Nonequilibrium fluctuation theorems from equilibrium fluctuations

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\textbf{Abstract.} A system can be driven to nonequilibrium behavior in the presence of thermodynamic imbalances in its environment, such as temperature or chemical potential differences. In derivations of far-from-equilibrium fluctuation theorems, such imbalances are typically modeled as fixed, externally imposed thermodynamic forces. Here, we argue that fluctuation theorems can instead be understood in terms of the \textit{equilibrium} dynamics of a larger supersystem, containing both the system of interest and its thermal surroundings. To this end, we consider rare fluctuations that spontaneously produce imbalances in the surroundings. In the aftermath of such fluctuations, the system of interest transiently behaves as though it were in the presence of an externally applied thermodynamic force. By applying the principle of detailed balance to these rare events, we recover the fluctuation theorem in both its transient and steady-state formulations.
1. Introduction

The disparity between our understanding of the behavior of systems in and out of thermal equilibrium is widely appreciated. Although a well-developed theory exists for systems in equilibrium, general statements regarding the dynamics of systems away from the equilibrium are scarce. A notable exception is the fluctuation theorem (FT) [1]. This term refers to a family of results, with similar structure (see equation (1) below), which describes the production of entropy in systems arbitrarily far from thermal equilibrium. The FT was first identified in computer simulations of sheared fluids [2]. Theoretical derivations for thermostated and stochastic systems soon followed [3–8], together with related predictions for the work performed on systems driven away from the equilibrium by an external agent [9, 10]. It was later appreciated that these results are closely related to an earlier body of research by Bochkov and Kuzovlev [11–14]; see [15–19] for detailed discussions.

The FT came as a surprise when it was discovered. It was described as ‘apparently bizarre’ [6] and ‘highly non-obvious’ [7], and its lack of adjustable parameters was noted [20]. Despite extensive research in this area, as summarized in numerous reviews [15–17, 21–32], relatively little attention has been paid to developing an intuitive understanding of why the FT holds. With the benefit of hindsight, should we have expected a result of this sort?

In this paper, we argue that the FT emerges naturally from the consideration of large fluctuations of a system in thermal equilibrium. Roughly speaking, if we wait sufficiently long for the system to spontaneously exhibit the nonequilibrium behavior in which we are
interested, then the principle of detailed balance, applied to these rare fluctuations, leads directly to equation (1). In somewhat more detail, the following picture emerges from our analysis.

FTs apply in contexts where a system is either maintained in a nonequilibrium state by a fixed, externally applied thermodynamic force, or else driven away from the equilibrium by the time-dependent manipulation of a mechanical parameter. In this paper, we will focus on the former case. We will use the term control variable, denoted by $x$, to refer to the applied thermodynamic force, and without loss of generality we take the value $x = 0$ to indicate the equilibrium situation. This control variable might be an externally maintained temperature difference or chemical potential difference, or the magnitude of shear flow imposed by appropriate boundary conditions in a numerical simulation [2], among other examples.

In modeling the microscopic evolution of the system of interest, the control variable typically appears as a fixed parameter of the dynamics: when $x = 0$ those dynamics satisfy detailed balance, and when $x \neq 0$ they do not. We will instead imagine that $x$ is itself a dynamic degree of freedom, and we will consider its equilibrium fluctuations. Specifically, we will embed our system of interest within a much larger ‘supersystem’, in which $x$ appears as a collective coordinate with large effective inertia. In the equilibrium, the control variable fluctuates mostly near the value $x = 0$, consequently the system of interest mostly exhibits equilibrium-like fluctuations. From time to time, however, the variable $x$ undergoes spontaneous fluctuations to unusually large (positive or negative) values, followed by relaxation back to zero. During such excursions, the system of interest transiently behaves as though it were out of equilibrium. By applying the principle of detailed balance to the relaxation of these rare equilibrium fluctuations of the supersystem, we will arrive at the nonequilibrium FT for the system of interest, in both its transient and steady-state forms.

In taking this approach, we adopt the point of view that a nonequilibrium steady state can be interpreted as a limiting instance of slow relaxation toward equilibrium. For instance, the steady-state conduction of heat through a metal bar whose ends are maintained at two different temperatures, can be described in terms of a larger system, consisting of the bar and two thermal reservoirs, relaxing slowly toward an eventual state in which all of the three bodies are at the same temperature. In the limit of reservoirs with infinite heat capacities, this ‘relaxation’ lasts forever.

Moreover, we assume that the slow process of relaxing toward the equilibrium does not depend on whether the initial state is prepared deliberately, or arises spontaneously from the thermal fluctuations of the larger system. Of course, the probability of observing a spontaneous fluctuation that would create a macroscopic temperature gradient is fantastically small. Nevertheless, as a point of principle we can imagine and analyze such a situation.

This perspective echoes Onsager’s comments, made in the context of heat conduction in a crystal (see [33, p 415]):

We also expect that an asymmetric distribution of energy will be exactly the same whether it has arisen accidentally from fluctuations or has been produced purposely by means of suitable external heating and cooling. Once a given distribution of energy is present its history is immaterial, but . . . the distribution that is present at any given time determines an average expectancy for the rates of the subsequent changes.

By following this line of thought, Onsager [33, 34] obtained his classic derivation of the reciprocal relations. Since he was interested in linear response coefficients, Onsager restricted his attention to suitably small fluctuations. Stratonovich [35, 36] later dropped this restriction,
thereby deriving a set of higher-order relations that effectively extend Onsager’s results to the nonlinear, far-from-equilibrium regime. Bochkov and Kuzovlev [11, 12] adopted a similar perspective in applying their generalized fluctuation–dissipation relations to nonlinear oscillator circuits [37, 38] as well as hydrodynamic fluctuations [39, 40]. Independently, nonlinear generalizations of Onsager’s approach were obtained by Grabert and Green [41], using a variational approach, and by Hänggi [42], using a generalized detailed balance symmetry. Nonlinear Onsager relations have also been obtained in the specific contexts of chemical reactions, by Grabert et al [43], and hydrodynamic fluctuations, by Shneidman and Hänggi [44].

In the present paper, we will continue in this tradition. As indicated above our analysis of rare fluctuations will lead directly to the TFT and the SSFT.

Although we believe our conclusions are quite general, we will analyze the specific case of a system that makes stochastic jumps among \( n \) microscopic states, governed by a transition matrix that gives rise to a nonequilibrium steady state. This is the setting considered by Lebowitz and Spohn [7], in their derivation of a SSFT for discrete Markov processes. We will map this model onto a hypothetical chemical reaction system involving a single, \( n \)-state enzyme molecule immersed in a dilute solution of substrate molecules of various chemical species. The enzyme causes interconversions among the substrates. This larger supersystem (enzyme + substrates) is assumed to be in equilibrium, and therefore satisfies detailed balance. By considering the behavior of the enzyme during those rare fluctuations in which the substrate concentrations stray substantially far from their typical equilibrium values, we will recover the FT.

Several extensions of Onsager’s ideas, or of Onsager–Machlup theory [45], to nonequilibrium systems have appeared in the recent literature. In their macroscopic fluctuation theory Bertini et al [46] show that an emerging spontaneous fluctuation in a nonequilibrium system is the time reversal of the corresponding relaxation in an adjoint process. (See also [47] for a review.) Maes and Netočný [48] have expressed the large deviation function of a nonequilibrium process as a sum of contributions from a reference equilibrium process and an additional local driving field. In these papers one modifies Onsager’s theory so that it will hold for systems away from thermal equilibrium. In contrast, in the current approach it is not Onsager’s theory which is modified but rather the system, which becomes embedded in a supersystem whose equilibrium fluctuations become the object of our attention.

In section 2, we review the FT for discrete Markov processes, introducing the notation and nomenclature we will use in the remainder of the paper. In section 3, we illustrate our analysis in the context of a simple three-state system, showing that both the TFT and the SSFT for this system can be obtained by consideration of the equilibrium fluctuations of a larger supersystem. In section 4, we extend these results to arbitrary \( n \)-state Markov processes. We end with a brief discussion in section 5.

2. Background and notation

In section 2 of [7], Lebowitz and Spohn—building on previous work by Gallavotti and Cohen [4, 5] and Kurchan [6]—derived an FT for continuous time Markov jump processes. The setting is abstract, and consequently quite general. A system jumps randomly among \( n \) states. The jump rates are collected in a fixed transition matrix \( r^0 \), whose off-diagonal element \( r^0_{ij} \geq 0 \) gives the probability rate to make a jump to state \( j \), starting from state \( i \). The diagonal elements are given by \( r^0_{ii} = -\sum_{j \neq i} r^0_{ij} \), and the probability distribution \( p(t) = (p_1, p_2, \ldots, p_n)^T \) satisfies
the master equation
\[ \frac{dp}{dt} = r^0 p. \]  
(2)

Some of the rates \( r^0_{ij} \) may be equal to zero, indicating that the corresponding transitions are not allowed. Two constraints are imposed on \( r^0 \). Firstly, if \( r^0_{ij} > 0 \), then also \( r^0_{ji} > 0 \), for any \( i \neq j \). Secondly, for any pair of states \( i \) and \( j \), there exists some path of allowed transitions connecting \( i \) to \( j \). Under these conditions, the dynamics support a unique steady state \( \pi \), satisfying
\[ r^0 \pi = 0. \]  
(3)

For future convenience, let
\[ J^S_{ij} ≡ r^0_{ij} \pi_j - r^0_{ji} \pi_i \]  
(4)
de note the average probability current from state \( j \) to state \( i \), in the steady state. We assume that the dynamics encoded by \( r^0 \) violate detailed balance (see e.g. equation (10)), hence, \( \pi \) represents a genuinely nonequilibrium steady state, with \( J^S_{ij} \neq 0 \) for some pairs of microstates.

If we observe this process over a time interval from \( t = 0 \) to \( \tau \), then the trajectory followed by the system can be represented symbolically:
\[ γ ≡ i_0 \rightarrow i_1 \rightarrow i_2 \rightarrow \cdots \rightarrow i_K, \]  
(5)

where the \( i_k \)'s represent the states visited by the system, and the \( t_k \)'s are the times at which jumps occurred during this interval. For this trajectory, let us consider a quantity
\[ \Delta S_m[γ] = \sum_{k=1}^{K} \delta S_m(i_{k-1} \rightarrow i_k), \]  
(6)

where
\[ \delta S_m(i \rightarrow j) = \ln \frac{r^0_{ji}}{r^0_{ij}}. \]  
(7)

Within the framework of stochastic thermodynamics [32, 49], \( \delta S_m(i \rightarrow j) \) is interpreted as the change in the entropy of the surrounding medium when the system makes a jump from state \( i \) to state \( j \) [16]. \( \Delta S_m[γ] \) is then the net entropy produced in the medium over the entire interval \( 0 < t < \tau \).

Now, let \( p^\text{NESS}_\tau(\Delta S_m) \) denote the probability distribution to observe a medium entropy production \( \Delta S_m \), during a time interval of duration \( \tau \) in the nonequilibrium steady state. This distribution obeys the symmetry relation
\[ \frac{p^\text{NESS}_\tau(+\Delta S_m)}{p^\text{NESS}_\tau(-\Delta S_m)} \sim e^{\Delta S_m}, \]  
(8)

where \( \sim \) denotes that this result becomes valid asymptotically, as \( \tau \rightarrow \infty \). More precisely, the time-averaged entropy production, \( \zeta = \Delta S_m/\tau \), obeys
\[ \lim_{\tau \rightarrow \infty} \frac{1}{\tau} \ln \frac{p^\text{NESS}_\tau(+\zeta)}{p^\text{NESS}_\tau(-\zeta)} = \zeta. \]  
(9)

This is the SSFT for this jump process. It is essentially a large deviation result, elegantly obtained from a symmetry property of the corresponding generating function [7]. A transient version of
the FT—first derived by Evans and Searles [3] for deterministic dynamics—holds for any value of $\tau$. 

The Markov jump process just described is abstract, and equation (9) is a meaningful mathematical result quite apart from any physical interpretation. In this paper, however, we aim to develop a physically motivated understanding of FTs, by showing that they follow from the equilibrium fluctuations of an appropriately defined supersystem. To accomplish this, we must connect the formal Markov process to an underlying physical system. 

Inspired by the work of Gaspard and co-workers [50–53] and Schmiedl and Seifert [54], we will consider an idealized chemical system whose dynamics obey a Markov jump process. We first introduce a nonequilibrium system of interest (NS) with $n$ discrete states, which obeys the FT, equation (9). We then separately consider an equilibrium supersystem (ES) that consists of an enzyme molecule with $n$ distinct conformations, interacting with a chemical bath of substrate molecules. We argue that, in the appropriate limit, the nonequilibrium dynamics of the former system emerge from the equilibrium dynamics of the latter; in effect, the enzyme molecule in solution mimics the nonequilibrium behavior of our original system of interest. With this identification in place, the FT for the nonequilibrium system follows as a natural consequence of detailed balance for the ES. We first obtain our results for a simple system with $n = 3$ states, deferring a more general treatment to section 4.

3. Three-state example

Consider the three-state system depicted in figure 1. The vertices of the triangle represent the states, and the edges represent bi-directional transitions, with rates given by a fixed transition matrix $r^0$. This graph contains a single cycle (closed loop), to which we assign a directionality by defining clockwise transitions ($1 \rightarrow 2 \rightarrow 3 \rightarrow 1$) to constitute a positive current. We explicitly assume that the affinity [52] associated with this cycle is nonzero,

$$A^0_c \equiv \ln \frac{r^0_{32} r^0_{21} r^0_{13}}{r^0_{23} r^0_{12} r^0_{31}} \neq 0,$$

hence the stationary solution associated with these dynamics supports a nonzero current, $J^S_c = J^S_{32} = J^S_{21} = J^S_{13} \neq 0$, with $\text{sign}(J^S_c) = \text{sign}(A^0_c)$. This three-state system is our NS. If we observe this system over an interval of duration $\tau$, then the entropy production in the medium is...
given by
\[ \Delta S_m = \nu \mathcal{A}_c^0, \]  
where \( \nu \) is the net number of clockwise excursions around the cycle\(^4\). Therefore, the SSFT for this system reads
\[ \lim_{\tau \to \infty} \frac{1}{\tau} \ln \frac{p_{\text{ess}}^\tau (+\omega)}{p_{\text{ess}}^\tau (-\omega)} = \omega \mathcal{A}_c^0, \]  
where
\[ \omega = \frac{\nu}{\tau} \]  
is the time-averaged rate of clockwise circulation.

Now let us consider another process, involving a larger and more explicitly ‘physical’ supersystem, with the idea that the dynamics of NS will emerge from those of the supersystem. Imagine a single molecule with three distinct conformational states, \( i = 1, 2, 3 \), in one-to-one correspondence with the three states of NS. This molecule, \( M \), is immersed in a solution that also contains two substrate species, \( A \) and \( B \). These are present in large numbers, \( N_A, N_B \gg 1 \), but at dilute concentrations, hence their chemical potentials are given by
\[ \mu_k = \mu_k^0 + \beta^{-1} \ln \frac{N_k}{V}, \quad k = A, B, \]  
where \( \beta^{-1} \) is the temperature of the solution. For convenience we will take the reference state chemical potentials of the substrates to be identical,
\[ \mu_A^0 = \mu_B^0, \]  
so that in equilibrium the concentrations of the substrates are equal, \( [A]^{\text{eq}} = [B]^{\text{eq}} \). Without this simplifying assumption, our analysis would be more cumbersome, but the central conclusion would remain the same.

We assume that \( M \) makes thermally activated transitions between states 1 and 2, and between states 1 and 3, without the involvement of either substrate. However, every jump from 2 to 3 is accompanied by the conversion of one \( A \) molecule to a \( B \) molecule, and vice versa for the reverse transition; see figure 2. Thus \( M \) acts as a catalyst for the interconversion between the two substrate species.

If the substrate concentrations were externally maintained at fixed but unequal values, \( [A] \neq [B] \), by appropriately adding and removing substrate molecules, then the enzyme would settle into a nonequilibrium steady state. For instance, a fixed surplus of \( A \)'s would induce clockwise transitions around the cycle. However, we will instead treat the enzyme molecule \( M \), the bath of substrates \( A \) and \( B \), and the surrounding solvent (e.g. water) as a large, closed ES, with a fixed total number of substrate molecules, \( N_A + N_B \). This supersystem is characterized by an equilibrium probability distribution
\[ P^{\text{eq}}(i, N_A, N_B) \propto e^{-\beta \varepsilon_i} \frac{N!}{N_A!N_B!} \delta_{N_A+N_B}, \]  
\(^4\) Strictly speaking, equation (11) applies only if the system begins and ends in the same state, but this caveat becomes irrelevant in the limit \( \tau \to \infty \).
Figure 2. The FT can be related to detailed balance by embedding the three-state molecule in a larger supersystem. The molecule is placed in a closed vessel with two species of substrate molecules $A$ and $B$, denoted by stars (\textasteriskcentered) and circles (\textcircled{}), respectively. One of the transitions of the enzyme molecule is coupled with a chemical reaction $A \leftrightarrow B$. If the system is left alone in the closed vessel it will eventually reach thermal equilibrium. A nonequilibrium steady state is achieved by externally fixing the substrate concentrations.

where $\varepsilon_i$ is the (free) energy of the enzyme molecule in state $i \in \{1, 2, 3\}$, and the Kronecker delta function constrains the total number of substrate molecules to be fixed at $N$. By the principle of detailed balance, the transition rates for this supersystem obey:

$$
\frac{R(1, N_A, N_B \rightarrow 2, N_A, N_B)}{R(1, N_A, N_B \leftarrow 2, N_A, N_B)} = \frac{P_{\text{eq}}(2, N_A, N_B)}{P_{\text{eq}}(1, N_A, N_B)} = e^{-\beta(\varepsilon_2 - \varepsilon_1)},
$$

$$
\frac{R(1, N_A, N_B \rightarrow 3, N_A, N_B)}{R(1, N_A, N_B \leftarrow 3, N_A, N_B)} = \frac{P_{\text{eq}}(3, N_A, N_B)}{P_{\text{eq}}(1, N_A, N_B)} = e^{-\beta(\varepsilon_3 - \varepsilon_1)},
$$

$$
\frac{R(2, N_A, N_B \rightarrow 3, N_A^-, N_B^+)}{R(2, N_A, N_B \leftarrow 3, N_A^-, N_B^+)} = \frac{P_{\text{eq}}(3, N_A^-, N_B^+)}{P_{\text{eq}}(2, N_A, N_B)} = e^{-\beta(\varepsilon_3 - \varepsilon_2)} \frac{N_A}{N_B^+},
$$

where the arrows indicate the directions of the transitions, and we have introduced the compact notation $N_A^- \equiv N_A - 1$ and $N_B^+ \equiv N_B + 1$. In each of the three lines in equation (16), the first equality expresses the condition of detailed balance, applied to a given pair of transitions, and the second equality follows from equation (15).

These transition rates describe a Markov jump process along a linear chain consisting of $3(2N + 1)$ states, illustrated in figure 3. Let us now define an order parameter

$$
x = \frac{N_A - N_B}{N},
$$

in terms of which the equilibrium distribution in equation (15) can be rewritten as

$$
p_{\text{eq}}(i, x) \propto e^{-\beta \varepsilon_i - N \phi(x)},
$$

with

$$
\phi(x) = \frac{1 + x}{2} \ln \left(\frac{1 + x}{2}\right) + \frac{1 - x}{2} \ln \left(\frac{1 - x}{2}\right),
$$

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Figure 3. Network of $3(2N+1)$ states describing a single three-state enzyme molecule $M$ interacting with a total of $N$ substrate molecules. Each box corresponds to a particular balance between $A$ and $B$ substrate molecules, and therefore a particular order parameter value $x$. The connectivity reflects the catalytic action of $M$ discussed in the text.

as obtained by the application of Stirling’s approximation to the binomial distribution in equation (15). The function $\phi(x)$ is convex ($\phi'' > 0$) with a minimum at $x = 0$, and $\beta^{-1}N\phi(x)$ is a potential of mean force. On summing over the states $i$, the equilibrium distribution of $x$ is given by

$$p_{eq}^{x}(x) \propto e^{-N\phi(x)}.$$  

(20)

By introducing this order parameter, we can effectively reduce the dynamics of our supersystem to that of a three-state system $M$ interacting with a quasi-continuous variable $x$. The former makes transitions described by a $3 \times 3$ rate matrix $r(x)$, and the value of $x$ in turn is updated by a small amount every time $M$ makes a transition from 2 to 3 or vice versa. Equation (16) places the following constraints on the elements of $r(x)$, to leading order in $N^{-1}$:

$$\frac{r_{21}}{r_{12}} = e^{-\beta(\epsilon_2 - \epsilon_1)}, \quad \frac{r_{31}}{r_{13}} = e^{-\beta(\epsilon_3 - \epsilon_1)}, \quad \frac{r_{32}}{r_{23}} = e^{-\beta(\epsilon_3 - \epsilon_2)} \frac{1 + x}{1 - x}.$$  

(21)

Since $N \gg 1$, there is a separation of timescales: $M$ makes many transitions among its three states before the value of $x$ changes substantially. In view of this, let us define an $x$-dependent affinity,

$$A_c(x) \equiv \ln \frac{r_{32}r_{21}r_{13}}{r_{23}r_{12}r_{31}} = \ln \frac{1 + x}{1 - x} = 2 \frac{\partial \phi}{\partial x} = \frac{\beta N_A}{N_B} = \beta(\mu_A - \mu_B).$$  

(22)

Unlike the fixed affinity $A_0^s$ associated with the NS (equation (10)) the value of $A_c$ fluctuates with time, reflecting the evolving balance between the substrate concentrations. In agreement with Le Châtelier’s principle, the affinity $A_c$ acts as a restoring force: when $x > 0$ this affinity is positive (equation (22)), therefore it drives the catalysis of $A’s$ to $B’s$, which in turn reduces the value of $x$; analogous comments apply when $x < 0$. Thus, as the enzyme $M$ converts $A’s$ to $B’s$ and vice versa, the variable $x$ typically fluctuates near the minimum of $\phi(x)$, at $x = 0$, occasionally making larger excursions up either the left slope or the right slope of the potential of mean force. The further the system strays from the minimum, the greater the magnitude of the force $A_c(x)$ pulling it back toward a state of balance between the substrates. In the following two paragraphs, we will derive a result that describes the evolution of the catalyst molecule $M$, following a large, equilibrium fluctuation of the order parameter (equation (27)). We will then
relate this result directly to the evolution of $M$ under nonequilibrium conditions corresponding to externally fixed substrate concentrations (equation (29)).

For a time interval of duration $\tau$, let $p_\tau^{\text{eq}}(x^1|x^0)$ denote the conditional probability to observe a particular final value of the order parameter, $x^1$, given an initial value, $x^0$. To be more precise, consider an infinitely long equilibrium trajectory of the supersystem, divided into consecutive segments of duration $\tau$, and now imagine discarding all of the segments except those for which the order parameter takes on a given initial value $x^0$. We will use the term conditioned ensemble to refer to the remaining ensemble of trajectory segments, and the probability $p_\tau^{\text{eq}}(x^1|x^0)$ is defined with respect to this conditioned ensemble.

Owing to the separation of the timescales mentioned above, we can view the evolution of $x$ as a Markov process. The condition of detailed balance then gives us

$$
p_\tau^{\text{eq}}(x^1|x^0) = \frac{p^{\text{eq}}(x^1)}{p^{\text{eq}}(x^0)} = \frac{\exp[-N\phi(x^1)]}{\exp[-N\phi(x^0)]} \approx \exp[vA_c(x^0)],
$$

where

$$
v = \frac{N}{2}(x^0 - x^1)
$$

is the net number of $A$-to-$B$ conversions during this interval. The first equality in equation (23) is a statement of detailed balance for the variable $x$; the second equality follows from equation (20); and in the last step we have used equation (22) and assumed $|x^1 - x^0| \ll 1$. By replacing $x^1$ with $x^0 - 2v/N$, we can reformulate the approximation in equation (23) as a limit:

$$
\lim_{N \to \infty} \frac{p_\tau^{\text{eq}}(x^0 - \frac{2v}{N} | x^0)}{p_\tau^{\text{eq}}(x^0 | x^0 - \frac{2v}{N})} = \lim_{N \to \infty} \frac{\exp[-N\phi(x^0 - \frac{2v}{N})]}{\exp[-N\phi(x^0)]} = \exp[vA_c(x^0)]
$$

with $\tau$, $v$ and $x^0$ held fixed. If we now let $p_\tau^{\text{eq}}(v | x)$ denote the probability of observing a net number $v$ of $A$-to-$B$ conversions during an interval of duration $\tau$, conditioned on the initial order parameter value, then equation (25) becomes

$$
\lim_{N \to \infty} \frac{p_\tau^{\text{eq}}(+v | x^0)}{p_\tau^{\text{eq}}(-v | x^0 - \frac{2v}{N})} = \exp[vA_c(x^0)].
$$

Equivalently,

$$
\lim_{N \to \infty} \frac{p_\tau^{\text{eq}}(+v | x^0)}{p_\tau^{\text{eq}}(-v | x^0)} = \exp[vA_c(x^0)].
$$

We emphasize that equation (27) describes equilibrium dynamics during a finite time interval, in the aftermath of an unusually large, spontaneous fluctuation away from the typical balance of substrate concentrations. We have obtained this result directly from the principle of detailed balance. Although fluctuations of this magnitude become vanishingly rare as $N \to \infty$ (for any fixed $x^0 \neq 0$), the conditional probability $p_\tau^{\text{eq}}(v | x^0)$ remains well defined and finite, in this limit. Let us now establish a connection between this result (equation (27)) and the nonequilibrium behavior of $M$ under fixed substrate concentrations.

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5 We assume that the volume of the vessel in figure 2 scales with $N$, so that the total concentration of the substrate molecules remains constant as we take this limit.
In the conditioned ensemble of equilibrium trajectory segments, defined above, the initial state of the molecule $M$ satisfies
\[ p_i(0) \propto e^{-\beta \epsilon_i}, \tag{28} \]
by equation (18). The order parameter begins at the definite value $x^0$, by construction, and then it fluctuates as the $A$'s are converted to $B$'s and vice versa. In the limit $N \to \infty$ these fluctuations become negligible over the finite interval $0 \leq t \leq \tau$, hence the order parameter effectively remains fixed at $x^0$. The dynamics of $M$ then become statistically identical to its dynamics in the case when the substrate concentrations are externally maintained at fixed values. In other words,
\[ \lim_{N \to \infty} p_{\tau}^{\text{eq}}(v | x^0) = \lim_{N \to \infty} p_{\tau}^{\text{neq}}(v), \tag{29} \]
where $p_{\tau}^{\text{neq}}(v)$ is defined as the probability to observe $v$ net conversions from $A$ to $B$ over an interval of duration $\tau$, at fixed substrate concentrations corresponding to the order parameter value $x^0$, with the initial conditions for $M$ sampled from the equilibrium (equation (28)). Choosing $x^0$ so that $A_c(x^0) = A_c^0$ (see equation (10)) and by combining equations (27) and (29), we obtain
\[ \lim_{N \to \infty} \frac{p_{\tau, x^0}^{\text{neq}}(v)}{p_{\tau, x^0}^{\text{neq}}(-v)} = \exp[v A_c^0]. \tag{30} \]
In the remaining paragraphs of this section, the limit $N \to \infty$ will be assumed.

Equation (30) is the TFT, and is valid for any $\tau > 0$. It pertains to evolution under fixed, nonequilibrium dynamics, with initial conditions for the system of interest drawn from the equilibrium: $p_i(0) \propto e^{-\beta \epsilon_i}$. These dynamics obey the master equation $\dot{p} = r^0 p$ (equation (2)), with the matrix $r^0$ corresponding to the fixed value $x^0 \neq 0$. Although the system begins in equilibrium at $t = 0$, it subsequently relaxes toward a unique nonequilibrium steady state $\pi$ (equation (3)), over a characteristic timescale $t_{\text{rel}}$.

The steps that we have taken to arrive at equation (30) may seem like an overly complicated derivation of the TFT, which indeed follows more easily from the analysis of the fixed transition matrix $r^0$. However, in taking these steps we have shown, for this simple three-state example, that the TFT follows from the equilibrium fluctuations of the supersystem, evaluated in the appropriate limit.

In order to make contact with the SSFT, we now assume that $\tau \gg t_{\text{rel}}$, so that after an initial transient the molecule $M$ spends most of the interval $0 \leq t \leq \tau$ in the steady state. In this case, intuition suggests that the statistics of medium entropy production, $\Delta S_m = v A_c^0$ (see equation (11)), are dominated by the steady-state behavior, i.e.
\[ p_{\tau, x^0}^{\text{neq}}(v) \approx p_{\tau, x^0}^{\text{ness}}(v). \tag{31} \]
Here, $p_{\tau, x^0}^{\text{ness}}$ is defined exactly as $p_{\tau, x^0}^{\text{neq}}$, except that $M$ begins (and remains) in the nonequilibrium steady state, $p(0) = \pi$, rather than in equilibrium (equation (28)).

To proceed from this intuition to the SSFT, let us consider the probability distributions of the quantity $\omega = v/\tau$ (see equation (13)), rather than the distributions of $v$. We can express these distributions as follows:
\[ p_{\tau, x^0}^{\text{neq}}(\omega) = \sum_{i=1}^{3} p_{\tau, x^0}^{\text{eq}}(\omega | i), \quad p_{\tau, x^0}^{\text{ness}}(\omega) = \sum_{i=1}^{3} \pi_i p_{\tau, x^0}(\omega | i), \tag{32} \]
where $p_{\tau,x^0}(\omega|i)$ is the probability distribution of $\omega$, conditioned on the initial microscopic state of $M$. On defining $f_i \equiv \pi_i / p_i^{eq} > 0$, we have

$$p_{\text{ness}}^{\tau,x^0}(\omega) = \sum_i q_i(\omega, \tau) f_i = \bar{f}(\omega, \tau),$$

where

$$q_i(\omega, \tau) = \frac{p_i^{eq} p_{\tau,x^0}(\omega|i)}{\sum_j p_j^{eq} p_{\tau,x^0}(\omega|j)}.$$  

(34)

Since $q_i \geq 0$ and $\sum_i q_i = 1$ (for any $\omega, \tau$), we can view $\bar{f}(\omega, \tau)$ as an average of $f_i$ with respect to a probability distribution $q_i(\omega, \tau)$. Therefore,

$$\min_i \{f_i\} \leq \bar{f}(\omega, \tau) \leq \max_i \{f_i\}.  \tag{35}$$

By combining equations (30), (33) and (35), we obtain

$$\lim_{\tau \to \infty} \frac{1}{\tau} \ln p^{\text{ness}}_{\tau,x^0}(+\omega) = \lim_{\tau \to \infty} \frac{1}{\tau} \ln \left[ \frac{p^{\text{ness}}_{\tau,x^0}(+\omega)}{p^{\text{ness}}_{\tau,x^0}(-\omega)} \frac{\bar{f}(+\omega, \tau)}{\bar{f}(-\omega, \tau)} \right] = \omega A^0_c,$$  

(36)

which is the SSFT for this three-state model (equation (12)).

For this simple three-state system, we have obtained both the TFT and the SSFTs by first applying detailed balance to the equilibrium fluctuations in the supersystem, and then taking the limits $N \to \infty$ and $\tau \to \infty$. These limits do not commute, and their order is important. The limit $N \to \infty$, which allows us to identify the conditioned equilibrium fluctuations of ES with the stationary, nonequilibrium dynamics of NS, must be taken first, at finite $\tau$.

By embedding our three-state system within a larger supersystem, we have effectively ‘unfolded’ the three-state network of figure 1 into the $3(2N + 1)$-state network of figure 3. In the following section, we will extend this approach to $n$-state networks containing multiple cycles (closed loops). Each cycle will be unfolded, as above, by coupling individual transitions to the conversion of substrate molecules in the surrounding medium.

4. Embedding $n$-state jump processes in an equilibrium supersystem

As in section 2, let us consider an $n$-state Markov jump process, whose fixed transition matrix $r^0$ satisfies the conditions described in the paragraph containing equation (2). This will be our NS. We also want to construct an ES containing a single $n$-state molecule $M$ immersed in a bath of substrate molecules, so that at a specific set of substrate concentrations the transition rates for $M$ reproduce those of NS.

To accomplish this we will make use of the network representation of jump processes [51, 52, 55, 56], in which the $n$ states of NS correspond to the nodes of a graph, while the bi-directional transitions correspond to the graph’s links, or edges. In this approach, the graph is decomposed into a set of fundamental cycles (as described below). The steady state of the jump process is then described in terms of the probability currents flowing around these cycles, and each cycle is characterized by a thermodynamic affinity, which acts as a driving force. The application of this approach to the characterization of steady states of jump processes was reviewed by Schnakenberg [56], and later applied by Andrieux and Gaspard [51, 52] within the context of the SSFT.

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The decomposition into fundamental cycles is achieved by following a few simple steps, which we sketch here and illustrate in figure 4, referring the reader to [56] for a more detailed treatment. First, a maximal tree covering the graph representing NS is identified. This maximal tree is a graph that connects all of the \( n \) states while having no closed loops of transitions (cycles). In other words, for any pair of states \((i, j)\), there is a unique nonrepeating path connecting state \(i\) to state \(j\), along the links of the maximal tree. A maximal tree is constructed by temporarily removing links from the original graph while ensuring that the remaining graph is still connected. Once a maximal tree has been identified, cycles are defined by separately reintroducing each removed link. Every reintroduced link creates a single fundamental cycle—a nonrepeating path starting and returning to the same state. The reintroduced links are termed chords. In the simple example shown in figure 4, the original graph has four nodes and five edges (figure 4(a)); the maximal tree has four nodes and three edges (figure 4(b)); and figures 4(c) and (d) show the two chords and fundamental cycles corresponding to this decomposition. Note that the decomposition of a given graph into fundamental cycles is not unique: it depends on the choice of links to be removed when constructing the maximal tree.

Let us now use this decomposition to characterize the NS and specifically its steady state, described by the probability distribution \( \pi \) and set of currents \( \{J_{ij}\} \) (see section 2). By construction, the number of fundamental cycles, \( L \), is equal to the number of chords. To each fundamental cycle \( \alpha \) one assigns a probability current, \( J_\alpha \), defined to be the steady-state probability current flowing through the corresponding chord. The steady-state currents flowing through all of the other links in the graph can then be expressed as linear combinations of the currents \( \{J_1, \ldots, J_L\} \) [56]. For each cycle one also defines an affinity

\[
\mathcal{A}_\alpha^0 = \ln \prod_{(i,j) \in \alpha} \frac{\pi_{ij}^0}{\pi_{ji}^0},
\]

Figure 4. (a) A graph corresponding to a four-state jump process with five bidirectional transitions (edges). (b) A maximal tree of the graph. (c), (d) The two fundamental cycles (thick blue solid and dashed lines) obtained from the tree by reintroducing the missing links, or chords (dashed lines).
where the product is over the links traversing the cycle in a directed manner\(^6\). This affinity acts as a thermodynamic driving force for the fundamental cycle \(\alpha\). The medium entropy production during a time interval \(\tau\) takes the form
\[
\Delta S_m = \sum_{\alpha=1}^{L} v_\alpha A^{0}_\alpha,
\]
where \(v_\alpha\) is the number of excursions around the \(\alpha\)th cycle \([52, 56]\). The \(v_\alpha\)’s can be obtained by counting the number of times that the system makes the transitions corresponding to the chords of the graph: \(v_\alpha\) is increased or decreased by 1 when the system makes the transition corresponding to the \(\alpha\)th chord, depending on its direction. While equation (38) is exact only when the system begins and ends in the same state, the corrections to it are bounded, and become negligible in the limit \(\tau \to \infty\).

We turn now to find an ES embedding the original \(n\)-state jump process. The idea is a simple generalization of the approach taken in section 3: in the ES each fundamental cycle is coupled with a catalysis of a chemical reaction. We therefore imagine an enzyme molecule, \(M\), with \(n\) internal states, immersed in solution in a closed container that also includes several other species of molecules. To each fundamental cycle we match two substrate species, \(A_\alpha\) and \(B_\alpha\). Transitions between the states of \(M\) that correspond to links on the maximal tree are not coupled with any chemical reactions, whereas transitions corresponding to the \(\alpha\)th chord are coupled with the chemical process \(A_\alpha \leftrightarrow B_\alpha\). (In the three-state example in section 3, with one fundamental cycle, the edges 12 and 13 constitute the maximal tree, and the edge 23 is the chord.) Our molecule \(M\) is therefore a catalyst to \(L\) independent chemical reactions. Since the container is assumed to be closed, the reactions satisfy the set of constraints
\[
N_{A_\alpha} + N_{B_\alpha} = N_\alpha, \quad \alpha = 1, \ldots, L
\]
with fixed values of \(N_1\) to \(N_L\). All of the substrate molecules are assumed to be present in large numbers, but with dilute concentrations, so that their corresponding chemical potentials \(\mu_{A_\alpha}\) and \(\mu_{B_\alpha}\) satisfy equation (14).

This prescription leads to an ES whose state at time \(t\) can be characterized by the internal state of the enzyme, \(i \in \{1, \ldots, n\}\), together with the values \((N_{A_1}, N_{A_2}, \ldots, N_{A_L})\). The dynamics of the ES consist of transitions in the internal state of the enzyme, \(i \to j\), and if such a jump occurs along one of the chords of the graph, then the corresponding value of \(N_{A_\alpha}\) (and \(N_{B_\alpha}\)) changes as well. We will refer to jumps that occur along the chords as enzymatic transitions—because they are associated with the catalysis of substrate molecules—and jumps that occur along other links as nonenzymatic transitions.

We will assume that the nonenzymatic transition rates for the ES are identical to their counterparts for the NS:
\[
R(i \to j) = r^0_{ji}.
\]
(To keep the notation compact we express only the properties of the ES state that change during a transition.) We can then use the principle of detailed balance to assign energies \(\varepsilon_i\) to the internal states of \(M\):
\[
\frac{R(i \to j)}{R(i \leftarrow j)} = \frac{r^0_{ji}}{r^0_{ij}} = e^{-\beta(\varepsilon_j - \varepsilon_i)}.
\]

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We have one such equation for every link in the maximal tree, and these equations define a set of energies \( \{\epsilon_1, \ldots, \epsilon_N\} \), up to an overall additive constant. Once these energies have been assigned, detailed balance imposes restrictions on the enzymatic transitions. Specifically, if the enzymatic transition \( i \rightarrow j \) catalyzes the reaction \( A_\alpha \rightarrow B_\alpha \), then

\[
\frac{R(i, N_{A_\alpha}, N_{B_\alpha} \rightarrow j, N_{A_\alpha}' N_{B_\alpha}')}{R(i, N_{A_\alpha}, N_{B_\alpha} \leftarrow j, N_{A_\alpha}' N_{B_\alpha}')} = e^{-\beta(\epsilon_j - \epsilon_i)} \frac{N_{A_\alpha}}{N_{B_\alpha}}.
\]

Equations (41) and (42) generalize equation (16) to jump processes with multiple fundamental cycles. The equilibrium probability distribution corresponding to these rates is given by

\[
P^{eq}(i, N_{A_1}, \ldots, N_{A_L}) = \frac{1}{Z} e^{-\beta x_i} \prod_{j=1}^{L} \frac{1}{2N_{\alpha}} \left( \frac{N_{\alpha}}{N_{\alpha}} \right)
\]

with \( Z = \sum_{i=1}^{n} e^{-\beta x_i} \).

The rest of the argument, sketched below, closely follows that of section 3. We first define a set of order parameters

\[
x_\alpha = \frac{N_{A_\alpha} - N_{B_\alpha}}{N_\alpha}, \quad \alpha \in \{1, \ldots, L\}
\]

and we treat each \( x_\alpha \) as a quasi-continuous variable in the range \([-1, 1]\). In terms of these order parameters we can assign affinities to the fundamental cycles of the \( n \)-state enzyme

\[
A_\alpha = \ln \frac{N_{A_\alpha}}{N_{B_\alpha}} = \ln \frac{1 + x_\alpha}{1 - x_\alpha} = 2 \frac{\partial \phi}{\partial x_\alpha}
\]

to leading order in \( N_\alpha^{-1} \). A nonzero value of \( A_\alpha \) represents a driving force that arises due to the imbalance between the \( A_\alpha \) and \( B_\alpha \) substrate molecules. These affinities fluctuate in time, as substrate molecules are catalyzed. Let \( x^0 \) denote the set of order parameter values for which these affinities match those of the NS, defined by equation (37):

\[
A_\alpha (x^0_\alpha) = A^0_\alpha.
\]

Using the Stirling approximation, equation (43) becomes

\[
p^{eq}(i, x) \propto e^{-\beta x_i} e^{-\sum_{\alpha=1}^{L} N_\alpha \phi(x_\alpha)},
\]

where \( \phi(x) \) is defined by equation (19). Hence, \( \beta^{-1}N_\alpha \phi(x_\alpha) \) plays the role of a potential of mean force for the order parameter \( x_\alpha \). Its minimum is located at \( x_\alpha = 0 \) and since \( N_\alpha \) is very large, fluctuations where \( x_\alpha \) appreciatively deviates from its minimum are exceedingly rare.

Now, let \( p_{eq}^0(x^1|x^0) \) denote the probability of observing a set of order parameter values \( x^1 \) at a final time \( t = \tau \), conditioned on initial order parameter values \( x^0 \) at \( t = 0 \), and let

\[
v_\alpha = \frac{N_\alpha}{2}(x^0_\alpha - x^1_\alpha)
\]

denote the number of \( A \rightarrow B \) conversions for each of the reactions, during this interval of time. On applying the principle of detailed balance to the equilibrium fluctuations of the order parameters, we find

\[
\frac{p_{eq}^0(x^1|x^0)}{p_{eq}^0(x^0|x^1)} = \frac{p_{eq}^0(x^1)}{p_{eq}^0(x^0)} = \frac{\exp[-N \sum_\alpha \phi(x^1_\alpha)]}{\exp[-N \sum_\alpha \phi(x^0_\alpha)]} \approx \exp \left[ \sum_\alpha v_\alpha A_\alpha (x^0_\alpha) \right],
\]
which generalizes equation (23). By taking the limits $N_\alpha \to \infty$, for all of the values of $\alpha$, this result becomes

$$
\lim_{N_\alpha \to \infty} \frac{p_{\tau}^{\text{eq}}(+\nu \mid x^0)}{p_{\tau}^{\text{eq}}(-\nu \mid x^0)} = \exp \left[ \sum_\alpha v_\alpha A_\alpha(x^0) \right] = \exp \left[ \sum_\alpha v_\alpha A_\alpha^0 \right].
$$

(50)

This result has been derived by consideration of the ES, in which the substrate concentrations fluctuate with time. However, when $N_\alpha \to \infty$ (for all $\alpha$) the conditional probability $p_{\tau}^{\text{eq}}(\nu \mid x^0)$ becomes statistically identical to the corresponding probability in a nonequilibrium process in which $x^0$ is kept fixed, $p_{\tau,x^0}^{\text{neq}}(\nu)$, with the initial conditions for $M$ sampled from the Boltzmann distribution, $p_i \propto \exp(-\beta \varepsilon_i)$. This finally gives us the TFT

$$
\lim_{N \to \infty} \frac{p_{\tau,x^0}^{\text{neq}}(+\nu)}{p_{\tau,x^0}^{\text{neq}}(-\nu)} = \exp \left[ \sum_\alpha v_\alpha A_\alpha^0 \right]
$$

(51)

for a jump process with $n$ states and $L$ fundamental cycles. The remaining arguments of section 3 (equations (32)–(36)) apply here as well, leading to the result

$$
\lim_{\tau \to \infty} \frac{1}{\tau} \ln \frac{p_{\tau,x^0}^{\text{neq}}(+\omega)}{p_{\tau,x^0}^{\text{neq}}(-\omega)} = \sum_\alpha \omega_\alpha A_\alpha^0,
$$

(52)

where $\omega_\alpha = v_\alpha / \tau$ is the rate of transitions corresponding to the $\alpha$th chord. This SSFT was previously derived by Andrieux and Gaspard [52] directly from consideration of the NS. Here, we have shown that the same result follows by applying the principle of detailed balance to an ES and by taking the appropriate limit.

5. Summary and discussion

Thermodynamic forces, arising from imbalances in a system’s thermal surroundings, drive that system away from equilibrium. If these imbalances persist indefinitely, the system reaches a nonequilibrium steady state, characterized by stationary out-of-equilibrium fluctuations that obey the TFT and/or the SSFTs. Most derivations of these results assume a fixed thermodynamic force that is externally imposed, or simply appears in the statement of the problem. Here, we have explored a different point of view, in which the system of interest and its surroundings are treated as a large, undisturbed supersystem. In its state of perpetual equilibrium, this supersystem exhibits fluctuations that obey the property of detailed balance. On occasion, these fluctuations give rise to temporary imbalances in the system’s surroundings, followed by the inevitable regression back to a state of balance. During these spontaneous excursions away from typical behavior, the system behaves as though it were subject to an externally imposed thermodynamic force. We contend that the TFT and the SSFTs both emerge directly from the application of the principle of detailed balance to these rare, equilibrium fluctuations of the supersystem.

To make our case, we considered an $n$-state Markov jump process—with dynamics that violate detailed balance—as the NS. Our strategy was then to construct a larger, explicitly physical ES, such that the dynamics of the NS would somehow emerge from those of the ES. We found it convenient to work within a simple chemical kinetic framework, imagining an enzyme molecule $M$ with $n$ distinct conformations, immersed in a solution containing various species of substrate molecules, with transitions among the states of $M$ coupled directly with chemical
reactions among the substrates. Within this setup, imbalances of substrate concentrations give rise to thermodynamic driving forces acting on $M$, and ultimately both the TFT and the SSFT emerge (as we have shown) from the regression of large equilibrium fluctuations away from the typical balance of substrate concentrations.

The large-$N$ (or large-$N_\alpha$) limit played a crucial role in our analysis. In this limit, the probability of achieving an imbalance of magnitude $x^0$ (or $x^0$) becomes exceedingly rare, but once it occurs, it persists for a long time, allowing us to connect the dynamics of the ES to those of the NS. In effect, the substrate concentrations have a large ‘thermodynamic inertia’ in this limit.

This framework of chemical kinetics offers a natural and tractable context for addressing the nonequilibrium fluctuations of a discrete-state system of interest by studying the equilibrium fluctuations of an extended supersystem. We expect, however, that our central conclusion is more general, and in principle similar results could be derived by analyzing a situation in which (for example) a spontaneous temperature difference arises due to equilibrium fluctuations.

Finally, as mentioned in our introduction, FTs for entropy production are closely related to analogous results for the work performed on a system by the external manipulation of a mechanical parameter [31]. We speculate that the approach taken in the present paper could be extended to that setting, by replacing the mechanical parameter with a massive dynamic degree of freedom, in equilibrium with the system of interest as well as with an external thermal reservoir. By analyzing the behavior of the system of interest, conditioned on unusually large fluctuations of this degree of freedom, one might recover the far-from-equilibrium work relations of [9, 10].

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