

# B 5 Stochastic thermodynamics

In: *Lecture Notes: 'Soft Matter. From Synthetic to Biological Materials'*.

39th IFF Spring School, Institut of Solid State Research, Research Centre Jülich (2008).

U. Seifert

II. Institut für Theoretische Physik

Universität Stuttgart

## Contents

<b>1</b>	<b>Classical vs. stochastic thermodynamics</b>	<b>2</b>
<b>2</b>	<b>Principles</b>	<b>4</b>
2.1	Stochastic dynamics . . . . .	4
2.2	First law . . . . .	5
2.3	Entropy production . . . . .	7
2.4	Jarzynski relation . . . . .	9
2.5	Optimal finite-time processes . . . . .	11
<b>3</b>	<b>Non-equilibrium steady states</b>	<b>12</b>
3.1	Characterization . . . . .	12
3.2	Detailed fluctuation theorem . . . . .	13
3.3	Generalized Einstein relation and generalized fluctuation-dissipation-theorem . . . . .	14
<b>4</b>	<b>Stochastic dynamics on a network</b>	<b>16</b>
4.1	Entropy production for a general master equation . . . . .	16
4.2	Driven enzyme or protein with internal states . . . . .	20
4.3	Chemical reaction network . . . . .	22
<b>A</b>	<b>Path integral representation</b>	<b>25</b>
<b>B</b>	<b>Proof of the integral fluctuation theorem</b>	<b>26</b>

# 1 Classical vs. stochastic thermodynamics

Stochastic thermodynamics provides a conceptual framework for describing a large class of soft and bio matter systems under well specified but still fairly general non-equilibrium conditions. Typical examples comprise colloidal particles driven by time-dependent laser traps and polymers or biomolecules like RNA, DNA or proteins manipulated by optical tweezers, micropipets or AFM tips. Three features are characteristic for such systems: (i) the source of non-equilibrium are external mechanical forces or unbalanced chemical potentials; (ii) these small systems are inevitably embedded in an aqueous solution which serves as a heat bath of well defined temperature  $T$ ; (iii) fluctuations play a prominent role.

As the main idea behind stochastic thermodynamics, notions like applied work, exchanged heat and entropy developed in classical thermodynamics about 200 years ago are adapted to this micro- or nano-world. Specifically, the stochastic energetics approach introduced a decade ago by Sekimoto [1] is combined with the observation that entropy can consistently be assigned to a single fluctuating trajectory [2].

For a juxtaposition of classical and stochastic thermodynamics we consider for each a paradigmatic experiment. For the classical compression of a gas or fluid in contact with a heat reservoir of temperature  $T$  (see Fig. 1), the first law

$$W = \Delta V + Q \quad (1)$$

expresses energy conservation. The work  $W$  applied to the system either increases the internal energy  $V$  of the system or is dissipated as heat  $Q = T\Delta S_m$  in the surrounding medium, where  $\Delta S_m$  is the entropy change of the medium.

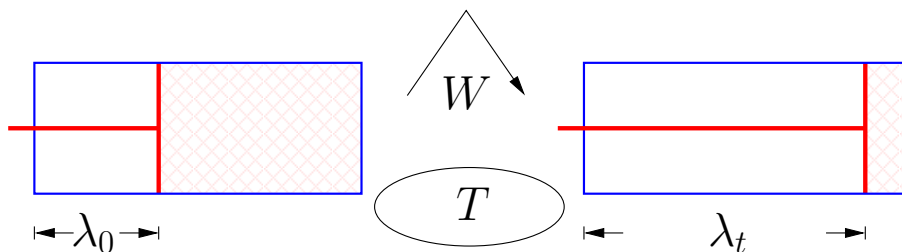
The second law

$$\Delta S_{\text{tot}} \equiv \Delta S + \Delta S_m \geq 0 \quad (2)$$

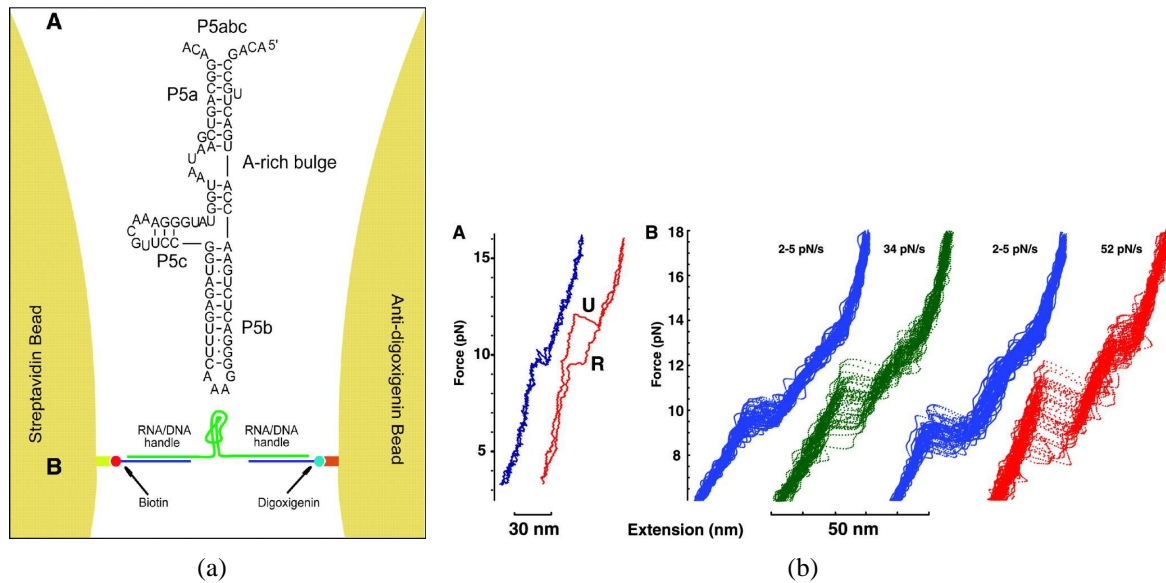
combined with the first law leads to an inequality

$$W_{\text{diss}} \equiv W - \Delta F \geq 0 \quad (3)$$

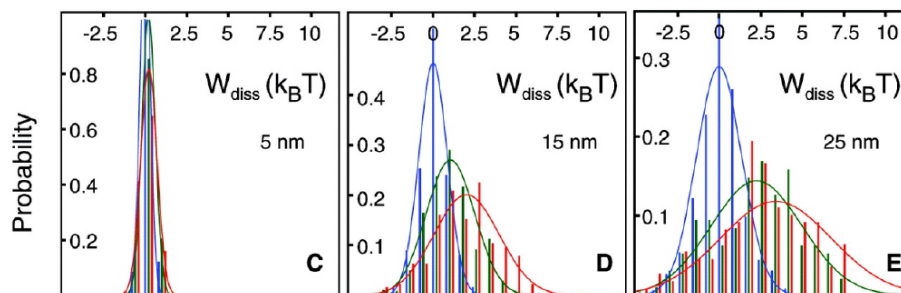
expressing the fact that the work put in is never smaller than the free energy difference  $\Delta F$  between final and initial state. This difference, the dissipated work  $W_{\text{diss}}$ , is zero only if the process takes place quasistatically.



**Fig. 1:** Typical experiment in classical thermodynamics: Starting from an initial position at  $\lambda_0$ , an external control parameter is changed according to a protocol  $\lambda(\tau)$  during time  $0 \leq \tau \leq t$  to a final position  $\lambda_t$ . This process requires work  $W$  while the system remains in contact with a heat bath at temperature  $T$ .



**Fig. 2:** Typical experiment in stochastic thermodynamics: The two ends of an RNA molecule are attached to two beads (yellow) which can be manipulated by micropipets. By pulling these beads, the hairpin structure of the RNA can be unfolded leading to force extension curves. For slow pulling (blue) these curves are almost reversible whereas for medium pulling speed (green) and large pulling speed (red) the curves show pronounced hysteresis which is a signature of non-equilibrium. In all cases, the overlay of several traces shows the role of fluctuation; adapted from [3].



**Fig. 3:** Measured distributions for dissipative work  $W_{\text{diss}}$ . The three panels correspond to different extensions whereas the colours refer to different pulling speeds; adapted from [3].

A similar experiment on a nano-scale, the stretching of RNA, is shown in Fig. 2. Two conceptual issues must be faced if one wants to use the same macroscopic notions to describe such an experiment. First, how should work, exchanged heat and internal energy be defined on this scale. Second, these quantities do not acquire sharp values but rather lead to distributions, as shown in Fig. 3.

The occurrence of negative value of the dissipated work  $W_{\text{diss}}$  is typical for such distributions. The quest to quantify and understand these events which seem to be in conflict with too narrow an interpretation of the second law lies at the origin of stochastic thermodynamics which got started by two originally independent discoveries. First, the (detailed) fluctuation theorem

dealing with non-equilibrium steady states provides a symmetry between the probability for observing asymptotically a certain entropy production and the probability for the corresponding entropy annihilation [4–7]. Second, the Jarzynski relation expresses the free energy difference between two equilibrium states as a non-linear average over the non-equilibrium work required to drive the system from one state to the other in a finite time [8–11]. Within stochastic thermodynamics both of these relations can easily be derived and the latter shown to be a special case of a more general relation [2].

The purpose of these lecture notes is to introduce the principles of stochastic thermodynamics using simple systems in a systematic way and to sketch a few examples following the exposition in [12]. No attempt is made to achieve a comprehensive historical presentation. Several (mostly) review articles can provide complementary and occasionally broader perspectives [13–25].

## 2 Principles

### 2.1 Stochastic dynamics

In this section, three equivalent but complementary descriptions of stochastic dynamics, the Langevin equation, the Fokker-Planck equation, and the path integral, are introduced [26–28]. We start with the Langevin equation for the overdamped motion  $x(\tau)$  of a “particle” or “system”

$$\dot{x} = \mu F(x, \lambda) + \zeta \quad (4)$$

where  $F(x, \lambda)$  is a systematic force and  $\zeta$  thermal noise with correlation

$$\langle \zeta(\tau)\zeta(\tau') \rangle = 2D\delta(\tau - \tau') \quad (5)$$

where  $D$  is the diffusion constant. In equilibrium,  $D$  and the mobility  $\mu$  are related by the Einstein relation

$$D = T\mu \quad (6)$$

where  $T$  is the temperature of the surrounding medium with Boltzmann’s constant  $k_B$  set to unity throughout the paper to make entropy dimensionless. In stochastic thermodynamics, one assumes that the strength of the noise is 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 force

$$F(x, \lambda) = -\partial_x V(x, \lambda) + f(x, \lambda) \quad (7)$$

can arise from a conservative potential  $V(x, \lambda)$  and/or be applied to the particle directly as  $f(x, \lambda)$ . Both sources 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 experimental protocol. To keep the notation simple, we treat the coordinate  $x$  as if it were a single degree of freedom. In fact, all results discussed in the following hold for an arbitrary number of coupled degrees of freedom for which  $x$  and  $F$  become vectors and  $D$  and  $\mu$  (possibly  $x$ -dependent) matrices [29].

Equivalent to the Langevin equation is the corresponding Fokker-Planck equation for the probability  $p(x, \tau)$  to find the particle at  $x$  at time  $\tau$  as

$$\begin{aligned} \partial_\tau p(x, \tau) &= -\partial_x j(x, \tau) \\ &= -\partial_x (\mu F(x, \lambda)p(x, \tau) - D\partial_x p(x, \tau)) \end{aligned} \quad (8)$$

where  $j(x, \tau)$  is the probability current. This partial differential equation must be augmented by a normalized initial distribution  $p(x, 0) \equiv p_0(x)$ . It will become crucial to distinguish the dynamical solution  $p(x, \tau)$  of this Fokker-Planck equation, which depends on this given initial condition, from the solution  $p^s(x, \lambda)$  for which the right hand side of (8) vanishes at any fixed  $\lambda$ . The latter corresponds either to a steady state for a non-vanishing non-conservative force  $f \neq 0$  or to equilibrium for  $f = 0$ , respectively.

A third equivalent description of the dynamics is given by assigning a weight

$$p[x(\tau)|x_0] = \exp \left[ - \int_0^t d\tau [(\dot{x} - \mu F)^2/4D + \mu \partial_x F/2] \right] \quad (9)$$

to each path or trajectory, as derived in Appendix A. Path dependent observables can then be averaged using this weight in a path integral which requires a path-independent normalization such that summing the weight (9) over all paths is 1.

## 2.2 First law

Following Sekimoto within his stochastic energetics approach [1], we first identify the first-law-like energy balance

$$dw = dV + dq \quad (10)$$

for the Langevin equation (4). The increment in work applied to the system

$$dw = (\partial V/\partial \lambda) \dot{\lambda} d\tau + f dx \quad (11)$$

consists of two contributions. The first term arises from changing the potential (at fixed particle position) and the second from applying a non-conservative force to the particle directly. If one accepts these quite natural definitions, for the first law to hold along a trajectory the heat dissipated into the medium must be identified with

$$dq = F dx. \quad (12)$$

This relation is quite physical since in an overdamped system the total force times the displacement corresponds to dissipation. Integrated along a trajectory of given length one obtains the expressions

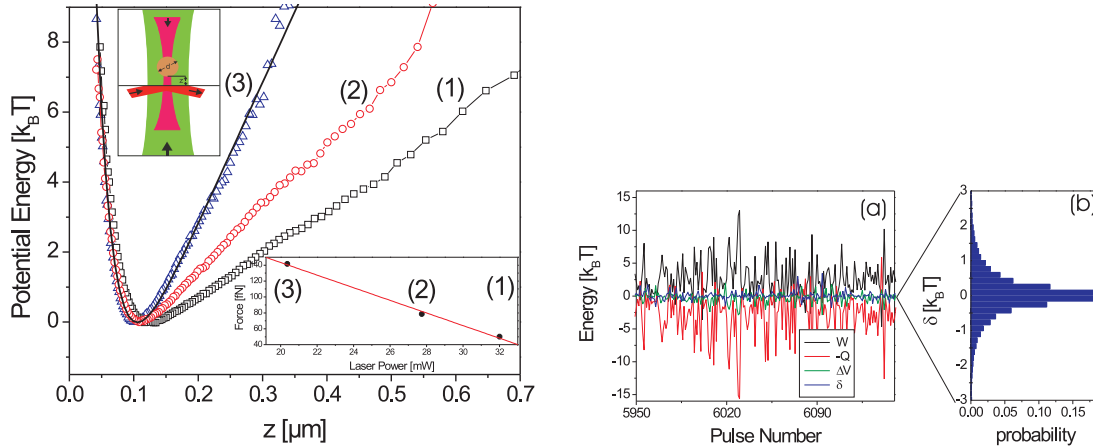
$$w[x(\tau)] = \int_0^t [(\partial V/\partial \lambda) \dot{\lambda} + f \dot{x}] d\tau \quad \text{and} \quad q[x(\tau)] = \int_0^t F \dot{x} d\tau \quad (13)$$

and the first law

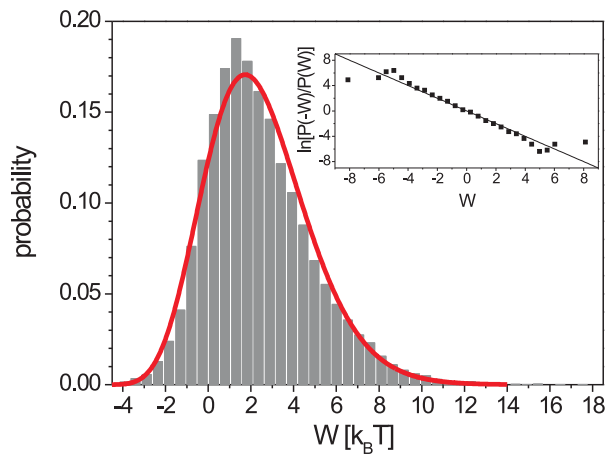
$$w[x(\tau)] = q[x(\tau)] + \Delta V = q[x(\tau)] + V(x_t, \lambda_t) - V(x_0, \lambda_0) \quad (14)$$

on the level of a single trajectory.

In a recent experiment [30], the three quantities applied work, exchanged heat and internal energy were inferred from the trajectory of a colloidal particle pushed periodically by a laser trap against a repulsive substrate, see Fig. 4. The measured non-Gaussian distribution for the applied work shown in Fig. 5 indicates that this system is driven beyond the linear response regime since it has been proven that within the linear response regime the work distribution is always Gaussian [31]. Moreover, the good agreement between the experimentally measured distribution and the theoretically calculated one indicates that the assumption of noise correlations being unaffected by the driving is still valid in this regime beyond linear response.



**Fig. 4:** *Experimental illustration of the first law. A colloidal particle is pushed by a laser towards a repulsive substrate. The (almost) linear attractive part of the potential depends linearly (see insert) on the laser intensity. For fixed laser intensity, the potential can be extracted by inverting the Boltzmann factor. If the laser intensity is modulated periodically, the potential becomes time-dependent. For each period (or pulse) the work  $W$ , heat  $Q$  and change in internal energy  $\Delta V$  can be inferred from the trajectory using (10-11). Ideally, these quantities should add up to zero for each pulse, while the histogram shows the small ( $\delta \lesssim 1k_B T$ ) experimental error; adapted from [30].*



**Fig. 5:** *Work distribution for a fixed trajectory length for the experiment shown in Fig. 4. The grey histogram are experimental data, the red curve shows the theoretical prediction with no free fit parameters. The non-Gaussian shape proves that the experimental condition probe the regime beyond linear response. The insert shows that the work distribution obeys the detailed fluctuation theorem introduced in Section 3.2 below; adapted from [30].*

## 2.3 Entropy production

For a refinement of the second law on the level of single trajectories, we need to define the corresponding entropy as well which turns out to have two contributions. First, the heat dissipated into the environment should be identified with an increase in entropy of the medium

$$\Delta s_m[x(\tau)] \equiv q[x(\tau)]/T. \quad (15)$$

Second, one defines as a stochastic or trajectory dependent entropy of the system the quantity [2]

$$s(\tau) \equiv -\ln p(x(\tau), \tau) \quad (16)$$

where the probability  $p(x, \tau)$  obtained by first solving the Fokker-Planck equation is evaluated along the stochastic trajectory  $x(\tau)$ . Since introducing this stochastic entropy in the main new concept within this approach, we first discuss some of its properties.

- **Relation to non-equilibrium ensemble entropy**

Obviously, for any given trajectory  $x(\tau)$ , the entropy  $s(\tau)$  depends on the given initial data  $p_0(x)$  and thus contains information on the whole ensemble. Indeed, upon averaging with the given ensemble  $p(x, \tau)$ , this trajectory-dependent entropy becomes the usual ensemble entropy

$$S(\tau) \equiv -\int dx p(x, \tau) \ln p(x, \tau) = \langle s(\tau) \rangle. \quad (17)$$

Here and throughout the manuscript the brackets  $\langle \dots \rangle$  denote the non-equilibrium average generated by the Langevin dynamics from some given initial distribution  $p(x, 0) = p_0(x)$ .

- **Relation to thermodynamics in equilibrium**

It is interesting to note that in equilibrium, i.e. for  $f \equiv 0$  and constant  $\lambda$ , the stochastic entropy  $s(\tau)$  obeys the well-known thermodynamic relation between entropy, internal energy and free energy

$$s(\tau) = (V(x(\tau), \lambda) - \mathcal{F}(\lambda))/T, \quad (18)$$

along the fluctuating trajectory at any time with the free energy

$$\mathcal{F}(\lambda) \equiv -T \ln \int dx \exp[-V(x, \lambda)/T]. \quad (19)$$

- **Invariance under coordinate transformations**

The entropy as defined in (16) has the formal deficiency that strictly speaking  $\ln p(x(\tau), \tau)$  is not defined since  $p(x, \tau)$  is a density. Apparently more disturbingly, this expression is not invariant under non-linear transformations of the coordinates. In fact, both deficiencies which also hold for the ensemble entropy (17) are related and can be cured easily as follows by implicitly invoking the notion of relative entropy [12].

A formally proper definition of the stochastic entropy starts by describing the trajectory using canonical variables. After integrating out the momenta, for a system with  $N$  particles with Cartesian positions  $\{x_i\}$ , one should define the entropy as

$$s(\{x_i(\tau)\}) \equiv -\ln[p(\{x_i(\tau)\}, \tau)\lambda_T^{3N}] \quad (20)$$

where  $\lambda_T$  is the thermal de Broglie length. If one now considers this dynamics in other coordinates  $\{y_i\}$ , one should use

$$s(\{y_i(\tau)\}) \equiv -\ln[p(\{y_i(\tau)\}, \tau) \det\{\partial y/\partial x\} \lambda_T^{3N}]. \quad (21)$$

This correction with the Jacobian ensures that the entropy both on the trajectory as well as on the ensemble level is independent of the coordinates used to describe the stochastic motion. Of course, this statement is no longer true if the transformation from  $\{x_i\}$  to  $\{y_i\}$  is not one to one. Indeed, if some degrees of freedom are integrated out the entropy does and should change. For ease of notation, we will in the following keep the simple form (16).

### • Equations of motion

The rate of change of the entropy of the system (16) is given by [2]

$$\begin{aligned} \dot{s}(\tau) &= -\frac{\partial_\tau p(x, \tau)}{p(x, \tau)} \Big|_{x(\tau)} - \frac{\partial_x p(x, \tau)}{p(x, \tau)} \Big|_{x(\tau)} \dot{x} \\ &= -\frac{\partial_\tau p(x, \tau)}{p(x, \tau)} \Big|_{x(\tau)} + \frac{j(x, \tau)}{Dp(x, \tau)} \Big|_{x(\tau)} \dot{x} - \frac{\mu F(x, \lambda)}{D} \Big|_{x(\tau)} \dot{x}. \end{aligned} \quad (22)$$

The first equality identifies the explicit and the implicit time-dependence. The second one uses the Fokker-Planck equation (8) for the current. The third term in the second line can be related to the rate of heat dissipation in the medium (15)

$$\dot{q}(\tau) = F(x, \lambda) \dot{x} = T \dot{s}_m(\tau) \quad (23)$$

using the Einstein relation  $D = T\mu$ . Then (22) can be written as a balance equation for the trajectory-dependent total entropy production

$$\dot{s}_{\text{tot}}(\tau) = \dot{s}_m(\tau) + \dot{s}(\tau) = -\frac{\partial_\tau p(x, \tau)}{p(x, \tau)} \Big|_{x(\tau)} + \frac{j(x, \tau)}{Dp(x, \tau)} \Big|_{x(\tau)} \dot{x}. \quad (24)$$

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

Upon averaging, the total entropy production rate  $\dot{s}_{\text{tot}}(\tau)$  has to become positive as required by the second law. This ensemble average proceeds in two steps. First, we conditionally average over all trajectories which are at time  $\tau$  at a given  $x$  leading to

$$\langle \dot{x} | x, \tau \rangle = j(x, \tau) / p(x, \tau). \quad (25)$$

Second, with  $\int dx \partial_\tau p(x, \tau) = 0$  due to probability conservation, averaging over all  $x$  with  $p(x, \tau)$  leads to

$$\dot{S}_{\text{tot}}(\tau) \equiv \langle \dot{s}_{\text{tot}}(\tau) \rangle = \int dx \frac{j(x, \tau)^2}{Dp(x, \tau)} \geq 0, \quad (26)$$

where equality holds in equilibrium only. Averaging the increase in entropy of the medium along similar lines leads to

$$\dot{S}_m(\tau) \equiv \langle \dot{s}_m(\tau) \rangle = \langle F(x, \tau) \dot{x} \rangle / T \quad (27)$$

$$= \int dx F(x, \tau) j(x, \tau) / T. \quad (28)$$



Hence upon averaging, the increase in entropy of the system itself becomes  $\dot{S}(\tau) \equiv \langle \dot{s}(\tau) \rangle = \dot{S}_{\text{tot}}(\tau) - \dot{S}_{\text{m}}(\tau)$ . On the ensemble level, this balance equation for the averaged quantities can also be derived directly from the ensemble definition (17) [32].

- **Integral fluctuation theorem (IFT)**

The total entropy change along a trajectory follows from (15) and (16)

$$\Delta s_{\text{tot}} \equiv \Delta s_{\text{m}} + \Delta s \quad (29)$$

with

$$\Delta s \equiv -\ln p(x_t, \lambda_t) + \ln p(x_0, \lambda_0). \quad (30)$$

It obeys a remarkable integral fluctuation theorem (IFT) [2]

$$\langle e^{-\Delta s_{\text{tot}}} \rangle = 1 \quad (31)$$

which can be interpreted as a refinement of the second law  $\langle \Delta s_{\text{tot}} \rangle \geq 0$ . The latter follows from (31) by Jensen's inequality  $\langle \exp x \rangle \geq \exp \langle x \rangle$ . This integral fluctuation theorem for  $\Delta s_{\text{tot}}$  is quite universal since it holds for any kind of initial condition (not only for  $p_0(x_0) = p^s(x_0, \lambda_0)$ ), any time-dependence of force and potential, with (for  $f = 0$ ) and without (for  $f \neq 0$ ) detailed balance at fixed  $\lambda$ , and any length of trajectory  $t$ .

As shown in Appendix B, the IFT for entropy production (31) follows from a more general fluctuation theorem which unifies several relations previously derived independently. Based on the concept of time-reversed trajectories and time-reversed protocol [6, 11, 17], it is easy to prove the relation [2]

$$\langle \exp[-\Delta s_{\text{m}}] p_1(x_t)/p_0(x_0) \rangle = 1 \quad (32)$$

for any function  $p_1(x)$  with normalization  $\int dx p_1(x) = 1$ . Here, the initial distribution  $p_0(x)$  is arbitrary. By using the first law (14), this relation can also be written in the form

$$\langle \exp[-(w - \Delta V)/T] p_1(x_t)/p_0(x_0) \rangle = 1 \quad (33)$$

with no reference to an entropy change.

The arguably most natural choice for the function  $p_1(x)$  is to take the solution  $p(x, \tau)$  of the Fokker-Planck equation at time  $t$  which leads to the IFT (31) for the total entropy production. Other choices lead to similar relations originally derived differently among which the Jarzynski relation is the most famous and useful.

## 2.4 Jarzynski relation

The Jarzynski relation (JR) originally derived using Hamiltonian dynamics [8]

$$\langle \exp[-w/T] \rangle = \exp[-\Delta \mathcal{F}/T] \quad (34)$$

expresses the free energy difference  $\Delta \mathcal{F} \equiv \mathcal{F}(\lambda_t) - \mathcal{F}(\lambda_0)$  between two equilibrium states characterized by the initial value  $\lambda_0$  and the final value  $\lambda_t$  of the control parameter, respectively, as a non-linear average over the work required to drive the system from one equilibrium state

to another. At first sight, this is a surprising relation since on the left hand side there is a non-equilibrium average which should in principle depend on the protocol  $\lambda(\tau)$ , whereas the free energy difference on the right hand side is a pure equilibrium quantity.

Within stochastic thermodynamics the JR follows, a posteriori, from the more general relation (33), by specializing to the following conditions: (i) There is only a time-dependent potential  $V(x, \lambda(\tau))$  and no non-conservative force ( $f \equiv 0$ ), (ii) initially the system is in thermal equilibrium with the distribution

$$p_0(x) = \exp[-(V(x, \lambda_0) - \mathcal{F}(\lambda_0))/T]. \quad (35)$$

Plugging this expression with the free choice  $p_1(x) = \exp[-(V(x, \lambda_t) - \mathcal{F}(\lambda_t))/T]$  into (33), the JR indeed follows within two lines. It is crucial to note that its validity does not require that the system has relaxed at time  $t$  into the new equilibrium. In fact, the actual distribution at the end will be  $p(x, t)$ .

As an important application, based on a slight generalization [33], the Jarzynski relation can be used to reconstruct the free energy landscape of a biomolecule  $G(x)$  where  $x$  denotes a ‘‘reaction coordinate’’ like the end-to-end distance in forced protein folding as reviewed in [20]. Indeed, the experiment on unfolding RNA described in the introduction [3] has been one of the first real-world test of the Jarzynski relation.

In this context, it might be instructive to resolve some confusion in the literature concerning an earlier relation derived by Bochkov and Kuzolev [34, 35]. For a system initially in equilibrium in a time-independent potential  $V_0(x)$  and for  $0 \leq \tau \leq t$  subject to an additional space and time-dependent force  $f(x, \tau)$ , one obtains from (33) the Bochkov-Kuzolev relation (BKR)

$$\langle \exp[-\tilde{w}/T] \rangle = 1 \quad (36)$$

with

$$\tilde{w} \equiv \int_{x_0}^{x_t} f(x, \lambda(\tau)) dx \quad (37)$$

by choosing  $p_1(x) = p_0(x) = \exp[-(V_0(x) - \mathcal{F}_0)/T]$ . Under these conditions,  $\tilde{w}$  is the work performed at the system. Since this relation derived much earlier by Bochkov and Kuzolev [34, 35] looks almost like the Jarzynski relation there have been both claims that the two are the same and some confusion around the apparent contradiction that  $\exp[-w/T]$  seems to be both  $\exp[-\Delta\mathcal{F}/T]$  or 1. The present derivation shows that the two relations are different since they apply a priori to somewhat different situations. The JR as discussed above applies to processes in a time-dependent potential, whereas the BKR as discussed here 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,  $f(x, \tau) = -V_1'(x, \tau)$ , there still seems to be an ambiguity. It can be resolved by recognizing that in this case the work entering the BKR (36)

$$\tilde{w} = \int dx f = - \int dx V_1'(x) = -\Delta V_1 + w \quad (38)$$

differs by a boundary term from the definition of work  $w$  given in eq. (11) and used throughout this paper. Thus, if the force arises from a time-dependent but conservative potential both the BKR in the form  $\langle \exp[-\tilde{w}/T] \rangle = 1$  and the JR (34) hold. The connection between the two relations can also be discussed within a Hamiltonian dynamics approach [36]. Further relation that can be derived from the IFT (32) can be found in Ref. [12].

## 2.5 Optimal finite-time processes

So far, we have discussed relations that hold for any protocol  $\lambda(\tau)$ . For various applications it is important to know an optimal protocol  $\lambda^*(\tau)$ . In this section we investigate the optimal protocol  $\lambda^*(\tau)$  that minimizes the mean work required to drive such a system from one equilibrium state to another in a *finite* time  $t$  [37]. The emphasis on a finite time is crucial since for infinite time the work spent in any quasi-static process is equal to the free energy difference of the two states. For finite time the mean work is larger and will depend on the protocol  $\lambda(\tau)$ . A priori, one might expect the optimal protocol connecting the given initial and final values to be smooth as it was found in a case study within the linear response regime [38]. In contrast, it turns out that for genuine finite-time driving the optimal protocol involves discontinuities both at the beginning and the end of the process.

As an instructive example [37], we consider a colloidal particle dragged through a viscous fluid by an optical tweezer with harmonic potential

$$V(x, \tau) = (x - \lambda(\tau))^2 / 2. \quad (39)$$

For notational simplicity, we set  $T = \mu = 1$  in this section by choosing natural units for energies and times. The focus of the optical tweezer is moved according to a protocol  $\lambda(\tau)$ . The optimal protocol  $\lambda^*(\tau)$  connecting given boundary values  $\lambda_0 = 0$  and  $\lambda_t$  in a time  $t$  minimizes the dimensionless mean total work

$$W[\lambda(\tau)] \equiv \int_0^t d\tau \dot{\lambda} \left\langle \frac{\partial V}{\partial \lambda}(x(\tau), \lambda(\tau)) \right\rangle \quad (40)$$

which we express as a functional of the mean position of the particle  $u(\tau) \equiv \langle x(\tau) \rangle$  as

$$\begin{aligned} W[\lambda(\tau)] &= \int_0^t d\tau \dot{\lambda} (\lambda - u) = \int_0^t d\tau (\dot{u} + \ddot{u}) \dot{u} \\ &= \int_0^t d\tau \dot{u}^2 + [\dot{u}^2]_0^t / 2. \end{aligned} \quad (41)$$

Here, we have used

$$\dot{u} = (\lambda - u) \quad (42)$$

which follows from averaging the Langevin equation (4). The Euler-Lagrange equation corresponding to (41),  $\ddot{u} = 0$ , is solved by  $u(\tau) = m\tau$ , where  $u(0) = 0$  is enforced by the initial condition. Eq. (42) then requires the boundary conditions  $\dot{u}(0) = \lambda_0 - u(0) = 0$  and  $\dot{u}(t) = \lambda_t - mt$  which can only be met by discontinuities in  $\dot{u}$  at the boundaries which correspond to jumps in  $\lambda$ . Note that these “kinks” do not contribute to the integral in the second line of (41). The yet unknown parameter  $m$  follows from minimizing the mean total work

$$W = m^2 t + (\lambda_t - mt)^2 / 2 \quad (43)$$

which yields  $m^* = \lambda_t / (t + 2)$ . The minimal mean work  $W^* = \lambda_t^2 / (t + 2)$  vanishes in the quasi-static limit  $t \rightarrow \infty$ . The optimal protocol then follows from (42) as

$$\lambda^*(\tau) = \lambda_t (\tau + 1) / (t + 2), \quad (44)$$

for  $0 < \tau < t$ . As a surprising result, this optimal protocol implies two distinct symmetrical jumps of size

$$\Delta\lambda \equiv \lambda(0^+) - \lambda_0 = \lambda_t - \lambda(t^-) = \lambda_t / (t + 2) \quad (45)$$

at the beginning and the end of the process. A priori, one might have expected a continuous linear protocol  $\lambda^{\text{lin}}(\tau) = \lambda_t \tau/t$  to yield the lowest work but the explicit calculation yields

$$W^{\text{lin}} = (\lambda_t/t)^2(t + e^{-t} - 1) > W^* \quad (46)$$

for any  $t > 0$ , with a maximal value  $W^{\text{lin}}/W^* \simeq 1.14$  at  $t \simeq 2.69$ . A further case study and more general consideration indeed show that such jumps at the beginning and end of the protocol are generic [37].

This approach of optimizing protocols can be extended to cyclic processes. Specifically, one can ask for the optimal protocol to achieve maximum power for stochastic heat engines [39] or in models for molecular motors, combining mechanical steps with chemical reactions given a finite cycle time. This perspective demonstrates that this optimization problem in stochastic thermodynamics has not only a broad fundamental significance. Its ramifications could ultimately also lead to the construction of “optimal” nano-machines.

### 3 Non-equilibrium steady states

#### 3.1 Characterization

Non-equilibrium does not necessarily require that the system is driven by time-dependent potentials or forces as discussed so far. A non-equilibrium steady state (NESS) is generated if time-independent but non-conservative forces  $f(x)$  act on the system. Such systems are characterized by a time-independent or stationary distribution

$$p^s(x) \equiv \exp[-\phi(x)]. \quad (47)$$

As a fundamental difficulty, there is no simple way to calculate  $p^s(x)$  or, equivalently, the “non-equilibrium potential”  $\phi(x)$ . In one dimension, it follows from quadratures but for more degrees of freedom, setting the right hand side of the Fokker-Plank equation (8) to zero represents a formidable partial differential equation. Physically, the complexity arises from the fact that detailed balance is broken, i.e. non-zero stationary currents arise. In technical terms, broken detailed balance means

$$p(x_2(t')|x_1(t))p^s(x_1) \neq p(x_1(t')|x_2(t))p^s(x_2) \quad (48)$$

where the first factor on both sides represents the conditional probability. In genuine equilibrium, the equal sign holds with  $p^{\text{eq}}(x)$  replacing  $p^s(x)$ . Equivalently, in a genuine NESS, one has a non-zero stationary current (in the full configuration space)

$$j^s(x) = \mu F(x)p^s(x) - D\partial_x p^s(x) \equiv v^s(x)p^s(x) \quad (49)$$

with the mean local velocity

$$v^s(x) = \langle \dot{x} | x \rangle. \quad (50)$$

This local mean velocity  $v_s(x)$  is the average of the stochastic velocity  $\dot{x}$  over the subset of trajectories passing through  $x$ . Since it enters  $j_s(x)$ , it can thus be regarded as a measure of the local violation of detailed balance.

This current leads to a mean entropy production rate (26)

$$\sigma \equiv \langle \Delta s_{\text{tot}} \rangle / t = \int dx \frac{j^s(x)^2}{Dp^s(x)}. \quad (51)$$

Even though the stationary distribution and currents can not be calculated in general, an exact relation concerning entropy production can be derived.

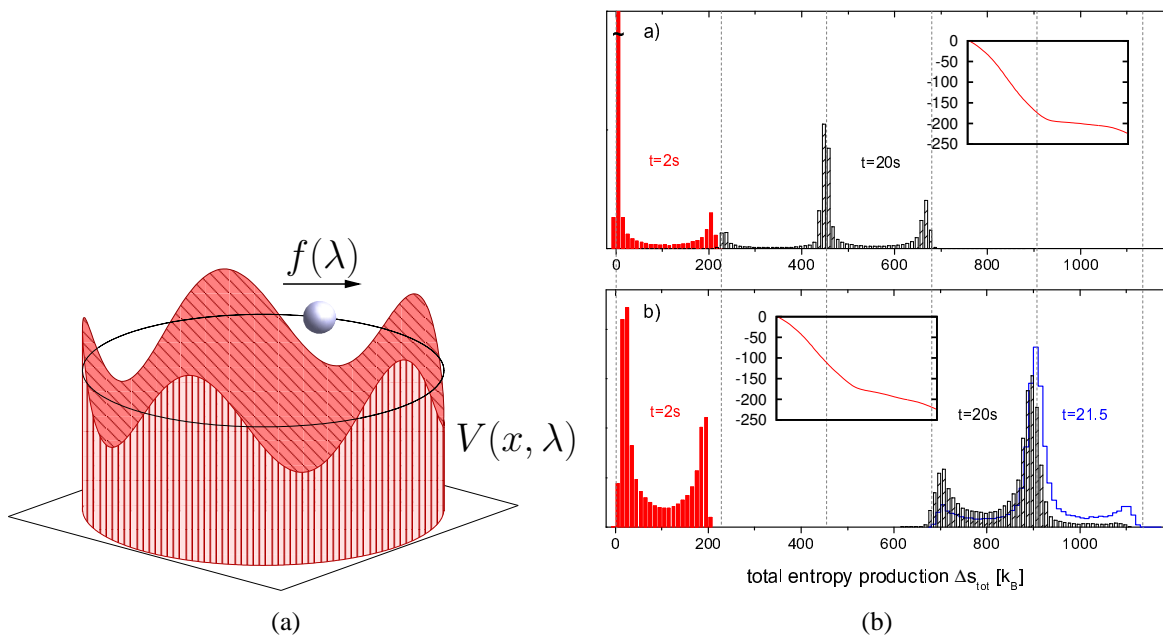
### 3.2 Detailed fluctuation theorem

In a NESS, the (detailed) fluctuation theorem

$$p(-\Delta s_{\text{tot}})/p(\Delta s_{\text{tot}}) = \exp[-\Delta s_{\text{tot}}] \quad (52)$$

expresses a symmetry of the probability distribution  $p(\Delta s_{\text{tot}})$  for the total entropy production accumulated after time  $t$  in the steady state. This relation has first been found in simulations of two-dimensional sheared fluids [4] and then been proven by Gallavotti and Cohen [5] using assumptions about chaotic dynamics. A much simpler proof has later been given by Kurchan [6] and Lebowitz and Spohn [7] using a stochastic dynamics for diffusive motion. Strictly speaking, in all these works the relation holds only asymptotically in the long-time limit since entropy production had been associated with what is called entropy production in the medium here. If one includes the entropy change of the system (30), the DFT holds even for finite times in the steady state [2]. This fact shows again the benefit of the definition of an entropy along a single trajectory.

While the DFT for (medium) entropy production has been tested experimentally for quite a number of systems, see e.g. [40–45], a first test including the system entropy has recently been achieved for a colloidal particle driven by a constant force along a periodic potential, see Fig. 6 [46]. This experimental set-up constitutes the simplest realization of a genuine NESS. The same set-up has been used to test other recent aspects of stochastic thermodynamics like the possibility to infer the potential  $V(x)$  from the measured stationary distribution and current [47] or a generalization of the Einstein relation beyond the linear response regime [48, 49] discussed below.



**Fig. 6:** a) Colloidal particle driven by a non-conservative force  $f(\lambda)$  along a potential  $V(x, \lambda)$  to generate a NESS. b) Corresponding histograms of the total entropy production  $p(\Delta s_{\text{tot}})$  for different lengths of trajectories and two different strengths of the applied force  $f$ . The inserts show the total potential  $V(x) - fx$  in the two cases; adapted from [46].

The DFT for total entropy production holds even under the more general situation of periodic driving  $F(x, \tau) = F(x, \tau + \tau_p)$ , where  $\tau_p$  is the period, if (i) the system has settled into a periodic distribution  $p(x, \tau) = p(x, \tau + \tau_p)$ , and (ii) the trajectory length  $t$  is an integer multiple of  $\tau_p$ . For the distribution of work  $p(W)$ , a similar DFT can be proven provided the protocol is symmetric  $\lambda(\tau) = \lambda(t - \tau)$ , the non-conservative force zero, and the systems starts in equilibrium initially. For such conditions, the DFT for work was recently tested experimentally using a colloidal particle pushed periodically by a laser trap against a repulsive substrate [30], as shown in the insert of Fig. 5 above.

### 3.3 Generalized Einstein relation and generalized fluctuation-dissipation-theorem

In a NESS, the relation between fluctuation, response to an external perturbation and dissipation is more involved than in equilibrium. The main principle can be understood by discussing the well-known Einstein relation. First, for a free particle in a thermal environment, the diffusion constant  $D_0$  and the mobility  $\mu_0$  are related by

$$D_0 = T\mu_0. \quad (53)$$

If this diffusion is modelled by a Langevin equation the strength of the noise becomes also  $D_0$  as introduced in section 2.1. For notational simplicity, we have ignored the subscript “0” in all but the present section of these lecture notes. Second, if the particle is not free but rather diffuses in a potential  $V(x)$ , the diffusion coefficient

$$D \equiv \lim_{t \rightarrow \infty} [\langle x^2(t) \rangle - \langle x(t) \rangle^2] / (2t), \quad (54)$$

and the effective mobility

$$\mu \equiv \frac{\partial \langle \dot{x} \rangle}{\partial f} \quad (55)$$

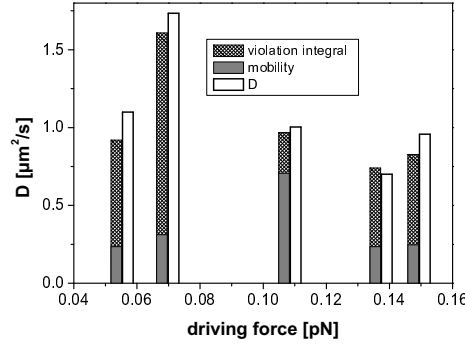
which quantifies the response of the mean velocity  $\langle \dot{x} \rangle$  to a small external force  $f$  still obey  $D = T\mu$  for any potential  $V(x)$ . Note that with this notation  $D < D_0$  for any non-zero potential, since it is more difficult to surmount barriers by thermal excitation. Third, one can ask how the relation between the diffusion coefficient and mobility changes in a genuine NESS as shown in the set-up of Fig. 6a. Both definitions (54) and (55) are then still applicable if in the latter the derivative is taken at non-zero force. Using path-integral techniques, one can derive a generalized Einstein relation of the form [48]

$$D = T\mu + \int_0^\infty d\tau I(\tau), \quad (56)$$

with

$$I(\tau) \equiv \langle [\dot{x}(t + \tau) - \langle \dot{x} \rangle][v_s(x(t)) - \langle \dot{x} \rangle] \rangle. \quad (57)$$

The “violation” function  $I(\tau)$  correlates the *actual* velocity  $\dot{x}(t)$  with the *local* mean velocity  $v_s(x)$  introduced in (50) subtracting from both the *global* mean velocity  $\langle \dot{x} \rangle = \int v_s(x) p^s(x) = 2\pi R j_s$  that is given by the net particle flux  $j_s$  along the ring of radius  $R$ . In one dimension for a steady state, the current must be the same everywhere and hence  $j_s$  is a constant. The offset  $t$  is arbitrary because of time-translational invariance in a steady state. Since in equilibrium detailed



**Fig. 7:** Experimental test of the generalized Einstein relation (56) for different driving forces  $f$ , using the set up shown in Fig. 6. The open bars show the measured diffusion coefficients  $D$ . The stacked bars are mobility  $\mu$  (grey bar) and integrated violation  $I$  (hatched bar); adapted from [46].

balance holds and therefore  $v_s(x) = \langle \dot{x} \rangle = 0$ , the violation (57) vanishes and (56) reduces to the equilibrium relation.

For an experimental test of the non-equilibrium Einstein relation (56), trajectories of a single colloidal particle for different driving forces  $f$  were measured and evaluated [46]. Fig. 7 shows the three terms in (56) for five different values of the driving force in the set-up shown in Fig. 6a. Their sum is in good agreement with the independently measured diffusion coefficient directly obtained from the particles trajectory using (54). For very small driving forces, the bead is close to equilibrium and its motion can be described using linear response theory. As a result, the violation integral is negligible. Experimentally, this regime is difficult to access since  $D$  and  $\mu$  become exponentially small and cannot be measured at reasonable time scales for small forces and potentials as deep as  $40 T$ . For very large driving forces, the relative magnitude of the violation term becomes smaller as well. In this limit, the imposed potential becomes irrelevant and the spatial dependence of the local mean velocity, which is the source of the violation term, vanishes. The fact that the violation term is about four times larger than the mobility proves that this experiment indeed probes the regime beyond linear response. Still, the description of the colloidal motion by a Markovian (memory-less) Brownian motion with drift as implicit in the analysis remains obviously a faithful representation since the theoretical results are derived from such a framework.

For an even broader perspective, it should be noted that this generalized Einstein relation in fact is the time-integrated version of a generalized fluctuation-dissipation-theorem (FDT) of the form [48]

$$T \frac{\partial \langle \dot{x}(t) \rangle}{\partial f(\tau)} = \langle \dot{x}(t) \dot{x}(\tau) \rangle - \langle \dot{x}(t) v_s(x(\tau)) \rangle \quad (58)$$

The left hand side quantifies the response of the mean velocity at time  $t$  to an additional force pulse at the earlier time  $\tau$ . In equilibrium, i.e. more strictly speaking in the linear response regime, this response function is given by the velocity-velocity correlation function which is the first term on the right hand side. In non-equilibrium, i.e. beyond the linear response regime, an additive second term on the right hand side contributes which involves again the crucial mean velocity  $v_s$ . Note that this formulation with an additive correction is quite different from

introducing an effective temperature  $T_{\text{eff}}$  on the left hand side and ignoring this last term. The equilibrium form of the FDT can be restored by referring the velocity to the local mean velocity according to

$$v(t) \equiv \dot{x}(t) - v_s(x(t)) \quad (59)$$

for which the form

$$T \frac{\partial \langle v(t) \rangle}{\partial f(\tau)} = \langle v(t) v(\tau) \rangle \quad (60)$$

holds even in non-equilibrium [48].

Since the generalized FDT (58) and the restoration (60) hold for a coupled interacting system of Langevin equations as well, the perspective of using such relations for an analysis of, e.g., sheared colloidal suspensions arises. The main challenge is to find useful approximation schemes for replacing the phase space variables  $x(\tau)$  and  $v_s(x)$  by real space quantities like correlation functions.

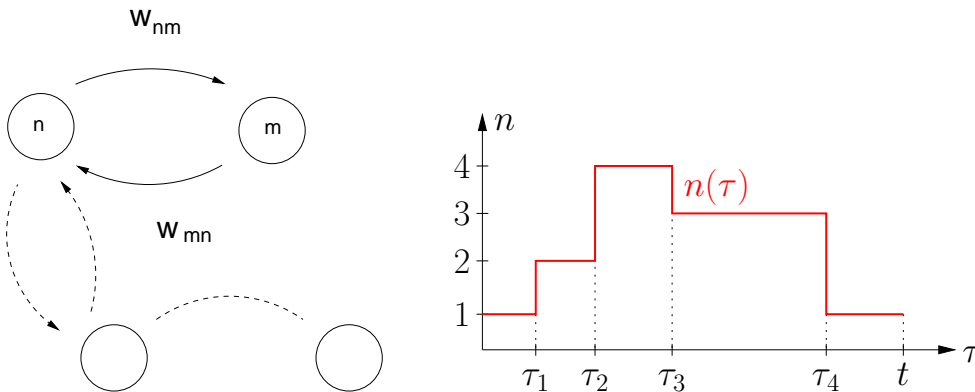
## 4 Stochastic dynamics on a network

### 4.1 Entropy production for a general master equation

For systems driven by mechanical forces described so far, the identification of a first law is simple since both internal energy and applied work are rather clear concepts. On the other hand the proof of both the IFT and the DFT shows that the first law does not crucially enter. In fact, the proof of these theorems exploits only the fact that under time-reversal entropy production changes sign. Hence, similar relations can be derived for a much larger class of stochastic dynamic models without reference to a first law.

We consider stochastic dynamics on an arbitrary set of states  $\{n\}$  where transitions between state  $m$  and  $n$  occur with a rate  $w_{mn}(\lambda)$ , which may depend on an externally controlled time-dependent parameter  $\lambda(\tau)$ , see Fig. 8. The master equation for the time-dependent probability  $p_n(\tau)$  then reads [27]

$$\partial_\tau p_n(\tau) = \sum_{m \neq n} [w_{mn}(\lambda) p_m(\tau) - w_{nm}(\lambda) p_n(\tau)]. \quad (61)$$



**Fig. 8:** Network with states  $\{n, m, \dots\}$  connected by rates  $w_{nm}$  and trajectory  $n(\tau)$  jumping at times  $\tau_j$ .



The analogue of the fluctuating trajectory  $x(\tau)$  in the mechanical case becomes a stochastic trajectory  $n(\tau)$  that starts at  $n_0$  and jumps at times  $\tau_j$  from  $n_j^-$  to  $n_j^+$  ending up at  $n_t$ , see Fig. 8. For any fixed  $\lambda$ , such networks relax into a unique steady state  $p_n^s$ . Two classes of networks must be distinguished depending on whether or not this stationary distribution  $p_n^s$  for fixed  $\lambda$  obeys the detailed balance condition

$$p_n^s(\lambda)w_{nm}(\lambda) = p_m^s(\lambda)w_{mn}(\lambda). \quad (62)$$

If this condition is violated, the network is in a genuine NESS. For large networks, there is no simple way to obtain the stationary distribution  $p_n^s$ . For small networks, a graphical method, recalled in [24] is usually more helpful than solving the set of linear equation resulting from setting the right hand side of (61) to zero.

Systems which obey detailed balance formally resemble mechanically driven systems without non-conservative force since for the latter, at fixed potential, detailed balance holds as well. Exploiting this analogy, one can assign a (dimensionless) internal “energy”

$$\epsilon_n(\lambda) \equiv -\ln p_n^s(\lambda) \quad (63)$$

to each state. The ratio of the rates then obeys

$$\frac{w_{nm}(\lambda)}{w_{mn}(\lambda)} = \exp[\epsilon_n(\lambda) - \epsilon_m(\lambda)] \quad (64)$$

which looks like the familiar detailed balance condition in equilibrium. For time-dependent rates  $w_{nm}(\lambda(\tau))$ , one can now formally associate an analogue of work in the form

$$w \equiv \int_0^t d\tau \dot{\lambda} \partial_\lambda \epsilon_n(\lambda(t)) = \sum_j \ln \frac{w_{n_j^- n_j^+}}{w_{n_j^+ n_j^-}} + \epsilon_{n(t)}(\lambda_t) - \epsilon_{n(0)}(\lambda_0), \quad (65)$$

where the sum is over all jumps along the trajectory. Even though one should not put too much physical meaning into this definition of work for an abstract stochastic dynamics, the analogy helps to see immediately that the fluctuation relations quoted above for zero non-conservative force hold for these more general systems as well [50]. Specifically, one has the “generalized” JR (34) with  $\Delta\mathcal{F} = 0$  and  $T = 1$ . Similarly, with the identification

$$\tilde{w} \equiv \sum_j [\epsilon_{n_{j^+}}(\tau_j) - \epsilon_{n_{j^-}}(\tau_j)] - [\epsilon_{n_{j^+}}(0) - \epsilon_{n_{j^-}}(0)] \quad (66)$$

the analogue of the BKR (36) with  $T = 1$  holds for such a master equation dynamics. The initial state in all cases is the steady state corresponding to  $\lambda_0$ .

For both classes of networks, one can define a stochastic entropy as [2]

$$s(\tau) \equiv -\ln p_{n(\tau)}(\tau) \quad (67)$$

where  $p_{n(\tau)}(\tau)$  is the solution  $p_n(\tau)$  of the master equation (61) for a given initial distribution  $p_n(0)$  taken along the specific trajectory  $n(\tau)$ . As above, this entropy will depend on the chosen initial distribution.

The entropy  $s(\tau)$  becomes time-dependent due to two sources. First, even if the system does not jump,  $p_{n(\tau)}(\tau)$  can be time-dependent either for time-independent rates due to possible

relaxation from a non-stationary initial state or, for time-dependent rates, due to the explicit time-dependence of  $p_n(\tau)$ . Including the jumps, the change of system entropy reads

$$\dot{s}(\tau) = -\frac{\partial_\tau p_n(\tau)(\tau)}{p_n(\tau)(\tau)} - \sum_j \delta(\tau - \tau_j) \ln \frac{p_{n_j^+}}{p_{n_j^-}} \quad (68)$$

$$\equiv \dot{s}_{\text{tot}}(\tau) - \dot{s}_{\text{m}}(\tau). \quad (69)$$

where we define the change in medium entropy to be

$$\dot{s}_{\text{m}}(\tau) \equiv \sum_j \delta(\tau - \tau_j) \ln \frac{w_{n_j^- n_j^+}}{w_{n_j^+ n_j^-}}. \quad (70)$$

For a general system, associating the logarithm of the ratio between forward jump rate and backward jump rate with an entropy change of the medium seems to be an arbitrary definition. Three facts motivate this choice. First, it corresponds precisely to what in Appendix A is identified as exchanged heat in the mechanically driven case. Second, upon averaging one recovers and generalizes results for the non-equilibrium ensemble entropy balance in the steady state [7, 51]. Specifically, for averaging over many trajectories, we need the probability for a jump to occur at  $\tau = \tau_j$  from  $n_j^-$  to  $n_j^+$  which is  $p_{n_j^-}(\tau_j)w_{n_j^- n_j^+}(\tau_j)$ . Hence, one gets

$$\dot{S}_{\text{m}}(\tau) \equiv \langle \dot{s}_{\text{m}}(\tau) \rangle = \sum_{n,k} p_n w_{nk} \ln \frac{w_{nk}}{w_{kn}}, \quad (71)$$

$$\dot{S}_{\text{tot}}(\tau) \equiv \langle \dot{s}_{\text{tot}}(\tau) \rangle = \sum_{n,k} p_n w_{nk} \ln \frac{p_n w_{nk}}{p_k w_{kn}} \quad (72)$$

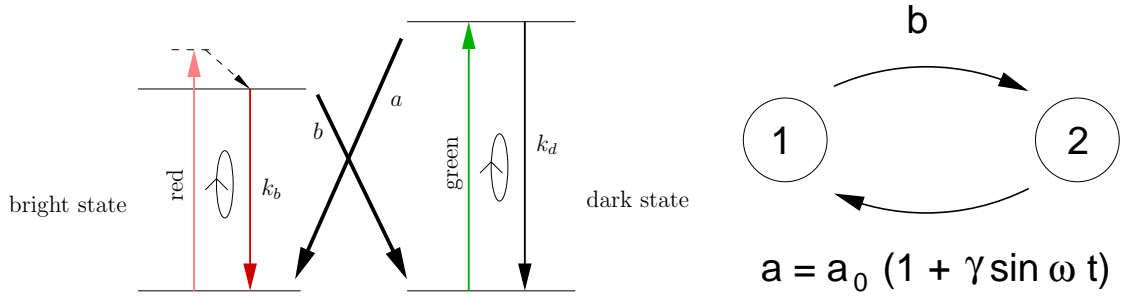
and

$$\dot{S}(\tau) \equiv \langle \dot{s}(\tau) \rangle = \sum_{n,k} p_n w_{nk} \ln \frac{p_n}{p_k} \quad (73)$$

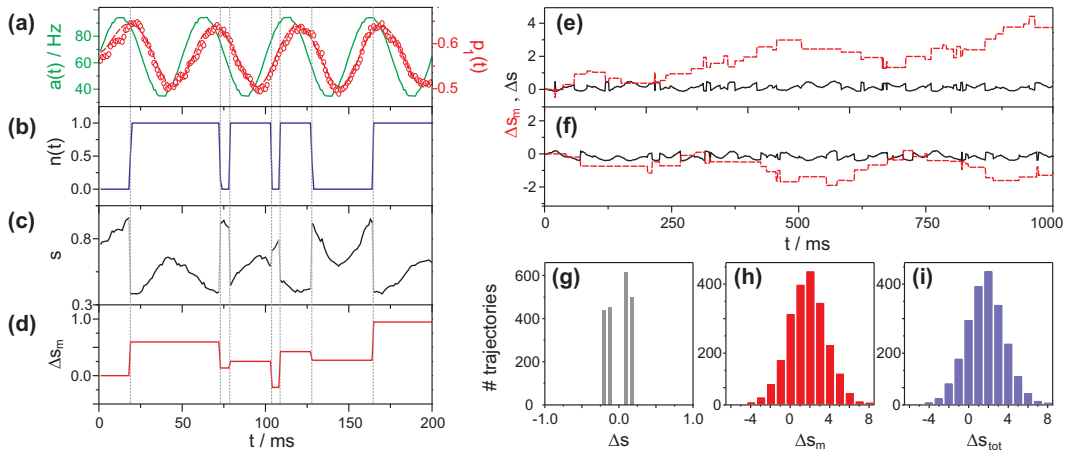
such that the global balance  $\dot{S}_{\text{tot}}(\tau) = \dot{S}_{\text{m}}(\tau) + \dot{S}(\tau)$  with  $\dot{S}_{\text{tot}}(\tau) \geq 0$  is valid. Here, we suppress the  $\tau$ -dependence of  $p_n(\tau)$  and  $w_{nk}(\tau)$ .

Third, following the proof given in Appendix A for the mechanically driven case, one can easily show [2] that with this choice the total entropy production  $\Delta_{S_{\text{tot}}}$  fulfills both the IFT (32) for arbitrary initial condition, arbitrary driving and any length of trajectory. Moreover,  $\Delta_{S_{\text{tot}}}$  obeys the DFT (52) in the steady state, i.e. for constant rates. Of course, in a general system, there is no justification to identify the change in medium entropy with an exchanged heat.

These fluctuation theorems have been illustrated in recent experiments [52, 53], using an optically driven defect center in diamond. For this system, the IFT for total entropy production and the analogue of the Jarzynski relation for such a general stochastic dynamics [50] have been tested, see Fig. 9 and 10 and their captions.

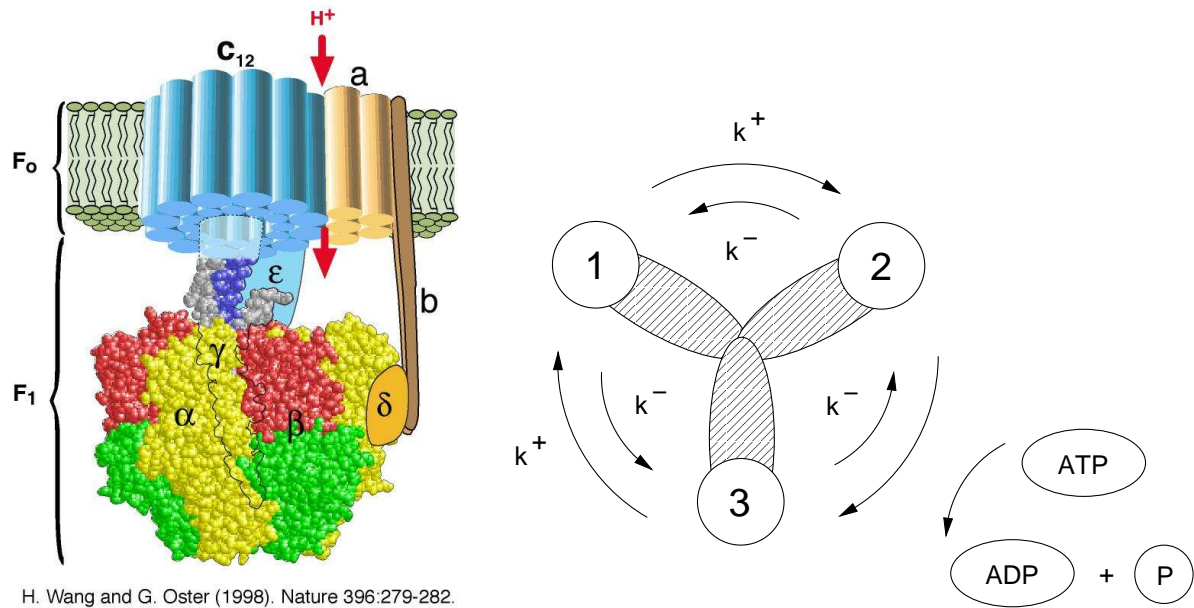


**Fig. 9:** Effective level scheme of a defect center in diamond (left) which corresponds to a two state system with one rate modulated sinusoidally (right). The photochromic defect center can be excited by red light responding with a Stokes-shifted fluorescence. In addition to this bright state the defect exhibits a nonfluorescent dark state. The transition rates  $a$  (from dark to bright) and  $b$  (from bright to dark) depend linearly on the intensity of green and red light, respectively, turning the defect center into an effective two-level system  $0$  (dark)  $\xrightleftharpoons[b]{a}$   $1$  (bright) with controllable transition rates  $a$  and  $b$ . The system can be found in state  $n$  with probability  $p_n$ , where  $n$  takes either the value  $0$  or  $1$ . To drive the system out of equilibrium, the rate  $a$  (from dark to bright) was modulated according to the sinusoidal protocol  $a(t) = a_0[1 + \gamma \sin(2\pi t/t_m)]$ , whereas the rate  $b$  is held constant. The parameters are the equilibrium rates  $a_0$  and  $b$ , the period  $t_m$ , and the modulation depth  $0 \leq \gamma < 1$ , for the data, see Fig. 10; adapted from [52].



**Fig. 10:** Measured entropy production for the single two-level system of Fig. 9 with parameters  $a_0 = (15.6 \text{ ms})^{-1}$ ,  $b = (21.8 \text{ ms})^{-1}$ ,  $t_m = 50 \text{ ms}$ , and  $\gamma = 0.46$ . (a) Transition rate  $a(t)$  [green] and probability of the bright state  $p_1(t)$  [red, circles are measured; line is the theoretical prediction] over 4 periods. (b) Single trajectory  $n(t)$  (c) Evolution of the system entropy. The gray lines correspond to jumps (vertical dotted lines) of the system whereas the dark lines show the continuous evolution due to the driving. (d) Entropy change of the medium, where only jumps contribute. (e), (f) Examples of (e) entropy producing and (f) entropy annihilating trajectories. The change of system entropy  $\Delta s = s(t) - s(0)$  [black] fluctuates around zero without effective entropy production, whereas in (e)  $\Delta s_m$  [red] produces a net entropy over time. In (f)  $\Delta s_m$  consumes an entropy of about 1 after 20 periods. (g), (h), (i) Histograms taken from 2000 trajectories of the system (g), medium (h), and total entropy change (i). The system entropy shows four peaks corresponding to four possibilities for the trajectory to start and end ( $0 \mapsto 1$ ,  $1 \mapsto 0$ ,  $0 \mapsto 0$ , and  $1 \mapsto 1$ ); adapted from [53].

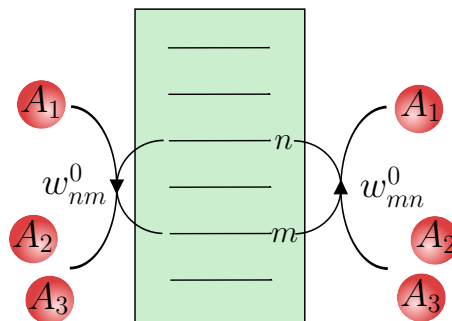
## 4.2 Driven enzyme or protein with internal states



**Fig. 11:** Molecular structure of the  $F_1$ -ATPase and schematic reaction network for the hydrolysis of ATP. The position of the  $\gamma$  subunit relative to the membrane plane advances  $120^\circ$  in each reaction step.

Chemical reaction networks comprise an important class for stochastic dynamics on a discrete set of states. Non-equilibrium conditions arise whenever at least one reaction is not balanced. For a typical example, see Fig. 11, which shows the  $F_1$ -ATPase. Driven by a proton-gradient across the membrane this membrane-bound enzyme usually synthesizes ATP. It can, however, also hydrolyze ATP and perform work against an external load. More generally, any enzyme or molecular motor can be considered as a system which stochastically undergoes transitions from one state  $m$  to another state  $n$ , see Fig. 12.

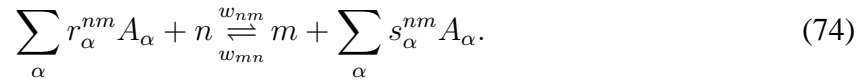
In such a transition, a chemical reaction like hydrolysis may be involved which transforms one molecule ATP to ADP and a phosphate. These three molecular species are externally maintained



**Fig. 12:** Protein or enzyme with internal states. A forward transition (left) from  $n$  to  $m$  involves the chemical reaction  $A_1 + n \rightarrow m + A_2 + A_3$  and similarly for the backward reaction (right). The rates  $w_{nm}^0$  and  $w_{mn}^0$  are the concentration-independent bare rates.

at non-equilibrium conditions thereby providing a source of chemical energy, i.e., chemical work, to the system. In each transition, this work will be transformed into mechanical work, dissipated heat, or changes in the internal energy (with any combination of positive and negative contributions). The formalism of stochastic thermodynamics allows to identify work, heat, and internal energy for each single transition in close analogy to the mechanically driven case [29, 54].

We consider a protein with  $M$  internal states  $\{1, 2, \dots, M\}$ . Each state  $n$  has internal energy  $E_n$ . Transitions between these states involve some other molecules  $A_\alpha$ , where  $\alpha = 1, \dots, N_A$  labels the different chemical species. A transition from state  $n$  to state  $m$  implies the reaction



Here,  $r_{\alpha}^{nm}$ ,  $s_{\alpha}^{nm}$  are the numbers of species  $A_{\alpha}$  involved in this transition. We assume that the chemical potentials, i.e., the concentrations  $c_{\alpha}$  of these molecules are controlled or clamped externally by chemiostats. In principle, this implies that after a reaction event has taken place, the used  $A_{\alpha}$  are “refilled” and the produced ones are “extracted”. This procedure guarantees that the chemiostats undergo no entropy change.

The chemical potential for species  $\alpha$  at concentration  $c_{\alpha}$  quite generally reads

$$\mu_{\alpha} \equiv E_{\alpha} + T \ln c_{\alpha} \omega_{\alpha} \quad (75)$$

which for equilibrium becomes  $\mu_{\alpha}^{\text{eq}} = E_{\alpha} + T \ln c_{\alpha}^{\text{eq}} \omega_{\alpha}$ . Here,  $\omega_{\alpha}$  is a suitable normalization volume chosen such that  $E_{\alpha}$  is the energy of a single  $A_{\alpha}$  molecule. If the  $A_{\alpha}$  molecules were an ideal monoatomic gas, we would have  $\omega_{\alpha} = \lambda_{\alpha}^3 e^{-3/2}$  where  $\lambda_{\alpha}$  is the thermal de Broglie wavelength and the factor  $e^{-3/2}$  compensates for making the kinetic energy  $E_{\alpha} = 3T/2$  explicit. Mass action law kinetics with respect to the  $A_{\alpha}$  molecules is a good approximation if we assume a dilute solution of  $A_{\alpha}$  molecules. The ratio between forward rate  $w_{nm}$  and backward rate  $w_{mn}$  is then given by

$$\frac{w_{nm}}{w_{mn}} = \frac{w_{nm}^0}{w_{mn}^0} \prod_{\alpha} (c_{\alpha} \omega_{\alpha})^{r_{\alpha}^{nm} - s_{\alpha}^{nm}}. \quad (76)$$

Here, we separate the concentration dependence from some “intrinsic” or bare rates  $w_{nm}^0, w_{mn}^0$ . Their ratio can be determined by considering a hypothetical equilibrium condition for this reaction. In fact, if the reaction took place in equilibrium with concentrations  $c_{\alpha}^{\text{eq}}$ , we would have the detailed balance relation

$$\frac{w_{nm}^{\text{eq}}}{w_{mn}^{\text{eq}}} = \frac{w_{nm}^0}{w_{mn}^0} \prod_{\alpha} (c_{\alpha}^{\text{eq}})^{r_{\alpha}^{nm} - s_{\alpha}^{nm}} \omega_{\alpha} = \frac{p_m^{\text{eq}}}{p_n^{\text{eq}}} = \exp(-\Delta G/T), \quad (77)$$

where

$$\Delta G \equiv -[E_n - E_m + \sum_{\alpha} (r_{\alpha}^{nm} - s_{\alpha}^{nm}) \mu_{\alpha}^{\text{eq}}] \quad (78)$$

is the equilibrium free energy difference for this reaction and  $p_{m,n}^{\text{eq}}$  are the equilibrium probabilities of states  $m$  and  $n$ , respectively. Combining (75)—(78) shows that the ratio of the intrinsic rates

$$\frac{w_{nm}^0}{w_{mn}^0} = \exp \left[ \left( E_n - E_m + \sum_{\alpha} (r_{\alpha}^{nm} - s_{\alpha}^{nm}) E_{\alpha} \right) / T \right] \quad (79)$$

involves only the energy-terms and is independent of concentrations. The ratio (76) under non-equilibrium conditions then becomes

$$\ln \frac{w_{nm}}{w_{mn}} = [E_n - E_m + \sum_{\alpha} (r_{\alpha}^{nm} - s_{\alpha}^{nm}) \mu_{\alpha}] / T \equiv (-\Delta E + w_{\text{chem}}^{nm}) / T. \quad (80)$$

The right hand side corresponds to the difference between applied chemical work

$$w_{\text{chem}}^{nm} = \sum_{\alpha} (r_{\alpha}^{nm} - s_{\alpha}^{nm}) \mu_{\alpha} \quad (81)$$

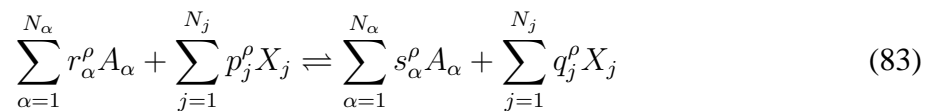
(since every transformed  $A_{\alpha}$  molecule gives rise to a chemical work  $\mu_{\alpha}$ ) and the difference in internal energy  $\Delta E$ . For the first law to hold for this transition, we then have to identify the left hand side of (80) with the heat delivered to the medium, i.e. with the change in entropy of the medium

$$\ln \frac{w_{nm}}{w_{mn}} = \Delta S_m^{nm}. \quad (82)$$

This identification of heat dissipated in one reaction step as the logarithm of the ratio between forward rate and backward rate corresponds precisely to the definition (70) introduced for general dynamics on a network thus proving the consistency of this approach.

### 4.3 Chemical reaction network

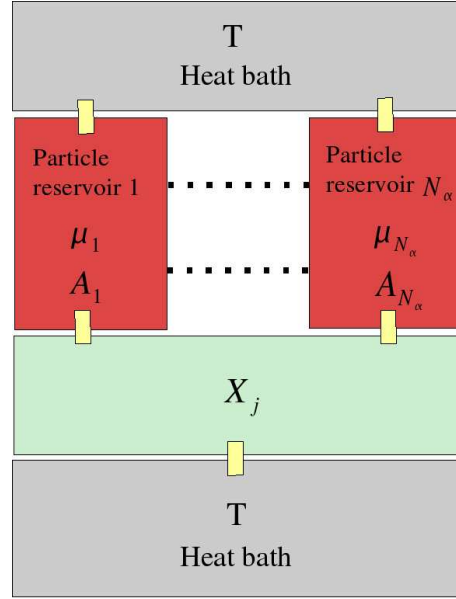
Finally, such a scheme can be extended to an arbitrary chemical reaction network which consists of  $N_j$  reactions of the type



with  $1 \leq \rho \leq N_{\rho}$  labeling the single (reversible) reactions. We distinguish two types of reacting species. The  $X_j$  molecules ( $j = 1, \dots, N_j$ ) are those species whose numbers  $\mathbf{n} = (n_1, \dots, n_{N_j})$  can, in principle, be measured along a chain of reaction events. In practice, these numbers should be small. The  $A_{\alpha}$  molecules ( $\alpha = 1, \dots, N_{\alpha}$ ) correspond to those species whose overall concentrations  $c_{\alpha}$  are controlled externally by a chemostat due to a (generally) time dependent protocol  $c_{\alpha}(\tau)$ . In principle, this implies that after a reaction event has taken place, the used  $A_{\alpha}$  are “refilled” and the produced ones are “extracted”. As above, these chemostats have chemical potential

$$\mu_{\alpha} = E_{\alpha} + T \ln (c_{\alpha} \omega_{\alpha}) \quad (84)$$

where  $T$  is the temperature of the heat bath to which both type of particles are coupled, see Fig. 13.



**Fig. 13:** Coupling of the system with species  $X_j$ ,  $j = (1, \dots, N_j)$  to the  $N_\alpha$  particle reservoirs for species  $A_\alpha$  at chemical potential  $\mu_\alpha$  and to a heat bath at constant temperature  $T$ .

We assume that the reacting species have no internal degrees of freedom. However, internal degrees of freedom as the ones introduced for a single enzyme could easily be treated within this approach by labeling different internal states as different species and defining “reactions” (transitions) between them.

The stoichiometric coefficients  $r_\alpha^\rho$ ,  $p_j^\rho$ ,  $s_\alpha^\rho$  and  $q_j^\rho$  enter the stoichiometric matrix  $\mathbf{V}$  with entries

$$v_j^\rho \equiv q_j^\rho - p_j^\rho \quad (85)$$

and the stoichiometric matrix of the reservoir species  $\mathbf{U}$  with entries

$$u_\alpha^\rho \equiv s_\alpha^\rho - r_\alpha^\rho. \quad (86)$$

For the externally controlled concentrations  $c_\alpha$  of  $A_\alpha$ , we use the vector notation  $\mathbf{c} = (c_1, \dots, c_{N_\alpha})$ . We assume a dilute solution of reacting species in a solvent (heat bath) and therefore the transition probabilities per unit time for the  $N_\rho$  reactions (83) take the text book form [26, 27]

$$w_+^\rho(\mathbf{n}, \mathbf{c}) = \Omega k_+^\rho \prod_\alpha (c_\alpha \omega_\alpha)^{r_\alpha^\rho} \prod_j \frac{n_j!}{(n_j - p_j^\rho)! (\Omega/\omega_j)^{p_j^\rho}} \quad (87)$$

$$w_-^\rho(\mathbf{n}, \mathbf{c}) = \Omega k_-^\rho \prod_\alpha (c_\alpha \omega_\alpha)^{s_\alpha^\rho} \prod_j \frac{n_j!}{(n_j - q_j^\rho)! (\Omega/\omega_j)^{q_j^\rho}} \quad (88)$$

where  $+$  denotes a forward reaction,  $-$  denotes a backward reaction and  $\Omega$  is the reaction volume. The bare rates  $k_{+,-}^\rho$  are the transition probabilities per unit time per unit volume per unit concentration (in terms of  $1/\omega_\alpha$  and  $1/\omega_j$ , respectively) of every educt reactant. Note that while  $w_{+,-}^\rho(\mathbf{n}, \mathbf{c})$ , in principle, can be measured experimentally, the bare rates  $k_{+,-}^\rho$  depend on the normalizing volumes  $\omega_\alpha$  and  $\omega_j$  whose unique definition requires a microscopic Hamiltonian [55].

The transition probabilities depend only on the current state and therefore define a Markov process with the master equation

$$\begin{aligned} \partial_\tau p(\mathbf{n}, \tau) &= \sum_{\rho} [w_+^{\rho}(\mathbf{n} - \mathbf{v}^{\rho}, \mathbf{c}) \cdot p(\mathbf{n} - \mathbf{v}^{\rho}, \tau) + w_-^{\rho}(\mathbf{n} + \mathbf{v}^{\rho}, \mathbf{c}) \cdot p(\mathbf{n} + \mathbf{v}^{\rho}, \tau)] \\ &\quad - \sum_{\rho} [w_+^{\rho}(\mathbf{n}, \mathbf{c}) \cdot p(\mathbf{n}, \tau) + w_-^{\rho}(\mathbf{n}, \mathbf{c}) \cdot p(\mathbf{n}, \tau)] \end{aligned} \quad (89)$$

governing the time evolution of the probability distribution  $p(\mathbf{n}, \tau)$  to have  $n_j$  molecules  $X_j$  at time  $\tau$ . Here, we have used the vector notation  $\mathbf{v}^{\rho} = (v_1^{\rho}, \dots, v_{N_j}^{\rho})$  for the entries of the stoichiometric matrix.

The stochastic dynamics of the networks has thus been uniquely defined. For fixed concentrations  $c_{\alpha}$ , this network acquires a stationary state which may or may not obey detailed balance, i.e. may or may not correspond to genuine equilibrium. The first law, entropy change of both the medium, i.e. the heat bath, and the network can consistently be defined and various fluctuation theorems be proven as detailed in [55]. So far, no experiments illustrating these concepts using measured data are available.

The notion ‘‘stochastic thermodynamics’’ had been introduced two decades ago for an interpretation of such chemical reaction networks in terms of thermodynamic notions on the ensemble level [56]. From the present perspective, it seems even more appropriate to use this term for the refined description along the fluctuating trajectory for any stochastic dynamics. As we have seen, both for mechanically and chemically driven systems in a surrounding heat bath, the thermodynamic concepts can literally and consistently be applied on this level. As a generalization to arbitrary stochastic dynamics, analogues of work, heat and internal energy obey similar exact relations which ultimately all arise from the behaviour of the dynamics under time-reversal. How much closer such an approach can lead us towards a systematic understanding of non-equilibrium phenomena in general is a question posed too early to be answered yet.



## Appendix

### A Path integral representation

We first derive the path integral representation of the Langevin dynamics. We start with the Langevin equation (4) in the form

$$\dot{x}(\tau) = \mu F(x(\tau), \lambda(\tau)) + \zeta(\tau) \quad (90)$$

and discretize time  $t \equiv i\epsilon$  ( $i = 0, \dots, N$ ). Writing  $x_i \equiv x(i\epsilon)$  and  $\lambda_i \equiv \lambda(i\epsilon)$ , we get

$$\frac{x_i - x_{i-1}}{\epsilon} = \frac{\mu}{2} [F_i(x_i) + F_{i-1}(x_{i-1})] + \zeta_i \quad (91)$$

with  $F_i(x_i) \equiv F(x_i, \lambda_i)$  using the mid-point (or Stratonovich) rule. In such a discrete time description, the stochastic noise obeys

$$\langle \zeta_i \rangle = 0 \quad \text{and} \quad \langle \zeta_i \zeta_j \rangle = 2(D/\epsilon)\delta_{ij} \quad (92)$$

These correlations follow from the weight

$$p(\zeta_1, \dots, \zeta_N) = \left(\frac{\epsilon}{4\pi D}\right)^{N/2} \exp\left[-\frac{\epsilon}{4D} \sum_i \zeta_i^2\right] \quad (93)$$

For the transition from  $p(\zeta_1, \dots, \zeta_N)$  to  $p(x_1, \dots, x_N|x_0)$  we have

$$p(x_1, \dots, x_N|x_0) = \det\left(\frac{\partial \zeta_i}{\partial x_j}\right) p(\zeta_1, \dots, \zeta_N) \quad (94)$$

with the Jacobi matrix

$$\frac{\partial \zeta_i}{\partial x_j} = \begin{pmatrix} \frac{1}{\epsilon} - \frac{\mu}{2} F'_1(x_1) & 0 & \dots & \dots \\ -\frac{1}{\epsilon} - \frac{\mu}{2} F'_1(x_2) & \frac{1}{\epsilon} - \frac{\mu}{2} F'_2(x_2) & 0 & \dots \\ \dots & \dots & \dots & \dots \end{pmatrix}. \quad (95)$$

The Jacobi determinant becomes

$$\begin{aligned} \det\left(\frac{\partial \zeta_i}{\partial x_j}\right) &= \left(\frac{1}{\epsilon}\right)^N \prod_{i=1}^N \left(1 - \frac{\epsilon\mu}{2} F'_i(x_i)\right) \\ &= \left(\frac{1}{\epsilon}\right)^N \exp\left[\sum_{i=1}^N \ln(1 - \epsilon\mu F'_i(x_i)/2)\right] \\ &\approx \left(\frac{1}{\epsilon}\right)^N \exp\left[-\sum_{i=1}^N \epsilon\mu F'_i(x_i)/2\right]. \end{aligned} \quad (96)$$

The weight for a discretized trajectory thus becomes

$$p(x_1, \dots, x_N|x_0) = \frac{1}{(4\pi D\epsilon)^{N/2}} \exp\left[-\frac{1}{4D\epsilon} \left[\sum_{i=1}^N (x_i - x_{i-1} - \epsilon\mu F_i(x_i))^2\right] - \frac{\epsilon\mu}{2} \sum_{i=1}^N F'_i(x_i)\right]. \quad (97)$$

In the continuum limit ( $\epsilon \rightarrow 0$ ,  $N \rightarrow \infty$ ,  $N\epsilon = t$  fixed) this expression becomes up to normalization

$$\begin{aligned} p[x(\tau)|x_0] &\equiv \exp\left[-\frac{1}{4D} \int_0^t [\dot{x} - \mu F(x(\tau), \lambda(\tau))]^2 d\tau - \frac{\mu}{2} \int_0^t F'(x(\tau), \lambda(\tau)) d\tau\right] \\ &\equiv \exp[-\mathcal{A}[x(\tau)]] \end{aligned} \quad (98)$$

with the ‘‘action’’

$$\mathcal{A}[x(\tau)] \equiv \frac{1}{D} \int_0^t d\tau L(x(\tau), \dot{x}(\tau); \lambda(\tau)) \quad (99)$$

and the ‘‘Lagrange function’’

$$L(x, \dot{x}, \lambda(\tau)) \equiv \frac{1}{4}(\dot{x} - \mu F)^2 + \frac{\mu D}{2} F'. \quad (100)$$

We include the normalization into the definition of the path-integral measure writing

$$\int_{x_0} d[x(\tau)] \equiv \lim_{\epsilon \rightarrow 0, N \rightarrow \infty, \epsilon N = t} \left(\frac{1}{4\pi D\epsilon}\right)^{N/2} \prod_{i=1}^N \int_{-\infty}^{+\infty} dx_i \quad (101)$$

for integration over all paths starting at  $x_0$ . Thus, we have

$$\int_{x_0} d[x(\tau)] p[x(\tau)|x_0] = 1 \quad (102)$$

and, including a normalized probability distribution  $p_0(x_0)$  for the initial point

$$\int d[x(\tau)] p[x(\tau)|x_0] p_0(x_0) = 1. \quad (103)$$

## B Proof of the integral fluctuation theorem

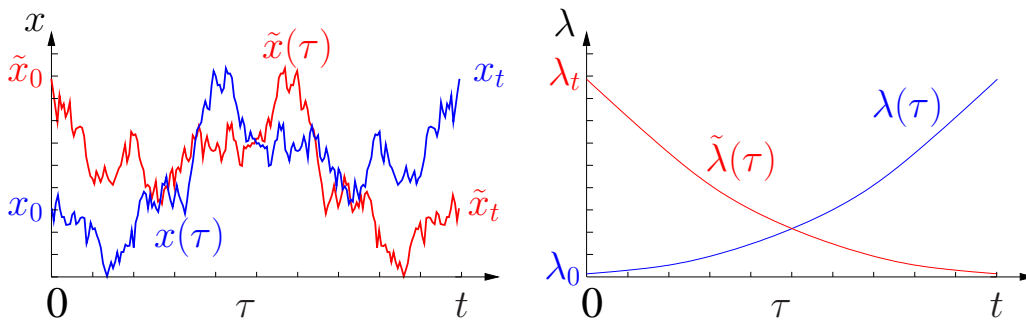
For the proof of the fluctuation theorem the crucial concept is the notion of the reversed protocol

$$\tilde{\lambda}(\tau) \equiv \lambda(t - \tau) \quad (104)$$

and the reversed trajectory

$$\tilde{x}(\tau) \equiv x(t - \tau), \quad (105)$$

see Fig. 14.



**Fig. 14:** Forward trajectory  $x(\tau)$  under the forward protocol  $\lambda(\tau)$  and reversed trajectory  $\tilde{x}(\tau) \equiv x(t - \tau)$  and reversed protocol  $\tilde{\lambda}(\tau) \equiv \lambda(t - \tau)$ .

The weight for the reversed path under the reversed protocol is given by

$$p[\tilde{x}(\tau)|\tilde{x}_0] = \exp[-\tilde{\mathcal{A}}[\tilde{x}(\tau)]] \quad (106)$$

with

$$\tilde{\mathcal{A}}[\tilde{x}(\tau)] = \mathcal{A}[x(\tau)] + \frac{1}{T} \int_0^t d\tau \dot{x}(\tau) F(x(\tau), \lambda(\tau)) \quad (107)$$

from which one obtains the relation

$$\frac{p[x(\tau)|x_0]}{p[\tilde{x}(\tau)|\tilde{x}_0]} = \exp[q[x(\tau)]/T] = \exp \Delta s_m. \quad (108)$$

Thus, the more heat, i.e. entropy in the medium, is generated in the forward process, the less likely is the reverse process to happen. In this sense, entropy generation in the medium is associated with broken time reversal symmetry.

The proof of the integral fluctuation theorem follows with a few lines: The normalization condition for the backward paths reads

$$1 = \int d[\tilde{x}(\tau)] p[\tilde{x}(\tau)|\tilde{x}_0] p_1(\tilde{x}_0), \quad (109)$$

where  $p_1(\tilde{x}_0)$  is an arbitrary normalized function of  $\tilde{x}_0$ . We introduce the given initial distribution of the forward process  $p_0(x_0)$  and the weight  $p[x(\tau)|x_0]$  of the forward process leading to

$$1 = \int d[\tilde{x}(\tau)] \frac{p[\tilde{x}(\tau)|\tilde{x}_0] p_1(\tilde{x}_0)}{p[x(\tau)|x_0] p_0(x_0)} p[x(\tau)|x_0] p_0(x_0) \quad (110)$$

The sum over all backward paths  $\int d[\tilde{x}(\tau)]$  can be replaced with a sum over all forward paths  $\int d[x(\tau)]$ . With relation (108) one then has

$$1 = \int d[x(\tau)] \left( \exp[-\Delta s_m] \frac{p_1(x_t)}{p_0(x_0)} \right) p[x(\tau)|x_0] p_0(x_0) \quad (111)$$

where we have used  $\tilde{x}_0 = x_t$ . Since this path integral is the non-equilibrium average  $\langle \dots \rangle$ , we get the integral fluctuation theorem (32) quoted in the main part. The proof of the detailed fluctuation theorem for a stationary or periodic state follows from quite similar reasoning [2, 10, 17].

## References

- [1] K. Sekimoto, *Prog. Theor. Phys. Supp.* **130**, 17 (1998).
- [2] U. Seifert, *Phys. Rev. Lett.* **95**, 040602 (2005).
- [3] J. Liphardt, S. Dumont, S. B. Smith, I. Tinoco Jr, and C. Bustamante, *Science* **296**, 1832 (2002).
- [4] D. J. Evans, E. G. D. Cohen, and G. P. Morriss, *Phys. Rev. Lett.* **71**, 2401 (1993).
- [5] G. Gallavotti and E. G. D. Cohen, *Phys. Rev. Lett.* **74**, 2694 (1995).
- [6] J. Kurchan, *J. Phys. A: Math. Gen.* **31**, 3719 (1998).
- [7] J. L. Lebowitz and H. Spohn, *J. Stat. Phys.* **95**, 333 (1999).
- [8] C. Jarzynski, *Phys. Rev. Lett.* **78**, 2690 (1997).
- [9] C. Jarzynski, *Phys. Rev. E* **56**, 5018 (1997).
- [10] G. E. Crooks, *Phys. Rev. E* **60**, 2721 (1999).
- [11] G. E. Crooks, *Phys. Rev. E* **61**, 2361 (2000).
- [12] U. Seifert, arXiv:0710.1187, *Eur. Phys. J. B*, in press (2008).
- [13] D. J. Evans and D. J. Searles, *Adv. Phys.* **51**, 1529 (2002).
- [14] R. D. Astumian and P. Hänggi, *Physics Today* **55(11)**, 33 (2002).
- [15] J. Vollmer, *Phys. Rep.* **372**, 131 (2002).
- [16] J. M. R. Parrondo and B. J. D. Cisneros, *Applied Physics A* **75**, 179 (2002).
- [17] C. Maes, *Sém. Poincaré* **2**, 29 (2003).
- [18] D. Andrieux and P. Gaspard, *J. Chem. Phys.* **121**, 6167 (2004).
- [19] C. Bustamante, J. Liphardt, and F. Ritort, *Physics Today* **58(7)**, 43 (2005).
- [20] F. Ritort, *J. Phys.: Condens. Matter* **18**, R531 (2006).
- [21] H. Qian, *J. Phys. Chem. B* **110**, 15063 (2006).
- [22] A. Imparato and L. Peliti, *C. R. Physique* **8**, 556 (2007).
- [23] R. J. Harris and G. M. Schütz, *J. Stat. Mech.: Theor. Exp.* P07020 (2007).
- [24] R. K. P. Zia and B. Schmittmann, *J. Stat. Mech.: Theor. Exp.* P07012 (2007).
- [25] R. Kawai, J. M. R. Parrondo, and C. V. den Broeck, *Phys. Rev. Lett.* **98**, 080602 (2007).
- [26] C. W. Gardiner, *Handbook of Stochastic Methods*, 3rd ed. (Springer-Verlag, Berlin, 2004).

- [27] N. G. van Kampen, *Stochastic processes in physics and chemistry* (North-Holland, Amsterdam, 1981).
- [28] H. Risken, *The Fokker-Planck Equation*, 2nd ed. (Springer-Verlag, Berlin, 1989).
- [29] T. Schmiedl, T. Speck, and U. Seifert, *J. Stat. Phys.* **128**, 77 (2007).
- [30] V. Blickle, T. Speck, L. Helden, U. Seifert, and C. Bechinger, *Phys. Rev. Lett.* **96**, 070603 (2006).
- [31] T. Speck and U. Seifert, *Phys. Rev. E* **70**, 066112 (2004).
- [32] H. Qian, *Phys. Rev. E* **64**, 022101 (2001).
- [33] G. Hummer and A. Szabo, *Proc. Natl. Acad. Sci. U.S.A.* **98**, 3658 (2001).
- [34] G. N. Bochkov and Y. E. Kuzovlev, *Physica A* **106**, 443 (1981).
- [35] G. N. Bochkov and Y. E. Kuzovlev, *Physica A* **106**, 480 (1981).
- [36] C. Jarzynski, *C. R. Physique* **8**, 495 (2007).
- [37] T. Schmiedl and U. Seifert, *Phys. Rev. Lett.* **98**, 108301 (2007).
- [38] M. de Koning, *J. Chem. Phys.* **122**, 104106 (2005).
- [39] T. Schmiedl and U. Seifert, *EPL* **81**, 20003 (2008).
- [40] S. Ciliberto and C. Laroche, *J. Phys. IV France* **8 (P6)**, 215 (1998).
- [41] W. I. Goldberg, Y. Y. Goldschmidt, and H. Kellay, *Phys. Rev. Lett.* **87**, 245502 (2001).
- [42] K. Feitosa and N. Menon, *Phys. Rev. Lett.* **92**, 164301 (2004).
- [43] S. Ciliberto, N. Garnier, S. Hernandez, C. Lacpatia, J.-F. Pinton, and G. R. Chavarria, *Physica A* **340**, 240 (2004).
- [44] G. M. Wang, J. C. Reid, D. M. Carberry, D. R. M. Williams, E. M. Sevick, and D. J. Evans, *Phys. Rev. E* **71**, 046142 (2005).
- [45] D. Andrieux, P. Gaspard, S. Ciliberto, N. Garnier, S. Joubaud, and A. Petrosyan, *Phys. Rev. Lett.* **98**, 150601 (2007).
- [46] T. Speck, V. Blickle, C. Bechinger, and U. Seifert, *EPL* **79**, 30002 (2007).
- [47] V. Blickle, T. Speck, U. Seifert, and C. Bechinger, *Phys. Rev. E* **75**, 060101 (2007).
- [48] T. Speck and U. Seifert, *Europhys. Lett.* **74**, 391 (2006).
- [49] V. Blickle, T. Speck, C. Lutz, U. Seifert, and C. Bechinger, *Phys. Rev. Lett.* **98**, 210601 (2007).
- [50] U. Seifert, *J. Phys. A: Math. Gen.* **37**, L517 (2004).
- [51] J. Schnakenberg, *Rev. Mod. Phys.* **48**, 571 (1976).

- 
- [52] S. Schuler, T. Speck, C. Tietz, J. Wrachtrup, and U. Seifert, *Phys. Rev. Lett.* **94**, 180602 (2005).
- [53] C. Tietz, S. Schuler, T. Speck, U. Seifert, and J. Wrachtrup, *Phys. Rev. Lett.* **97**, 050602 (2006).
- [54] U. Seifert, *Europhys. Lett.* **70**, 36 (2005).
- [55] T. Schmiedl and U. Seifert, *J. Chem. Phys.* **126**, 044101 (2007).
- [56] C. Y. Mou, J.-L. Luo, and G. Nicolis, *J. Chem. Phys.* **84**, 7011 (1986).