

Fluctuation theorem for nonequilibrium reactions

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A fluctuation theorem is derived for stochastic nonequilibrium reactions ruled by the chemical master equation. The theorem is expressed in terms of the generating and large-deviation functions characterizing the fluctuations of a quantity which measures the loss of detailed balance out of thermodynamic equilibrium. The relationship to entropy production is established and discussed. The fluctuation theorem is verified in the Schlögl model of far-from-equilibrium bistability.

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I. INTRODUCTION

Reacting systems can be driven out of equilibrium when in contact with several particle reservoirs or chemiostats generating fluxes of matter across the system. The fluxes are caused by the differences of chemical potentials between the chemiostats. Such an open system may be thought of as a reactor with inlets for reactants and an outlet for the products. In this case, the open system is driven out of equilibrium at the boundaries with the chemiostats. Even if detailed balance is satisfied for all the reactions in the bulk of the reactor, the nonequilibrium boundary conditions will break detailed balance for the reactions establishing the contact with the chemiostats. According to the second law of thermodynamics, the resulting nonequilibrium states are characterized by the production of entropy inside the open system.

Above the nanoscale, the reactions taking place in the system can be described in terms of the numbers of molecules of the different species. These numbers undergo random jumps on time scales longer than the time scale of the elementary reacting steps because of the randomness of the elastic and inelastic collisions among the molecules composing the system. The random jumps in the numbers of reacting particles form a stochastic process ruled by a master equation proposed in the seventies by Nicolis and coworkers¹⁻⁴. This master equation obeys a H -theorem, which leads to a mesoscopic expression for the entropy production in terms of probability distributions^{5,6}. In this theoretical framework, the master equation rules the relaxation of the probability distribution toward an invariant distribution called a *nonequilibrium steady state* even if the open system is driven far from equilibrium in a regime which would be identified as time-dependent in the macroscopic description. This invariant probability distribution describes the molecular fluctuations around the trajectory of the macroscopic (deterministic) time evolution.

In a stroboscopic observation at regular time intervals, the system randomly visit successive states, forming a path in the state space. The probability of such a path can be compared with the probability of the time-reversed path. If the system is at equilibrium, both probabilities are in balance on average since detailed balance holds. In contrast, if the system is driven out of equilibrium, the probabilities are no longer in balance. This nonequilibrium loss of balance manifests itself on average as well as for individual paths.

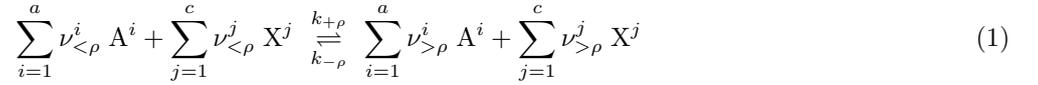
The purpose of the present paper is to show that the ratio of the forward- and backward-path probabilities decays on average according to the entropy production of the nonequilibrium reactions taking place in the open system and that, moreover, the large deviations of this ratio with respect to its average behavior obey a remarkable property called a *fluctuation theorem*. This result has its origins in recent work on a symmetry property for Markov stochastic processes obtained by Kurchan⁷, Lebowitz and Spohn⁸, as well as Maes⁹, who were inspired by previous work on dynamical chaos in the many-particle systems of statistical mechanics¹⁰⁻¹⁶. Here, our goal is to establish a fluctuation theorem for reactions in NESS including far-from-equilibrium situations. This fluctuation theorem is derived in the framework of the master equation by Nicolis and coworkers and is applied to a bistable far-from-equilibrium reaction.

The paper is organized as follows. Section II describes the theoretical framework used here for describing nonequilibrium reactions. The fluctuation theorem is obtained in Sec. III. In Sec. IV, the fluctuation theorem is applied to the Schlögl trimolecular model of bistability^{17,18}. Conclusions are drawn in Sec. V

II. STOCHASTIC APPROACH TO NONEQUILIBRIUM REACTIONS

A. Reaction as a stochastic process

We consider a network of reactions $\rho = 1, 2, \dots, r$:



involving the intermediate species $\{X^j\}_{j=1}^c$ and the species $\{A^i\}_{i=1}^a$ supplied at constant concentration by reservoirs, also called chemiostats. We impose that the reactions take place in a homogeneously system such as a continuously stirred tank reactor connected to the chemiostats. The system is assumed to be isothermal.

A reversed reaction is associated with each reaction so that each process can be balanced by the reversed process. An elementary event of the reaction $\rho \in \{\pm 1, \pm 2, \dots, \pm r\}$ changes the integer numbers $X^j \in \mathbb{N}$ of molecules of the intermediate species X^j by an amount equal to the stoichiometric coefficients

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

($j = 1, 2, \dots, c$). \mathbb{N} denotes the set of non-negative integer numbers.

We introduce the numbers of molecules of the different species X^j inside a fictitious boundary separating the reactor (i.e., the open system) from the chemiostats. We denote by $\mathbf{X} = \{X^j\}_{j=1}^c \in \mathbb{N}^c$ the vector of the numbers of molecules of the different species and by $\boldsymbol{\nu}_{\rho} = \{\nu_{\rho}^j\}_{j=1}^c$ the vector of the stoichiometric coefficients. An elementary event of the reaction ρ induces the random jump

$$\mathbf{X} \xrightarrow{\rho} \mathbf{X} + \boldsymbol{\nu}_{\rho} \quad (3)$$

with the transition rate $W_{\rho}(\mathbf{X}|\mathbf{X} + \boldsymbol{\nu}_{\rho})$. On the other hand, an elementary event of the reversed reaction $-\rho$ induces the random jump

$$\mathbf{X} \xrightarrow{-\rho} \mathbf{X} - \boldsymbol{\nu}_{\rho} \quad (4)$$

with the transition rate $W_{-\rho}(\mathbf{X}|\mathbf{X} - \boldsymbol{\nu}_{\rho})$.

The random jumps and the waiting times between the jumps can be generated by Gillespie's algorithm^{19,20}. If the system is in the state \mathbf{X} the next reaction ρ to occur is a random variable with probabilities

$$P_{\rho} = \frac{W_{\rho}(\mathbf{X}|\mathbf{X} + \boldsymbol{\nu}_{\rho})}{\sum_{\rho'=\pm 1}^{\pm r} W_{\rho'}(\mathbf{X}|\mathbf{X} + \boldsymbol{\nu}_{\rho'})} \quad (5)$$

while the waiting time τ is another random variable which is exponentially distributed with the probability density

$$p(\tau) = \kappa \exp(-\kappa\tau) \quad \text{with} \quad \kappa = \sum_{\rho'=\pm 1}^{\pm r} W_{\rho'}(\mathbf{X}|\mathbf{X} + \boldsymbol{\nu}_{\rho'}) \quad (6)$$

The successive jumps are statistically independent.

For reactions among diluted species, the transition rates are given by the mass-action law according to¹⁻⁴

$$W_{\rho}(\mathbf{X}|\mathbf{X} + \boldsymbol{\nu}_{\rho}) = \Omega k_{\rho} \prod_{i=1}^a [A^i]^{\nu_{<\rho}^i} \prod_{j=1}^c \frac{X^j}{\Omega} \frac{X^j - 1}{\Omega} \frac{X^j - 2}{\Omega} \dots \frac{X^j - \nu_{<\rho}^j + 1}{\Omega} \quad (7)$$

($\rho = \pm 1, \pm 2, \dots, \pm r$) where Ω is the so-called extensivity parameter which is proportional to the total number of particles in the open system, while k_{ρ} is the reaction coefficient. In the case the reaction ρ involves some species A^i supplied by a chemiostat, the transition rate is proportional to the product of the concentrations $[A^i]$ of the species A^i from the chemiostats.

B. Master equation

The master equation ruling the reactive stochastic process described here above is given by¹⁻⁴

$$\frac{d}{dt}P(\mathbf{X};t) = \sum_{\rho=\pm 1}^{\pm r} [W_{\rho}(\mathbf{X} - \boldsymbol{\nu}_{\rho}|\mathbf{X}) P(\mathbf{X} - \boldsymbol{\nu}_{\rho};t) - W_{-\rho}(\mathbf{X}|\mathbf{X} - \boldsymbol{\nu}_{\rho}) P(\mathbf{X};t)] \quad (8)$$

where $P(\mathbf{X};t)$ is the probability that the reactor contains the numbers \mathbf{X} of molecules of the intermediate species at time t . In Eq. (8), the sum over the reactions runs over both the direct and reversed reactions $\rho = \pm 1, \pm 2, \dots, \pm r$.

In general, the probabilities $P(\mathbf{X};t)$ relax in time toward stationary values $P_{\text{st}}(\mathbf{X})$, defining some nonequilibrium steady state (NESS) or the state of thermodynamic equilibrium.

In a stationary state, *detailed balance* is satisfied for reaction ρ if

$$W_{\rho}(\mathbf{X} - \boldsymbol{\nu}_{\rho}|\mathbf{X}) P_{\text{st}}(\mathbf{X} - \boldsymbol{\nu}_{\rho}) = W_{-\rho}(\mathbf{X}|\mathbf{X} - \boldsymbol{\nu}_{\rho}) P_{\text{st}}(\mathbf{X}) \quad (9)$$

If the system is closed, detailed balance holds for all the reactions $\rho \in \{\pm 1, \pm 2, \dots, \pm r\}$ and the stationary state becomes the equilibrium state $P_{\text{st}}(\mathbf{X}) = P_{\text{eq}}(\mathbf{X})$. If the system is open and in contact with out-of-equilibrium chemiostats, there is no detailed balance for the reactions involving the chemiostats. The loss of detailed balance is a consequence of the nonequilibrium boundary conditions imposed at the contacts of the reactor with the chemiostats.

C. Entropy production

The entropy of the open system in a state described by the probabilities $P(\mathbf{X};t)$ is given by

$$S(t) = \sum_{\mathbf{X}} S^0(\mathbf{X})P(\mathbf{X};t) - \sum_{\mathbf{X}} P(\mathbf{X};t) \ln P(\mathbf{X};t) \quad (10)$$

in units where Boltzmann's constant takes the unit value, $k_{\text{B}} = 1$. The first term of Eq. (10) is the average of the entropy $S^0(\mathbf{X})$ of a system with the fixed numbers \mathbf{X} of molecules due to the disorder in the degrees of freedom other than the numbers \mathbf{X} themselves. The second term of Eq. (10) is the contribution to entropy due to the probability distribution of these numbers \mathbf{X} of molecules, i.e., due to the disorder in the probability distribution of the numbers \mathbf{X} of molecules.

Nicolis and coworkers⁶ have proved the following H -theorem according to which the time variation of the entropy splits as

$$\frac{dS}{dt} = \frac{d_e S}{dt} + \frac{d_i S}{dt} \quad (11)$$

into the entropy flow $\frac{d_e S}{dt}$ and the entropy production $\frac{d_i S}{dt}$. If we define the reaction rates

$$J_{\rho}(\mathbf{X};t) \equiv W_{\rho}(\mathbf{X} - \boldsymbol{\nu}_{\rho}|\mathbf{X}) P(\mathbf{X} - \boldsymbol{\nu}_{\rho};t) - W_{-\rho}(\mathbf{X}|\mathbf{X} - \boldsymbol{\nu}_{\rho}) P(\mathbf{X};t) \quad (12)$$

and the reaction affinities

$$A_{\rho}(\mathbf{X};t) \equiv \ln \frac{W_{\rho}(\mathbf{X} - \boldsymbol{\nu}_{\rho}|\mathbf{X}) P(\mathbf{X} - \boldsymbol{\nu}_{\rho};t)}{W_{-\rho}(\mathbf{X}|\mathbf{X} - \boldsymbol{\nu}_{\rho}) P(\mathbf{X};t)} \quad (13)$$

associated with the reactions $\rho = \pm 1, \pm 2, \dots, \pm r$, the *entropy flow* is given by

$$\frac{d_e S}{dt} = \underbrace{\sum_{\mathbf{X},\rho} S^0(\mathbf{X}) J_{\rho}(\mathbf{X};t)}_{\frac{d_e S}{dt}} - \underbrace{\frac{1}{2} \sum_{\mathbf{X},\rho} J_{\rho}(\mathbf{X};t) \ln \frac{W_{\rho}(\mathbf{X} - \boldsymbol{\nu}_{\rho}|\mathbf{X})}{W_{-\rho}(\mathbf{X}|\mathbf{X} + \boldsymbol{\nu}_{\rho})}}_{\frac{d_i S}{dt}} \quad (14)$$

and the *entropy production* by

$$\frac{d_i S}{dt} = \frac{1}{2} \sum_{\mathbf{X},\rho} J_{\rho}(\mathbf{X};t) A_{\rho}(\mathbf{X};t) \geq 0 \quad (15)$$

The entropy flow (14) has a passive contribution $\frac{d'_e S}{dt}$ due to the simple advection of the entropy $S^0(\mathbf{X})$ and an active contribution $\frac{d''_e S}{dt}$ due to changes in the numbers \mathbf{X} of molecules.

Because of the inequality $(R_+ - R_-) \ln(R_+/R_-) \geq 0$, the entropy production (15) is always non-negative in agreement with the second law of thermodynamics^{5,6}. The entropy production vanishes at equilibrium because detailed balance (9) is then satisfied for all the reactions. Out of equilibrium, the entropy production is always positive.

We notice that the master equation (8) takes the form

$$\frac{d}{dt}P(\mathbf{X}; t) = \sum_{\rho} J_{\rho}(\mathbf{X}; t) \quad (16)$$

in terms of the reaction rates (12).

III. FLUCTUATION THEOREM

A. The fluctuating quantity Z

As aforementioned, the reactive process can be considered as a succession of random jumps

$$\begin{cases} \mathbf{X}_k = \mathbf{X}_{k-1} + \boldsymbol{\nu}_{\rho_k} \\ t_k = t_{k-1} + \tau_k \end{cases} \quad (17)$$

each occurring at some time t_k because of some reaction $\rho_k \in \{\pm 1, \pm 2, \dots, \pm r\}$. These random jumps are for instance generated by Gillespie's algorithm^{19,20}. The successive numbers of molecules \mathbf{X}_k form the *path*:

$$\mathcal{X}(t) = \mathbf{X}_0 \xrightarrow{\rho_1} \mathbf{X}_1 \xrightarrow{\rho_2} \mathbf{X}_2 \xrightarrow{\rho_3} \dots \xrightarrow{\rho_n} \mathbf{X}_n \quad (18)$$

with $0 < t_1 < t_2 < \dots < t_n < t$. In order to compare the probability of the path (18) with the probability of the time-reversed path

$$\mathcal{X}^R(t) = \mathbf{X}_n \xrightarrow{-\rho_n} \dots \xrightarrow{-\rho_3} \mathbf{X}_2 \xrightarrow{-\rho_2} \mathbf{X}_1 \xrightarrow{-\rho_1} \mathbf{X}_0 \quad (19)$$

we introduce the quantity

$$Z(t) \equiv \ln \frac{W_{\rho_1}(\mathbf{X}_0|\mathbf{X}_1) W_{\rho_2}(\mathbf{X}_1|\mathbf{X}_2) \dots W_{\rho_n}(\mathbf{X}_{n-1}|\mathbf{X}_n)}{W_{-\rho_1}(\mathbf{X}_1|\mathbf{X}_0) W_{-\rho_2}(\mathbf{X}_2|\mathbf{X}_1) \dots W_{-\rho_n}(\mathbf{X}_n|\mathbf{X}_{n-1})} \quad (20)$$

which is the analog for nonequilibrium reactions of the action functional defined by Lebowitz and Spohn for general jump processes⁸. The quantity (20) can be thought of as the logarithm of the ratio between the probabilities of the forward and backward paths given by Eqs. (18) and (19). Indeed, the probability of a given path is the product of the probabilities (5) of the individual reactive events composing the path. Accordingly, we have that

$$Z(t) \simeq \ln \frac{P_{\text{st}}[\mathcal{X}(t)]}{P_{\text{st}}[\mathcal{X}^R(t)]} \quad (21)$$

after a long enough time, where P_{st} denotes the stationary probability.

B. The fluctuation theorem in terms of the generating function

The generating function of the statistical moments of the quantity (20) is defined as

$$Q(\eta) \equiv \lim_{t \rightarrow \infty} -\frac{1}{t} \ln \langle e^{-\eta Z(t)} \rangle \quad (22)$$

where $\langle \cdot \rangle$ denotes the statistical average

$$\langle e^{-\eta Z(t)} \rangle = \sum_{\mathcal{X}(t)} P_{\text{st}}[\mathcal{X}(t)] e^{-\eta Z(t)} \quad (23)$$

with respect to the stationary probability distribution of the process, which satisfies the normalization condition

$$\sum_{\mathcal{X}(t)} P_{\text{st}}[\mathcal{X}(t)] = 1 \quad (24)$$

According to Eq. (21), the following equalities hold

$$\langle e^{-\eta Z(t)} \rangle \simeq \sum_{\mathcal{X}(t)} P_{\text{st}}[\mathcal{X}(t)] \left\{ \frac{P_{\text{st}}[\mathcal{X}^{\text{R}}(t)]}{P_{\text{st}}[\mathcal{X}(t)]} \right\}^{\eta} \quad (25)$$

$$= \sum_{\mathcal{X}(t)} P_{\text{st}}[\mathcal{X}^{\text{R}}(t)] \left\{ \frac{P_{\text{st}}[\mathcal{X}(t)]}{P_{\text{st}}[\mathcal{X}^{\text{R}}(t)]} \right\}^{1-\eta} \quad (26)$$

$$= \sum_{\mathcal{X}^{\text{R}}(t)} P_{\text{st}}[\mathcal{X}(t)] \left\{ \frac{P_{\text{st}}[\mathcal{X}^{\text{R}}(t)]}{P_{\text{st}}[\mathcal{X}(t)]} \right\}^{1-\eta} \quad (27)$$

$$\simeq \langle e^{-(1-\eta)Z(t)} \rangle \quad (28)$$

where the third equality uses the fact that summing over the time-reversed paths is the same as summing over the paths since both sums cover all the possible paths. If we substitute the result (28) in the generating function (22), we obtain the *fluctuation theorem* which states that

$$Q(\eta) = Q(1 - \eta) \quad (29)$$

A consequence of the fluctuation theorem (29) and of the definition (22) is that

$$Q(0) = Q(1) = 0 \quad (30)$$

Furthermore, the derivatives of the generating function at $\eta = 0$ and $\eta = 1$ are related to the mean growth rate of the quantity (20) according to

$$\frac{dQ}{d\eta}(0) = -\frac{dQ}{d\eta}(1) = \lim_{t \rightarrow \infty} \frac{1}{t} \langle Z(t) \rangle \quad (31)$$

C. The fluctuation theorem in terms of the large-deviation function

We now consider the large-deviation function

$$R(\zeta) \equiv \lim_{t \rightarrow \infty} -\frac{1}{t} \ln P_{\text{st}} \left[\frac{Z(t)}{t} \in (\zeta, \zeta + d\zeta) \right] \quad (32)$$

This function controls the exponential decay of the probability that the quantity $\frac{Z(t)}{t}$ takes its value in the interval $(\zeta, \zeta + d\zeta)$. Indeed, Eq. (32) is a consequence of the assumption that this probability behaves as

$$P_{\text{st}} \left[\frac{Z(t)}{t} \in (\zeta, \zeta + d\zeta) \right] = C(\zeta; t) e^{-R(\zeta)t} d\zeta \quad (33)$$

where $C(\zeta; t)$ varies with the time t less rapidly than an exponential:

$$\lim_{t \rightarrow \infty} -\frac{1}{t} \ln C(\zeta; t) = 0 \quad (34)$$

The large-deviation function (32) is related to the generating function (22) by the following calculation. Since we suppose that $Z(t) \simeq \zeta t$, the average (23) can be evaluated in terms of the probability (33) according to

$$\langle e^{-\eta Z(t)} \rangle = \int P_{\text{st}} \left[\frac{Z(t)}{t} \in (\zeta, \zeta + d\zeta) \right] e^{-\eta \zeta t} = \int C(\zeta; t) e^{-[R(\zeta) + \eta \zeta]t} d\zeta \quad (35)$$

By a steepest-descent integration, the generating function is thus obtained as

$$Q(\eta) = R[\zeta(\eta)] + \eta \zeta(\eta) \quad (36)$$

where $\zeta(\eta)$ is the solution of the implicit equation

$$\eta = -\frac{dR}{d\zeta}(\zeta) \quad (37)$$

The generating function is therefore given by the Legendre transform of the large-deviation function $R(\zeta)$.

Reciprocally, the large-deviation function is given by the Legendre transform of the generating function as

$$R(\zeta) = Q[\eta(\zeta)] - \zeta \eta(\zeta) \quad (38)$$

where $\eta(\zeta)$ is the solution of the implicit equation

$$\zeta = \frac{dQ}{d\eta}(\eta) \quad (39)$$

In the case the generating function $Q(\eta)$ is non-differentiable, the large-deviation function is given by

$$R(\zeta) = \max_{\eta} [Q(\eta) - \zeta \eta] \quad (40)$$

Since the generating function is convex downward, its Legendre transform $R(\zeta)$ is convex upward.

The fluctuation theorem (29) has for corollary that the large-deviation function (32) satisfies the identity

$$R(\zeta) - R(-\zeta) = -\zeta \quad (41)$$

As a further consequence, the ratio between the probabilities that $\frac{Z(t)}{t} \simeq \zeta$ and $\frac{Z(t)}{t} \simeq -\zeta$ behaves as

$$\frac{P_{\text{st}} \left[\frac{Z(t)}{t} \in (\zeta, \zeta + d\zeta) \right]}{P_{\text{st}} \left[\frac{Z(t)}{t} \in (-\zeta, -\zeta + d\zeta) \right]} \simeq e^{\zeta t} \quad \text{for } t \rightarrow +\infty \quad (42)$$

which is another form of the fluctuation theorem^{10–14}, here established for reactions in nonequilibrium steady states.

D. The fluctuation theorem and the entropy production

The relationship to the second law of thermodynamics and the entropy production is established as follows. We notice that the statistical average $\langle Z(t) \rangle$ of the quantity (20) over the path $\mathcal{X}(t)$ is given in terms of the active contribution to the entropy flow (14) as

$$\langle Z(t) \rangle \simeq - \int_0^t \frac{d_e'' S}{d\tau} d\tau \quad (43)$$

The reason is that the average of the quantity $Z(t)$ is the sum of the logarithms

$$\ln \frac{W_{\rho_k}(\mathbf{X}_{k-1}|\mathbf{X}_k)}{W_{-\rho_k}(\mathbf{X}_k|\mathbf{X}_{k-1})} \quad (44)$$

for the reactive events ρ_k occurring along the path $\mathcal{X}(t)$. The logarithms (44) are weighted by the probabilities of occurrence of the reactions ρ_k , which are given by the time integrals of the reaction rates (12) so that

$$\langle Z(t) \rangle \simeq \int_0^t \frac{1}{2} \sum_{\mathbf{X}, \rho} J_{\rho}(\mathbf{X}; \tau) \ln \frac{W_{\rho}(\mathbf{X} - \boldsymbol{\nu}_{\rho}|\mathbf{X})}{W_{-\rho}(\mathbf{X}|\mathbf{X} + \boldsymbol{\nu}_{\rho})} d\tau \quad (45)$$

By comparing with the definition of $\frac{d_e'' S}{dt}$ in Eq. (14), we get the result (43).

On the other hand, in a stationary state, the time variation of the entropy is vanishing so that

$$\frac{dS}{dt} = \underbrace{\frac{d_e S}{dt}}_{=0} + \frac{d_e'' S}{dt} + \frac{d_i S}{dt} = 0 \quad (46)$$

where the overline denotes the time average

$$\overline{(\cdot)} = \lim_{t \rightarrow \infty} \frac{1}{t} \int_0^t (\cdot) d\tau \quad (47)$$

Moreover, the time average of the passive contribution $\frac{d''S}{dt}$ to the entropy flow also vanishes since $\frac{d}{dt}P_{\text{st}} = \sum_{\rho} J_{\rho} = 0$ for a stationary state according to Eq. (16). Therefore, we find that, in a stationary state, the derivative (31) of the generating function is equal to the time average of the entropy production (15) whereupon

$$\zeta_0 = \frac{dQ}{d\eta}(0) = \lim_{t \rightarrow \infty} \frac{1}{t} \langle Z(t) \rangle_{\text{st}} = \overline{\frac{d_i S}{dt}} \Big|_{\text{st}} \geq 0 \quad (48)$$

The statistical average of the quantity (20) may thus be interpreted as the entropy irreversibly produced inside the open system along the path $\mathcal{X}(t)$, i.e., as the work dissipated along this path divided by the temperature.

According to Eqs. (37) and (38), we have that

$$R(\zeta_0) = 0 \quad \text{and} \quad \frac{dR}{d\zeta}(\zeta_0) = 0 \quad (49)$$

i.e., the large-deviation function presents a minimum at the value ζ_0 equal to the entropy production of the NESS.

We notice that both the generating and large-deviation functions identically vanish at the thermodynamic equilibrium where detailed balance is satisfied for all the reactions. Indeed, the probabilities of the forward and backward paths (18) and (19) are in balance at equilibrium, i.e., $P_{\text{eq}}[\mathcal{X}(t)] \sim P_{\text{eq}}[\mathcal{X}^{\text{R}}(t)]$ up to subexponential factors so that $Q(\eta) = R(\zeta) = 0$ at equilibrium. Therefore, the generating and large-deviation functions characterize the nonequilibrium properties of the reaction network.

E. Method of calculation

A method to compute the generating function (22) is to integrate the differential equations

$$\frac{d}{dt}G(\mathbf{X}; t) = \sum_{\rho=\pm 1}^{\pm r} [W_{\rho}(\mathbf{X} - \boldsymbol{\nu}_{\rho} | \mathbf{X})^{\eta} W_{-\rho}(\mathbf{X} | \mathbf{X} - \boldsymbol{\nu}_{\rho})^{1-\eta} G(\mathbf{X} - \boldsymbol{\nu}_{\rho}; t) - W_{-\rho}(\mathbf{X} | \mathbf{X} - \boldsymbol{\nu}_{\rho}) G(\mathbf{X}; t)] \quad (50)$$

for the conditional expectation values $G(\mathbf{X}; t)$ of $e^{-\eta Z(t)}$ given that the system is initially in the state \mathbf{X} , as shown by Lebowitz and Spohn⁸. By consistency with Eq. (22), these conditional expectation values should decay in time at a rate given by the generating function

$$G(\mathbf{X}; t) = \langle e^{-\eta Z(t)} \rangle_{\mathbf{X}} \sim e^{-Q(\eta) t} \quad (51)$$

which gives a practical way to calculate the generating function by numerically integrating Eq. (50). We notice that Eq. (50) reduces to the master equation (8) for $\eta = 1$ and to the adjoint equation for $\eta = 0$.

IV. APPLICATION TO A MODEL OF BISTABLE REACTION

In the present section, we apply the theory to a model of far-from-equilibrium bistability. We consider Schlögl's trimolecular reaction^{17,18}



The transition rates of the reactions are

$$\begin{aligned} W_{+1}(X|X+1) &= k_{+1} [\text{A}] \Omega \\ W_{-1}(X|X-1) &= k_{-1} X \\ W_{+2}(X|X-1) &= k_{+2} X \frac{X-1}{\Omega} \frac{X-2}{\Omega} \\ W_{-2}(X|X+1) &= k_{-2} [\text{B}] X \frac{X-1}{\Omega} \end{aligned} \quad (53)$$

The macroscopic kinetic equation for the concentration

$$[X] = \frac{1}{\Omega} \sum_{X=0}^{\infty} X P(X; t) \quad (54)$$

of the intermediate species X is given by

$$\frac{d}{dt}[X] = \underbrace{k_{+1}[A]}_{w_{+1}} - \underbrace{k_{-1}[X]}_{w_{-1}} - \underbrace{k_{+2}[X]^3}_{w_{+2}} + \underbrace{k_{-2}[B][X]^2}_{w_{-2}} \quad (55)$$

which is obtained from the master equation by neglecting the effects of fluctuations at $O(1/\Omega)$ in the limit $\Omega \rightarrow \infty$. In the same limit, the entropy production is given by

$$\frac{1}{\Omega} \frac{d_i S}{dt} \simeq \frac{d_i s}{dt} = (w_{+1} - w_{-1}) \ln \frac{w_{+1}}{w_{-1}} + (w_{+2} - w_{-2}) \ln \frac{w_{+2}}{w_{-2}} \geq 0 \quad (56)$$

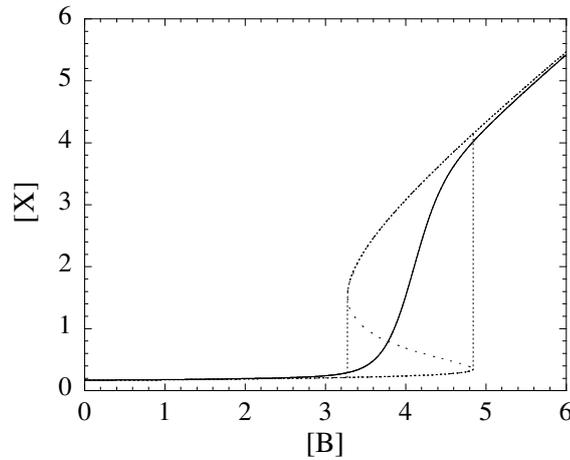


FIG. 1: Bifurcation diagram of the concentration $[X]$ versus the control concentration $[B]$ in the Schlögl model (52) for $k_{+1}[A] = 0.5$, $k_{-1} = 3$, and $k_{+2} = k_{-2} = 1$, obtained from the macroscopic equation (55) (dashed lines) and given by Eq. (54) in the stochastic description (solid line).

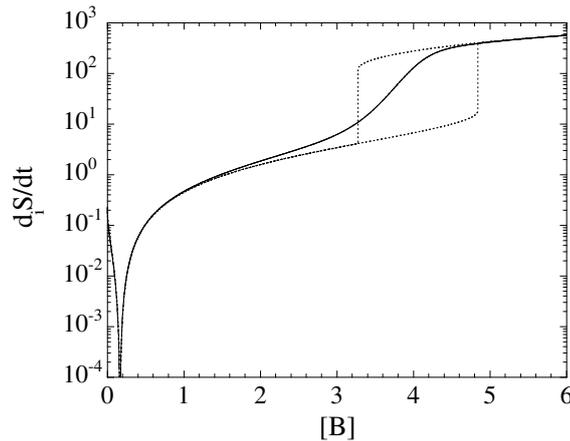


FIG. 2: Entropy production versus the control concentration $[B]$ in the Schlögl model (52) for $k_{+1}[A] = 0.5$, $k_{-1} = 3$, and $k_{+2} = k_{-2} = 1$, given by the macroscopic formula (56) (dashed lines) or by Eq. (15) in the stochastic description for $\Omega = 10$ (solid line). The thermodynamic equilibrium is located at $[B]_{\text{eq}} = \frac{1}{6}$.

The thermodynamic equilibrium corresponds to the state where detailed balance is satisfied

$$[X]_{\text{eq}} = \frac{k_{+1}}{k_{-1}} [A] = \frac{k_{-2}}{k_{+2}} [B]_{\text{eq}} \quad (57)$$

which relates the concentrations of the species A and B. As a consequence, the entropy production (56) vanishes at equilibrium.

In NESS', the concentration is solution of the cubic polynomial equation (55) with the stationary condition $\frac{d}{dt}[X]_{\text{st}} = 0$. Accordingly, the system may sustain two stable and one unstable steady states in some regime far from equilibrium. In the space of the control concentrations [A] and [B], the region of bistability forms a cusp located at the point:

$$[A]_{\text{cusp}} = \frac{k_{-1}}{3k_{+1}} \sqrt{\frac{k_{-1}}{3k_{+2}}} \quad (58)$$

$$[B]_{\text{cusp}} = \frac{\sqrt{3k_{-1}k_{+2}}}{k_{-2}} \quad (59)$$

Figure 1 depicts the bifurcation diagram of the concentration [X] as a function of the control concentration [B] across the region of bistability. The entropy production (56) is depicted in Fig. 2 in the same region. As expected, the entropy production vanishes at the thermodynamic equilibrium.

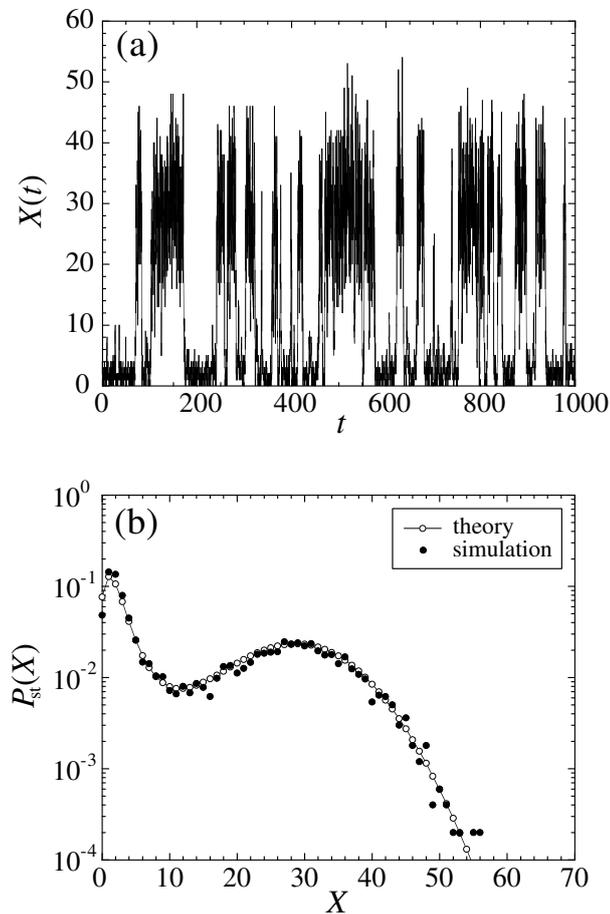


FIG. 3: (a) Stochastic time evolution of the number X of molecules of the intermediate species X , simulated with Gillespie's algorithm in the Schlögl model (52) for $k_{+1}[A] = 0.5$, $k_{-1} = 3$, $k_{+2} = k_{-2} = 1$, $[B] = 4$, and $\Omega = 10$. (b) Corresponding stationary probability distribution $P_{\text{st}}(X)$ of the intermediate species X obtained from the master equation (8) (open circles) and from the statistics of the stochastic simulation (a) (filled circles).

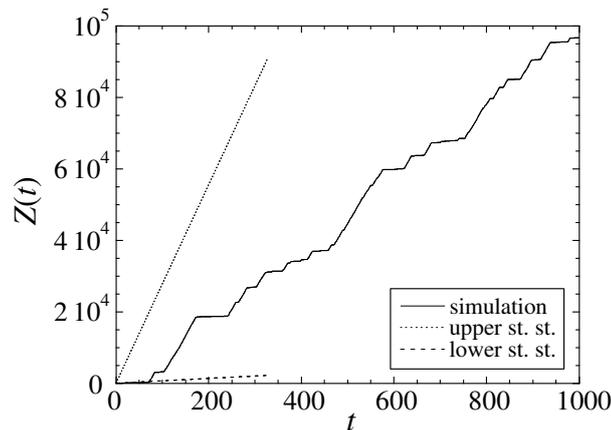


FIG. 4: Stochastic time evolution of the quantity $Z(t)$ for the trajectory of Fig. 3a, in the Schlögl model (52) with $k_{+1}[A] = 0.5$, $k_{-1} = 3$, $k_{+2} = k_{-2} = 1$, $[B] = 4$, and $\Omega = 10$. The increase of $Z(t)$ fluctuates between the entropy production rate of the lower (long-dashed line) and upper (dashed line) stationary macroscopic concentrations, in correlation with the jumps seen in Fig. 3a.

In the stochastic description based on the master equation (8) with the rates (53), the equilibrium state is described by the Poissonian distribution

$$P_{\text{eq}}(X) = \frac{e^{-\langle X \rangle_{\text{eq}}}}{X!} \langle X \rangle_{\text{eq}}^X \quad (60)$$

with $\langle X \rangle_{\text{eq}} = \Omega[X]_{\text{eq}}^4$.

Far from equilibrium, in the region of bistability, a stochastic trajectory simulated by Gillespie's algorithm performs random jumps between the low and high concentration states as depicted in Fig. 3a. Accordingly, the stationary probability distribution is bimodal as seen in Fig. 3b. The knowledge of the stationary probability distribution allows us to calculate the average concentration by Eq. (54) in the NESS and to compare it with the macroscopic value (see Fig. 1). In the region of monostability, the macroscopic concentration which is solution of Eq. (55) is very close to the average concentration calculated with Eq. (54). In the region of bistability, the macroscopic concentration presents a hysteresis while the average concentration (54) of the stochastic description interpolates between the low and high stationary macroscopic concentrations. The origin of the hysteresis in the macroscopic description holds in the fact that the macroscopic equation (55) describes the most probable states of the stochastic description, i.e., the concentrations corresponding to the maxima in the bimodal stationary probability distribution $P_{\text{st}}(X)$. Indeed, in the macroscopic limit $\Omega \rightarrow \infty$, this bimodal distribution becomes more and more peaked around the two stable stationary concentrations of Eq. (55) (see Fig. 1).

A similar comparison can be carried out between the entropy production of the stochastic description given by Eq. (15) and of the macroscopic description given by Eq. (56) (see Fig. 2). The entropy production vanishes at equilibrium. In the regions of monostability, the agreement between the stochastic and macroscopic descriptions is excellent. On the other hand, the region of bistability is characterized by a hysteresis in the macroscopic description. In this region, the entropy production of the stochastic description smoothly interpolates between the low and high entropy production of the two NESS' (see Fig. 2).

In the stochastic simulation with Gillespie's algorithm, the quantity $Z(t)$ is a fluctuating quantity which increases on average with time at a mean rate equal to the entropy production (56). At equilibrium, the entropy production vanishes so that the quantity $Z(t)$ fluctuates around a constant value. In the far-from-equilibrium region of bistability, the quantity $Z(t)$ presents successive regimes of increases at the two rates equal to the macroscopic entropy productions of the low and high stationary concentrations (see Fig. 4).

The generating function of the quantity $Z(t)$ has been computed by the method presented in Subsection III E and the result is depicted as a function of the parameter η in Fig. 5 for increasing values of the control concentration $[B]$. At the equilibrium (57), the generating function $Q(\eta)$ vanishes identically. Close to equilibrium, the generating function is very well approximated by the parabola

$$Q(\eta) \simeq \zeta_0 \eta(1 - \eta) \quad \text{for } 0 \leq \eta \leq 1 \quad (61)$$

with $\zeta_0 = \left. \frac{d_i S}{dt} \right|_{\text{st}}$. Far from equilibrium, the slopes at $\eta = 0$ and $\eta = 1$ are very steep because the entropy production is very large in these nonequilibrium regimes. In contrast, the maximum value $Q(\eta = \frac{1}{2})$ increases moderately so that

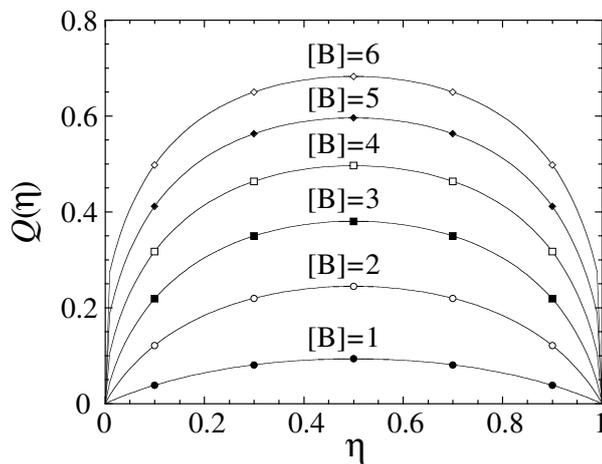


FIG. 5: Generating function (22) of the fluctuating quantity $Z(t)$ versus η in the Schlögl model (52) for $k_{+1}[A] = 0.5$, $k_{-1} = 3$, $k_{+2} = k_{-2} = 1$, $[B] = 1, 2, \dots, 6$, and $\Omega = 10$. We notice that $Q(\eta) = 0$ at the equilibrium $[B]_{\text{eq}} = \frac{1}{6}$.

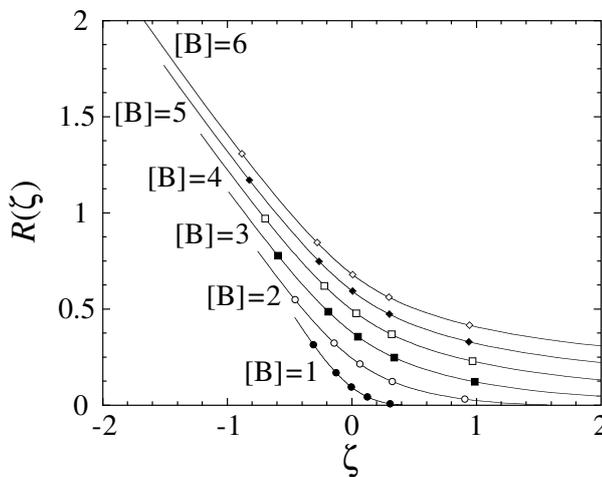


FIG. 6: Large-deviation function (32) of the fluctuating quantity $Z(t)$ versus ζ in the Schlögl model (52) for $k_{+1}[A] = 0.5$, $k_{-1} = 3$, $k_{+2} = k_{-2} = 1$, $[B] = 1, 2, \dots, 6$, and $\Omega = 10$ obtained by the numerical Legendre transform of the generating functions depicted in Fig. 5.

the generating function strongly deviate from the parabola (61) and presents strong nonlinearities. The bistability influences the generating function only to the extent that its slope at $\eta = 0$ and $\eta = 1$ steeply increases in the region of bistability. We observe in Fig. 5 that the fluctuation theorem (29) is remarkably satisfied. Thank to the algorithm described in Subsection III E, the equality (29) is verified in our numerical calculation with a precision of 6 digits and more.

The large-deviation function $R(\zeta)$ has been numerically calculated by Legendre transform according to Eqs. (38)-(39) and is depicted in Fig. 6. Close to equilibrium, the large-deviation function is very well approximated by the half parabola

$$R(\zeta) \simeq \frac{1}{4\zeta_0}(\zeta - \zeta_0)^2 \quad \text{with } \zeta \leq \zeta_0 \quad (62)$$

which is the Legendre transform of Eq. (61). In the far-from equilibrium regimes, we here also observe strong deviations with respect to the parabola (62). For $1 \ll \zeta < \zeta_0$, the large-deviation function becomes flatter and flatter as the entropy production ζ_0 increases: $R(\zeta) \simeq 0$. On the other, for $-\zeta_0 < \zeta \ll -1$, the large-deviation function tends to the straight line $R(\zeta) \simeq -\zeta$ as the entropy production ζ_0 increases. The fluctuation theorem (41) is also remarkably satisfied in terms of the large-deviation function $R(\zeta)$: the difference $R(\zeta) - R(-\zeta) + \zeta$ vanishes up to an error only due to the direct numerical derivative $\zeta \simeq \frac{\Delta Q}{\Delta \eta}$ used to perform the Legendre transform.

V. CONCLUSIONS

In this paper, we have derived a fluctuation theorem for nonequilibrium reactions. The fluctuation theorem is a symmetry property in the large fluctuations of the quantity (20) which measures the deviations with respect to detailed balance along a stochastic path followed by the reaction network. The fluctuations of $Z(t)$ are characterized by the generating function (22) of its moments and by its Legendre transform which is the large-deviation function (32). The consequences of microreversibility are therefore the symmetry properties Eq. (29) for the generating function, Eq. (41) for the large-deviation function, and Eq. (42) for the ratio between the probability of positive and negative deviations with respect to detailed balance. These symmetry relations are known under the name of fluctuation theorem. In a nonequilibrium steady state, the mean value of the quantity $Z(t)$ is given by the entropy production multiplied by the time interval t according to Eq. (48). Therefore, the fluctuation theorem here derived directly concerns the irreversible entropy production of the reactions evolving in the steady state.

The Yamamoto-Zwanzig formula giving the reaction rate as the integral of a time autocorrelation function^{21,22} as well as the Onsager reciprocity relations²³ can be deduced from the fluctuation theorem close to the thermodynamic equilibrium, as will be reported in future publication. A most remarkable feature of the symmetry relations of the fluctuation theorem is that they continue to hold far from the thermodynamic equilibrium, as we have here shown in the Schlögl model of bistability. We may therefore expect to obtain, in out-of-equilibrium regimes, general properties similar to the Yamamoto-Zwanzig formula and the Onsager reciprocity relations such as higher-order reciprocity relations.

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