Comment on "Validity of path thermodynamics in reactive systems"

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The paper by Malek Mansour and Garcia [Phys. Rev. E **101**, 052135 (2020)] is shown to be based on misconceptions in the stochastic formulation of chemical thermodynamics in reactive systems. Their erroneous claims, asserting that entropy production cannot be correctly evaluated using path probabilities whenever the reactive system involves more than one elementary reaction leading to the same composition changes, are refuted.
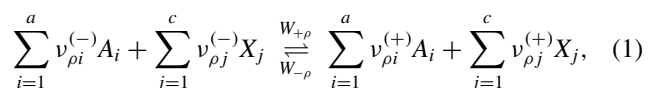
I. REFUTATION

In Ref. [1], Malek Mansour *et al.* have raised doubts on the validity of the stochastic approach, they call "path thermodynamics," to evaluate thermodynamic quantities (especially, entropy production) using path probabilities in reactive systems. In particular, they claim that "nowadays the general belief is that path thermodynamics is the ultimate theoretical formalism for physicochemical systems ranging from macroscopic to nanometer scale. [...] Yet, we shall prove that the resulting properties will be wrong whenever the reactive system involves more than one elementary reaction leading to the same composition changes." Similar criticisms have already been expressed by Malek Mansour *et al.* in Ref. [2].

The aim of this Comment is to show that such criticisms are ill founded because they result from basic misconceptions in the stochastic formulation of chemical thermodynamics in reactive systems.

The reactive systems that are here considered are networks of elementary chemical reactions $\rho = 1, 2, \ldots, r$:

$$\sum_{i=1}^{a} \nu_{\rho i}^{(-)} A_i + \sum_{j=1}^{c} \nu_{\rho j}^{(-)} X_j \underset{W_{-\rho}}{\overset{W_{+\rho}}{\rightleftharpoons}} \sum_{i=1}^{a} \nu_{\rho i}^{(+)} A_i + \sum_{j=1}^{c} \nu_{\rho j}^{(+)} X_j, \quad (1)$$

where $\{A_i\}_{i=1}^{a}$ are reactant and product species, $\{X_j\}_{j=1}^{c}$ intermediate ones, and $\nu_{\rho j}^{(\mp)} \in \mathbb{N}$ the numbers of molecules entering the forward and backward reactions $\pm\rho$ of respective rates $W_{\pm\rho}$. For a system of volume V, the molecular concentrations are given by $a_i = A_i/V$ and $x_j = X_j/V$, where A_i and X_j are the numbers of molecules of corresponding species. These concentrations are supposed to be uniform because of efficient mixing.

If the intermediate species are assumed to have lower concentrations than reactants and products ($a_i \gg x_j$) either at initial time or by supply from outside, the system may reach a stationary state determined by the reactant and product concentrations. This stationary state is either the equilibrium steady state if the conditions of detailed balance are satisfied, or a nonequilibrium steady state (NESS) if this is not the case.

At the mesoscopic level of description, the numbers A_i and X_j are erratically changing in time because of reactive events occurring at random upon inelastic collisions between molecules. Such physicochemical systems can be described in the framework of the theory of stochastic processes. If the reactive events are fast enough with respect to the mean time between their occurrences, these stochastic processes may be taken as continuous-time discrete-state Markov processes defined in terms of transition rates $W_{\pm\rho}$. The theory of such Markovian processes has been developed since classic works by Kolmogorov [3] and Feller [4,5]. A famous theorem by them states that the probabilities of such a process are given by the solutions of a master equation and that these solutions are essentially unique. This master equation can be written in terms of the transition rates $W_{\pm\rho}$ and it can be solved to obtain the probability distributions of the random variables at a given time, as well as the probabilities of the paths taken by these variables at successive instants of time.

In Ref. [1], Malek Mansour *et al.* claim that "... we are entirely free to define a 'path' any way we want. But then it is *not* always possible to associate a stochastic process to an arbitrary constructed path. This misinterpretation of the Kolmogorov's theorem is at the origin of the wrong result of Gaspard and Andrieux" [6,7]. The fallacy of this statement is that Malek Mansour *et al.* [1] here suppose that the uniqueness theorem of Kolmogorov and Feller imposes some limitations in the description of a physicochemical system by different possible stochastic processes. Actually, the stochastic processes concerned by the uniqueness theorem of Kolmogorov and Feller are defined by choosing given random variables, although different sets of random variables may be chosen for the description of a physicochemical system, thus leading to the definition of several possible stochastic processes. Therefore, the uniqueness theorem does not establish the uniqueness of the stochastic process associated with a given physicochemical system. The misuse of the uniqueness theorem in Ref. [1] is misleading Malek Mansour *et al.* to incorrect conclusions that will now be refuted.

As a matter of fact, there exist different properties of interest in reactive systems. These properties may be the numbers X_j of molecules of the intermediate species in the reaction network (1), or the amounts of reactants and chemical free energy that are consumed when the reaction network is driven out of equilibrium, or also the entropy that is produced due to dissipation. Establishing the balances of energy and entropy is the goal of thermodynamics. Besides, depending on the set of random variables chosen to describe physicochemical systems, the stochastic process may be reversible or not, whenever the system is at equilibrium or not, as can be illustrated in many physicochemical systems. The choice of random variables is thus crucial for the description of nonequilibrium systems and their thermodynamics. Fully aware of these fundamental issues, the author of this Comment proposed in 2004 to describe the time evolution of a stochastic reactive system in terms of the paths

$$\mathcal{X}(t) = X_0 \xrightarrow{\rho_1} X_1 \xrightarrow{\rho_2} \cdots \xrightarrow{\rho_n} X_n, \tag{2}$$

where X_l are the numbers of molecules of intermediate species at the successive times $t_1 < t_2 < \cdots < t_n$ and ρ_l the reactions occurring along the path, while the initial condition is sampled according to the stationary probability distribution $P_{st}(X_0)$ [6]. The successive random reactive events can be generated with Gillespie's algorithm [8,9] based on the following reaction rates of the network (1):

$$W_\rho(X|X') \qquad \text{for the transition} \quad X \xrightarrow{\rho} X' = X + \nu_\rho \tag{3}$$

with $\rho = \pm 1, \pm 2, \ldots, \pm r$ and the stoichiometric coefficients $\nu_\rho = \{\nu_{\rho j} \equiv \nu_{\rho j}^{(+)} - \nu_{\rho j}^{(-)}\}_{j=1}^c$. Far from being superfluous, the reaction sequence $\{\rho_1, \rho_2, \ldots, \rho_n\}$ is playing a key role and it must be specified to be consistent with the Gillespie algorithm simulating the reactive events. Indeed, Gillespie's algorithm provides an exact Monte Carlo method for simulating the stochastic time evolution of coupled chemical reactions described by jump Markov processes [8,9]. Moreover, it is worth pointing out that the aim of the original algorithm is the simulation of the reactive events, instead of the jumps of the molecular numbers X.

Apparently, Malek Mansour *et al.* in Refs. [1,2] have overlooked these essential aspects and they have wrongly assumed that the paths are defined in Ref. [6] as

$$\mathcal{X}_0(t) = X_0 \rightarrow X_1 \rightarrow \cdots \rightarrow X_n \tag{4}$$

by omitting the reaction sequence. The stochastic process resulting from this omission is defined in terms of the sole random variables X_l that are the molecular numbers of intermediate species. The rates of this other stochastic process are given by summing the rates of all the elementary reactions having equal stoichiometric coefficients for the intermediate species considered, according to

$$W(X|X') \equiv \sum_\rho \delta_{X'-X, \nu_\rho} W_\rho(X|X'). \tag{5}$$

This other stochastic process is thus different from the previous one if the reactive system involves more than one elementary reaction leading to the same composition changes. For numerical purposes, the rates (5) define a different Gillespie algorithm, which can have the advantage of speeding

up simulations. However, the limitation is that this other stochastic process does not contain enough information to evaluate the entropy production, which instead requires the knowledge of the elementary chemical reactions taking place in the reactive system [10]. The theorem by Kolmogorov and Feller certainly guarantees the uniqueness of the path probabilities $P_{st}[\mathcal{X}(t)]$ and $P_{st}[\mathcal{X}_0(t)]$ associated with each of the two stochastic processes, but, contrary to the erroneous claims by Malek Mansour *et al.* in Ref. [1], this theorem does not disprove the existence of either one or the other of those processes.

Now, we continue with the issue of evaluating the entropy production using path probabilities. Inspired by Ref. [11], the author of the present Comment proposed in Ref. [6] that entropy production can be evaluated in reactive systems using the ratio of the probability $P_{st}[\mathcal{X}(t)]$ of the path (2) to the probability of its time reversal

$$\mathcal{X}^R(t) = X_n \xrightarrow{-\rho_n} \cdots \xrightarrow{-\rho_2} X_1 \xrightarrow{-\rho_1} X_0. \tag{6}$$

The logarithm of this ratio can be written as

$$\ln \frac{P_{st}[\mathcal{X}(t)]}{P_{st}[\mathcal{X}^R(t)]} = Z(t) + \ln \frac{P_{st}(X_0)}{P_{st}(X_n)} \tag{7}$$

in terms of the quantity

$$Z(t) \equiv \ln \prod_{l=1}^n \frac{W_{\rho_l}(X_{l-1}|X_l)}{W_{-\rho_l}(X_l|X_{l-1})}. \tag{8}$$

In the long-time limit, the last term in Eq. (7) becomes negligible in front of $Z(t)$. This latter is linearly growing with time under nonequilibrium conditions, giving the entropy production rate

$$\left. \frac{d_i S}{dt} \right|_{st} = R \equiv \lim_{t \to \infty} \frac{1}{t} \langle Z(t) \rangle \tag{9}$$

in terms of the mean value of the quantity (8) with respect to the path probability of the stochastic process, Boltzmann's constant being set equal to 1 [6]. This method leads to the standard expression for entropy production in reactive systems [10]

$$\left. \frac{d_i S}{dt} \right|_{st} = \sum_X \sum_{\rho=1}^r [W_\rho(X - \nu_\rho|X) P_{st}(X - \nu_\rho)$$
$$- W_{-\rho}(X|X - \nu_\rho) P_{st}(X)]$$
$$\times \ln \frac{W_\rho(X - \nu_\rho|X) P_{st}(X - \nu_\rho)}{W_{-\rho}(X|X - \nu_\rho) P_{st}(X)} \geqslant 0. \tag{10}$$

In contradistinction with what is written in Ref. [6], Malek Mansour *et al.* have supposed in Refs. [1,2] that the paths (4) omitting the reaction sequence and their time reversal would have been considered in Ref. [6]. This allegation is misleading Malek Mansour *et al.* to consider a quantity looking like Eq. (7) but for the paths (4) instead of (2) and $Z(t)$ replaced by

$$Z_0(t) \equiv \ln \prod_{l=1}^n \frac{W(X_{l-1}|X_l)}{W(X_l|X_{l-1})}, \tag{11}$$

which is defined with the rates (5) instead of (3). Given that the assumptions are different, it is not a surprise that this is also the case for the conclusions that are reached.

Actually, the mean growth rate of the quantity (11) is always smaller than or equal to the entropy production rate given by Eq. (9): $R_0 \equiv \lim_{t \to \infty} \langle Z_0(t) \rangle / t \leqslant R$. If the stochastic process of the paths (4) is reversible although the system is out of equilibrium, the rate R_0 is equal to zero, confirming that the paths (4) may not be used to correctly evaluate the entropy production rate.

As proved in Ref. [6], it is the rate (9) that gives the entropy production rate in reactive systems since the paths (2) are needed to identify the transitions associated with the elementary chemical reactions, as required by the principles of chemical thermodynamics [10].

Finally, Malek Mansour *et al.* are trying in Eqs. (14)–(16) of Ref. [1] to disprove the fluctuation theorem given by their Eq. (7) for the quantity $Z(t)$. What is wrong with this attempt is that it is again confusing the properties of the two different stochastic processes associated with the paths defined by either (2) or (4). On the one hand, the quantity $Z(t)$ in Eq. (14) of Ref. [1] can only be defined for the paths $\mathcal{X}(t)$ defined by Eq. (2) including the sequence $\{\rho_l\}_{l=1}^n$ of elementary reactions in the path, but the probability of this path is not equal to the probability of its time reversal, $P_{st}[\mathcal{X}(t)] \neq P_{st}[\mathcal{X}^R(t)]$, in contradiction with the so-called "fundamental relation" used to obtain Eq. (16) of Ref. [1]. On the other hand, for the Schlögl model [12,13] considered in this part of Ref. [1], the stochastic process based on the paths $\mathcal{X}_0(t)$ defined by Eq. (4) omitting the reaction sequence is a reversible process, for which $P_{st}[\mathcal{X}_0(t)] = P_{st}[\mathcal{X}_0^R(t)]$ indeed holds. However, for the stochastic process corresponding to the paths $\mathcal{X}_0(t)$ where the reaction sequence is omitted, the quantity $Z(t)$ defined in Eq. (14) of Ref. [1] is undefined since the sequence $\{\rho_l\}_{l=1}^n$ of elementary reactions is not specified, contradicting the premises. Consequently, in both alternatives, Eq. (16) of Ref. [1] does not invalidate the fluctuation theorem given by Eq. (7) of the same paper.

Thus, the claims by Malek Mansour *et al.* in Ref. [1], according to which the results of Refs. [6,7] would be wrong, are inconsistent due to basic mistakes in the stochastic formulation required to evaluate entropy production in reactive systems.

II. ILLUSTRATIVE EXAMPLE

These issues are easily illustrated with the following simple reaction network,

$$A \underset{W_{-1}}{\overset{W_{+1}}{\rightleftharpoons}} X \underset{W_{+2}}{\overset{W_{-2}}{\rightleftharpoons}} B, \tag{12}$$

where A and B are the reactant or product species, while X is the intermediate species. The transition rates of this reaction network are given by

$$W_{+1} = k_{+1}A, \quad W_{-1} = k_{-1}X,$$
$$W_{+2} = k_{+2}B, \quad W_{-2} = k_{-2}X. \tag{13}$$

The Gillespie algorithm simulating this process is based on the distinct rates $W_{\pm 1}$ and $W_{\pm 2}$ and it generates the paths (2) specified not only by the molecule numbers X_l, but also the

reactive events $\rho_l \in \{\pm 1, \pm 2\}$. The knowledge of the reaction sequence allows us to reconstruct the time evolution of the number A of reactant or product molecules that is consumed during the process. Therefore, every path (2) is equivalent to

$$\mathcal{X}(t) = (A_0, X_0) \rightarrow (A_1, X_1) \rightarrow \cdots \rightarrow (A_n, X_n). \tag{14}$$

The stochastic process of the paths (2) is thus here identical to the process defined for the paths (14) in terms of the random variables A and X. The master equation of this process is given by

$$\frac{d}{dt}P(A, X, t) = W_{+1}(A + 1, X - 1)P(A + 1, X - 1, t)$$
$$+ W_{-1}(A - 1, X + 1)P(A - 1, X + 1, t)$$
$$+ W_{+2}(A, X - 1)P(A, X - 1, t)$$
$$+ W_{-2}(A, X + 1)P(A, X + 1, t)$$
$$- \sum_{\rho = \pm 1}^{\pm 2} W_\rho(A, X)P(A, X, t), \tag{15}$$

ruling the time evolution of the probability $P(A, X, t)$ that the system contains the molecule numbers A and X at time t.

Now, we may consider the stochastic process associated with the paths (4) obtained by omitting the reaction sequence or, equivalently, from the paths (14) by erasing the random variables $\{A_0, A_1, \ldots, A_n\}$. Clearly, the information contained in the paths (4) is too limited to reconstruct the paths (14) and thus to determine the sequence of elementary chemical reactions that have been followed during the process, in order to evaluate the entropy production.

In the literature [10,12–19], it is often assumed that the concentrations $a = A/V$ and $b = B/V$ of reactant and product are held constant during the process, because these species are in excess with respect to the intermediate ones. Under such circumstances, the rates $W_{+1} \simeq k_{+1}aV$ and $W_{+2} \simeq k_{+2}bV$ no longer depend on the random variable A in the master equation (15). We may thus deduce the following master equation ruling the marginal probability distribution $P(X, t) \equiv \sum_A P(A, X, t)$ for the sole random variable X,

$$\frac{d}{dt}P(X, t) = W_+(X-1)P(X-1, t) + W_-(X+1)P(X + 1, t)$$
$$- [W_+(X) + W_-(X)]P(X, t) \tag{16}$$

with the cumulative transition rates $W_\pm \equiv W_{\pm 1} + W_{\pm 2}$. The paths of this reduced stochastic process are given by Eq. (4).

Now, we can compare the growth rates R and R_0 of the quantities (8) and (11), respectively. Under the conditions where $A \simeq aV$ and $B \simeq bV$ are constant, the stationary solution of Eq. (16) is a Poisson distribution of mean value $\langle X \rangle_{st} = Vx_{st}$ with $x_{st} = (k_{+1}a + k_{+2}b)/(k_{-1} + k_{-2})$. In this stationary state, the macroscopic rates $w_\rho \equiv W_\rho/V$ are satisfying the condition $w_{+1} + w_{-1} = w_{+2} + w_{-2}$. In the limit where the volume V is large enough, the Poisson distribution becomes Gaussian and peaked around $\langle X \rangle_{st} = Vx_{st}$, so that the mean growth rate of the quantity (8) is obtained from Eq. (10), giving

$$R = \left. \frac{d_i S}{dt} \right|_{st} \simeq V \sum_{\rho=1}^{2} \left[(w_{+\rho} - w_{-\rho}) \ln \frac{w_{+\rho}}{w_{-\rho}} \right]_{st}. \tag{17}$$

This entropy production rate is equal to zero at equilibrium when the conditions of detailed balance hold: $w_{+\rho} = w_{-\rho}$ for $\rho = 1, 2$. Otherwise, it takes a positive value in NESS. The stochastic process associated with the paths (2) is thus reversible at equilibrium, but not in NESS.

However, the mean growth rate of the quantity (11) has the value

$$R_0 \simeq V(w_+ - w_-) \ln \frac{w_+}{w_-} \qquad (18)$$

with the cumulative reaction rates $w_\pm \equiv w_{\pm 1} + w_{\pm 2}$. Under stationary conditions where $w_+ = w_-$, Eq. (18) is thus vanishing in consistency with the reversibility of the stochastic process associated with the paths (4) for the reaction network (12), although the system may be in NESS.

These considerations demonstrate that several stochastic processes may describe a reactive system and that the entropy production is correctly evaluated using one giving complete information on the reaction sequence.

III. CHEMICAL MASTER EQUATIONS

The difficulties met by Malek Mansour *et al.* [1,2] in formulating chemical thermodynamics for stochastic processes is probably pointing towards some lack in the literature about Gillespie's algorithm. Indeed, the complete master equation of this process is rarely considered.

One way to establish this complete master equation is by introducing the numbers $\boldsymbol{n} = \{n_\rho\}_{\rho=\pm 1}^{\pm r}$ counting the reactive events that have occurred since the beginning of the simulation with the rates (3) of the elementary reactions. If the jump of these counters upon the reaction ρ is denoted $\Delta \boldsymbol{n}_\rho = -\Delta \boldsymbol{n}_{-\rho}$, the complete master equation can be written as [20]

$$\frac{d}{dt} P(\boldsymbol{X}, \boldsymbol{n}, t) = \sum_{\rho=\pm 1}^{\pm r} [W_\rho(\boldsymbol{X} - \boldsymbol{\nu}_\rho | \boldsymbol{X}) P(\boldsymbol{X} - \boldsymbol{\nu}_\rho, \boldsymbol{n} - \Delta \boldsymbol{n}_\rho, t)$$
$$- W_{-\rho}(\boldsymbol{X} | \boldsymbol{X} - \boldsymbol{\nu}_\rho) P(\boldsymbol{X}, \boldsymbol{n}, t)], \qquad (19)$$

because the rates do not depend on the counters $\boldsymbol{n}$. The inclusion of such counters has also been considered in other contexts, in particular, for charge transport in quantum dots [21].

This powerful method can be used to investigate the statistical properties of reactions. In particular, the generating function of the statistical moments of the reactive events can be defined as $F(\boldsymbol{X}, \boldsymbol{\lambda}, t) \equiv \sum_{\boldsymbol{n}} P(\boldsymbol{X}, \boldsymbol{n}, t) e^{-\boldsymbol{\lambda} \cdot \boldsymbol{n}}$ by introducing the counting parameters $\boldsymbol{\lambda}$. The equation ruling this generating function can be deduced from the complete master equation (19). We note that the standard chemical master equation [14–17] is recovered for $P(\boldsymbol{X}, t) = F(\boldsymbol{X}, \boldsymbol{\lambda} = \boldsymbol{0}, t)$. This method is used to establish the fluctuation theorem for currents in Ref. [22]. With this method, the entropy production can be determined with the random rates $\boldsymbol{n}(t)/t$ and the macroscopic affinities driving the process.

IV. CONCLUSION

As explained in this Comment, the doubts and criticisms expressed by Malek Mansour *et al.* in Refs. [1,2] about the validity of the stochastic approach to evaluate entropy production in reactive systems are ill founded.

Contrary to what is claimed in Refs. [1,2], several Markov processes can be defined for a given reactive system, depending on the set of random variables that are chosen. Each of these stochastic processes is associated with a specific Gillespie algorithm and, in parallel, the theorem of Kolmogorov and Feller establishes the uniqueness of the associated path probabilities.

Since the entropy production is defined in terms of the elementary chemical reactions [10], it is the process generated by the Gillespie algorithm simulating the random events of these elementary chemical reactions that should be considered in stochastic thermodynamics.

Omitting observables may lead to lower values than expected for entropy production, because such omission is further coarse graining the description of the process, up to being so coarse that its nonequilibrium character may become unobservable. This general feature can also be illustrated in other physicochemical systems. For instance, Brownian motion in a constant external force can be described by the stochastic process for the random variables of position and velocity, as ruled by Kramers' master equation [23]. However, the stochastic process for the sole random velocity is in one-to-one correspondence with the Ornstein-Uhlenbeck stochastic process, which is known to be reversible. The situation is thus analogous to what happens for the reaction network of Sec. II. In both systems, the observation of the sole random variable defining a reversible process does not give direct evidence for the nonequilibrium character of the system.

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