



# On the stochastic thermodynamics of reactive systems

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## HIGHLIGHTS

- We develop a framework for the stochastic thermodynamics of reactive systems.
- We derive constraints acting on the transition probabilities of reactive events.
- The constraints make the stochastic picture coherent with classical thermodynamics.
- They affect the properties of stochastic fluxes, forces and entropy production.
- We show how they can be used to derive various types of fluctuation theorems.

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## ABSTRACT

We develop a theoretical framework for the stochastic thermodynamics of reactive systems. We show that the transition probabilities per unit time of reactive events must satisfy specific constraints, in order for stochastic approaches to lead to physically meaningful results in the macroscopic limit. We discuss how these constraints affect the properties of stochastic fluxes and forces, and entropy production. We also see how they can be used to derive various expressions of fluctuation theorems.

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## 1. Introduction

The recent years have witnessed important advances in the development of non-equilibrium thermodynamics. Stochastic thermodynamics proved to be an especially fruitful and powerful way to assess the properties of small systems, since they naturally include the effect of fluctuations of energy, mass, etc. Stochastic analogues of the laws of thermodynamics have been put forward [1–6], and new relations describing the properties of fluctuating thermodynamic variables, known as fluctuation theorems, have been proposed [2,5,7–13].

Despite such impressive developments, the author's opinion is that stochastic thermodynamics has not reached full maturity yet. The plethora of high-quality contributions has led to a multitude of approaches using different conventions and definitions, which can make the interpretation and comparison of the various works difficult. This difficulty arises in particular for the connection between the stochastic approach and its traditional, macroscopic counterpart. As an example, (free) energy is sometimes introduced as a stochastic variable [2,5,6] or alternatively as the logarithm of the probability distribution [3,4]. Furthermore, in most applications to reactive systems, chemical reactions are considered to modify the internal energy of the system [2,5], while according to macroscopic thermodynamics this is not the case as long as the properties of the particles that are responsible for the interaction with external fields are conserved [14]. Examples

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include reactions in a gravitational field (because of the conservation of mass), and in electrical fields (since the charge is conserved). There are also several coexisting definitions of entropy, as stochastic thermodynamics is often treated in terms of the Shannon (informational) entropy, which is different from the thermodynamic (Gibbs) entropy. As a consequence, one can find oneself confronted with different expressions for the exchange of entropy with the environment, depending on the definition used. As a last example, we note that in some stochastic approaches the mechanical work is considered to contribute to the entropy flow [6], which is not the case in traditional thermodynamics. These examples show the apparently contradictory conclusions that can be drawn from stochastic descriptions, and illustrate the need to rationalize the different approaches and to build a coherent theoretical framework.

The goal of this work is to propose a self-consistent stochastic thermodynamics, in such a way that all the principles of macroscopic, non-equilibrium thermodynamics are respected in the appropriate limit. We use for this a theoretical framework based on the master equation. For the sake of illustration, we will consider the case of open, spatially uniform reactive systems. The corresponding macroscopic description is first outlined in Section 2. Section 3 is devoted to a general presentation of the problem. The master equation is introduced and the different stochastic thermodynamic quantities are defined. The main results are presented in Section 4. We discuss how compatibility with the laws of thermodynamics puts constraints on the transition probabilities of the different processes, including the reactions. In Section 5, we illustrate these results on a simple chemical reaction and show how they can help to clarify the ambiguities mentioned above. In Section 6, we analyze how these constraints affect the properties of fluxes, forces and entropy production. We also discuss there how they contribute to the different types of fluctuation theorems. We finally conclude and point towards possible future developments.

## 2. Thermodynamics of open reactive systems

We start by a short presentation of the traditional macroscopic thermodynamics of open reactive systems. We consider the case of a spatially uniform system with no bulk velocity, in contact with an environment at a temperature  $T$  and a pressure  $p$ . Here, we define the system as being a given region of space being delimited by boundaries with well-defined properties, which allows defining its volume unambiguously. The only force acting on the system is the uniform pressure exerted by the environment on its boundaries, in other words we consider systems that are not subjected to external forces acting on its bulk properties. These choices are here justified because we want to focus on the contributions of chemical reactions to the different thermodynamic quantities, which appears to be at the source of most of the contradictory statements found in the literature. The thermodynamic state of such a system is supposed to be entirely defined by a set of macroscopic variables. Here we choose to work with the internal energy  $E$ , the volume  $V$ , and the number of molecules of each of the  $c$  chemical species  $\mathbf{N} = \{N_\gamma\} = (N_1, N_2 \dots N_c)$ .

The first principle of thermodynamics postulates that the total energy of a system can vary only because of exchanges with the environment. Since under the above assumptions the internal energy  $E$  is itself equal to the total energy, it changes according to

$$\frac{dE}{dt} = \frac{d_e E}{dt} + \frac{d_i E}{dt} = \frac{d\Phi}{dt} - p \frac{dV}{dt}; \quad \frac{d_i E}{dt} = 0, \quad (1)$$

where  $d\Phi/dt$  is a combination of energy transferred as heat, and energy transferred with mass. It is often referred to as the generalized heat [15]. The term  $-p dV/dt$  accounts for the energy exchanged in the form of mechanical work. In the above equations, the subscripts  $e$  and  $i$  represent, respectively, contributions due to exchanges with the environment and contributions related to internal processes.

In the presence of chemical reactions, the number of moles of each species can vary either because matter is being exchanged with the environment, or because of the reactions themselves:

$$\frac{dN_\gamma}{dt} = \frac{d_e N_\gamma}{dt} + \frac{d_i N_\gamma}{dt}. \quad (2)$$

Note that the internal changes are connected to the advancement  $\xi_\rho$  of each elementary reaction  $\rho$

$$\sum_{\gamma=1}^c \vec{v}_{\gamma\rho} M_\gamma = \sum_{\gamma=1}^c \overleftarrow{v}_{\gamma\rho} M_\gamma, \quad (3)$$

by

$$\frac{d_i N_\gamma}{dt} = \sum_{\rho=1}^r v_{\gamma\rho} \frac{d\xi_\rho}{dt} \equiv \sum_{\rho=1}^r v_{\gamma\rho} J_\rho, \quad (4)$$

in which

$$v_{\gamma\rho} = \overleftarrow{v}_{\gamma\rho} - \overrightarrow{v}_{\gamma\rho} \quad (5)$$

is the stoichiometric coefficient of the species  $M_\gamma$  in the corresponding reaction and where  $d\xi_\rho = dN_\gamma/v_{\gamma\rho}$ .

The second principle states that the entropy of the system evolves according to

$$\frac{dS}{dt} = \frac{d_e S}{dt} + \frac{d_i S}{dt}; \quad \frac{d_i S}{dt} \geq 0. \quad (6)$$

Entropy can increase or decrease, but the contribution of internal processes to its evolution can only be positive. A connection with the other thermodynamic variables can be obtained by considering the Gibbs formula

$$\frac{dS}{dt} = \frac{1}{T} \frac{dE}{dt} + \frac{p}{T} \frac{dV}{dt} - \sum_{\gamma=1}^c \frac{\mu_\gamma}{T} \frac{dN_\gamma}{dt}, \quad (7)$$

where one introduces the chemical potential of each species,  $\mu_\gamma = -T \left( \partial S / \partial N_\gamma \right)_{E,V,N_{\gamma' \neq \gamma}}$ . Combining (7), (1) and (2) leads to

$$\frac{dS}{dt} = \frac{1}{T} \frac{d\Phi}{dt} - \sum_{\gamma=1}^c \frac{\mu_\gamma}{T} \frac{d_e N_\gamma}{dt} - \sum_{\gamma=1}^c \frac{\mu_\gamma}{T} \frac{d_i N_\gamma}{dt}. \quad (8)$$

Remember that our main focus is here on the contribution of chemical reactions to the thermodynamic potentials. In the following we will hence restrict ourselves to the case of systems for which the temperature, the pressure and the chemical potentials are at all times very close to those of the environment. Such systems can be thought of as being in a state of thermal, mechanical and diffusional equilibrium. The flow of entropy is then given by

$$\frac{d_e S}{dt} = \frac{1}{T} \frac{d\Phi}{dt} - \sum_{\gamma=1}^c \frac{\mu_\gamma}{T} \frac{d_e N_\gamma}{dt}. \quad (9)$$

Note that it is proportional to the heat flux, since one can show that  $d\Phi/dt = dQ/dt + \sum_{\gamma=1}^c \mu_\gamma d_e N_\gamma/dt$ . The entropy production reads

$$\frac{d_i S}{dt} = - \sum_{\gamma=1}^c \frac{\mu_\gamma}{T} \frac{d_i N_\gamma}{dt} = \sum_{\rho=1}^r J_\rho \frac{\mathcal{A}_\rho}{T}. \quad (10)$$

In the last equation, the affinity of reaction  $\mathcal{A}_\rho = - \sum_{\gamma=1}^c \nu_{\gamma\rho} \mu_\gamma$  has been introduced. Because of our assumptions, only chemical reactions contribute to the production of entropy. In other situations, the flows of energy and mass also lead to entropy production terms [14]. Viscous terms can also be found when the hypothesis of zero bulk velocity is relaxed.

Combining the above equations, one can easily obtain the differential of the enthalpy  $H = E - P V$ , the free energy  $F = E - T S$ , the free enthalpy  $G = H - T S$ , etc. As discussed already long ago, all these equations are supposed to hold out of equilibrium, whenever the system can be considered to be in a state of *local* equilibrium. From a microscopic point of view, this assumption means that the degrees of freedom that are disregarded in the theory (the positions and velocities of particles, and the molecular degrees of freedom) are expected to follow an equilibrium distribution. We will now discuss how these ideas connect with a stochastic description.

### 3. Stochastic approach

The philosophy behind the stochastic approach is intuitively appealing, but retains a somewhat heuristic character. The main idea is that, instead of trying to solve the full probabilistic problem given by the Liouville (or von Neumann) equation in phase space, one considers that the natural variables of thermodynamics can be used but must be seen as stochastic processes. In the framework we use, this would mean that the internal energy, the volume and the number of particles fluctuate over time. Consequently, one can associate to the corresponding stochastic processes a probability  $P(X, t)$ , where  $X = (\tilde{E}_X, \tilde{V}_X, \tilde{N}_{1,X}, \tilde{N}_{2,X}, \dots, \tilde{N}_{c,X}) = (\tilde{E}_X, \tilde{V}_X, \tilde{N}_X)$  represents a set of possible values for these processes. We will often refer to such a set as an *instantaneous configuration*.

Additional assumptions need to be made to reach a tractable evolution equation for the above probability. We will adopt the usual hypothesis that the stochastic processes are Markovian. The probability then obeys the master equation

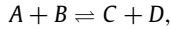
$$\frac{d}{dt} P(X, T) = \sum_{X' \neq X} [W(X | X') P(X', t) - W(X' | X) P(X, t)], \quad (11)$$

in which the  $W$ s stand for the transition probabilities per unit time. The validity of the Markovian hypothesis rests on the idea that there exists a clearcut separation of time scales between the dynamics of the macroscopic observables and that of the comparatively much faster (microscopic) degrees of freedom that are not included in the stochastic processes. This separation of time scales has the consequence that the microscopic degrees of freedom follow an equilibrium distribution all along the stochastic trajectories, i.e. that they are in a state of local equilibrium. The properties of the transition probabilities introduced in this way must reflect the physicochemical properties of the processes taking place in the system. They will be discussed in more detail in the next section. For now, we will simply state the hypothesis that they can be split into two groups:

- The probabilities to have transitions thanks to a coupling of the system with its environment, which we will call  $W_e(X | X')$ , and
- The probabilities related to internal processes, denoted  $W_i(X | X')$ . These processes, by definition, leave the environment unchanged.

With this choice, the master equation can be decomposed into an “exchange” and “internal” parts  $dP(X, T)/dt = \mathcal{L}_e + \mathcal{L}_i$ .

The distinction that we just made between exchange and internal processes is actually the same as what is done in classical thermodynamics. Exchange processes would include for example (i) the transfer of mass between the system and a reservoir of matter, (ii) the transfer of heat through the walls of the system in contact with a thermostat, or (iii) the exchange of energy in the form of work because of a change in the volume of the system, driven by a difference of pressure across the walls. Internal processes would essentially be chemical reactions for the type of systems we are considering here. In most situations, we should expect a system to be subject to different exchange and internal processes simultaneously. Consider for example a chemical reaction of the type



where the concentrations of  $A$  and  $D$  would be maintained constant to keep the system out of equilibrium. On top of the (internal) reactive event itself, mass exchange processes are also present to ensure the constancy of the concentrations. One would have to include then transfer processes such as

$$A_e \rightleftharpoons A \tag{12}$$

$$D_e \rightleftharpoons D, \tag{13}$$

where  $A_e$  and  $D_e$  would be the same species in the environment, which would play the role of a chemostat.

In order to connect the above stochastic description with the traditional, macroscopic approach, a clear connection must be established between the values the stochastic processes take and the thermodynamic variables. We will adopt here the idea that *the macroscopic observables correspond to the ensemble average of the fluctuating processes*. This choice ensures that the stochastic description coincides with equilibrium statistical mechanics in the absence of non-equilibrium constraints.<sup>1</sup> We thus define the thermodynamic number of particles, internal energy and volume as

$$N_\gamma \equiv \langle \tilde{N}_{\gamma, X} \rangle (t) = \sum_X \tilde{N}_{\gamma, X} P(X, t) \tag{14}$$

$$E \equiv \langle \tilde{E}_X \rangle (t) = \sum_X \tilde{E}_X P(X, t) \tag{15}$$

$$V \equiv \langle \tilde{V}_X \rangle (t) = \sum_X \tilde{V}_X P(X, t). \tag{16}$$

Similarly, the entropy can be defined as

$$S \equiv \sum_X \tilde{S}_X P(X, t) - k_B \sum_X P(X, t) \ln P(X, t), \tag{17}$$

in which  $k_B$  is Boltzmann’s constant. In this definition,  $\tilde{S}_X$  represents the entropy of the microscopic degrees of freedom for a given set  $(\tilde{E}_X, \tilde{V}_X, \tilde{N}_X)$ . The second term is the Shannon (or informational) entropy. Note that, because of the assumption of local equilibrium,  $\tilde{S}_X$  takes the same form as it does at the “true” equilibrium state, and it is thus related to the degeneracy of the system,  $g(X)$ , by

$$\tilde{S}_X = k_B \ln g(X), \tag{18}$$

as discussed earlier [2,5].

Now that we have defined all the thermodynamic quantities of interest, we turn to the stochastic expression for the laws of thermodynamics.

#### 4. The stochastic laws of thermodynamics

The above expressions for the thermodynamic observables, together with the master equation, lead to evolution laws that bear strong similarities with the laws of thermodynamics. We will first discuss the balance equation for the internal energy.

<sup>1</sup> Another approach would consist in considering that the observables correspond to the maximum of the probability distribution at a given time. These two points of view are equivalent for monomodal distributions whose maximum coincides with the means, but differ for highly asymmetric distributions or for multimodal probability distributions. In a sense, one could say that the predictions of the framework we use should apply to measures obtained from the averaging of a large amount of experiments. The other framework would be more relevant when doing predictions on the single trajectories of large systems. In any case, the latter choice leads as a rule to evolution equations that are much more difficult to handle than those generated by the averaging procedure.

#### 4.1. Energy balance and the first principle

Combining (15) and (11), one gets

$$\begin{aligned}\frac{dE}{dt} &= \sum_{X,X'} [\tilde{E}_X - \tilde{E}_{X'}] W_e(X | X') P(X', t) + \sum_{X,X'} [\tilde{E}_X - \tilde{E}_{X'}] W_i(X | X') P(X', t) \\ &= \frac{d_e E}{dt} + \frac{d_i E}{dt}.\end{aligned}\quad (19)$$

For this equation to be equivalent to the first principle of thermodynamics, the following statement should apply:

1. *The stochastic processes representing internal transitions leave the total energy of a system unchanged.*

In the framework we chose to work with, such internal processes are nothing but the chemical reactions.

The idea that chemical reactions leave the internal energy of a system unchanged is a well established property in classical thermodynamics [14,15] (remember that we ignore here the cases where the molecular properties responsible for the interaction with external fields of force are not conserved by the reactions). This view is fully consistent with the fact that, at a microscopic level, reactive events can be seen as inelastic collisions, which conserve the total energy and the total momentum but do not conserve the kinetic energy. Reactions thus simply induce a redistribution of the total energy between its potential and kinetic contributions. It is that change in the kinetic energy of the particles that leads to the exothermic or endothermic character of chemical reactions.

It is relevant to compare this constraint with what has been proposed previously for the stochastic thermodynamics of reactive systems. The property mentioned above might indeed at first appear to be in contradiction with the framework proposed by Seifert et al. [2,5,11], in which under similar constraints (no external force) each chemical reaction is inducing a change in the internal energy of the system. This contradiction is, however, only apparent. In their works, these authors consider chemical reactions in dilute solutions. They define the system as the collection of reacting molecules, with the solvent playing the role of a heat bath. In this approach, the energy released or absorbed by the reacting molecules is instantaneously transmitted to the solvent, so that the total energy of the system made of the solutes *and* the solvent remains unchanged. Note also that the approach developed in Refs. [2,5,11] is consistent, generally speaking, with the above mentioned classical result of reactive non-equilibrium thermodynamics: The system defined in this way is embedded in a force field generated by the molecules of the solvent. The molecular properties that are responsible for the interaction with this field (such as the dipole moment of the solutes) are not especially conserved during the reaction, and so one can expect the energy of the system defined in this way to vary. The two frameworks are thus equivalent, but focus on different aspects of reactive stochastic thermodynamics through their choices for the definitions of the system and of the environment. In the author's opinion, though, the main advantage of the framework proposed here is that it can be applied equally to dilute and concentrated solutions, to gas phase reactions with no solvent or to solid systems, for example.

We now go further in the comparison between the macroscopic and stochastic expressions of the first principle. The stochastic energy exchange consists in a single contribution while the first law of thermodynamics makes a clear difference between energy exchanged as work, and energy exchanged as (generalized) heat. The two approaches can be shown to be equivalent, though. A stochastic expression for the work can be deduced from the master equation. Indeed, one has

$$\begin{aligned}\frac{dV}{dt} &= \sum_{X,X'} [\tilde{V}_X - \tilde{V}_{X'}] W_e(X | X') P(X', t) + \sum_{X,X'} [\tilde{V}_X - \tilde{V}_{X'}] W_i(X | X') P(X', t) \\ &= \frac{d_e V}{dt} + \frac{d_i V}{dt}.\end{aligned}\quad (20)$$

Since by definition internal transitions are processes that leave the environment unchanged,<sup>2</sup>  $d_i V(t)/dt = 0$  and one can conclude that

2. *The stochastic processes representing internal transitions leave the volume of a system unchanged.*

Consequently, the stochastic work reads

$$-p \frac{dV}{dt} = - \sum_{X,X'} p [\tilde{V}_X - \tilde{V}_{X'}] W_e(X | X') P(X', t).\quad (21)$$

Thanks to this definition, one also finds the evolution ruling the temporal evolution of the stochastic generalized heat

$$\frac{d\Phi}{dt} = \sum_{X,X'} \left[ (\tilde{E}_X + p \tilde{V}_X) - (\tilde{E}_{X'} + p \tilde{V}_{X'}) \right] W_e(X | X') P(X', t).\quad (22)$$

<sup>2</sup> We disregard here the specific (and unrealistic) case where the externally applied pressure would be exactly zero.

Note that it can be seen as a flow of enthalpy,  $H \equiv \langle \tilde{H}_X \rangle (t) = \sum_X (\tilde{E}_X + p \tilde{V}_X) P(X, t)$ . This conclusion is in accordance with the macroscopic approach, since at constant pressure  $d\Phi/dt = dH/dt$  [15].

In view of the situation we consider here, the above statement concerning the variations of volume means that chemical reactions leave the volume of a system unchanged. This assertion might sound surprising at first glance. It is indeed a simple matter of observation that chemical reactions can make a system contract, or expand. However, from a microscopic point of view, reactions consist in the redistribution of atoms, electrons, ions, etc. between two particles. The idea that a local event like the transfer of, say, an electron from one molecule to another could lead to the macroscopic displacement of the wall of a reactor makes very little physical sense. We should thus not expect the transition probabilities per unit time of reactive events to modify the volume for the kind of situation we address here. But as mentioned above, reactions result in a redistribution of the total energy such that kinetic energy is not conserved. Consequently, they induce a change of the pressure exerted by the particles of the system on its boundaries, which can lead to the expansion or the contraction of the reactor. In the framework we propose here, the pressure-related event we just mentioned would be an exchange process, because it implies a transfer of energy in the form of work. In Section 5, we illustrate this point with a simple example. Before we do this, though, we will first turn to the expression for the evolution of entropy.

#### 4.2. Entropy and the second principle

The evolution equation for the entropy takes the form

$$\begin{aligned} \frac{dS}{dt} = & \sum_{X, X'} \left[ \tilde{S}_X - \tilde{S}_{X'} - k_B \ln \frac{P(X, t)}{P(X', t)} \right] W_e(X | X') P(X', t) \\ & + \sum_{X, X'} \left[ \tilde{S}_X - \tilde{S}_{X'} - k_B \ln \frac{P(X, t)}{P(X', t)} \right] W_i(X | X') P(X', t). \end{aligned} \quad (23)$$

It is illustrative to consider separately the terms coming from exchanges with the environment, and the terms related to internal processes.

##### Contribution of the exchange terms

The first contribution can be rewritten as

$$\sum_{X, X'} \left[ \tilde{S}_X - \tilde{S}_{X'} + k_B \ln \frac{W_e(X' | X)}{W_e(X | X')} + k_B \ln \frac{W_e(X | X') P(X', t)}{W_e(X' | X) P(X, t)} \right] W_e(X | X') P(X', t). \quad (24)$$

In order to reach a more transparent expression, and inspired by Ref. [6], we make use of the detailed balance assumption. The idea behind this assumption is that

##### 3. The environment remains at equilibrium all along the transformations of the system.

Consequently, the ratio of the transition probabilities standing for the coupling with the environment is the same as it is at equilibrium:

$$\frac{W_e(X' | X)}{W_e(X | X')} = \frac{P(X', eq)}{P(X, eq)}, \quad (25)$$

where  $P(X, eq)$  stands for the equilibrium distribution of an open system in contact with a reservoir at constant temperature, pressure and chemical potentials [16]:

$$P(X, eq) = \frac{\exp \left[ \frac{\tilde{S}_X}{k_B} - \frac{\tilde{E}_X}{k_B T} + \sum_{\gamma} \frac{\mu_{\gamma}}{k_B T} \tilde{N}_{\gamma, X} - \frac{p \tilde{V}_X}{k_B T} \right]}{\Gamma}, \quad (26)$$

where

$$\Gamma \equiv \sum_{X'} \exp \left[ \frac{\tilde{S}_{X'}}{k_B} - \frac{\tilde{E}_{X'}}{k_B T} + \sum_{\gamma} \frac{\mu_{\gamma}}{k_B T} \tilde{N}_{\gamma, X'} - \frac{p \tilde{V}_{X'}}{k_B T} \right] \quad (27)$$

is the corresponding partition function.

Using the above expression for the equilibrium distribution, one finds that

$$k_B \ln \frac{W_e(X' | X)}{W_e(X | X')} = \frac{[\tilde{E}_X - \tilde{E}_{X'}]}{T} + \frac{p}{T} [\tilde{V}_X - \tilde{V}_{X'}] - [\tilde{S}_X - \tilde{S}_{X'}] - \sum_{\gamma=1}^c \frac{\mu_{\gamma}}{T} [\tilde{N}_{\gamma, X} - \tilde{N}_{\gamma, X'}]. \quad (28)$$

The contribution to entropy due to exchange terms thus reads

$$\frac{1}{T} \frac{d\Phi}{dt} - \sum_{\gamma=1}^c \frac{\mu_{\gamma}}{T} \frac{d_e N_{\gamma}}{dt} + \left( \frac{d_i S}{dt} \right)_I \quad (29)$$

where we introduced

$$\begin{aligned} \frac{dN_{\gamma}}{dt} &= \sum_{X, X'} [\tilde{N}_{\gamma, X} - \tilde{N}_{\gamma, X'}] W_e(X | X') P(X', t) + \sum_{X, X'} [\tilde{N}_{\gamma, X} - \tilde{N}_{\gamma, X'}] W_i(X | X') P(X', t) \\ &= \frac{d_e N_{\gamma}}{dt} + \frac{d_i N_{\gamma}}{dt} \end{aligned} \quad (30)$$

and

$$\left( \frac{d_i S}{dt} \right)_I = k_B \sum_{X, X'} \ln \frac{W_e(X | X') P(X', t)}{W_e(X' | X) P(X, t)} W_e(X | X') P(X', t) \geq 0. \quad (31)$$

This term is representative of the dissipation due to the exchange processes and would be zero for transformation at mechanical, thermal and diffusional equilibrium as considered in Section 2, because the corresponding changes can then be considered as quasi-static transformations [6]. We can now turn to the contribution of the internal processes.

### Internal processes

The internal processes contribute to the change of entropy with terms that are similar to those encountered above

$$\sum_{X, X'} \left[ \tilde{S}_{X'} - \tilde{S}_X + k_B \ln \frac{W_i(X' | X)}{W_i(X | X')} + k_B \ln \frac{W_i(X | X') P(X', t)}{W_i(X' | X) P(X, t)} \right] W_i(X | X') P(X', t). \quad (32)$$

However, one cannot use the assumption of detailed local equilibrium including the environment, like before. Indeed, the internal transitions cannot be related to an environment being itself at equilibrium. The transition probabilities per unit time corresponding to internal transitions are not arbitrary, though. An important constraint acting on them can be deduced, as explained below.

One recognizes in the above equation the classical stochastic expression for an entropy production,

$$\left( \frac{d_i S}{dt} \right)_{II} = k_B \sum_{X, X'} \ln \frac{W_i(X | X') P(X', t)}{W_i(X' | X) P(X, t)} W_i(X | X') P(X', t) \geq 0. \quad (33)$$

In principle, the remaining terms would stand for an exchange of entropy with the environment. Their presence would mean that systems in which the internal processes are the only ones taking place, would present a non-vanishing entropic flow. This conclusion has no physical meaning whatsoever in view of the very definition of exchange and internal processes. As a consequence,

#### 4. Internal stochastic processes cannot contribute to the flow of entropy.

This statement translates into

$$\frac{W_i(X' | X)}{W_i(X | X')} = \exp \frac{\tilde{S}_{X'} - \tilde{S}_X}{k_B} = g(X') - g(X). \quad (34)$$

This relation shows that the difference of degeneracy between the final and initial states acts as a driving force for chemical reactions. It should be noted that this constraint is not new: It has been used before to establish constraints on the transition probabilities of reactive events (see for example Ref. [17]), and a very similar relation has been shown to hold in the framework put forth by Seifert et al. [18] for mass-action kinetics. The above result shows that these conclusions can be generalized to any type of rate equations. Interestingly, the ratio takes a form that looks very much like a local detailed balance involving a “purely entropic” reservoir with constant energy, volume and number of particles [19]. In that sense, one could say that the reacting molecules are in contact with an entropic reservoir that finds its origins in the microscopic degrees of freedom, which always remain in a state of equilibrium and with which the mesoscopic degrees of freedom can exchange entropy.

### Evolution equation for the entropy

Summarizing all the contributions, one gets for the entropy a *stochastic Gibbs equation*

$$\frac{dS}{dt} = \frac{1}{T} \frac{d\Phi}{dt} - \sum_{\gamma=1}^c \frac{\mu_{\gamma}}{T} \frac{d_e N_{\gamma}(t)}{dt} + \frac{d_i S}{dt}, \quad (35)$$

in which the entropy production term contains two contributions: one from the processes ensuring the exchanges with the environment, and one from the internal processes. Thanks to the self-consistent definitions we used, work does not enter



the entropy flow. It is remarkable that the evolution equation for the entropy has exactly the same structure as the one found in the macroscopic limit under the local equilibrium assumption. This does not mean, however, that the thermodynamic and the stochastic quantities coincide whatever the conditions. The fluctuations affect the dynamics of the system and we expect this influence to be stronger for small systems or for systems with strong nonlinearities, in particular in the vicinity of bifurcation points. But the connection between the stochastic thermodynamic quantities remains the same, in any case.

It is instructive to compare this result with that of the approaches used in Refs. [6,13], which are also based on the local balance assumption. The theory developed in these works is to some extent more general in the sense that it includes time-varying constraints. There is however a major difference in the way the volume is introduced in the present framework and in these approaches. We consider  $V$  as a stochastic variable, while it is implicitly included in the form of an external driving force in Refs. [6,13]. More precisely, the balance equation for the energy in these works takes the form

$$\frac{dE}{dt} = \sum_{X,X'} [\tilde{E}_X - \tilde{E}_{X'}] W_e(X | X') P(X', t) + \frac{d\lambda}{dt} \frac{\partial E}{\partial \lambda}, \quad (36)$$

an equation in which  $\lambda$  stands for the externally driven parameter(s). The connection with heat  $Q$  and work  $W$  has been established to be

$$\frac{dQ}{dt} = \sum_{X,X'} [\tilde{E}_X - \tilde{E}_{X'}] W_e(X | X') P(X', t) \quad (37)$$

$$\frac{dW}{dt} = \frac{d\lambda}{dt} \frac{\partial E}{\partial \lambda}. \quad (38)$$

Note that we consider here the case of closed system, since our focus is on the role played by the volume. The second law is given in the above references by

$$\begin{aligned} \frac{dS}{dt} &= \frac{1}{T} \frac{dQ}{dt} + \frac{d\lambda}{dt} \frac{\partial S}{\partial \lambda} + \frac{d_i S}{dt} \\ &= \frac{1}{T} \frac{dE}{dt} + \frac{d\lambda}{dt} \left[ \frac{\partial S}{\partial \lambda} - \frac{1}{T} \frac{\partial E}{\partial \lambda} \right] + \frac{d_i S}{dt} \end{aligned} \quad (39)$$

with the entropy production term having the same form as in the present work. A comparison between (36) and the traditional form of the first law (1) suggests that when pressure is the only external force,  $\lambda = V$ . The equations (36)–(39) thus lead to correct expressions for the first principle and for the Gibbs equation in the macroscopic limit, but only if  $\partial_V S = 0$  and  $\partial_V E = -p$ . Unfortunately, the conditions under which such equalities would hold are not really discussed in these works. It is for example simply stated in Ref. [6] that it is “often the case”. A possible explanation is that, in order for  $\partial_V E = -p$  in the macroscopic limit, one has to consider a quasi-static transformation at constant entropy and number of moles, since then  $(\partial_V E)_{S,N} = -p$ . In such conditions, the derivative of the entropy would indeed be zero. Alternatively, Ref. [13] considers the case of non-degenerate systems, for which the derivative of  $S$  with respect to  $\lambda$  is identically null. The latter level of description cannot be applied straightforwardly to the case of reactive systems. Indeed, in the case of non-degenerate systems, the entropy of the system is identified with the Shannon entropy  $S_{Sh} = -k_B \sum_X P(X, t) \ln P(X, t)$ . With this definition, a flow of entropy out of isolated systems becomes inevitable when chemical processes are included since the constraint acting on them cannot be enforced. It is thus not an appropriate choice when it comes to using stochastic approaches for the thermodynamic properties of reactive systems.

We will now illustrate some of the main results we obtained with the help of a simple reactive system.

## 5. A simple example

We consider here a simple instance of chemical reaction, to illustrate some of the major features of the stochastic thermodynamic approach that we propose. Let  $A$  be an atomic species of mass  $m$  in an ideal gas phase, which can form the corresponding dimer:



For simplicity we assume that  $A$  can be described as a hard sphere and  $A_2$  as a harmonic oscillator and a rigid rotator, but the inclusion of additional internal degrees of freedom is straightforward. We start by discussing our conclusion that chemical reactions must leave the energy unchanged.

### 5.1. Internal processes do not affect the energy of a system

As discussed in Section 4, the separation of the processes into internal and exchange contributions led us to the conclusions that the internal transitions, including chemical reactions, must leave the energy of a system unaltered. This proposition might seem to be in contradiction with the fact that chemical reactions can be exothermic or endothermic.



To show that it is in fact not the case, consider the above reaction taking place in an isolated system. In such case, the kinetics reads in the macroscopic limit

$$\frac{dN_{A_2}}{dt} = \frac{k_1(T_s)}{V} N_A^2 - k_{-1}(T_s) N_{A_2} = -\frac{1}{2} \frac{dN_A}{dt} \quad (41)$$

or, equivalently in terms of the concentrations  $c_A = N_A/V$  and  $c_{A_2} = N_{A_2}/V$ ,

$$\frac{dc_{A_2}}{dt} = k_1(T_s) c_A^2 - k_{-1}(T_s) c_{A_2} = -\frac{1}{2} \frac{dc_A}{dt} \quad (42)$$

in which the kinetic rate constants depend on the temperature of the system,  $T_s$ . The instantaneous internal energy of the system is given by Ref. [2]

$$\tilde{E} = \sum_{\gamma} E_{\gamma} \tilde{N}_{\gamma}, \quad (43)$$

along any stochastic trajectory. In this equation,  $E_{\gamma}$  is the energy of a single molecule of the species  $\gamma$  as defined by a microscopic Hamiltonian. In whole generality, one could expect each chemical event to induce a change of the internal energy:

$$\delta E_1 = E_{A_2} - 2 E_A = -\delta E_{-1}. \quad (44)$$

However, one has for the mean energy in the macroscopic limit

$$\frac{dE}{dt} = E_A \frac{dN_A}{dt} + E_{A_2} \frac{dN_{A_2}}{dt} = \delta E_1 \frac{dN_{A_2}}{dt}. \quad (45)$$

This equation is supposed to hold whatever the boundary conditions, since  $\delta E_1$  is defined through purely microscopic quantities and the rate of reaction can take a priori any value. Obviously, the need to respect the first law in an isolated system imposes that  $\delta E_1 = 0$ , and that it should be so for closed or open reactors as well. This result corresponds to the statement we made in the previous section.

As briefly discussed above, this conclusion might seem to contradict the fact that a chemical reaction can be exothermic or endothermic. Thermodynamics tells us that in a system at constant volume (like here), the exo- or endothermicity refers to the sign of the isochoric heat of reaction  $u_{T,V} = (\partial E / \partial \xi)_{T,V}$ . It corresponds to the heat released or absorbed, or equivalently to the change of internal energy if the reaction were taking place *in a closed system at constant volume and temperature*. Since we are under the local equilibrium hypothesis, one can define in the example we are analyzing a time-dependent temperature of the system  $T_s$  through

$$E = \frac{3}{2} N_A k_B T_s + \frac{7}{2} N_{A_2} k_B T_s. \quad (46)$$

Consequently, the heat of reaction is equal to  $1/2 k_B T_s$ , in other words the reaction is endothermic. This is due to the fact that part of the kinetic energy contained in the monoatomic species  $A$  can be converted into potential energy in  $A_2$  (rotation, vibration). This endothermicity appears, for an isolated system, in the form of a decrease of the temperature. Since in such cases  $dE/dt = 0$ , the derivative of Eq. (46) gives

$$\left[ \frac{3}{2} N_A k_B + \frac{7}{2} N_{A_2} k_B \right] \frac{dT_s}{dt} = C_V \frac{dT_s}{dt} = -\frac{1}{2} k_B T_s \frac{dN_{A_2}}{dt} = -u_{T,V} \frac{dN_{A_2}}{dt}, \quad (47)$$

which is nothing but the evolution law for the temperature predicted by macroscopic, non-equilibrium thermodynamics. This equation shows that the temperature of the system will change as a function of time, although its internal energy remains constant.

These considerations can easily be extended to the case of closed or open systems. As was shown in Ref. [17], adding jumps in the energy through contact with an environment leads in the appropriate limit to the addition of a Newton cooling law in Eq. (47). The constraint that we propose on the internal energy thus means that it is the difference of temperature between a system and its environment that drives the release of heat, not an “internal production” of energy that would be released immediately.

## 5.2. Internal processes leave the volume of a system unchanged

With the separation that we propose comes the idea that internal processes leave the volume of a system unchanged. In a way that is similar to the case of exo- and endothermicity, this statement seems to contradict the observation that reactions can in fact affect the volume of a reactor. As mentioned before, thanks to the local hypothesis assumption, one can define an internal temperature directly in terms of the internal energy and the number of particles. Knowing the volume of the

reactor, one can define in a similar fashion a thermodynamic pressure inside the system. For the example considered here, one would have in the macroscopic limit

$$p_s = \frac{(N_A + N_{A_2}) k_B T_s}{V}. \quad (48)$$

Generally speaking, the evolution equation for this quantity will depend on the form of the transition probabilities for both internal and exchange processes. It will thus depend on the mechanism of transfer of energy between the particles in the system and the boundaries and is highly system-specific.

As our goal here is to show that the above mentioned contradiction is only apparent, we consider instead the case of reaction (40) taking place in a closed reactor at thermal and mechanical equilibrium with its environment, in such a way that  $T_s = T$  and  $p_s = p$  are constant. The time derivative of (48) then leads to a direct coupling between the temporal evolution of the mean number of moles and of the mean volume, since

$$\frac{dp_s}{dt} = \frac{k_B T_s}{V} \left[ \frac{d(N_A + N_{A_2})}{dt} - \frac{N_A + N_{A_2}}{V} \frac{dV}{dt} \right] = 0, \quad (49)$$

which leads to

$$\frac{dV}{dt} = -\frac{V}{N_A + N_{A_2}} \frac{dN_{A_2}}{dt} = -\left( \frac{k_B T_s}{p_s} \right) \frac{dN_{A_2}}{dt}. \quad (50)$$

The latter equation is nothing but the macroscopic prediction for the type of system under consideration. This result shows that reactions can induce a change of volume in the framework we present, because they enter the evolution equation of the pressure inside the system. Note that the limit we considered to show this corresponds to the above mentioned strong coupling. It would be interesting to study how a decoupling of these processes could affect the evolution law of the volume.

### 5.3. Constraint on the transition probabilities of reactive events

We finish by commenting on the physical meaning of the constraint (34), which in our view must be imposed on the transition probabilities of the reactions, so that internal processes do not contribute to the flow of entropy. We will show now that this condition actually corresponds to a well-known property of the rate constants. Indeed, consider again the above case of a system at constant temperature. The two reactions can then be characterized by two time-independent transition probabilities per unit time:

$$W_1(\tilde{N}_A, \tilde{N}_{A_2}) = \frac{k_1}{V} \tilde{N}_A (\tilde{N}_A - 1); \quad W_{-1}(\tilde{N}_A, \tilde{N}_{A_2}) = k_{-1} \tilde{N}_{A_2}. \quad (51)$$

The constraint that we propose to act on these probabilities reads

$$\frac{W_1(\tilde{N}_A, \tilde{N}_{A_2})}{W_{-1}(\tilde{N}_A - 2, \tilde{N}_{A_2} + 1)} = \exp \left[ \frac{\tilde{S}_{\tilde{N}_{A_2}+1, \tilde{N}_A-2} - \tilde{S}_{\tilde{N}_{A_2}, \tilde{N}_A}}{k_B} \right] = \frac{P(\tilde{N}_A - 2, \tilde{N}_{A_2} + 1, eq)}{P(\tilde{N}_A, \tilde{N}_{A_2}, eq)}, \quad (52)$$

because of Einstein's formula for the equilibrium entropy [20]. Since the system is ideal, the equilibrium distribution is a multivariate Poissonian for mesoscopic sizes,

$$P(\tilde{N}_{A_2}, \tilde{N}_A, eq) = \frac{N_A(eq)^{\tilde{N}_A} e^{-N_A(eq)}}{\tilde{N}_A!} \times \frac{N_{A_2}(eq)^{\tilde{N}_{A_2}} e^{-N_{A_2}(eq)}}{\tilde{N}_{A_2}!} \quad (53)$$

so that the above ratio gives

$$\frac{W_1(\tilde{N}_A, \tilde{N}_{A_2})}{W_{-1}(\tilde{N}_A - 2, \tilde{N}_{A_2} + 1)} = \left( \frac{c_{A_2}}{c_A^2} \right)_{eq} \frac{\tilde{N}_A (\tilde{N}_A - 1)}{V (\tilde{N}_{A_2} + 1)} = K_{eq} \frac{\tilde{N}_A (\tilde{N}_A - 1)}{V (\tilde{N}_{A_2} + 1)}, \quad (54)$$

where  $K_{eq}$  is the equilibrium constant at the temperature of interest. Comparing (54) and (51), we observe that the constraint acting on the transition probabilities means that the ratio of the forward and the backward rate constants must be equal to the equilibrium constant. This relation is a well known feature of elementary reactive events as evidenced in the transition state theory, for example. This means that if the expressions for the transition probabilities are chosen on physically sound grounds, the fictitious entropy exchange emerging from the stochastic description should vanish consistently for reactions. Transition probabilities that do not respect the criterion we propose would on the contrary lead to two physically unacceptable results simultaneously.

Now that self-consistent equations governing stochastic thermodynamics have been established and illustrated, we can analyze in further detail the properties of the quantity that has traditionally been at the center of studies on non-equilibrium thermodynamics, namely the (stochastic) entropy production.

## 6. Some properties of the stochastic entropy production

The expression for the total stochastic entropy production has the same familiar bilinear form as its macroscopic counterpart. This property appears most clearly when expressing the transitions in the master equation in terms of an ensemble of elementary events. The exchange part can be rewritten as

$$\mathcal{L}_e = \sum_{k=\pm 1}^{\pm K} [W_k(X | X - \xi_k) P(X - \xi_k, t) - W_{-k}(X - \xi_k | X) P(X, t)], \quad (55)$$

in which  $k$  stands for each of the possible environment-related processes inducing a transition. In this notation,  $\xi_k = (\delta_k \tilde{E}_X, \delta_k \tilde{V}_X, \delta_k \tilde{\mathbf{N}}_X)$  is a vector of changes for the state  $X$ . Similarly, the reactive part can be written as

$$\mathcal{L}_i = \sum_{\rho=\pm 1}^{\pm r} [W_\rho(X | X - \nu_\rho) P(X - \nu_\rho, t) - W_{-\rho}(X - \nu_\rho | X) P(X, t)], \quad (56)$$

where  $\rho$  stands for the different chemical reactions. During a reactive transition, only the number of particles changes from  $\tilde{\mathbf{N}}_X$  to  $\tilde{\mathbf{N}}_{X'} = \tilde{\mathbf{N}}_X + \nu_\rho$ , where  $\nu_\rho = \{v_{\gamma\rho}\}$  is the vector of stoichiometric coefficients (note that  $\nu_{-\rho} = -\nu_\rho$ ). Consequently, the two entropy production terms (31)–(33) become

$$\begin{aligned} \left( \frac{d_i S}{dt} \right)_I &= \frac{k_B}{2} \sum_X \sum_{k=\pm 1}^{\pm K} [W_k(X | X - \xi_k) P(X - \xi_k, t) - W_{-k}(X - \xi_k | X) P(X, t)] \\ &\quad \times \ln \frac{W_k(X | X - \xi_k) P(X - \xi_k, t)}{W_{-k}(X - \xi_k | X) P(X, t)} \end{aligned} \quad (57)$$

and

$$\begin{aligned} \left( \frac{d_i S}{dt} \right)_{II} &= \frac{k_B}{2} \sum_X \sum_{\rho=\pm 1}^{\pm r} [W_\rho(X | X - \nu_\rho) P(X - \nu_\rho, t) - W_{-\rho}(X - \nu_\rho | X) P(X, t)] \\ &\quad \times \ln \frac{W_\rho(X | X - \nu_\rho) P(X - \nu_\rho, t)}{W_{-\rho}(X - \nu_\rho | X) P(X, t)}. \end{aligned} \quad (58)$$

The total entropy production thus has the form

$$\frac{d_i S}{dt} = \frac{k_B}{2} \sum_{m,X} \tilde{\mathcal{F}}_m(X) \tilde{\mathcal{X}}_m(X) \quad (59)$$

where  $m$  stands for both internal and exchange processes, and in which one introduces the stochastic fluxes

$$\tilde{\mathcal{F}}_m(X) \equiv [W_m(X | X') P(X', t) - W_{-m}(X' | X) P(X, t)] = \tilde{\mathcal{F}}_m^+(X) - \tilde{\mathcal{F}}_m^-(X) \quad (60)$$

and the corresponding stochastic forces

$$\tilde{\mathcal{X}}_m(X) \equiv \ln \frac{W_m(X | X') P(X', t)}{W_{-m}(X' | X) P(X, t)} = \ln \frac{\tilde{\mathcal{F}}_m^+(X)}{\tilde{\mathcal{F}}_m^-(X)}. \quad (61)$$

Note that, at equilibrium, all the fluxes and forces are equal to zero, because of the detailed balance. In the following, we will assess some of the properties of such stochastic entropy production. We will first discuss the properties of the fluxes and forces *per se*, and see how they are connected to the traditional macroscopic expressions. Then, we will present some consequences that the constraints acting on the transition probabilities have on the fluctuation theorem(s), with a special emphasis on the connection between entropy production and irreversibility.

### 6.1. Stochastic fluxes and forces

There exists a simple relation connecting each of the stochastic fluxes to its corresponding force, since by combining (60) and (61) one finds

$$\tilde{\mathcal{F}}_m(X) = \tilde{\mathcal{F}}_m^+(X) \left[ 1 - e^{-\tilde{\mathcal{X}}_m(X)} \right] = \tilde{\mathcal{F}}_m^-(X) \left[ e^{\tilde{\mathcal{X}}_m(X)} - 1 \right]. \quad (62)$$

This expression is supposed to hold whatever the distance from equilibrium, i.e. for arbitrarily large values of the forces and the fluxes. Remarkably, it appears that the intensity of the stochastic fluxes associated to each elementary stochastic event

depends *only* on the stochastic force of that very event. Close to equilibrium, since the forces are small, one can develop the exponential and the forward flux in series and obtain to the first order:

$$\tilde{\mathcal{F}}_m(X) \approx \tilde{\mathcal{F}}_m^+(eq) \tilde{\mathcal{X}}_m(X), \quad (63)$$

so that the matrix relating the stochastic fluxes and forces is diagonal, which means that the stochastic fluxes are uncoupled.

This conclusion might look to be at odds with the fact that fluxes can be coupled to each other in the traditional, thermodynamic description of non-equilibrium systems. It is important in that respect to remember that in macroscopic thermodynamics, the entropy production is expressed (by construction) in terms of flows of energy, of mass and chemical reactions. In the stochastic approach, it is expressed in terms of the stochastic processes, each of which can in principle contribute to changes of the energy, volume or number of particles. The macroscopic fluxes are thus non-trivial combinations of the stochastic fluxes. To illustrate this, consider a non-reactive system containing a single monoatomic species  $A$ , such that the exchange of energy with the environment occurs solely through the exchange of particles. A physical realization of such system could be a box with rigid and non-conducting walls, but having holes whose diameter is much smaller than the mean free path of the particles in the box (i.e. it could be a Knudsen exchanger [21]). There exists then a single stochastic process  $\tilde{\mathcal{J}}(X)$  and a single force  $\tilde{\mathcal{X}}(X)$ . Because of Eq. (28), one has

$$\tilde{\mathcal{X}}(X) = -\frac{\delta\tilde{E}}{k_B T} + \frac{\delta\tilde{\Sigma}}{k_B} + \frac{\mu\delta\tilde{N}}{k_B T}. \quad (64)$$

In the above equation,  $\delta\tilde{E}$  and  $\delta\tilde{N}$  stand for the change of energy and change in the number of particles induced by the Knudsen exchange mechanism. The expression

$$\delta\tilde{\Sigma} = \tilde{\Sigma}_{\tilde{E}_X + \delta\tilde{E}, \tilde{N}_X + \delta\tilde{N}} - \tilde{\Sigma}_{\tilde{E}_X, \tilde{N}_X},$$

where  $\tilde{\Sigma}_X \equiv \tilde{S}_X - k_B \ln P(X, t)$  can be seen as an “instantaneous” entropy, in the sense that its ensemble average gives the entropy as defined earlier. It is the quantity that is used, for example, for the path-dependent properties found in the fluctuation theorems, as we will see later on.

Consider now the limit of a macroscopic system. It is convenient to introduce then the densities of the state variables,  $x = X\Omega$ , where  $\Omega$  is a parameter that is representative of the size of the system. The entropy can then be expressed as an integral of the probability density  $\mathcal{P}(x, t) = \Omega^s P(X, t)$ , in which  $s$  stands for the total number of stochastic variables:

$$S(t) = \int \left[ \tilde{S}_x - k_B \ln \mathcal{P}(x, t) \right] \mathcal{P}(x, t) dx = \int \tilde{\Sigma}_x \mathcal{P}(x, t) dx. \quad (65)$$

If the macroscopic system admits a unique macroscopic trajectory (which is always the case close to equilibrium), the probability density can be replaced by a Dirac delta function so that  $S$  and  $\Sigma$  become identical. The stochastic force can be developed as

$$\begin{aligned} \tilde{\mathcal{X}}(x) &\approx -\frac{\delta\tilde{E}}{k_B T} + \frac{1}{k_B} \left[ \delta\tilde{E} \left( \frac{\partial S}{\partial E} \right)_{N,V} + \delta\tilde{N} \left( \frac{\partial S}{\partial N} \right)_{E,V} \right] + \frac{\mu\delta\tilde{N}}{k_B T} \\ &= \frac{\delta\tilde{E}}{k_B} \left[ \frac{1}{T_s} - \frac{1}{T} \right] - \frac{\delta\tilde{N}}{k_B} \left[ \frac{\mu_s}{T_s} - \frac{\mu}{T} \right]. \end{aligned}$$

In this expression, one finds the thermodynamic definition for the internal temperature  $T_s$  and the chemical potential  $\mu_s$  of the system, expressed in terms of the derivatives of the state functions. Consequently, the entropy production can be divided into two parts: one due to the flow of energy, and one due to the flow of matter. The forces associated with each of the flows is the one predicted in the macroscopic description as well [14]. There is thus no contradiction between the two approaches in the macroscopic limit, because stochastic forces (and fluxes) can be divided into distinct contributions to the flows of mass and energy. Moreover, the stochastic expressions could be used as a basis for the study of the role of fluctuations on the production of entropy by replacing, for example, the probability density by a Gaussian distribution with an appropriate variance.

It should also be noted that the expression connecting the forward and backward flows (62) is similar to the De Donder relation for the rate of chemical reactions:

$$\frac{J_\rho^+}{J_\rho^-} = \exp \frac{\mathcal{A}_\rho}{k_B T}, \quad (66)$$

in which  $J_\rho^+$  ( $J_\rho^-$ ) stands for the rate of the reaction  $\rho$  in the direct (reverse) direction. This macroscopic relation can in fact easily be deduced from the connection between the stochastic fluxes and forces associated with chemical events. We obtain from the very definition of these quantities

$$\ln \frac{J_\rho^+}{J_\rho^-} \equiv \sum_X \ln \frac{\tilde{\mathcal{F}}_\rho^+(X)}{\tilde{\mathcal{F}}_\rho^-(X)} P(X, t) = \sum_X \tilde{\mathcal{X}}_\rho(X) P(X, t), \quad (67)$$

which is equivalent to the De Donder relation if one assumes that  $\mathcal{A}_\rho/(k_B T) \equiv \langle \tilde{\mathcal{X}}_\rho(X) \rangle$ . This stochastic definition of the affinities of reaction is consistent with the known macroscopic expression. Indeed, the stochastic force associated with each chemical event reads, because of (34),

$$\begin{aligned} \tilde{\mathcal{X}}_\rho(X) &= \ln \frac{W_\rho(X | X') P(X', t)}{W_{-\rho}(X' | X) P(X, t)} \\ &= \frac{\tilde{\Sigma}_X - \tilde{\Sigma}_{X'}}{k_B}. \end{aligned} \quad (68)$$

Since chemical reactions change the number of particles but keep the energy and the volume constant,  $X = (\tilde{E}_X, \tilde{V}_X, \tilde{\mathbf{N}}_X)$  and  $X' = (\tilde{E}_X, \tilde{V}_X, \tilde{\mathbf{N}}_X - \nu_\rho)$ . The stochastic affinity is thus a measure of how the instantaneous entropy changes when the number of particles changes because of a reactive event. Just like above, in the macroscopic limit and along a single trajectory, one would then have

$$\tilde{\mathcal{X}}_\rho(x) \approx \frac{1}{k_B} \sum_{\gamma=1}^c \nu_{\gamma\rho} \left( \frac{\partial S}{\partial N_\gamma} \right)_{E,V,N_{\gamma' \neq \gamma}} = -\frac{1}{k_B T_s} \sum_{\gamma=1}^c \nu_{\gamma\rho} \mu_\gamma. \quad (69)$$

Under these conditions, the stochastic definition and the macroscopic values of the affinities of the reactions thus become essentially the same.

We have just seen that the constraints acting on the transition probabilities allow us to (re)derive known macroscopic expressions for the entropy production as well as the forces and fluxes entering it. We note in particular that the fact that chemical reactions should not affect the energy of the system is necessary to keep the fluxes of energy and chemical reactions uncoupled, as they should be. Including a reaction-induced change of the energy would lead to non-zero Onsager coefficient between these two fluxes and, consequently, one could have a reaction-induced flow of energy. We thus believe that such a reaction induced change would not be consistent with what is known, as of today, on the macroscopic entropy production. As we will see now, the constraints we highlighted also have consequences on the different expressions of the fluctuation theorem(s).

## 6.2. Fluctuation theorems

We finish with a few remarks concerning fluctuation theorems. The fluctuation theorems are expressions that provide information on the behavior of thermodynamic quantities along the (stochastic) *trajectories* of a system. To do this, one introduces random variables such as the “instantaneous” entropy  $\tilde{\Sigma}_X$  encountered above, which should be distinguished from their ensemble averages ( $S$ , in this case). In this way, one can define a new stochastic quantity for every transition  $m$  bringing the system from a state  $X$  to a state  $X'$ :

$$\delta_i \tilde{\Sigma} \equiv \delta \tilde{\Sigma} - \frac{\delta \tilde{E}}{T} - p \frac{\delta \tilde{V}}{T} + \sum_{\gamma=1}^c \frac{\mu_\gamma}{T} \delta_e \tilde{N}_\gamma. \quad (70)$$

In this equation the  $\delta$ s represent the difference between the final and initial states. Remember that the subscript  $e$  stands for transitions due to exchange processes only. The ensemble average of  $\delta_i \tilde{\Sigma}$  gives the entropy production associated with the transition, and has thus a clear thermodynamic meaning. There is still an ongoing debate on whether the “instantaneous” value  $\delta_i \tilde{\Sigma}$  would correspond to an entropy production along a single trajectory, as would be measured experimentally. We will not engage into this question but will rather focus on how the constraints that we derived influence the conclusions drawn earlier in the literature concerning this quantity.

### Path probabilities

The fluctuation theorems focus on the connections between the trajectories of a fluctuating system, and the corresponding time-reversed trajectories. Two central quantities to be introduced are thus the forward path

$$\omega = X_0 \xrightarrow{m_0} X_1 \xrightarrow{m_1} \dots X_{n-2} \xrightarrow{m_{n-2}} X_{n-1} \xrightarrow{m_{n-1}} X_n, \quad (71)$$

during which the system jumps between the state because of a well-given succession of events  $\{m_i\}$ , and the corresponding reverse path

$$\omega_R = X_n \xrightarrow{-m_{n-1}} X_{n-1} \xrightarrow{m_{n-2}} X_2 \dots \xrightarrow{-m_1} X_1 \xrightarrow{-m_0} X_0 \quad (72)$$

where the system goes back to its initial state thanks to the backward transitions. The ratio of the probabilities of these paths is often introduced as a measure of irreversibility. More precisely, we define

$$\begin{aligned} P(\omega) &\equiv P(X_0, t_0; X_1, t_1; \dots X_{n-1}, t_{n-1}; X_n, t_n) \\ &= P(X_0, t_0) W_{m_0}(X_1|X_0) W_{m_1}(X_2|X_1) \dots W_{m_{n-1}}(X_n|X_{n-1}) \end{aligned} \quad (73)$$

and

$$\begin{aligned} P(\omega_R) &\equiv P(X_n, t_n; X_{n-1}, t_{n+1}; \dots X_1, t_{2n-1}; X_0, t_{2n}) \\ &= P(X_n, t_n) W_{-m_{n-1}}(X_{n-1}|X_n) \dots W_{-m_1}(X_1|X_2) W_{-m_0}(X_0|X_1). \end{aligned} \quad (74)$$

In the two above relations, we have used both the property of Markovianity and the time-independence of the transition probabilities per unit time. The central quantity in most fluctuation theorems is the logarithm of the ratio of these probabilities,

$$\tilde{R}(\omega) \equiv \ln \frac{P(\omega)}{P(\omega_R)} = \ln \frac{P(X_0, t_0) W_{m_0}(X_1|X_0) W_{m_1}(X_2|X_1) \dots W_{m_{n-1}}(X_n|X_{n-1})}{P(X_n, t_n) W_{-m_{n-1}}(X_{n-1}|X_n) \dots W_{-m_1}(X_1|X_2) W_{-m_0}(X_0|X_1)}. \quad (75)$$

A transparent connection can be established between  $R(\omega)$  and the thermodynamic functions thanks to the constraints that we identified in this work. Indeed, noting that (28) and (34) act on the transition probabilities appearing in the above ratio, and using the Gibbs-like Eq. (70), one readily arrives to the conclusion that

$$\begin{aligned} \tilde{R}(\omega) &= \frac{\Delta \tilde{\Sigma}}{k_B} - \frac{\Delta \tilde{E}}{k_B T} - p \frac{\Delta \tilde{V}}{k_B T} + \sum_{\gamma=1}^c \frac{\mu_\gamma}{k_B T} \Delta_e \tilde{N}_\gamma \\ &= \frac{\Delta_i \tilde{\Sigma}}{k_B}. \end{aligned} \quad (76)$$

Here, the  $\Delta$ s stand for differences between the final and initial values of the corresponding stochastic quantities. Note however  $\Delta_e$  counts the change in number of particles that is due only to exchanges with the environment. The stochastic entropy production of a system is thus a measure of the degree of irreversibility of trajectories it can go through, in the sense that  $\sum_\omega \tilde{R}(\omega) P(\omega) = \langle \tilde{R}(\omega) \rangle = \Delta_i S/k_B$ .

### Integral and detailed fluctuation theorems

The ratio  $R(\omega)$  is known to respect simple relations, such as

$$\sum_\omega e^{-\tilde{R}(\omega)} P(\omega) = \langle e^{-\tilde{R}(\omega)} \rangle = \sum_\omega P(\omega) = 1. \quad (77)$$

This identity is usually called an integral fluctuation theorem. With the constraints we derived earlier, we get straightforwardly that

$$\langle e^{-\Delta_i \tilde{\Sigma}/k_B} \rangle = 1. \quad (78)$$

The latter result can be seen, to some extent, as a generalization of the second principle within the framework of stochastic dynamics. Note that, by Jensen's inequality ( $\langle e^x \rangle \geq e^{\langle x \rangle}$ ), one has  $\Delta_i S \geq 0$ . Moreover, as shown by Van den Broeck and Esposito [12], the above equality also has the direct consequence that  $\Delta_i \tilde{\Sigma}$  obeys a detailed fluctuation theorem

$$\frac{P(\Delta_i \tilde{\Sigma})}{P(-\Delta_i \tilde{\Sigma})} = e^{\Delta_i \tilde{\Sigma}/k_B}. \quad (79)$$

The expression we arrive to differs slightly from previous presentations for stochastic reactive systems, in which one finds in the exponential the variation of the total entropy, i.e. the entropy of the system plus that of the environment [2,5]. This is due to the fact that we consider here an environment that is at equilibrium at all times, so that the internal production of entropy is actually equal to the total change of entropy. Consequently, these expressions quantify irreversibility in terms of internal changes taking place in a system, without any explicit reference to external reservoirs.

The fluctuation theorems can serve as a basis for the interpretation of the connection between entropy production and irreversibility in systems far from equilibrium. They also form the starting point for a series of equations connecting the statistics of the work produced by (or delivered to) a system, with changes in thermodynamic quantities. As an example, we can introduce here an “instantaneous” chemical work with  $(k_B T) \tilde{W}_{Ch} \equiv \sum_{\gamma=1}^c \mu_\gamma \Delta_e \tilde{N}_\gamma$  and similarly a free enthalpy  $\tilde{G}_X \equiv \tilde{E}_X + p \tilde{V}_X - T \tilde{\Sigma}_X$ , so that the relation (77) reads

$$\left\langle \exp \left( -\frac{\tilde{W}_{Ch}}{k_B T} \right) \right\rangle = \left\langle \exp \left( -\frac{\Delta \tilde{G}}{k_B T} \right) \right\rangle. \quad (80)$$

In particular, for trajectories connecting two equilibrium states,  $\Delta \tilde{G}$  is expected to be path-independent [2] so that one gets

$$\left\langle \exp \left( -\frac{\tilde{W}_{Ch}}{k_B T} \right) \right\rangle = \exp \left( -\frac{\Delta \tilde{G}}{k_B T} \right), \quad (81)$$

which can also be written so as to make the mechanical work  $\tilde{W} = -p \Delta\tilde{V}$  appear explicitly

$$\left\langle \exp \left( -\frac{\tilde{W} + \tilde{W}_{Ch}}{k_B T} \right) \right\rangle = \exp \left( -\frac{\Delta\tilde{F}}{k_B T} \right), \quad (82)$$

by using the following definition of the free energy  $\tilde{F}_X \equiv \tilde{G}_X - p\tilde{V}_X$ . Note that this equation relates the difference of free energy between two equilibrium states to the statistics of the chemo-mechanical work as a whole. Such equations are known as Jarzynski relations, following the early work of this author [22].

We will now summarize the most important outcomes of this paper.

## 7. Conclusions

In this work, we have investigated some of the properties of the stochastic thermodynamics of reactive systems. An important result is that specific constraints must be put on the transition probabilities, and that these restrictions are not the same for the internal processes (such as chemical reactions) and for exchange processes (which are related to a coupling with the environment). We derived these constraints by imposing that the laws of thermodynamics be respected in the macroscopic limit. The four postulates that we obtain in this way can thus be thought of as a mesoscopic expression of the laws of thermodynamics, here corresponding to spatially uniform systems with no bulk velocity. Indeed,

1. Our requirement that the system is put in contact with an environment that remains at equilibrium is similar to the zeroth law of thermodynamics, in the sense that it defines the notion of thermal equilibrium and, thus, of temperature.
2. We found out that internal processes must leave the internal energy of a system unchanged, and that consequently they cannot contribute to the flow of energy (here, in the form of mechanical work). These statements are the equivalent of the first law of thermodynamics.
3. We arrived to the conclusion that the variation of entropy can be subdivided in two contributions: A flow term in which one finds only contributions due to stochastic exchange processes, and a production term (which is definite positive), to which both the exchange and internal processes contribute. These conclusions can be seen as forming a mesoscopic second law.

Finally, we note that the fourth law of thermodynamics is implicitly introduced in the definition of the stochastic entropy, since the latter is connected to the degeneracy of the system.

Based on these laws of stochastic thermodynamics, one finds that the entropy follows a stochastic version of the Gibbs equation, which should prove useful for the evaluation of stochastic thermodynamic properties, generally speaking. The constraints we highlighted moreover ensure that the entropy production, as well as the thermodynamic forces and fluxes converge to their macroscopic expression when they should. Now that a transparent connection has been established with the macroscopic limit, a systematic investigation of the effects of fluctuations on the thermodynamic quantities (in particular on the entropy production) should be instigated. A first step in this direction would be to consider relatively general solutions of the master equation, such as multivariate Gaussian distributions, together with the constraints we found.

Another interesting point to assess would be the development of a similar approach for systems with multiple baths, or for situations in which an external driving is present, like for example a time-dependent change of the applied external forces. These changes could affect both the exchange and the creation of energy and entropy in the system. One could wonder to what extent the set of constraints that we found could be generalized to such situations.

We also started to analyze how the restrictions acting on the transition probabilities per unit time influence the results obtained in the context of fluctuation theorems. Relations between the chemo-mechanical work and the changes of thermodynamic potentials were obtained. Engaging further in this avenue should certainly be worth the while, by studying for example the behavior of simple models of chemically driven nanomotors. It would of course be particularly interesting to see whether these results can be verified experimentally.

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