quad (55)
 \end{aligned}$$

The response coefficients are obtained by identification with the expansion (19). Hence, the linear response coefficients are given by

$$L_{\alpha\alpha} = \frac{k_{+r}\langle R_r \rangle}{k_{-r}} k_{-\alpha} \left(1 - \frac{k_{-\alpha}}{\sum_{\rho=1}^r k_{-\rho}} \right), \quad (56)$$

$$L_{\alpha\beta} = -\frac{k_{+r}\langle R_r \rangle}{k_{-r}} \frac{k_{-\alpha} k_{-\beta}}{\sum_{\rho=1}^r k_{-\rho}} \quad (\alpha \neq \beta), \quad (57)$$

and we can check that they satisfy the Onsager reciprocity relations $L_{\alpha\beta} = L_{\beta\alpha}$.

For the reaction network (29), the higher-order response coefficients can be related to the linear response coefficients as follows:

$$L_{\alpha\alpha} = M_{\alpha\alpha\alpha} = N_{\alpha\alpha\alpha} = \cdots, \quad (58)$$

$$L_{\alpha\beta} = M_{\alpha\beta\beta} = N_{\alpha\beta\beta} = \cdots \quad (\alpha \neq \beta), \quad (59)$$

$$0 = M_{\alpha\beta\gamma} = N_{\alpha\beta\gamma\delta} = \cdots \quad (\beta \neq \gamma \text{ or } \beta \neq \delta \text{ or } \dots). \quad (60)$$

We notice that, in spite of the linearity of the kinetic equations (33), the mean fluxes (54) have a strong nonlinear dependence on the affinities. Moreover, each flux depends on all the independent affinities of the network in such a way that the response coefficients are coupling at most pairs of independent affinities, as revealed by Eqs. (58)–(60).

In order to verify the new relations (23) in the case of the present system, we calculate the diffusivities (24) in the non-equilibrium steady state

$$D_{\alpha\alpha} = \frac{k_{+r}\langle R_r \rangle}{2k_{-r}} \frac{k_{-\alpha}}{\sum_{\rho=1}^r k_{-\rho}} \left(\sum_{\rho=1}^r k_{-\rho} e^{A_\rho} + e^{A_\alpha} \sum_{\rho=1}^r k_{-\rho} \right), \quad (61)$$

$$D_{\alpha\beta} = -\frac{k_{+r}\langle R_r \rangle}{2k_{-r}} \frac{k_{-\alpha} k_{-\beta}}{\sum_{\rho=1}^r k_{-\rho}} (e^{A_\alpha} + e^{A_\beta}) \quad (\alpha \neq \beta). \quad (62)$$

We notice that the diffusivities (61) and (62) reduce to the linear response coefficients (56) and (57) at equilibrium $A = 0$. For $A \neq 0$, we can now confirm by direct calculation that the diffusivities (61) and (62) are indeed related to the

second-order response coefficients (21) by our formulas (23), showing that microreversibility imposes non trivial relations between response and fluctuations far from equilibrium as well.

E. Temporal disorder and entropy production

In the steady state (34), the temporal disorder of the stochastic reactions (29) is characterized by the τ entropy per unit time (25) as follows:

$$\begin{aligned}
 h(\tau) &= \sum_{\rho=1}^r k_{+\rho}\langle R_\rho \rangle \ln \frac{e}{\tau k_{+\rho}\langle R_\rho \rangle} + \sum_{\rho=1}^r k_{-\rho}\langle X \rangle \ln \frac{e}{\tau k_{-\rho}\chi(\langle X \rangle)} \\
 &\quad + O(\tau), \quad (63)
 \end{aligned}$$

where we have introduced the special function

$$\chi(\langle X \rangle) \equiv \exp(\ln(X+1)) \quad (64)$$

of the average $\langle X \rangle$ of the Poisson distribution (34) (see the Appendix).

On the other hand, the time-reversed τ entropy per unit time is given by

$$\begin{aligned}
 h^R(\tau) &= \sum_{\rho=1}^r k_{+\rho}\langle R_\rho \rangle \ln \frac{e}{\tau k_{-\rho}\chi(\langle X \rangle)} + \sum_{\rho=1}^r k_{-\rho}\langle X \rangle \ln \frac{e}{\tau k_{+\rho}\langle R_\rho \rangle} \\
 &\quad + O(\tau). \quad (65)
 \end{aligned}$$

The difference between the time-reversed and the direct τ entropies per unit time is a measure of the time asymmetry in the temporal disorder and gives the thermodynamic entropy production in the steady state according to Eq. (28) as follows:

$$\left. \frac{d_i S}{dt} \right|_{\text{st}} = \sum_{\rho=1}^r (k_{+\rho}\langle R_\rho \rangle - k_{-\rho}\langle X \rangle) \ln \frac{k_{+\rho}\langle R_\rho \rangle}{k_{-\rho}\langle X \rangle} \geq 0. \quad (66)$$

The entropy production is non-negative as expected from the second law of thermodynamics. It is positive out of equilibrium and vanishes at equilibrium where the detailed balance conditions (37) are satisfied.

The entropy production (66) can be expressed in terms of the $r-1$ independent macroscopic fluxes (54) and the associated macroscopic affinities (36). Indeed, the fluxes (54) can be written as

$$J_\alpha = k_{+\alpha}\langle R_\alpha \rangle - k_{-\alpha}\langle X \rangle. \quad (67)$$

Now, Eq. (66) can be transformed as follows:

$$\begin{aligned}
 \left. \frac{d_i S}{dt} \right|_{\text{st}} &= \sum_{\rho=1}^{r-1} (k_{+\rho}\langle R_\rho \rangle - k_{-\rho}\langle X \rangle) \ln \frac{k_{-\rho} k_{+\rho}\langle R_\rho \rangle}{k_{-\rho} k_{+\rho}\langle R_\rho \rangle} \\
 &\quad + \underbrace{\sum_{\rho=1}^r (k_{+\rho}\langle R_\rho \rangle - k_{-\rho}\langle X \rangle) \ln \frac{k_{+r}\langle R_r \rangle}{k_{-r}\langle X \rangle}}_{=0} \quad (68)
 \end{aligned}$$

$$= \sum_{\alpha=1}^{r-1} J_{\alpha} A_{\alpha}, \quad (69)$$

and we get Eq. (13) since the last term of the first line of Eq. (69) vanishes by Eq. (35).

Finally, the generating function (16) of the Lebowitz-Spohn action functional (15) is obtained if we consider the eigenvalue problem of Eq. (42) with all the parameters set equal to $\eta_{\rho} = \eta$.

$$q(\eta) = \Phi(\eta, \dots, \eta). \quad (70)$$

According to the generating function (46) with Eq. (45), we thus find that

$$q(\eta) = \left(\sum_{\rho=1}^r k_{+\rho} \langle R_{\rho} \rangle \right) [1 - \gamma(\eta) \gamma(1 - \eta)], \quad (71)$$

with the function

$$\gamma(\eta) = \frac{1}{r} \sum_{\rho=1}^r k_{-\rho} \exp\left(\eta \ln \frac{k_{+\rho} \langle R_{\rho} \rangle}{k_{-\rho} \langle X \rangle}\right), \quad (72)$$

such that $\gamma(0) = \gamma(1) = 1$. The generating function (71) obeys the fluctuation theorem (17) and, here also, we recover the entropy production (66) according to Eq. (18).

IV. REACTIONS BETWEEN TWO RESERVOIRS

In this section, we consider the case of the reaction network (29) between two reservoirs $r=2$. Besides explicating for this case the concepts developed in the previous sections, our purpose is to show that the fluctuation theorem is here satisfied over finite time intervals, before holding asymptotically in the long-time limit.

A. Reaction network and affinity

The simplest reaction network sustaining a nonequilibrium steady state in the family (29) is the case of an intermediate species X between $r=2$ reservoirs as follows:



The transition rates entering the chemical master equation (32) are obtained from Eqs. (30) and (31) with $\rho=1, 2$.

In the graph G of the corresponding Markovian process, there is one cycle between any two states X and $X+1$ (cf. Fig. 1 with $r=2$). The ratio of the products of transition rates along the two possible orientations of this cycle is given by

$$A \equiv \ln \frac{W_{+1}(X|X+1)W_{-2}(X+1|X)}{W_{-1}(X+1|X)W_{+2}(X|X+1)} = \ln \frac{k_{-2}k_{+1}\langle R_1 \rangle}{k_{-1}k_{+2}\langle R_2 \rangle}, \quad (74)$$

which is independent of the state X and defines the single macroscopic affinity A of this reaction network in terms of the enthalpy change of the overall reaction $R_1 \rightarrow R_2$. The as-

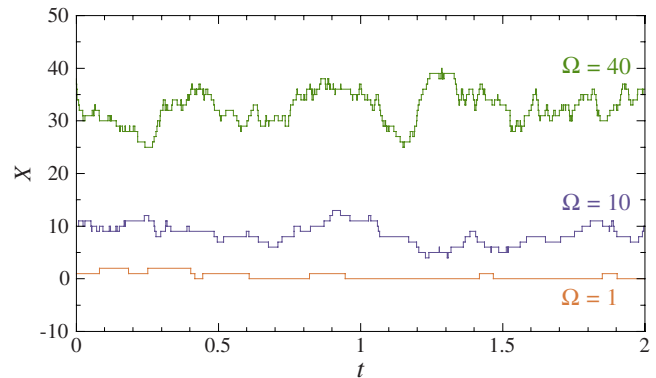


FIG. 2. (Color online) The fluctuating number $X(t)$ of molecules of the intermediate species in the reaction network (73) with $k_{+1} = k_{-1} = k_{+2} = 1$, $k_{-2} = 1.5$, $[R_1] = [R_2] = 1$ for different sizes $\Omega = 1, 10, 40$. The affinity (74) here takes the value $A = \ln 1.5 = 0.405$, the mean flux is equal to $J = \Omega/5$, and the entropy production is positive $\frac{d_i S}{dt} = (\Omega/5) \ln 1.5$. In these nonequilibrium steady states, the mean number of molecules is equal to $\langle X \rangle = 4\Omega/5$. The τ entropy per unit time of each path is given by $h(\tau) \approx 4\Omega \ln[2.691/(\tau\Omega)]$ for $\Omega \gg 1$. The larger Ω , the larger the τ entropy and, therefore, the larger the temporal disorder of the path.

sociated macroflux is the number of molecules R_1 which are transformed into the molecules R_2 per unit time.

The stochastic process can be simulated by Gillespie's algorithm [39,40]. Several random paths are depicted in Fig. 2 under different conditions. The temporal disorder of the fluctuations and its time-reversal symmetry are characterized in terms of the τ entropy per unit time (63) and the corresponding time-reversed quantity (65). We observe in Fig. 2 that the path which looks most random is indeed the one with the largest τ entropy per unit time. On the other hand, we can verify that the difference between the time-reversed and the direct τ entropies per unit time gives the thermodynamic entropy production (66).

B. Fluctuation theorem in the long-time limit

Different fluctuating quantities are now considered. There is the instantaneous flux $j_1(t)$ defined by Eq. (8) when the reaction 1 is completed (see Fig. 3) or $j_2(t)$ when the reaction 2 is completed. On the other hand, there is the Lebowitz-Spohn quantity (15) (see Fig. 4). Since there is only a single independent flux in this reaction network, the three fluctuating quantities are related to one another and they share similar probability distributions.

The generating function of the fluctuating flux $j_1(t)$ is analytically given by Eq. (52) for $r=2$, which can be rewritten as

$$Q(\lambda) = L(e^\lambda - 1)(e^{A-\lambda} - 1), \quad (75)$$

with

$$L = \frac{k_{-1}k_{+2}\langle R_2 \rangle}{k_{-1} + k_{-2}}, \quad (76)$$

and the affinity (74). This generating function obeys the symmetry relation (53) of the infinite-time fluctuation theorem.

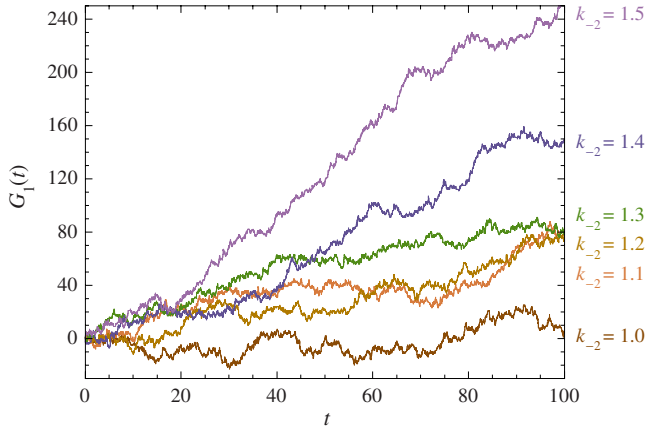


FIG. 3. (Color online) The fluctuating cumulated flux $G_1(t) = \int_0^t dt' j_1(t')$ of the reaction 1 versus time t in the network (73) with $k_{+1}=k_{-1}=k_{+2}=1$, $[R_1]=[R_2]=1$, $\Omega=10$, for different values of $k_{-2} = 1.0, 1.1, 1.2, 1.3, 1.4, 1.5$. The affinity (74) is $A = \ln k_{-2}$ and it vanishes if $k_{-2}=1.0$, which corresponds to the state of thermodynamic equilibrium. The other cases correspond to nonequilibrium steady states. The mean slope of the curves is the associated mean flux (77), which here takes the value $J = \langle j_1 \rangle = \Omega(k_{-2}-1)/(k_{-2}+1)$, vanishing consistently at equilibrium.

In nonequilibrium steady states, the mean value of the flux $j_1(t)$ is given by

$$J \equiv \langle j_1 \rangle = \frac{dQ}{d\lambda}(0) = L(e^A - 1) = \frac{k_{-2}k_{+1}\langle R_1 \rangle - k_{-1}k_{+2}\langle R_2 \rangle}{k_{-1} + k_{-2}}. \quad (77)$$

This flux rapidly increases for $A \rightarrow +\infty$, but saturates at the constant negative value $-L$ for $A \rightarrow -\infty$. This behavior is reminiscent of the electric current in a diode. We notice that

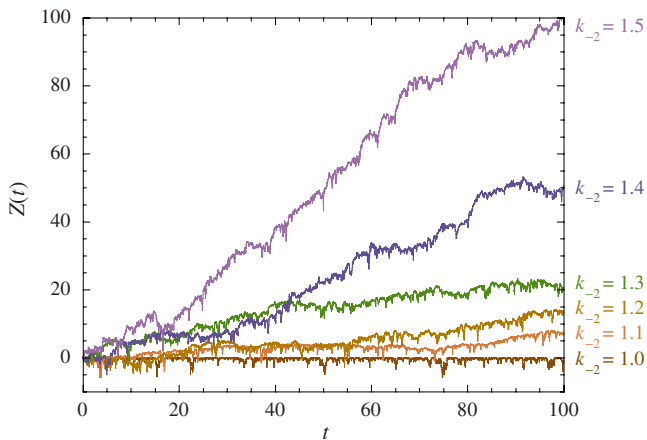


FIG. 4. (Color online) The fluctuating Lebowitz-Spohn quantity (15) versus time t in the reaction network (73) with the same parameter values, affinity A , and mean flux J as in Fig. 3. The mean slope of the curves is equal to the entropy production $\frac{dS}{dt} = JA$, which vanishes at equilibrium when $k_{-2}=1.0$. Comparing with Fig. 3, we observe that the mean slope is indeed reduced by the affinity $A = \ln k_{-2}$.

Eq. (76) gives the Onsager coefficient obtained by expanding the flux in powers of the affinity according to Eq. (19).

The decay rate of the probability that the cumulated flux takes a value around ξt ,

$$\text{Prob} \left[\frac{1}{t} \int_0^t dt' j_1(t') \in (\xi, \xi + d\xi) \right] \sim e^{-H(\xi)t} \quad (t \rightarrow \infty), \quad (78)$$

is obtained as the Legendre transform of the generating function

$$H(\xi) = Q(\lambda) - \lambda \xi \quad \text{with} \quad \xi = \frac{dQ}{d\lambda} \quad \text{or} \quad \lambda = -\frac{dH}{d\xi}. \quad (79)$$

From Eq. (75), we get the Legendre transform

$$H(\xi) = L \left[1 + e^A - 2 \sqrt{\left(\frac{\xi}{2L} \right)^2 + e^A} \right] - \xi \ln \left[-\frac{\xi}{2L} + \sqrt{\left(\frac{\xi}{2L} \right)^2 + e^A} \right], \quad (80)$$

which satisfies the symmetry

$$\xi A = H(-\xi) - H(\xi), \quad (81)$$

leading to the following form of the fluctuation theorem:

$$\frac{\text{Prob} \left[\frac{1}{t} \int_0^t dt' j_1(t') \in (\xi, \xi + d\xi) \right]}{\text{Prob} \left[\frac{1}{t} \int_0^t dt' j_1(t') \in (-\xi, -\xi + d\xi) \right]} \simeq \exp \xi A t \quad (t \rightarrow \infty). \quad (82)$$

We notice that the maximal tree could have been chosen as consisting of the reaction 1 edges. For this choice, each cycle is formed with a chord made of an edge due to reaction 2, resulting into similar results for the fluctuating flux $j_2(t)$.

The fluctuating quantity (15) by Lebowitz and Spohn [15] has the generating function (71) with Eq. (72), which here reduces to

$$q(\eta) = L(e^{A\eta} - 1)(e^{A-A\eta} - 1) = Q(A\eta), \quad (83)$$

showing that the quantity $Z(t)$ is proportional to the cumulated flux over long-time intervals according to $Z(t) \simeq A G_1(t) = A \int_0^t dt' j_1(t')$. The entropy production is thus given by

$$\left. \frac{d_i S}{dt} \right|_{\text{st}} = \left. \frac{dq}{d\eta} \right|_0 = LA(e^A - 1) = JA = H(-J), \quad (84)$$

and $H(J)=0$, as it should. The generating function (83) is depicted in Fig. 5, which shows the agreement between the analytical formula and the numerical computation of this function. As seen in Fig. 5, the generating function is symmetric under the reflection $\eta \rightarrow 1 - \eta$. This symmetry is the expression of the fluctuation theorem.

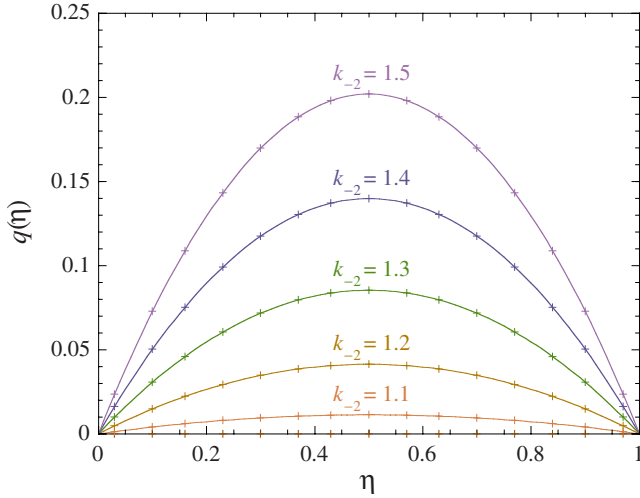


FIG. 5. (Color online) The generating function (83) of the fluctuating Lebowitz-Spohn quantity (15) versus its parameter η in the reaction network (73) with $k_{+1}=k_{-1}=k_{+2}=1$, $[R_1]=[R_2]=1$, $\Omega=10$ for different values of $k_{-2}=1.0, 1.1, 1.2, 1.3, 1.4, 1.5$, as in Figs. 3 and 4. The solid lines depict the generating function computed by solving numerically Eq. (42) with all the parameters $\eta_\rho=\eta$. The crosses give the values of the analytical formula (83), showing the agreement. We notice that the generating function vanishes identically at equilibrium when $k_{-2}=1.0$.

C. Finite-time symmetry relation

For the linear reaction network (73), it is possible to derive the exact probability distribution of the fluxes at every time t . The following derivation can be carried out for the reaction networks (29) between any number r of reservoirs, but for simplicity we illustrate the method in the simple case of the reaction network (73) between two reservoirs. The exact solution allows us to evaluate explicitly in this example the importance of the finite-time corrections to the fluctuation theorem.

Let us introduce the probability $P(X, l, m, t)$ to have X particles at time t while having the signed cumulated fluxes l and m for the reactions 1 and 2. The evolution equation of this quantity is the following:

$$\begin{aligned} \frac{dP(X, l, m, t)}{dt} &= k_{+1}\langle R_1 \rangle P(X-1, l-1, m, t) - k_{+1}\langle R_1 \rangle P(X, l, m, t) \\ &\quad + k_{-1}(X+1)P(X+1, l+1, m, t) - k_{-1}XP(X, l, m, t) \\ &\quad + k_{+2}\langle R_2 \rangle P(X-1, l, m-1, t) - k_{+2}\langle R_2 \rangle P(X, l, m, t) \\ &\quad + k_{-2}(X+1)P(X+1, l, m+1, t) - k_{-2}XP(X, l, m, t). \end{aligned} \quad (85)$$

The finite-time generating function of the signed cumulated fluxes is defined by [8,38]

$$G(s, s_1, s_2, t) \equiv \sum_{X=0}^{\infty} \sum_{l, m=-\infty}^{+\infty} s^X s_1^l s_2^m P(X, l, m, t). \quad (86)$$

The various probabilities can be recovered by expanding this generating function in powers of s , s_1 , and s_2 , or equivalently by differentiating the generating function. We notice that we can trace out the information we do not need by setting the corresponding variable s equal to unity. Normalization requires that $G(1, 1, 1, t)=1$ for all time t .

Since we are interested in the properties of the steady state, the initial condition is taken to be

$$P(X, l, m, t=0) = e^{-\langle X \rangle} \frac{\langle X \rangle^X}{X!} \delta_{0,l} \delta_{0,m}, \quad (87)$$

so that

$$G(s, s_1, s_2, t=0) = e^{\langle X \rangle (s-1)}. \quad (88)$$

The evolution equation for the generating function $G(s, s_1, s_2, t)$ can be deduced from Eq. (85) to get

$$\begin{aligned} \frac{\partial G(s, s_1, s_2, t)}{\partial t} &= [k_{+1}\langle R_1 \rangle (s s_1 - 1) + k_{+2}\langle R_2 \rangle (s s_2 - 1)] \\ &\quad \times G(s, s_1, s_2, t) + \left[k_{-1} \left(\frac{1}{s_1} - s \right) \right. \\ &\quad \left. + k_{-2} \left(\frac{1}{s_2} - s \right) \right] \frac{\partial G(s, s_1, s_2, t)}{\partial s}. \end{aligned} \quad (89)$$

This first-order partial differential equation can be solved by using the method of characteristics starting from the initial condition (88). We find

$$\begin{aligned} G(s, s_1, s_2, t) &= \exp \left[t \frac{AC - BD}{D} - \frac{B}{D} - \frac{(A-B)C}{D^2} (1 - e^{-Dt}) \right] \\ &\quad \times \exp \left\{ s \left[\frac{B}{D} e^{-Dt} + \frac{A}{D} (1 - e^{-Dt}) \right] \right\}, \end{aligned} \quad (90)$$

with

$$A = k_{+1}\langle R_1 \rangle s_1 + k_{+2}\langle R_2 \rangle s_2, \quad (91)$$

$$B = k_{+1}\langle R_1 \rangle + k_{+2}\langle R_2 \rangle, \quad (92)$$

$$C = \frac{k_{-1}}{s_1} + \frac{k_{-2}}{s_2}, \quad (93)$$

$$D = k_{-1} + k_{-2}, \quad (94)$$

such that $\langle X \rangle = B/D$. This solution satisfies the normalization condition and the steady-state solution (88) is recovered if $s_1=s_2=1$.

Since we are interested in the flux, we must evaluate the solution (90) at $s=1$ with $s_1=e^{-\lambda_1}$ and $s_2=e^{-\lambda_2}$ to find

$$\begin{aligned}
 G(1, s_1, s_2, t) &= \sum_{X=0}^{\infty} \sum_{l, m=-\infty}^{+\infty} s_1^l s_2^m P(X, l, m, t) \\
 &= \left\langle \exp \left[-\lambda_1 \int_0^t dt' j_1(t') - \lambda_2 \int_0^t dt' j_2(t') \right] \right\rangle \\
 &\sim e^{-\Psi(\lambda_1, \lambda_2)t}.
 \end{aligned} \tag{95}$$

By Eq. (90), we get

$$\begin{aligned}
 G(1, s_1, s_2, t) &= \exp \left[t \frac{\mathcal{AC} - \mathcal{BD}}{\mathcal{D}} - \frac{(A - \mathcal{B})(C - \mathcal{D})}{\mathcal{D}^2} (1 - e^{-\mathcal{D}t}) \right] \\
 &\sim e^{-\Psi(\lambda_1, \lambda_2)t}.
 \end{aligned} \tag{96}$$

By the way, we can check that the infinite-time generating function $\Psi(\lambda_1, \lambda_2) = \mathcal{B} - \mathcal{AC}/\mathcal{D}$ is indeed given by Eq. (49).

The signed cumulated flux of reaction 1 is given by setting $s_2 = 1$ in Eq. (96) to get the following finite-time generating function:

$$\begin{aligned}
 G(1, s_1, 1, t) &= \exp \left\{ \frac{t}{\mathcal{D}} \left[k_{-2} k_{+1} \langle R_1 \rangle (s_1 - 1) + k_{-1} k_{+2} \langle R_2 \rangle \right. \right. \\
 &\quad \times \left. \left. \left(\frac{1}{s_1} - 1 \right) \right] + \frac{1 - e^{-\mathcal{D}t}}{\mathcal{D}^2} k_{-1} k_{+1} \langle R_1 \rangle \right. \\
 &\quad \left. \times \left(s_1 + \frac{1}{s_1} - 2 \right) \right\}.
 \end{aligned} \tag{97}$$

The probability distribution $P(l, t)$ to have a signed cumulated flux l up to time t for the reaction 1 can be obtained using the generating series of the Bessel functions given by Eq. (9.6.33) of Ref. [47].

$$e^{z/2(\theta+1/\theta)} = \sum_{l=-\infty}^{+\infty} \theta^l I_l(z) \quad (\theta \neq 0). \tag{98}$$

This probability distribution is thus given by

$$\begin{aligned}
 P(l, t) &= \mathcal{N}(t) \left[\frac{k_{-2} k_{+1} \langle R_1 \rangle \mathcal{D}t + k_{-1} k_{+1} \langle R_1 \rangle (1 - e^{-\mathcal{D}t})}{k_{-1} k_{+2} \langle R_2 \rangle \mathcal{D}t + k_{-1} k_{+1} \langle R_1 \rangle (1 - e^{-\mathcal{D}t})} \right]^{l/2} \\
 &\quad \times I_l \left[\frac{2}{\mathcal{D}^2} \sqrt{k_{-2} k_{+1} \langle R_1 \rangle \mathcal{D}t + k_{-1} k_{+1} \langle R_1 \rangle (1 - e^{-\mathcal{D}t})} \sqrt{k_{-1} k_{+2} \langle R_2 \rangle \mathcal{D}t + k_{-1} k_{+1} \langle R_1 \rangle (1 - e^{-\mathcal{D}t})} \right],
 \end{aligned} \tag{99}$$

where $I_l(z)$ denotes the Bessel functions of integer order [47] and

$$\begin{aligned}
 \mathcal{N}(t) &= \exp \left[-\frac{t}{\mathcal{D}} (k_{-2} k_{+1} \langle R_1 \rangle + k_{-1} k_{+2} \langle R_2 \rangle) \right. \\
 &\quad \left. - 2 \frac{1 - e^{-\mathcal{D}t}}{\mathcal{D}^2} k_{-1} k_{+1} \langle R_1 \rangle \right]
 \end{aligned} \tag{100}$$

is the normalization constant with $\mathcal{D} = k_{-1} + k_{-2}$.

According to the following property of the Bessel functions [47]

$$I_l(z) = I_{-l}(z), \tag{101}$$

the ratio $P(l, t)/P(-l, t)$ obeys the following symmetry relation:

$$\frac{P(l, t)}{P(-l, t)} = \left[\frac{k_{-2} k_{+1} \langle R_1 \rangle \mathcal{D}t + k_{-1} k_{+1} \langle R_1 \rangle (1 - e^{-\mathcal{D}t})}{k_{-1} k_{+2} \langle R_2 \rangle \mathcal{D}t + k_{-1} k_{+1} \langle R_1 \rangle (1 - e^{-\mathcal{D}t})} \right]^l. \tag{102}$$

In the long-time limit, we thus recover the fluctuation theorem (82) with $l = \xi t$.

$$\frac{P(l, t)}{P(-l, t)} \simeq \left(\frac{k_{-2} k_{+1} \langle R_1 \rangle}{k_{-1} k_{+2} \langle R_2 \rangle} \right)^l = e^{A l} \quad \text{for } t \rightarrow \infty, \tag{103}$$

where A is the affinity (74).

The finite-time generating function of the flux can be found by calculating the sum

$$\begin{aligned}
 G(1, s_1 = e^{-\lambda}, 1, t) &= \sum_{l=-\infty}^{+\infty} e^{-\lambda l} P(l, t) \\
 &= \left\langle \exp \left[-\lambda \int_0^t dt' j_1(t') \right] \right\rangle \equiv e^{-\tilde{Q}(\lambda, t)t},
 \end{aligned} \tag{104}$$

with $\lambda = \lambda_1$. According to Eq. (97), we thus have

$$\begin{aligned}
 \tilde{Q}(\lambda, t) &\equiv -\frac{1}{t} \ln \left\langle \exp \left[-\lambda \int_0^t dt' j_1(t') \right] \right\rangle \\
 &= \tilde{Q}(\lambda, \infty) + 2k_{-1} k_{+1} \langle R_1 \rangle (1 - \cosh \lambda) \frac{1 - e^{-\mathcal{D}t}}{\mathcal{D}^2 t},
 \end{aligned} \tag{105}$$

where $\tilde{Q}(\lambda, \infty) = Q(\lambda)$ is given by Eq. (75) and the finite-time correction is observed to decrease as $1/t$. We notice that the symmetry of the fluctuation theorem is not valid at finite t , but we have instead the following time-dependent symmetry:

$$\tilde{Q}(\lambda, t) = \tilde{Q}(\tilde{A}(t) - \lambda, t), \tag{106}$$

with

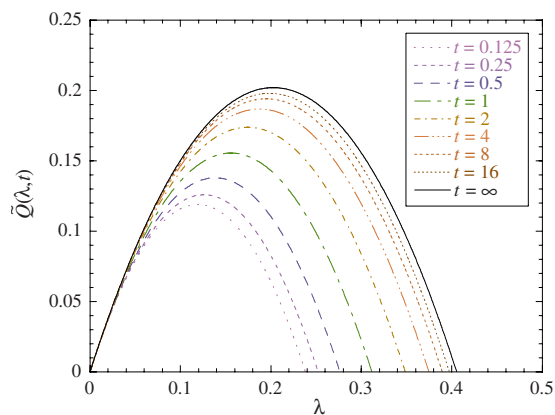


FIG. 6. (Color online) The finite-time generating function (105) of the fluctuating flux 1 versus its parameter λ for different values of the time t , in the reaction network (73) with $k_{+1}=k_{-1}=k_{+2}=1$, $k_{-2}=1.5$, $[R_1]=[R_2]=1$, and $\Omega=10$. In this case, the affinity is $A=\ln 1.5$, the mean flux is $J=2$, and the mean number of molecules is $\langle X \rangle=8$, $L=4$, and $\mathcal{D}=2.5$. The solid lines depict the asymptotic generating function (75) in the limit $t \rightarrow \infty$. The generating function vanishes at $\lambda=0$ and $\lambda=\tilde{A}(t)$. Moreover, we observe that it is symmetric under the reflection $\lambda \rightarrow \tilde{A}(t)-\lambda$, as predicted by Eq. (106).

$$\tilde{A}(t) = \ln \frac{k_{-2}k_{+1}\langle R_1 \rangle + k_{-1}k_{+1}\langle R_1 \rangle(1 - e^{-\mathcal{D}t})/(\mathcal{D}t)}{k_{-1}k_{+2}\langle R_2 \rangle + k_{-1}k_{+1}\langle R_1 \rangle(1 - e^{-\mathcal{D}t})/(\mathcal{D}t)}. \quad (107)$$

The finite-time generating function (105) is depicted in Fig. 6 for different values of the time t , together with the asymptotic generating function (75), which is reached in the long-time limit $t \rightarrow \infty$. We observe that, for each value of the time, the generating function is symmetric under the reflection $\lambda \rightarrow \tilde{A}(t)-\lambda$ with respect to the time-dependent affinity (107). This result shows that the symmetry of the fluctuation theorem still holds at finite times for this class of stochastic processes in the sense of Eq. (106).

V. CONCLUSIONS

In this paper, we have analyzed a class of chemical reactions described by birth-and-death stochastic processes in the framework of nonequilibrium statistical thermodynamics. In this theory, relationships are established between the concepts of macroscopic nonequilibrium thermodynamics such as the entropy production or the De Donder affinities (also called the thermodynamic forces) [1–3] and the probability distributions of the nonequilibrium molecular fluctuations. A landmark in the early developments of this theory is the work by Onsager and Machlup in the fifties [48]. In the seventies, great advances were achieved for chemical reactions in mesoscopic nonequilibrium systems. These systems are ruled by a master equation with transition rates given by the mass action law of chemical kinetics, as shown by Nicolis and co-workers [4–9].

In this framework, the detailed balance conditions defining the state of thermodynamic equilibrium can be extended

into nonequilibrium conditions by using the cycles of the stochastic process, as shown by Hill, Schnakenberg, and others [32–34]. Although the transition rates of the master equation depend both on the concentrations of the reactants in the external reservoirs and on the instantaneous state of the system, the products of transition rates over each cycle and its time reversal have a ratio which only depends on the macroscopic De Donder affinities according to Eq. (6). The De Donder affinities are fixed by the reactant concentrations and are nonvanishing if the system is out of equilibrium, i.e., if the system is crossed by fluxes of matter. At the mesoscopic level, these fluxes or currents are fluctuating together with the numbers of molecules involved in the reactions. Along a path of the stochastic process, these fluxes or currents jump at random each time a cycle or its time reversal is completed. As the consequence of the nonequilibrium conditions (6) by Hill, Schnakenberg, and others [32–34], the fluctuations of the fluxes or currents obey remarkable relationships known under the name of fluctuation theorem. A further remarkable result is that the thermodynamic entropy production—which is given by combining the statistical averages of the fluxes with the affinities—finds its origin in the time asymmetry of the temporal disorder developed by the stochastic process, as shown by Eq. (28) [37,43–46]. The temporal disorder is characterized by the quantities (25) and (26), which are reminiscent of the Kolmogorov-Sinai entropy per unit time [36,49].

In the present paper, the connections between these fundamental concepts have been analytically established for a class of stochastic chemical reactions with one intermediate species produced from several reactants flowing from and to external reservoirs. For these reactions, we have rigorously deduced the generating function of the fluctuating fluxes and shown that the symmetry of the fluctuation theorem for the currents is satisfied. Moreover, we have verified fundamental relations obeyed by the nonlinear response coefficients [31], which are the consequences of the fluctuation theorem for the currents beyond the Onsager reciprocity relations of linear response [35]. The generating function of the Lebowitz-Spohn action functional [15] is also obtained analytically. In our chemical reaction models, we have explicitly shown that this fluctuating quantity grows on average as the thermodynamic entropy production and obeys the corresponding fluctuation theorem.

Besides, we have calculated the characteristic quantities of temporal disorder, which are the so-called τ entropy per unit time (63) and (65). The asymmetry between the forward and reversed temporal disorders turns out to be directly related to the thermodynamic entropy production (66) of the reaction network, confirming the results of Refs. [37,43–46] for stochastic chemical reactions.

Furthermore, we have also studied the fluctuations of the chemical reactions over finite-time intervals. The probability distributions to have a signed cumulated flux up to a given finite time have been analytically calculated in terms of Bessel functions by using the chemical master equation. Remarkably, the probabilities to have opposite fluctuations obey a time-dependent symmetry relation which is reminiscent of the fluctuation theorem. The steady-state fluctuation theorem is recovered in the long-time limit.

In conclusion, the nonequilibrium chemical reactions that we have here studied are multilevel complex systems. At the mesoscopic level, they are described as stochastic processes ruled by a master equation which can be analytically solved in spite of their complexity. The probability distributions of their nonequilibrium fluctuations are highly nontrivial and differ considerably from Gaussian distributions. Yet, they obey general relationships valid away from equilibrium and provide the foundations for the science of complex systems [50].

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APPENDIX: SPECIAL FUNCTION

In this appendix, we study the function introduced in Eq. (64) as

$$\chi(a) \equiv \exp\langle \ln(X+1) \rangle, \tag{A1}$$

where the statistical average $\langle \rangle$ is carried out over the Poisson distribution (34) of mean value $a = \langle X \rangle$. We consider the Taylor expansion around $a=0$ as well as the asymptotic expansion for $a \rightarrow \infty$.

1. Taylor expansion

For small mean value, we can use the definition of the statistical average and write:

$$\langle \ln(X+1) \rangle = e^{-a} \left(a \ln 2 + \frac{a^2}{2} \ln 3 + \frac{a^3}{6} \ln 4 + \frac{a^4}{24} \ln 5 + \dots \right). \tag{A2}$$

Accordingly, we find that $\chi(a) = 1 + a \ln 2 + O(a^2)$ and, more precisely,

$$\begin{aligned} \chi(a) = & 1 + 0.693\,147a + 0.096\,385\,5a^2 - 0.015\,882\,4a^3 \\ & + 0.000\,175\,723a^4 + 0.000\,606\,519a^5 \\ & - 0.000\,151\,533a^6 + O(a^7), \end{aligned} \tag{A3}$$

for $a \rightarrow 0$.

2. Asymptotic expansion

For the asymptotic expansion, we need the central moments of the Poisson distribution. These moments can be deduced from the characteristic function according to

$$g(s) = \sum_{n=0}^{\infty} \frac{1}{n!} \langle (X-a)^n \rangle s^n = \langle e^{(X-a)s} \rangle = e^{a(e^s-1-s)}. \tag{A4}$$

Now, the average of the logarithm of $(X+1)$ can be transformed as follows:

$$\begin{aligned} \langle \ln(X+1) \rangle &= \ln \langle X+1 \rangle + \langle \ln(1+\delta) \rangle \\ &= \ln \langle X+1 \rangle + \sum_{n=0}^{\infty} \frac{(-1)^{n-1}}{n} \langle \delta^n \rangle, \end{aligned} \tag{A5}$$

with

$$\delta \equiv \frac{X - \langle X \rangle}{\langle X+1 \rangle} = \frac{X-a}{a+1}. \tag{A6}$$

Performing the Taylor series around $a^{-1}=0$, we get

$$\begin{aligned} \langle \ln(X+1) \rangle = & \ln a + \frac{1}{2a} + \frac{1}{12a^2} + \frac{1}{12a^3} + \frac{19}{120a^4} \\ & + \frac{9}{20a^5} + \frac{863}{504a^6} + O\left(\frac{1}{a^7}\right), \end{aligned} \tag{A7}$$

and finally,

$$\begin{aligned} \chi(a) = & a + \frac{1}{2} + \frac{5}{24a} + \frac{7}{48a^2} + \frac{1247}{5760a^3} + \frac{2113}{3840a^4} \\ & + \frac{5747257}{2903040a^5} + O\left(\frac{1}{a^6}\right). \end{aligned} \tag{A8}$$

[1] T. De Donder and P. Van Rysselberghe, *Thermodynamic Theory of Affinity* (Stanford University Press, Menlo Park, CA, 1936).
 [2] I. Prigogine, *Introduction to Thermodynamics of Irreversible Processes* (Wiley, New York, 1967).
 [3] D. Kondepudi and I. Prigogine, *Modern Thermodynamics: From Heat Engines to Dissipative Structures* (Wiley, Chichester, 1998).
 [4] G. Nicolis and I. Prigogine, Proc. Natl. Acad. Sci. U.S.A. **68**, 2102 (1971).
 [5] G. Nicolis, J. Stat. Phys. **6**, 195 (1972).
 [6] M. Malek-Mansour and G. Nicolis, J. Stat. Phys. **13**, 197 (1975).
 [7] G. Nicolis and J. W. Turner, Physica A **89**, 326 (1977).
 [8] G. Nicolis and I. Prigogine, *Self-Organization in Nonequilibrium Systems* (Wiley, New York, 1977).
 [9] Luo Jiu-li, C. Van den Broeck, and G. Nicolis, Z. Phys. B: Condens. Matter **56**, 165 (1984).
 [10] D. J. Evans, E. G. D. Cohen, and G. P. Morriss, Phys. Rev. Lett. **71**, 2401 (1993).
 [11] D. J. Evans and D. J. Searles, Phys. Rev. E **50**, 1645 (1994).
 [12] G. Gallavotti and E. G. D. Cohen, Phys. Rev. Lett. **74**, 2694 (1995).
 [13] G. Gallavotti, Phys. Rev. Lett. **77**, 4334 (1996).
 [14] J. Kurchan, J. Phys. A **31**, 3719 (1998).
 [15] J. L. Lebowitz and H. Spohn, J. Stat. Phys. **95**, 333 (1999).

- [16] C. Maes, *J. Stat. Phys.* **95**, 367 (1999).
- [17] C. Maes and K. Netocny, *J. Stat. Phys.* **110**, 269 (2003).
- [18] G. E. Crooks, *Phys. Rev. E* **60**, 2721 (1999).
- [19] R. van Zon, S. Ciliberto, and E. G. D. Cohen, *Phys. Rev. Lett.* **92**, 130601 (2004).
- [20] U. Seifert, *Phys. Rev. Lett.* **95**, 040602 (2005).
- [21] B. Cleuren, C. Van den Broeck, and R. Kawai, *Phys. Rev. E* **74**, 021117 (2006).
- [22] S. Rahav and C. Jarzynski, *J. Stat. Mech.: Theory Exp.* (2007), P09012.
- [23] B. Derrida, *J. Stat. Mech.: Theory Exp.* (2007), P07023.
- [24] P. Gaspard, *J. Chem. Phys.* **120**, 8898 (2004).
- [25] D. Andrieux and P. Gaspard, *J. Chem. Phys.* **121**, 6167 (2004); **125**, 219902(E) (2006).
- [26] U. Seifert, *J. Phys. A* **37**, L517 (2004).
- [27] U. Seifert, *Europhys. Lett.* **70**, 36 (2005).
- [28] D. Andrieux and P. Gaspard, *Phys. Rev. E* **74**, 011906 (2006).
- [29] D. Andrieux and P. Gaspard, *J. Stat. Mech.: Theory Exp.* (2006), P01011.
- [30] D. Andrieux and P. Gaspard, *J. Stat. Phys.* **127**, 107 (2007).
- [31] D. Andrieux and P. Gaspard, *J. Stat. Mech.: Theory Exp.* (2006), P02006.
- [32] T. L. Hill, *Free Energy Transduction and Biochemical Cycle Kinetics* (Dover, New York, 2005).
- [33] J. Schnakenberg, *Rev. Mod. Phys.* **48**, 571 (1976).
- [34] D.-Q. Jiang, M. Qian, and M.-P. Qian, *Mathematical Theory of Nonequilibrium Steady States* (Springer, Berlin, 2004).
- [35] L. Onsager, *Phys. Rev.* **37**, 405 (1931).
- [36] P. Gaspard and X.-J. Wang, *Phys. Rep.* **235**, 291 (1993).
- [37] P. Gaspard, *J. Stat. Phys.* **117**, 599 (2004); **126**, 1109 (2006).
- [38] C. W. Gardiner, *Handbook of Stochastic Methods for Physics, Chemistry and the Natural Sciences*, 3rd ed. (Springer, Berlin, 2004).
- [39] D. T. Gillespie, *J. Comput. Phys.* **22**, 403 (1976).
- [40] D. T. Gillespie, *J. Phys. Chem.* **81**, 2340 (1977).
- [41] H. B. Callen, *Thermodynamics and an Introduction to Thermostatistics*, 2nd ed. (Wiley, New York, 1985).
- [42] E. Helfand, *Phys. Rev.* **119**, 1 (1960).
- [43] P. Gaspard, *New J. Phys.* **7**, 77 (2005).
- [44] D. Andrieux, P. Gaspard, S. Ciliberto, N. Garnier, S. Joubaud, and A. Petrosyan, *Phys. Rev. Lett.* **98**, 150601 (2007).
- [45] D. Andrieux, P. Gaspard, S. Ciliberto, N. Garnier, S. Joubaud, and A. Petrosyan, *J. Stat. Mech.: Theory Exp.* (2008), P01002.
- [46] P. Gaspard, *C. R. Phys.* **8**, 598 (2007).
- [47] M. Abramowitz and I. A. Stegun, *Handbook of Mathematical Functions* (Dover, New York, 1972).
- [48] L. Onsager and S. Machlup, *Phys. Rev.* **91**, 1505 (1953).
- [49] P. Gaspard, *Chaos, Scattering and Statistical Mechanics* (Cambridge University Press, Cambridge, UK, 1998).
- [50] G. Nicolis and C. Nicolis, *Foundations of Complex Systems* (World Scientific, New Jersey, 2007).