A general theory for irreversible thermodynamics

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We demonstrate that irreversibility arises from the principles of microscopic reversibility and the presence of memory in the time evolution of a single copy of a system driven by a protocol. We introduce microscopic reversibility by using the concept of protocol- and pathway-dependent thermodynamic function, as defined in J.R. Arias-Gonzalez, arXiv:1511.08017 [cond-mat.stat-mech], and memory by using the concept of non-Markovianity, as in J.R. Arias-Gonzalez, arXiv:1511.06139 [cond-mat.stat-mech]. We define work as the change in free energy and heat as the change in entropy for microscopic, individual pathways of a system subject to a protocol. We find that all non-equilibrium statistics emerge naturally. In particular, we derive most known fluctuation theorems and formulate two others. While the conservation of energy is invoked both at the level of the individual pathway and in ensemble-average processes, the second law of thermodynamics and the time arrow, which are only fulfilled in ensemble-average processes, are shown to be consequences of microscopic reversibility and non-Markovianity.

Non-equilibrium thermodynamics seeks to understand irreversible processes, namely, those for which the initial state of a system becomes irrecoverable without energy expenditure. Statistical Mechanics, in turn, explains from first physical laws how microscopic fluctuations lead to equilibrium processes in the macroscopic limit [1,2]. It is known that irreversible processes devalue the energy of a system, that is, part of the energy that a system exchanges with the environment is wasted in the sense that it cannot be transformed into useful work. This is the second law of thermodynamics, which is obeyed by ensemble-averaged (time-averaged if ergodicity can be applied) systems, not under an individual pathway along which the system fluctuates sometimes generating so-called transient violations of this law.

Fluctuation theorems have appeared in recent years explaining quantitatively energy imbalances between forward and reverse processes or between equilibrium and non-equilibrium processes that connect an initially equilibrium state with a final, generally non-equilibrium state of a system [3,4]. These theorems have been tested experimentally [5–7], mostly in biomolecular systems analyzed on a one by one basis [8]. However, a fundamental theory based on general principles underlying those theorems has not been established. In other words, there is to date no formal framework that uses statistics and first physical laws to precisely describe how irreversibility arises from fluctuations.

Thermodynamics establishes relationships among ensemble-average values of the thermodynamic potentials, what ultimately neglects the individuality of a single copy of the system or the single pathway that the system describes. Single-molecule biophysics is bringing to the foreground of the statistical discussion the importance of single pathways and single systems because biochemical reactions do not occur in ensembles in the cell [8]. It is then legitimized analyzing energy exchanges from the single object viewpoint.

We previously developed a general framework for microscopic reversible pathways based on Non-Markovian relations between the present and the previous states of a system and the fact that it is fair to define thermodynamic functions for a single copy of the system [9,10]. Here, we use these concepts, namely, (1), Microscopic reversibility, (2), Non-Markovianity and (3), what we may call here individuality, to explain non-equilibrium processes. The third one is clear at least for classical systems, which are distinguishable, and, as introduced, can be followed experimentally at the single copy level. We will illustrate our theory by deducing the most known fluctuation theorems and by introducing two new closing relations.

We suppose that our system is in contact with a thermal bath at temperature $T$ at all times. We recognize the existence of a protocol that stochastically drives the evolution of the system through privileged pathways, each comprised of a set of successive possible states according to a directional, stochastic chain with memory [8]. In the following, we will use the terms substate (or event), quasistate and state as defined in our previous work [10]: substates will refer to the sequential stages that a system traverses in its evolution, a quasistate will refer to a certain substate at time $t$ plus the history of substates that the system recalls and a state will refer to the ensemble of quasistates that comply with the constraints fixed by the protocol at time $t$. In addition, here, we will use the term pathway to refer to a single microscopic trajectory in the phase space, as defined by a sequence of substates, and will reserve the term process for the ensemble average over the pathways that the system can follow under the existing protocol. This ensemble average is different from a time average if the memory of the
system is long enough (i.e., if it comprises a sufficiently large number of previous substates) with respect to the number of substates that the system goes through in its evolution along a pathway under the protocol. In these conditions, the average over the ensemble of substates adopted by the system along a certain pathway under a certain protocol may not be the same that the average over an ensemble of copies of the system, each describing a certain pathway driven by the same protocol, making the ergodic hypothesis not valid in general.

We denote by \( \lambda \) and \( \lambda^{-1} \) the direct and inverse protocols, respectively, and their associated set of control parameters. The inverse protocol denotes the time-reversed forward protocol, hence it is characterized by the same set of parameters with opposite evolution; the superindex label \( \lterms{-1} \) may be then dropped down when there is no confusion on time direction. Given two temporal instants \( t > \tau \), we associate a directional, stochastic chain with memory [9], \( \nu \), to a pathway, as defined by a temporal sequence of substates, that shares a common segment and that has been constructed under protocol \( \lambda \) as:

\[
\nu_t^\lambda = \{x_{0}^\lambda, \ldots, x_{\tau}^\lambda, \ldots, x_{t}^\lambda\},
\]

\[
\nu_{\tau}^\lambda = \{x_{\tau}^\lambda, \ldots, x_{t}^\lambda\}.
\]

When there is no confusion about the protocol, we will drop the superindex \( \lambda \). Likewise, when there is no confusion by the time instants, we will drop subindices \( t \) and \( \tau \) from the sequence index.

A thermodynamic function, “\( A \)”, can be averaged over the phase-space pathways that the system can follow complying with the evolving constraints prescribed by the protocol \( \lambda \) as [10]

\[
A^{\lambda} \equiv \left< A^{\nu^\lambda}_\nu \right>_{\lambda} = \sum_{\nu=1}^{N} p^{\lambda}_{\nu} A^{\lambda}_{\nu},
\]

where \( p^{\lambda}_{\nu} \) is the probability distribution according to protocol \( \lambda \). Probabilities are normalized by their corresponding sequence-dependent partition function [9, 10]:

\[
p^{\lambda}_{\nu} = \frac{e^{-\beta E_{\nu}}}{Z^{\lambda}_{\nu}},
\]

such that \( \sum_{\nu=1}^{N} p^{\lambda}_{\nu} = 1 \) and \( \beta = 1/kT \). As explained earlier [9, 10], the standard partition function, \( Z \), which defines the equilibrium probabilities \( p_{\nu} = \exp(-\beta E_{\nu})/Z \), does not make any assumptions on a particular protocol, it comprises all the possibilities for all the protocols and therefore it is independent of time. Time, according to this scheme, can be conceived as implicitly determined, on the one hand, by the number of states, \( n \), that the system adopts between \( \tau \) and \( t \) (\( n \) is the cardinality of \( \nu_t \) minus that of \( \nu_{\tau} \), namely, \( n = |\nu_t| - |\nu_{\tau}| = t - \tau \) and, on the other hand, by the protocol \( \lambda \). We may then formally express \( t = \tau(n, \lambda) \).

Ensemble-average equilibrium thermodynamic functions are describable in a similar fashion within this formalism as \( A \equiv \left< A_{\nu} \right> = \sum_{\nu=1}^{N} p_{\nu} A_{\nu} \). It is important to note that if “\( A \)” is a thermodynamic potential, \( A^{\lambda}_{\nu} \) and \( A^{\lambda} \) are not state functions in the sense of ensemble-average processes because their values are both pathway- and protocol-dependent for \( A^{\lambda}_{\nu} \) and protocol-dependent for \( A^{\lambda} \). Within the framework of the microcanonical and canonical ensembles, we will characterize the system by the Internal Energy, “\( U^{\lambda} \)”, the Helmholtz Free Energy, “\( F^{\lambda} \)”, and the Entropy, “\( S^{\lambda} \)”, thermodynamic potentials using their protocol- and pathway-dependent definitions [10].

We introduce the reversible, microscopic work between two states \( x_t \) and \( x_{\tau} \) along sequence \( \nu \) under protocol \( \lambda \) as the Helmholtz free energy difference:

\[
W^{\nu}_{\nu}(t, \tau) \equiv F^{\nu}_{\nu}(t) - F^{\nu}_{\nu}(\tau).
\]

We can associate to each sequence \( \nu \) an inverse counterpart \( \nu^{-1} \), which mathematically reads \( \nu^{-1} = \{x_t, x_{t-1}, \ldots, x_{\tau+1}, x_{\tau}, x_{\tau-1}, \ldots, x_1, x_0\} \). The associated reversible work is

\[
W^{(\nu^{-1})}_{\nu}(\tau, t) = F^{(\nu^{-1})}_{\nu}(\tau) - F^{(\nu^{-1})}_{\nu}(t) = -W^{\nu}_{\nu}(t, \tau).
\]

It is indeed possible to return to the initial substate \( x_{\tau} \) from the final substate \( x_t \) along many pathways. Let \( \nu' \) be a sequence that shares a common path with \( \nu \) until \( \tau \) and differs from it between \( \tau \) and \( t \), namely, \( \nu' = \{x_0, x_1, \ldots, x_{\tau-1}, x_{\tau}, x_{\tau+1}', \ldots, x_{t-1}', x_t\} \). Then, \( W^{(\nu^{-1})}_{\nu'}(\tau, t) = F^{(\nu^{-1})}_{\nu'}(\tau) - F^{(\nu^{-1})}_{\nu'}(t) \neq -W^{\nu}_{\nu}(t, \tau) \), the equality holding when there are no interactions with previous events [9].

The equilibrium, ensemble-average (macroscopic) work reads \( W(t, \tau) = F(t) - F(\tau) \). It is also possible to define the protocol-dependent ensemble-average work as \( W^{\lambda}(t, \tau) = F^{\lambda}(t) - F^{\lambda}(\tau) \), which follows from \( W^{\lambda} = \left< W^{\nu}_{\nu} \right>_{\lambda} \) by using Eq. [3].

We now set the heat from the definition of entropy in macroscopic, reversible processes. Equilibrium thermodynamics relates the differential entropy in a reversible process at constant temperature \( T \) to the change in heat divided by the temperature, i.e. \( dS \equiv \delta Q/T \), where \( \delta \) stands for inexact differential. For a macroscopic, reversible cycle, \( \Delta S = 0 \) and the heat exchanged with the environment equals zero. For an irreversible cycle, the Clausius theorem expresses the second law of Thermodynamics as \( \delta Q/T < 0 \) [11].

Following our previous work [10], we will assume that all evolutions of the system at the single pathway level are microscopically reversible. For reasons that will become clearer later, we will use the term non-equilibrium (or irreversible) for a process that is protocol-dependent, preserving the term equilibrium when the process does
not dependent on a protocol, as explained above. Clausius theorem can be extended to a general irreversible process that connects an initial state, 1, and a final state, 2, by splitting an irreversible cycle 1 → 2 → 1 into a forward non-equilibrium process 1 → 2 with entropy change \( \Delta S(1) \equiv S_2^{(1)} - S_1^{(1)} = f_1^2 \delta Q(1)/T \) and a backward equilibrium process 2 → 1 with entropy change \( -\Delta S = S_1 - S_2 = f_2^2 \delta Q/T \). Then, it follows that \( \Delta S > \Delta S(1) \), in accord with the extended version of Clausius theorem \([11]\). For a system in contact with a thermal bath, it is clear that \( T \Delta S > Q(1) \), which expresses that part of the heat generated by the system is wasted and released into the environment. If the system is isolated, the internal energy is conserved, \( \Delta U = 0 \), which means that the system does not exchange heat or work with the environment, only internal transformations are allowed. Transformations are thus adiabatic, \( Q(1) = 0 \), and then \( \Delta S > 0 \). This is the most known expression of the second law of Thermodynamics, which states that the entropy of an isolated system either increases (irreversible process) or is zero (reversible process).

By applying the principle of microscopic reversibility to a time-directional, stochastic chain with memory, the heat that the system exchanges with the environment at constant temperature, \( T \), set by the thermal bath reads:

\[
Q_{\nu}(t, \tau) \equiv T \left( S_{\nu}^{(1)}(t) - S_{\nu}^{(1)}(\tau) \right).
\]

Likewise, the protocol-dependent ensemble-average heat and the equilibrium heat are \( Q^{(1)}(t, \tau) = T \left( S^{(1)}(t) - S^{(1)}(\tau) \right) \) and \( Q(t, \tau) = T \left( S(t) - S(\tau) \right) \), respectively. The energy conservation imposes that \( \Delta E_{\nu}(t, \tau) = W_{\nu}(t, \tau) + Q_{\nu}(t, \tau) = \Delta F_{\nu}(t, \tau) + T \Delta S_{\nu}(t, \tau) \) for single temporal trajectories. These relations are formally the same for protocol-dependent ensemble-averages and equilibrium quantities. We consider positive both the heat absorbed by the system and the work supplied to the system.

We next derive Jarzynski’s equality \([12]\) from our formalism. We consider a system that is initially in an equilibrium state \( x_\tau \), namely, it is conformed by an ensemble of statistically similar states, and that evolves to a final state \( x_\tau \), which might be non-equilibrium or achieve equilibrium afterwards, through irreversible pathways controlled by a protocol \( \lambda \). The equilibrium Helmholtz free energy difference, \( \Delta F \), between state \( x_\tau \) and the equilibrium equivalent of the final state was shown to be related to the work, \( W \), needed to drive the transition by \( \langle \exp(-\beta W) \rangle = \exp(-\beta \Delta F) \).

To better understand this picture, we will consider the example of DNA replication, in which the initial state at \( \tau \) is an ensemble of free, non-interacting deoxyribonucleotide triphosphates (dNTP), which represents a macroscopic equilibrium similar to that of an ideal gas.

The final quasistate at \( t \) is in turn a linear arrangement of deoxyribonucleotide monophosphates (dNMP) directionally-constructed by a DNA polymerase (DNAp) by sequentially arranging the dNMPs according to a prescribed DNA template (single-molecule case \([8]\)). The final state corresponds to the ensemble of directionally-constructed stochastic chains of dNMPs (bulk case \([8]\), each chain sequentially assembled by a DNAp according to the prescribed DNA template \([13, 14]\). The final equilibrium state represents the spontaneous process in which dNMPs are non-enzymatically arranged on the template, which is a similar case to the spin chain construction studied by Ising and which can be approximated by an enzymatically-driven polymerization with proofreading at infinitely slow replication rates \([14]\).

The Helmholtz free energy of the initial state is a fixed parameter that we will denote \( F(\tau) \). We want to calculate the free energy difference \( \Delta F = F(t) - F(\tau) \), where \( F(t) \) is the equilibrium free energy of the final state, i.e. \( F(t) = -(1/\beta) \ln \mathbb{Z}(t) \), by following microscopically reversible trajectories instead of obtaining it from the equilibrium thermalization, which is either an inexistent process (polymerization is in reality a protein-mediated process) or needs an infinite amount of time despite its spontaneity. The change in free energy for each chain constructed under a protocol will be denoted by \( \Delta F_{\nu}(t) = F_{\nu}^{(1)}(t) - F(\tau) \).

Microscopically reversible transformations impose that \( W_{\nu}(t) = \Delta F_{\nu}(t) \). Then

\[
\langle e^{-\beta \Delta F_{\nu}(t)} \rangle_{\lambda} = \langle e^{-\beta (F_{\nu}(t) - F(\tau))} \rangle_{\lambda} = \frac{Z_{\nu}^{(1)}(t)}{Z(\tau)} = \frac{Z(t)}{Z(\tau)} = e^{-\beta \Delta F},
\]

where we have used \( Z_{\nu}(t) = Z(t) \), as demonstrated elsewhere \([8, 11]\). It is important to note that the ensemble-average final free energy is \( F^{(1)} = \langle F_{\nu}(t) \rangle_{\lambda} \neq F \). What is actually true is the inequality \([10]\)

\[
F^{(1)}(t) \geq F(t),
\]

which means that the reversible work to build an ensemble of directional, stochastic chains with memory by microscopically reversible trajectories, \( W^{(1)} = \Delta F^{(1)} \), always supersedes that of the ensemble of chains with memory that results from an equilibrium thermalization,

\[
W \geq \Delta F:
\]

Inequality \([10]\) can also be deduced from Eq. 8, as formerly shown by Jarzynski \([12]\), by using the fact that the exponential is a convex function, namely,

\[
\langle e^{-\beta \Delta F_{\nu}} \rangle_{\lambda} \geq e^{-\beta (\Delta F_{\nu})_{\lambda}} = e^{-\beta \Delta F^{(1)}} \implies \Delta F^{(1)} \geq \Delta F.
\]
Inequalities (10) and (11) state that when memory is present, the ensemble-average work employed to construct a stochastic chain of events through microscopically reversible trajectories is always greater than the process that involves an equilibrium thermalization.

Next, we derive Crooks theorem [15], which relates the transition probabilities between microscopically reversible forward and backward pathways. The system, as in Jarzynski equality, starts in an equilibrium state. More in depth, it starts in one substate, \( x_{\tau} \), out of an ensemble of substates, \( \nu_\tau = \{x_{\tau(1)}, \ldots, x_{\tau(m_0)}\} \), that have been adopted under equilibrium conditions. We use subindices \( \tau(k), k = 1, \ldots, m_0 \) to note that time is not defined when the system experiences transitions in phase space in equilibrium. Then, the system ends up in a general non-equilibrium substate, \( x_\lambda^{(i)} \), which might eventually thermalize into a final equilibrium substate, \( x_t \). As previously, \( x_t \) represents one substate out of an ensemble of substates \( \nu_t = \{x_{t(1)}, \ldots, x_{t(m_f)}\} \) (with \( t(k), k = 1, \ldots, m_f \)) that have been achieved under protocol-independent pathways.

It is important to note that although time is not defined for a system that experiences equilibrium processes, a global time goes by from a macroscopic point of view because other nearby systems involved in non-equilibrium processes mark this global time arrow. More in depth, since equilibrium states are idealizations because all systems are in the end interacting with one another, a global time can be defined. We will then use the term proper time to refer to the time coordinate of a specific system, which, as explained, may pause if the system stays in equilibrium with respect to the global time.

We introduce in Fig. 1 the extended phase-space, which is the phase space representation that we believe suitable for both equilibrium and non-equilibrium processes. The scheme shows the propagation of the phase space of a system along its proper time coordinate. Hyperplanes orthogonal to the proper time coordinate represent phase-spaces at each instant on which the system may explore equilibrium configurations. Hypersurfaces on individual phase-spaces correspond to states, either equilibrium or non-equilibrium, although rigorously speaking the former must exclusively sit on hyperplanes perpendicular to the proper time coordinate.

Now, our system evolves from substate \( x_{\tau} \) to \( x_\lambda^{(i)} \) under the influence of the protocol by following a pathway, namely, \( \nu_{\tau \to t} = \{x_{\tau}, x_{\tau+1}, \ldots, x_t\} \), see Eqs. (11) and (12). These conditions are applied for the reverse

FIG. 1. Extended phase space. The scheme represents a reduced \((2D + 1)\)-dimensional space of \(2D\) generalized space and momentum coordinates, \((q_\nu, p_\nu)\), \( h = 1, \ldots, D \) \((D\) is the number of degrees of freedom), plus a proper time coordinate (see the text for details). The system starts its evolution in an initial quasistate at \( \tau \) and ends in a final quasistate at \( t \). Blue hypersurfaces orthogonal to the temporal coordinate correspond to equilibrium states and red ones to non-equilibrium states; the extent and shape of these \(2D\)-dimensional hypersurfaces represent the widths of the probability distributions at a definite height. The red-shaded tube represents a non-equilibrium process, which is the ensemble average over the individual pathways (black curve) that the system can follow under protocol \( \lambda \) by traversing individual substates (black dots). The blue-shaded tube represents the equilibrium process, which envelopes the equilibrium-probability hypersurfaces between the two proper time instants. Although a global time elapses along every pathway that the system describes, the system does not age when pathways are orthogonal to the proper time coordinate.
process, where now \( x_t \) is the equilibrium initial state and \( x_t^{(\lambda^{-1})} \) is the general non-equilibrium final state. The transition forward probability, \( P_F \), equals the probability \( p_v(\tau) \) of starting in equilibrium times the probability \( p_v^{(\lambda)}(t) \), of ending in a general state through a non-equilibrium pathway controlled by protocol \( \lambda \). The transition reverse probability, \( P_R \), follows the same rationale, namely, \( P_R = p_v(t) \times p_v^{(\lambda^{-1})}(\tau) \). Then, the ratio of forward and reverse probabilities read

\[
\frac{P_F}{P_R} = \frac{p_v(\tau) \times p_v^{(\lambda)}(t)}{p_v(t) \times p_v^{(\lambda^{-1})}(\tau)} = \frac{\exp(-\beta E_{v_f}) \exp(-\beta E_{v_i})}{Z(\tau)Z_v^{(\lambda)}(t)} \times \left( \frac{\exp(-\beta E_{v_f})}{Z(t)} \frac{\exp(-\beta E_{v_i})}{Z_v^{(\lambda^{-1})}(\tau)} \right)^{-1} \nonumber
\]

\[
= \frac{Z(t)Z_v^{(\lambda^{-1})}(\tau)}{Z(\tau)Z_v^{(\lambda)}(t)}. \tag{12}
\]

The partition functions in Eq. (12) can be expressed in terms of the free energies,

\[
Z(t) = \exp(-\beta F(t)), \tag{13}
\]

\[
Z_v^{(\lambda)}(t) = \exp(-\beta F_v^{(\lambda)}(t)); \tag{14}
\]

\[
Z(\tau) = \exp(-\beta F(\tau)), \tag{15}
\]

\[
Z_v^{(\lambda^{-1})}(\tau) = \exp(-\beta F_v^{(\lambda^{-1})}(\tau)). \tag{16}
\]

Then,

\[
\frac{P_F}{P_R} = \exp\left( \frac{W_v^{(\lambda)}(t, \tau) - \Delta F}{kT} \right), \tag{17}
\]

where we have used the definition of the reversible microscopic work, Eq. (10), and that \( \Delta F = F(t) - F(\tau) \).

In the following, we will use our formalism to derive two new fluctuation theorems for the relationship between the entropy and the heat exchanged between the system and the environment in general, irreversible trajectories. These theorems are the analogues of Crooks and Jarzynski theorems for the relationship between the Helmholtz free energy and the work. We express the protocol-dependent probability in terms of the entropy of a single trajectory \( n \) as

\[
p_v^{(\lambda)} = \exp\left( -\frac{1}{k} S_v^{(\lambda)} \right). \tag{18}
\]

Like for the Crooks theorem, the system starts in an equilibrium state both for the forward and reverse processes but this time the equilibrium is defined under the microcanonical ensemble, that is, equilibrium states are those with defined energy hence corresponding to the isolated system. The non-equilibrium, forward pathways transform the system from an equilibrium state with energy \( U(\tau) \) into a non-equilibrium quasistate with energy \( E_v(t) \) belonging to a set that complies with an internal energy \( U^{(\lambda)}(t) \). This non-equilibrium state may eventually thermalize into the corresponding equilibrium state with energy \( U(t) \geq U^{(\lambda)}(t) \), that is, the final energies \( E_v(t) \) \( (\nu = 1, \ldots, N) \), may relax either by redistributing into equal degenerate energies \( U(t) \) (so that \( U(t) = U^{(\lambda)}(t) \)) or the system may just become a subsystem of a bigger system that contains the bath (so that \( U(t) > U^{(\lambda)}(t) \)). In the reverse process, we similarly conceive that the system starts in this equilibrium state and transforms into a non-equilibrium state with energy \( U^{(\lambda^{-1})}(\tau) \), which may eventually relax into an equilibrium state with energy \( U(\tau) \).

The transition forward microcanonical probability, \( p_F \), equals the probability \( \exp(-S(\tau)/k) \) of starting in equilibrium times the probability, \( \exp(-S_v^{(\lambda)}(t)/k) \), of ending in a general state through a non-equilibrium pathway controlled by protocol \( \lambda \). The transition reverse probability, \( p_R \), follows the same rationale, namely, \( p_R = \exp(-S(t)/k) \times \exp(-S_v^{(\lambda^{-1})}(\tau)/k) \). Then, the ratio of forward and reverse probabilities read

\[
\frac{p_F}{p_R} = \frac{\exp\left(\frac{S(t) - S(\tau)}{k}\right)}{\exp\left(\frac{S_v^{(\lambda)}(t) - S_v^{(\lambda^{-1})}(\tau)}{k}\right)}. \tag{19}
\]

Using the definition of the reversible microscopic heat, Eq. (7), the first, new fluctuation theorem states:

\[
p_F = \exp\left(\frac{\Delta S}{k} - \frac{Q_v^{(\lambda)}(t, \tau)}{kT}\right). \tag{20}
\]

Theorem (20) relates the heat exchanged between the system and the environment under general, non-equilibrium processes to the ratio of the forward and reverse probabilities. It is important to note that the system is in contact with a thermal bath at temperature \( T \) and therefore, the heat \( Q_v^{(\lambda)} \) is that generated by the system when it connects an equilibrium state with defined energy to a generally non-equilibrium state. Equation (20) can be simply expressed as

\[
``\frac{p_F}{p_R} = \exp\left(\frac{\Delta S}{k} - \frac{Q_v^{(\lambda)}(t, \tau)}{kT}\right)``
\]

as the counterpart expression of Crooks theorem appeared elsewhere (see, for example [3]), keeping in mind that \( Q \) is the heat exchanged over irreversible paths, in contrast to the notation used in this paper, where \( Q \) is the reversible heat, \( Q \equiv T\Delta S \).

Like for the derivation of Jarzynski equality from Crooks theorem [13], that is, by summing over the heat on both sides of Eq. (20), it is easy to obtain the second,
new fluctuation theorem in this paper:

$$\left\langle \exp \left( \frac{Q^{(\lambda)}}{kT} \right) \right\rangle_\lambda = \exp \left( \frac{\Delta S}{k} \right),$$

(21)

which may be invoked as 

$$\left\langle \exp \left( \frac{Q}{kT} \right) \right\rangle = \exp \left( \frac{\Delta S}{k} \right)$$

keeping in mind that the expected value must be taken in experiments always driven by the same protocol between an initially equilibrium state with defined internal energy and a generally non-equilibrium state with final energy $E_f$, and that $Q$ is a generally irreversible heat.

Like for the demonstration of Jarzynski theorem, Eq. (8), we can show how Eq. (21) naturally arises from our formalism. Namely, microscopically reversible transformations impose that $Q^{(\lambda)} = T\Delta S^{(\lambda)}$, see Eq. (7). Then:

$$\left\langle e^{\frac{1}{T\Delta t}\Delta S^{(\lambda)}} \right\rangle_\lambda = \left\langle e^{\frac{1}{T} \left( S^{(\lambda)}(t) - S(\tau) \right)} \right\rangle_\lambda = \left\langle \frac{p_\nu(\tau)}{p_0^{(\lambda)}} \right\rangle_\lambda = \frac{p_\nu(\tau)}{1/N}$$

$$= e^{\frac{1}{T\Delta t}\Delta S},$$

(22)

where we have used that $N$ is the number of configurations compatible with a final energy $U^{(\lambda)}(t)$ which thermalizes into $U(t)$.

Fluctuation theorem (21) relates the heat exchanged between the system and the environment between two states to their entropy difference $\Delta S$. Using Jensen’s inequality, it follows from Eq. (21) that

$$\frac{1}{T} \left\langle Q^{(\lambda)} \right\rangle_\lambda = \frac{Q^{(\lambda)}}{T} \leq \frac{Q}{T} = \Delta S,$$

(23)

which is the extended version of the Clausius theorem [11] at constant temperature $T$, as described above (remember that here $Q$ is the heat exchanged in a reversible process and $Q^{(\lambda)}$ is the heat exchanged in a general process under protocol $\lambda$). Inequality (23) is the heat-entropy counterpart to inequality (10).

Inequality (23) can be expressed as $\Delta S^{(\lambda)} \leq \Delta S$, which can directly be deduced from (10)

$$S(t) - S^{(\lambda)}(t) \geq \frac{1}{T} \left( U(t) - U^{(\lambda)}(t) \right),$$

(24)

by using the fact that $U - U^{(\lambda)} \geq 0$ for the final, equilibrium state of the isolated system (see above). Inequality (21) expresses in the end that the entropy of the isolated system always increases (see above). On the contrary, when the system is not isolated it can be taken to states of lower or higher entropy through non-equilibrium processes by appropriately favouring pathways (i.e., by using certain protocols $\lambda$). In particular, the system may increase its entropy with respect to the equilibrium level at the cost of energy absorption ($S - S^{(\lambda)} < 0$, $U - U^{(\lambda)} < 0$), as was shown for a DNA replication protocol in which dNTPs were directionally assembled [14], or may decrease its entropy at the cost of energy dissipation ($S - S^{(\lambda)} > 0$, $U - U^{(\lambda)} > 0$), as was also shown for the same system in a protocol in which dNMPs were removable [14]. Note that in [14], the DNAp was considered a passive element that couples dNTP hydrolysis to dNMP incorporation and strand hybridization, but this protein is actually an active nanomachine that uses part of the dNTP energy to fuel its motor, which activity includes translocation and accurate nucleotide incorporation. DNAp action can thus be rightly included in the protocol $\lambda$ that drives polymerization to the real, high fidelities [13, 17].

The lower the entropy of the final state (or the information acquisition) the larger the energy dissipation [10], which, as explained above, can be achieved in DNA replication by more complex protocols than the simply passive, directional mechanism proposed in [14]. Like for the dissipated work, $W^{(\lambda)}_{diss} \equiv W^{(\lambda)} - \Delta F$ (see, for example, [12]), it is possible to define the dissipated heat, $Q^{(\lambda)}_{diss} \equiv -(Q^{(\lambda)} - T\Delta S)$, which better illustrates this tradeoff. $Q^{(\lambda)}_{diss}$ is the heat that cannot be used to decrease the entropy of the system and that is eventually released to the environment.

We now introduce the rate, $\sigma^{(\lambda)}$, at which the system exchanges heat with the bath under a certain protocol $\lambda$:

$$\sigma^{(\lambda)} \equiv \frac{1}{T\Delta t} Q^{(\lambda)}_{diss} = -\frac{Q^{(\lambda)} - Q}{T\Delta t} = -\frac{\Delta S^{(\lambda)} - \Delta S}{\Delta t},$$

(25)

where $\Delta t \equiv t - \tau$ is the time interval. With this definition, it is straightforward to derive the Gallavotti-Cohen expression [18], which emerges from the so-called Fluctuation Theorem [19, 20]. This theorem connects the forward and reverse heat-rate probability distributions for steady-state, non-equilibrium processes. It is demonstrated by following a similar argument as the one we used for Eq. (20), namely, by using Eq. (25) for steady-state conditions in the derivation of Eq. (20), it follows that

$$\lim_{\Delta t \to \infty} k \Delta t \ln \frac{p_f}{p_r} = \sigma^{(\lambda)},$$

(26)

where $p_f = \exp(-S(\tau)/k)\times \exp\left(-S^{(\lambda)}(t)/k\right)$ and $p_r = \exp(-S(t)/k)\times \exp\left(-S^{(\lambda)}(\tau)/k\right)$. Here, exp $(-S^{(\lambda)}(t)/k)$ and exp $(-S^{(\lambda)}(\tau)/k)$ are the probabilities of finding the system with steady-state energies $U^{(\lambda)}(t)$ and $U^{(\lambda)}(\tau)$. In a cycle, $Q^{(\lambda)}_{diss} = -Q^{(\lambda)}$ and $\sigma^{(\lambda)} = -Q^{(\lambda)}/T\Delta t$, since the reversible heat is zero, and the internal energy change of the system is $U^{(\lambda)}(t) - U^{(\lambda)}(\tau)$. The fact that $\sigma^{(\lambda)} = -Q^{(\lambda)}/T\Delta t$ in a closed loop can also be understood from the fact that the system does not necessarily returns to the initial state through the same pathway or with the inverse protocol.
We have used microscopic reversibility, non-Markovianity and the fact that a system can be experimentally followed at the single copy level to explain that irreversibility arises from the average over the ensemble of pathways that the system can follow in its evolution under time-dependent constraints. Just by using conservation laws it is possible to consider that no temporal evolution of a system is irreversible at the single-pathway level and to deduce irreversibility as a consequence of protocol-biased stochasticity in the presence of memory. A system may be then said to evolve through a non-equilibrium process when there are memory effects between each present substate and its corresponding past substates along every available pathway driven by a protocol. We have proposed extended phase-space diagrams to represent both equilibrium and non-equilibrium processes.

In the absence of memory, all processes take place in equilibrium, as was early demonstrated (see the Independence limit theorem [9]); non-equilibrium is just a consequence of the impossibility to explore all substates to connect arbitrary states in a definite time. In this regard, protocols that drive the system between two states at high velocities decrease the chances of the system to explore a significant number of substates in each possible pathway, thus decreasing the probability that the reverse pathways that may be used to recover the system become similar to the time-reversed of the forward ones, thus driving the system out of equilibrium. Specifically, let’s consider two identical protocols, \( \lambda \) and \( \lambda' \), except for the velocity, being the latter faster than the former. Then, protocol \( \lambda \) allows the system to explore more substates within the same microscopically reversible pathway to connect arbitrary quasistates than \( \lambda' \). In a cycle, protocol \( \lambda \) is more likely to drive the system in the forward direction through pathways that can be aproximately mapped reversely in the backward direction (by inverse protocol \( \lambda^{-1} \)) than protocol \( \lambda' \). The system would then evolve farther from equilibrium by protocol \( \lambda' \) than by protocol \( \lambda \). In the limit in which a protocol is infinitely slowly, the system visits all substates to connect arbitrary states both for the forward and the backward directions, hence making the process in equilibrium.

We have deduced Jarzynski, Crooks and Gallavotti-Cohen theorems and have presented two closing fluctuation theorems that relate the heat exchanged by a system when it transforms irreversibly between an equilibrium state and a final, general quasistate. We have shown that dissipated heat (or friction) appears as a consequence of the unlikelihood for the system to describe overlapping forward and backward pathways.

The second law of Thermodynamics can be definitely observed as a consequence of both microscopic reversibility and memory effects, as defined by stochastic interactions among the substrates that the system adopts along its evolution. Therefore, it may not be considered as a fundamental law of Physics but rather a consequence of conservation laws. Note that unlike the first law of Thermodynamics, the second law only arises after ensemble averages, whereas the energy conservation is fulfilled at both individual pathways and in ensemble-average processes. The time arrow may also be considered a consequence of microscopic reversibility and non-Markovianity. In fact, in equilibrium and in systems where memory effects can be neglected, the time coordinate is not defined, which indicates that a system does not age in these conditions. This makes possible to define a proper time for each system, which indicates how the system ages. The fact that systems are not isolated make proper times correlate into a global time with which aging in different systems can be compared. The proper time that elapses while a system evolves irreversibly between two states is determined by the number of intermediate states that are gone through under a defined protocol.

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