New Journal of Physics
The open access journal at the forefront of physics

Deutsche Physikalische Gesellschaft DPG
IOP Institute of Physics

Published in partnership with: Deutsche Physikalische Gesellschaft and the Institute of Physics

Check for updates

PAPER

Non-equilibrium symmetry of cyclic first-passage times

Daniel Maria Busiello[1,2,3,7,*], **Shiling Liang**[2,4,5,6,7] and **Simone Pigolotti**[4,7]

[1] Department of Physics and Astronomy 'G. Galilei', University of Padova, 35131 Padova, Italy
[2] Max Planck Institute for the Physics of Complex Systems, 01187 Dresden, Germany
[3] Theoretical Sciences Visiting Program (TSVP), Okinawa Institute of Science and Technology Graduate University, Onna, Okinawa 904-0495, Japan
[4] Biological Complexity Unit, Okinawa Institute of Science and Technology Graduate University, Onna, Okinawa 904-0495, Japan
[5] Center for Systems Biology Dresden, 01307 Dresden, Germany
[6] Max Planck Institute of Molecular Cell Biology and Genetics, 01307 Dresden, Germany
[7] The authors are listed in alphabetical order.
[*] Author to whom any correspondence should be addressed.

E-mail: danielmaria.busiello@unipd.it, shiling@pks.mpg.de and simone.pigolotti@oist.jp

Keywords: stochastic processes, stochastic thermodynamics, first-passage times, fluctuation theorems, entropy production

OPEN ACCESS

RECEIVED
28 January 2026

REVISED
29 April 2026

ACCEPTED FOR PUBLICATION
19 May 2026

PUBLISHED
8 June 2026

Original Content from this work may be used under the terms of the Creative Commons Attribution 4.0 licence.

Any further distribution of this work must maintain attribution to the author(s) and the title of the work, journal citation and DOI.

Abstract

We study the sum of first passage times along an arbitrary cycle made up of $N > 2$ states of a small physical system. We show that, if the system is at thermodynamic equilibrium, this sum follows the same probability distribution regardless of whether the cycle is explored clockwise or counter-clockwise (CCW). Out of equilibrium, the distributions of clockwise and CCW cyclic first passage times are related by a detailed fluctuation theorem. This result descends from a symmetry of clockwise and CCW trajectories, which combines time reversal with swapping portions of the trajectories. We then relate the entropy produced along the cycle with the entropy production of the whole system using large deviation theory. Our results reveal a novel symmetry in stochastic systems, of potential broad applicability in non-equilibrium physics.

1. Introduction

First-passage times are of central importance in the theory of stochastic processes [1] and find widespread applications in physics and biology, including in reaction rate theory [2], spin models [3], epigenetics [4], and neural dynamics [5]. Our focus in this paper are first-passage times in physical systems, where stochasticity originates from interactions with a heat reservoir. Such systems present universal statistical properties, whose understanding is the subject of stochastic thermodynamics [6]. Some properties of first-passage times have been considered in this context. For example, it has been shown that irreversibility sets a bound on the relative fluctuations of first-passage times [7–10].

The statistical behavior of key observables in stochastic thermodynamics drastically depend on whether the system is at equilibrium or not. A main reason is that systems at thermodynamic equilibrium present an invariance under time reversal; this symmetry constrains the behavior of thermodynamic observables. However, this general idea cannot be naively applied to first-passage times. For example, the first-passage time τ_{xy} from a certain state y to a certain state x of a stochastic system is not generally related with τ_{yx}, even if the system is at thermodynamic equilibrium. The reason is that τ_{xy} and τ_{yx} are statistical quantities pertaining to two different ensembles, in which either x or y are absorbing states, so that one of them is not trivially connected with the other by an operation of time reversal.

In this manuscript, we explore a symmetry that instead involves sums of first-passage times along a closed path in a stationary stochastic system. Specifically, we consider a sequence of $N > 2$ distinct states $x_0, x_1 \dots x_{N-1}$, with $x_N \equiv x_0$ to close the path. We define the cyclic first-passage time as:

$$\tau_{\rm CW} = \sum_{j=1}^{N} \tau_{x_j, x_{j-1}}\,, \tag{1}$$

© 2026 The Author(s). Published by IOP Publishing Ltd on behalf of the Institute of Physics and Deutsche Physikalische Gesellschaft

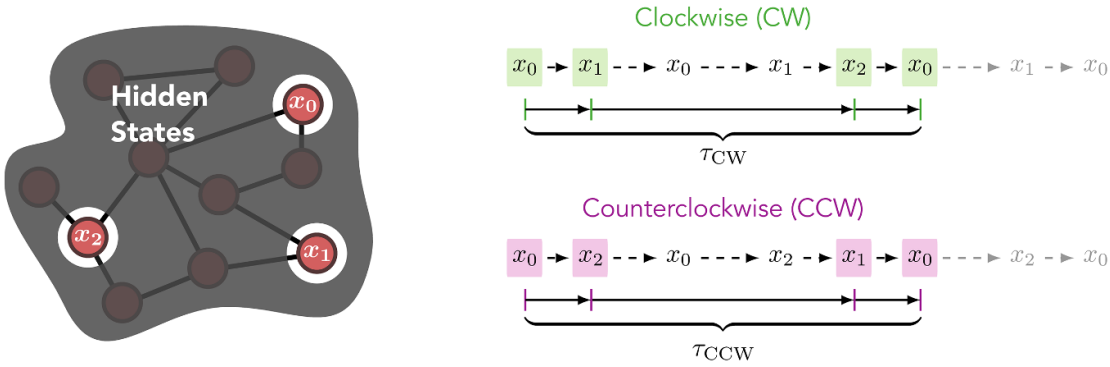


Figure 1. Clockwise (CW) and counterclockwise (CCW) trajectories over a set of three visible states, x_0, x_1, and x_2, among many hidden states in the system. In the right representation, the CW (top) and CCW (bottom) trajectories are highlighted.

where the subscript 'CW' stands for clockwise. Similarly, we define the counterclockwise (CCW) cyclic first-passage time as $\tau_{\rm CCW} = \sum_{j=1}^{N} \tau_{x_{j-1},x_j}$ (see figure 1). We shall also call these quantities 'clockwise time' and 'CCW time' for shortness. We have restricted ourselves to $N > 2$ because the case $N = 2$ is trivial, in that clockwise and CCW times coincide. From a practical point of view, measuring clockwise and CCW times only requires observing the N chosen states. This means that these quantities are measurable also in situations where only a small subset of a system's states is visible, while the remaining states are hidden.

As for individual first-passage times, CW and CCW cyclic first-passage are not related by a simple time-reversal operation, in general. However, we shall see that, at thermodynamic equilibrium, $\tau_{\rm CQ}$ and $\tau_{\rm CCW}$ follow the same probability distribution, independently of the system and of choice of the states composing the path. Additionally, out of equilibrium, the distributions of $\tau_{\rm CQ}$ and $\tau_{\rm CCW}$ are connected by a detailed fluctuation theorem. In stochastic thermodynamics, fluctuation theorems often descend from a time-reversal symmetry at the trajectory level [6, 11–13]. In our case, we shall see that the symmetry relating CW and CCW trajectories is related with time reversal, but requires cutting and pasting different portions of each trajectory. Besides its fundamental relevance, our finding implies that a difference between the distributions of $\tau_{\rm CW}$ and $\tau_{\rm CCW}$ can be taken as evidence that the system is out of thermodynamic equilibrium. We make this link explicit by deriving a direct connection between the statistics of cyclic first-passage times and those of the entropy production rate.

The paper is organized as follows. Section 2 presents the detailed fluctuation theorem for cyclic first passage times. Section 3 explains the symmetry between clockwise and CCW trajectories that underlies this detailed fluctuation theorem. Section 4 connects the scaled cumulants of the entropy production rate with those of cyclic first passage times, using tools of large deviation theory. Section 5 presents an application of our theory to a model of an enzymatic cycle. Section 6 presents conclusions and perspectives.

2. Detailed fluctuation theorem for cyclic first-passage times

We consider a sequence of $N > 2$ states explored by a stationary stochastic system. The theory that follows is valid for both discrete and continuous phase space; we only require the dynamics to be Markovian. We introduce the joint distribution $p_{\rm CW}(\tau, s)$ of observing a clockwise time $\tau_{\rm CW} = \tau$ along the sequence while producing a total entropy s. We define $p_{\rm CCW}(\tau, s)$ in a similar way. Our first main result is a detailed fluctuation theorem:

$$\frac{p_{\rm CW}(\tau, s)}{p_{\rm CCW}(\tau, -s)} = e^{s}. \tag{2}$$

Here and in the following, we choose units so that the Boltzmann constant and the temperature are both equal to one. Equation (2) implies that, at equilibrium, the marginalized clockwise and CCW distributions are identical:

$$p_{\rm CW}(\tau) = p_{\rm CCW}(\tau) \qquad \text{(equilibrium)}\,, \tag{3}$$

while in general the two distributions are related by

$$p_{\rm CW}(\tau) = \int_{-\infty}^{+\infty} {\rm d}s\, p_{\rm CCW}(\tau, s)\, {\rm e}^{-s}\,. \tag{4}$$

To prove this result, we first introduce the notation $\boldsymbol{x}$ for a stochastic trajectory, and indicate its path probability with $\mathcal{P}(\boldsymbol{x})$. Given a sequence of $N > 2$ states, we define a 'clockwise trajectory' as a trajectory associated with a clockwise time, and similarly for CCW trajectories. Any clockwise or CCW trajectory starts and ends at $x = x_0$, by definition. We now express the joint probability $p_{\rm CQ}(\tau, s)$ in terms of path probabilities:

$$p_{\rm CW}(\tau, s) = \int_{{\rm CW}_x} \mathcal{D}\boldsymbol{x}\mathcal{P}(\boldsymbol{x})\,\delta_\tau\delta_s \tag{5}$$

where ${\rm CW}_x$ is the set of all clockwise trajectories, δ_τ is a short-hand notation for $\delta(\tau(\boldsymbol{x}) - \tau)$, where $\tau(\boldsymbol{x})$ is the duration of the trajectory, and similarly $\delta_s = \delta(s(\boldsymbol{x}) - s)$ where $s(\boldsymbol{x})$ is the entropy produced along the trajectory.

Our proof is centered on the existence of a combined operator $\hat{T}\hat{C}$ that maps a clockwise trajectory into a CCW one. Here, the operator $\hat{T}$ represents time reversal, while $\hat{C}$ is an operator that preserves both path probability and entropy production, and that we will present in detail in the next section. Importantly, the operation $\hat{T}\hat{C}$ is an involution, meaning that $\hat{T}\hat{C}\hat{T}\hat{C} = \hat{I}$, where $\hat{I}$ is the identity operator on ${\rm CW}_x$ (or ${\rm CCW}_x$, the analogous of ${\rm CW}_x$ for CCW trajectories). By applying the $\hat{T}\hat{C}$ operator, we have:

$$\begin{aligned} p_{\rm CW}(\tau, s) &= \int_{{\rm CW}_x} \mathcal{D}\boldsymbol{x}\frac{\mathcal{P}(\boldsymbol{x})}{\mathcal{P}\left(\hat{T}\hat{C}\boldsymbol{x}\right)}\mathcal{P}\left(\hat{T}\hat{C}\boldsymbol{x}\right)\delta_\tau\delta_s \\ &= \int_{{\rm CCW}_x} \mathcal{D}\boldsymbol{x}\mathcal{P}(\boldsymbol{x})\,{\rm e}^{-s(\boldsymbol{x})}\delta_\tau\delta_{-s} = p_{\rm CCW}(\tau, -s)\,{\rm e}^{s}\,. \end{aligned} \tag{6}$$

We obtained this result by the following steps. In the first line, we multiplied and divided by $\mathcal{P}(\hat{T}\hat{C}\boldsymbol{x})$. In the second line, we changed the integration domain into the set of CCW trajectories, and used the irreversibility relation $\mathcal{P}(\hat{T}\hat{C}\boldsymbol{x})/\mathcal{P}(\boldsymbol{x}) = {\rm e}^{-s(\boldsymbol{x})}$ [6].

3. The symmetry leading to the detailed fluctuation theorem

We now properly introduce the operator $\hat{C}$ and its properties. Given a set of N visible states, we represent trajectories as discrete sequence of visited states among the visible ones. These sequences always start and end in x_0, and have variable length l. We call K the set of such cyclic sequences. A CW trajectory has therefore the form

$$\boldsymbol{x} = \left\{ \overbrace{x_0, \underbrace{\dots}_{\nexists\, x_1} x_1}^{x_0 \to x_1}, \underbrace{\dots}_{\nexists\, x_2} x_2, \dots \overbrace{x_{N-1}, \underbrace{\dots}_{\nexists\, x_0} x_0}^{x_{N-1} \to x_0} \right\} \in {\rm CW}_x\,.$$

A clockwise trajectory can visit x_0 several times. We also define the sets $\overline{\rm CW}_x$ and $\overline{\rm CCW}_x$. A trajectory belongs to $\overline{\rm CW}_x$ ($\overline{\rm CCW}_x$) if its time-reverse is a CW (CCW) trajectory, i.e. if it belongs to ${\rm CW}_x$ (${\rm CCW}_x$). Our goal is to establish a relation between the sets ${\rm CW}_x$ and $\overline{\rm CCW}_x$. There exist trajectories that are both in ${\rm CW}_x$ and in $\overline{\rm CCW}_x$, e.g. for $N = 4$,

$$\boldsymbol{x} = \{x_0, x_1, x_2, x_3, x_0\} \in {\rm CW}_x, \overline{\rm CCW}_x\,,$$

but this is not always the case, e.g.

$$\boldsymbol{x} = \{x_0, x_1, x_2, x_3, x_0, x_2, x_0\} \in \overline{\rm CCW}_x\,,\ \boldsymbol{x} \notin {\rm CW}_x\,.$$

This means that, in general, CCW trajectories cannot be constructed from CW trajectories by just reversing the time.

Given a generic set of trajectories S, we define as S-minimal trajectory a trajectory belonging to S that does not contain any proper subsequence of length $l > 1$ which also belongs to S. We define a K-minimal trajectory as a 'block', i.e. a block is a trajectory that only visits x_0 at its start and end. We call

n the number of blocks in a trajectory, so that the number of intermediate x_0s in the given trajectory is equal to $n-1$. Furthermore, we define as 'minimal cycle' a CW_x-minimal trajectory and indicate it as $\{x_0, B_x, x_0\}$. We remark that a minimal cycle may or may not be a block. A minimal cycle is a $\overline{\mathrm{CCW}}_x$-minimal trajectory as well. In fact, the states in a minimal cycle are visited in the CW order forward in time and in the CCW order when moving backward in time. Furthermore, when moving backward in time, the minimal cycle terminates as soon as it completes the CCW cycle, thus meeting the conditions for being a CCW trajectory.

A CW trajectory can contain an arbitrary number of blocks, but it must contain one and only one minimal cycle at its end, i.e. it must be of the form

$$\boldsymbol{x} = \{x_0, \ldots, x_0, B_x, x_0\} \in \mathrm{CW}_x \,, \tag{7}$$

since it has to end after having completed the cycle. Similarly, a $\overline{\mathrm{CCW}}$ trajectory must contain one and only one minimal cycle at its beginning:

$$\boldsymbol{x} = \{x_0, B_x, x_0, \ldots, x_0\} \in \overline{\mathrm{CCW}}_x \,. \tag{8}$$

CW trajectories that are themselves minimal cycles belong to both CW_x and $\overline{\mathrm{CCW}}_x$.

We now introduce cut operators $\hat{C}_i$, $i = 1 \ldots n-1$ acting on a trajectory containing $n-1$ intermediate x_0s. The cut operator $\hat{C}_i$ swaps the two portions of the trajectory before and after the ith intermediate x_0. As an example,

$$\begin{aligned} \{x\} &= \{x_0, \ldots, x_0, B_x, x_0\} \in \mathrm{CW}_x \\ \hat{C}_1\{x\} &= \{x_0, B_x, x_0, \ldots, x_0\} \in \overline{\mathrm{CCW}}_x . \end{aligned} \tag{9}$$

Each operator $\hat{C}_i$ preserves the path probability. To see that, we call $\boldsymbol{x}^A$ and $\boldsymbol{x}^B$ the two portions of trajectory before and after the time at which the ith intermediate x_0 is reached. Since the dynamics is Markovian, the path probability factorizes as

$$\mathcal{P}(\boldsymbol{x}|x_0) = \mathcal{P}\left(\boldsymbol{x}^A|x_0\right)\mathcal{P}\left(\boldsymbol{x}^B|x_0\right) \,. \tag{10}$$

The invariance of the path probability under application of $\hat{C}_i$ trivially follows from the commutative property of the product in the right hand side of equation (10).

The family of cut operators $\hat{C}_i$, $i = 1 \ldots n-1$ maps a trajectory into $n-1$ trajectories of the same length. This relation defines an equivalence class, in the sense that each of the n trajectories (including the original one) is mapped into all the others by one of the $\hat{C}_i$s.

We graphically represent this equivalence class by an oriented ring of states, see figure 2(a). In this representation, each trajectory in the equivalence class corresponds to a choice of a particular x_0 as a starting and end point along the ring. We represent minimal cycles as arches on top of the ring.

We shall prove that each equivalence class contains the same number of CW and $\overline{\mathrm{CCW}}$ trajectories. Thanks to this property, one can define a bijection between CW_x and $\overline{\mathrm{CCW}}_x$ by arbitrarily pairing CW and $\overline{\mathrm{CCW}}$ trajectories in each of the equivalence classes. Calling $\hat{C}$ the choice of cut corresponding to this pairing, then $\hat{T}\hat{C}$ is a bijection between the sets CW_x and CCW_x.

To prove this property, we define a function $\phi(x)$ that depends on the state x along the ring and counts the number of 'surviving' minimal cycles if a trajectory is created by opening the ring at position x (see figure 2(a)). By definition, $\phi(x)$ is a periodic function. We notice that only one minimal cycle can start (or end) at each x_0. The reason is that one of the two minimal cycles starting/ending at the same point would contain the other, and therefore it would not be minimal. This property implies that $\phi(x)$ can only change by one unit at a step, i.e. from $n \to n \pm 1$. It is however possible that one minimal cycle ends at the same point in which another (or the same) minimal cycle starts. We represent these events as 'spikes' in the function $\phi(x)$, i.e. transitions from $n \to n+1$ immediately followed by transitions from $n+1 \to n$, see figure 2(f).

We now note that transitions of $\phi(x)$ from 1 to 0 mark the beginning of a single surviving minimal cycle in the trajectory. Therefore, such points $x = x_0$ are associated with a $\overline{\mathrm{CCW}}_x$ trajectory. Similarly, transitions from 0 to 1 denote the end points of single surviving minimal cycles and, as such, mark the x_0s associated with a CW trajectory. Since $\phi(x)$ is a periodic function and can only change by one unit at a step, the numbers of transitions $1 \to 0$ and $0 \to 1$ must be equal. This directly implies that each equivalence class contains equal numbers of CW and $\overline{\mathrm{CCW}}$ trajectories, as we were meant to show. Examples of equivalence classes and corresponding function $\phi(x)$ are shown in figures 2(a)–(f).

In appendix, we also provide an alternative proof of equation (2) based on renewal theory.

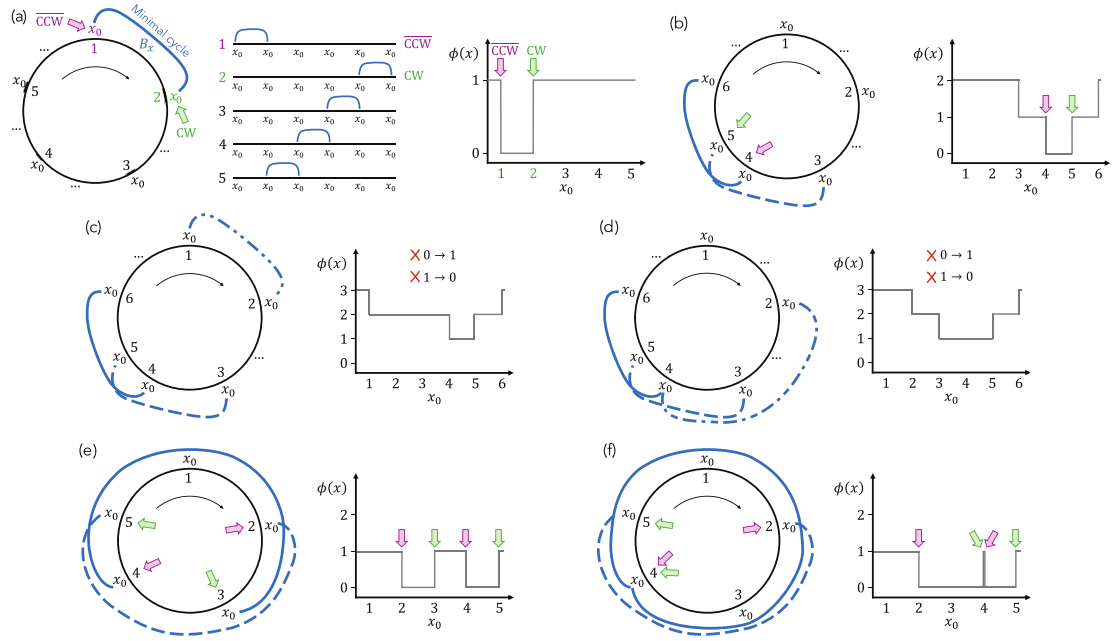


Figure 2. Equivalence class of cyclic trajectories in six examples of increasing complexity. (a) Example of a trajectory including a single minimal cycle. The two x_0s whose cuts lead to a CW and a $\overline{\text{CCW}}$ trajectory are marked with arrows. To avoid confusion, we remark that the arrows are not meant to indicate the direction of cycles. The five trajectories associated with all possible cuts are shown in the right, alongside the position of the minimal cycle. The function $\phi(x)$ associated with the equivalence class is also shown. (b) Two overlapping minimal cycles are present and two different cuts lead to a CW and a $\overline{\text{CCW}}$ trajectory. (c)–(d) Two cases in which none of the cuts lead to either CW or $\overline{\text{CCW}}$ trajectories, due to the presence of multiple non-overlapping minimal cycles. (e)–(f) Examples in which multiple CW and $\overline{\text{CCW}}$ trajectories are present in the same equivalence class. In example (f), one of the trajectories belongs to both CW and $\overline{\text{CCW}}$. In all examples, the number of CW trajectories in each equivalence class is equal to the number of $\overline{\text{CCW}}$ trajectories.

4. Cyclic first-passage times and entropy production rate

We now assume to know the probability $p_{\text{CW}}(\tau, s)$, or equivalently $p_{\overline{\text{CCW}}}(\tau, s)$, for a given cycle. Our goal is to use this information to compute the large deviation function of the total entropy production.

We consider a long trajectory that completes the cycle N_C times, and define the intensive variables

$$j_{\tilde{s}} = \frac{1}{N_C}\sum_{i=1}^{N_C} s^{(i)} \qquad \text{and} \qquad j_\tau = \frac{1}{N_C}\sum_{i=1}^{N_C} \tau^{(i)}\,, \tag{11}$$

where $s^{(i)}$ and $\tau^{(i)}$ are the entropy production and time associated with the ith cycle, respectively. Each sum is composed of i.i.d. random variables, although $s^{(i)}$ and $\tau^{(j)}$ are correlated for $i = j$. Therefore, the joint scaled cumulant generating function is given by

$$\Phi(k_s, k_\tau) = \lim_{N_C\to\infty} \frac{1}{N_C} \ln\left\langle \mathrm{e}^{N_C[k_s j_{\tilde{s}} + k_\tau j_\tau]}\right\rangle = \ln\left\langle \mathrm{e}^{k_s s + k_\tau \tau}\right\rangle\,. \tag{12}$$

Also, the variables $j_{\tilde{s}}$ and j_τ obey a large deviation principle, meaning that $P(j_{\tilde{s}}, j_\tau) \asymp \mathrm{e}^{-N_C I(j_{\tilde{s}}, j_\tau)}$. The Gartner-Ellis theorem states that the rate function can be obtained by a Legendre transform [14]:

$$I(j_{\tilde{s}}, j_\tau) = \sup_{k_s, k_\tau \in \Re} \left[k_s j_{\tilde{s}} + k_\tau j_\tau - \Phi(k_s, k_\tau)\right]\,. \tag{13}$$

In this case, we fix $T = \sum_{i=1}^{N_C} \tau^{(i)}$ and introduce the new random variables $n_C = N_C/T$ and $j_s = j_{\tilde{s}} N_C/T$. By changing of variables in the probability distribution and using that the Jacobian does not contribute to the leading exponential order, we find that the joint large-deviation function $J(j_s, n_C)$ is given by

$$J(j_s, n_C) = n_C I(j_s/n_C, 1/n_C) \tag{14}$$

in terms of these new variables. We now use the contraction principle of large deviation theory to obtain

$$J(j_s) = \inf_{n_C \in \Re^+} J(j_s, n_C)\,. \tag{15}$$

At this point, we can interpret $J(j_s)$ as the large-deviation function associated with the empirical entropy production rate, since we marginalized over n_C.

By combining equations (13)–(15), we have

$$J(j_s) = \inf_{n_C} n_C I(j_s/n_C, 1/n_C) = \inf_{n_C} n_C \sup_{k_s,k_\tau} \left[\frac{k_s j_s + k_\tau}{n_C} - \Phi(k_s,k_\tau) \right]. \tag{16}$$

Assuming convexity, we swap the order of the supremum and infimum, and rewrite equation (16) as

$$J(j_s) = \sup_{k_s} \left[k_s j_s - \inf_{n_C,k_\tau} \left(n_C \Phi(k_s,k_\tau) - k_\tau \right) \right]. \tag{17}$$

Again from the Gartner-Ellis theorem, the scaled cumulant generating function of the empirical entropy production rate is expressed by

$$\psi(k_s) = \lim_{T\to\infty} \frac{1}{T} \ln \left\langle e^{T k_s j_s} \right\rangle = \inf_{n_C,k_\tau} \left(n_C \Phi(k_s,k_\tau) - k_\tau \right). \tag{18}$$

The extremality conditions are

$$\begin{aligned} &\Phi\left(k_s, k_\tau^{\inf}\right) = 0 \qquad \text{or} \qquad n_C^{\inf} = 0\,, \qquad \text{and} \\ &n_C^{\inf} \partial_{k_\tau} \Phi(k_s,k_\tau)\big|_{k_\tau = k_\tau^{\inf}} = 1\,. \end{aligned} \tag{19}$$

These conditions are derived by simply taking derivatives to find the infimum or, in the case of the condition $n_C^{\inf} = 0$, by noticing that the infimum might be attained at the boundary of the interval. We focus on the first of these conditions. Substituting this back into equation (18), we obtain the remarkably simple relationship

$$\psi(k_s) = -k_\tau^{\inf}. \tag{20}$$

We further assume that the non-trivial case $n_C^{\inf} > 0$ always holds (otherwise the second condition in equation (19) cannot be satisfied). This implies that $k_\tau^{\inf}$ can be obtained from the following relationship

$$\left\langle e^{k_s s + k_\tau^{\inf} \tau} \right\rangle = 1\,. \tag{21}$$

Or, equivalently,

$$\left\langle e^{k_s s - \psi(k_s)\tau} \right\rangle = 1. \tag{22}$$

Equations (21) and (22) are our second main result. The scaled cumulants of the entropy production rate can be obtained by expanding equation (22) around $k_s = 0$, and imposing that each term vanishes (since the function is equal to a constant). At the first order we obtain

$$\langle j_s \rangle = \mu_s = \frac{\langle s \rangle}{\langle \tau \rangle}\,. \tag{23}$$

The second order term yields the scaled variance

$$\sigma_s = \left\langle (j_s - \mu_s)^2 \right\rangle = \frac{\mathrm{d}^2}{\mathrm{d}k_s^2} \psi(k_s)\big|_{k_s=0} = \frac{1}{\langle \tau \rangle} \left\langle \left(s - \frac{\langle s \rangle}{\langle \tau \rangle} \tau \right)^2 \right\rangle = \frac{1}{\langle \tau \rangle} \left\langle (s - \mu_s \tau)^2 \right\rangle. \tag{24}$$

Finally, we compute the third central moment:

$$\langle (j_s - \mu_s)^3 \rangle = \frac{1}{\langle \tau \rangle} \left[\left\langle (s - \mu_s \tau)^3 \right\rangle - 3\sigma_s \langle \tau (s - \mu_s \tau) \rangle \right]. \tag{25}$$

We remark that we did not specify whether these N_C cycles are performed clockwise or CCW. As a consequence, we can equivalently compute all averages in equations (23)–(25) over clockwise or CCW distributions.

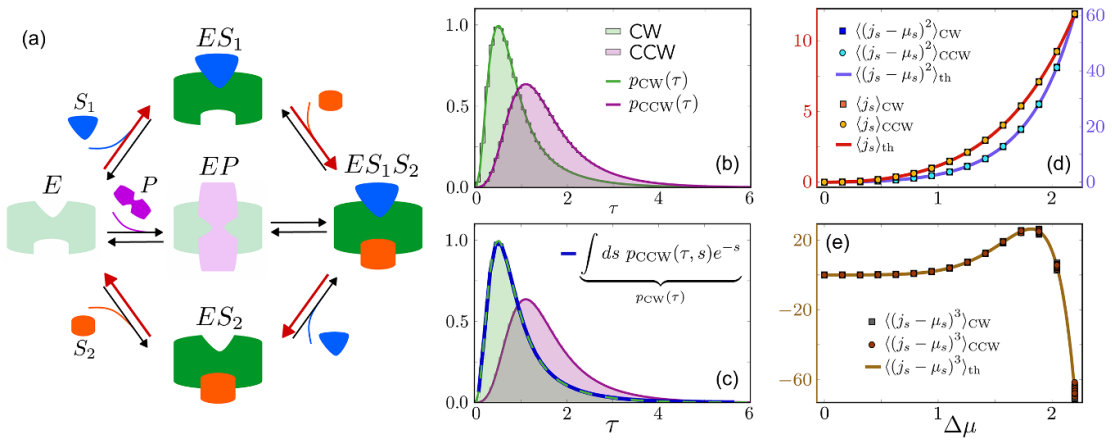


Figure 3. (a) Enzymatic cycle in which two substrates, S_1 and S_2, are converted into a product, P. Substrates and product concentrations are chemostatted. Only substrate-bound states are visible (not shaded) and the system is externally driven to cycle clockwise (red arrows). (b) Distribution of the first passage time associated with clockwise ($ES_1 - ES_1S_2 - ES_2 - ES_1$) and CCW ($ES_1 - ES_2 - ES_1S_2 - ES_1$) visible cycles. Simulations were performed using a Gillespie algorithm. The distributions were then computed by enumerating CW and CCW events together with their total entropy production, and constructing the corresponding histograms. (c) Numerical validation of the fluctuation theorem in equation (2). The clockwise distribution is recovered from the CCW statistics upon integration over all possible values of the entropy production. (d) Mean and variance of the entropy production rate estimated from the large-deviation argument in equation (22) (applied to clockwise and CCW cycles) coincide with their corresponding theoretical values. Here we denote by $\langle\cdot\rangle_{CQ}$ an average performed over the distribution of clockwise cycles (and similarly for $\langle\cdot\rangle_{CCW}$), while $\langle\cdot\rangle_{th}$ indicates the corresponding theoretical expression. (e) The same comparison is shown for the third central moment. Numerical values have been obtained from 20 different realizations for each cycle direction (clockwise and CCW), all reported in the figure. Energies (ϵ_i) and energetic barriers (B_{ij}) are: $\epsilon_E = 0, \epsilon_{ES_1} = 0.023, \epsilon_{ES_1S_2} = 0.20, \epsilon_{ES_2} = 0.023, \epsilon_{EP} = 0.19, B_{E,ES_1} = 0.24, B_{E,ES_2} = 0.28, B_{E,EP} = 0.27, B_{ES_1,ES_1S_2} = 0.28, B_{ES_2,ES_1S_2} = 0.23, B_{ES_1S_2,EP} = 0.26$. We take $k_BT = 1$, $[S_1] = [S_2] = [P] = 1$, and the nonequilibrium driving equal to $\Delta\mu = 2$ in panels (a)–(c).

5. Example: enzymatic cycle

We test our results using a model of an enzymatic cycle, see figure 3(a). We consider an enzyme E that can bind two different substrates, S_1 and S_2, thereby forming two distinct complexes, ES_1 and ES_2, with rates $k_{E\to ES_1}$ and $k_{E\to ES_2}$, respectively. These complexes can further bind to the other substrate, thus forming the trimer ES_1S_2. The enzyme catalyzes the conversion of both bound substrates into a product P, i.e. ES_1S_2 transforms into EP with a rate $k_{ES_1S_2\to EP}$. This product is then released into the environment, thereby freeing the enzyme. For thermodynamic consistency, we take all reactions to be reversible, i.e. if a chemical rate connecting any two states i and j, $k_{i\to j}$, is different from zero, then $k_{j\to i} \neq 0$. The entire set of chemical reactions is

$$E + S_1 \leftrightharpoons ES_1 \qquad E + S_2 \leftrightharpoons ES_2$$
$$ES_1 + S_2 \leftrightharpoons ES_1S_2 \qquad ES_2 + S_1 \leftrightharpoons ES_1S_2$$
$$E + P \leftrightharpoons EP \qquad ES_1S_2 \leftrightharpoons EP$$

with the transition rates parametrized as:

$$k_{i\to j} = \mathrm{e}^{-\left(B_{ij}-\epsilon_i\right)} . \tag{26}$$

Here, ϵ_i is the energy of the state i, and $B_{ij} = B_{ji}$ the energetic barrier associated with the interconversion of i into j. We consider the concentrations of substrates and product to be chemostatted at their equilibrium values, i.e. $[S_1][S_2]/[P] = 1$ in this case, for simplicity. This condition implies that, in the absence of any additional driving, the system satisfies detailed balance, and $p_{CQ}(\tau) = p_{CCW}(\tau)$. We further consider the presence of a nonequilibrium driving $\Delta\mu$ that induces the enzyme to preferentially bind first S_1 and then S_2, and unbind first S_2 and then S_1. In figure 3(a), the red arrows indicate the rates modified by the driving as

$$k_{i\to j} \to k^{\mathrm{neq}}_{i\to j} = k_{i\to j}\mathrm{e}^{\Delta\mu} . \tag{27}$$

We consider the scenario in which the enzyme can be observed only when bound to (one or both) substrates, see figure 3(a). We track clockwise and CCW first-passage cycles in this reduced 3-state system and record their associated completion times at stationarity. We thereby compute and compare $p_{CQ}(\tau)$

and $p_{\rm CCW}(\tau)$, see figure 3(b). As expected, clockwise cycles are completed, on average, in shorter times out of equilibrium.

Since we are dealing with a discrete-state system, given a cyclic trajectory visiting N states, at stationarity, we compute the entropy production by the expression [6]:

$$s(\boldsymbol{x}) = \sum_{j=1}^{N} \log \frac{k_{x_{j-1}\to x_j}}{k_{x_j\to x_{j-1}}} \,. \tag{28}$$

We find excellent agreement between simulations and the fluctuation theorem embodied in equation (4), see figure 3(c). We now test our ability to infer the statistics of the entropy production rate j_s from the entropy produced during clockwise or CCW cycles. The expressions of mean, variance, and third central moment are respectively shown in equations (23)–(25). In figure 3(d) and (e), we compare the numerical results obtained by these formulas (both considering clockwise and CCW cycles) with their exact analytical values, computed with the graphical method detailed in [15, 16]. We find once again an excellent agreement that validates our theoretical results.

6. Discussion

In this work, we uncovered a nonequilibrium symmetry of cyclic first-passage times among an arbitrary subset of states of a stochastic system. This symmetry leads to a detailed fluctuation theorem that relates the timing of such cycles with the entropy dissipated in the process. Our approach makes minimal assumptions on the underlying dynamics and requires observing an arbitrary subset of $N > 2$ states. These features make our approach particularly apt to probe the nonequilibrium behavior of biological stochastic systems that operate through cyclic processes.

Experimental advancements have made it possible to measure first-passage times at the molecular level, raising growing interest in this topic [17–19]. In particular, mesoscopic processes in which first-passage-time statistics are experimentally accessible include unimolecular strand displacement in DNA [20]; colloidal particles diffusing in fractal landscapes [21]; and mechanical stepping events in single-molecule studies of chemomechanical kinesin networks [22, 23]. In this context, our result can be applied to identify the main dissipative macroscopic cycles in a system, by comparing clockwise and CCW trajectories between different subsets of visible states. Additionally, the connection we revealed between statistics of cyclic first passage times and entropy production rate complements previous efforts to infer entropy production from partial information [23–26]. However, estimating the dissipation associated with each cycle might be experimentally challenging, and potentially require additional information, such as the amount of consumed ATP in chemically active systems. Nevertheless, our alternative approach exploits this additional information to infer, in principle, the entire statistics of the total entropy production.

Our theory can be extended in several directions to facilitate experimental application. In particular, experimentally accessible states are often coarse-grained, including unresolved internal degrees of freedom. Extending the nonequilibrium symmetry uncovered here to such situations is a nontrivial problem that we leave for future investigations. Another promising extension is to consider intertwined clockwise and CCW cycles, with the goal of using this nested structure to probe additional nonequilibrium features of a system.

Acknowledgments

We thank Izaak Neri for a critical reading of the manuscript and for suggesting [19]. DMB conducted part of this research while visiting the Okinawa Institute of Science and Technology (OIST) through the Theoretical Sciences Visiting Program (TSVP). All authors thank the TSVP since part of initial discussions on this study were conducted during a TSVP workshop. DMB is funded by the STARS@UNIPD program through the project 'ActiveInfo'.

Data availability statement

No new data were created or analysed in this study.

Appendix. Alternative derivation of the detailed fluctuation theorem

Here we use an alternative approach based on Laplace transform and renewal theory to prove the detailed fluctuation theorem for the cyclic first-passage-time distribution in equation (2). The cyclic first-passage probability is defined as the probability of sequential first-passage events, following the order $[x_0, x_1, \cdots, x_{N-1}, x_0]$. The probability of completing the cycle in a time τ and producing an entropy s can be written as the (bivariate) convolution of first-passage distributions between adjacent states:

$$p_{\rm CW}(\tau, s) = \bigstar_{j=1}^{N} f_{x_j, x_{j-1}}(\tau, s) \ , \tag{A1}$$

where $\star$ denotes convolution in (τ, s):

$$(f \star g)(\tau, s) = \int_0^{\tau} {\rm d}t' \int_{-\infty}^{\infty} {\rm d}s' \, f(t', s') \, g(\tau - t', s - s') \ .$$

Taking the Laplace transform in (τ, s) (unilateral in τ, bilateral in s), here indicated as $\mathcal{L}_{\tau,s}$ and defined as

$$\mathcal{L}_{\tau,s}\{\phi(\tau, s)\} = \int_0^{+\infty} {\rm d}\tau \int_{-\infty}^{+\infty} {\rm d}s \, {\rm e}^{-u\tau} {\rm e}^{-vs} \phi(\tau, s) \tag{A2}$$

for a generic function $\phi(\tau, s)$, we obtain

$$P_{\rm CW}(u, v) = \mathcal{L}_{\tau,s}\{p_{\rm CW}(\tau, s)\} = \prod_{j=1}^{N} F_{x_j, x_{j-1}}(u, v) \ . \tag{A3}$$

where $F_{x_j, x_{j-1}}(u, v) = \mathcal{L}_{\tau,s}\{f_{x_j, x_{j-1}}(\tau, s)\}$. A classic result in renewal theory [1, 27] relates the Laplace transforms of the first-passage distribution and propagators:

$$F_{x_j, x_{j-1}}(u, v) = \frac{P_{x_j, x_{j-1}}(u, v)}{P_{x_j, x_j}(u, v)} \ , \tag{A4}$$

with $P_{x,y}(u, v) = \mathcal{L}_{\tau,s}\{p_{x,y}(\tau, s)\}$, being $p_{x,y}(\tau, s)$ the probability of going from y to x in a time interval τ while producing a total entropy s. So that we have

$$P_{\rm CW}(u, v) = \prod_{j=1}^{N} \frac{P_{x_j, x_{j-1}}(u, v)}{P_{x_j, x_j}(u, v)} \ . \tag{A5}$$

For the CCW cycle $[x_0, x_{N-1}, \ldots, x_1, x_0]$, this means

$$P_{\rm CCW}(u, v) = \prod_{j=1}^{N} \frac{P_{x_{j-1}, x_j}(u, v)}{P_{x_{j-1}, x_{j-1}}(u, v)} \ . \tag{A6}$$

We now use the fluctuation theorem for propagators [6, 13]:

$$\frac{p_{x,y}(\tau, s)}{p_{y,x}(\tau, -s)} = {\rm e}^{s} \qquad \Longleftrightarrow \qquad P_{x,y}(u, v) = P_{y,x}(u, 1 - v) \, . \tag{A7}$$

Setting $x = y$ also yields $P_{x,x}(u, v) = P_{x,x}(u, 1 - v)$. Applying $P_{x_j, x_{j-1}}(u, v) = P_{x_{j-1}, x_j}(u, 1 - v)$ and $P_{x_j, x_j}(u, v) = P_{x_j, x_j}(u, 1 - v)$ to (A5), we have:

$$P_{\rm CW}(u, v) = \prod_{j=1}^{N} \frac{P_{x_{j-1}, x_j}(u, 1 - v)}{P_{x_{j-1}, x_{j-1}}(u, 1 - v)} = P_{\rm CCW}(u, 1 - v) \, . \tag{A8}$$

This is the detailed fluctuation theorem in the Laplace domain. Taking the inverse Laplace transforms for u and v directly yields equation (2).

ORCID iDs

Daniel Maria Busiello 0000-0002-6754-5019
Shiling Liang 0000-0001-8968-8443
Simone Pigolotti 0000-0002-6157-6906

References

[1] Redner S 2001 *A Guide to First-Passage Processes* (Cambridge University Press)
[2] Hänggi P, Talkner P and Borkovec M 1990 Reaction-rate theory: fifty years after kramers *Rev. Mod. Phys.* **62** 251
[3] Bray A J, Majumdar S N and Schehr G 2013 Persistence and first-passage properties in nonequilibrium systems *Adv. Phys.* **62** 225
[4] Aurell E and Sneppen K 2002 Epigenetics as a first exit problem *Phys. Rev. Lett.* **88** 048101
[5] Burkitt A N 2006 A review of the integrate-and-fire neuron model: I. homogeneous synaptic input *Biol. Cybern.* **95** 1–19
[6] Peliti L and Pigolotti S 2021 *Stochastic Thermodynamics: an Introduction* (Princeton University Press)
[7] Gingrich T R and Horowitz J M 2017 Fundamental bounds on first passage time fluctuations for currents *Phys. Rev. Lett.* **119** 170601
[8] Hiura K and Sasa S-I 2021 Kinetic uncertainty relation on first-passage time for accumulated current *Phys. Rev. E* **103** L050103
[9] Pal A, Reuveni S and Rahav S 2021 Thermodynamic uncertainty relation for first-passage times on Markov chains *Phys. Rev. Res.* **3** L032034
[10] Raghu A and Neri I 2025 Thermodynamic bounds and symmetries in first-passage problems of fluctuating currents *New J. Phys.* **27** 124602
[11] Chetrite R and Gawędzki K 2008 Fluctuation relations for diffusion processes *Commun. Math. Phys.* **282** 469
[12] Harris R J and Schütz G M 2007 Fluctuation theorems for stochastic dynamics *J. Stat. Mech.* 07020
[13] Seifert U 2012 Stochastic thermodynamics, fluctuation theorems and molecular machines *Rep. Prog. Phys.* **75** 126001
[14] Ellis R S 2007 *Entropy, Large Deviations and Statistical Mechanics* (Springer)
[15] Busiello D M and Fiore C 2022 Hyperaccurate bounds in discrete-state Markovian systems *J. Phys. A: Math. Theor.* **55** 485004
[16] Padmanabha P, Busiello D M, Maritan A and Gupta D 2023 Fluctuations of entropy production of a run-and-tumble particle *Phys. Rev. E* **107** 014129
[17] Grebenkov D S, Metzler R and Oshanin G 2018 Towards a full quantitative description of single-molecule reaction kinetics in biological cells *Phys. Chem. Chem. Phys.* **20** 16393
[18] Berezhkovskii A M and Makarov D E 2021 On distributions of barrier crossing times as observed in single-molecule studies of biomolecules *Biophys. Rep.* **1** 100029
[19] Jia C, Jiang D-Q and Qian M-P 2016 Cycle symmetries and circulation fluctuations for discrete-time and continuous-time Markov chains *Ann. Appl. Probab.* **26** 2454
[20] Broadwater D B, Cook A W and Kim H D 2021 First passage time study of DNA strand displacement *Biophys. J.* **120** 2400
[21] Zunke C, Bewerunge J, Platten F, Egelhaaf S U and Godec A 2022 First-passage statistics of colloids on fractals: theory and experimental realization *Sci. Adv.* **8** eabk0627
[22] Carter N J and Cross R 2005 Mechanics of the kinesin step *Nature* **435** 308
[23] Harunari P E, Dutta A, Polettini M and Roldán E 2022 What to learn from a few visible transitions'statistics? *Phys. Rev. X* **12** 041026
[24] Li J, Horowitz J M, Gingrich T R and Fakhri N 2019 Quantifying dissipation using fluctuating currents *Nat. Commun.* **10** 1666
[25] Skinner D J and Dunkel J 2021 Improved bounds on entropy production in living systems *Proc. Natl Acad. Sci.* vol 118 p e2024300118
[26] Van der Meer J, Ertel B and Seifert U 2022 Thermodynamic inference in partially accessible Markov networks: a unifying perspective from transition-based waiting time distributions *Phys. Rev. X* **12** 031025
[27] Montroll E W and Weiss G H 1965 Random walks on lattices. II *J. Math. Phys.* **6** 167