REVIEW ARTICLE

Stochastic thermodynamics, fluctuation theorems and molecular machines

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Stochastic thermodynamics, fluctuation theorems and molecular machines

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Abstract

Stochastic thermodynamics as reviewed here systematically provides a framework for extending the notions of classical thermodynamics such as work, heat and entropy production to the level of individual trajectories of well-defined non-equilibrium ensembles. It applies whenever a non-equilibrium process is still coupled to one (or several) heat bath(s) of constant temperature. Paradigmatic systems are single colloidal particles in time-dependent laser traps, polymers in external flow, enzymes and molecular motors in single molecule assays, small biochemical networks and thermoelectric devices involving single electron transport. For such systems, a first-law like energy balance can be identified along fluctuating trajectories. For a basic Markovian dynamics implemented either on the continuum level with Langevin equations or on a discrete set of states as a master equation, thermodynamic consistency imposes a local-detailed balance constraint on noise and rates, respectively. Various integral and detailed fluctuation theorems, which are derived here in a unifying approach from one master theorem, constrain the probability distributions for work, heat and entropy production depending on the nature of the system and the choice of non-equilibrium conditions. For non-equilibrium steady states, particularly strong results hold like a generalized fluctuation–dissipation theorem involving entropy production. Ramifications and applications of these concepts include optimal driving between specified states in finite time, the role of measurement-based feedback processes and the relation between dissipation and irreversibility. Efficiency and, in particular, efficiency at maximum power can be discussed systematically beyond the linear response regime for two classes of molecular machines, isothermal ones such as molecular motors, and heat engines such as thermoelectric devices, using a common framework based on a cycle decomposition of entropy production.

(Some figures may appear in colour only in the online journal)

This article was invited by Erwin Frey.

Contents

1. Introduction

1.1. From classical to stochastic thermodynamics

Classical thermodynamics, at its heart, deals with general laws governing the transformations of a system, in particular, those involving the exchange of heat, work and matter with an environment. As a central result, total entropy production is identified that in any such process never decreases, leading, *inter alia*, to fundamental limits on the efficiency of heat engines and refrigerators. The thermodynamic characterization of systems in equilibrium gets its microscopic justification from equilibrium statistical mechanics which states that for a system in contact with a heat bath the probability to find it in any specific microstate is given by the Boltzmann factor. For small deviations from equilibrium, linear response theory allows one to express transport properties caused by small external fields through equilibrium correlation functions. On a more phenomenological level, linear irreversible thermodynamics provides a relation between such transport coefficients and entropy production in terms of forces and fluxes. Beyond this linear response regime, for a long time, no universal exact results were available.

Over the last 20 years fresh approaches have revealed general laws applicable to non-equilibrium system thus pushing the range of validity of exact thermodynamic statements beyond the realm of linear response deep into the genuine non-equilibrium region. These exact results, which become particularly relevant for small systems with appreciable (typically non-Gaussian) fluctuations, generically refer to distribution functions of thermodynamic quantities such as exchanged heat, applied work or entropy production.

First, for a thermostatted shear-driven fluid in contact with a heat bath, a remarkable symmetry of the probability distribution of entropy production in the steady state was discovered numerically and justified heuristically by Evans *et al* [1]. Now known as the (steady-state) fluctuation theorem (FT), it was first proven for a large class of systems using concepts from chaotic dynamics by Gallavotti and Cohen [2], later for driven Langevin dynamics by Kurchan [3] and for driven diffusive dynamics by Lebowitz and Spohn [4]. As a variant, a transient fluctuation theorem valid for relaxation toward the steady state was found by Evans and Searles [5].

Second, Jarzynski proved a remarkable relation which allows one to express the free energy difference between two equilibrium states by a non-linear average over the work required to drive the system in a non-equilibrium process from one state to the other [6, 7]. By comparing probability distributions for the work spent in the original process with the time-reversed one, Crooks found a 'refinement' of the Jarzynski relation (JR), now called the Crooks fluctuation theorem [8, 9]. Both this relation and another refinement of the JR, the Hummer–Szabo relation (HSR) [10], became particularly useful for determining free energy differences and landscapes of biomolecules. These relations are the most prominent ones within a class of exact results (some of which

were found even earlier [11, 12] and then rediscovered) valid for non-equilibrium systems driven by time-dependent forces. A close analogy to the JR, which relates different equilibrium states, is the Hatano–Sasa relation that applies to transitions between two different non-equilibrium steady states [13].

Third, for driven Brownian motion, Sekimoto realized that two central concepts of classical thermodynamics, namely the exchanged heat and the applied work, can be meaningfully defined on the level of individual trajectories [14, 15]. These quantities entering the first law become fluctuating ones giving birth to what he called stochastic energetics as described in his monograph [16]. Fourth, Maes emphasized that entropy production in the medium is related to that part of the stochastic action which determines the weight of trajectories that is odd under time reversal [17, 18].

Finally, building systematically on a concept briefly noticed previously [8, 19], a unifying perspective on these developments emerged by realizing that in addition to the fluctuations of the entropy production in the heat bath one should similarly assign a fluctuating, or 'stochastic', entropy to the system proper [20]. Once this is carried out, the key quantities known from classical thermodynamics are defined along individual trajectories where they become accessible to experimental or numerical measurements. This approach of taking both energy conservation, i.e. the first law, and entropy production seriously on this mesoscopic level has been called stochastic thermodynamics [21], thus revitalizing a notion originally introduced by the Brussels school in the mid-1980s where it was used on the ensemble level for chemical non-equilibrium systems [22, 23].

1.2. Main features of stochastic thermodynamics

Stochastic thermodynamics as understood here applies to (small) systems such as colloidal particles, (bio)polymers (such as DNA, RNA and proteins), enzymes and molecular motors. All these systems are embedded in an aqueous solution. Three types of non-equilibrium situations can be distinguished for these systems. First, one could prepare the system in a non-equilibrium initial state and study the relaxation toward equilibrium. Second, genuine driving can be caused by the action of time-dependent external forces, fields, flows or unbalanced chemical reactions. Third, if the external driving is time-independent the system will reach a non-equilibrium steady state (NESS). For this latter class, particularly strong exact results exist. In all cases, even under such non-equilibrium conditions, the temperature of the system, which is the same as that of the embedding solution, remains well-defined. This property together with the related necessary time-scale separation between the observable, typically slow, degrees of freedom of the system and the unobservable fast ones made up by the thermal bath (and, in the case of biopolymers, by fast internal ones of the system) allows for a consistent thermodynamic description.

The collection of the relevant slow degrees of freedom makes up the state of the system. Since this state changes either due to the driving or due to the ever present fluctuations, it leads to a trajectory of the system. Such trajectories belong to an ensemble which is fully characterized by the distribution of the initial state, by the properties of the thermal noise acting on the system and by specifying the (possibly time-dependent) external driving. The thermodynamic quantities defined along the trajectory like applied work and exchanged heat thus follow a distribution which can be measured experimentally or be determined in numerical simulations.

Theoretically, the time-scale separation implies that the dynamics becomes Markovian, i.e. the future state of the system depends only on the present one with no memory of the past. If the states are made up by continuous variables (such as position), the dynamics follows a Langevin equation for an individual system and a Fokker–Planck equation for the whole ensemble. Sometimes it is more convenient to identify discrete states with transition rates governing the dynamics which, on the ensemble level, leads to a master equation.

Within such a stochastic dynamics, the exact results quoted above for the distribution functions of certain thermodynamic quantities follow universally for any system from rather unsophisticated mathematics. It is sufficient to invoke a 'conjugate' dynamics, typically, but not exclusively, time reversal, to derive these theorems in a few lines. Essentially, they lead to universal constraints on these distributions. One inevitable consequence of these theorems is the occurrence of trajectories with negative total entropy production. Such events have occasionally been called (transient) violations of the second law. In fairness to classical thermodynamics, however, one should emphasize that this classical theory ignores fluctuations. If the second law is understood as referring to the mean entropy production, it is indeed confirmed by these more recent exact relations. Moreover, they show that the probability for such events becomes typically exponentially small in the relevant system size which means that one has to sample exponentially many trajectories in order to observe these 'violations'.

Since these constraints on the distributions are so universal, one might suspect that they are useless for uncovering system-specific properties. Quite to the contrary, some of them offer a surprising relation between equilibrium and non-equilibrium properties with the JR as the most prominent and useful example. Moreover, such constraints can be used as an obvious check whether the assumptions of the model apply to any particular system. Finally, studying non-universal features of these distribution functions and trying to find further common aspects in these has become an important part of the activities in this field.

Going beyond the thermodynamic framework, it turns out that many of the FTs hold formally true for any kind of Markovian stochastic dynamics. The thermodynamic interpretation of the involved quantities as heat and work is not mandatory to derive such *a priori* surprising relationships between functionals defined along dynamic trajectories.

1.3. Hamiltonian, thermostatted and open quantum dynamics

Even though I will focus in the main part of this review on systems described by a stochastic dynamics, it is appropriate to mention briefly alternative approaches as some of the FTs have originally been derived using a deterministic framework.

Hamiltonian dynamics works, in principle, if the external driving is modeled by a time-dependent potential arising, e.g., from a movable piston, tip of an atomic force microscope, or optical tweezer. Conceptually, one typically requires thermalized initial conditions, then cuts off the system from the heat bath leading to the deterministic motion and finally one has to reconnect the heat bath again. In a second variant, the heat bath is considered to be part of the system but one then has to follow all degrees of freedom. One disadvantage of Hamiltonian dynamics is that it cannot deal with a genuine NESS, which is driven by a time-independent external field or flow, since such a setting inevitably heats up the system.

Thermostatted dynamics can deal with NESSs. Here, one keeps deterministic equations of motion and introduces a friction term making sure that on average the relevant energy (kinetic or total, depending on the scheme) does not change [24].

Even though a deterministic dynamics is sometimes considered to be more fundamental than a stochastic one, the latter has at least three advantages from the perspective held in this review. First, from a practical point of view, in soft matter and biophysics a description focusing on the relevant (and measurable) degrees of freedom and ignoring water molecules from the outset has a certain economical appeal. Second, stochastic dynamics can describe transitions between discrete states as in (bio)chemical reactions with essentially the same conceptual framework used for systems with continuous degrees of freedom. Third, the mathematics required for deriving the exact relations and for stating their range of validity is surprisingly simple compared with what is required for dealing with NESSs in the deterministic setting.

Open quantum systems will not be discussed explicitly in this review. Some of the FTs can indeed be formulated for these systems, sometimes at the cost of requiring somewhat unrealistic measurements at the beginning and end of a process, as reviewed in [25, 26]. The results derived and discussed in the following, however, are directly applicable to open quantum systems whenever coherences, i.e. the role of non-diagonal elements in the density matrix, can be ignored. The dynamics of the driven or open quantum system is then equivalent to a classical stochastic one. For the validity of the exact relations in these cases, the quantum-mechanical origin of the transition rates is inconsequential.

1.4. Scope and organization of this review

In writing this review, apart from focusing entirely on systems governed by Markovian stochastic dynamics, I have been guided by the following principles concerning format and content.

First, I have tried to present the field in a systematic order (and notation) rather than to follow the historical development which has been briefly alluded to in the introductory section above. Such an approach leads to a more concise and coherent presentation. Moreover, I have tried to keep most of the more technical parts (some of which are original) still self-contained. Both features should help those using this material as a basis for courses such as those which I have given several times at the University of Stuttgart and at summer schools in Beijing, Boulder and Jülich.

Second, as a consequence of the more systematic presentation, experimental, analytical and numerical case studies of specific systems are mostly grouped together and typically placed after the general theory where they fit best.

Third, for the exact results the notions 'theorem', 'equality' and 'relation' are used here in no particular hierarchy. I rather try to follow the practice established in the field so far. In particular, it is not implied that a result called here 'theorem' is in any sense deeper than another one called 'relation'.

This review starts in section 2 by introducing a paradigm for this field which is a colloidal particle driven by a time-dependent force as it has been realized in several experiments. Using this system, the main concepts of stochastic thermodynamics, such as work, heat and entropy changes along individual trajectories, will be introduced. At the end of this section, simple generalizations of driven one-dimensional motion such as three-dimensional motion, coupled degrees of freedom and motion in external flow are discussed.

A general classification and a physical discussion of the major FTs dealing with work and the various contributions to entropy production follows in section 3. In section 4, I present a unifying perspective on basically all known FTs for stochastic dynamics using the concept of a conjugate dynamics. It is shown explicitly how these FTs follow from one master theorem. Section 5 contains an overview of experimental, analytical or numerical studies of Langevin-type dynamics in specific systems. Section 6 deals with Markovian dynamics on a discrete set of states for which FTs hold even without assuming a thermodynamic structure.

The second part of the review deals with ramifications, consequences and applications of these concepts. In section 7, the optimal driving of such processes is discussed and the relation between irreversibility and the amount of dissipation derived. Both concepts can then be used to discuss the role of measurements and (optimal) feedback in these systems. Section 8 deals with generalizations of the well-known fluctuation–dissipation theorem (FDT) to NESSs where it is shown that stochastic entropy plays a crucial role.

As one paradigm for more complex systems, biomolecular systems are discussed in section 9 where special emphasis is given to the role of time-scale separation between the fast (unobservable) degrees of freedom making up a well-defined heat bath for the non-equilibrium processes and the slow variables caused by mechanical or chemical imbalances. From a conceptual point of view the second essential new aspect of these systems is that each of the states is composed of many microstates which leads to the crucial notion of intrinsic entropy that enters some of the exact relations in a non-trivial way.

Coming back to the issues that stood at the origin of thermodynamics, the final two sections discuss the efficiency and optimization of nano- and micro-engines and devices where it is useful to distinguish isothermal engines such as molecular motors discussed in section 10 from heat engines

such as thermoelectric devices treated in section 11. A brief summary and a few perspectives are sketched in section 12.

1.5. Complementary reviews

A selection of further reviews dealing with the topics discussed in the first part of this paper can roughly be grouped as follows.[1]

The influential essay [27] had an introductory character. More recent non-technical accounts have been given by Jarzynski [28] and van den Broeck [29] who both emphasize the relation of the FTs with irreversibility and time's arrow. Other brief reviews by some of the main proponents include [17, 30–32] and the contributions in the collection [33]. Ritort has written a review on the role of non-equilibrium fluctuations in small systems with special emphasis on the applications to biomolecular systems [34]. A review focusing on experimental work by one of the main groups working on FTs is [35].

For stochastic dynamics based on the master equation, a comprehensive derivation of FTs has been given by Harris and Schütz [36]. The FT in the context of thermostatted dynamics has been systematically reviewed by Evans and Searles [37]. From the perspective of chaotic dynamics it is treated in Gallavotti's monograph [38]. The links between different approaches and rigorous mathematical statements are surveyed in [39–42].

Stochastic thermodynamics focuses on a description of individual trajectories as does an alternative approach by Attard introducing a 'second entropy' [43]. On a more coarse-grained level, phenomenological thermodynamic theories of non-equilibrium systems have been developed *inter alia* under the label of 'extended irreversible thermodynamics' [44], 'GENERIC' [45], 'mesoscopic dynamics of thermodynamic systems' [46] and 'steady-state thermodynamics' [47, 48].

Nice reviews covering related recent topics in non-equilibrium physics are [49, 50].

2. Colloidal particle as paradigm

The main concepts of stochastic thermodynamics can be introduced using as a simple model system a colloidal particle confined to one spatial dimension, which can arguably serve as *the* paradigm for the field.

2.1. Stochastic dynamics

The overdamped motion $x(\tau)$ of a colloidal particle (or any other system with a single continuous degree of freedom) can be described using three equivalent but complementary descriptions of stochastic dynamics, the Langevin equation, the path integral and the Fokker–Planck equation.

The Langevin equation reads

$$\dot{x} = \mu F(x,\lambda) + \zeta = \mu(-\partial_x V(x,\lambda) + f(x,\lambda)) + \zeta. \quad (1)$$

The systematic force $F(x,\lambda)$ can arise from a conservative potential $V(x,\lambda)$ and/or be applied to the particle directly as $f(x,\lambda)$. In one dimension, a force $f(x,\lambda)$ can always be written as the gradient of a global potential except for the important case of motion on a ring which imposes periodic boundary conditions. Still, from a physical point of view the two contributions to the total mechanical force should be distinguished as will become clear when discussing the first law below. Moreover, in two or more dimensions, there are forces which cannot even locally be written as a gradient. Both contributions to the force may be time-dependent through an external control parameter $\lambda(\tau)$ varied from $\lambda(0) \equiv \lambda_0$ to $\lambda(t) \equiv \lambda_t$ according to some prescribed protocol.

The thermal noise is Gaussian with correlations

$$\langle \zeta(\tau)\zeta(\tau')\rangle = 2D\delta(\tau - \tau'). \quad (2)$$

In equilibrium, D becomes the diffusion constant, which is related to the mobility μ by the Einstein relation

$$D = T\mu \quad (3)$$

where T is the temperature of the surrounding medium with Boltzmann's constant k_B set to unity throughout this review to make entropy dimensionless. In stochastic thermodynamics, one assumes that the strength of the noise as given by D still obeys the Einstein relation (3) and is thus not affected by the presence of a time-dependent force. The range of validity of this crucial assumption can be tested experimentally or in simulations by comparing with theoretical results derived on the basis of this assumption.

The Langevin dynamics generates trajectories $x(\tau)$ starting at $x(0) \equiv x_0$ with a weight

$$p[x(\tau)|x_0] = \mathcal{N}\exp[-\mathcal{A}([x(\tau),\lambda(\tau)])] \quad (4)$$

where

$$\mathcal{A}([x(\tau),\lambda(\tau)]) \equiv \int_0^t d\tau[(\dot{x} - \mu F)^2/4D + \mu\partial_x F/2] \quad (5)$$

is the 'action' associated with the trajectory. The last term arises from the Stratonovich convention for the discretization in the Jacobian when the weight for a noise history $[\zeta(\tau)]$ is expressed by $[x(\tau)]$. This symmetric discretization is used implicitly throughout this review. Path-dependent observables $\Omega[x(\tau)]$ can then be averaged using this weight in a path integral which requires a path-independent normalization $\mathcal{N}$ such that summing the weight equations (4), (5) over all paths is 1. Throughout the review averages using this weight and a given initial distribution $p_0(x)$ will be denoted by $\langle\ldots\rangle$ as in

$$\langle\Omega[x(\tau)]\rangle \equiv \int dx_0 \int d[x(\tau)]\Omega[x(\tau)]p[x(\tau)|x_0]p_0(x_0) \quad (6)$$

for any functional $\Omega[x(\tau)]$.

Equivalently, the Fokker–Planck equation for the probability $p(x,\tau)$ to find the particle at x at time τ is

$$\begin{aligned}\partial_\tau p(x,\tau) &= -\partial_x j(x,\tau)\\ &= -\partial_x\left(\mu F(x,\lambda)p(x,\tau) - D\partial_x p(x,\tau)\right), \end{aligned} \quad (7)$$

where $j(x,\tau)$ is the probability current. This partial differential equation must be augmented by a normalized initial distribution $p(x,0) \equiv p_0(x)$. For further calculations, it is useful to define a (time-dependent) mean local velocity

$$v(x,\tau) \equiv j(x,\tau)/p(x,\tau). \quad (8)$$

[1] Relevant reviews for the more specific topics treated in the second part of this review will be mentioned in the respective sections.

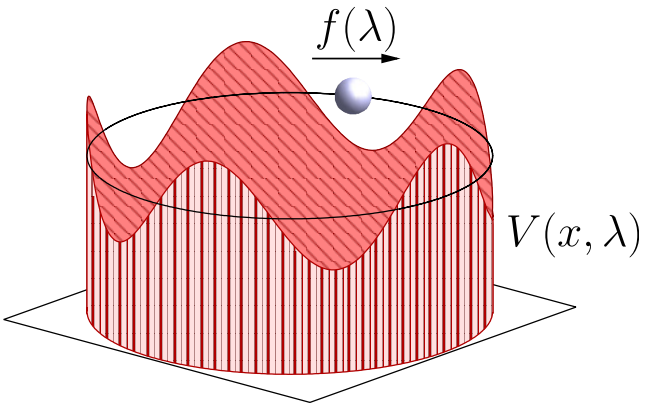

Figure 1. Colloidal particle driven along a periodic potential $V(x,\lambda)$ by a non-conservative force $f(\lambda)$. In a NESS, the external parameter λ is independent of time.

More technical background concerning these three equivalent descriptions of Markovian stochastics dynamics of a continuous degree of freedom is provided in the monographs [51–54].

2.2. Non-equilibrium steady states

For a time-independent control parameter λ, any initial distribution will finally reach a stationary state $p^s(x,\lambda)$. For $f = 0$, this stationary state is the thermal equilibrium[2],

$$p^{\rm eq}(x,\lambda) = \exp[-(V(x,\lambda) - \mathcal{F}(\lambda))/T], \tag{9}$$

with the free energy

$$\mathcal{F}(\lambda) \equiv -T \ln \int {\rm d}x \exp[-V(x,\lambda)/T]. \tag{10}$$

A non-conservative force acting on a ring as shown in figure 1 generates a paradigm for a genuine NESS with a stationary distribution

$$p^s(x,\lambda) \equiv \exp[-\phi(x,\lambda)], \tag{11}$$

where $\phi(x,\lambda)$ is the 'non-equilibrium' potential. In one dimension, $p^s(x,\lambda)$ can be obtained explicitly by quadratures [52] or by an intriguing mapping to an equilibrium problem [55]. Characteristic for such a NESS is a steady current

$$j^s(x) = \mu F(x) p^s(x) - D\partial_x p^s(x) \equiv v^s(x) p^s(x) \tag{12}$$

with the stationary mean local velocity $v^s(x)$. Even for time-dependent driving, one can express the total mechanical force

$$F(x,\lambda) = [v^s(x,\lambda) - D\partial_x \phi(x,\lambda)]/\mu \tag{13}$$

through quantities refering to the corresponding stationary state which is sometimes helpful.

Occasionally, we will use $\langle \ldots \rangle^{\rm eq}$ and $\langle \ldots \rangle^s$ to emphasize when averages or correlation functions are taken in genuine equilibrium and in a NESS, respectively.

[2] Strictly speaking, one has to exclude the case where boundary conditions on a finite interval for x impose a stationary current.

2.3. Stochastic energetics

2.3.1. The first law. Sekimoto suggested to endow the Langevin dynamics with a thermodynamic interpretation by applying the notions appearing in the first law

$$đw = {\rm d}E + đq \tag{14}$$

to an individual fluctuating trajectory [14, 15]. Throughout the paper, we use the convention that work applied to the particle (or more generally system) is positive as is heat transferred or dissipated into the environment.

It is instructive first to identify the first law for a particle in equilibrium, i.e. for $f = 0$ and constant λ. In this case, no work is applied to the system and hence an increase in internal energy, defined by the position in the potential, ${\rm d}E = {\rm d}V = (\partial_x V)\,{\rm d}x = -đq$, must be associated with heat taken up from the reservoir.

Applying work to the particle either requires a time-dependent potential $V(x,\lambda(\tau))$ and (or) an external force $f(x,\lambda(\tau))$. The increment in work applied to the particle then reads

$$đw = (\partial V/\partial\lambda)\,{\rm d}\lambda + f\,{\rm d}x, \tag{15}$$

where the first term arises from changing the potential at fixed particle position. Consequently, the heat dissipated into the medium must be identified with

$$đq = đw - {\rm d}V = F\,{\rm d}x. \tag{16}$$

This relation makes physical sense since in an overdamped system the total mechanical force times the displacement corresponds to dissipation. Integrated over a time interval t, one obtains the expressions

$$w[x(\tau)] = \int_0^t [(\partial V/\partial\lambda)\dot\lambda + f\dot x]\,{\rm d}\tau \tag{17}$$

and

$$q[x(\tau)] = \int_0^t {\rm d}\tau\, \dot q = \int_0^t F\dot x\,{\rm d}\tau \tag{18}$$

and the integrated first law

$$w[x(\tau)] = q[x(\tau)] + \Delta V = q[x(\tau)] + V(x_t,\lambda_t) - V(x_0,\lambda_0) \tag{19}$$

on the level of an individual trajectory.

The expression for the heat requires a prescription of how to evaluate $F\dot x$. As above in the path integral, one has to use the mid-point, i.e. Stratonovich rule for which the ordinary rules of calculus for differentials and integrals apply.

The expression for the heat dissipated along the trajectory $x(\tau)$ can also be written in the form

$$\begin{aligned} q[x(\tau)] &= -T(\mathcal{A}([x(\tau),\lambda(\tau)]) - \mathcal{A}([x(t-\tau),\lambda(t-\tau)]) \\ &= T\ln\frac{p[x(\tau),\lambda(\tau)]}{p[\tilde x(\tau),\tilde\lambda(\tau)]} \end{aligned} \tag{20}$$

as a ratio involving the weight (5) for this trajectory given its initial point x_0 compared with the weight of the time-reversed trajectory $\tilde x(\tau) \equiv x(t-\tau)$ under the reversed protocol $\tilde\lambda(\tau) \equiv \lambda(t-\tau)$ for $\tilde x_0 = x(t) \equiv x_t$. This formulation points to the deep relation between dissipation and time reversal which repeatedly shows up in this field.

2.3.2. Housekeeping and 'excess' heat. Motivated by steady-state thermodynamics, it will be convenient to split the dissipated heat into two contributions [13, 47]

$$q \equiv q^{\rm hk} + q^{\rm ex}. \tag{21}$$

The housekeeping heat is the heat inevitably dissipated in maintaining the corresponding NESS. For a Langevin dynamics, it reads

$$q^{\rm hk} \equiv \int_0^t {\rm d}\tau \dot{x}(\tau)\mu^{-1}v^s(x(\tau),\lambda(\tau)). \tag{22}$$

The 'excess' heat

$$\begin{aligned} q^{\rm ex} &= -(D/\mu)\int_0^t {\rm d}\tau \dot{x}(\tau)\partial_x\phi(x,\lambda) \\ &= T[-\Delta\phi + \int_0^t {\rm d}\tau \dot{\lambda}\partial_\lambda\phi] \end{aligned} \tag{23}$$

is the heat associated with changing the external control parameter where we have used (13) and (18).

2.3.3. Heat and strong coupling. This interpretation of the first law and, in particular, of heat relies on the implicit assumption that the unavoidable coupling between particle (or, more generally, system) described by the slow variable x and the degrees of freedom making up the heat bath neither depends crucially on x nor on the control parameter λ. Such an idealization may well apply to a colloidal particle in a laser trap but will certainly fail for more complex systems like biomolecules. In the following, we first continue with this simple assumption. In section 9.2, we discuss the general case and point out which of the results derived in the following will require a ramification. Roughly speaking, most of the FTs hold true with minor modifications whereas inferring heat correctly indeed requires one more term compared with (16).

2.3.4. Alternative identification of work. The definition of work (15) has been criticized for supposedly being in conflict with a more conventional view that work should be given by force times displacement, see [56] and, for rebuttals, [57–59]. In principle, such a view could be integrated into the present scheme by splitting the potential into two contributions,

$$V(x,\lambda) = V^0(x,\lambda_0) + V^{\rm ext}(x,\lambda), \tag{24}$$

the first being an intrinsic time-independent potential, and the second one a time-dependent external potential used to transmit the external force. If one defines work as

$$đw^{\rm ext} \equiv (-\partial_x V^{\rm ext}(x,\lambda) + f)\,{\rm d}x, \tag{25}$$

it is trivial to check that the first law then holds in the form

$$đw^{\rm ext} = {\rm d}E^{\rm ext} + đq \tag{26}$$

with the corresponding change in internal energy ${\rm d}E^{\rm ext} \equiv {\rm d}V^0 = \partial_x V^0\,{\rm d}x$ and the identification of heat (16) unchanged. Clearly, within such a framework, it would be appropriate to identify the internal energy with changes in the intrinsic potential only. Integrated over a trajectory, this definition of work differs from the previous one by a boundary term, $\Delta w = \Delta w^{\rm ext} + \Delta V^{\rm ext}$.

It is crucial to appreciate that exchanged heat as a physical concept is, and should be, independent of the convention regarding how it is split into work and changes in internal energy. The latter freedom is inconsequential as long as one stays within one scheme. A clear disadvantage of this alternative scheme, however, is that changes in the free energy of a system are no longer given by the quasi-static work relating two states. In this review, we will keep the definitions as introduced in section 2.3.1 and only occasionally quote results for the alternative expression for work introduced in this section.

2.4. Stochastic entropy

Having expressed the first law along an individual trajectory, it seems natural to ask whether entropy can be identified on this level as well. For a simple colloidal particle, the corresponding quantity turns out to have two contributions. First, the heat dissipated into the environment should obviously be identified with an increase in entropy of the medium

$$\Delta s^{\rm m}[x(\tau)] \equiv q[x(\tau)]/T. \tag{27}$$

Second, one identifies as a stochastic or trajectory dependent entropy of the system the quantity [20]

$$s(\tau) \equiv -\ln p(x(\tau),\tau) \tag{28}$$

where the probability $p(x,\tau)$ obtained by first solving the Fokker–Planck equation is evaluated along the stochastic trajectory $x(\tau)$. Thus, the stochastic entropy depends not only on the individual trajectory but also on the ensemble. If the same trajectory $x(\tau)$ is taken from an ensemble generated by another initial condition $p(x,0)$, it will lead to a different value for $s(\tau)$.

In equilibrium, i.e. for $f \equiv 0$ and constant λ, the stochastic entropy $s(\tau)$ just defined obeys the well-known thermodynamic relation, $TS = E - F$, between entropy, internal energy and free energy in the form

$$Ts(\tau) = V(x(\tau),\lambda) - \mathcal{F}(\lambda), \tag{29}$$

now along the fluctuating trajectory at any time with the free energy defined in (10) above.

Using the Fokker–Planck equation the rate of change of the entropy of the system (28) follows as [20]

$$\dot{s}(\tau) = -\frac{\partial_\tau p(x,\tau)}{p(x,\tau)}\bigg|_{x(\tau)} + \left(\frac{j(x,\tau)}{Dp(x,\tau)} - \frac{\mu F(x,\lambda)}{D}\right)_{x(\tau)}\dot{x}. \tag{30}$$

Since the very last term can be related to the rate of heat dissipation in the medium (18), using $D = T\mu$, one obtains a balance equation for the trajectory-dependent total entropy production as

$$\dot{s}^{\rm tot}(t) \equiv \dot{s}^{\rm m}(t) + \dot{s}(\tau) = -\frac{\partial_\tau p(x,\tau)}{p(x,\tau)}\bigg|_{x(\tau)} + \frac{j(x,\tau)}{Dp(x,\tau)}\bigg|_{x(\tau)}\dot{x}. \tag{31}$$

The first term on the right-hand side (rhs) signifies a change in $p(x,\tau)$ which can be due to a time-dependent $\lambda(\tau)$ or, even for a constant λ_0, due to relaxation from a non-stationary initial state $p_0(x) \neq p^s(x,\lambda_0)$.

As a variant on the trajectory level, occasionally $\phi(x,\lambda) = -\ln p^s(x,\lambda)$ has been suggested as a definition of system entropy. Such a choice is physically questionable as the following example shows. Consider diffusive relaxation of a localized initial distribution $p_0(x)$ in a finite region $0 \leqslant x \leqslant L$. Since $p^s(x) = 1/L$, $\phi(x)$ will not change during this process. On the other hand, such a diffusive relaxation should clearly lead to an entropy increase. Only in cases where one starts in a NESS and waits for final relaxation, the change in system entropy can also be expressed by a change in the non-equilibrium potential according to $\Delta s = \Delta\phi$.

2.5. Ensemble averages

Upon averaging, the expressions for the thermodynamic quantities along the individual trajectory should become the ensemble quantities of non-equilibrium thermodynamics derived previously for such Fokker–Planck systems, see, e.g., [19].

Averages for quantities involving the position $x(\tau)$ of the particle are most easily performed using the probability $p(x,\tau)$. Somewhat more delicate are averages over quantities such as heat that involve products of the velocity $\dot{x}$ and a function $g(x)$. These can be performed in two steps. First, one can evaluate the average $\langle \dot{x}|x,\tau\rangle$ conditioned on the position x in the spirit of the Stratonovich discretization as

$$\langle \dot{x}|x,\tau\rangle \equiv \lim_{\Delta\tau\to 0} \left(\langle x(\tau+\Delta\tau) - x(\tau)|x(\tau)=x\rangle + \langle x(\tau) - x(\tau-\Delta\tau)|x(\tau)=x\rangle\right)/(2\Delta\tau). \quad (32)$$

The averages in the brackets on the rhs can be evaluated by discretizing the path integral (equations (4) and (5)) for one step. The first term straightforwardly yields $\mu F(x,\tau)\Delta\tau$. In the second one, the end-point conditioning is crucial which leads to an additional contribution if the distribution is not uniform[3]. The final result is [20]

$$\langle \dot{x}|x(\tau)=x\rangle = \mu F(x,\tau) - D\partial_x \ln p(x,\tau) \equiv v(x,\tau). \quad (33)$$

Any subsequent average over position is now trivial leading to

$$\langle g(x)\dot{x}\rangle = \langle g(x)v(x,\tau)\rangle = \int \mathrm{d}x\, g(x)\, j(x,\tau). \quad (34)$$

With these relations, one obtains, e.g., for the averaged total entropy production rate from (31) the expression

$$\dot{S}^{\mathrm{tot}}(\tau) \equiv \langle \dot{s}^{\mathrm{tot}}(\tau)\rangle = \int \mathrm{d}x \frac{j(x,\tau)^2}{Dp(x,\tau)} = \langle v(x,\tau)^2\rangle/D \geqslant 0, \quad (35)$$

where equality holds in equilibrium only. In a NESS, $v(x,\tau) = v^s(x)$ which thus determines the mean dissipation rate. Averaging the increase in entropy of the medium along similar lines leads to

$$\dot{S}^{\mathrm{m}}(\tau) \equiv \langle \dot{s}^{\mathrm{m}}(t)\rangle = \int \mathrm{d}x\, F(x,\tau)\, j(x,\tau)/T. \quad (36)$$

Hence upon averaging, the increase in entropy of the system proper becomes $\dot{S}(\tau) \equiv \langle \dot{s}(\tau)\rangle = \dot{S}^{\mathrm{tot}}(\tau) - \dot{S}^{\mathrm{m}}(\tau)$. On the ensemble level, this balance equation for the averaged quantities can also be derived directly from the ensemble definition of the system entropy

$$S(\tau) \equiv -\int \mathrm{d}x\; p(x,\tau)\ln p(x,\tau) = \langle s(\tau)\rangle \quad (37)$$

using the Fokker–Planck equation (7).

2.6. Generalizations

2.6.1. Underdamped motion. For some systems, it is necessary to keep the inertial term which leads with mass m and damping constant γ to the Langevin equation

$$m\ddot{x} + \gamma\dot{x} = -\partial_x V(x,\lambda) + f(\lambda) + \xi \quad (38)$$

with the noise correlations $\langle \xi(\tau)\xi(\tau')\rangle = 2\gamma T\delta(\tau-\tau')$.

The internal energy now must include the kinetic energy, $\mathrm{d}E = \mathrm{d}V + mv\,\mathrm{d}v$, with $v \equiv \dot{x}$. Since the identification of work (15) remains valid, the first law becomes

$$đq = đw - \mathrm{d}E = F\,\mathrm{d}x - mv\,\mathrm{d}v. \quad (39)$$

Evaluating the stochastic entropy

$$s(\tau) \equiv -\ln p(x(\tau), v(\tau), \tau) \quad (40)$$

now requires a solution of the corresponding Fokker–Planck equation

$$\partial_\tau p = -\partial_x(vp) - \partial_v[[(-\gamma v + F)/m] - T(\gamma/m^2)\partial_v]p \quad (41)$$

for $p = p(x,v,\tau)$ with an appropriate initial condition $p_0(x,v)$.

2.6.2. Interacting degrees of freedom. The framework introduced for a single degree of freedom can easily be generalized to several degrees of freedom $\boldsymbol{x}$ obeying the coupled Langevin equations

$$\dot{\boldsymbol{x}} = \underline{\underline{\mu}}[-\boldsymbol{\nabla} V(\boldsymbol{x},\lambda) + \boldsymbol{f}(\boldsymbol{x},\lambda)] + \boldsymbol{\zeta}, \quad (42)$$

where $V(\boldsymbol{x},\lambda)$ is a potential and $\boldsymbol{f}(\boldsymbol{x},\lambda)$ a non-conservative force. The noise correlations

$$\langle \boldsymbol{\zeta}(\tau) : \boldsymbol{\zeta}(\tau')\rangle = 2T\underline{\underline{\mu}}\delta(\tau-\tau'), \quad (43)$$

where : denotes a dyadic product, involve the mobility tensor $\underline{\underline{\mu}}$. Simple examples of such system comprise a colloidal particle in three dimensions, several interacting colloidal particles, or a polymer where $\boldsymbol{x}$ labels the positions of monomers. If

[3] Specifically, using Bayes' theorem, with

$$p[x(\tau-\Delta\tau) = x-y \mid x(\tau)=x)] = p[x(\tau) = x \mid x(\tau-\Delta\tau) = x-y] \times p(x-y,\tau-\Delta\tau)/p(x,\tau) \approx p[x(\tau)=x \mid x(\tau-\Delta\tau)=x-y] \times (1 - y\partial_x \ln p(x,\tau) - \Delta\tau\partial_\tau \ln p(x,\tau)),$$

the conditioned probability becomes an ordinary forward term. The conditioned mean value of the increment $y = x(\tau) - x(\tau-\Delta\tau)$ now follows easily as $\langle y|x(\tau)=x\rangle = [\mu F(x,\tau) - 2D\partial_x \ln p(x,\tau)]\Delta\tau + O(\Delta\tau^2)$.

hydrodynamic interactions are relevant, the mobility tensor will depend on the coordinates $\boldsymbol{x}$.

The corresponding Fokker–Planck equation becomes

$$\partial_\tau p(\boldsymbol{x},\tau) = -\boldsymbol{\nabla}\boldsymbol{j} = -\boldsymbol{\nabla}(\underline{\underline{\mu}}(-\boldsymbol{\nabla}V + \boldsymbol{f})p - T\underline{\underline{\mu}}\boldsymbol{\nabla}p) \quad (44)$$

with the local (probability) current $\boldsymbol{j}$.

In particular for a NESS, there are two major formal differences compared with the one-dimensional case. First, the stationary current $\boldsymbol{j}^s(\boldsymbol{x})$ becomes $\boldsymbol{x}$ dependent and, second, the stationary distribution $p^s(\boldsymbol{x}) \equiv \exp[-\phi(\boldsymbol{x})]$ or, equivalently, the non-equilibrium potential is not known analytically except for the trivial case that the total forces are linear in $\boldsymbol{x}$.

The path integral for such a multivariate process has been pioneered by Onsager and Machlup for linear processes [60, 61] and by Graham for non-linear processes including a spatially dependent diffusion constant [62, 63]. On a formal level, all expressions discussed above for the simple colloidal particle can easily be generalized to this multidimensional case by replacing scalar operations by the corresponding vector or matrix ones.

2.6.3. Systems in external flow. So far, we have assumed that there is no overall hydrodynamic flow imposed on the system. For colloids, however, external flow is a common situation. Likewise, as we will see, colloids in moving traps can also be described in a co-moving frame as being subject to some flow. We therefore recall the modifications required for the basic notions of stochastic thermodynamics in the presence of an external flow field $\boldsymbol{u}(\boldsymbol{r})$ [64].

The Langevin equations for $k = 1,\ldots,N$ coupled particles at positions $\boldsymbol{r}_k$ reads

$$\dot{\boldsymbol{r}}_k = \boldsymbol{u}(\boldsymbol{r}_k) + \sum_l \underline{\underline{\mu}}_{kl}(-\boldsymbol{\nabla}_l V + \boldsymbol{f}_l) + \boldsymbol{\zeta}_k \quad (45)$$

with the usual noise correlations

$$\langle \boldsymbol{\zeta}_k(\tau) : \boldsymbol{\zeta}_l(\tau')\rangle = 2T\underline{\underline{\mu}}_{kl}\delta(\tau-\tau'). \quad (46)$$

In such a system, the increments in external work and dissipated heat are given by

$$đw \equiv ([\partial_\tau + \boldsymbol{u}(\boldsymbol{r}_k)\boldsymbol{\nabla}_k]V + \boldsymbol{f}_k[\dot{\boldsymbol{r}}_k - \boldsymbol{u}(\boldsymbol{r}_k)])\,\mathrm{d}t \quad (47)$$

and

$$đq = đw - dV = ([\dot{\boldsymbol{r}}_k - \boldsymbol{u}(\boldsymbol{r}_k)][-\boldsymbol{\nabla}_k V + \boldsymbol{f}_k])\,\mathrm{d}t, \quad (48)$$

respectively. Compared with the case without flow, the two modifications involve replacing the partial derivative by the convective one and measuring the velocity relative to the external flow velocity. These expressions guarantee frame invariance of stochastic thermodynamics [64].

For the experimentally studied case of one-dimensional colloid motion in a flow of constant velocity u discussed in section 5.2.2, the Langevin equation simplifies to

$$\dot{x} = u + \mu(-\partial_x V + f) + \zeta \quad (49)$$

and the ingredients of the first law become

$$đw = (\partial_\tau V + u\partial_x V)\,\mathrm{d}t + f(\dot{x}-u)\,\mathrm{d}t \quad (50)$$

and

$$đq = (\dot{x}-u)[-\partial_x V + f]\,\mathrm{d}t. \quad (51)$$

2.6.4. Inhomogeneous temperature. So far, it has been assumed that the temperature of the surrounding heat bath is uniform. The present formalism can be extended to a system embedded in an externally imposed stationary temperature gradient. In this case, the quantity T in (43) must be evaluated at the instantaneous position of the corresponding particle.[4] The same ramification has to be applied to all relations linking exchanged heat with entropy changes of the medium. For studying heat transport, similar models for particles on a lattice coupled at the boundaries to heat baths of different temperature using Langevin equations have been investigated as reviewed in [65].

Thermophoresis of particles and thermodiffusion of molecules (Soret effect) as reviewed in [66, 67] are further effects of an inhomogeneous temperature. These phenomena require a direct microscopic interaction between the molecule or colloidal particle and the solvent which give rise to an effective force that needs to be included in the Langevin or Fokker–Planck description since in the absence of external forces and interactions, a temperature gradient is not sufficient to generate biased diffusion, i.e. a non-uniform distribution.

Finally, an even more subtle case is the phenomenon of 'hot Brownian motion' where a diffusing particle heated by a laser acts as a local heat source [68–71]. The resulting temperature field is now coupled to the motion of the particle. It will be interesting to see whether and how the concepts of stochastic thermodynamics and the FTs to be discussed next can be adapted to this type of system.

3. Fluctuation theorems

Fluctuation theorems express universal properties of the probability distribution $p(\Omega)$ for functionals $\Omega[x(\tau)]$, like work, heat or entropy change, evaluated along the fluctuating trajectories taken from ensembles with well-specified initial distributions $p_0(x_0)$. In this section, we give a phenomenological classification into three classes according to their mathematical appearance and point out some general mathematical consequences. The most prominent ones will then be discussed in physical terms with references to their original derivation. For proofs of these relations within stochastic dynamics from the present perspective, we provide in section 4 the unifying one for all FTs that also shows that there is essentially an infinity of such relations.

3.1. Phenomenological classification

3.1.1. Integral fluctuation theorems. A non-dimensionalized functional $\Omega[x(\tau)]$ with probability distribution function $p(\Omega)$ obeys an integral fluctuation theorem (IFT) if

$$\langle \exp(-\Omega)\rangle \equiv \int \mathrm{d}\Omega\; p(\Omega)\exp(-\Omega) = 1. \quad (52)$$

The convexity of the exponential functions then implies the inequality

$$\langle \Omega\rangle \geqslant 0 \quad (53)$$

[4] Obviously, a complication occurs if hydrodynamically induced non-local interactions between the particles are included since then it is not clear at which of the two positions the temperature should be evaluated.

which often represents a well-known thermodynamic inequality related to the second law. With the exception of the degenerate case, $p(\Omega) = \delta(\Omega)$, the IFT implies that there are trajectories for which Ω is negative. Such events have sometimes then been characterized as 'violating' the second law. Such a formulation is controversial since classical thermodynamics, which ignores fluctuations from the very beginning, is silent on issues beyond its range of applicability. The probability of such events quickly diminishes for negative Ω. Using (52), it is easy to derive for $\omega > 0$ [72]

$$\text{prob}[\Omega < -\omega] \leqslant \int_{-\infty}^{-\omega} \mathrm{d}\Omega\; p(\Omega)\, \mathrm{e}^{-\omega-\Omega} \leqslant \mathrm{e}^{-\omega}. \qquad (54)$$

This estimate shows that relevant 'violations' occur for Ω of order 1. Restoring the dimensions in a system with N relevant degrees of freedom, Ω will typically be of order $Nk_{\mathrm{B}}T$ which implies that in a large system such events are exponentially small, i.e. occur exponentially rarely. This observation essentially reconciles the effective validity of thermodynamics at the macro-scale with the still correct mathematical statement that even for large systems, in principle, such events must occur.

An IFT represents one constraint on the probability distribution $p(\Omega)$. If it is somehow known that $p(\Omega)$ is a Gaussian, the IFT implies the relation

$$\langle(\Omega - \langle\Omega\rangle)^2\rangle = 2\langle\Omega\rangle \qquad (55)$$

between variance and mean of Ω.

3.1.2. Detailed fluctuation theorems. A detailed fluctuation theorem (DFT) corresponds to the stronger relation

$$p(-\Omega)/p(\Omega) = \exp(-\Omega) \qquad (56)$$

for the pdf $p(\Omega)$. Such a symmetry constrains 'one half' of the pdf which means, e.g., that the even moments of Ω can be expressed by the odd ones and vice versa. A DFT implies the corresponding IFT trivially. Further statistical properties of $p(\Omega)$ following from the validity of the DFT (and some from the IFT) are derived in [73].

Depending on the physical situation, a variable obeying the DFT has often been called to obey either a TFT or a steady-state FT (SSFT). These notions will be explained below for the specific cases.

3.1.3. (Generalized) Crooks fluctuation theorems. These relations compare the pdf $p(\Omega)$ of the original process one is interested in with the pdf $p^\dagger(\Omega)$ of the *same* physical quantity for a 'conjugate' (mostly the time-reversed) process. The general statement then is that

$$p^\dagger(-\Omega) = p(\Omega)\mathrm{e}^{-\Omega} \qquad (57)$$

which implies the IFT (but not the DFT) for Ω since $p^\dagger$ is normalized.

3.2. Non-equilibrium work theorems

These relations deal with the probability distribution $p(w)$ for work spent in driving the system from a (mostly equilibrium) initial state to another (not necessarily equilibrium) state. They require only a notion of work defined along the trajectory but not yet the concept of stochastic entropy.

3.2.1. Jarzynski relation. In 1997, Jarzynski showed that the work spent in driving the system from an initial equilibrium state at λ_0 via a time-dependent potential $V(x, \lambda(\tau))$ for a time t obeys [6]

$$\langle\exp(-w/T)\rangle = \exp(-\Delta\mathcal{F}/T), \qquad (58)$$

where $\Delta\mathcal{F} \equiv \mathcal{F}(\lambda_t) - \mathcal{F}(\lambda_0)$ is the free energy difference between the equilibrium state corresponding to the final value λ_t of the control parameter and the initial state. In the classification scheme proposed here, it can technically be seen as the IFT for the (scaled) dissipated work

$$w_d \equiv (w - \Delta\mathcal{F})/T. \qquad (59)$$

The paramount relevance of this relation—and its originally so surprising feature—is that it allows one to determine the free energy difference, which is a genuine equilibrium property, from non-equilibrium measurements (or simulations). It represents a strengthening of the familiar second law $\langle w\rangle \geqslant \Delta F$ which follows as the corresponding inequality. It was originally derived using a Hamiltonian dynamics but was soon shown to hold for stochastic dynamics as well [7–9]. Its validity requires that one starts in the equilibrium distribution but not that the system has relaxed at time t into the new equilibrium. In fact, the actual distribution at the end will be $p(x, t)$ but any further relaxation at constant λ would not contribute to the work anyway.

Within stochastic dynamics, the validity of the JR (as of any other FT with a thermodynamic interpretation) essentially rests on assuming that the noise in the Langevin equation (1) is not affected by the driving. A related issue arises in the Hamiltonian derivation of the JR which requires some care in identifying the proper role of the heat bath during the process, and, for the strongly coupled case, an appropriately defined free energy [74, 75].

The JR has been studied for many systems analytically, numerically and experimentally. Specific case studies for stochastic dynamics will be classified and quoted in section 5. As an important application, based on a generalization introduced by Hummer and Szabo [10], the JR can be used to reconstruct the free energy landscape of a biomolecule as discussed in section 9.3.

3.2.2. Bochkov–Kuzovlev relation. The JR should be distinguished from an earlier relation derived by Bochkov and Kuzovlev [11, 12]. For a system initially in equilibrium in a time-independent potential $V_0(x)$, which is for $0 \leqslant \tau \leqslant t$ subject to an additional space and time-dependent force (possibly arising from an additional potential), the work

(25) integrated over a trajectory obeys the Bochkov–Kuzovlev relation (BKR)

$$\langle \exp[-w^{\rm ext}/T]\rangle = 1. \tag{60}$$

In contrast to some claims, the BKR is different from the JR since they apply *a priori* to somewhat different situations [21, 76, 77]. The JR as discussed above applies to processes in a time-dependent potential, whereas the BKR applies to a process in a constant potential with some additional force. If, however, in the latter case, this explicit force arises from a potential as well, both the BKR and the JR (58) hold for the respective forms of work.

3.2.3. Crooks fluctuation theorem. In the Crooks relation, the pdf for work $p(w)$ spent in the original (the 'forward') process is related to the pdf for work $\tilde{p}(w)$ applied in the reversed process where the control parameter is driven according to $\tilde{\lambda}(\tau) = \lambda(t-\tau)$ and one starts in the equilibrium distribution corresponding to $\tilde{\lambda}_0 = \lambda_t$. These two pdfs obey [8, 9]

$$\tilde{p}(-w)/p(w) = \exp[-(w-\Delta\mathcal{F})/T]. \tag{61}$$

Hence, $\Delta\mathcal{F}$ can be obtained by locating the crossing of the two pdfs which for biomolecular applications turned out to be a more reliable method than using the JR. Clearly, the Crooks relation implies the JR since $\tilde{p}(w)$ is normalized. Technically, the Crooks relation is of the type (57) for $\Omega = w_d$ with the conjugate process being the reversed one.

3.2.4. Further general results on $p(w)$. Beyond the JR and the CFT, further exact results on $p(w)$ are scarce. For systems with linear equations of motion, the pdf for work (but not for heat) is a Gaussian for arbitrary time-dependent driving [78, 79]. For slow driving, i.e. for $t_{\rm rel}/t \ll 1$ where $t_{\rm rel}$ is the typical relaxation time of the system at fixed λ and t the duration of the process, an expansion based on this time-scale separation yields a Gaussian for any potential [80]. Such a result has previously been expected [81, 82] or justified by invoking arguments based on the central limit theorem [83]. Two observations show, however, that such an expansion is somewhat delicate. First, even in simple examples there occur terms that are non-analytic in $t_{\rm rel}/t$ [80]. Second, for the special case of a 'breathing parabola', $V(x,\lambda) = \lambda(\tau)x^2/2$, any protocol with $\dot{\lambda} > 0$ leads to $p(w) \equiv 0$ for $w < 0$ which is obviously violated by a Gaussian. How the latter effectively emerges in the limit of slow driving is investigated in [84].

From another perspective, Engel [85, 86] investigated the asymptotic behavior of $p(w)$ for small T using a saddle point analysis. The value of this approach is that it can provide exact results for the tail of the distribution. Specific examples show an exponential decay. Saha *et al* [87] suggest that the work distribution for quite different systems can be mapped to a class of universal distributions.

3.3. FTs for entropy production

3.3.1. Integral fluctuation theorem. The total entropy production along a trajectory as given by

$$\Delta s^{\rm tot} \equiv \Delta s^{\rm m} + \Delta s, \tag{62}$$

with

$$\Delta s \equiv -\ln p(x_t,\lambda_t) + \ln p(x_0,\lambda_0) \tag{63}$$

and $\Delta s^{\rm m}$ defined in (27), obeys the IFT [20]

$$\langle \exp(-\Delta s^{\rm tot})\rangle = 1 \tag{64}$$

for arbitrary initial distribution $p(x,0)$, arbitrary time-dependent driving $\lambda(\tau)$ and an arbitrary length t of the process.

Formally, this IFT can be considered as a refinement of the second law, $\langle \Delta s^{\rm tot}\rangle \geqslant 0$, which is the corresponding inequality. Physically, however, it must be stressed that by using the Langevin equation a fundamental irreversibility has been implemented from the very beginning. Thus, this IFT should definitely not be considered to constitute a fundamental proof of the second law.

3.3.2. Steady-state fluctuation theorem. In a NESS with fixed λ, the total entropy production obeys the stronger SSFT

$$p(-\Delta s^{\rm tot})/p(\Delta s^{\rm tot}) = \exp(-\Delta s^{\rm tot}) \tag{65}$$

again for arbitrary length t. This relation corresponds to the genuine 'fluctuation theorem'. It was first found in simulations of two-dimensional sheared fluids [1] and then proven by Gallavotti and Cohen [2] using assumptions about chaotic dynamics. For stochastic diffusive dynamics as considered specifically in this review, it has been proven by Kurchan [3] and Lebowitz and Spohn [4]. Strictly speaking, in these early works the relation holds only asymptotically in the long-time limit since entropy production had been associated with what is here called entropy production in the medium. If one includes the entropy change of the system (63), the SSFT holds even for finite times in the steady state [20].

3.3.3. Transient fluctuation theorem. The TFT pioneered by Evans and Searles applies to relaxation toward a steady state [5, 37, 88]. The 'dissipation function' Ω_t, which as defined more precisely in section 4.4.5 is related to, but, in general, different from total entropy production $\Delta s^{\rm tot}$, obeys

$$p(-\Omega_t)/p(\Omega_t) = \exp(-\Omega_t) \tag{66}$$

for any length of trajectories t.

3.3.4. Hatano–Sasa relation. The Hatano–Sasa relation applies to systems with steady states $p^s(x,\lambda) = \exp[-\phi(x,\lambda)]$. With the splitting of the dissipated heat into a housekeeping and excess one (21), the IFT [13]

$$\langle \exp[-(\Delta\phi + q^{\rm ex}/T)]\rangle = 1 \tag{67}$$

holds for any length of trajectory with $\Delta\phi \equiv \phi(x_t,\lambda_t) - \phi(x_0,\lambda_0)$. The corresponding inequality

$$\langle \Delta\phi\rangle \geqslant -\langle q^{\rm ex}\rangle/T \tag{68}$$

allows an interesting thermodynamic interpretation. The left-hand side (lhs) can be seen as the ensemble entropy change of the system in a transition from one steady state

to another. Within the framework discussed in this review, this interpretation is literally true provided one waits for final relaxation at constant λ_t since then $\Delta s = \Delta\phi$. A recent generalization of the HS relation leads to a variational scheme for approximating the stationary state [89].

With the interpretation of the lhs as entropy change in the system, the inequality (68) provides for transitions between NESSs what the famous Clausius inequality does for transitions between equilibrium states. The entropy change in the system is at least as big as the excess heat flowing into the system. For transitions between NESSs, the inequality (68) is sharper than the Clausius one (which still applies in this case and becomes just $\langle\Delta s\rangle \geqslant -q/T$) since q scales with the transition time whereas $q^{\rm ex}$ can remain bounded and can actually approach equality in (68) for quasi-static transitions.

Experimentally, the Hatano–Sasa relation has been verified for a colloidal particle pulled through a viscous liquid at different velocities which corresponds to different steady states [90].

3.3.5. IFT for housekeeping heat. Finally, it should be noted that the second contribution to heat, the housekeeping heat, also obeys an IFT [91]

$$\langle\exp[-q^{\rm hk}/T]\rangle = 1 \tag{69}$$

for arbitrary initial state, driving and length of trajectories.

4. Unification of FTs

Originally, the FTs have been found and derived on a case by case approach. However, it has soon become clear that within stochastic dynamics a unifying strategy is to investigate the behavior of the system under time reversal. Subsequently, it turned out that comparing the dynamics with its 'dual' one [13, 92, 93], eventually also in connection with time reversal, allows a further unification. In this section, we outline this general approach and show how the prominent FTs discussed above (and a few further ones mentioned below) fit into, or derive from, this framework. Even though this section is inevitably somewhat technical and dense, it is self-contained. It could be skipped by readers not interested in the proofs or systematics of the FTs. For related mathematically rigorous approaches to derive FTs for diffusive dynamics, see [94–97].

4.1. Conjugate dynamics

FTs for the original process with trajectories $x(\tau)$, $0 \leqslant \tau \leqslant t$, an initial distribution $p_0(x_0)$ and a conditional weight $p[x(\tau)|x_0]$ are most generally derived by formally invoking a 'conjugate' dynamics for trajectories $x^\dagger(\tau)$. These are supposed to obey a Langevin equation

$$\dot{x}^\dagger = \mu^\dagger F^\dagger(x^\dagger, \lambda^\dagger) + \zeta^\dagger \tag{70}$$

with $\langle\zeta^\dagger(\tau)\zeta^\dagger(\tau')\rangle = 2\mu^\dagger T^\dagger\delta(\tau-\tau')$. The trajectories with weight $p^\dagger[x^\dagger(\tau)|x_0^\dagger]$ run over a time t and start with an initial distribution $p^\dagger(x_0^\dagger)$. Averages of the conjugate dynamics will be denoted by $\langle\ldots\rangle^\dagger$.

This conjugate dynamics is related to the original process by a one-to-one mapping

$$\{x(\tau), \lambda(\tau), F, \mu, T\} \to \{x^\dagger(\tau), \lambda^\dagger(\tau), F^\dagger, \mu^\dagger, T^\dagger\} \tag{71}$$

which allows one to express all quantities occurring in the conjugate dynamics in terms of the original ones.

The crucial quantity leading to the FTs is a master functional given by the log-ratio of the unconditioned path weights

$$\begin{aligned} R[x(\tau)] &\equiv \ln\frac{p[x(\tau)]}{p^\dagger[x^\dagger(\tau)]} \\ &= \ln\frac{p_0(x_0)}{p_0^\dagger(x_0^\dagger)} + \ln\frac{p[x(\tau)|x_0]}{p^\dagger[x^\dagger(\tau)|x_0^\dagger]} \equiv R_0 + R_1 \end{aligned} \tag{72}$$

that consists of a 'boundary' term R_0 coming from the two initial distributions and a 'bulk' term R_1.

Three choices for the conjugate dynamics and the associated mapping have been considered so far. In all cases, neither the temperature nor the functional form of the mobilities have been changed for the conjugate dynamics, i.e. $T^\dagger = T$ and $\mu^\dagger = \mu$.

(i) *Reversed dynamics:* this choice corresponds to 'time reversal'. The mapping reads

$$x^\dagger(\tau) \equiv x(t-\tau) \qquad \text{and} \qquad \lambda^\dagger(\tau) \equiv \lambda(t-\tau) \tag{73}$$

with no changes at the functional dependence of the force from its arguments, i.e. $F^\dagger(x^\dagger, \lambda^\dagger) = F(x^\dagger, \lambda^\dagger)$.
The weight of the conjugate trajectories is easily calculated using the mapping (73) in the weight (equations (4), (5)) leading to

$$\begin{aligned} R_1 &= \mathcal{A}([x^\dagger(\tau), \lambda^\dagger(\tau)]) - \mathcal{A}([x(\tau), \lambda(\tau)])] \\ &= \Delta s^{\rm m} = q/T, \end{aligned} \tag{74}$$

which is the part of the action $\mathcal{A}([x(\tau), \lambda(\tau)])$ that is odd under time reversal.
This relation allows a deep physical interpretation. For given initial point x_0 and final point x_t, the log-ratio between the probability to observe a certain forward trajectory and the probability to observe the time-reversed trajectory is given by the heat dissipated along the forward trajectory.

(ii) *Dual dynamics:* this choice alters the equations of motion for the $x^\dagger(\tau)$ trajectories such that (i) the stationary distribution remains the same for both processes and that (ii) the stationary current for the dual dynamics is minus the original one. Specifically, this mapping reads [92]

$$F^\dagger(x^\dagger, \lambda^\dagger) = F(x^\dagger, \lambda^\dagger) - 2v^s(x^\dagger, \lambda^\dagger)/\mu \tag{75}$$

which enters the conjugate Langevin equation (70) and no modification for x and λ, i.e. $x^\dagger(\tau) \equiv x(\tau)$ and $\lambda^\dagger(\tau) \equiv \lambda(\tau)$.
Calculating the action for the dual dynamics (70), the functional R_1 becomes

$$R_1 = q^{\rm hk}/T \equiv \Delta s^{\rm hk}. \tag{76}$$

(iii) *Dual-reversed dynamics:* for this choice, the dual dynamics is driven with the time-reversed protocol, i.e. the mapping of the force (75) is combined with the time reversal (73). In this case, the functional R_1 becomes [92]

$$R_1 = q^{\rm ex}/T \equiv \Delta s^{\rm ex}. \tag{77}$$

In summary, depending on the form of the conjugate dynamics, different parts of the dissipated heat form the functional R_1. For later reference, we have introduced in the last two equations for the scaled contributions to the dissipated heat the corresponding entropies.

4.2. The master FT

4.2.1. Functionals with definite parity. The FTs apply to functionals $S_\alpha[x(\tau)]$ of the original dynamics that map with a definite parity $\epsilon_\alpha = \pm 1$ to the conjugate dynamics according to

$$S_\alpha^\dagger\left([x^\dagger(\tau)], \lambda^\dagger, F^\dagger\right) = \epsilon_\alpha S_\alpha\left([x(\tau)], \lambda, F\right) \tag{78}$$

such that $S_\alpha^\dagger[x^\dagger(\tau)]$ represents the *same* physical quantity for the conjugate dynamics as $S_\alpha[x(\tau)]$ does for the original one.

Examples for such functionals are work and heat that both are odd ($\epsilon_\alpha = -1$) for the reversed dynamics. For dual or dual-reversed dynamics, however, these two functionals have no definite parity since both cases involve a different dynamics. Explicitly, the heat behaves under time reversal as $q^\dagger \equiv \int_0^t {\rm d}\tau \dot{x}^\dagger F^\dagger = -\int_0^t {\rm d}\tau \dot{x} F = -q$. For dual dynamics, the heat transforms as $q^\dagger \equiv \int_0^t {\rm d}\tau \dot{x}^\dagger F^\dagger = \int_0^t {\rm d}\tau \dot{x}(F - 2v^s/\mu) = q - 2q^{\rm hk}$ which has, in general, no definite parity. On the other hand, the housekeeping heat is odd for the dual dynamics and even for both the reversed and the dual-reversed dynamics.

The stochastic entropy Δs, in general, has no definite parity under time reversal since $s(\tau)$ is defined through the solution $p(x,\tau)$ of the Fokker–Planck equation which is not odd under time reversal. In particular, $p(x, t-\tau)$ does not solve the Fokker–Planck equation for the time-reversed process even if one starts the reversed process with the final distribution $p(x,t)$ of the original process. The change in the non-equilibrium potential $\Delta\phi$, however, is odd under time reversal. This difference between Δs and $\Delta\phi$ implies that $\Delta\phi$ occurs more frequently in FTs.

4.2.2. Proof. With these preparations, one can easily derive the master FT

$$\begin{aligned}
&\langle g(\{\epsilon_\alpha\ S_\alpha^\dagger[x^\dagger(\tau)]\})\rangle^\dagger \\
&\quad = \int {\rm d}x_0^\dagger \int {\rm d}[x^\dagger(\tau)] p_0^\dagger(x_0^\dagger) p[x^\dagger(\tau)|x_0^\dagger] g(\{\epsilon_\alpha S_\alpha^\dagger\}) \\
&\quad = \int {\rm d}x_0^\dagger \int {\rm d}[x^\dagger(\tau)] p_0(x_0) p[x(\tau)|x_0] \exp[-R] g(\{S_\alpha\}) \\
&\quad = \int {\rm d}x_0 \int {\rm d}[x(\tau)] p_0(x_0) p[x(\tau)|x_0] \exp[-R] g(\{S_\alpha\}) \\
&\quad = \langle g(\{S_\alpha[x(\tau)]\}) \exp(-R[x(\tau)])\rangle
\end{aligned} \tag{79}$$

for any function g depending on an arbitrary number of such functionals S_α. For the second equality, we use the definitions (72) and the parity relation (78); for the third we recognize that summing over all daggered trajectories is equivalent to summing over all original ones both for $x^\dagger(\tau) = x(\tau)$ and $x^\dagger(\tau) = x(t-\tau)$. With the choice $g \equiv 1$, this FT leads to the most general IFT $\langle {\rm e}^{-R}\rangle = 1$ from which all known IFT-like relations follow, as shown in section 4.3.

By choosing for g the characteristic function, one obtains a generalized FT for joint probabilities in the form

$$\frac{p^\dagger(\{S_\alpha^\dagger = \epsilon_\alpha s_\alpha\})}{p(\{S_\alpha = s_\alpha\})} = \langle \exp(-R)|\{S_\alpha\} = \{s_\alpha\}\rangle \tag{80}$$

that relates the pdf for the conjugate process to the pdf of the original one and a conditional average. Basically all known DFTs for stochastic dynamics follow as special cases of this general theorem as shown in section 4.4. The key point is to (i) select the appropriate conjugate process for which the quantity of interest Ω has a unique parity, which is most often just the reversed dynamics, (ii) identify for the generally free initial distribution $p_0^\dagger(x)$ an appropriate function and (iii) express the functional R using physical quantities, preferentially the quantity of interest Ω.

4.3. General IFTs

The simplest choice for the function g in (79) is the identity, $g = 1$, leading to the IFT $\langle {\rm e}^{-R}\rangle = 1$. Explicitly, one obtains for the three types of conjugate dynamics.

(i) By choosing the reversed dynamics (73) and with (74), the class of IFTs

$$\left\langle \frac{p_1(x_t)}{p_0(x_0)} \exp[-\Delta s^{\rm m}] \right\rangle = 1 \tag{81}$$

follows for any initial condition $p_0(x_0)$, any length of trajectories t, and any normalized function $p_1(x_t) = p_0^\dagger(x_t)$ [20]. By specializing the latter to the solution of the Fokker–Planck equation for $\tau = t$ one obtains the IFT for total entropy production (64).

For a system in a time-dependent potential $V(x,\lambda)$ and by starting in an initial distribution given by the corresponding Boltzmann factor, $p_0(x) = \exp[-(V(x,\lambda_0) - \mathcal{F}(\lambda_0))/T]$, one obtains the JR (58) for the choice $p_1(x_t) = \exp[-(V(x,\lambda_t) - \mathcal{F}(\lambda_t))/T]$ corresponding to the Boltzmann distribution for the final value of the control parameter.

A variety of 'end-point' relations can be generated from (81) as follows. By choosing $p_1(x) = p(x,t)g(x)/\langle g(x_t)\rangle$, one obtains

$$\langle g(x_t) \exp[-\Delta s^{\rm tot}]\rangle = \langle g(x_t)\rangle \tag{82}$$

for any function $g(x)$ [98]. Likewise, for $f \equiv 0$ and $V(x,\lambda(\tau))$, by choosing $p_1(x) = g(x)\exp[-(V(x,\lambda_t) - \mathcal{F}(\lambda_t))/T]/\langle g(x)\rangle_{\lambda_t}^{\rm eq}$, one obtains

$$\langle g(x_t) \exp[-(w - \Delta\mathcal{F})/T]\rangle = \langle g(x)\rangle_{\lambda_t}^{\rm eq} \tag{83}$$

which has been first derived by Crooks [9]. Here, the average on the rhs is the equilibrium average at the final

value of the control parameter. In the same fashion, one can derive

$$\langle g(x_t)\exp[-w^{\rm ext}/T]\rangle = \langle g(x)\rangle^{\rm eq}_{\lambda_0} \tag{84}$$

by choosing $p_1(x) = g(x)\exp[-(V(x,\lambda_0) - \mathcal{F}(\lambda_0)))/T]/\langle g(x)\rangle^{\rm eq}_{\lambda_0}$ for a time-independent potential and arbitrary force $f(x,\tau)$ which is the end-point relation corresponding to the BKR (60). The latter follows trivially by choosing $g(x) = 1$.

For processes with feedback control as discussed in section 7.3, it will be convenient to exploit the end-point conditioned average

$$\left\langle \frac{1}{p_0(x_0)}\exp[-\Delta s^{\rm m}]\big|x_t = x\right\rangle p(x,t) = 1 \tag{85}$$

valid for any x which follows from (81) by choosing $p_1(x_t) = \delta(x_t - x)$. Equivalently, by choosing $p_1(x_t) = p(x,t)$,

$$\int {\rm d}x_0 \langle \exp[-\Delta s^{\rm m}]p(x_t,t)|x_0\rangle = 1 \tag{86}$$

holds for summing over the initial point conditioned average.

(ii) Using the dual dynamics with $p_0^\dagger(x_0) = p_0(x_0)$, the IFT for the housekeeping heat [91]

$$\langle \exp[-q^{\rm hk}/T]\rangle = 1 \tag{87}$$

valid for any initial distribution follows.

(iii) For the dual-reversed dynamics, one obtains the class of IFTs from

$$\left\langle \frac{p_1(x_t)}{p_0(x_0)}\exp[-q^{\rm ex}/T]\right\rangle = 1 \tag{88}$$

valid for any initial distribution $p_0(x_0)$ and any normalized function $p_1(x_t)$. By choosing $p_0(x_0) = \exp[-\phi(x_0,\lambda_0)]$ and $p_1(x_t) = \exp[-\phi(x_t,\lambda_t)]$, one obtains the Hatano–Sasa relation (67). Similarly, another class of end-point relations could be generated starting from (88).

Finally, since the IFTs, $\langle\exp[-\Omega]\rangle = 1$, do not explicitly involve the conjugate process, one might wonder whether they can be derived in an alternative way. Indeed, some of them can be obtained by deriving an appropriate Fokker–Planck-type equation for the joint pdf $p(\Omega,x,\tau)$ and then showing $\partial_\tau\langle {\rm e}^{-\Omega}\rangle = \partial_\tau \int {\rm d}\Omega \int {\rm d}x\ {\rm e}^{-\Omega}p(\Omega,x,\tau) = 0$ directly, see for the JR [7], for the housekeeping heat [91], and for another large class of IFTs [92]. Both the JR and (82) can also be derived by a Feynman–Kac approach [10].

4.4. FTs derived from time reversal

In this section, the FTs following from using time reversal as conjugate dynamics are derived systematically from (80) by specializing to the various scenarios concerning initial conditions and type of driving. More or less reversing the chronological development, we start with the more general cases and end with the more specific ones, for which the strongest constraints on these pdfs follow.

4.4.1. *CFTs involving reversed dynamics.*

By starting original and reversed dynamics in the respective stationary state, the functional R becomes

$$R = \Delta\phi + \Delta s^{\rm m}. \tag{89}$$

Hence, one obtains from (80) the FT

$$\frac{p^\dagger(\{S^\dagger_\alpha = \epsilon_\alpha s_\alpha\})}{p(\{S_\alpha = s_\alpha\})} = \langle\, {\rm e}^{-(\Delta\phi+\Delta s^{\rm m})}|\{S_\alpha\} = \{s_\alpha\}\rangle. \tag{90}$$

For the special case that $\sum_\alpha S_\alpha = \Delta\phi + \Delta s^{\rm m}$, this relation has first been derived by Garcia-Garcia *et al* [99]. Note that in general the change in stochastic entropy Δs is not an admissible choice for S_α since it lacks definite parity under time reversal.

By choosing for S_α the work w, one obtains

$$p^\dagger(-w) = p(w)\langle {\rm e}^{-(\Delta\phi+\Delta s^{\rm m})}|w\rangle. \tag{91}$$

From this relation, the Crooks FT (57) follows for a time-dependent $V(x,\lambda(\tau))$ and $f = 0$, if one samples both processes from the respective initial equilibria, since then $\Delta\phi = \Delta(V - \mathcal{F})/T$ and hence $R = (w - \Delta\mathcal{F})/T$.

Likewise, by choosing $S_\alpha = w\chi_A(x_0)\chi_b(x_t)$, where $\chi_{A,B} \equiv 1(0)$ if $x \in (\notin)A, B$ are the characteristic functions of two regions A and B, one obtains the variants derived and discussed in [100, 101] which allow one to extend the CFT to 'partially equilibrated' initial and final states. These variants have become useful in recovering free energy branches in single molecule experiments.

As another variant, by choosing for S_α the work $w^{\rm ext}$ and by starting the reverse process in the initial equilibrium, one obtains with $\Delta\phi = \Delta V^0$ and $R = (\Delta V^0 + q)/T = w^{\rm ext}$ the Crooks relation for $w^{\rm ext}$ [77]

$$p^\dagger(-w^{\rm ext})/p(w^{\rm ext}) = \exp[-w^{\rm ext}/T]. \tag{92}$$

4.4.2. *DFTs for symmetric and periodic driving.*

For symmetric driving, $\lambda(\tau) = \lambda(t-\tau)$, and for $p_0^\dagger(x_0^\dagger) = p_0(x_0)$, the reversed dynamics becomes the original one. Hence, the FTs (90,91) derived in the previous subsection remain valid in this case if one replaces $p^\dagger$ on the lhs with p. In this case, as in those in the following subsections, the FTs no longer involve the conjugate dynamics explicitly which thus has become a mere mathematical tool to derive these relations most efficiently. In particular, for starting in the initial equilibrium, $R = w/T$ and one obtains for the pdf of work [102, 103]

$$p(-w)/p(w) = \exp[-w/T]. \tag{93}$$

Likewise, for a periodically driven system with an integer number of symmetric periods of length t_p, i.e. $\lambda(t_p - \tau) = \lambda(\tau)$, the reversed dynamics is the original one. If the distribution has settled into a periodic stationary state, one has the DFT-like relation for total entropy production [104, 105]. Note that it is crucial to choose not only a periodic but also a symmetric protocol since otherwise the reversed dynamics is not the original one.

4.4.3. SSFTs for NESSs. For a NESS, i.e. for time-independent driving and starting in the stationary state, the reversed dynamics becomes the original one and thus $R = \Delta s^{\rm tot}$. Then (80) implies the generalized SSFT for joint probabilities in the form

$$\frac{p(\{S_\alpha = \epsilon_\alpha s_\alpha\})}{p(\{S_\alpha = s_\alpha\})} = \langle {\rm e}^{-\Delta s_{\rm tot}} | \{S_\alpha\} = \{s_\alpha\}\rangle. \qquad (94)$$

For this case, system entropy is indeed odd, and hence one also has, in particular, by choosing $S_\alpha = \Delta s^{\rm tot}$ the genuine SSFT (65) for total entropy production and arbitrary length t. As variants, illustrating the potency of the general theorem, one easily gets from (94)

$$p(-\Delta s) = p(\Delta s){\rm e}^{-\Delta s}\langle {\rm e}^{-\Delta s^{\rm m}} | \Delta s\rangle \qquad (95)$$

and

$$p(-\Delta s^{\rm m}) = p(\Delta s^{\rm m}){\rm e}^{-\Delta s^{\rm m}}\langle {\rm e}^{-\Delta s} | \Delta s^{\rm m}\rangle \qquad (96)$$

involving conditional averages. Such relations seem not to have been explored in specific systems yet.

4.4.4. Expression for the NESS distribution. Using an initial and end-point conditioned variant of (80), Komatsu *et al* manage to express the stationary distribution $p^s(x)$ in a NESS by non-linear averages over the difference in 'excess' heat required either to reach x from the steady state or to reach the NESS starting in x [106–108] which leads to Clausius-type relations for NESSs [109]. For a related expression for $p^s(x)$ in terms of an expansion around a corresponding equilibrium state, see [110] which contains a valuable introduction into the history of such approaches. Following similar lines an exact non-equilibrium extension of the Clausius heat theorem has been derived in [111].

4.4.5. TFT. This relation applies to *time-independent* driving and arbitrary initial condition $p_0(x_0)$. If the reversed dynamics is sampled using the same initial condition, $p_0^\dagger(x_0^\dagger) = p_0(x_0)$, then the functional R becomes

$$R = -\ln[p_0(x_t)/p_0(x_0)] + q/T \equiv \Omega_t \qquad (97)$$

which has been called dissipation functional by Evans and Searles [37]. Under these conditions, it is related via

$$\Omega_t = \Delta s^{\rm tot} - \ln[p_0(x_t)/p(x_t, t)] \qquad (98)$$

to total entropy production. Physically, Ω_t corresponds to the log-ratio between the probability to observe the original trajectory and the one for observing the time-reversed one. Since under these conditions Ω_t is odd and the reversed dynamics is equivalent to the original one, one has from (80) the TFT (66) valid for any length t and initial condition. Specifically, if the system is originally equilibrated in a potential $V_0(x)$ and then suddenly subject to a force $f(x)$ the dissipation functional becomes $\Omega_t = w/T$ which implies that in this case the TFT holds for work.

4.5. FTs for variants

4.5.1. FTs for underdamped motion. For underdamped motion as introduced in section 2.6.1, the functional R_1 defined in (72) under time reversal is still given by the dissipated heat, i.e., by (39) integrated over the trajectory [112]. This fact follows by directly evaluating the action for the path integral corresponding to the underdamped Langevin equation (38). Hence, FTs based on time reversal hold true also for underdamped dynamics with the obvious modification that initial (and daggered) distributions now depend on x and v.

4.5.2. FTs in the presence of external flow. In the presence of flow, one has to specify how the flow changes in the conjugate dynamics. For genuine time reversal, the physically appropriate choice is $\boldsymbol{u}(\boldsymbol{r})^\dagger = -\boldsymbol{u}(\boldsymbol{r})$ which leads with the definitions of work and heat (equations (47), (48)) to an odd parity for these two functionals. Consequently, the FTs then hold as in the case without flow. Formally, however, one could also keep the flow unchanged for the conjugate dynamics, $\boldsymbol{u}(\boldsymbol{r})^\dagger = \boldsymbol{u}(\boldsymbol{r})$, which would lead to another class of FTs. For a specific example illustrating this freedom, see the discussion in [64] for a dumbbell in shear flow first investigated in [113].

4.5.3. FT with magnetic field. In the presence of a (possibly time-dependent) magnetic field, the FTs hold true essentially unchanged as proven in great generality for the JR and the CFT for interacting particles on a curved surface [114]. This work generalized earlier case studies on the validity of the JR for specific situations involving a magnetic field as mentioned in section 5.2. A second motivation for this work was to refute earlier claims based on simulations that the Bohr–van-Leeuven theorem stating the absence of classical diamagnetism could fail for a closed topology [115].

4.5.4. Further 'detailed theorems'. Esposito and van den Broeck have derived what they call DFTs for $\Delta s^{\rm tot}$, $\Delta s^{\rm hk}$, (called 'adiabatic' entropy change $\Delta s^{\rm ad}$) and for the 'non-adiabatic' entropy change $\Delta s^{\rm na} \equiv \Delta s^{\rm ex} + \Delta s$ under even more general conditions [116–118]. Their relations are beyond the realm of the present systematics since they compare the pdf for *different* physical quantities for the original and the conjugate process whereas we always compare the pdfs of the *same* physical quantities[5]. A unification of FTs within this broader sense involving joint distributions of these decompositions of entropy production is achieved in [93] and a generalization of the Hatano–Sasa relation in [119]. The crucial role of odd variables in such a scheme is emphasized in [120, 121].

4.6. FTs for athermal systems

4.6.1. General Langevin systems. The derivation of the master FT in section 4.2 shows that for obtaining these mathematical relations the main requirement is the existence of a conjugate dynamics such as time reversal. Therefore, imposing a relation between the strength of the noise and the

[5] The IFT $\langle \exp[-\Delta s^{\rm na}]\rangle = 1$, however, follows directly from (88) by choosing $p_1(x_t) = p(x, t)$.

mobility as carried out in section 2.1 for colloidal particles is not really necessary. Neither is it necessary to interpret the Langevin equation using concepts of work and heat. We therefore sketch in this section the general FT for a system of Langevin equations

$$\dot{\boldsymbol{x}} = \boldsymbol{K}(\boldsymbol{x}, \lambda) + \boldsymbol{\zeta} \tag{99}$$

with arbitrary 'force' $\boldsymbol{K}$ and noise correlations

$$\langle \boldsymbol{\zeta}(\tau) : \boldsymbol{\zeta}(\tau') \rangle = 2\underline{\underline{D}}\delta(\tau - \tau'). \tag{100}$$

The corresponding Fokker–Planck equation becomes

$$\partial_\tau p(\boldsymbol{x}, \tau) = -\boldsymbol{\nabla}\boldsymbol{j} = -\boldsymbol{\nabla}(\boldsymbol{K}p - \underline{\underline{D}}\boldsymbol{\nabla}p) \tag{101}$$

and the local (probability) current $\boldsymbol{j}(\boldsymbol{x}, \lambda)$. For constant λ, one has the local mean velocity

$$\boldsymbol{\nu}^s(\boldsymbol{x}, \lambda) \equiv \boldsymbol{j}^s(\boldsymbol{x}, \lambda)/p^s(\boldsymbol{x}, \lambda) = \boldsymbol{K}(\boldsymbol{x}, \lambda) - \underline{\underline{D}}\boldsymbol{\nabla} \ln p^s. \tag{102}$$

For time reversal as conjugate dynamics, by evaluating the corresponding weight one obtains for the master functional (74)

$$R_1 = \int_0^t \mathrm{d}\tau \dot{\boldsymbol{x}} \underline{\underline{D}}^{-1}\boldsymbol{K} \equiv \Delta s^{\mathrm{m}} \tag{103}$$

where the identification with Δs^{m} is now purely formal. If one adds the stochastic entropy change along a trajectory

$$\Delta s \equiv -\ln[p(\boldsymbol{x}_t, \lambda_t)/p(\boldsymbol{x}_0, \lambda_0)] \tag{104}$$

one obtains the total entropy production Δs^{tot}. Likewise, in analogy to the colloidal case, Δs^{m} can be split into

$$\Delta s^{\mathrm{hk}} \equiv \int_0^t \mathrm{d}\tau \dot{x} \underline{\underline{D}}^{-1}\boldsymbol{\nu}^s \tag{105}$$

and

$$\Delta s^{\mathrm{ex}} \equiv \Delta s^{\mathrm{m}} - \Delta s^{\mathrm{hk}} = \int_0^t \mathrm{d}\tau \dot{\boldsymbol{x}}\boldsymbol{\nabla} \ln p^s = -\Delta\phi + \int_0^t \mathrm{d}\tau \dot{\lambda}\partial_\lambda \phi. \tag{106}$$

With these identifications all FTs involving the various forms of entropy production derived and discussed in sections 3.3 and 4 hold true for such Langevin systems as well.

The identification of a generalized work makes immediate sense only if $\boldsymbol{K} = -(\underline{\underline{D}}/T)\boldsymbol{\nabla}V(\boldsymbol{x}, \lambda)$ with some potential $V(\boldsymbol{x}, \lambda)$ and effective temperature T in which case one is back to the thermal model with interacting degrees of freedom introduced in section 2.6.2. If $\boldsymbol{K}$ cannot be derived in this way from a gradient field there seems to be no gain by trying to impose a genuine thermodynamic interpretation without further physical input.

4.6.2. Stochastic fields. The generalization of the results in the previous section for coupled Langevin equations to stochastic field equations is trivially possible [21]. Consider a scalar field $\Psi(\boldsymbol{r}, \tau)$ that obeys

$$\partial_\tau \Psi(\boldsymbol{r}, \tau) = K[\Psi(\boldsymbol{r}, \tau), \lambda(\tau)] + \zeta(\boldsymbol{r}, \tau) \tag{107}$$

with some functional $K[\Psi(\boldsymbol{r}, \tau), \lambda(\tau)]$ and

$$\langle \zeta(\boldsymbol{r}, \tau)\zeta(\boldsymbol{r}', \tau') \rangle = 2D(\boldsymbol{r} - \boldsymbol{r}')\delta(\tau - \tau') \tag{108}$$

with arbitrary spatial correlation $D(\boldsymbol{r} - \boldsymbol{r}')$. The expressions for the entropy terms can easily be inferred; e.g. the analogy of the entropy change in the medium becomes

$$\Delta s^{\mathrm{m}} \equiv \int_0^t \mathrm{d}\tau \int \mathrm{d}\boldsymbol{r} \int \mathrm{d}\boldsymbol{r}' \partial_\tau \Psi(\boldsymbol{r}, \tau) D^{-1}(\boldsymbol{r} - \boldsymbol{r}') \times K[\Psi(\boldsymbol{r}', \tau), \lambda(\tau)]. \tag{109}$$

By now, it should be obvious how to derive the corresponding FTs and how to generalize all these also to the case when $\Psi(\boldsymbol{r}, \tau)$ is a multi-component field. Likewise, it would be a trivial task to specialize all this to driven or relaxing 'thermal' field theories for which $\boldsymbol{K}$ includes the derivative of some Landau–Ginzburg type free energy and where the noise obeys an FDT [122].

An interesting application concerns enstrophy dissipation in two-dimensional turbulence [123]. Field-theoretic techniques are used in [124] to derive generalized JRs and to explore the role of supersymmetry in this context. Quite generally, it will be interesting to investigate stochastic versions of the field equations of active matter [125] from this perspective.

4.6.3. FTs in evolutionary dynamics. The framework of FTs has recently been applied to the stochastic evolution of molecular biological systems where it leads to an IFT for fitness flux [126].

5. Experimental, analytical and numerical work for specific systems with continuous degrees of freedom

5.1. Principal aspects

The various relations derived and discussed above have the status of mathematically exact statements. As such they require neither a 'test' nor a 'verification'. The justification for, and the value of, the large body of experimental and numerical work that has appeared in this field over the last decade rather arises from the following considerations.

First, experimental and numerical measurements of the distributions $p(\Omega)$ entering the theorems provide non-trivial information about the specific system under consideration. Integral and detailed theorems give only one constraint on, and constrain only one half of, the distribution, respectively. Beyond the constraints imposed by the exact relations, the distributions are non-universal in particular for short times.

Second, the theorems involve non-linear averages. The necessarily limited number of data entering experimental or numerical estimates can cause deviations from the predicted exact behavior. It is important to get experience of how large such statistical errors are. Systematic theoretical investigations concerning the error due to finite sampling are mentioned in section 9.3.

Third, the thermodynamic interpretation of the mathematical relations in terms of work, heat and entropy rests on the

crucial assumption that the noise in the Langevin equation is not affected by the driving. While this condition can trivially be guaranteed in simulations, it could be violated in experiments. A statistically significant deviation of experimental results from a theoretical prediction could be rooted in the violation of this assumption.

These remarks apply to systems where one expects at least in principle that a stochastic description of the relevant degrees of freedom well-separated in time-scale from an equilibrated heat bath is applicable. There are, however, systems that *a priori* do not belong to this class like sheared molecular fluids, shaken granular matter and alike. The proof of FTs given above will not apply to such systems. Still, FTs have been proved for other types of dynamics and experimentally investigated in such systems.

In the following we first focus on a review of experimental and numerical work of the first category and then briefly mention systems for which it is less clear whether they comply with the assumptions of a stochastic dynamics. When referring to the experiments and the numerical work, we will use the notions and notations established in this review, which may occasionally differ from those given by the original authors.

5.2. Overdamped motion: colloidal particles and other systems

5.2.1. Equilibrium pdf for heat. Even in equilibrium, explicit calculations of the pdf for heat are typically non-trivial. In the long time $t \to \infty$, low temperature $T \to 0$ limit, it has been calculated for an arbitrary potential with multiple minima [127]. For a harmonic potential and any t and T, it is given by an expression involving a Bessel function [128]. It has also been derived analytically in the presence of a magnetic field [129].

5.2.2. Moving harmonic traps and electric circuits. Wang *et al* [130] measured the distribution of what amounts to work (called Σ_t in their equation (2)) for a colloidal particle initially in equilibrium in a harmonic trap which was then displaced with constant velocity. The authors found that the pdf obeys a relation corresponding to the TFT which is strictly speaking the correct interpretation only within the co-moving frame. Interpreted in the lab frame, the driving is time-dependent. However, since for linear forces the work distribution is a Gaussian which moreover has to obey the JR with $\Delta\mathcal{F} = 0$, it is clear that such a Gaussian also obeys the TFT formally.

In a sequel, Wang *et al* [131] considered the same set-up for a quasi-steady-state situation at constant velocity. The authors showed in particular that a quantity $(\Omega_t(\boldsymbol{r})$ as defined in their equation (19)) which is equal to $\Delta s^{\rm tot}$ obeys the DFT also for short times as it should since this set-up seen in the co-moving frame corresponds to a genuine NESS.

For traps moving with constant velocity, explicit expressions for the Gaussian work distribution, i.e. for its mean and variance, have been calculated in [78, 132]. In all cases, the DFT type relation is fulfilled. In contrast, the pdf for the dissipated heat is non-Gaussian with exponential tails. An explicit expression is not available, but its characteristic function and in consequence its large deviation form can be determined analytically [133, 134]. The pdf for work in a moving trap (and the pdf for heat in a stationary trap) was also measured and compared with theoretical results by Imparato *et al* [135]. For a harmonically bound particle subject to a time-dependent force, Saha *et al* calculated pdfs for total entropy production, in particular, for non-equilibrated initial conditions [136].

For a charged particle in a harmonic trap, work fluctuations and the JR have been studied theoretically for a time-independent magnetic field and a moving trap or time-dependent electric field in [137–141], and for a time-dependent magnetic field in [142], respectively.

Trepagnier *et al* [90] studied experimentally the transition from one NESS to another by changing the speed of the moving trap. If interpreted in the co-moving frame, their experiment constituted the first experimental verification of the Hatano–Sasa relation (67).

Simple electric circuits can formally be mapped to the dragged colloidal particle. Corresponding FTs and pdfs have been investigated by Ciliberto and co-workers [143–145], by Falcon and Falcon [146] and by Bonaldi *et al* [147] for actively cooled resonators used in a gravitational wave detector. A similar mapping was used by Berg to study the JR applied to gene expression dynamics [148].

5.2.3. Harmonic traps with changing stiffness. Carberry *et al* [149] investigated the motion of a colloidal particle in a harmonic trap whose stiffness is suddenly changed from one value to another thus verifying the TFT (66). For strongly localized initial conditions, this TFT has been verified experimentally in [150]. Gomez-Solano *et al* inferred the fluctuations of the heat exchanged between a colloidal particle and an aging gel which bears some similarity to a time-dependent stiffness [151].

5.2.4. Non-linear potentials. Blickle *et al* [152] measured the work distribution for a colloidal particle pushed periodically by a laser toward a repulsive substrate. This experimental set-up was the first one for colloidal particles that used effectively non-harmonic potentials. The pdf for work is distinctly non-Gaussian but still in good agreement with theoretical predictions based on solving the Fokker–Planck equation. This agreement justifies *a posteriori* the crucial assumption that the noise correlations are not affected by the time-dependent driving. Moreover, a DFT for $p(w)$ (93) was checked for this periodic driving with a symmetric protocol. Sun determines $p(w)$ for a potential that switches between a single well and a double well [153].

5.2.5. Stochastic resonance. For a colloidal particle in a double-well potential that is additionally subject to a modulated linear potential to generate conditions of stochastic resonance [154], distributions for work, heat and entropy were measured and calculated in [155, 156]. Other numerical work using the concepts of stochastic thermodynamics to investigate stochastic resonance includes [157–159].

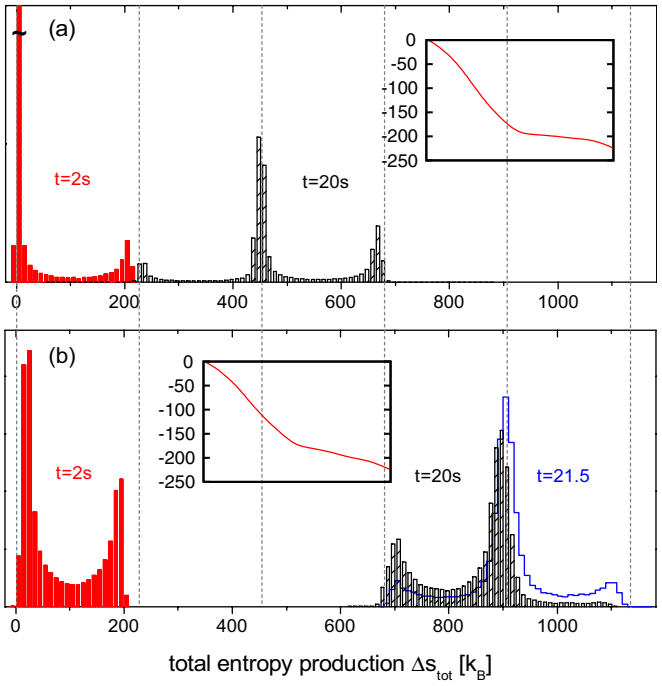

Figure 2. Distribution of entropy production $p(\Delta s^{\rm tot})$ for a colloidal particle driven along a periodic potential for two different values of external force f. The insets show the total potential $V(x) - fx$. The different histograms refer to different trajectory lengths. Reproduced with permission from [160]. Copyright 2007 European Physical Society.

5.2.6. NESS in a periodic potential. In an experiment for this paradigmatic geometry shown in figure 1 which corresponds to the Langevin equation (1), the pdf for total entropy production has been measured and compared with theoretical predictions [160], see figure 2. Characteristically, for short times, this pdf exhibits several peaks corresponding to the number of barriers the particle has surmounted. Examples for the pdf for entropy production have also been calculated in [161]. For long times, the asymptotic behavior of this pdf in the form of a large deviation function has been calculated numerically in [162] where an interesting kink-like singularity was found. The same quantity has also been derived using a variational principle [163].

5.3. Underdamped motion

5.3.1. Torsion pendulum as experimental realization. A driven torsion pendulum differs fundamentally from colloidal particles since here the inertia term becomes accessible. In a series of experiments reviewed in [35], Ciliberto and co-workers have investigated the pdf for various quantities with the aim of checking which ones obey FT-like relationships.

In [164, 165], the JR and the Crooks relation were used to determine the 'free energy difference' for the torsion pendulum for linear and periodic forcing. In [166], pdfs for the external work were determined for three different types of protocols for the time-dependent force in (38). (i) For a linearly ramped force, the pdf for starting in equilibrium was found to obey a TFT relation even for short times. Since a linear ramp corresponds to a time-dependent driving, one would, in fact, not expect a TFT. It is found here only because the work distribution for this linear system is Gaussian and should obey the JR which constrains mean and variance such that the TFT is valid. Alternatively, an explicit calculation of the pdf shows the same result. (ii) Starting in a quasi-steady state of the linear ramp, the pdf for $w^{\rm ext}$ no longer obeys the TFT for short times as expected. (iii) Likewise, for periodic driving, a DFT type for the work distribution is found only in the long-time limit as expected. For the latter two cases, the finite time corrections have been calculated.

The same group investigated the pdf for the heat for similar protocols [167]. In agreement with both the general theoretical expectations and their explicit calculations the pdf for heat neither obeys a TFT for short times nor even the DFT asymptotically for long times since the internal energy is not bounded for a harmonic oscillator.

The pdf for changes in the stochastic entropy and the total one were reported for periodic driving of this system in [145]. Once the system has settled in the periodic steady state, for an integer multiple of the period the functional R becomes the total entropy change which thus fulfills a DFT as found experimentally.

5.3.2. General theoretical results. Using path integral techniques, Farago determined the statistics of the power injected by the thermal forces into an underdamped particle and found it to be independent of an underlying confining potential [168].

In a series of papers for a moving trap, Taniguchi and Cohen investigated pdfs for work and heat as well as various FTs using the path integral representation [169–172]. They also point out the ambiguity (or freedom) to define time reversal in this particular system.

For both a moving and a breathing trap, Minh *et al* calculated work weighted propagators for underdamped motion [173]. FTs for underdamped Brownian motion were studied by Lev and Kiselev by transforming from the momentum to the energy variable [174], by Fingerle for the relativistic version [175] and by Iso *et al* for motion near black holes [176]. Sabhapandit determined the work fluctuations of a randomly driven harmonic oscillator [177] which was studied experimentally in [178].

5.3.3. Heat transport. Underdamped Langevin equations have been used to study heat transport through harmonic chains or lattices coupled at the end to heat reservoirs of different temperatures [65]. Relevant in our context is work concerning not only the average heat current but also the distribution of exchanged heat and the corresponding FT. These issues have been studied for a single particle attached to two heat baths in [179–181], for two coupled particles attached to two different baths in [182], for harmonic chains in [183–185] and an anharmonic lattice in [186].

5.4. Other systems

Ever since the DFT for entropy production was formulated, there have been attempts to show whether it is fulfilled in a

specific system both numerically and experimentally. Beyond the 'clean' cases discussed above for which the dynamics of the relevant degrees of freedom is clearly compatible with a stochastic Markovian dynamics, there are a number of studies for other systems where a theoretical understanding is more challenging. Such studies include an early theoretical work with three simple dissipative deterministic models [187], experimental [188–192] and numerical [193–200] work for granular matter or dense colloids, experimental work for turbulence [201–203], numerical work for a shell model in turbulence [204] and one on the role of hydrodynamic interactions [205], and experimental work for liquid crystals [206, 207], a vibrating plate [208] and self-propelled particles [209]. Characteristically for the experimental systems just mentioned, one cannot necessarily expect that these can be described by a stochastic Markovian dynamics for the relevant variables. Similarly, in the numerical works either the equations of motion are not of the Langevin type (or deterministic thermostatted ones) or, if they are, not all variables are monitored which effectively amounts to some coarse graining. Since for these cases, the FTs have not been proven, such tests give valuable hints on possible extensions beyond their established realm of validity.

Two general aspects for putting results of such case studies in perspective are the following ones. First, the putative validity of a DFT for the quantity R is typically cast in the form of checking for a constant slope of the quantity $\lim_{t\to\infty}[\ln[p(\rho_t)/p(-\rho_t)]/t$ where ρ_t is the time averaged rate corresponding to the quantity $R = t\rho_t$ for which we have formulated the FT. Since such a plot is necessarily antisymmetric in ρ_t [194], for a non-trivial statement the contribution of higher order terms such as ρ_t^3 must be shown to be negligible which requires a large enough range of studied ρ_t-values. Moreover, a large enough t is necessary. Second, in bulk systems often only 'local' quantities can be investigated which would require local forms of the FTs. From the perspective of a stochastic dynamics, this amounts to integrating out other slow degrees of freedom or some type of coarse graining under which one cannot expect the FTs to hold necessarily. We will come back to this issue at the very end of this review.

6. Dynamics on a discrete set of states

6.1. Master equation dynamics

The derivation of the FTs in section 4 is based on the behavior of the weight for a stochastic trajectory under time reversal or the other operations generating the conjugate dynamics. Therefore, they hold for any kind of stochastic dynamics, in particular, for a master equation type of dynamics [210, 211] on a discrete set of states $\{n\}$, see figure 3.

Examples of such systems include random walks and, more generally, diffusive processes on a lattice, birth–death processes, growth processes on a lattice, conformational changes between discrete states of a biomolecule or chemical reaction networks. The latter two classes of systems differ from the previous ones since they typically occur in a well-defined thermal environment. This feature imposes additional

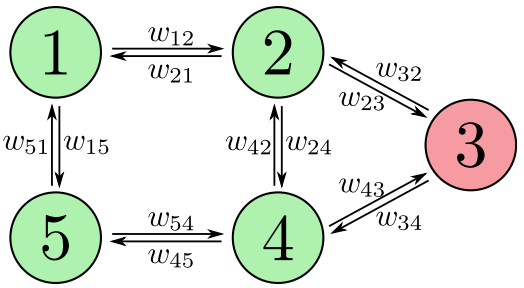

Figure 3. Network with five states comprising three cycles (1245), (234), and (12345) and the corresponding transition rates. Without the state 3, this network would be a unicyclic one.

constraints on the dynamics as discussed in section 9. In this section, we focus on the stochastic dynamics with arbitrary transition rates.

6.1.1. Transition rates and probability currents. Transitions from a state m to a state n occur with a rate $w_{mn}(\lambda)$ which may be time-dependent according to the external protocol $\lambda(\tau)$. For ease of notation, we will write $w_{mn}(\tau)$ or $w_{mn}(\lambda)$ for the more explicit $w_{mn}(\lambda(\tau))$. In principle, one could distinguish different transitions or 'channels' connecting the same two states from which we refrain here for notational simplicity.

The probability $p_n(\tau)$ to find the system at time τ in state n evolves according to the master equation

$$\partial_\tau p_n(\tau) = \sum_{m\neq n}[p_m(\tau)w_{mn}(\tau) - p_n(\tau)w_{nm}(\tau)] \qquad (110)$$

given an initial distribution $p_n(0)$. To each link (mn) one can associate a (directed) probability current

$$j_{mn}(\tau) = p_m(\tau)w_{mn}(\tau) - p_n(\tau)w_{nm}(\tau) = -j_{nm}(\tau). \qquad (111)$$

6.1.2. Two classes of steady states. For time-independent λ, the system eventually reaches a steady state provided the network is 'ergodic', i.e. any two states are connected through a series of links as we will always assume in the following. The time-independent stationary probabilities can be written as

$$p_n^s(\lambda) \equiv \exp[-\phi_n(\lambda)] \qquad (112)$$

which defines the analog of the non-equilibrium potential. For small networks, there is an elegant graphical method to determine p_n^s from given rates [211, 212].

Steady states fall into two classes depending on whether or not the detailed balance condition (DBC),

$$p_n^s(\lambda)w_{nm}(\lambda) = p_m^s(\lambda)w_{mn}(\lambda), \qquad (113)$$

is fulfilled. The first case corresponds to genuine equilibrium, the second one to a NESS. In the latter case, there are non-vanishing steady-state probability currents

$$j_{mn}^s \equiv p_m^s w_{mn} - p_n^s w_{nm} = -j_{nm}^s. \qquad (114)$$

Since knowing p_n^s is not sufficient to distinguish a genuine equilibrium from a NESS, Zia and Schmittmann [213, 214]

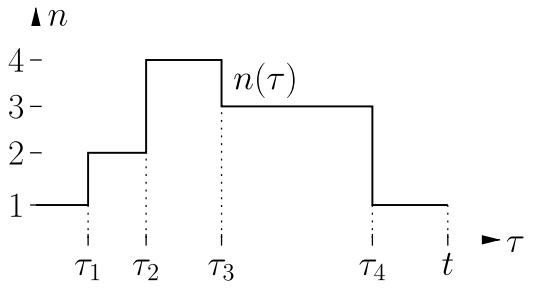

Figure 4. Trajectory $n(\tau)$ of total length t jumping at discrete times $\{\tau_j\}$ between states.

suggested to characterize a NESS by its stationary distribution p^s_n *and* its stationary currents j^s_{mn}. Then the same NESS could be generated by a whole equivalence class of possible rates w_{mn} since any two sets of rates with

$$p^s_m(w_{mn} - w'_{mn}) = p^s_n(w_{nm} - w'_{nm}) \tag{115}$$

would lead to the same NESS, i.e. the same stationary distribution and currents. In the following, we will adapt the view that a system is characterized by a definite set of rates $w_{mn}(\lambda)$ and a protocol $\lambda(\tau)$ from which all other quantities can, in principle, be derived.[6]

A 'distance' from equilibrium quantifying the amount of violation of the DBC has been introduced in [220]. A Lyapunov function for relaxation toward a NESS is discussed in [221]. Master equation dynamics as a gauge theory is formulated in [222]. A mapping to a dynamics in the dual space of cycles is discussed in [223].

6.1.3. Path weight and dynamical action. We first characterize the fluctuating trajectories. A trajectory $n(\tau)$ with $0 \leqslant \tau \leqslant t$ starts at n_0 and jumps at times τ_j from n_j^- to n_j^+ ending up at state n_t after J jumps, see figure 4. Defining for each state the instantaneous total exit rate

$$r_n(\tau) \equiv \sum_{m \neq n} w_{nm}(\tau) \tag{116}$$

the conditional weight for a trajectory exhibiting no jump at all is given by

$$p[n(\tau) = n_0|n_0] = \exp[-\int_0^t \mathrm{d}\tau r_{n_0}(\tau)]. \tag{117}$$

The weight for a trajectory with $J \geqslant 1$ jumps at times $\{\tau_j\}$ is given by

$$p[n(\tau)|n_0] = \exp[-\int_0^{\tau_1} \mathrm{d}\tau r_{n_0}(\tau)] \times \prod_{j=1}^{J} w_{n_j^- n_j^+}(\tau_j) \exp\left[-\int_{\tau_j}^{\tau_{j+1}} \mathrm{d}\tau r_{n_j^+}(\tau)\right] \tag{118}$$

with $\tau_{J+1} \equiv t$. Averages with these weights will be denoted by $\langle \ldots \rangle$ in the following.

[6] For completeness, we mention a complementary approach where rates are derived by imposing mean currents as constraints [215–218]. For a relation to the minimum entropy production principle, see [219] and references therein.

In analogy with the continuous case (5), these expressions define an 'action'

$$\mathcal{A}[n(\tau)] \equiv -\ln p[n(\tau)|n_0] = \int_0^{\tau_1} \mathrm{d}\tau r_{n_0}(\tau) - \sum_{j=1}^{J} \left[\ln w_{n_j^- n_j^+}(\tau_j) - \int_{\tau_j}^{\tau_{j+1}} \mathrm{d}\tau r_{n_j^+}(\tau)\right]. \tag{119}$$

6.2. Entropy production

6.2.1. Stochastic entropy. The concept of stochastic entropy can be transferred immediately from the Langevin case to the discrete one as [20]

$$s(\tau) \equiv -\ln p_{n(\tau)}(\tau). \tag{120}$$

It is obtained by first solving the master equation (110) for $p_n(\tau)$ with a given initial distribution and then plugging into it the specific trajectory $n(\tau)$ taken from this ensemble.

The equation of motion for stochastic entropy becomes

$$\dot{s}(\tau) = -\left.\frac{\partial_\tau p_n(\tau)}{p_n(\tau)}\right|_{n(\tau)} - \sum_j \delta(\tau - \tau_j) \ln \frac{p_{n_j^+}(\tau_j)}{p_{n_j^-}(\tau_j)}. \tag{121}$$

The first term shows that even if the system remains in the same state, stochastic entropy will change whenever the ensemble is time-dependent either due to a non-equilibrated initial state or due to time-dependent rates. The second term shows the contributions from each transition. The change in stochastic entropy during time t is given by

$$\Delta s = \int_0^t \mathrm{d}\tau \dot{s}(\tau) = -\ln p_{n_t}(t) + \ln p_{n_0}(0). \tag{122}$$

6.2.2. Time reversal. Time reversal as a choice for the conjugate dynamics works analogously to the Langevin case with $n^\dagger(\tau) = n(t - \tau)$ and $\lambda^\dagger(\tau) = \lambda(t - \tau)$. Using the weights (equations (117) and (118)), it is trivial to check that

$$R_1 \equiv \ln \frac{p[n(\tau)|n_0]}{p^\dagger[n^\dagger(\tau)|n_0^\dagger]} = \sum_j \ln \frac{w_{n_j^- n_j^+}(\tau_j)}{w_{n_j^+ n_j^-}(\tau_j)} \equiv \Delta s^{\mathrm{m}}. \tag{123}$$

There are two justifications for identifying R_1 with the entropy change of the surrounding medium Δs^{m}. The first is the analogy to the Langevin case, where this term turned out to be the dissipated heat (divided by temperature). In the absence of a first law for the master equation dynamics, which would require further physical input not available at this general stage, this identification is by analogy only. Second, it turns out that the sum of the system entropy change as defined in (122) and the so identified medium entropy,

$$\Delta s^{\mathrm{tot}} \equiv \Delta s + \Delta s^{\mathrm{m}}, \tag{124}$$

will obey the same FTs as discussed above for the Langevin dynamics. In fact, for Δs^{m} Lebowitz and Spohn had derived the SSFT in the long-time limit [4].

From the expression (123) an instantaneous entropy production rate in the medium can be identified as

$$\dot{s}^{\rm m}(\tau) = \sum_j \delta(\tau - \tau_j) \ln \frac{w_{n_j^- n_j^+}(\tau_j)}{w_{n_j^+ n_j^-}(\tau_j)} \tag{125}$$

that makes the contributions from the individual jumps obvious. Combining this relation with (121), one obtains

$$\dot{s}^{\rm tot}(\tau) = -\left.\frac{\partial_\tau p_n(\tau)}{p_n(\tau)}\right|_{n(\tau)} + \sum_j \delta(\tau - \tau_j) \ln \frac{p_{n_j^-}(\tau_j) w_{n_j^- n_j^+}(\tau_j)}{p_{n_j^+}(\tau_j) w_{n_j^+ n_j^-}(\tau_j)}. \tag{126}$$

6.2.3. Ensemble level. By averaging these trajectory-dependent contributions for entropy production, one obtains expressions derived much earlier within the ensemble approach [23, 211, 212, 224]. On a technical level, using

$$\left\langle \sum_j \delta(\tau - \tau_j) d_{n_j^- n_j^+}(\tau) \right\rangle = \sum_{mn} p_m(\tau) w_{mn}(\tau) d_{mn}(\tau) \tag{127}$$

valid for any set of quantities $\{d_{mn}\}$, one obtains

$$\dot{S}^{\rm tot}(\tau) \equiv \langle \dot{s}^{\rm tot} \rangle = \sum_{mn} p_m(\tau) w_{mn}(\tau) \ln \frac{p_m(\tau) w_{mn}(\tau)}{p_n(\tau) w_{nm}(\tau)}, \tag{128}$$

and

$$\dot{S}^{\rm m}(\tau) \equiv \langle \dot{s}^{\rm m} \rangle = \sum_{mn} p_m(\tau) w_{mn}(\tau) \ln \frac{w_{mn}(\tau)}{w_{nm}(\tau)} \tag{129}$$

which should be compared with (35) and (36), respectively.

6.2.4. Splitting entropy production. Following the Langevin case, we can split the entropy production in the medium (123) into two contributions

$$\Delta s^{\rm m} = \Delta s^{\rm hk} + \Delta s^{\rm ex} \tag{130}$$

with

$$\Delta s^{\rm hk} \equiv \sum_j \ln \frac{p^s_{n_j^-}(\lambda_j) w_{n_j^- n_j^+}(\lambda_j)}{p^s_{n_j^+}(\lambda_j) w_{n_j^+ n_j^-}(\lambda_j)} \tag{131}$$

where $\lambda_j \equiv \lambda(\tau_j)$ and

$$\Delta s^{\rm ex} \equiv -\sum_j \ln \frac{p^s_{n_j^-}(\lambda_j)}{p^s_{n_j^+}(\lambda_j)} \tag{132}$$

characterizing the entropy change associated with maintaining the corresponding steady state and the one associated with time-dependent driving, respectively. It is simple to rewrite $\Delta s^{\rm ex}$ as the discretized version of $-\Delta\phi + \partial_\lambda \phi$ as in (23). This excess entropy production has a nice geometrical interpretation along a path in the parameter space analogous to the Berry phase in quantum mechanics [225].

A somewhat different splitting of total entropy production on the trajectory level was introduced in [116–118] writing

$$\Delta s^{\rm tot} = \Delta s^{\rm ad} + \Delta s^{\rm na} \tag{133}$$

with the adiabatic entropy change $\Delta s^{\rm ad} \equiv \Delta s^{\rm hk}$ and the non-adiabatic one $\Delta s^{\rm na} \equiv \Delta s^{\rm ex} + \Delta s$.

6.2.5. Dual dynamics. The dual dynamics is defined by rates

$$w^\dagger_{mn}(\lambda) \equiv w_{nm}(\lambda) p^s_n(\lambda) / p^s_m(\lambda). \tag{134}$$

These rates lead to the same stationary state as the original dynamics, $p^{\dagger s}_m = p^s_m$. However, the stationary currents are reversed according to

$$j^{\dagger s}_{mn}(\lambda) = -j^s_{nm}(\lambda). \tag{135}$$

In complete analogy to the Langevin case, by comparing the weights for the original with the dual and the dual-reversed dynamics, one obtains

$$R_1 = \Delta s^{\rm hk} \qquad \text{and} \qquad R_1 = \Delta s^{\rm ex}, \tag{136}$$

respectively.

6.3. FTs for entropy production and 'work'

6.3.1. General validity. With these identifications, all FTs from sections 3.3 and 4 involving the various forms of entropy changes apply under exactly the same conditions as stated there provided the occasional x (and x_0, x_t) is trivially replaced by n (and n_0, n_t).

The only variable not defined yet is the analog of work. For networks that at constant λ fulfill the DBC (113), one can identify a (dimensionless) internal energy as $\phi_n(\lambda) \equiv -\ln p^s_n(\lambda)$ that plays the role of the potential $V(x,\lambda)/T$ in the Langevin case with a free energy identical to zero. At this stage, there is indeed no point in identifying a non-trivial λ-dependent free energy. Consequently, work along a trajectory corresponds to dissipated work and can be identified in analogy to (15) with

$$w \equiv \int_0^t {\rm d}\tau \, \partial_\lambda \phi_n(\lambda)_{|n(\tau)} \dot{\lambda}. \tag{137}$$

With this identification of work, the FTs from sections 3.2 and 4 involving work hold for this master equation dynamics as well (setting there $T = 1$). It should be stressed, however, that without a more physical microscopic understanding of the network, this concept of work (and heat, if one wanted to promote $\Delta s^{\rm m}$ to this status) is a purely formal one without real physical meaning.

For networks that do not fulfill the DBC (113), there is no unique way of assigning internal energy to a state without further physical input, and, hence, no sensible way of identifying work even formally. Naively keeping (137), as sometimes suggested [226], fails as the counter-example of a discretized version of the driven overdamped motion on a flat ring easily shows, since $\phi_n = {\rm const}$ implies $w = 0$.

The statistics of rare events contributing to these FTs can also be studied through a 'mapping' of the master equation to a Schrödinger equation and then analyzing the corresponding path integral [227, 228]. Finally, a somewhat formal general IFT was derived in [229].

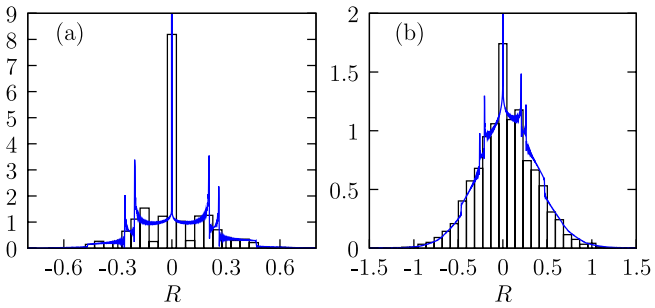

Figure 5. Probability distribution for the 'work' (137), denoted here R, in a driven two-level system for two different lengths of trajectories. The histogram shows experimental data, the full curve a theoretical calculation; for more details, see [102]. Reproduced with permission from [102]. Copyright 2005 American Physical Society.

6.3.2. Experimental case studies. Experimental work measuring the distributions of these quantities with the perspective of 'testing' the FTs is yet scarce. The arguably simplest non-trivial network is a two-state system with time-dependent rates. Any such two-state system necessarily obeys the DB condition. Such a two-state system was realized experimentally by driving an optical defect center into diamond with two lasers. The distributions for work (137) and for the entropy change of system, medium and total, were measured and compared with the theoretical predictions [102, 104]. Characteristically, for comparably short times these distributions show quite intricate, distinctively non-Gaussian, features, see figure 5.

6.3.3. Analytical and numerical case studies. Entropy production and the FT for the simplest discrete system which is in essence a random walk biased in one direction by applying an external field was studied quite generally in [230], in the context of a ratchet model in [231], for a rotary motor in [232, 233] and for transport through a membrane channel in [234]. Simple three and four state systems were investigated in [235, 236]. The statistics of dissipated heat for a driven two-level system modeling single electron transport has been calculated in [237].

Entropy production on a lattice model both for a simple reaction–diffusion scheme and for transport was investigated in [238] with an attempt to clarify the occurrence of a kink in the rate function at zero entropy production. In another variant of the reaction–diffusion scheme, the violation of an FT caused by breaking microscopic reversibility in the sense that some backward transitions are forbidden were studied in [239, 240]. Entropy production for a model of cyclic population dynamics was investigated in [241] and for effusion of a relativistic ideal gas in [242]. FTs in the presence of local heating have been studied in [243].

The analog of work distributions for a spin system in time-dependent magnetic fields was investigated in [244, 245] and for time-dependent coupling constants in [246]. The surface tension in the three-dimensional Ising model is determined through simulations using the analogy of the JR in [247].

The interplay between a non-equilibrium phase transition and singularities in the entropy production has been investigated for a majority vote model [248], for driven lattice gases [249, 250], for wetting [251] and for kinetically constrained lattice models [252]. For the latter, the FT was investigated in [253, 254].

6.4. FT for currents

For a network in a NESS, currents obey an FT as derived by Gaspard and Andrieux [255–258] exploiting the decomposition of such a network in cycles as introduced by Schnakenberg [211] and using concepts from large deviation theory [259]. For a concise derivation of the current FT using the formalism developed in section 4, we write the total entropy production along a trajectory in the form

$$\Delta s^{\rm tot} = \sum_a n_a \Delta S_a + \Delta s_r. \tag{138}$$

Here, n_a is the number of times a cycle a has been completed in clockwise ($n_a > 0$) or anti-clockwise ($n_a < 0$) direction during this trajectory leading to a fluctuating current $\mathcal{J}_a \equiv n_a/t$ for each cycle, see figure 3 for an example of cycles in a network. The entropy production associated with each cycle

$$\Delta S_a = \sum_{(mn)\in a} \ln \frac{w_{mn}}{w_{nm}} \tag{139}$$

is also called the affinity of this cycle. The remainder Δs_r collects the contributions arising from those parts of the trajectory that do not contribute to a full cycle. Clearly, the current $\mathcal{J}_a$ is odd under time reversal and hence qualifies as a possible variable S_α with $\epsilon_\alpha = -1$ for the general SSFT (94) which thus becomes

$$\frac{p(\{-\mathcal{J}_a\})}{p(\{\mathcal{J}_a\})} = \exp[-t\sum_a \Delta S_a \mathcal{J}_a]\langle \mathrm{e}^{-\Delta s_r}|\{\mathcal{J}_a\}\rangle. \tag{140}$$

For large t, Δs_r and hence the second factor remains of order 1. It can thus be ignored when taking the logarithm in the long-time limit leading to the current FT

$$\lim_{t\to\infty} \frac{1}{t} \ln \frac{p(\{\mathcal{J}_a\})}{p(\{-\mathcal{J}_a\})} = \sum_a \Delta S_a \mathcal{J}_a. \tag{141}$$

For a network coupled to different reservoirs at different temperatures or chemical potentials, the cycle affinities ΔS_a arise from externally imposed affinities $\mathcal{F}_k$ as discussed in more detail in section 10.2. These affinities give rise to mesoscopic currents

$$\mathcal{J}_k = \sum_a \mathcal{J}_a d_a^k \tag{142}$$

where d_a^k are a generalized distance counting how much each cycle contributes to the respective current. Expressed in these currents, the FT reads

$$\lim_{t\to\infty} \frac{1}{t} \ln \frac{p(\{\mathcal{J}_k\})}{p(\{-\mathcal{J}_k\})} = \sum_k \mathcal{F}_k \mathcal{J}_k. \tag{143}$$

In this derivation, it is crucial that all currents that contribute to the entropy production (either on the cycle or on the mesoscopic level) are included.

Generalizations of such an FT have been derived for just one current in [260], for networks with multiple transitions between states in [261], to currents not related to entropy production in [262–264]. Geometrical and topologial aspects were studied in [265–268]. Periodically driven systems were investigated in [269] and a relation to supersymmetry is made in [270]. In another extension, Hurtado *et al* have derived an 'isometric fluctuation relation' that compares pdfs for currents with different orientations [271].

The FT for entropy production has been discussed for various chemical reaction networks in the papers by Gaspard and Andrieux quoted above, and, more recently, has been applied to transport in mesoscopic devices which, despite their quantum character, can often still be described by a master equation whenever coherences can be, or are, ignored. For a few recent examples, see, e.g., [227, 228, 272–282].

There is a large literature arising from the recent progress of understanding current fluctuations in NESSs in general, not necessarily related to the FT, for which the review by Derrida could serve as a point of departure [283].

7. Optimization, irreversibility, information and feedback

7.1. Optimal protocols

7.1.1. General aspects. The IFTs such as the JR hold for any external protocol $\lambda(\tau)$ and any time interval t. An optimal protocol $\lambda^*(\tau)$ is the one that extremizes the mean of a functional of the trajectory like work or heat for given initial value $\lambda_i \equiv \lambda(0)$ and final value $\lambda_f \equiv \lambda(t)$ of a control parameter and a fixed total time t allocated to this process.

Mean work and total entropy production as objective functions are arguably the most relevant cases. For $t \to \infty$, the minimal mean work required for a transition is given by the free energy difference $\Delta\mathcal{F} \equiv \mathcal{F}(\lambda_f) - \mathcal{F}(\lambda_i)$. For any finite time t, the mean work should be larger and the question for the optimal protocol becomes non-trivial. Understanding this problem will allow one to extract the maximum amount of work from a given free energy difference in finite time.

Formulated as a variational problem, the optimal protocol obeys a quite complicated Euler–Lagrange equation which is non-local in time since changing the control parameter at time t_1 affects the work increment at all later times t_2. Crucial insight into general features of the solution, however, has been obtained by investigating case studies involving harmonic potentials [284]. As a general feature, jumps of the optimal protocol were found that are absent in a linear response treatment [285].

A second motivation for minimizing the work could be an attempt to improve convergence of the Jarzynski estimate to obtain free energy differences since one might expect that a small mean work may also to lead to a smaller variance. Due to the non-linearity of $\exp[-w/T]$, however, one should rather find the optimal protocol for minimizing $\langle\exp[-2w/T]\rangle$ which turns out to have jumps as well [286].

7.1.2. Overdamped dynamics. The generic jumps in the optimal protocol were first found in case studies involving harmonic potentials [284]. The simplest case is a process where the center of a harmonic potential $V(x,\lambda) = (x-\lambda)^2/2$ is shifted from $\lambda_i = 0$ to λ_f in a finite time t. Such a shift does not involve any free energy difference. Hence, the mean work required for this task will approach 0 for $t \to \infty$. For a finite time, the optimal protocol can be calculated analytically by expressing the mean work as a functional of the mean position of the particle which renders the problem local in time. The optimal protocol (in dimensionless units for time)

$$\lambda(\tau) = \lambda_f(\tau+1)/(t+2) \tag{144}$$

involves two jumps

$$\Delta\lambda \equiv \lambda(0+) - \lambda_0 = \lambda_f - \lambda(t-) = \lambda_f/(t+2) \tag{145}$$

at the beginning and the end of the process. The physical reason for, e.g., the first jump is the fact that with this jump the dissipation rate is constant throughout the process. If the trap moved with constant speed without initial jump, the friction would slowly build up at the beginning of the process which ultimately would imply stronger dissipation. The size of the, in this case, symmetric jumps at the beginning and end vanishes as $t \to \infty$.

Similar jumps have also been found in a second case study where the stiffness of a harmonic potential $V(\lambda, x) = \lambda x^2/2$ is changed in finite time from an initial value λ_i to λ_f [284]. For overdamped motion of a dipole in a magnetic field that switches the orientation, the optimal protocol can even show a degeneracy [287]. Further examples for optimal protocols involving non-linear potentials were studied numerically in [286].

An intriguing mapping of this optimization problem to deterministic optimal transport like mass transport by a Burgers velocity field has been discussed in [288, 289]. For total entropy production as objective function, turning an earlier scaling argument [290] into a mathematical proof, a general bound can thus be derived, $\Delta S^{\rm tot} \geqslant C/t$ valid for any t, where C depends on the given initial and final distributions [291]. The key point is that this optimization takes place in the space of all probability distributions rather than in a restricted space of driving potentials with a few variational parameters. In the latter case, the $\sim 1/t$ behavior will hold only for long times.

7.1.3. Underdamped dynamics. For underdamped dynamics, the optimal protocol involves even stronger singularities at the beginning and end of the process given by additional δ-peaks in the protocol [292]. Physically, these terms guarantee that the particle at the beginning acquires, and at the end loses, a finite mean momentum instantaneously which minimizes total dissipation.

7.1.4. Discrete dynamics. Optimal protocols can also be investigated for master equation dynamics on a discrete set of states. A simple case has been studied as a model for a quantum dot with a single energy level E connected to a reservoir with chemical potential $\mu \equiv E - \epsilon(\tau)$. The optimal protocol for an externally controllable gap $\epsilon(\tau)$ and given $\epsilon(0)$ and $\epsilon(t)$ minimizing the mean work $W \equiv \int_0^t {\rm d}\tau p(\tau)\dot{\epsilon}(\tau)$, where $p(\tau)$

is the probability that the energy level is occupied, shows jumps in the optimal $\epsilon^*(\tau)$ at beginning and end which are nicely explained in physical terms in [293]. A more general approach to the optimal protocol connecting arbitrary given initial and final distributions is given in [294].

7.2. Quantifying irreversibility

The concepts developed for deriving the FTs can also lead to a more quantitative understanding of irreversibility. In section 4, the time-reversed process was introduced as a mere tool for deriving the FTs. By considering such a time-reversed process seriously and comparing it with the original time-forward process, one can indeed derive an interesting relation between dissipation and irreversibility. An essential tool in this analysis is the relative entropy or Kullback–Leibler distance

$$D[p||q] \equiv \int \mathrm{d}y p(y) \ln[p(y)/q(y)] \geqslant 0 \tag{146}$$

between two distributions $p(y)$ and $q(y)$. Essentially, this quantity measures how distinct the two distributions are [295].

We present here the stochastic version of the basic idea first introduced using Hamiltonian dynamics [296, 297]. For a process with a time-dependent potential $V(\boldsymbol{x}, \lambda)$ and its time reversal, which start and end in the respective equilibrium states, the quantity R in the generalized FT (80) becomes $R = w - \Delta\mathcal{F}$. This FT thus implies

$$\langle \exp[-(w - \Delta F)] | s_\alpha \rangle = p^\dagger(\epsilon_\alpha s_\alpha)/p(s_\alpha) \tag{147}$$

where the average is conditioned on the value s_α of an arbitrary functional $S_\alpha[\boldsymbol{x}(\tau)]$ along the trajectory with a definite parity ϵ_α under time reversal. By choosing $S_\alpha = w - \Delta\mathcal{F}$, averaging the logarithm of (147) yields

$$\langle w \rangle - \Delta\mathcal{F} = D[p(w - \Delta\mathcal{F})||p^\dagger(-(w - \Delta\mathcal{F})]. \tag{148}$$

This relation, which can be seen as a consequence of the CFT (61), shows that the dissipated work determines how different the distributions for this quantity along the forward and the backward paths are. Likewise, a large difference of these two distributions implies a substantial dissipated work.

By choosing $S_\alpha = \boldsymbol{x}(t_1) = \boldsymbol{x}^\dagger(t - t_1)$, i.e. the state of the system at any intermediate time t_1, one obtains from (147) the lower bound

$$\langle w \rangle - \Delta\mathcal{F} \geqslant D[p(\boldsymbol{x}(t_1))||p^\dagger(\boldsymbol{x}^\dagger(t_1))] \tag{149}$$

on the dissipated work. In contrast to this stochastic case, for a Hamiltonian dynamics, one obtains an equality in (149) due to Liouville's theorem [296]. For both types of dynamics, further coarse graining, i.e. looking at the distributions for a variable $y = y(\boldsymbol{x}(t_1))$, leads to a lower bound on the dissipated work since relative entropy decreases under coarse graining [295] as nicely illustrated in the present context in [298].

Similarly, by choosing $t_1 = t$, one immediately obtains the inequality

$$\langle w \rangle - \Delta\mathcal{F} \geqslant D[p(\boldsymbol{x}(t))||p^{\mathrm{eq}}(\boldsymbol{x}(t))] \tag{150}$$

which bounds dissipation by the distinguishability of the instantaneous distribution with the corresponding equilibrium distribution as derived and discussed in [299].

It is trivial to derive similar relations for processes involving genuine steady states that at constant control parameters reach a NESS rather than equilibrium as pointed out in [300]. Essentially, in (147)–(150), one has to replace both $\langle w \rangle - \Delta\mathcal{F}$ by $\langle \Delta s^{\mathrm{m}} + \Delta\phi \rangle$ where ϕ is the non-equilibrium potential (11) and p^{eq} by p^s.

Related inequalities have been discussed for transitions between specified initial and final states [301]. Relations between other information-theoretic measures and non-linear averages of work and entropy along non-equilibrium trajectories have been derived in [302–304]. An intriguing relation between generating information and dissipation has been made for DNA replication in [305] with a corresponding pedagogical introduction in [306] and an analysis in terms of a thermodynamic machine in [307].

7.3. Measurement and feedback

7.3.1. Feedback and the second law. According to the Kelvin–Planck formulation of the second law, one cannot extract work from an equilibrated system at constant temperature without leaving any traces of this process somewhere else. The situation becomes apparently different if information about the state of the system during this process becomes available through a measurement as the classical example of Maxwell's demon and the Szilard engine reviewed in [308, 309] demonstrate.[7] Based on the result of a measurement, one can choose a particular protocol for a control parameter which will indeed allow either to extract work in a cyclic process or, in a non-cyclic process, to extract more work than the corresponding free energy difference of initial and final equilibrium state. These statements are still compatible with the second law since erasing the information acquired will cost free energy according to Landauer's principle. Taking this additional effect into account, the ordinary second law is restored. Typically, for discussing these processes within stochastic thermodynamics the cost of measurement and erasure process is first ignored in the problem of how to convert the acquired information into work (most efficiently) as it also will be ignored in the following discussion of the main concept where we use an approach based on FTs. Related earlier work will be briefly mentioned in section 7.3.5.

7.3.2. Measurement and information. For a quantitative description, we assume a system evolving according to a master equation as introduced in section 6. If the system at time t_1 is in state $n_1 = n(t_1)$, a measurement at this time yields a result y_1 with the probability $p(y_1, t_1|n_1) = p(n_1, t_1|y_1)p(y_1, t_1)/p(n_1, t_1)$. Here, $p(n, t)$ is the ordinary solution of the master equation for the given initial condition and $p(y_1, t_1)$ the probability for obtaining the result y_1 irrespective of n_1. The (trajectory-dependent) information acquired in this measurement is [311]

$$\begin{aligned} \mathcal{I}(n_1, y_1) &\equiv \ln[p(n_1, t_1|y_1)/p(n_1, t_1)] \\ &= \ln[p(y_1, t_1|n_1)/p(y_1, t_1)]. \end{aligned} \tag{151}$$

[7] For an instructive criticism of one of the assumptions of the Szilard engine, see [310].

Upon averaging with $p(y_1|n_1)$, this trajectory-dependent information becomes the relative entropy $D[p(n_1,t_1|y_1)||p(n_1,t_1)]$ which still depends on the result y_1 of the measurement. Further averaging over y_1 leads to the mutual information

$$\mathcal{I} \equiv \int \mathrm{d}y_1\, p(y_1,t_1) D[p(n_1,t_1|y_1)||p(n_1,t_1)] \quad (152)$$

$$= \int \mathrm{d}y_1 \int \mathrm{d}n_1\, p(n_1,y_1,t_1)\mathcal{I}(n_1,y_1). \quad (153)$$

7.3.3. Sagawa–Ueda equality and a generalization. After a measurement, the control parameter $\lambda(\tau,y_1)$ for the subsequent evolution $t_1 \leqslant \tau \leqslant t$ is assumed to depend uniquely on the outcome y_1 leading to the probability distribution $p_1(n,\tau|y_1)$. For a system with a time-dependent potential $V(n,\lambda)$, i.e. a system that at any fixed λ reaches a genuine equilibrium state, Sagawa and Ueda have generalized the JR (58) to this feedback-driven process in the form [311, 312]

$$\langle \exp[-(w - \Delta\mathcal{F} + \mathcal{I})]\rangle = 1 \quad (154)$$

which implies for the maximal mean extractable work $W^{\mathrm{out}} \equiv -\langle w\rangle$ the bound

$$W^{\mathrm{out}} \leqslant -\Delta\mathcal{F} + \mathcal{I} \quad (155)$$

with $\mathcal{I} \equiv \langle \mathcal{I}\rangle$. Thus, acquiring information through a measurement allows one to extract more work than what one would get from a process without feedback.

The original formulation of the SUE requires the notion of a free energy difference for initial and final state. For transitions involving genuine non-equilibrium states, i.e. those that at constant control parameters reach a NESS, the analogous relation

$$\langle \exp[-(\Delta s^{\mathrm{tot}} + \mathcal{I})]\rangle = 1 \quad (156)$$

with the inequality

$$\langle \Delta s^{\mathrm{tot}}\rangle \geqslant -\mathcal{I} \quad (157)$$

holds true as well.[8]

A concise proof of (156), which will be valid with a minor modification for (154) as well[9], not requiring explicit time reversal follows from exploiting the IFTs (equations (85) and (86)) [313]. Using $\Delta s^{\mathrm{tot}} = \Delta s + \Delta s^{\mathrm{m}}$, splitting the last term into the two contributions associated with the two time intervals $i = (0 \leqslant \tau < t_1)$ and $ii = (t_1 \leqslant \tau \leqslant t)$, making the total entropy change of the system explicit with $\Delta s = -\ln p(n_t,t|y) + \ln p_0(n_0,0)$, and the specific expression for the information (151), the lhs of (156) can be written as

$$\left\langle \frac{1}{p_0(n_0)} \mathrm{e}^{-\Delta s_i^{\mathrm{m}}} \frac{p(n_1,t_1)}{p_1(n_1,t_1|y_1)} \mathrm{e}^{-\Delta s_{ii}^{\mathrm{m}}} p_1(n_t,t|y_1) \right\rangle$$

$$= \sum_{m_1} \left\langle \frac{1}{p_0(n_0)} \mathrm{e}^{-\Delta s_i^{\mathrm{m}}} | n_1 = m_1 \right\rangle_i p(n_1,t_1)$$

$$\times \left\langle \mathrm{e}^{-\Delta s_{ii}^{\mathrm{ex}}} p_1(n_t,t|y_1)|n_1\right\rangle_{ii} = 1. \quad (158)$$

Introducing conditioned averages on the two intervals i and ii eliminates the explicit factor $1/p_1(n_1,t_1|y_1)$. The underlined term is 1 for any m_1 due to (85). Likewise, the subsequent summation over m_1 is 1 due to (86). The SUE thus holds for trajectory-averages still conditioned on the results y_1. Of course, further averaging over all possible outcomes y_1 is allowed. This proof (as the original one) is easily extended to multiple measurements. Thus, the Sagawa–Ueda equality (SUE) and its variant (156) with the corresponding inequalities hold for any number of measurements [312–316].

For processes involving genuine non-equilibrium states, the generalization of the Hatano–Sasa relation (67) to processes with feedback in the form [313]

$$\langle \exp[-(\Delta s^{\mathrm{tot}} - \Delta s^{\mathrm{hk}} + \mathcal{I})]\rangle = 1 \quad (159)$$

with the inequality

$$\langle \Delta s^{\mathrm{tot}}\rangle \geqslant \langle \Delta s^{\mathrm{hk}}\rangle - \mathcal{I} \quad (160)$$

follows as easily starting with conditioned variants of (88). The bound (160) is much stronger than (157) since $\langle \Delta s^{\mathrm{hk}}\rangle$ will typically scale with the total time t. For systems that at constant λ exhibit detailed balance, $\Delta s^{\mathrm{hk}} = 0$, in which case (159) and (160) become (156) and (157).

7.3.4. Efficiency of Brownian information machines. For a cyclically operating information machine, where measurements are repeated at regular intervals separated by t_m [317], the inequality (157) implies that one can extract at most a mean power $\dot{W}^{\mathrm{out}}$ bounded by

$$\dot{W}^{\mathrm{out}} \leqslant \dot{\mathcal{I}}, \quad (161)$$

where $\dot{\mathcal{I}}$ is the rate with which information is acquired. Likewise, for processes involving transitions between genuine non-equilibrium states, the inequality (160) implies

$$\dot{W}^{\mathrm{out}} \leqslant \dot{W}^{\mathrm{in}} - \langle \dot{q}^{\mathrm{hk}}\rangle + \dot{\mathcal{I}}. \quad (162)$$

If the rate of acquiring information is large enough, i.e. if $\dot{\mathcal{I}} > \langle \dot{q}^{\mathrm{hk}}\rangle$, the extracted power can exceed the power $\dot{W}^{\mathrm{in}}$ required to sustain these non-equilibrium steady states as demonstrated explicitly with a simple example in [313]. Characteristically, the power extracted from such a machine becomes larger, the smaller the intervals t_m between the measurements are.

A quite natural definition for the efficiency [317, 318] of such a Brownian information machines obeying $0 \leqslant \eta \leqslant 1$ is in the first case

$$\eta \equiv \dot{W}^{\mathrm{out}}/\dot{\mathcal{I}} \quad (163)$$

and, analogously,

$$\eta \equiv \dot{W}^{\mathrm{out}}/[\dot{W}^{\mathrm{in}} - \langle \dot{q}^{\mathrm{hk}}\rangle + \dot{\mathcal{I}}] \quad (164)$$

for the second case.

7.3.5. Further theoretical work and case studies. Several theoretical studies have investigated various aspects of such feedback-driven processes for stochastic dynamics. Kim and Qian have considered an underdamped particle controlled by a velocity-dependent force [319, 320]. This problem has been

[8] Note that even for detailed balanced systems, the equalities (154) and (156) are different since, in general $w - \Delta\mathcal{F} \neq \Delta s^{\mathrm{tot}}$.

[9] For proving the SUE (154), one only needs to replace $p_1(n_t,t|y_1)$ by $p^{\mathrm{eq}}(n_t,t|y_1)$ in (158).

analyzed from the perspective of total entropy production in [321]. Suzuki and Fujitani investigate Brownian motion both under a time-dependent force [322] and for linear systems more generally [323]. Similarly, Sagawa and Ueda illustrated their concept using a particle that is transported in a movable harmonic trap and can still extract work from the surrounding heat bath [311]. Feedback-driven transport for ratchet-type systems has been optimized in [324–326]. Maximum power for such a model has been studied in [327]. Information-theoretic and thermodynamic concepts have been combined in [318, 328–331]. The thermodynamic cost of a measurement has been modeled in [332]. Recent reviews on the relation between information and feedback control are [333, 334].

The optimal protocol for extracting the maximal work from cyclic processes for particles in harmonic traps with adjustable center and stiffness based on imperfect positional measurements has been calculated in [335] where it was shown that the bound (155) cannot be saturated if only the center of the trap is under control. Only by additionally adjusting the stiffness can all the information be recovered provided an infinite time is allocated to the process. For such a machine, the efficiency at finite cycle time has been calculated in [317]. The issue of saturating this bound has been investigated in more depth introducing the notion of 'reversible' feedback by Horowitz and Parrondo [336, 337]. A model for the cost of erasing information using a Brownian particle in a double-well potential was discussed in [338].

7.3.6. Experimental illustrations. Experimentally, the SUE has been demonstrated using an ingenious set-up involving electric fields that upon measuring the position of a colloidal particle on a 'stair' prevent that the particle slides down a step that it has just climbed by thermal excitation [339]. In another experiment, Landauer's principle has been illustrated using a colloidal particle trapped in a modulated double-well potential. The mean dissipated heat indeed saturates at the Landauer bound in the limit of long erasure cycles [340].

7.3.7. Hamiltonian dynamics for microcanonical initial conditions. Deviating from the restriction to stochastic dynamics as applied generally in this review, I mention a few recent studies that use Hamiltonian dynamics and feedback since they provide an additional perspective on what has just been described. The Kelvin–Planck statement of the second law does not hold for microcanonical initial conditions which indeed allow one to extract work, i.e. to decrease the mean energy from a Hamiltonian system by manipulating an external control parameter [341]. Specific examples have been given for a harmonic oscillator [342], for a particle between movable walls [343] and for motion in a double-well potential [344]. While for such microcanonical initial conditions no measurement is necessary, these results could be applied to an initially canonical ensemble if the energy of the system is measured with subsequent adaptation of the protocol of the control parameter in a feedback process. As shown explicitly in [344], the full analysis including the cost of erasing information exorcizes this 'demon' and restores the ordinary second law.

8. FDT in a NESS

8.1. Overview

8.1.1. FDT in equilibrium. Equilibrium systems react to small perturbations in a quite predictable way formally expressed by the FDT, see, e.g., [345]. The response of an observable A at time τ_2 to a perturbation h applied at time τ_1 can be written in the form of an equilibrium correlation function as

$$T\delta\langle A(\tau_2)\rangle/\delta h(\tau_1)_{|h=0} \equiv T R_A^{\rm eq}(\tau_2-\tau_1) = \partial_{\tau_1}\langle A(\tau_2)B(\tau_1)\rangle^{\rm eq}, \tag{165}$$

where the conjugate variable

$$B = -\partial_h E \tag{166}$$

follows from the energy $E(h)$ of the system. Here it is assumed that for any small fixed h the energy of the system is still well-defined. This FDT is the formalization and generalization of Onsager's regression hypothesis that states that the decay of an excitation is independent of whether it has been generated externally by a force (or field) h or by a thermal fluctuation. This theorem is of great practical significance since it allows one to predict the response to a perturbation without ever applying one just by sampling the corresponding equilibrium fluctuations either in experiments or in simulations. Characteristically, the same B holds for any A and any time difference $\tau_2 - \tau_1$.

8.1.2. FDT in a NESS. Whether a similarly universal relation exists for NESSs has been addressed using various approaches since the seventies. For an underlying stochastic dynamics, Agarwal has expressed the response function by a correlation function involving the typically unknown stationary distribution [346]. Bochkov and Kuzovlev [12, 347, 348] and Hänggi and Thomas [349] have derived a variety of formal expressions for stochastic processes. A comprehensive review of the general relation between fluctuations and response including, in particular, deterministic chaotic systems is given in [350].

More recently, taking up a theme introduced earlier [351], Harada and Sasa derived a relation where the 'violation' of the equilibrium FDT in a NESS was related to the rate of energy dissipation for a Langevin system [352, 353] later generalized to a description in terms of a density field [354]. For the special case of a driven colloidal particle it was shown in [355] that the FDT in the NESS could be obtained from the equilibrium FDT (165) by subtracting from the rhs a second correlation function involving the local mean velocity. This result suggested that in the locally co-moving frame the Onsager hypothesis could be restored which was later extended to sheared systems [356] and proven for general diffusive dynamics in [357, 358]. Thus, for these systems, the decay of an excitation around a local NESS is still the same whether generated externally or by the thermal fluctuations still present in the NESS.

A concise formal derivation and discussion of the general FDT in a NESS has been given by Baiesi *et al* [359–361]. The response of particular observables was treated at the same

time by Prost *et al* [362]. In [363], it was then shown that the latter result holds indeed for any observable and that the FDT for a NESS becomes particularly transparent when using the concept of stochastic entropy with its splitting into a total and a medium one. In this latter work, the apparent multitude of FDTs in a NESS was rationalized in terms of an equivalence relation holding for observables in NESS correlation functions.

An elegant synthesis using mathematically somewhat more demanding concepts has just been given in [364]. An extension of these concepts to obtain an FDT around non-stationary non-equilibrium states is derived in [365]. A connection with gauge fields is made in the geometrical approach of [366]. For a nice review on the FDT for NESSs, see the recent [367].

8.1.3. Effective temperature. The derivation of recent exact versions of the FDT for a NESS which as a result typically express the response function by a sum of two correlation functions should be distinguished from the phenomenological concept of an effective temperature that has been reviewed in [368]. Originally introduced in the context of aging systems, it can be formulated also for a NESS. Simply stated, guided by the equilibrium form (165) an effective temperature is defined as

$$T^{\rm eff}(A,\tau_2-\tau_1)\equiv \partial_{\tau_1}\langle A(\tau_2)B(\tau_1)\rangle^s/R_A(\tau_2-\tau_1), \quad (167)$$

where R_A is now taken in the NESS. In general, $T^{\rm eff}$ will depend on both the observable A and the time difference $\tau_2-\tau_1$ which upon Fourier transformation corresponds to frequency ω. Obviously, this concept can become meaningful only if these dependences are not very pronounced.

From a theoretical point of view, a strictly observable and frequency-independent $T^{\rm eff}$ follows for a Langevin system like (42) with $\boldsymbol{f}=0$ if the non-equilibrium conditions are caused by an additional 'active' noise $\boldsymbol{\eta}$ with correlations $\langle\boldsymbol{\eta}(\tau_2)\boldsymbol{\eta}(\tau_1)\rangle = 2(T^{\rm eff}-T)\underline{\underline{\mu}}\delta(\tau_2-\tau_1)$. For a linear system and active noise correlated on a scale $\tau^{\rm ac}$, $T^{\rm eff}$ will depend on frequency. For $\omega\tau^{\rm ac}\gg 1$, one obtains the ordinary temperature, whereas for $\omega\tau^{\rm ac}\ll 1$ the enhanced fluctuations lead to a larger $T^{\rm eff}$.

On the other hand, if the non-equilibrium is generated by a non-conservative force or field, such a simple reasoning is no longer possible. Still, in interacting systems one often finds numerically good agreement with the concept of an effective temperature as briefly mentioned in section 8.4 below for sheared suspensions. A fundamental understanding of when and why this is the case in general seems still to be missing.

For insight into the frequency and observable dependence for specific models and systems, see, e.g., [369, 370] for a binary Lennard-Jones mixture in a simple shear flow, [371] for a glassy model system, [372–375] for simple interacting model systems, [376–378] for simple Langevin systems, and [379] for field-theoretical models. For the phenomenon of 'hot Brownian motion' mentioned in section 2.6.3, various 'effective temperatures' were determined in simulations [380].

Examples of investigating biophysical systems using an effective temperature include [381] for hair bundle oscillations, [382, 383] for the cytoskeleton, [384, 385] for filament oscillations in an active medium, [386] for self-propelled particles, [387] for vesicle and [388, 389] for red-blood-cell fluctuations. If the response of such a system acts effectively 'against' the perturbation, the effective temperature becomes negative as occasionally found in these studies. Such an observation shows that this concept should not be taken very literally.

8.2. Derivation and discussion

In this section, we sketch the derivation of the various forms of the FDT in a NESS from a unifying perspective for a general Markovian dynamics on a discrete set of states. Since overdamped Langevin systems can always be discretized, this case is a very general one. We follow the concepts introduced in [359, 363] which were briefly reviewed in their continuum version in [390]. Earlier related work for a Markovian dynamics on a discrete set of states making somewhat more explicit assumptions on observable and rates for spin models include [391–398] and for aging in supercooled liquids [399].

8.2.1. Equivalent correlation functions in a NESS. We consider a class of NESSs with rates $w_{mn}(h)$ that depend on a perturbation h. The stationary distribution of the master equation dynamics (110) obeys

$$\sum_n L_{mn}(h)p_n^s(h)=0 \quad (168)$$

with the generator

$$L_{mn}(h)\equiv w_{nm}(h)-\delta_{mn}\sum_k w_{mk}(h). \quad (169)$$

For fixed h, any dynamic information is fully contained in the propagator

$$G_{kl}(\tau)\equiv p[n(\tau)=k|n(0)=l] \quad (170)$$

for which the master equation (110) implies the evolution

$$\partial_\tau G_{kl}(\tau)=\sum_m L_{km}G_{ml}(\tau)=\sum_m G_{km}(\tau)L_{ml}. \quad (171)$$

In a NESS, denoted in the following with $\langle\ldots\rangle^s$, two-point correlation functions for state variables of the form $A(\tau)=\sum_m A_m\delta_{n(\tau)m}$ are given by

$$\langle A(\tau_2)B(\tau_1)\rangle^s=\sum_{mn}A_mG_{mn}(\tau_2-\tau_1)B_np_n^s \quad (172)$$

if $\tau_2>\tau_1$. Using (169) and (171), a time derivative with respect to the earlier time can thus be written as an ordinary two-point correlation function

$$\partial_{\tau_1}\langle A(\tau_2)B(\tau_1)\rangle^s=\langle A(\tau_2)C(\tau_1)\rangle^s \quad (173)$$

with

$$\begin{aligned}C_n&=B_n\sum_m w_{nm}-\sum_m B_m w_{mn}p_m^s/p_n^s\\&=\sum_m(B_n-B_m)p_m^s w_{mn}/p_n^s.\end{aligned} \quad (174)$$

In addition to state variables as observables we will also need current variables of the type

$$D(\tau) \equiv \sum_j \delta(\tau - \tau_j) d_{n_j^- n_j^+} \tag{175}$$

that yield $d_{n_j^- n_j^+}$ whenever a corresponding transition takes place. Their NESS average is given by $\langle D(\tau)\rangle^s = \sum_{mn} p_m^s w_{mn} d_{mn}$. If $D(\tau)$ shows up in a correlation function at the earlier time τ_1, we obtain

$$\langle A(\tau_2) D(\tau_1)\rangle^s = \sum_{mkl} A_m G_{ml}(\tau_2 - \tau_1) p_k^s w_{kl} d_{kl} \tag{176}$$

$$= \langle A(\tau_2) E(\tau_1)\rangle^s \tag{177}$$

with

$$E_n = \sum_k p_k^s w_{kn} d_{kn} / p_n^s. \tag{178}$$

These relations imply, in particular, that the formal current variable

$$\dot{B}(\tau) \equiv \sum_j \delta(\tau - \tau_j)(B_{n_j^+} - B_{n_j^-}) \tag{179}$$

obeys

$$\langle A(\tau_2)\dot{B}(\tau_1)\rangle^s = \partial_{\tau_1}\langle A(\tau_2) B(\tau_1)\rangle^s \tag{180}$$

which demonstrates, quite expectedly, that even in this discrete case time derivatives can be pulled in and out of a NESS correlation function straightforwardly.

The fact that NESS correlation functions can have the same value if the variable at the earlier time is written differently gives rise to an equivalence relation denoted by

$$O^{(1)}(\tau) \cong O^{(2)}(\tau) \tag{181}$$

if

$$\langle A(\tau_2) O^{(1)}(\tau_1)\rangle^s = \langle A(\tau_2) O^{(2)}(\tau_1)\rangle^s \tag{182}$$

holds for all A and times $\tau_1 < \tau_2$ [363]. For the variables defined above we obviously have

$$D(\tau) \cong E(\tau) \qquad \text{and} \qquad \dot{B}(\tau) \cong C(\tau) \tag{183}$$

which summarizes how current variables and time derivatives can be replaced by state variables in NESS correlation functions. This freedom will explain why apparently so different looking FDTs can be derived for a NESS.

8.2.2. Equivalent forms of the FDT. The apparent plethora of FDTs can be rationalized by starting with an expression for the response function using the path weight (119). In the presence of a time-dependent perturbation $h(\tau)$, the mean value of the observable $A(\tau)$ is given by [359, 363]

$$\langle A(\tau)\rangle = \sum_{n(\tau)} A(\tau) p[n(\tau); h(\tau)|n_0] p_{n_0}^s$$
$$= \sum_{n(\tau)} A(\tau) \frac{p[n(\tau); h(\tau)|n_0]}{p[n(\tau)|n_0]} p[n(\tau)|n_0] p_{n_0}^s. \tag{184}$$

The response function

$$R_A(\tau_2 - \tau_1) \equiv \delta\langle A(\tau_2)\rangle / \delta h(\tau_1)|_{h=0} \equiv \langle A(\tau_2) B^p(\tau_1)\rangle^s \tag{185}$$

can be expressed by a two-point correlation function in the unperturbed NESS by evaluating (184) with the action (119) as

$$B^p(\tau_1) = -\delta \mathcal{A}[n(\tau); h(\tau)]/\delta h(\tau_1)|_{h=0} \tag{186}$$

$$= -\sum_k w_{n(\tau)k} \alpha_{n(\tau)k} + \sum_j \delta(t - \tau_j) \alpha_{n_j^- n_j^+} \tag{187}$$

where

$$\alpha_{mn} \equiv \partial_h \ln w_{mn}(h)_{|h=0}. \tag{188}$$

This form of the conjugate variable (with the superscript p alluding to the derivation through the path weight) is convenient since it allows one to determine the response function by measuring a correlation function that requires only knowledge about how the rates depend on the control parameter which is easily available in simulations. The more formal aspect that the first term in (187) arises from the time-symmetric part of the action and the second one from its time-antisymmetric one is emphasized and further exploited in [359–361].

A second equivalent representation of the conjugate variable is obtained by replacing (by following the scheme (175)–(178)) the second (current) part in B^p by its equivalent state variable form which leads to $B^p \cong B^a$ with

$$B_n^a = -\sum_k w_{nk}\alpha_{nk} + \sum_k w_{kn}\alpha_{kn} p_k^s / p_n^s \tag{189}$$

$$= \sum_k \partial_h L_{nk}(h)|_{h=0}\, p_k^s / p_n^s. \tag{190}$$

The last equality follows from expanding (169) in h and the definition (188). This expression for the conjugate variable involving only state variables can also be derived by straightforward time-dependent perturbation theory of the Fokker–Planck equation as originally derived by Agarwal (hence, the superscript a) [346]. Using this expression, however, requires knowledge of the stationary distribution which for interacting systems with many degrees of freedom is not easily available in either simulations or experiments.

Finally, as a third, arguably physically most transparent form of the conjugate variable, it is easy to check explicitly that $-\partial_h \dot{s} \cong B^a$ by expanding (168) in h and following the recipe of how to pull a time derivative into a correlation function given in the previous subsection. Consequently, one has [363]

$$R_A(\tau_2 - \tau_1) = -\langle A(\tau_2)\partial_h \dot{s}(\tau_1)\rangle^s \tag{191}$$

$$= \langle A(\tau_2)\partial_h \dot{s}^{\mathrm{m}}(\tau_1)\rangle^s - \langle A(\tau_2)\partial_h \dot{s}^{\mathrm{tot}}(\tau_1)\rangle^s. \tag{192}$$

The first form expresses the response function as a time derivative of a correlation function where the observable $A(\tau_2)$ is correlated with the h-derivative of the stochastic entropy at τ_1. This form of the conjugate variable is actually unique if one wants to write the response function as a time derivative of a correlation function. Moreover, it allows a physically transparent interpretation by splitting it into the sum of medium and total entropy production as shown in the second line.

8.2.3. Comparison with equilibrium FDT. For a comparison with the equilibrium FDT, assume that the steady state is a genuine equilibrium state for $h = 0$. In fact, two classes of such systems should be distinguished.

First, if the system is not only in equilibrium at $h = 0$ but also at small h, the stationary distribution is given by the Boltzmann distribution

$$p_n^{\rm eq}(h) = \exp\{-[E_n(h) - \mathcal{F}(h)]/T\}, \tag{193}$$

where $E_n(h)$ is the internal energy and $\mathcal{F}(h)$ the h-dependent free energy of the system. The stochastic entropy obeys $s_n(h) = -\ln p_n^{\rm eq}(h) = [E_n(h) - \mathcal{F}(h)]/T$. Along an individual trajectory, $\mathcal{F}(h)$ is constant and hence we have

$$T\,\partial_h \dot{s}_n(h)_{|h=0} = \partial_h \dot{E}_n(h)_{|h=0}. \tag{194}$$

Inserting this equivalence into (191), the FDT acquires its well-known equilibrium form (equations (165) and (166)) involving the observable conjugated to h with respect to energy.

Second, a system may be in equilibrium at $h = 0$ but driven into a NESS even at constant small h. The paradigmatic example is a perturbation through shear flow for which there is no corresponding $E(h)$ for any $h \neq 0$. For such systems, the equilibrium FDT can still be written in the form (191) but also in the pure state form with B^a from (equations (189) and (190)).

8.2.4. Systems with local-detailed balance. A further comparison between the equilibrium and the NESS-FDT is instructive for systems for which the perturbation enters the ratio of the rates in the form of a local-DBC

$$\frac{w_{mn}(h)}{w_{nm}(h)} = \frac{w_{mn}(0)}{w_{nm}(0)} \exp[h d_{mn}/T], \tag{195}$$

where $d_{mn} = -d_{nm}$ is the distance conjugate to the field covered by the transition $m \to n$. For $h = 0$, the system is supposed to be in genuine equilibrium with averages denoted by $\langle \ldots \rangle^{\rm eq}$; for $h = h_0 \neq 0$ a genuine NESS denoted by $\langle \ldots \rangle^s$ is reached. In equilibrium, using the global DBC (113), one easily verifies $\partial_h \dot{s}^{\rm m} \cong B^a$ and hence one has the equilibrium FDT

$$T R_A^{\rm eq}(\tau_2 - \tau_1) = \langle A(\tau_2) B^a(\tau_1)\rangle^{\rm eq} = \langle A(\tau_2)\partial_h \dot{s}^{\rm m}(\tau_1)\rangle^{\rm eq}. \tag{196}$$

On the other hand, the NESS-FDT in the form (192) always holds. Since for such systems

$$\partial_h \dot{s}^{\rm m} = \sum_j \delta(\tau - \tau_j) d_{n_j^-, n_j^+}/T \tag{197}$$

is independent of h, the recipe for getting the FDT in a NESS from the equilibrium FDT is to keep as a first term the observables showing up in the correlation function but to evaluate the latter under NESS conditions and to subtract an expression involving the total entropy production [363].

8.2.5. Generalized Green–Kubo relations. In equilibrium, the Green–Kubo relations express transport coefficients like conductivity or viscosity by time-integrals over equilibrium correlation functions of the corresponding currents. Based on the FDT derived above, it is possible to derive similar relations between transport coefficients in a NESS and appropriate current–current correlation functions [400] as illustrated for a simple model of molecular motors in [401]. This approach of studying the linear response of a NESS should be distinguished from extensions of the Onsager symmetry relations to the non-linear response coefficients of an equilibrium system [402].

8.3. Colloidal particle on a ring as paradigm

The overdamped particle driven along a periodic potential, see figure 1, as discussed in section 2.2 can serve as paradigm for illustrating the different versions of the FDT [363].

8.3.1. Equivalent correlation functions. The equivalence relation introduced in section 8.2.1 for variables occurring in correlation functions in a NESS exists for continuous variables as well. For a discretized position variable, jump rates can easily be derived from discretizing the path integral. Going then through the steps as in section 8.2.2 shows that the equivalence

$$\dot{x} \cong 2v^s(x) - \mu F(x) \tag{198}$$

can be used in a NESS correlation function at the earlier time.[10] The mean local velocity $v^s(x)$ has been introduced in (12). Sometimes, the generalization

$$g(x)\dot{x} \cong g(x)[2v^s(x) - \mu F(x)] - \mu T\,\partial_x g(x) \tag{199}$$

is useful which can be derived similarly[11].

8.3.2. Three equivalent forms. First, consider a NESS generated by a force f_0 which is further perturbed by an additional delta-like force impulse acting at time τ_1. The response function can be written as a correlation function in the three equivalent forms

$$T R_A(\tau_2 - \tau_1)_{|f_0 \neq 0} = \langle A(\tau_2)[\dot{x} - \mu F(x)]_{|\tau_1}/2\rangle^s \tag{200}$$

$$= \langle A(\tau_2)[v^s(x) - \mu F(x)]_{|\tau_1}\rangle^s \tag{201}$$

$$= \langle A(\tau_2)[\dot{x} - v^s(x)]_{|\tau_1}\rangle^s. \tag{202}$$

The first form follows from applying perturbation theory to the path integral expression. The advantage of this expression is that it does not require explicit knowledge of the stationary distribution. By replacing the velocity with the corresponding state variable as shown in (198) one obtains the second form. This expression can also easily be obtained from perturbation theory of the Fokker–Planck equation as in the original derivation [346]. Finally, a simple linear combination of the first two lines leads to the third form originally first derived in [355]. In this form, both the additive correction to the equilibrium form $T R_A(\tau_2 - \tau_1) = \langle A(\tau_2)\dot{x}(\tau_1)\rangle^{\rm eq}$ and the significance of a locally co-moving frame become apparent.

[10] In equilibrium, this equivalence becomes $\dot{x} \cong \mu \partial_x V(x)$ where the crucial sign difference compared with naively ignoring the noise in the Langevin equation (1) should be noted.

[11] Applied to a NESS correlation function with $A(\tau_2) = 1$, this relation leads to $\langle g(x)\dot{x}\rangle^s = \langle g(x)[2v^s(x) - \mu F(x)]\rangle^s - \mu T\langle \partial_x g(x)\rangle^s = \langle g(x)v^s(x)\rangle^s$ which corresponds to (34) applied to a NESS.

8.3.3. Generalized Einstein relation. The Einstein relation (3) connecting the bare mobility μ of a particle embedded in a viscous fluid with its diffusion constant D has arguably been the first form of an FDT which was based on a microscopic understanding of thermal motion. This relation has many manifestations in more complex soft matter systems as reviewed in [49]. If such a particle is in a periodic potential $V(x)$, the diffusion coefficient

$$D[V(x)] = \lim_{t\to\infty}[\langle x^2(t)\rangle - \langle x(t)\rangle^2]/2t \tag{203}$$

and the effective mobility

$$\mu[V(x)] = \partial_f \langle \dot{x}\rangle_{|f=0} \tag{204}$$

still obey $D[V(x)] = T\mu[V(x)]$ even though both terms are exponentially suppressed if the barriers exceed the thermal energy.

In the presence of a non-zero base force, an effective diffusion constant $D[V(x), f]$ and a mobility $\mu[V(x), f]$ as in (203) and (204) evaluated at a finite force, respectively, are still defined. The effective mobility is the time-integrated response function. Hence, the generalized Einstein relation between $D[V(x), f]$ and $\mu[V(x), f]$ follows from integrating (202) from $\tau_2 = \tau_1$ to $\tau_2 = \infty$ as [355]

$$T\mu[V(x), f] = D[V(x), f] + \int_0^\infty \mathrm{d}\tau[\langle \dot{x}(\tau) - \langle \dot{x}\rangle][v^s(x(0)) - \langle \dot{x}\rangle^s] \tag{205}$$

which shows how the 'violation' of the usual Einstein relation can be expressed as an integral over velocity correlation functions. This relation is a simple example of a Green–Kubo relation generalized to a NESS [400]. Another form of this generalized Einstein relation has been studied in [403] for two-dimensional motion in the presence of a magnetic field and for a discrete model showing anomalous diffusion in [404], respectively.

8.3.4. Experiments. The generalized Einstein relation (205) has been measured experimentally in [405]. Significantly, in this experiment, the extra integral term in (205) can be about four times as big as $T\mu[V(x), f]$ which shows clearly that this experiment probes a genuine NESS far from any linear response regime of an equilibrium system. Still, the description of the colloidal motion by a Markovian Brownian motion with unaltered thermal noise and a drift obviously remains a faithful representation. The very fact that around a critical force $f \simeq \max|\partial_x V(x)|$ the diffusion coefficient becomes quite large is known as giant diffusion [406, 407].

The time-resolved version of this FDT has been studied experimentally in [408] where it was shown that even though the different correlation functions (equations (200)–(202)) are theoretically equivalent their statistics can be vastly different. Not surprisingly, the variant (201) involving only state functions shows better convergence properties than the ones requiring $\dot{x}$. The response not to a force but to a change in the amplitude of the periodic potential was studied experimentally in [409, 410].

8.4. Sheared suspensions

For studying the relation between fluctuations and response in interacting non-equilibrium systems, a colloidal suspension in shear flow provides a paradigmatic case. Such a system follows a dynamics as introduced in section 2.6.3 with $\boldsymbol{u}(\boldsymbol{r}) = \dot{\gamma} y \boldsymbol{e}_x$ (or the corresponding underdamped version) and some pair interaction V.

One obvious question is to investigate the generalized Einstein relation between the self-diffusion coefficient $D_{ij}(\dot{\gamma})$ and the mobility $\mu_{ij}(\dot{\gamma})$ of a tagged particle which both become tensorial quantities in such an anisotropic system. Szamel [411] studied these quantities analytically using the memory-function formalism. Krüger and Fuchs [412] have studied this relation analytically and numerically near the glass transition. Our numerical study in the fluid phase [413] revealed that for moderate densities the results can surpringly well be expressed as an effective temperature since the ratios $D_{ii}(\dot{\gamma})/\mu_{ii}(\dot{\gamma})$ of the diagonal elements become isotropic with a roughly quadratic increase with shear rate. This effective temperature which turns out to be the kinetic one can be rationalized by comparing this interacting system with a harmonically bound single particle in shear flow [414]. The response to a perturbation in the shear rate has been investigated in [356] and the one to a static external long wave-length perturbation in [415, 416].

Further studies of the general FDT for sheared suspensions include the integration through transient formalism [417, 418]. One advantage of this approach is that all quantities can be expressed in terms of (albeit complicated) equilibrium correlation functions. The response to a time-dependent additional shear strain has been studied numerically in [356] using essentially the form (191) that makes the excess compared with the equilibrium case explicit. The relation between the violation of the equilibrium FDT and energy dissipation using field variables has been addressed in [354].

9. Biomolecular systems

9.1. Overview

Single molecules and (small) biomolecular networks constitute a paradigmatic class of systems to which the concepts of stochastic thermodynamics can be applied. Conformational changes of single molecules have become observable through a variety of methods often summarized as single molecule techniques [419–421]. There are essentially two ways of exposing such a molecule that is embedded in an aqueous solution of well-defined temperature containing different solutes at specified concentrations to non-equilibrium conditions. First, one can apply a (possibly time-dependent) mechanical force if one end is connected via polymeric spacers to the tip of an AFM or to beads in an optical tweezer. This set-up allows one to study, e.g., force-induced unfolding of proteins. Another source of non-equilibrium are unbalanced chemical reactions catalyzed by the enzyme under study. In combination with a mechanical force, this set-up allows one in particular to resolve individual steps of a molecular motor

and to measure force–velocity curves of such a molecular machine [422, 423].

The fluctuating conformations of biomolecules in non-equilibrium can be described in two ways [34, 424, 425]. First, one can model the observable degrees of freedom like the end to end-distance of a protein by a continuous degree of freedom subject to a Langevin equation. Such an approach is particularly appropriate for studying force-induced un- and refolding of biopolymers, in particular, with the perspective of recovering free energy differences and even landscapes from non-equilibrium experiments as reviewed in section 9.3.

Second, one can identify discrete, distinguishable states between which (sudden) transitions take place as has often been carried out to model molecular motors [426–442]. In most of these works the focus has been put on elucidating the cycles involved in the action of the motor and on deriving force–velocity curves and their dependence on ATP and ADP concentrations. A combination of both types of models has been used for describing molecular motors by a Langevin dynamics in a ratchet potential that depends explicitly on the current chemical state of the motor as reviewed in [443–446].

From the perspective of stochastic thermodynamics, one would like to formulate a first law, discuss entropy production and derive the corresponding fluctuation theorems on the single molecule level. Within a discrete state description, a first law along an individual trajectory has been discussed for single enzymes in [98, 232, 447], for molecular motors in [430, 434–439], and for small biochemical reaction networks in [255, 448, 449]. Fluctuation theorems without explicit reference to a first law were discussed for such systems in [431, 440, 450–456].

From a theoretical point of view, there are essentially two new aspects that enter the stochastic thermodynamics of biomolecular systems beyond a naive combination of the stochastic thermodynamics of colloids as developed in section 2 and the discrete dynamics as introduced in section 6. First, the rates are not arbitrary as in section 6 but are rather constrained by thermodynamic consistency [211, 212, 457] as discussed in detail below. Second, each of the states visited along a stochastic trajectory contains many microstates. Transitions between these (unobserved) microstates are fast so that thermal equilibrium is reached within each state. Transitions between the states, however, are slower, observable and can be driven by external forces, flows or chemical gradients. As a consequence, each of the states described by stochastic thermodynamics carries an intrinsic entropy arising from the coupling to the fast polymeric degrees of freedom and to those of the heat bath. This effect must be taken into account in any consistent identification of heat on the single trajectory level [98, 438, 458, 459]. Some of the earlier studies quoted above missed this contribution and, hence, failed to identify the dissipated heat correctly.

How these systems can be described from the perspective of a thermodynamic engine will be pursued in section 10.

9.2. Role of fast hidden degrees of freedom

In this section, we show how for a system with a separation of time-scales the first law and entropy production along a trajectory as well as the FTs can be formulated by extending to this case the formalism developed for systems without relevant internal degrees of freedom like the colloidal particle of section 2. Whether for any specific system such as the paradigmatic biomolecule used here as illustration such a separation is a realistic assumption would have to be studied on a case by case basis by investigating its specific molecular dynamics. We first use a description with continuous degrees of freedom and address the discrete case in section 9.4.

9.2.1. Thermodynamic states from a microscopic model. A biopolymer contains a large number of coupled microscopic degrees of freedom most of which will not be accessible in experiments. Still, these microscopic degrees of freedom affect processes on a larger scale that are described by stochastic thermodynamics. The microscopic configurational degrees of freedom collectively denoted by ξ are subject to a microscopic potential energy $\Phi(\xi, \lambda)$ containing the interactions within the molecule (and possibly with some of the surrounding solvent and solute molecules). The dependence on λ allows for an external potential arising from an AFM or an optical tweezer whose positions can be controlled through λ.

Under non-equilibrium conditions, an external force (or field or flow) is applied to the molecule leading to conformational changes apparent through, e.g., a changing end-to-end distance. Such a quantity is an example of a meso-scale description that involves a certain number of variables denoted by $\boldsymbol{x}$. Each such state effectively comprises many microstates. Formally, one can split all microstates $\{\xi\}$ in classes $\mathcal{C}_{\boldsymbol{x}}$ such that each ξ belongs to exactly one $\mathcal{C}_{\boldsymbol{x}}$. The dynamics of $\boldsymbol{x}$ is supposed to be slow and observable whereas equilibration among the microstates making up one state $\boldsymbol{x}$ is fast. Under this crucial assumption, the conditioned probability $p(\xi|\boldsymbol{x}, \lambda)$ that a microstate is occupied is given by

$$p(\xi|\boldsymbol{x}, \lambda) = \exp[-(\Phi(\xi, \lambda) - F(\boldsymbol{x}, \lambda))/T] \tag{206}$$

with the constrained free energy

$$\begin{aligned} F(\boldsymbol{x}, \lambda) &\equiv E(\boldsymbol{x}, \lambda) - TS(\boldsymbol{x}, \lambda) \\ &\equiv -T \ln \sum_{\xi \in \mathcal{C}_{\boldsymbol{x}}} \exp[-\Phi(\xi, \lambda)/T], \end{aligned} \tag{207}$$

the constrained intrinsic entropy

$$S(\boldsymbol{x}, \lambda) \equiv -\partial_T F(\boldsymbol{x}, \lambda) = -\sum_{\xi \in \mathcal{C}_{\boldsymbol{x}}} p(\xi|\boldsymbol{x}, \lambda) \ln p(\xi|\boldsymbol{x}, \lambda) \tag{208}$$

and constrained internal energy

$$E(\boldsymbol{x}, \lambda) = \sum_{\xi \in \mathcal{C}_{\boldsymbol{x}}} \Phi(\xi, \lambda) p(\xi|\boldsymbol{x}, \lambda). \tag{209}$$

This model includes but is more general than a more conventional description of the configurational potential in the additive form

$$\Phi(\boldsymbol{x}, \xi, \lambda) = \Phi^0(\boldsymbol{x}, \lambda) + \Phi^{\text{int}}(\boldsymbol{x}, \xi, \lambda) + \Phi^{\text{med}}(\xi, \lambda) \tag{210}$$

made up, respectively, by a system, a coupling (of arbitrary strength) and a potential for the degrees of freedom of the

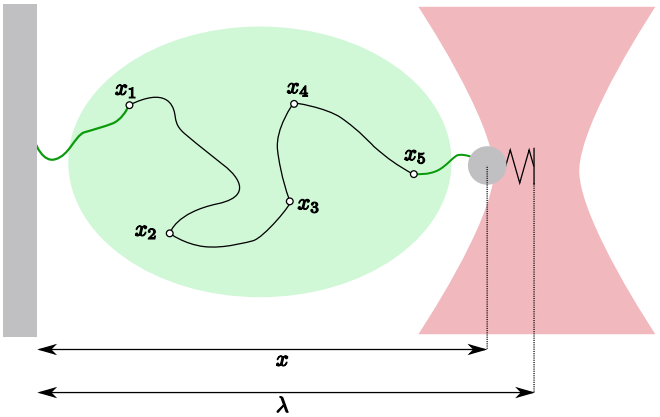

Figure 6. Schematic view of a protein stretched by a bead in a laser trap. In a meso-scale description, the configuration is characterized by the positions $\boldsymbol{x} = \{x_1, x_2, x_3, x_4, x_5, x)\}$ where x is the position of the bead. The control parameter λ denotes the center of the trap.

medium, which all may depend on the control parameter. Here, all degrees of freedom are split into those of the system $\boldsymbol{x}$ and those of the heat bath ξ. By replacing $\Phi(\xi, \lambda)$ in (206) and (207) with $\Phi(\boldsymbol{x}, \xi, \lambda)$ and summing without constraint over all ξ, the relations (206)–(209) remain true for the potential (210).

9.2.2. First law. For a time-dependent $\lambda(\tau)$, representing, e.g., the center of a moving laser trap, the increment in applied work reads

$$đw = \sum_{\xi \in \mathcal{C}_x} \partial_\lambda \Phi(\xi, \lambda) p(\xi|\boldsymbol{x}, \lambda)\, \mathrm{d}\lambda \tag{211}$$

$$= \partial_\lambda F(\boldsymbol{x}, \lambda)\, \mathrm{d}\lambda = \mathrm{d}F(\boldsymbol{x}, \lambda) - \boldsymbol{\nabla} F(\boldsymbol{x}, \lambda)\, \mathrm{d}\boldsymbol{x}. \tag{212}$$

In the first equality, for a changing external parameter the work arising from the microscopic interaction $\Phi(\boldsymbol{x}, \lambda)$ is expressed as an average over all microstates contributing to the state with (fixed) $\boldsymbol{x}$. The second equality follows with (206). Compared with the expression in the colloidal case (15), the essential difference here is that $F(\boldsymbol{x}, \lambda)$ is a free energy rather than a bare potential, i.e. internal energy. Consequently, the first law that, of course, should involve internal energies becomes

$$đw = \mathrm{d}E(\boldsymbol{x}, \lambda) + đq = \mathrm{d}F(\boldsymbol{x}, \lambda) + T\, \mathrm{d}S(\boldsymbol{x}, \lambda) + đq. \tag{213}$$

This relation together with (212) implies for the increment in heat

$$đq = -\boldsymbol{\nabla} F(\boldsymbol{x}, \lambda)\, \mathrm{d}\boldsymbol{x} - T\, \mathrm{d}S(\boldsymbol{x}, \lambda), \tag{214}$$

which makes the contribution to heat that arises from the intrinsic entropy $S(\boldsymbol{x}, \lambda)$ clear.

For a practical evaluation of the work, one would have to know $F(\boldsymbol{x}, \lambda)$, which, in general, has a complicated λ-dependence if the microscopic potential $\Phi(\xi, \lambda)$ is genuinely λ-dependent. However, if the external potential couples only to the slow degrees of freedom $\boldsymbol{x}$ as typically assumed, see figure 6, a significant simplification occurs. In this case, one can write

$$F(\boldsymbol{x}, \lambda) = F^0(\boldsymbol{x}) + V(\boldsymbol{x}, \lambda) = E^0(\boldsymbol{x}) - TS^0(\boldsymbol{x}) + V(\boldsymbol{x}, \lambda), \tag{215}$$

where the quantities with superscript 0 are the thermodynamic potentials (207)–(209) of the molecule for constrained slow variables $\boldsymbol{x}$ in the absence of the external potential. As a consequence

$$đw = \partial_\lambda V(\boldsymbol{x}, \lambda) d\lambda, \tag{216}$$

which becomes trivial for the typical case of a harmonic potential $V(\boldsymbol{x}, \lambda) = k(x_\mathrm{i} - \lambda)^2/2$, with x_i the relevant coordinate for the coupling and k the effective stiffness of the AFM tip or optical trap centered at $\lambda(\tau)$.

9.2.3. Dynamics. For the dynamics of the slow degrees of freedom one has the Langevin equation

$$\dot{\boldsymbol{x}} = \underline{\underline{\mu}}[-\boldsymbol{\nabla} F(\boldsymbol{x}, \lambda)] + \boldsymbol{\zeta} \tag{217}$$

with the noise correlations as in (43). Likewise, the Fokker–Planck equation reads

$$\partial_\tau p(\boldsymbol{x}, \tau) = \boldsymbol{\nabla}(\underline{\underline{\mu}} \boldsymbol{\nabla} F(\boldsymbol{x}, \lambda) p(\boldsymbol{x}, \tau) + T \underline{\underline{\mu}} \boldsymbol{\nabla} p(\boldsymbol{x}, \tau)). \tag{218}$$

Compared with the discussion in section 2.6.2 the key point here is that whenever states carry intrinsic entropy, the gradient of the free energy (rather than of internal energy) has to show up in the Langevin and Fokker–Planck equations since for any fixed λ, the system has to reach equilibrium with the Boltzmann factor

$$p^{\mathrm{eq}}(\boldsymbol{x}, \lambda) = \exp[-(F(\boldsymbol{x}, \lambda) - \mathcal{F}(\lambda)/T] \tag{219}$$

with the λ-dependent free energy

$$\mathcal{F}(\lambda) \equiv -T \ln \int \mathrm{d}\boldsymbol{x} \exp[-F(\boldsymbol{x}, \lambda)/T]. \tag{220}$$

9.2.4. Entropy production. The stochastic entropy along the trajectory $\boldsymbol{x}(\tau)$ becomes

$$s(\tau) \equiv -\ln p(\boldsymbol{x}(\tau), \tau) \tag{221}$$

where $p(\boldsymbol{x}, \tau)$ follows from solving the Fokker–Planck equation (218) with an appropriate initial condition. For such a system with intrinsic entropy, the total entropy production along a trajectory during time t

$$\Delta s^{\mathrm{tot}} \equiv \int_0^t \mathrm{d}\tau \dot{s}^{\mathrm{tot}} = \int_0^t \mathrm{d}\tau [\dot{s}(\tau) + \dot{S}(\boldsymbol{x}, \lambda) + \dot{q}/T] \tag{222}$$

contains three contributions rather than two as in the case without relevant intrinsic degrees of freedom.

9.2.5. Fluctuation theorems. In principle, the FT hold true in the presence of intrinsic entropy as well provided the latter is taken into account properly. The crucial point is that the master functional R_1 defined in (72) when using as conjugate process the time-reversed one becomes

$$R_1 = \Delta s^{\mathrm{int}} + q/T \tag{223}$$

where

$$\Delta s^{\mathrm{int}} \equiv S(\boldsymbol{x}_t, \lambda_t) - S(\boldsymbol{x}_0, \lambda_0) \tag{224}$$

is the change in intrinsic entropy along the forward trajectory. This result follows from evaluating the action in the path weight

corresponding to the Langevin equation (217) and using the first law (213) integrated along the trajectory.

As a consequence, the FTs involving entropy production discussed in sections 3.3 and 4 essentially hold true with the replacement

$$\Delta s^{\mathrm{m}} \to \Delta s^{\mathrm{m}} + \Delta s^{\mathrm{int}}. \tag{225}$$

All FTs involving total entropy production hold true unmodified.

The FTs involving work as defined in (212) hold true as well. In particular, the JR stands with $\Delta\mathcal{F} = \mathcal{F}(\lambda_t) - \mathcal{F}(\lambda_0)$ where the free energies have been defined in (220). The reason why the intrinsic entropy does not spoil these relations is the fact that both the work and the force in the Langevin equation are determined by the free energy $F(\boldsymbol{x}, \lambda)$ very much in the same way as the bare potential $V(x, \lambda)$ determines the corresponding quantities in the colloidal case. Loosely speaking, the results of the simpler case hold true provided one replaces the potential $V(x, \lambda)$ by the free energy (i.e. potential of mean force) $F(\boldsymbol{x}, \lambda)$.

In the presence of intrinsic entropy, the FDT (192) must be modified accordingly by replacing $\dot{s}^{\mathrm{m}}$ by $\dot{s}^{\mathrm{m}} + \dot{s}^{\mathrm{int}}$.

9.3. Free energy recovery from non-equilibrium data

9.3.1. HSR and variants. From a practical perspective, arguably the most relevant FT for biomolecules is the HSR [10, 460]. As a kind of JR resolved along a reaction coordinate, it allows one to determine the free energy landscape $F^0(\boldsymbol{x})$ from non-equilibrium work measurements through an external potential $V(\boldsymbol{x}, \lambda)$ conditioned on a fixed value of $\boldsymbol{x}$. It reads

$$\exp[-F^0(\boldsymbol{x})/T] = \exp[(V(\boldsymbol{x}, \lambda_t) - \mathcal{F}(\lambda_0))/T] \times \langle \exp[-w/T]\delta(\boldsymbol{x}_t - \boldsymbol{x})\rangle. \tag{226}$$

The rhs is evaluated by measuring the accumulated work w as a function of position $\boldsymbol{x}_t$ irrespective of the particular t.

A concise derivation [21] of the HSR starts with the IFT (81). With the necessary replacement (225), the initial equilibrium distribution $p_0(\boldsymbol{x}, \lambda_0) = \exp[-(F(\boldsymbol{x}_0, \lambda_0) - \mathcal{F}(\lambda_0)/T]$, the free choice $p_1(\boldsymbol{x}_t) = \delta(\boldsymbol{x}_t - \boldsymbol{x})$, the first law (213) and the assumption (215), it follows within a couple of lines.

A variant of the HSR not requiring the position histograms in (226) can be derived for a harmonic coupling $V(\boldsymbol{x}, \lambda_t)$ [461]. Moreover, similarly as the CFT generalizes the JR by including information from the time-reversed process, bidirectional variants of the HSR have been derived and tested in model calculations [462, 463].

9.3.2. Experiments. The first experimental application of the JR to biomolecules was the determination of the free energy involved in partially unfolding RNA hairpins [464]. The CFT was first applied in another experiment measuring the free energies in RNA hairpins and RNA three-helix junctions [465]. In a series of experiments, Ritort and co-workers have used the CFT to determine the free energy involved in unfolding DNA hairpins [101, 466–468]. The free energy involved in unfolding the multidomain protein, titin, has been measured in [469] using a simplified variant of the JR leading to some criticism [470, 471]. The CFT has been used to determine free energy changes induced by mechanically unfolding coiled-coil structures [472, 473] and different topological variants of a protein [474]. Axis-dependent anisotropy in protein unfolding was investigated using the HSR in [475]. The free energy landscape derived from the HSR has been compared with equilibrium measurements in [476].

9.3.3. Numerical work. As relatively scarce as real experimental studies using the FTs still are, as large is the number of 'numerical' experiments illustrating the use of the HSR and its variants for recovering free energy landscapes. The following brief list is necessarily incomplete. Model calculations for a single coordinate deal with the advantage of applying a periodic force protocol [477], with random forcing [478], comparison with 'inherent structures' [479], with motion in a periodic potential [480], and with recovering an unknown spatially dependent mobility [481]. Multidimensional landscapes were reconstructed in [482]. Monte-Carlo or molecular dynamic simulations were used for an off-lattice model protein [483], for a protein domain in [484] and for a membrane protein in [485].

An important line of research in this context is to find methods for dealing with the error caused by having only finite (and even noisy) data for evaluating the non-linear averages involved in the JR and the HSR. Some of the papers dealing with this issue are [100, 153, 486–512].

9.4. Enzymes and molecular motors with discrete states

In this section, we show how the general framework for a Markovian dynamics on a discrete set of states can be adapted to describe the stochastic thermodynamics of enzymes and molecular motors in a thermal environment starting again from a microscopic model. Apart from keeping track of the intrinsic entropy of the states the essential point is to incorporate the enzymatic reactions involving solute molecules consistently.

9.4.1. Thermodynamic states. The enzyme is in an aqueous solution which consists of molecules of type i with concentrations $\{c_i\}$ and chemical potentials $\{\mu_i\}$ enclosed in a volume V at a temperature T. It exhibits a set of states such that equilibration among microstates corresponding to the same state is fast whereas transitions between these states are assumed to be slower and observable. Under these conditions, one can assign to each state n of the enzyme a free energy F_n^{enz}, an internal energy E_n^{enz}, and an intrinsic entropy S_n^{enz}. As explicitly discussed in [459], these quantities follow from any microscopic model that specifies the energy of the microstates of enzyme and solution. They obey the usual thermodynamic relation

$$F_n^{\mathrm{enz}} = E_n^{\mathrm{enz}} - T S_n^{\mathrm{enz}} \tag{227}$$

despite the fact that the enzyme is small. Moreover, there is no need to assume that the interaction between enzyme and solution is somehow weak. In general, these thermodynamic variables of the enzyme depend on the concentrations of the various solutes.

9.4.2. First law. In this section, we discuss the first law for the three classes of (i) pure conformational changes, (ii) enzymatic reactions including binding and release of solutes and (iii) motor proteins.

(i) *Conformational changes:* if the enzyme jumps from state m to state n, the change in internal energy

$$\Delta E^{\rm enz} \equiv E^{\rm enz}_n - E^{\rm enz}_m = -q \tag{228}$$

must be identified with an amount q of heat being released into (or, if negative, being taken up from) the surrounding heat bath since there is no external work involved.

(ii) *Enzymatic reactions:* the more interesting case are enzymatic transitions that involve binding of solute molecules A_i, their transformation while bound, and finally their release from the enzyme. Quite generally, one considers transitions written as

$$n^-_\rho + \sum_i r^\rho_i A_i \rightleftharpoons n^+_\rho + \sum_i s^\rho_i A_i \tag{229}$$

where $1 \leqslant \rho \leqslant N_\rho$ labels the possible transitions. Here, n^-_ρ and n^+_ρ denote the states of the enzyme before and after the reaction, respectively. For $s^\rho_i = 0$, this scheme describes pure binding of solutes, and for $r^\rho_i = 0$ release of bound solutes. A transformation (such as bound ATP to bound ADP + P_i) can also be described by the above scheme with $r^\rho_i = s^\rho_i = 0$ and the understanding that the enzyme states contain the bound solutes, see [459] for a more detailed discussion.

The free energy difference involved in such a transition

$$\Delta F_\rho = \Delta E_\rho - T\Delta S_\rho \equiv \Delta F^{\rm enz}_\rho + \Delta F^{\rm sol}_\rho \tag{230}$$

has two contributions where

$$\Delta F^{\rm enz}_\rho = \Delta E^{\rm enz}_\rho - T\Delta S^{\rm enz}_\rho \equiv F^{\rm enz}_{n^+_\rho} - F^{\rm enz}_{n^-_\rho} \tag{231}$$

denotes the free energy change of the enzyme and

$$\Delta F^{\rm sol}_\rho = \Delta E^{\rm sol}_\rho - T\Delta S^{\rm sol}_\rho \equiv \sum_i (s^\rho_i - r^\rho_i)\mu_i \equiv \Delta\mu_\rho \tag{232}$$

denotes the free energy change attributed to the solution in this reaction. Both free energy contributions can as usually be split into internal energy and intrinsic entropy. As in the case of pure conformational changes, one assigns a first law type energy balance to each reaction of type ρ (229). Once an initial state is prepared, in the closed system (enzyme plus solution) there is obviously no source of external work. Neither does the system perform any work. Hence, the heat released in this transition is given by minus the change of internal energy of the combined system [459]

$$q_\rho = -\Delta E_\rho = -\Delta E^{\rm enz}_\rho - \Delta\mu_\rho - T\Delta S^{\rm sol}_\rho. \tag{233}$$

This relation shows that the enzyme and the solution are treated on the same footing since only their combined change in internal energy enters. Since the heat is released into the solution acting as a thermal bath, the configurational change of the enzyme as well as binding and releasing solute molecules contribute to the same bath.

(iii) *Molecular motors:* essentially the same formalism applies to an enzyme acting as a molecular motor often described by such discrete states. Most generally, if the motor undergoes a forward transition of type ρ as in (229) it may advance a distance d_ρ in the direction of the applied force f (or, if $f < 0$, opposite to it). The special cases $d_\rho = 0$ (pure chemical step) or $s^\rho_i = r^\rho_i = 0$ (pure mechanical step) are allowed. For $d_\rho \neq 0$, the mechanical work

$$w^{\rm mech}_\rho \equiv f d_\rho \tag{234}$$

is applied to (or, if negative, delivered by) the motor.

The motor operates in an environment where the concentration of molecules such as ATP, ADP or P_i are essentially fixed. The first law for a single transition of type ρ becomes [459]

$$q_\rho = w^{\rm mech}_\rho - \Delta E_\rho = f d_\rho - \Delta E^{\rm enz}_\rho - \Delta\mu_\rho - T\Delta S^{\rm sol}_\rho. \tag{235}$$

9.4.3. Role of chemiostats: genuine NESS conditions. The more recent form (235) of the first law differs from an expression discussed previously for molecular motors [430, 434–438]. There, in the present notation and sign convention, the first law for a step like in (229) reads

$$\bar q_\rho = w^{\rm mech}_\rho - \Delta E^{\rm enz}_\rho - \Delta\mu_\rho. \tag{236}$$

The difference between the two expressions for the heat

$$\bar q_\rho - q_\rho = T\Delta S^{\rm sol}_\rho \tag{237}$$

involves the entropy change in the solution resulting from the reaction.

The physical origin of the two different forms arises from the fact that in the older work the enzyme is thought to be coupled to 'chemiostats' providing and accepting molecules at an energetic cost (or benefit) given by their chemical potential. Introducing the notion of a 'chemical work'

$$w^{\rm chem}_\rho \equiv -\Delta\mu_\rho \tag{238}$$

the first law is then written in the form

$$w^{\rm mech}_\rho + w^{\rm chem}_\rho = \Delta E^{\rm enz}_\rho + \bar q_\rho. \tag{239}$$

The concept of chemiostats is supposed to guarantee that the concentration of solute molecules remains strictly constant. Physically, it could be implemented by an ATP buffer of ATP-regeneration scheme that involves additional enzymes. From the perspective of stochastic thermodynamics as long as one focuses on single transitions, however, it would be more appropriate to treat these additional enzymes and the chemical reactions they catalyze in the same way as the reaction involving the motor protein. It turns out that if these additional reactions operate quasistatically, then $\bar q_\rho$ is the dissipated heat that under steady-state conditions would enter an ensemble average [459]. Therefore, choosing the heat $\bar q_\rho$ is appropriate whenever one deals with strict NESS conditions while not wanting to consider the heat involved in enforcing these conditions explicitly as an extra contribution. On the trajectory level for a single motor protein, there seems to be no sensible way for assigning $\bar q_\rho$ instead of q_ρ to an individual transition.

9.4.4. Stochastic trajectory and ensemble. A trajectory of the enzyme can be characterized by the sequence of jump times $\{\tau_j\}$ and the sequence of reactions $\{\rho_j^{\sigma_j}\}$ where ρ_j denotes the corresponding reactions (229) and $\sigma_j = \pm$ characterizes the direction in which the reaction takes place.

An ensemble is defined by specifying (i) the initial probability $p_n(0)$ for finding the enzyme in state n and (ii) the set of rates $w_\rho^\pm$ with which the reactions (229) take place in either direction. Both inputs will then determine the probability $p_n(\tau)$ to find the enzyme in state n at time τ.

9.4.5. Rates and local-detailed balance. An identification of entropy production along the trajectory requires some input from the rates determining the transitions. For the simple case of pure conformational changes, $m \rightleftharpoons n$, choosing rates that obey

$$\frac{w_{mn}}{w_{nm}} = \exp[-(F_n^{\rm enz} - F_m^{\rm enz})/T] \tag{240}$$

is required by thermodynamic consistency. Indeed, only this choice guarantees that irrespectively of the initial conditions the ensemble will eventually reach thermal equilibrium,

$$p_n(\tau) \to p_n^{\rm eq} \equiv \exp[-(F_n^{\rm enz} - \mathcal{F}^{\rm enz})/T], \tag{241}$$

with the free energy of the enzyme

$$\mathcal{F}^{\rm enz} \equiv -T \ln \sum_n \exp[-F_n^{\rm enz}/T]. \tag{242}$$

Fixing the ratio of the rates still leaves one free parameter per pair of states which can only be determined from knowing the dynamics of the underlying more microscopic model.

The corresponding relation for transitions that involve enzymatic reactions (229),

$$\frac{w_\rho^+}{w_\rho^-} = \exp[-\Delta F_\rho/T] = \exp[-(\Delta F_\rho^{\rm enz} + \Delta\mu_\rho)/T], \tag{243}$$

and for transitions of molecular motors,

$$\frac{w_\rho^+}{w_\rho^-} = \exp[-(\Delta F_\rho^{\rm enz} + \Delta\mu_\rho - w_\rho^{\rm mech})/T], \tag{244}$$

are somewhat less obvious. Essentially, three types of justifications for choosing such ratios can be given.

First, even though microreversibility is often invoked it seems unclear how to obtain these ratios rigorously using this concept if chemical reactions are involved.

Second, one can derive (243) using the following argument. For any enzymatic reaction there will be concentrations $\{c_i^{\rm eq}\}$ of the solutes such that the enzyme will reach equilibrium. For these particular equilibrium concentrations, a choice of rates respecting (243) is mandatory as in the case of pure conformational changes. If one now assumes that (i) the reaction rates obey the mass action law and that (ii) the concentrations and the chemical potentials are related by the ideal solution expression, $\mu_i(c_i) = \mu_i^{\rm eq} + T \ln(c_i/c_i^{\rm eq})$, then the form (243) follows.

Third, more recently it has been shown that by requiring a consistent stochastic thermodynamic description on the trajectory level, one can indeed derive these conditions on the rates using rather mild assumptions [459].

In all cases by invoking the respective first laws (equations (228), (233), (235)), the ratio of the rates can also be written in the form

$$\frac{w_\rho^+}{w_\rho^-} = \exp[\Delta S_\rho + q_\rho/T] \tag{245}$$

showing that this ratio is determined by the change of intrinsic and medium entropy involved in this transition. This important relation should be compared with (20) in the colloidal case where the continuum version of such a ratio involves only the dissipated heat since there is no relevant intrinsic entropy change given here by ΔS_ρ. Similarly, for a biopolymer within a continuum description, the relation (223) shows the contribution of intrinsic entropy.

9.4.6. Entropy production and FTs. The total entropy production involved in one forward transition ρ at time τ can be derived from the general expression (126) and using the ratio of the rates (245) as

$$\Delta s_\rho^{\rm tot}(\tau) = \ln \frac{p_{n_\rho^-}(\tau) w_\rho^+}{p_{n_\rho^+}(\tau) w_\rho^-} = \Delta s_\rho + \Delta S_\rho + q_\rho/T. \tag{246}$$

It consists of three contributions. The first is the change in stochastic entropy,

$$\Delta s_\rho(\tau) = -\ln[p_{n_\rho^+}(\tau)/p_{n_\rho^-}(\tau)]. \tag{247}$$

The second denotes the change in the intrinsic entropy (230) of the system which consists here of enzyme and surrounding solution. The third term arises from the dissipated heat (equations (233) and (235)).

Summing over all reactions taking place up to time t and adding the concomitant change in stochastic entropy, $\Delta s = -\ln p_{n_t}(t) + \ln p_{n_0}(0)$, one obtains the total entropy production along a trajectory

$$\Delta s^{\rm tot} = \Delta s + \sum_j \sigma_j [\Delta S_{\rho_j}(\tau_j) + q_{\rho_j}(\tau_j)/T], \tag{248}$$

where $\sigma_j = \pm 1$ denotes the direction in which the transition ρ_j takes place at time τ_j.

The arguably most relevant situation for an enzyme modeled by discrete states is a NESS generated by non-equilibrated solute concentrations and/or an applied external force in the case of a motor protein. In such a NESS, one has the SSFT (65) for the total entropy production as defined in (248).

9.4.7. Time-dependent rates and work. So far, it was implicitly assumed that the rates are time-independent. Time-dependent rates could arise either since the concentrations of the solutes are externally modulated (or, in a finite system, depleted due to the action of the enzymes) or since the forces applied to motor proteins are time-dependent. The ratio of the rates is then still constrained by equations (243) and (244).

However, under such time-dependent external conditions characterized by a parameter $\lambda(\tau)$, the thermodynamic state variables E_n, S_n and F_n can become time-dependent as well. In consequence, there are contributions to the first law and to entropy production even if the enzyme remains in the same state. Specifically, if the enzyme remains in state n, in analogy to (212) the first law becomes

$$đw_n = \partial_\lambda F_n \, \mathrm{d}\lambda = (\partial_\lambda E_n - T\partial_\lambda S_n)\, \mathrm{d}\lambda = \partial_\lambda E_n \, \mathrm{d}\lambda + đq_n. \tag{249}$$

Hence, there is exchanged heat, $đq_n = -T dS_n$, even if the system remains in the same state whenever the intrinsic entropy depends on a changing external parameter (such as the concentration of the solutes).

These expressions of heat and work resemble those of quasi-static processes as they should since it is implicitly assumed that the distribution of microstates that contribute to the state n adapts (almost) instantaneously to thermal equilibrium. Consequently, these contributions to work and heat enter the FTs trivially.

9.4.8. Experiments: F1-ATPase. Apart from free energy reconstructions described above, experimental work using the concepts of stochastic thermodynamics is still scarce. For the F1-ATPase, two groups have published work pointing in this direction. In an intriguing example of exploiting the SSFT, the torque exerted by the F1-ATPase on a bead in an optical trap could be measured without knowing the friction constant of the bead [513]. The implicit assumption, however, with this type of analysis is that no further dissipative mechanisms exist. In another study of this molecule [514, 515], it was inferred that this motor transfers almost the full free energy from ATP hydrolysis into loading the elastic element connecting the motor with the bead.

9.4.9. Biochemical reaction networks. The formalism described above for a single enzyme can easily be extended to networks involving several types of (different) enzymes [98] or ordinary chemical reaction networks using chemical master equations [255, 449]. Specific examples for which the distribution of entropy production has been calculated are [516–518].

10. Autonomous isothermal machines

10.1. General aspects

Enzymes and molecular motors as described in section 9 from the stochastic thermodynamics perspective provide a paradigm for isothermal machines. In contrast to heat engines, which in their classical form are the archetypical thermodynamic machines and which in their stochastic version will be described in section 11, isothermal machines do not transform heat but rather chemical energy into mechanical work (or vice versa) while the temperature of the surrounding medium remains constant. For an overall scheme introducing the classifications relevant to the content of the next two sections, see figure 7.

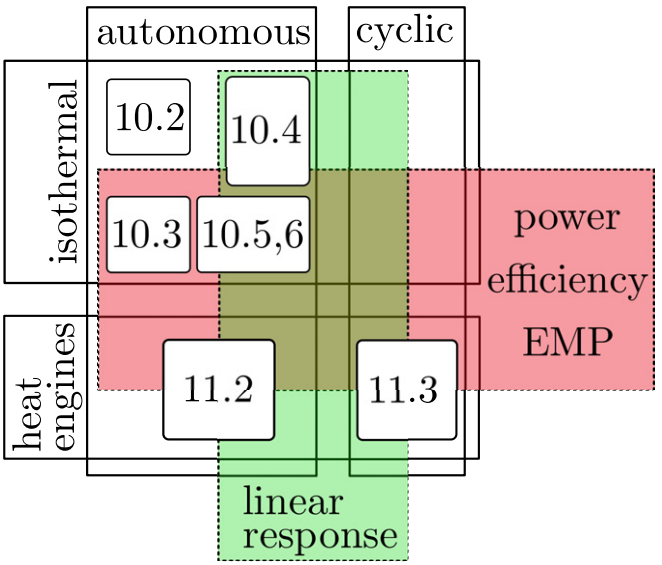

Figure 7. This scheme shows two pairs of classification (isothermal versus heat engines and autonomous versus cyclically driven), a few key notions (power, efficiency and efficiency at maximum power (EMP)) and a possible approximation (linear response) applicable to machines. The overlap of the white boxes with these alternatives indicates which case will be relevant to the respective sections.

An important classification is whether or not a machine operates autonomously. In the stochastic setting, an autonomous machine will typically correspond to a NESS generated by externally imposed time-independent boundary conditions. Any molecular motor is a typical example of such an autonomous isothermal machine, since single molecule assays typically provide conditions of constant non-equilibrium concentrations of 'fuel' molecules such as ATP. For a non-autonomous machine, some time-dependent external control is required that 'leads' the machine through its cycle. Building reliable artificial molecular motors in the lab still constitutes a major challenge as reviewed in [519–524].

In this section, we present a systematic theory for isothermal autonomous machines in the discrete state version based on the representation of the NESS in terms of cycles of the underlying network as introduced in section 6.4. As a main ingredient, a local-DBC as introduced in (195) and (245) is imposed on the rates thus guaranteeing thermodynamic consistency. Even though we focus on the discrete case, this approach includes earlier models based on continuous coordinates diffusing in a ratchet potential that depends on the chemical state of the motor since any continuum model can be discretized.

An important quantity for any type of machine is its efficiency defined as the ratio between the power delivered by the machine and the rate of 'fuel' consumption. Thermodynamics constrains this efficiency by 1 for isothermal machines and by the Carnot efficiency for thermal heat engines operating between heat baths of different temperatures. In both cases working at the highest possible efficiency comes at the cost of zero delivered power since reaching the thermodynamic bound requires a quasi-static, i.e. infinitely slow operation. A practically more relevant question then is about efficiency at maximum power (EMP). We will see that

Table 1. Affinities and generalized distance for isothermal machines.

Process	Affinity $\mathcal{F}_k$	Gen. distance d^k
Linear motion	Force f/T	Linear distance d
Rotation	Torque N/T	Angle $\Delta\phi$
Particle transport	$-\Delta\mu/T$	(typically) 1
Chemical reaction	$-\Delta\mu/T$	(typically) 1

in this thermodynamic framework rather general expressions for power, efficiency and EMP emerge.

It would be interesting to pursue these issues also for periodically driven machines, which are one step more complex than the autonomous ones. While there is a vast literature on how to generate transport by periodic modulation of system parameters as reviewed in [445, 525–527] the problem of efficiency and EMP, however, seems not to have been addressed systematically for such stochastic machines. One reason is that even making explicit statements about the periodic steady state is much harder than for the NESS engine at constant external parameters.

10.2. General framework for autonomous machines: Cycle representation and entropy production

An autonomously operating device or machine can be modeled as a Markov process on a network in a steady state. Transitions between different states in this NESS depend on rates that reflect both the coupling of the machine to reservoirs with different chemical potentials for solutes or particles and external forces or loads. These non-equilibrium conditions can be expressed by generalized thermodynamic forces or 'affinities' $\mathcal{F}_k$ as listed in table 1.

For a systematic presentation it is useful first to recall the representation of a NESS in terms of cycle currents [211, 212], see figure 3. Rather than summing over the individual transitions (mn) or reactions ρ as we have carried out so far, in a NESS probability currents can be expressed by a sum over directed cycle currents

$$j_a \equiv j_a^+ - j_a^- = j_a^+(1 - j_a^-/j_a^+) = j_a^+(1 - \prod_{\rho\in a} w_\rho^-/w_\rho^+) \quad (250)$$

where a labels the cycles and j_a^+ and j_a^- denote the inverse mean times required for completing the cycle in forward and backward directions, respectively[12]. These forward and backward (probability) currents can be expressed in a diagrammatic way by the transition rates of the whole network (not just those of the respective cycle). However, the ratio j_a^-/j_a^+, is given by the ratio between the product of all backward rates and the product of all forward rates contributing to the cycle a.

Thermodynamic consistency as formulated in (139) or (245) allows one to express this ratio

$$\prod_{\rho\in a} w_\rho^-/w_\rho^+ = \exp(-\Delta S_a) \quad (251)$$

[12] The directed cycle current $j_a \equiv \langle \mathcal{J}_a \rangle$ is the mean of the fluctuating current $\mathcal{J}_a$ introduced in section 6.4.

by the sum

$$\Delta S_a \equiv \sum_{\rho\in a} \left(q_\rho/T + \Delta S_\rho\right) \equiv q_a/T + \sum_{\rho\in a} \Delta S_\rho = \bar{q}_a/T \quad (252)$$

of the entropy changes in the reservoirs and heat baths associated with this cycle. The last equality recalls the definition of heat under strict steady-state conditions which includes the quasi-static refilling of the reservoirs as discussed in section 9.4.3. With the first law (239) summed along a cycle, this entropy change can also be written as

$$\Delta S_a = (w_a^{\rm mech} + w_a^{\rm chem})/T. \quad (253)$$

This representation alluding to the definition of a 'chemical work' introduced in section 9.4.3 becomes convenient when discussing the efficiency.

Alternatively, expressed in terms of affinities, the entropy change associated with a cycle becomes

$$\Delta S_a = \sum_k d_a^k \mathcal{F}_k, \quad (254)$$

where d_a^k is a generalized distance conjugate to the force $\mathcal{F}_k$ as listed in table 1. To each affinity $\mathcal{F}_k$, there corresponds a conjugate flux or current

$$J_k \equiv \sum_a (j_a^+ - j_a^-) d_a^k = \sum_a j_a^+ [1 - \exp(-\Delta S_a)] d_a^k \quad (255)$$

describing the rate with which the respective quantity is 'processed' by the machine.

The mean entropy production rate can be written as

$$\sigma = \sum_a (j_a^+ - j_a^-)\Delta S_a \quad (256)$$

$$= \sum_a j_a^+ [1 - \exp(-\Delta S_a)]\Delta S_a = \sum_k J_k \mathcal{F}_k. \quad (257)$$

These expressions are exact and do not imply any linear response assumption as the final bilinear form may suggest.

10.3. Power and efficiency

10.3.1. Input and output power. A device or machine is supposed to deliver some output from consuming some input. Characteristically for nano-machines, the role of output and input can easily be reversed as it depends on the signs of the corresponding affinities. Input has to be offered to the machine with a positive affinity $\mathcal{F}_{\rm i} > 0$ whereas output is associated with a current or flux that is opposite to an applied affinity $\mathcal{F}_{\rm o} < 0$.

Quite generally, for an isothermal machine in a NESS, the total rate of production of output and input, P_o and P_i, respectively, is given by the product between a pair of corresponding flux and affinity according to

$$P_{\rm o,i} = \epsilon_{\rm o,i} J_{\rm o,i} (T\mathcal{F}_{\rm o,i}) \quad (258)$$

$$= \epsilon_{\rm o,i} \sum_a j_a^+ [1 - \exp(-\Delta S_a)] d_a^{\rm o,i} (T\mathcal{F}_{\rm o,i}) \quad (259)$$

where $\epsilon_{\rm o} \equiv -1$ and $\epsilon_{\rm i} \equiv 1$ reflect the fact that the output is delivered against an external load $\mathcal{F}_{\rm o} < 0$. Expressed in terms

of a cycle-specific work input

$$w_{\mathrm{i},a} \equiv \mathcal{F}_{\mathrm{i}} d_a^{\mathrm{i}} \tag{260}$$

and work output

$$w_{\mathrm{o},a} \equiv -\mathcal{F}_{\mathrm{o}} d_a^{\mathrm{o}}, \tag{261}$$

the power can also be written as [528]

$$P_{\mathrm{o,i}} = \sum_a j_a^+ [1 - \exp(w_{\mathrm{o},a} - w_{\mathrm{i},a})] T w_{\{\mathrm{o,i}\}\mathrm{a}}. \tag{262}$$

In the contribution of each cycle, the expressions (259) and (262) separate a system-specific kinetic prefactor, $j_a^+ = j_a^+(\{\mathcal{F}_k\})$, from the remaining thermodynamic quantities.

10.3.2. Efficiency and EMP. The efficiency of a machine is defined as the ratio

$$\eta \equiv P_{\mathrm{o}}/P_{\mathrm{i}}. \tag{263}$$

It has occasionally been argued that the traditional definition of efficiency (263) should be modified for molecular motors pulling cargo in order to include the 'work' required for overcoming Stokes friction even in the absence of an external force [529, 530]. More recently, a 'sustainable' efficiency has been suggested as an alternative concept [531, 532]. In this review, we keep the traditional expression (263).

For the paradigmatic case of just two non-zero affinities, the entropy production rate (257) becomes

$$\sigma = (P_{\mathrm{i}} - P_{\mathrm{o}})/T \geqslant 0 \tag{264}$$

implying that efficiency of isothermal machines is bounded by $0 \leqslant \eta \leqslant 1$. Working at the highest possible efficiency comes at the cost of zero delivered power since reaching the thermodynamic bound requires a quasi-static, i.e. infinitely slow operation. A practically more relevant question then is about EMP.

The notion of EMP requires one or several parameters $\{\lambda_i\}$ with respect to the variation of which P_{o} can become maximal, i.e. $P_{\mathrm{o}}^* \equiv \max_{\{\lambda_i\}} P_{\mathrm{o}} \equiv P_{\mathrm{o}}(\{\lambda_{\mathrm{i}}^*\})$. EMP is then given by

$$\eta^* \equiv P_{\mathrm{o}}^*/P_{\mathrm{i}}(\{\lambda_{\mathrm{i}}^*\}). \tag{265}$$

In general, the result for EMP will depend strongly both on the choice and the allowed range of the variational parameters $\{\lambda_i\}$ [528, 533] which is a fact occasionally ignored when statements about *the* EMP are made. In particular, one should distinguish variation with respect to the externally imposed affinities from those with respect to structural or intrinsic parameters of the machine. Examples for the latter are the topology of the network and common prefactors for forward and backward rates that leave their ratio and thus the thermodynamics invariant.

10.4. Linear response: relation to phenomenological irreversible thermodynamics

At this point, it is instructive to consider a machine operating close to equilibrium and to cast the results into the framework of linear irreversible thermodynamics [534, 535]. This theory truncates an expansion of the fluxes in the first order of the affinities, i.e. assumes that

$$J_k = \sum_l L_{kl} \mathcal{F}_l \tag{266}$$

with the Onsager coefficients L_{kl}. By expanding (255) for small affinities and using (254), we obtain for the Onsager coefficients the cycle representation

$$L_{kl} = \sum_a j_a^{+\mathrm{eq}} d_a^k d_a^l. \tag{267}$$

Here, $j_a^{+\mathrm{eq}} \equiv j_a^+(\{\mathcal{F}_k\} = 0)$ is the equilibrium forward current of a cycle a. In this approach, the Onsager symmetry $L_{kl} = L_{lk}$ is satisfied automatically. Similarly, the rate of total entropy production (257) becomes

$$\sigma \approx \sum_a j_a^+ (\Delta S_a)^2 = \sum_{kl} L_{kl} \mathcal{F}_k \mathcal{F}_l. \tag{268}$$

In this lowest order, power input and output (259) become

$$P_{\mathrm{o,i}} = \epsilon_{\mathrm{o,i}} J_{\mathrm{o,i}} (T \mathcal{F}_{\mathrm{o,i}}) = \epsilon_{\mathrm{o,i}} T \sum_k L_{\{\mathrm{o,i}\}\mathrm{k}} \mathcal{F}_k \mathcal{F}_{\mathrm{o,i}}. \tag{269}$$

In the paradigmatic case of two affinities, for fixed input affinity $\mathcal{F}_{\mathrm{i}} > 0$ and choosing the output affinity as variational parameter $\mathcal{F}_{\mathrm{o}}$, maximum power is reached for

$$\mathcal{F}_{\mathrm{o}}^* = -L_{\mathrm{oi}} \mathcal{F}_{\mathrm{i}}/2L_{\mathrm{oo}} \tag{270}$$

leading to an EMP of [536]

$$\eta^* = L_{\mathrm{oi}}^2/[4L_{\mathrm{oo}}L_{\mathrm{ii}} - 2L_{\mathrm{oi}}L_{\mathrm{io}}] \leqslant 1/2. \tag{271}$$

The upper bound imposed by the positivity of entropy production is realized for a degenerate matrix of Onsager coefficients,

$$L_{\mathrm{oo}}L_{\mathrm{ii}} = L_{\mathrm{oi}}L_{\mathrm{io}}, \tag{272}$$

which implies that $J_{\mathrm{o}} \sim J_{\mathrm{i}}$. Possible realizations of this structural condition are (i) all unicyclic machines and (ii) tightly coupled multicyclic machines. These two classes and the third one of weakly coupled multicyclic machines will be defined and discussed in the next sections.

10.5. Unicyclic machines

Unicyclic machines consist of only one cycle which allows one to drop the cycle index a in this section, see figure 3 for an example. In general, the power delivered and used by a unicyclic motor becomes with (262)

$$P_{\mathrm{o,i}} = T j^+ [1 - \mathrm{e}^{w_{\mathrm{o}} - w_{\mathrm{i}}}] w_{\mathrm{o,i}}. \tag{273}$$

Its efficiency $\eta \equiv w_{\mathrm{o}}/w_{\mathrm{i}}$ depends thus trivially only on the externally imposed affinities $\mathcal{F}_k$ and the intrinsic properties $d^{\mathrm{o,i}}$ but is independent of the detailed kinetics. In the regime $0 < w_{\mathrm{o}} < w_{\mathrm{i}}$, the motor will work as intended. For $w_{\mathrm{o}} = w_{\mathrm{i}}$, the motor has optimal efficiency $\eta = 1$ but does not deliver any power since it then cycles as often in the forward as in the backward direction.

The concept of EMP requires one to identify the admissible variational parameters. A simple and physically transparent choice is to fix the input w_i and vary the output w_o, e.g., by changing the applied force or torque in the case of a molecular motor. The condition $\mathrm{d}P_\mathrm{o}/\mathrm{d}w_\mathrm{o} = 0$ leads to the implicit relation [528]

$$w_\mathrm{i} = w_\mathrm{o}^* + \ln[1 + w_\mathrm{o}^*/(1 + x_\mathrm{o} w_\mathrm{o}^*)] \tag{274}$$

for the optimal output w_o^* at fixed input w_i with

$$x_\mathrm{o} \equiv \mathrm{d}\ln j^+/\mathrm{d}w_\mathrm{o} \approx x_\mathrm{o}^\mathrm{eq} + O(w_\mathrm{i}, w_\mathrm{o}). \tag{275}$$

These expressions can easily be evaluated for any unicyclic machine with specified rates which determine the non-universal j^+.

The linear response regime is defined by the condition $w_\mathrm{o} < w_\mathrm{i} \ll 1$. By expanding (274), one obtains

$$\eta^* = w_\mathrm{o}^*/w_\mathrm{i} \approx 1/2 + (x_\mathrm{o}^\mathrm{eq} + 1/2) w_\mathrm{i}/8 + O(w_\mathrm{i}^2) \tag{276}$$

which shows how system-specific features like the coefficient x_o^eq enter EMP beyond the universal value 1/2. This expression proves that, depending on the value of the non-universal parameter x_o^eq, EMP may well rise beyond the linear response regime as found first in a case study of molecular motors [537]. These results seem to be at variance with another study along similar lines where a universal bound of 1/2 was found for EMP [531]. The difference, however, is that the latter authors constrain the optimization to a parameter space that leaves the stationary distribution invariant which seems to be a somewhat artificial condition. Further analytical and numerical results for EMP of unicyclic machines using w_o or both, w_i and w_o, as variation parameters can be found in [528]. Bounds on EMP on simple unicyclic machines have been derived in [538].

10.6. Multicyclic machines: strong versus weak coupling

A discussion of multicylic machines along similar lines does not require much additional conceptual effort [528]. The crucial distinction becomes the one between 'strong' (or tight) and 'weak' (or loose) coupling first introduced within the phenomenological linear response treatment in [536] and later stressed by van den Broeck and co-workers mostly in the context of heat engines as reviewed in the next section. In a strongly coupled multicylic machine, any cycle containing the input transition also contains the output transition (assuming for simplicity that input and output affect only one transition each). For such strongly coupled machines exactly the same formalism as for unicyclic machines applies with the only caveat that j^+ appearing there is now given by $j^+ \equiv \sum_a j_a^+$ where the sum runs over all cycles that include input and output transitions and the j_a^+ are the corresponding forward cycle currents. Thus, such strongly coupled machines obey the same relations for efficiency and EMP as unicyclic machines.

In the weak coupling case, there are cycles containing the input but not the output transition. Running through such a cycle the machine 'burns' the input without delivering any output which clearly decreases the efficiency. In particular, it turns out that in the linear response regime, EMP is less than 1/2, but may still rise when moving deeper into the non-equilibrium regime [528].

10.7. Efficiency and EMP of molecular motors

One important class of potential applications of the theory just described are molecular motors that transform chemical energy into mechanical energy (or vice versa). Traditionally, efficiency of molecular motors has been studied within ratchet models where the motor undergoes a continuous motion in a periodic potential that depends on the current chemical state of the motor [443–446, 539, 540]. Dissipation then involves both the continuous degree of freedom which should be treated along the lines discussed in section 2 and the discrete switching of the potential due to an enzymatic event. Model systems of this type have been investigated in [433, 541–544]. For a recent study of EMP in such a continuum description, see [545].

There is a second motivation for studying such models combining discrete with continuous dynamics. In the typical experimental set-up for measuring the efficiency of a molecular motor under load, an external force or torque is applied to a micrometer-sized bead that is connected to the molecular motor like in the recent example of the rotary motor F1-ATPase [514, 515, 546]. The discrete nano-sized steps of the motor become visible only through monitoring the biased Brownian motion of the bead which clearly is continuous. For a comprehensive description, both dissipation in the discrete steps of the motor and the one associated with the continuous motion of the bead should be combined [547].

For dynamics on a discrete set of states, efficiency (rather than EMP) has been investigated recently for various models [548, 549]. Genuine EMP has been studied for both the simplest unicyclic and a simple multicycle network in [537]. It would be interesting to do so for more intricate models such as the one introduced in [435], but also for artificial swimmers such as the one discussed in [550].

11. Efficiency of stochastic heat engines

11.1. Carnot, Curzon–Ahlborn and beyond

In classical thermodynamics, a heat engine, delivering work $-W$ by extracting heat $-Q_1$ from a hot bath at temperature T_1 and releasing heat Q_2 into a cold bath at temperature T_2, has an efficiency

$$\eta \equiv |W|/|Q_1| \leqslant \eta_\mathrm{C} \equiv 1 - T_2/T_1 \tag{277}$$

limited by the Carnot efficiency η_C which provides a universal bound that follows from combining the first and the second law. Reaching the upper bound comes at the price of zero power since this condition requires a quasi-static, i.e. infinitely slow operation. A practically more relevant efficiency is the one at maximum power (EMP), η^*, which becomes well-defined only if the parameter space available for the maximization is specified. For macroscopic thermodynamics, introducing this problem is often attributed to Curzon and Ahlborn [551] even though their result has been described earlier, see [552] and the comment made in reference [1] of [533]. Subsequent work for macroscopic engines pursued under the label of finite-time thermodynamics is reviewed in [553–556].

Curzon and Ahlborn (CA) assume ordinary heat conduction between the baths and the engine that is supposed

to operate without further internal losses. By optimizing the power with respect to the temperature difference responsible for the heat exchange between the baths and the machine, or, equivalently in their set-up, the duration of the two isothermal steps (while fixing a constant ratio between the time allocated to isothermal and adiabatic steps) they obtain for EMP the expression

$$\eta_{CA} \equiv 1 - (T_2/T_1)^{1/2} \approx \eta_C/2 + \eta_C^2/8 + O(\eta_C^3), \qquad (278)$$

which is independent of the thermal conductivities between baths and engine.

Whether or not the CA result can claim more universality than under the original 'endoreversible' assumptions, or is even a bound on EMP, is a subtle, if not even ill-defined, issue since maximum power depends crucially on the admissible parameter space. Beyond the original assumption there are conditions like for a cascade of intermediate engines [557, 558] and for 'weak symmetric dissipation' [559] where CA can be shown to hold for a rather reasonable choice of variational conditions. Numerical simulations of finite-time Carnot cycles for a weakly interacting gas have been analyzed for efficiency and EMP in [560–562].

A related question is the range of universal validity of the expansion in (278) for EMP. For tightly coupled machines defined by an output work flux that is proportional to the heat flux taken from the hot reservoir, the leading term, $\eta_C/2$, follows from simple linear irreversible thermodynamics for fixed input and variable output [536]. Such a result will hold both for macroscopic as for small engines.

The question of efficiency and EMP is indeed as relevant and applicable to small engines or devices as to macroscopic ones. The new aspect concerns the role of fluctuations not in the sense that a fluctuating efficiency is defined which might lead to ill-defined results given the fact that sometimes the heat taken from the hot bath would be zero or even negative. One rather keeps the definition (277) but now W and Q are mean values that are determined by averaging over the fluctuations[13]. A main advantage of a stochastic approach compared with the macroscopic phenomenological one is the fact that a thermodynamically consistent kinetics valid beyond the linear response regime can easily be imposed.

Whether the CA result has any relevance to these small thermal engines has been one of the main issues in the field especially since the coefficient 1/8 in the second term of an expansion of efficiency at maximum power in η_C was found in quite different systems [290, 564]. For an autonomous machine, i.e. in the steady-state regime, the 1/8 is indeed universal if the system possesses an additional (left-right) symmetry [565]. It should be stressed, however, that getting this coefficient requires a second (intrinsic or structural) variational parameter beyond the output control required for getting the 1/2. For such steady-state machines, beyond the second term in the expansion (278), the full CA result is irrelevant.

On the other hand, for small cyclic machines, which can be treated formally in a spirit closer to CA's original approach, obtaining the factor 1/8 requires a symmetry in the exchange with the hot and cold baths [565]. Moreover, for such a machine it is possible to obtain the CA result over the full temperature range for certain conditions [290, 565].

[13] The inequality (277) is a trivial consequence of the IFT for total entropy production, if the latter quantities are expressed by fluctuating work and heat contributions [563].

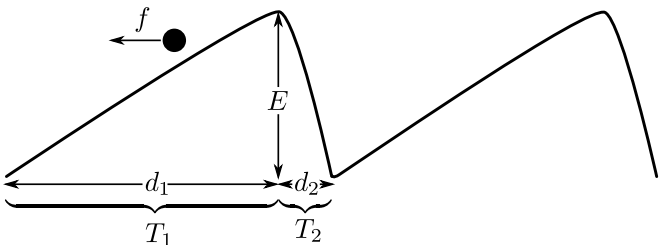

Figure 8. In a BL ratchet, a particle preferentially climbs a potential barrier with height E over a distance d_1 while in contact with a heat bath at T_1. It slides down a distance d_2 on the cold side with $T_2 = T_1 - \Delta T$. This temperature-difference driven motion to the right persists for a small enough force $f < 0$ pulling to the left.

In the following, we describe paradigmatically how small heat engines or devices fit into the stochastic framework from which these and further results for both autonomous (steady state) and periodically driven machines can easily be derived. We focus on both the formal similarities and differences with the isothermal machines and the issue of EMP[14]. Even though we restrict the following discussion to heat engines, similar concepts can be applied to refrigerators, see, e.g., [567, 568].

11.2. Autonomous heat engines

For understanding both the general issues and the necessary ramifications of the comparably simpler framework introduced in section 10 for the isothermal case, it is helpful to have a few specific examples in mind.

11.2.1. Büttiker–Landauer and Feynman ratchet. Transport of a colloidal particle in a periodic potential can be induced by an external force at constant temperature as discussed in section 2. As an alternative, in the absence of an external force, a spatially periodic temperature profile (out of phase with the potential) will also lead to net motion as discussed by Büttiker [569], van Kampen [570] and Landauer [571]. This set-up is one example of noise-induced transport which is comprehensively reviewed by Reimann [445]. From a more thermodynamic perspective, and in the presence of an additional opposing external force, such a Büttiker–Landauer (BL) ratchet is a simple example for a stochastic heat engine that transforms heat into mechanical work. One can then ask for the efficiency of such a device which is a subtle question especially when using the overdamped limit for a discontinuous temperature profile [14, 572–576]. The optimization of such a device for maximal power has been studied both for variation of the external force [577, 578] and for variation of the intrinsic potential [579, 580]. These issues become technically simpler in discretized versions [564, 581–584] as in the simple model sketched and described in figure 8. This system can also be seen as a simplified (one degree of

[14] Universality of the efficiency if other quantities are optimized has been studied in [566].

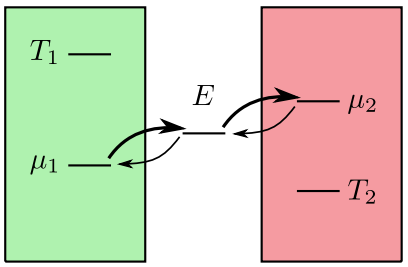

Figure 9. In a thermoelectric device, simplified here as a quantum dot with a single relevant energy level E, electrons are transported on average from a hot reservoir with μ_1 and T_1 to a cold reservoir with $\mu_2 = \mu_1 + \Delta\mu > \mu_1$ and $T_2 = T_1 - \Delta T$ using heat from the hot reservoir.

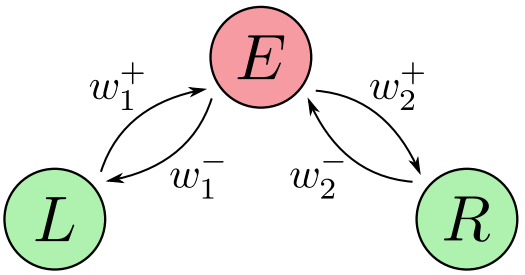

Figure 10. Common three-state diagram for the simplified BL ratchet (figure 8) and the thermo-electric device (figure 9). For the BL-ratchet L and R refer to the particle sitting in the minimum and E corresponds to the particle being on the barrier top. For the electronic device, L and R refer to the electron being in the left or right reservoir. E corresponds to the electron sitting on the quantum dot. In both cases, the state R should be identified with L after the electron or particle has been transported from left to right thus completing the cycle. The log-ratio of the transition rates is given in table 2.

freedom) version of the famous Feynman ratchet [585] that as a paradigm for rectification of thermal noise has its own conceptual subtleties [14, 586]. The Feynman ratchet has inspired various model systems which have been analyzed both analytically and in numerical simulations [587, 588]. A model system using two continuous degrees of freedom coupled anisotropically to two heat baths of different temperatures thus generating a systematic torque has been investigated in [589].

From an experimental perspective, realizing such ratchets in aqueous solution is not straightforward since one needs significant temperature differences on rather small length scales as realized in single particle studies of thermophoresis, see, e.g., [590].

11.2.2. Electronic devices. In electronic devices, temperature differences can be more easily imposed as it is carried out, e.g., in thermoelectrics where they are exploited to transport electrons against an electro-chemical potential. For such systems, thermodynamic considerations have been emphasized by Linke and co-workers who pointed out that such machines can indeed operate at the Carnot limit [591, 592]. More recent studies based on simple models for quantum dots have addressed in particular the issue of EMP [593–595]. The simple paradigm discussed in [593] is sketched in figure 9.

A particularly intriguing aspect of such devices is the observation that in the presence of a magnetic field the Onsager–Casimir symmetry relations, in principle, seem to allow Carnot efficiency at finite power [596]. This issue deserves further study through the analysis of microscopic models such as the one suggested in [597].

Likewise, any photo-electric device is also coupled to a reservoir of rather high temperature since the photons being absorbed from the sun come with the black-body distribution of the sun's temperature. Therefore, photo-electric devices are amenable to a thermodynamic description focusing of efficiency and EMP, see, e.g., [598].

11.2.3. General theory. For any discrete autonomous heat engines in contact with heat baths of at least two different temperatures, it must be specified for each transition at which temperature it takes place, i.e. with which heat bath the machine is in contact at this particular transition. As in the isothermal case, the assumption of local-detailed balance implies thermodynamic constraints on the ratios of forward and backward rates as given in figure 10 and table 2 for the two examples introduced above.

Table 2. Ratio of rates for the devices shown in figures 8 and 9 with their network representation figure 10.

	$\ln w_1^+/w_1^-$	$\ln w_2^+/w_2^-$
BL ratchet	$-(E + \lvert f\rvert d_1)/T_1$	$(E - \lvert f\rvert d_2)/T_2$
Thermo-electric device	$(\mu_1 - E)/T_1$	$(E - \mu_2)/T_2$

The thermodynamic constraints imply that the total entropy production along a cycle still fulfills (251). For the representation (254), one needs the affinities with the corresponding conjugate distances entering the conjugate fluxes given for the two examples in table 3. The general differences compared with the isothermal case arise from the presence of (at least) two different temperatures. First, there is a new affinity associated with the two heat baths with energy flow as the corresponding flux. Second, if matter is transported between baths of different chemical potentials and different temperatures, the corresponding affinity involves the two temperatures. As a consequence, in linear response, the latter affinity carries both a $\Delta\mu$ and a ΔT term. Finally, a force applied to a particle in a thermal ratchet subject to two different temperatures requires to introduce even two affinities with this force. As in the isothermal case, for an autonomous heat engine the total entropy production rate can be expressed by affinities and conjugate fluxes according to (257).

On the cycle level, the total entropy change becomes

$$\Delta S_a = \bar{q}_a^{(1)}/T_1 + \bar{q}_a^{(2)}/T_2, \tag{279}$$

where we use the heat as appropriate under NESS conditions. This heat fulfills first laws of the type

$$w_a^{\mathrm{mech}\,(1,2)} + w_a^{\mathrm{chem}\,(1,2)} = \bar{q}_a^{(1,2)} + \Delta E_a^{(1,2)} \tag{280}$$

where $\Delta E_a^{(1)} = -\Delta E_a^{(2)}$ is the change in internal energy of the system arising from the transitions associated with the respective heat baths labeled by superscripts. With this relation, the total entropy change along a cycle (279) can also

Table 3. Characteristic quantities for the two examples of unicyclic heat engines shown in figures 8 and 9.

	Relevant affinities $\mathcal{F}_k$	$\mathcal{F}_k$ in linear response	Conjugate distance d^k	Input $-\bar{q}^{(1)} = T_2 w_\mathrm{i}$	Output $T_2 w_\mathrm{o}$
BL	$1/T_2 - 1/T_1$	$\Delta T/T_2^2$	E	$E + \lvert f\rvert d_1$	
ratchet	$f/T_1, f/T_2$	$f/T_2, f/T_2$	d_1, d_2		$\lvert f\rvert(d_1 + d_2)$
Thermoelectric	$1/T_2 - 1/T_1$	$\Delta T/T_2^2$	E	$E - \mu_1$	
device	$\mu_1/T_1 - \mu_2/T_2$	$-(\Delta\mu/T_2 + \mu_1 \Delta T/T_2^2)$	1		$\mu_2 - \mu_1$

be expressed by the heat extracted from the hot reservoir as

$$\Delta S_a = -\bar{q}_a^{(1)} \eta_\mathrm{C}/T_2 + (w_a^\mathrm{mech} + w_a^\mathrm{chem})/T_2 \equiv w_{\mathrm{i},a}\eta_\mathrm{C} - w_{\mathrm{o},a}, \tag{281}$$

where the work terms refer to the sum of the contributions from the respective bath contacts. The definition of dimensionless input $w_{\mathrm{i},a}$ is motivated by the fact that for a heat engine the input is the heat extracted from the hotter bath. Dimensionless output denoted by $w_{\mathrm{o},a}$ is mechanical and/or chemical work delivered by the machine.

The power of the machine can now be expressed analogously to the isothermal case as

$$P_\mathrm{o,i} = \epsilon_\mathrm{o,i} \sum_a j_a^+ [1 - \exp(-w_{\mathrm{i},a}\eta_\mathrm{C} + w_{\mathrm{o},a})] T_2 w_{\{\mathrm{o,i}\}a} \tag{282}$$

where the occurrence of the Carnot efficiency η_C in the exponent compared with the isothermal case (262) is crucial. In the affinity representation, the difference to the isothermal case is even more drastic since output and input powers can no longer be written as simple products of a pair of conjugate flux $J_\mathrm{o,i}$ and affinity $T\mathcal{F}_\mathrm{o,i}$ as in (259). One could have anticipated this complication since with two baths it is not obvious which temperature should be chosen in (259) when trying to generalize to the non-isothermal case.

11.2.4. EMP for unicyclic machines. For unicyclic machines (and hence dropping the cycle index a), maximizing the power P_o with respect to the output w_o, which would physically correspond to varying the external force or chemical potentials, leads to the analog of (274) in the form

$$w_\mathrm{i} = (w_\mathrm{o}^* + \ln[1 + w_\mathrm{o}^*/(1 + x_\mathrm{o} w_\mathrm{o}^*)])/\eta_\mathrm{C}. \tag{283}$$

This relation implies immediately the universal $\eta^* \equiv w_\mathrm{o}^*/w_\mathrm{i} \approx \eta_\mathrm{C}/2 + O(\eta_\mathrm{C}^2)$ in the linear response regime which can also easily be obtained from a phenomenological treatment analogously to the one presented in section 10.4 [557].

Maximizing the power with respect to the input variable w_i leads to

$$w_\mathrm{i}^* = [w_\mathrm{o}^* + \ln(1 - \eta_\mathrm{C}/x_\mathrm{i})]/\eta_\mathrm{C} \tag{284}$$

with

$$x_\mathrm{i} \equiv d \ln j^+/d w_\mathrm{i} \approx x_\mathrm{i}^\mathrm{eq} + O(\eta_\mathrm{C}, w_\mathrm{o}). \tag{285}$$

As the respective column in table 3 shows, w_i involves an intrinsic parameter of the machine like the relevant energy level. Combining relations (283) and (284) and varying both w_o and w_i leads to the EMP

$$\eta^{**} = \eta_\mathrm{C}/[1 - (x_\mathrm{o} + x_\mathrm{i}/\eta_\mathrm{C}) \ln(1 - \eta_\mathrm{C}/x_\mathrm{i})] \tag{286}$$

$$\approx \eta_\mathrm{C}/2 - [(2x_\mathrm{o}^\mathrm{eq} + 1)/x_\mathrm{i}^\mathrm{eq}]\eta_\mathrm{C}^2/8 + O(\eta_\mathrm{C}^3) \tag{287}$$

which shows that the second order coefficient is system specific.

It can be checked that for a unicyclic device with spatial symmetry, for which the current j reverses sign when the affinities $\mathcal{F}_k$ change sign, the square-bracket prefactor of the second term is indeed -1 thus recovering the overall 1/8 as previously derived by extending the phenomenological irreversible thermodynamics approach to second order [565].

For an explicit evaluation of the EMP (286) one needs the specific form of $x_\mathrm{o,i} = x_\mathrm{o,i}(w_\mathrm{o}, w_\mathrm{i})$ which requires assumptions on the specific rates beyond the constraints imposed by thermodynamics exploited so far. For the mechanical BL ratchet, it is interesting to note that even for $d_1 \neq d_2$, an explicit calculation for $w_2^+ = w_1^- = 1$ (and the other rates as given in table 2) recovers the coefficient 1/8 despite the obvious breaking of the left-right symmetry. The case $d_2 = 0$ is discussed for the full temperature range in [564], where, not surprisingly, deviations from the CA result are found. The thermoelectric device is treated in [565, 593]. For a photo-electric device, explicit results can be found in [598], where also the role of non-radiative transition is discussed. Further examples of EMP in three and five state networks have been discussed in [533].

11.3. Periodically driven heat engines

The autonomous machines just discussed reach a NESS since they are permanently connected to both heat baths. For a periodically driven heat engine, contact with either one bath or, in an adiabatic step, with none, is periodically enforced externally.

11.3.1. Brownian heat engine. Within stochastic thermodynamics such a model was introduced in [290] for a Brownian particle in a time-dependent potential, see figure 11. Optimizing for both, the potential and the time interval spent in the isothermal transitions, EMP for fixed $T_{1,2}$ was shown to be

$$\eta^* = \eta_\mathrm{C}/(2 - \alpha\eta_\mathrm{C}) \approx \eta_\mathrm{C} + (\alpha/4)\eta_\mathrm{C}^2 + O(\eta_\mathrm{C}^3) \tag{288}$$

where

$$\alpha \equiv 1/[1 + (\mu(T_1)/\mu(T_2))^{1/2}] \tag{289}$$

is a system-specific coefficient given by the temperature-dependence of the mobility $\mu(T)$. If the latter is independent of temperature, one recovers the coefficient 1/8. Since $0 \leqslant \alpha \leqslant 1$, expression (288) implies the bounds

$$\eta_\mathrm{C}/2 \leqslant \eta^* \leqslant \eta_\mathrm{C}/(2 - \eta_\mathrm{C}) \tag{290}$$

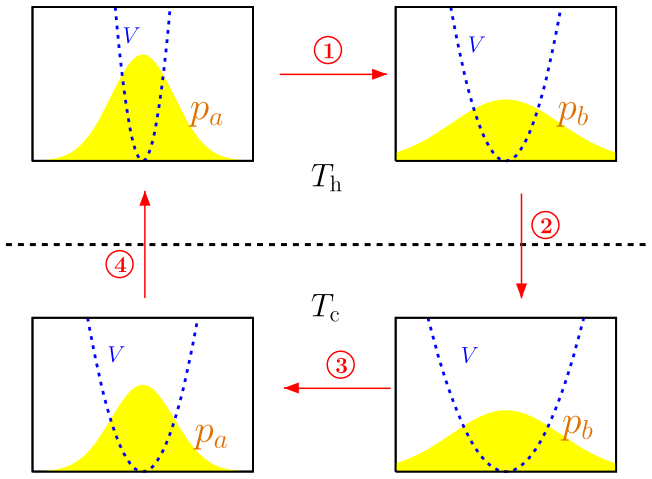

Figure 11. Paradigm for a stochastic heat engine based on a colloidal particle in a time-dependent harmonic laser trap in consecutive contact with a hot (T_h) and cold (T_c) bath. The steps 1 and 3 are isothermal; the steps 2 and 4 are instantaneous and adiabatic during which the distributions are p_b and p_a, respectively. Reproduced with permission from [290]. Copyright 2008 European Physical Society.

on EMP later also derived under the assumption of 'weak' dissipation which leads to a quite similar formalism [559, 599]. Further ramifications and classifications of such bounds have been discussed by Wang and Tu [600, 601] and in [602, 603]. The Onsager coefficients for a linear response treatment of this heat engine have been defined and calculated in [604].

A micrometer-sized heat engine based on the Stirling version of the scheme shown in figure 11 has been realized experimentally [605]. The colloidal particle as 'working fluid' in a laser trap acting as the analog of a piston can be heated locally thereby realizing the contact with a hot bath. By varying the cycle time both a maximum in the power at finite time and the approach to the maximal efficiency in the quasi-static limit could be demonstrated. For further interesting comments on this experiment, see [606].

11.3.2. Quantum dot. A similar analysis can be applied to a finite-time Carnot cycle of a quantum dot that can be connected to two different reservoirs similar as the set-up shown in figure 9 [607]. For a cyclic engine, the energy level $E(\tau)$ is controlled in both the isothermal steps when the dot is connected to either one bath and in the adiabatic steps when it is disconnected. Optimizing for the protocol $E(\tau)$ as well as for the duration of isothermal and adiabatic steps, one finds for EMP an expression similar to (288). In the limit of weak dissipation, i.e. for small deviations from the respective thermal population of the energy level, and symmetric conditions, the coefficient α turns out to be $\alpha = \eta_{CA}/\eta_C$ and hence one can here recover the CA result over the full temperature range. The distributions of work and heat for such a simple two-state engine have been calculated in [608].

12. Concluding perspective

After this long exposition it may be appropriate to recall the basic assumption of this approach, to summarize the main achievements and to raise a few open general issues.

12.1. Summary

Stochastic thermodynamics applies to systems where a few observable degrees of freedom such as the positions of colloidal particles or the gross conformations of biomolecules are in non-equilibrium due to the action of possibly time-dependent external forces, fields, flows or unbalanced chemical reactants. The unobserved degrees of freedom such as those making up the aqueous solution, however, are assumed to be fast and thus always in the constrained equilibrium imposed by the instantaneous values of the observed slow degrees of freedom. Then internal energy, intrinsic entropy and free energy are well-defined and, if a microscopic Hamiltonian was given, in principle, computable for fixed values of the slow variables. This assumption is sufficient to identify a first-law like energy balance along any fluctuating trajectory recording the changing state of the slow variables.

Entropy change along such a trajectory consists of three parts: heat exchanged with the bath, intrinsic entropy of the states and stochastic entropy. The latter requires in addition an ensemble from which this trajectory is taken. If the same trajectory is taken from a different ensemble it leads to a different stochastic entropy. Thermodynamic consistency of the Markovian dynamics generating the trajectory imposes a local-detailed balance condition constraining either the noise in a Langevin-type continuum dynamics or the ratio of transition rates in a discrete dynamics.

At their core, the fluctuation theorems are mathematical identities derived from properties of the weight of stochastic paths under time reversal or other transformations. They acquire physical meaning by associating the mathematical ingredients with the thermodynamic quantities identified within stochastic thermodynamics. The detailed fluctuation theorems then express a symmetry of the distribution function for thermodynamic quantities. An open question is whether the probability distributions of work, heat and entropy production can be grouped into 'universality classes' characterized, e.g., by the asymptotics of such distributions, and, if yes, which specific features of a system determine this class. The more generally applicable integral theorems often can be expressed as refinements of the second law for transitions between certain states. Still, these integral fluctuation theorems should not be considered a 'proof' of the second law since irreversibility has been implemented consistently from the beginning by choosing a stochastic dynamics including the local-detailed balance condition.

Conceptually, a major step has been to include feedback schemes based on perfect or imperfect measurements into this framework which requires surprisingly little additional effort due to the strong formal similarity of stochastic entropy with information. Achieving a full integration of measurement apparatus and the erasure process into the thermodynamic balance of the efficiency for specific information machines remains an important issue [609].

The crucial ingredient for the developments summarized so far is the notion of an individual trajectory and the concomitant concept of distributions for thermodynamic quantities which represents the main difference compared with classical thermodynamics.

New insights, however, have emerged from this approach even when focusing on averages and correlation functions as we have carried out in the second part of the review. The general fluctuation–dissipation theorem for non-equilibrium steady states shows how the response of any observable to a perturbation can be expressed as a sum of two correlation functions involving entropy production. In which cases this additive relation between response and correlation can be reformulated as a multiplicative one using the concept of an effective temperature is still not understood despite some insights gained from specific case studies.

Our discussion of molecular motors, machines and devices has been centered on the notion of efficiency and efficiency at maximum power. Despite the fundamental difference between isothermal engines operating at one temperature as do all cellular ones and genuine heat engines such as thermoelectric devices involving two baths of different temperatures, a common framework exists based on the representation of entropy production in terms of cycles of the underlying network of states. Clearly, more realistic networks need to be studied in the future, in particular, for applications and for modeling of specific biophysical systems but the basic concepts seem to be identified. One particularly intriguing perspective comes from the recent analysis of the energetic cost of sensory adaptation using the concepts of stochastic thermodynamics [610].

12.2. Beyond a Markovian dynamics: memory effects and coarse graining

The identification of states, of work and of internal energy, i.e. of the ingredients entering the first law on the level of trajectories, is logically independent of the assumption of a Markovian dynamics connecting these states. The crucial step is the splitting of all degrees of freedom into slow and fast ones, the latter always being in a constrained equilibrium imposed by the instantaneous values of the slow ones. Likewise, the identification of entropy production only requires the notion of an ensemble which determines stochastic entropy along an individual trajectory. Any dynamics guaranteeing that for fixed external parameters compatible with genuine equilibrium, this equilibrium will be reached for an arbitrary initial distribution of the slow variables could qualify as a thermodynamically consistent one.

12.2.1. Continuous states. A popular choice for a non-Markovian dynamics obeying these constraints is Langevin dynamics with a memory kernel that, for thermodynamics consistency, determines the correlations of the colored noise[15]. Under this assumption, the notions of stochastic thermodynamics are well-defined and the various fluctuation theorems hold true as shown quite generally in [378, 615–619]. Some of these papers contain illustrations for model systems as do the references [620–622]. One specific motivation to explore such a dynamics arises from the recent fascinating experimental data that show how hydrodynamic effects lead to a frequency dependent mobility for colloidal motion [623].

A somewhat different and more subtle situation occurs if not all slow variables are accessible in the experiment or the simulation. The effective dynamics for the observable ones will then no longer be Markovian and its specific form in the case on non-harmonic interactions between the slow ones is typically not accessible. The proper identification of, e.g., entropy production is then difficult if not impossible. Still, one might be inclined to infer an apparent entropy production by applying the rules for Markovian dynamics and to check whether this quantity obeys the FT. In a recent study using two coupled driven colloidal particles it turned out that the apparent entropy production based on the observation of just one particle shows an FT-like symmetry but with a different prefactor for a surprisingly large range of parameter values. However, there are also clear cases for which not even an effective FT can be identified [624]. This type of coarse graining in the context of the FDT for a NESS has been explored in [625].

12.2.2. Discrete states. For an underlying dynamics on a discrete set of states following a Markovian master equation, one option for coarse graining is to group several states into new 'meso-states' or aggregated states. Typically, the dynamics between these meso-states is then no longer Markovian. One question is whether one can then distinguish genuine equilibrium from a NESS if only the coarse-grained trajectory is accessible. For a three-state system coarse-grained into a two-state system, this issue has been addressed in [626, 627] and, for more general cases, in [628, 629].

Coarse graining of a discrete network becomes systematically possible if states among which the transitions are much faster are grouped together. From the perspective of stochastic thermodynamics, entropy production and fluctuation theorems this approach has been followed in [630–637].

12.3. Coupling of non-equilibrium steady states: a zeroth law?

In addition to the first and the second law, classical thermodynamics is founded on a zeroth law stating that the notion of temperature and chemical potential for equilibrium systems is transitive, i.e. if a system A is in separate equilibrium with system B and system C, then upon contact of B and C neither heat nor particle flow will occur between these two systems. A natural question is whether a similar equilibration also occurs for non-equilibrium systems brought into contact such that they can exchange energy or particles. Do then quantities exist resembling temperature or chemical potential that govern 'equilibration' between such steady states? On a phenomenological level this question has been introduced within the context of steady-state thermodynamics by Oono and Paniconi [47] and further refined by Sasa and Tasaki [48]. For simple one-dimensional model systems such as zero-range processes in contact a non-equilibrium chemical potential is indeed well-defined [638]. For two-dimensional driven lattice gases in contact, numerical work has revealed that in a large

[15] Stochastic thermodynamics for a non-Markovian dynamics not obeying such a constraint has been explored for generalized Langevin equations in [378, 611], for delayed Langevin systems in [612], for Poissonian shot noise in [613], and for non-Gaussian white noise in [614].

parameter range such a putative zeroth law and a corresponding thermodynamic structure is approximately valid [639, 640].

12.4. Final remark

From its very beginnings, thermodynamics has fascinated scientists by posing deep conceptual issues that needed to be resolved for understanding and optimizing quite practical matters such as the design of heat engines. With the experimentally realized micrometer-sized heat engine [605] discussed in one of the last sections of this review, these latest developments have brought us back to the very origins of classical thermodynamics albeit on quite different time and length scales and, quite importantly, with a much refined view on individual trajectories. Indeed, without the spectacular advances in experimental techniques concerning tracking and manipulation of single particles and molecules, stochastic thermodynamics could still have been conceived as a theoretical framework but would have not reached the broader appeal that it has gained over the last fifteen years. Whether the next decade of research in the field will be dominated by specific applications, most likely for biomolecular networks and devices facilitating transport of all sorts, or by further conceptual work exploring the ultimate limits of a thermodynamic approach to non-equilibrium beyond the Markovian paradigm into feedback-driven, information-processing, strongly interacting systems remains to be seen.

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