

## Generalization of the Jarzynski and Crooks nonequilibrium work theorems in molecular dynamics simulations

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The Jarzynski identity [C. Jarzynski, Phys. Rev. Lett. **78**, 2690 (1997)] and the Crooks equation [G. E. Crooks, J. Stat. Phys. **90**, 1481 (1998)] relate thermodynamic free energy differences to the work done on a system during a collection of nonequilibrium transformations. In the present Rapid Communication we provide generalized versions of these nonequilibrium work theorems, which hold for dissipative transformations where the system may undergo simultaneously mechanical work and pressure-temperature or volume-temperature changes. The proof is valid in the context of dynamic systems that evolve with *NPT*-based equations of motion according to the Martyna-Tobias-Klein algorithm [Martyna *et al.* J. Chem. Phys. **101**, 4177 (1994)]. An extension of the proof to dynamic systems that evolve through *NVT*-based equations of motion is also provided. The theorems may be effectively used in non-Hamiltonian molecular dynamics simulations for evaluating Helmholtz or Gibbs free energy differences, or the ratio of partition functions at different temperatures to be eventually used in thermodynamic cycles.

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In the field of molecular dynamics simulations, several routes to the free energy calculation along selected collective variables have been opened in the last decade. At variance with classical methods such as thermodynamic integration or free energy perturbation, which are based on equilibrium dynamics, most of these new approaches rely on the production of nonequilibrium trajectories. Typical examples are the recently developed adaptive bias potential methods, such as metadynamics [1] and self-healing umbrella sampling [2]. Since these techniques must in principle bring to a final equilibrium sampling in the subspace of the collective variables, they are [1] or must eventually mutate [2] into quasiequilibrium methodologies. A substantially different scenario was shown at the end of the 1990s by Jarzynski [3] and Crooks [4], who introduced “truly” nonequilibrium strategies for determining free energy differences. In particular they proposed a way to relate free energy differences between two thermodynamic states, differing in at least one (mechanical) collective variable, to the external work done on the system in an ensemble of nonequilibrium trajectories switching between the two states.

*Jarzynski identity (JI).* The JI relates an exponential average of the work  $W$  to drive the system from the state  $A$  to the state  $B$  at constant temperature to the free energy difference  $\Delta F = F(B) - F(A)$  between the two states,

$$\langle e^{-\beta W} \rangle = e^{-\beta \Delta F}, \quad (1)$$

where  $\beta = (k_B T)^{-1}$ ,  $k_B$  being the Boltzmann constant and  $T$  the temperature. The average quantity  $\langle \exp(-\beta W) \rangle$  is calculated over different nonequilibrium phase space trajectories whose initial points are canonically distributed. Note that, since we are dealing with nonequilibrium (irreversible) trajectories, the final phase space points are not canonically distributed. After the first demonstration [3], the JI has been proved for a variety of cases from Hamiltonian and non-Hamiltonian dynamics [5–8], to Langevin [9] and Markov-

chain [10] dynamics. The first experimental test of the JI was published by Liphardt *et al.* [11], who applied Eq. (1) to measurements of the irreversible work done to mechanically stretch a single molecule of RNA.

*Crooks equation (CE).* The CE relates the probability of a nonequilibrium phase space trajectory,  $\Gamma_0 \rightarrow \Gamma_\tau$ , to the probability of its time reversal,  $\Gamma_0^* \leftarrow \Gamma_\tau^*$ . The phase space points  $\Gamma_0$  and  $\Gamma_\tau$  may refer to different Hamiltonians (where, e.g., the distance between two molecules is constrained to different values). The CE establishes that

$$\frac{p(\Gamma_0 \rightarrow \Gamma_\tau)}{p(\Gamma_0^* \leftarrow \Gamma_\tau^*)} = \exp[\beta(W_{\Gamma_0 \rightarrow \Gamma_\tau} - \Delta F)], \quad (2)$$

where  $W_{\Gamma_0 \rightarrow \Gamma_\tau}$  is the work done on the system during the trajectory  $\Gamma_0 \rightarrow \Gamma_\tau$ . In Eq. (2),  $p(\Gamma_0 \rightarrow \Gamma_\tau)$  is the joint probability of taking the microstate  $\Gamma_0$  from a canonical distribution with an initial Hamiltonian and of performing the forward transformation to the microstate  $\Gamma_\tau$ .  $p(\Gamma_0^* \leftarrow \Gamma_\tau^*)$  is the analogous joint probability for the time reversal path.  $\Delta F$  is the free energy difference between the final and initial thermodynamic states. In Monte Carlo or molecular dynamics simulations, a more manageable but less general form of Eq. (2) is used [10]. This form is easily obtained from Eq. (2) by summing the probabilities of all possible trajectories during which the same amount of work  $W$  is done on the system. It reads as follows:

$$\frac{P_F(W)}{P_R(-W)} = \exp[\beta(W - \Delta F)], \quad (3)$$

where  $P_F(W)$  is the probability distribution of the work done on the system during all possible forward trajectories, while  $P_R(-W)$  is the analogous distribution for the reverse paths. Note that the JI [Eq. (1)] may be trivially recovered by rearranging Eq. (3) and by integrating over  $W$ . The CE was originally derived [4] for microscopically reversible Markov-

ian systems in the context of Monte Carlo simulations. Several other proofs followed [6,12–16]. In particular, in Ref. [13] Evans pointed out the connection between the CE and the fluctuation theorem [17–19]. From the experimental point of view the CE has been verified using atomic force microscopy for the process of unfolding and refolding of a small RNA hairpin and an RNA three-helix junction [20].

The Jarzynski and Crooks theorems share the fact that the external work  $W$  is of a mechanical nature and the thermodynamic conditions of the initial and final states are the same. These are indeed basic assumptions in the various proofs of the theorems and in the available computational [14] and experimental [11,20] tests. In the present Rapid Communication we propose a generalization of the JI and CE to realizations that drive the system out of equilibrium, not only using a mechanical force acting on the physical system, but also irreversibly changing the thermodynamic conditions of the physical system. This provides the opportunity of determining the relevant equilibrium quantities (the free energy difference or the ratio between the partition functions) of the initial and final states that may differ in the basic thermodynamic quantities ( $P$ ,  $T$ , and  $V$ ). We will also derive Eqs. (1) and (3) as special cases of such generalized equations.

In the following, we specifically address the proof for the generalized CE and we derive the corresponding generalized JI as stated above, that is by integration on the overall work variable. We start by considering a dynamic system with a given initial energy that evolves according to the Martyna-Tobias-Klein (MTK) equations of motion [21] ( $NPT$ -based dynamics). It has been shown [22] that for stationary systems such equations yield the proper  $NPT$  partition function both with and without momentum conservation. Here, we limit ourselves to the latter case, since it can be easily proved that the result does not change when the momentum conservation is applied. Suppose we drive such a system out of equilibrium by an arbitrary combination of the following mechanisms: (1) introduction of some time-dependent external potential  $U(t)$  that produces mechanical work on the system; (2) temperature variation through the thermostat; and (3) external pressure variation through the barostat. The time schedules for the mechanical work and the pressure and temperature variations are arbitrary and mutually independent. The effect of such a transformation is to change the energy of the global system from

$$\mathcal{H}(0) = H + U(0) + \psi_{\text{bar}} + VP(0) + \psi_{\text{th}} + \left[ (3N+1)\eta_1 + \sum_{k=2}^M \eta_k \right] \beta^{-1}(0) \quad (4)$$

to

$$\mathcal{H}(\tau) = H + U(\tau) + \psi_{\text{bar}} + VP(\tau) + \psi_{\text{th}} + \left[ (3N+1)\eta_1 + \sum_{k=2}^M \eta_k \right] \beta^{-1}(\tau), \quad (5)$$

where  $H$  is the (potential plus kinetic) energy of the physical system,  $\psi_{\text{bar}} = p_{\epsilon}^2 / (2M_b)$  is the kinetic energy associated to

the barostat with mass  $M_b$  and  $\psi_{\text{th}} = \sum_{k=1}^M p_{\eta_k}^2 / (2Q_k)$  is the kinetic energy associated to the thermostat (according to the MTK algorithm we use a Nosé-Hoover chain [23] with  $M$  coupled thermostats). It is important to note that, in Eqs. (4) and (5), the external potential  $U(t)$ , the external pressure  $P(t)$ , and the temperature  $[k_B\beta(t)]^{-1}$  depend explicitly on time. For convenience we separate the total energy of the global system at time  $t$ ,  $\mathcal{H}(t)$ , into two terms: the energy of the *physical system+barostat* (from now on called extended system) and the energy of the thermostat:

$$\mathcal{H}(t) = \mathcal{H}_{\text{es}}(t) + \mathcal{H}_{\text{th}}(t), \quad (6)$$

where

$$\mathcal{H}_{\text{es}}(t) = H + U(t) + \psi_{\text{bar}} + VP(t) \quad (7)$$

and

$$\mathcal{H}_{\text{th}}(t) = \psi_{\text{th}} + \left[ (3N+1)\eta_1 + \sum_{k=2}^M \eta_k \right] \beta^{-1}(t). \quad (8)$$

For simplicity of notation, in Eqs. (7) and (8) we have expressed the dependence on  $t$  only for those quantities that depend explicitly on time. The work done on the global system during the transformation is

$$W = \int_0^{\tau} \frac{\partial \mathcal{H}(t)}{\partial t} dt. \quad (9)$$

As stated above [see also Eqs. (7) and (8)], three terms of the total energy  $\mathcal{H}(t)$  depend explicitly on time. Correspondingly,  $W$  is given by the sum of three terms, namely

$$\begin{aligned} W &= W_m + W_{\text{bar}} + W_{\text{th}} \\ &= \int_0^{\tau} \frac{\partial U(t)}{\partial t} dt + \int_0^{\tau} V \frac{\partial P(t)}{\partial t} dt \\ &\quad + \int_0^{\tau} \left[ (3N+1)\eta_1 + \sum_{k=2}^M \eta_k \right] \frac{\partial \beta^{-1}(t)}{\partial t} dt, \end{aligned} \quad (10)$$

where  $W_m$ ,  $W_{\text{bar}}$ , and  $W_{\text{th}}$  are the mechanical work on the physical system, the work done to produce a pressure change, and the work done to produce a temperature change, respectively. The quantities  $W_m$ ,  $W_{\text{bar}}$ , and  $W_{\text{th}}$  can be directly calculated from molecular dynamics simulations, since the time schedules of  $U(t)$ ,  $P(t)$ , and  $\beta(t)$  are given.

For a thermostated system with an incorporated barostat, the thermal energy provided by the thermostat during the transformation can flow, not only from and to the physical system, but also from and to the barostat. The total energy change of the extended system can thus be expressed as

$$\mathcal{H}_{\text{es}}(\tau) - \mathcal{H}_{\text{es}}(0) = Q + W_m + W_{\text{bar}}, \quad (11)$$

where  $Q$  is the heat flowing in the extended system from the thermostat and  $W_m + W_{\text{bar}}$  is the total work done on the extended system. Analogously, from Eq. (8) we can derive the energy change of the thermostat during the transformation:

$$\mathcal{H}_{\text{th}}(\tau) - \mathcal{H}_{\text{th}}(0) = W_{\text{th}} + \int_0^\tau \dot{\psi}_{\text{th}} dt + \int_0^\tau \left[ (3N+1) \dot{\eta}_1 + \sum_{k=2}^M \dot{\eta}_k \right] \beta^{-1}(t) dt. \quad (12)$$

Since in Eq. (11) we have arbitrarily assumed that the heat entering into the extended system is positive, the sum of the last two terms of Eq. (12) corresponds to  $-\mathcal{Q}$ . Therefore

$$\mathcal{H}_{\text{th}}(\tau) - \mathcal{H}_{\text{th}}(0) = W_{\text{th}} - \mathcal{Q}. \quad (13)$$

The proof proceeds by considering the so-called transient fluctuation theorem by Evans *et al.* [17] that correlates the joint probabilities of Eq. (2) to the compressibility  $\nabla_\Gamma \cdot \dot{\Gamma}$  of the system and to the probabilities  $p(\Gamma_0)$  and  $p(\Gamma_\tau)$  of the initial and final phase space points:

$$\frac{p(\Gamma_0 \rightarrow \Gamma_\tau)}{p(\Gamma_0^* \leftarrow \Gamma_\tau^*)} = \frac{p(\Gamma_0)}{p(\Gamma_\tau)} \exp\left(-\int_0^\tau \nabla_\Gamma \cdot \dot{\Gamma} dt\right). \quad (14)$$

In our case the probabilities  $p(\Gamma_0)$  and  $p(\Gamma_\tau)$  are canonically distributed. Therefore considering the expression of the canonical probability of a phase space point  $\Gamma \equiv (\mathbf{p}, \mathbf{r}, p_\epsilon, V, p_\eta)$  provided by the MTK algorithm for a momentum conserving system [22], we can write

$$\frac{p(\Gamma_0)}{p(\Gamma_\tau)} = \frac{e^{-\beta(0)[H(0)+U(0)+\psi_{\text{bar}}(0)+\psi_{\text{th}}(0)+V(0)P(0)]} \omega_{p,T}^{(\tau)}}{e^{-\beta(\tau)[H(\tau)+U(\tau)+\psi_{\text{bar}}(\tau)+\psi_{\text{th}}(\tau)+V(\tau)P(\tau)]} \omega_{p,T}^{(0)}}, \quad (15)$$

where  $\omega_{p,T}^{(\tau)}$  and  $\omega_{p,T}^{(0)}$  are the partition functions of the final and initial thermodynamic states in the  $\Gamma$  phase space, respectively. In order to obtain the partition functions in the phase space of the coordinates and momenta of the physical system, the integrals over  $p_\epsilon$  and  $p_\eta$  in  $\omega_{p,T}^{(\tau)}$  and  $\omega_{p,T}^{(0)}$  must be calculated. Hence using Eq. (7), we rewrite Eq. (15) as follows:

$$\frac{p(\Gamma_0)}{p(\Gamma_\tau)} = \frac{e^{-\beta(0)[\mathcal{H}_{\text{es}}(0)+\psi_{\text{th}}(0)]} \left[ \frac{\beta(0)}{\beta(\tau)} \right]^m \frac{\Omega_{p,T}^{(\tau)}}{\Omega_{p,T}^{(0)}}}{e^{-\beta(\tau)[\mathcal{H}_{\text{es}}(\tau)+\psi_{\text{th}}(\tau)]} \left[ \frac{\beta(\tau)}{\beta(0)} \right]^m \frac{\Omega_{p,T}^{(0)}}{\Omega_{p,T}^{(\tau)}}}, \quad (16)$$

where  $\Omega_{p,T}^{(\tau)}$  and  $\Omega_{p,T}^{(0)}$  are the partition functions in the phase space of the physical system and  $m=(M+1)/2$ . To obtain the final expression for the ratio  $p(\Gamma_0 \rightarrow \Gamma_\tau)/p(\Gamma_0^* \leftarrow \Gamma_\tau^*)$ , we need to determine the exponential function in Eq. (14). The MTK equations of motion for a momentum conserving system give rise to the following compressibility [22]:

$$\nabla_\Gamma \cdot \dot{\Gamma} = -(3N+1) \dot{\eta}_1 - \sum_{k=2}^M \dot{\eta}_k. \quad (17)$$

Using Eq. (17), the exponential function in Eq. (14) can be written as

$$\exp\left(-\int_0^\tau \nabla_\Gamma \cdot \dot{\Gamma} dt\right) = \frac{e^{-(3N+1)\eta_1(0) - \sum_{k=2}^M \eta_k(0)}}{e^{-(3N+1)\eta_1(\tau) - \sum_{k=2}^M \eta_k(\tau)}}. \quad (18)$$

Upon substitution of Eqs. (16) and (18) into Eq. (14) and using Eqs. (6) and (8), we obtain

$$\frac{p(\Gamma_0 \rightarrow \Gamma_\tau)}{p(\Gamma_0^* \leftarrow \Gamma_\tau^*)} = \frac{e^{-\beta(0)\mathcal{H}(0)}}{e^{-\beta(\tau)\mathcal{H}(\tau)}} \left[ \frac{\beta(0)}{\beta(\tau)} \right]^m \frac{\Omega_{p,T}^{(\tau)}}{\Omega_{p,T}^{(0)}}. \quad (19)$$

By using Eqs. (6), (11), and (13),  $\mathcal{H}(\tau)$  can be expressed as a function of the quantities  $\mathcal{H}(0)$ ,  $W_m$ ,  $W_{\text{bar}}$ , and  $W_{\text{th}}$ :

$$\mathcal{H}(\tau) = \mathcal{H}(0) + W_m + W_{\text{bar}} + W_{\text{th}}. \quad (20)$$

Upon substitution of Eq. (20) into Eq. (19) we finally get

$$\frac{p(\Gamma_0 \rightarrow \Gamma_\tau)}{p(\Gamma_0^* \leftarrow \Gamma_\tau^*)} = \frac{\Omega_{p,T}^{(\tau)}}{\Omega_{p,T}^{(0)}} e^{\beta(\tau)W + [\beta(\tau) - \beta(0)]\mathcal{H}(0) + m \ln [\beta(0)/\beta(\tau)]}, \quad (21)$$

where  $W = W_m + W_{\text{bar}} + W_{\text{th}}$  and must be calculated following Eq. (10). Equation (21) relates the probability of a general nonequilibrium transformation (i.e., involving mechanical work and pressure and temperature changes) and its time reversal to the total work done on the global system in the forward process and to the partition functions of the initial and final states. Equation (19) [or equivalently Eq. (21)] is the generalized form of Eq. (2) and is the central result of the present Rapid Communication.

The extension of the CE to systems where the volume (instead of the external pressure) and the temperature change during the transformation due to external work is straightforward. In such case the MTK equations of motion reduce to the Nosé-Hoover chain equations [23] (*NVT* dynamics) and the energy of the global system is

$$\mathcal{H}(t) = H[V(t)] + U(t) + \psi_{\text{th}} + \left[ (3N+1)\eta_1 + \sum_{k=2}^M \eta_k \right] \beta^{-1}(t). \quad (22)$$

In Eq. (22), the dependence of the energy of the physical system on the volume is explicitly given because the volume, and hence the energy, may be arbitrarily changed during the transformation. Moreover, since the external pressure is constant, the relation  $W_{\text{bar}}=0$  holds. However, as previously stated, the physical system may undergo additional work, say  $W_{\text{vol}}$ , during the transformation

$$W_{\text{vol}} = \int_0^\tau \frac{\partial H(V)}{\partial V} \dot{V} dt. \quad (23)$$

By following the guideline that brought us to Eq. (21), we may recover the generalized CE for *NVT* dynamic systems:

$$\frac{p(\Gamma_0 \rightarrow \Gamma_\tau)}{p(\Gamma_0^* \leftarrow \Gamma_\tau^*)} = \frac{\Omega_{V,T}^{(\tau)}}{\Omega_{V,T}^{(0)}} e^{\beta(\tau)W + [\beta(\tau) - \beta(0)]\mathcal{H}(0) + m \ln [\beta(0)/\beta(\tau)]}, \quad (24)$$

where  $\mathcal{H}(0)$  is given by Eq. (22) (with  $t=0$ ),  $m=M/2$  (only the integrals over  $p_\eta$  are present in  $\omega_{V,T}^{(\tau)}$  and  $\omega_{V,T}^{(0)}$ ), and  $W = W_m + W_{\text{vol}} + W_{\text{th}}$ .

In order to recover the generalized versions of Eqs. (1) and (3), we define the following adimensional functional of a generic trajectory that brings the system from the state  $A$  at time 0 to the state  $B$  at time  $\tau$ :

$$\mathcal{W} \equiv \mathcal{W}_{AB} = \beta_B W + (\beta_B - \beta_A) \mathcal{H}_A + m \ln \frac{\beta_A}{\beta_B}, \quad (25)$$

where  $(k_B \beta_A)^{-1}$  and  $(k_B \beta_B)^{-1}$  are the temperatures of the initial and final states, respectively, and  $\mathcal{H}_A$  is the energy of the global system [Eq. (4)] in the initial state. Using the above definition, collecting all trajectories yielding the same  $\mathcal{W}$ , and exploiting the fact that  $\mathcal{W}_{BA} = -\mathcal{W}_{AB} \equiv -\mathcal{W}$ , Eq. (21) transforms as follows:

$$\frac{P_F(\mathcal{W})}{P_R(-\mathcal{W})} = e^{\mathcal{W} \frac{\Omega_B}{\Omega_A}}, \quad (26)$$

where  $P_F(\mathcal{W})$  and  $P_R(-\mathcal{W})$  are the normalized distribution functions of  $\mathcal{W}$  and  $-\mathcal{W}$  for the forward and backward transformations, respectively. Multiplying both sides of Eq. (26) by  $e^{-\mathcal{W}} P_R(-\mathcal{W})$  and integrating the resulting equation over  $\mathcal{W}$ , the generalized JI is obtained

$$\langle e^{-\mathcal{W}} \rangle = \frac{\Omega_B}{\Omega_A}. \quad (27)$$

With analogous considerations, it can be shown that the functional relations of Eqs. (26) and (27) are also valid for *NVT*-based dynamics [Eq. (24)]. The difference between *NVT* and *NPT* dynamic systems stems from the meaning of

the quantities  $W$ ,  $\mathcal{H}_A$ ,  $\Omega_A$ , and  $\Omega_B$  as discussed above.

It is now straightforward to derive Eqs. (1) and (3) as special cases of the nonequilibrium work theorems expressed by Eqs. (27) and (26). To this aim we consider the particular case in which the temperature of the thermodynamic states *A* and *B* is the same. Such condition implies that  $\beta_B = \beta_A = \beta$  in Eq. (25) and therefore  $\mathcal{W} = \beta W$ . The same condition allows us to relate the ratio  $\Omega_B/\Omega_A$  to the free energy difference between the states *A* and *B*. In particular:  $\Omega_B/\Omega_A = e^{-\beta \Delta G}$  for *NPT* dynamic systems and  $\Omega_B/\Omega_A = e^{-\beta \Delta F}$  for *NVT* dynamic systems. The CE and JI are easily recovered using the relations obtained for  $\mathcal{W}$  and  $\Omega_B/\Omega_A$  into Eqs. (26) and (27), respectively.

In conclusion the generalized nonequilibrium relations we present could be fruitfully exploited, not only for the direct determination of free energy differences, but also used in thermodynamic cycles. Our results may open interesting perspectives either into the computational or into the experimental field, providing a framework where both intensive and extensive thermodynamic variables can be freely manipulated during the nonequilibrium measurements.

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