Skewness and kurtosis in stochastic thermodynamics

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Abstract
The thermodynamic uncertainty relation is a prominent result in stochastic thermodynamics that provides a bound on the fluctuations of any thermodynamic flux, also known as current, in terms of the average rate of entropy production. Such fluctuations are quantified by the second moment of the probability distribution of the current. The role of higher order standardized moments such as skewness and kurtosis remains largely unexplored. We analyze the skewness and kurtosis associated with the first passage time of thermodynamic currents within the framework of stochastic thermodynamics. We develop a method to evaluate higher order standardized moments associated with the first passage time of any current. For systems with a unicyclic network of states, we conjecture upper and lower bounds on skewness and kurtosis associated with entropy production. These bounds depend on the number of states and the thermodynamic force that drives the system out of equilibrium. We show that these bounds for skewness and kurtosis do not hold for multicyclic networks. We discuss the application of our results to infer an underlying network of states.

Keywords: stochastic thermodynamics, first passage time, fluctuations

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

1. Introduction
The theory of thermodynamics developed in the 19th century is restricted to equilibrium macroscopic systems. Fluctuations in thermodynamic fluxes such as heat and work are negligible in standard thermodynamics. However, many small physical systems with non-negligible fluctuations such as colloids and single enzymes can be realized in the laboratory today. The
appropriate framework for some of these small nonequilibrium systems is stochastic thermodynamics [1]. In this theory, thermodynamic currents such as entropy production, heat, and work are stochastic variables.

A main goal in stochastic thermodynamics is to find universal relations concerning the statistics of thermodynamic currents. The most prominent such relation is the fluctuation theorem [1] that can be expressed as a symmetry for the probability distribution of the entropy production. A more recent development is the thermodynamic uncertainty relation [2], which is a lower bound on the fluctuations of any thermodynamic current that depends only on the average rate of entropy production. Much recent work has been done since the proposal of the thermodynamic uncertainty relation [3–27].

Instead of stochastic current for a fixed time interval one can consider an observable that is the first passage time to reach a certain threshold current. These observables are equivalent as the current distribution contains the information from the first passage time distribution. Both the fluctuation theorem and the thermodynamic uncertainty relation have been expressed in terms of first passage times in [28–31] (see also [32]), respectively.

In this paper we analyze skewness and kurtosis associated with the first passage time of a current. We develop a method to calculate the moments associated with the first passage time distribution in terms of the transition rates for discrete Markov processes. We conjecture lower and upper bounds on the skewness and kurtosis associated with the first passage time of entropy for unicyclic networks. For multicyclic networks, these bounds are shown to be violated. We discuss how our bounds are potentially applicable to the problem of inferring a network of states from statistical data of the first passage time of a current. For instance, this problem is relevant in statistical kinetics [33].

The paper is organized as follows. In section 2 we define stochastic currents and their first passage times. Section 3 contains the method we develop to calculate skewness and kurtosis associated with the first passage time distribution. The bounds for unicyclic networks are discussed in section 4. We show that these bounds are violated in a multicyclic networks in section 5. We conclude in section 6.

2. Currents and first passage time

2.1. Stochastic current

Our framework is valid for Markov processes with continuous time and with a finite number of states $\Omega$. The transition rate from a state $i$ to a state $j$ is denoted by $k_{ij}$. In stochastic thermodynamics, we typically consider processes such that if $k_{ij} \neq 0$ then $k_{ji} \neq 0$. Furthermore, thermodynamic fluxes, which are the observables of interest in this paper, are expressed as stochastic currents. These are functionals of a stochastic trajectory that changes by $\theta_{i^-j^+}$ whenever there is a jump from state $i$ to state $j$. For a stochastic trajectory with fixed time interval $T$, the time-integrated current $J$ is written as

$$J \equiv \sum_{\text{all jumps } l} \theta_{i^-j^+}$$

where $i^-$ is the state of the system before a jump $l$ and $i^+$ is the state of the system after jump $l$. For currents, the increments $\theta_{i^-j^+}$ are antisymmetric, i.e., $\theta_{i^-j^+} = -\theta_{i^+j^-}$. Physical examples of currents are heat or particle fluxes and entropy production. The results obtained in section 3 also hold for increments that do not fulfill this antisymmetry property.
In the long time limit $T \to \infty$, the statistics of $J$ is described by the scaled cumulant generating function

$$\lambda(z) \equiv \lim_{T \to \infty} \langle e^{-zJ} \rangle_T / T,$$

where the brackets with subscript $T$ denote an average over stochastic trajectories with fixed time interval $T$. This scaled cumulant generating function is the maximum eigenvalue of the modified generator \[34\]

$$L(z)_{ij} \equiv e^{-\theta}k_{ij}(1 - \delta_{ij}) - \delta_{ij}\sum_{k \neq i} k_{ik}.$$

2.2. First passage time

Instead of the current $J$ for a trajectory with fixed time $T$ we can consider the first passage time $T$ to reach a certain threshold current $J_t$. This first passage time is different from the persistence time to reach an absorbing state, which is also commonly considered in the literature. The statistics of $T$ in the limit $J_t \to \infty$ is described by another scaled cumulant generating function, given by

$$\rho(s) \equiv \lim_{J_t \to \infty} \ln \langle e^{-sT} \rangle / J_t,$$

where the brackets without any subscript denote an average over stochastic trajectories with fixed threshold current $J_t$. The derivatives of $\rho(s)$ at $s = 0$ give the cumulants associated with the first passage time $T$ through the relation

$$\kappa_i \equiv (\frac{-1}{J_t}) \frac{d^i \rho}{ds^i}(s = 0),$$

where $\kappa_i$ denotes the cumulant of order $i$ associated with $T$.

In particular, we are interested in skewness

$$S \equiv \frac{|J_t|}{\kappa_3^{1/2}} \frac{\kappa_3}{\kappa_2}$$

and the (excess) kurtosis

$$K \equiv \frac{|J_t|}{\kappa_4} \frac{\kappa_4}{\kappa_2^2}.$$

There are two relevant comments about these definitions. First, skewness and kurtosis are typically defined without the $J_t$ factors. We have scaled $S$ and $K$ by factors of $J_t$ so that they are finite in the limit $J_t \to \infty$, in agreement with equation (5). Hence, these quantities could be called scaled skewness and scaled kurtosis. Second, we have used the absolute value of $J_t$ in our definitions for the following reason. There are two possible first passage time distributions. One is the distribution for typical events that corresponds to a threshold current $J_t$ that has the same sign as the sign of the average of the stochastic current $\langle J \rangle_T$. The other is the first passage time distribution for rare events that corresponds to a $J_t$ that has an opposite sign in relation to the sign of $\langle J \rangle_T$. Here we consider the first passage distribution for typical events with $J_t$ and $\langle J \rangle_T$ with the same sign. Since we do not know the sign of the average current $\langle J \rangle_T$ in terms of the transition rates, our method must work for both positive and negative signs.
In order to account for the sign of $J_t$ we consider the first derivative in equation (5),

$$\text{sign } J_t = -\text{sign}(\rho') \equiv \epsilon,$$

(8)

where the prime denotes a derivative at $s = 0$. We can now write $S$ and $K$ in terms of derivatives of $\rho$ in a way consistent with both positive and negative $J_t$. Skewness in equation (6) and kurtosis in equation (7) can be written in terms of derivatives of $\rho(s)$ at $s = 0$ from equation (5), which gives the following relations,

$$S = -\epsilon \rho''' / (\epsilon \rho'')^{3/2},$$

(9)

and

$$K = \epsilon \rho'''' / (\epsilon \rho'')^2,$$

(10)

where the primes denote derivatives at $s = 0$. We reiterate that with $\epsilon$ we always consider the first passage time for typical events, with $J_t$ and the average current $\langle J \rangle_T$ with the same sign, independent of whether this sign is positive or negative.

The statistics of a stochastic current $\mathcal{J}$ for fixed time $T$ are connected to the statistics of the first passage time $T$ for fixed threshold current $J_t$. This connection is represented by the following relation between $\lambda(z)$ and $\rho(s)$. Consider the characteristic polynomial associated with the modified generator in equation (3)

$$\Xi(s, z) \equiv \text{det}(s \mathbb{I} - L(z)),$$

(11)

where $\mathbb{I}$ is the identity matrix and $L(z)$ is the matrix defined in equation (3). The maximal root of this polynomial in $s$ is the scaled cumulant generating function for a current $\lambda(z)$. The scaled cumulant generating function for the first passage time $\rho(s)$ is the inverse of $\lambda(z)$, i.e. $\lambda(\rho(s)) = s$. This relation leads to [31]

$$\Xi(s, \rho(s)) = 0.$$  

(12)

In principle, we can use this equation to determine $\rho(s)$ in terms of the transition rates $k_{ij}$. From $\rho(s)$ we can determine skewness $S$ from equation (9) and kurtosis $K$ from equation (10). However, the explicit form of $\rho(s)$ in terms of the transition rates $k_{ij}$ is hard to obtain even for systems with a small number of states. In the next section, we introduce a method to circumvent this issue, i.e. one can determine $S$ and $K$ in terms of the transition rates without the explicit form of $\rho(s)$.

3. Method to calculate standardized moments

Our method follows the same rationale of the method by Koza [35] to obtain the cumulants associated with the stochastic current for a fixed time without the explicit calculation of $\lambda(z)$. In Koza’s method one can obtain the derivatives of $\lambda(z)$ at $z = 0$ in terms of the coefficients of the characteristic polynomial in equation (11): there is no need to find the root of the polynomial $\lambda(z)$, which is a much more complicated problem. The coefficients $B(z)$ in Koza’s method are defined through the relation $\Xi(s, z) = \sum c_i B(z) s^i$.

Consider the characteristic polynomial $\Xi(s, \rho)$, defined in equation (11) as a function of two independent variables $s$ and $\rho$. A Taylor expansion of equation (12) in $\rho$ leads to

$$\sum_{i=0}^{\infty} c_i(s) \rho(s)^i = 0,$$

(13)
where $c_i$ is the $i$ derivative of $\Xi(s, \rho)$ with respect to $\rho$. We note that these derivatives are taken with $\rho$ as an independent variable. However, we now consider $c_i(s)$ and $\rho(s)$ as functions of $s$ in equation (13). For our final derivation we use the relation [31]

$$\rho(s = 0) = 0,$$

which is true for the typical first passage time distribution that corresponds to a threshold current with the same sign as the average current. Using this relation and taking derivatives with respect to $s$ at $s = 0$ in equation (13) we obtain,

$$\rho' = -\frac{c_0'}{c_1},$$

$$\rho'' = -\frac{c_0'' + 2c_2\rho'^2 + 2c_1\rho'}{c_1},$$

$$\rho''' = -\frac{c_0'''}{c_1} + 6c_2\rho''\rho' + 3c_1\rho'' + 3\rho'c_1'' + 6c_3\rho'(\rho')^3 + 6c_4\rho'(\rho')^2,$$

$$\rho'''' = -\frac{c_0''''}{c_1} + 8c_2\rho''\rho' + 4c_1\rho'' + 4\rho'c_1''' + 6c_2(\rho'')^2 + 6c_3\rho'' +$$

$$-36c_3(\rho'(\rho')^2\rho'' + 24c_1\rho'\rho'' + 12(\rho')^2c_2''' + 24c_4(\rho')^4 + 24c_3(\rho')^3).$$

This equation together with equations (9) and (10) allow us to obtain skewness $S$ and kurtosis $K$ in terms of the coefficients $c_i(s)$ in equation (13).

Summarizing, one can calculate $S$ and $K$ in terms of the transition rates $k_{ij}$ with the following algorithm. First, evaluate the characteristic polynomial in equation (11). Second, obtain the coefficients $c_i(s)$ up to $i = 4$ in the Taylor expansion in equation (13). Third, calculate the derivatives of $\rho$ at $s = 0$ in (15). The skewness $S$ can be obtained with equation (9) and the kurtosis $K$ can be obtained with equation (10). Hence, one can obtain the skewness and the kurtosis associated with first passage time of a current in terms of the transition rates without explicitly calculating roots of the polynomial in equation (11). This method is our first main result. The method can also be used to calculate higher order cumulants by simply calculating higher order derivatives of $\rho$. We reiterate that the method is not restricted to currents that have antisymmetric increments but also applies to any observable of the form given in equation (1).

4. Bound for unicyclic networks

4.1. Unicyclic networks and bound on second cumulant

We now consider a unicyclic network with $\Omega$ states. The transition rate from state $i$ to state $i + 1$ is denoted $k_i$ and the transition rate from state $i$ to state $i - 1$ is denoted $\overline{k}_i$. The unicyclic network has periodic boundary conditions, the transition rate from $i = \Omega$ to $j = 1$ ($j = \Omega$) is denoted $k_{\Omega}$ ($\overline{k}_1$). Possible physical interpretations for such a model are an enzyme with a single cycle or a colloid on a ring. The thermodynamic affinity is defined as [38]

$$A \equiv \ln \prod_{i=1}^{\Omega} \frac{k_i}{\overline{k}_i}.$$

If $A = 0$ the system is in equilibrium and if $A \neq 0$ the system is out of equilibrium. For an enzyme that burns one ATP in a cycle, the thermodynamic affinity is the free energy of ATP
hydrolysis and for a colloidal particle on a ring it is the work done by the force that drives the particle in one loop, both in units of $k_B T$, where $k_B$ is Boltzmann’s constant and $T$ is the temperature. Without loss of generality we will consider the case $A \geq 0$.

The entropy production has the following increments, $\theta_{\Omega,1} = -\theta_{1,\Omega} = A$. For any other jumps the increment is zero. We consider the entropy since this is a general current that can also be analyzed in multicyclic networks. However, since the network of states is unicyclic there is only one independent current due to Kirchhoff’s law and different increments lead to the same results up to a rescaling factor. We also consider the cases $\Omega = 1$ and $\Omega = 2$.

For $\Omega = 1$ we simply have a biased random walk that jumps to the right with rate $k e^A$ and to the left with rate $k$. For $\Omega = 2$ there must be two links between the two states. The modified generator in this case is a $2 \times 2$ matrix with elements $L_{11} = -(k_1^+ + k_1^-), L_{22} = -(k_2^+ + k_2^-), L_{21} = k_1^+ + k_1^- e^{A_1},$ and $L_{12} = k_2^+ e^{-A_1} + k_2^-.$

Before we present our results we mention the following existing bound. Consider the following quantity related to the second cumulant of the first passage time distribution,

$$ R \equiv J_T \frac{\langle (T - \langle T \rangle)^2 \rangle}{\langle T \rangle^2}, $$

which is known as randomness parameter in statistical kinetics [33]. For a fixed affinity $A$ and number of states $\Omega$, there is a lower bound on $R$ for unicyclic networks [36],

$$ R \geq A \Omega^{-1} \coth[A/(2\Omega)]. $$

The randomness parameter is a function of $2\Omega$ transition rates. If we use the affinity $A$ to fix one of the rates, it becomes a function of $2\Omega - 1$ variables. The minimum of $R$ for fixed $A$ and $\Omega$, expressed on the right-hand side of equation (18), is achieved for uniform rates that correspond to an asymmetric random walk (ARW), i.e. $k_i = k e^{A/(2\Omega)}$ and $L_i = k e^{-A/(2\Omega)}$ for all $i$.

For an ARW, we can obtain the maximum eigenvalue of the modified generator in equation (3), which is $\lambda_{\text{ARW}}(z) = k [\cosh \frac{4e^{A/\Omega}}{2\Omega}] - \cosh \frac{k}{2\Omega}/2$. Hence, the inverse function of $\lambda_{\text{ARW}}(z)$ is $\rho_{\text{ARW}}(s) = \frac{4}{k} \cosh^{-1}[s/(2k)] + \cosh \frac{k}{2\Omega} - 1$. Skewness and kurtosis for an ARW can be obtained from this expression together with equations (9) and (10), respectively.

4.2. Bounds on skewness

We used the method introduced in section 3 to evaluate the skewness and kurtosis for unicyclic networks as functions of the transition rates. Let us first consider the skewness $S$. If we consider an ARW, which corresponds to uniform rates, with affinity $A$ and number of states $\Omega$ the skewness is given by

$$ S_{\text{ARW}}(A, \Omega) = \frac{2\sqrt{A}}{\sqrt{\Omega}} \frac{1 + 4e^{A/\Omega} + e^{2A/\Omega}}{\sqrt{-1 + e^{A/\Omega}}(1 + e^{A/\Omega})}. $$

An important difference between the expression for $S$ in equation (19) and the lower bound on $R$ in equation (18) is that the lower bound on $R$ is a decreasing function of $\Omega$ while $S_{\text{ARW}}(A, \Omega)$ is not. For a given value of the affinity $A$ there is an optimal value of the integer $\Omega$ that minimizes $S_{\text{ARW}}(A, \Omega).$ For $0 \leq A \leq A_1^{\Omega}$ the function $S_{\text{ARW}}(A, 1)$ is the minimal one, where $A_1^{\Omega}$ is the solution of the transcendental equation $S_{\text{ARW}}(A_1^{\Omega}, 1) = S_{\text{ARW}}(A_1^{\Omega}, 2)$. In general, $S_{\text{ARW}}(A, i)$ is minimal for $A_{i-1}^{\Omega} \leq A \leq A_i^{\Omega}$, where $A_i^{\Omega}$ is the solution of the transcendental
Figure 1. Bounds on skewness for (a) $\Omega = 3$ and (b) $\Omega = 4$. We have plotted $S$ for randomly chosen rates, the exact lower bound in equation (20), $S_{\text{ARW}}(A, \Omega)$, the numerical minimum of $S$, and the numerical maximum of $S$.

Figure 2. (a) Illustration of the kink on the lower bound on $S$ for $\Omega = 4$. (b) Illustration of the kink and the asymptotic behavior for large $A$ of the upper bound on $S$. In the limit $A \to 0$ the skewness is $S = 6/\sqrt{2}$.

equation $S_{\text{ARW}}(A^f_i, i) = S_{\text{ARW}}(A^f_i, i + 1)$. Therefore, for a system with $\Omega$ states $S_{\text{ARW}}(A, \Omega)$ cannot be the lower bound for all $A$, since it is also possible to choose rates such that a system with $\Omega$ states behaves like an ARW with less than $\Omega$ states.

Performing a numerical investigation up to $\Omega = 8$ we arrive at the conjecture of the following lower bound on the skewness for fixed affinity $A$ and number of states $\Omega$,

$$S \lessgtr \min_{N \leq \Omega} \{ S_{\text{ARW}}(A, N) \}. \quad (20)$$

This bound and our numerical investigation is illustrated in figure 1 for $\Omega = 3$ and $\Omega = 4$. The lower bound for a system with $\Omega$ states has $\Omega - 1$ kinks, which happen at points $A^f_i$, with $i = 1, \ldots, \Omega - 1$. For $A > A^f_{\Omega-1}$ the lower bound becomes $S_{\text{ARW}}(A, \Omega)$. These kinks are illustrated in figure 2(a) for the case $\Omega = 4$. In our numerical investigation we have performed numerical minimization of $S$ with fixed affinity $A$ and number of states $\Omega$. We have also evaluated $S$ for random values for the transition rates and they all stay above the lower bound.
Table 1. Points for the kinks of the upper bounds for different system sizes.

| Ω  | $A^L_1$ | $A^L_2$ |
|----|---------|---------|
| 2  | 2.84    | 3.27    |
| 3  | 3.15    | 3.64    |
| 4  | 3.32    | 3.84    |
| 5  | 3.41    | 3.95    |
| 6  | 3.47    | 4.02    |
| 7  | 3.51    | 4.07    |
| 8  | 3.54    | 4.10    |

The skewness $S$ has an absolute minimum $S_{\text{min}}$, which is independent of the affinity $A$ and the number of states $\Omega$. Interestingly, for a system with $\Omega$ states, this minimum is reached in each of the $\Omega$ pieces of the lower bound in equation (19), as shown for $\Omega = 4$ in figure 2(a). This minimum value is $S_{\text{min}} \approx 3.90973$.

Besides this lower bound it turns out that the skewness also has an upper bound illustrated in figure 2(b). This upper bound has one kink at $A = A^L_2$ that depends on system size $\Omega$. Interestingly, for a system with $\Omega$ states, this minimum is reached in each of the $\Omega$ pieces of the lower bound in equation (19), as shown for $\Omega = 4$ in figure 2(a). This minimum value is $S_{\text{min}} \approx 3.90973$.

4.3. Bounds on kurtosis

Similar bounds also hold for the kurtosis $K$, as shown in figure 3. There is a lower bound for fixed $A$ and $\Omega$ given by

$$K \leq \min_{N \in \Omega} \{K_{\text{ARW}}(A, N)\},$$

where,

$$K_{\text{ARW}}(A, \Omega) = \frac{6A \Omega + 8e^{A/\Omega} + e^{2A/\Omega}}{1 + e^{2A/\Omega}}$$

is the kurtosis of an ARW. This lower bound also has $\Omega - 1$ kinks at points $A^L_i$, which are the solution of the equation $K_{\text{ARW}}(A^L_i, i) = K_{\text{ARW}}(A^L_{i+1}, i+1)$. For $A^L_{i+1} \leq A \leq A^L_i$ the lower bound is given by $K_{\text{ARW}}(A, i)$, where $i = 1, \ldots, \Omega - 1$ and for $i = 1$ we have $A^L_0 = 0$. In each of the $\Omega$ pieces of the lower bound the Kurtosis reaches an absolute minimum independent of $A$ and $\Omega$, which is given by $K_{\text{min}} \approx 25.0913$. These features of the lower bound are illustrated in figure 4(a) for the case $\Omega = 4$.

The upper bound on Kurtosis is shown in figure 4(b). This upper bound has a kink at a point $A^L_1$ that depends on system size $\Omega$. The values of $A^L_1$ up to $\Omega = 8$ are given in table 1. For
Figure 3. Bounds on kurtosis for $\Omega = 3$ and $\Omega = 4$. We have plotted $K$ for randomly chosen rates, the exact lower bound in equation (21), $K_{\text{ARW}}(A, \Omega)$, the numerical minimum of $K$, and the numerical maximum of $K$.

Figure 4. (a) Illustration of the kink of the lower bound on $K$ for $\Omega = 4$. (b) Illustration of the kink and the asymptotic behavior for large $A$ of the upper bound on $K$. In the limit $A \to 0$ the kurtosis is $K = 30$.

0 $\leq A \leq A^K$ the upper bound is given by $K_{\text{ARW}}(A, \Omega)$. For $A > A^K$ we can only determine the upper bound numerically. The asymptotic form of the upper bound for large affinity $A$ is $6A$, which corresponds to the asymptotic form of $K_{\text{ARW}}(A, 1)$ in equation (22).

In the linear response regime the lower and upper bounds for kurtosis also tend to the same value, as shown in figure 1. In this regime the kurtosis has a fixed value given by $K = 30$. This value can be obtained by taking the limit $A \to 0$ of $K_{\text{ARW}}(A, \Omega)$ in equation (22).

4.4. Inference of network topology

The idea of statistical kinetics [33] is to infer the topology of a network of states in an enzymatic reaction from data gathered in single molecule experiments. While we focus on the entropy production, which has increments $\theta_{\Omega,1} = -\theta_{1,\Omega} = \Delta$, the current analyzed in statistical kinetics has increments $\theta_{\Omega,1} = -\theta_{1,\Omega} = 1$. We define the randomness parameter, skewness and kurtosis associated with this current with increments 1 (instead of $A$) as $R^*$, $S^*$ and $K^*$, respectively. They
Figure 5. Multicyclic network with 4 states. The links between states represent non-zero transition rates.

are related to the same quantities for the entropy production in the following way \( R = AR^* \), \( S = A^{1/2}S^* \), and \( K = AK^* \).

A main bound in statistical kinetics is \( R^* \geq 2/\Omega \), which is valid in the limit \( A \to \infty \). One can infer the unknown number of states in an enzymatic reaction by measuring \( R \) and calculating the lower bound on the number of states \( 2/R \). As shown in [37], there are also lower bounds on skewness and kurtosis in the limit \( A \to \infty \), which are \( S^* \geq 2/\Omega^{1/2} \) and \( K^* \geq 6/\Omega \). These bounds are consistent with the more general lower bounds in equations (20) and (21). It turns out that the randomness parameter in equation (17) is the most effective for a direct estimation of the minimal number of states [37].

These bounds hold in the limit \( A \to \infty \). The lower bounds we found here for \( S \) and \( K \) are more general and take the affinity \( A \) into account. Hence, they can be potentially more effective to infer the number of states. The investigation on how to use the bounds conjectured here for skewness and kurtosis to infer the number of states of a unicyclic network is beyond the scope of this paper. However, we can make the following statements. For \( A \leq A_1^S \) for skewness and for \( A \leq A_1^K \) for kurtosis the lower bound is dominated by an ARW with \( \Omega = 1 \), hence the lower bounds cannot be used to infer number of states in this regime. The upper bounds for both skewness and kurtosis, for affinities smaller than the affinity for which the kink in the upper bounds take place, can, in principle, be used to infer the number of states. However, differences in the upper bounds due to the number of states are quite small, as shown in figure 2(b) for \( S \) and figure 4(b) for \( K \). Therefore, using the upper bound to infer the number of states does not look promising.

We point out that theoretical works on statistical kinetics frequently use models with irreversible transition rates. Such models correspond to the formal limit \( A \to \infty \) and are a reasonable description of experiments performed at high \( A \). Our results show that experiments performed with a controlled affinity \( A \) can lead to more information about the enzymatic scheme. While in stochastic thermodynamics the generalization of known results to the case of irreversible transition rates do require further elaboration [39, 40], our results directly apply to such case with the formal limit \( A \to \infty \), as explained above.
5. Violation of bounds in a multicyclic network

We now show that the lower bounds we found for unicyclic networks do not hold for multicyclic networks. We consider the multicyclic network with 4 states shown in figure 5. We have calculated skewness and kurtosis for the entropy production using the methods explained in section 3. The increments for the entropy production for general multicyclic networks are given by $\theta_{ij} = \ln(k_{ij}/k_{ji})$. We consider the skewness and kurtosis associated with the first passage time distribution of the entropy production.

Defining an affinity dependent bound for multicyclic networks is not so straightforward since there is more than one affinity for multicyclic networks. However, we can check whether for a multicyclic network $S$ and $K$ can cross the absolute minima, independent of affinity and system size, for unicyclic networks, which are given by $S_{\text{min}} \approx 3.90973$ and $K_{\text{min}} \approx 25.0913$.

As shown in figure 6, they do cross these absolute minima for the multicyclic network considered here. Hence, the lower bound for unicyclic networks does not apply to multicyclic networks. For the results shown in figure 6, there is a region for which $S < S_{\text{min}}$ but $K > K_{\text{min}}$. However, in our numerical investigation we also found regions for which $K < K_{\text{min}}$ and $S > S_{\text{min}}$. The crossing of at least one of the two absolute minima constitute a rather generic toll to infer whether a network of states is not unicyclic, which is also a relevant problem in statistical kinetics [33].

6. Conclusion

We introduced a method to calculate the cumulants associated with the first passage time distribution of an arbitrary current, or more generally associated with any observable of the form in equation (1). Our method circumvents the problem of evaluating the full scaled cumulant generating function $\rho(s)$, which can only be obtained in terms of the transition rates for quite simple models. Instead the cumulants are obtained in terms of certain coefficients that are much easier to evaluate.

The skewness and kurtosis related to the first passage time distribution of entropy production for unicyclic networks have been analyzed with our method. We conjectured lower and upper
bounds on these standardized moments. Interestingly, the lower bounds have several kinks, which comes from the fact that an ARW with $\Omega$ states does not minimize the skewness and kurtosis for any value of the affinity. This lower bound is different from a previously known lower bound associated with the second cumulant \cite{36}, which has no kinks and is minimized for an ARW with $\Omega$ states.

Skewness and kurtosis for unicyclic networks have absolute minima, independent of affinity and number of states. We have shown that for a multicyclic network both skewness and kurtosis can go below the minima for unicyclic networks. Hence, multicyclic networks are not bounded by the bounds we conjectured for unicyclic networks. Crossing of these minima provides a generic tool to infer whether an underlying network of states is indeed multicyclic.

As an interesting perspective for future work, the application of our bounds to statistical kinetics could lead to new ways to obtain information about an enzymatic scheme from data obtained in single molecule experiments. Our bounds take thermodynamic affinity into account, which, in principle, can be controlled in an experiment.

Data availability statement

The data that support the findings of this study are available upon reasonable request from the authors.

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References

[1] Seifert U 2012 Rep. Prog. Phys. 75 126001
[2] Barato A C and Seifert U 2015 Phys. Rev. Lett. 114 158101
[3] Gingrich T R, Horowitz J M, Perunov N and England J L 2016 Phys. Rev. Lett. 116 120601
[4] Pietzonka P, Barato A C and Seifert U 2016 Phys. Rev. E 93 052145
[5] Nguyen M and Vaikuntanathan S 2016 Proc. Natl Acad. Sci. 113 14231
[6] Pietzonka P and Seifert U 2018 Phys. Rev. Lett. 120 190602
[7] Polettini M, Lazarescu A and Esposito M 2016 Phys. Rev. E 94 052104
[8] Tsobgni Nyawo P and Touchette H 2016 Phys. Rev. E 94 032101
[9] Guioth J and Lacoste D 2016 Europhys. Lett. 115 60007
[10] Pietzonka P, Ritort F and Seifert U 2017 Phys. Rev. E 96 012101
[11] Horowitz J M and Gingrich T R 2017 Phys. Rev. E 96 020103
[12] Pigolotti S, Neri I, Roaldán E and Julicher F 2017 Phys. Rev. Lett. 119 140604
[13] Proesmans K and Van den Broeck C 2017 Europhys. Lett. 119 20001
[14] Maes C 2017 Phys. Rev. Lett. 119 160601
[15] Hyeon C and Hwang W 2017 Phys. Rev. E 96 012156
[16] Bisker G, Polettini M, Gingrich T R and Horowitz J M 2017 J. Stat. Mech. 093210
[17] Brandner K, Hanazato T and Saito K 2018 Phys. Rev. Lett. 120 090601
[18] Nardini C and Touchette H 2018 Eur. Phys. J. B 91 16 1434
[19] Chiuchiù D and Pigolotti S 2018 Phys. Rev. E 97 032109
[20] Barato A C, Chetrite R, Faggionato A and Gabrielli D 2018 New J. Phys. 20 103023
[21] Dechant A and Sasa S-i 2018 J. Stat. Mech. 063209
[22] Carollo F, Jack R L and Garrahan J P 2019 Phys. Rev. Lett. 122 130605
[23] Liu J and Segal D 2019 Phys. Rev. E 99 062141
[24] Guarnieri G, Landi G T, Clark S R and Goold J 2019 Phys. Rev. Res. 1 033021
[25] Koyuk T and Seifert U 2020 Phys. Rev. Lett. 125 260604
[26] Ito S and Dechant A 2020 Phys. Rev. X 10 021056
[27] Hasegawa Y 2021 Phys. Rev. Lett. 126 010602
[28] Roldán É, Neri I, Dörpinghaus M, Meyr H and Jülicher F 2015 Phys. Rev. Lett. 115 250602
[29] Saito K and Dhar A 2016 Europhys. Lett. 114 50004
[30] Neri I, Roldán E and Jülicher F 2017 Phys. Rev. X 7 011019
[31] Gingrich T R and Horowitz J M 2017 Phys. Rev. Lett. 119 170601
[32] Garrahan J P 2017 Phys. Rev. E 95 032134
[33] Moffitt J R and Bustamante C 2014 FEBS J. 281 498
[34] Lebowitz J L and Spohn H 1999 J. Stat. Phys. 95 333
[35] Koza Z 1999 J. Phys. A: Math. Gen. 32 7637
[36] Barato A C and Seifert U 2015 J. Phys. Chem. B 119 6555
[37] Barato A C and Seifert U 2015 Phys. Rev. Lett. 115 188103
[38] Schnakenberg J 1976 Rev. Mod. Phys. 48 571
[39] Pal A, Reuveni S and Rahav S 2021 Phys. Rev. Res. 3 013273
[40] Pal A, Reuveni S and Rahav S 2021 Phys. Rev. Res. 3 L032034