Failure of the Work-Hamiltonian Connection for Free-Energy Calculations

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Extensions of statistical mechanics are routinely being used to infer free energies from the work performed over single-molecule nonequilibrium trajectories. A key element of this approach is the ubiquitous expression $dW/dt = \partial H(x, t)/\partial t$, which connects the microscopic work W performed by a time-dependent force on the coordinate x with the corresponding Hamiltonian $H(x, t)$ at time t. Here we show that this connection, as pivotal as it is, cannot be used to estimate free-energy changes. We discuss the implications of this result for single-molecule experiments and atomistic molecular simulations and point out possible avenues to overcome these limitations.

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Hamiltonians provide two key ingredients to bridge the microscopic structure of nature with macroscopic thermodynamic properties: they completely specify the underlying dynamics, and they can be identified with the energy of the system [1]. At equilibrium in a thermal bath at a temperature T, the link with the thermodynamic properties is established through the partition function $Z = \int e^{-\beta H(x)} dx$, which here uses the Hamiltonian $H(x)$ in the coordinate space x as the energy of the system and $\beta \equiv 1/k_B T$ as the inverse of the characteristic thermal energy [2]. Thermodynamic properties, such as the free-energy $G = -\frac{1}{\beta} \ln Z$, play an important role because they provide information that is not readily available from the microscopic properties, including whether ($\Delta G < 0$) or not ($\Delta G > 0$) a given process happens spontaneously.

The connection between work and Hamiltonian expressed through the relation $\frac{d}{dt} W = \frac{\partial}{\partial t} H(x, t)$, or equivalently through its integral representation $W = \int_0^t \frac{\partial}{\partial t'} H(x(t'), t') dt'$, is typically used to extend statistical mechanics to far-from-equilibrium situations [3–5]. These relations are meant to imply that the work W performed on a system is used to change its energy. The potential advantage of this type of approach is its ability to infer thermodynamic properties even when the relevant details of the Hamiltonian are not known or when they are too complex for a direct analysis. Experiments and computer simulations can thus be performed to probe the microscopic mechanical properties from which to obtain thermodynamic properties. Time-dependent Hamiltonians, however, provide the energy up to an arbitrary factor that typically depends on time and on the microscopic history of the system. Such dependence, as we show below, prevents this approach from being generally applicable to compute thermodynamically consistent properties.

To illustrate how work and Hamiltonian fail to be generally connected, we consider a system described by the Hamiltonian $H_0(x)$ under the effects of an external time-dependent force $f(t)$. The total Hamiltonian is given by

$$H(x, t) = H_0(x) - f(t)x + g(t), \qquad (1)$$

where $g(t)$ is an arbitrary function of time. The function $g(t)$ does not affect the total force acting on the system, $F = -\partial H_0/\partial x + f(t)$, but it changes the Hamiltonian. Therefore, $g(t)$ has to be chosen so that the Hamiltonian can be identified with the energy of the system.

In general, the arbitrary time dependence of the Hamiltonian, $g(t)$, cannot be chosen so that the Hamiltonian gives a consistent energy. Consider, for instance, that the system, initially at x_0, is subjected to a sudden perturbation $f(t) \equiv f_0\Theta(t)$, where f_0 is a constant and $\Theta(t)$ is the Heaviside step function. The work performed on the system $W = f_0(x_t - x_0)$, where $x_t \equiv x(t)$ represents the value of the coordinate x at time t, is in general different from $\int_0^t \frac{\partial H(x_{t'}, t')}{\partial t'} dt' = -f_0 x_0 + g(t) - g(0)$, irrespective of the explicit form of the function $g(t)$.

To illustrate the consequences of the lack of connection between work and changes in the Hamiltonian, we focus on the domain of validity of nonequilibrium work relations [3] of the type

$$\langle e^{-\beta W} \rangle = e^{-\beta \Delta G_E}, \qquad (2)$$

which have been widely used recently to obtain estimates ΔG_E of free-energy changes from single-molecule pulling experiments [6] and atomistic computer simulations [7]. The promise of this type of relations is that they provide the values of the free-energy from irreversible trajectories and therefore do not require equilibration of the system. Yet, in almost all instances in which this approach has been applied, the agreement with the canonical thermodynamic results has not been complete and in some cases the discrepancies have been large. The discrepancies have typically been attributed to the lack of statistics in the estimation of the exponential average $\langle e^{-\beta W} \rangle$ [8].

Currently, the mathematical validity of these type of nonequilibrium work relations appears to be well established inasmuch as they have been derived using approximations [3,9] and mathematically rigorous methods for

systems described by Langevin equations [4,5]. All the derivations, however, rely in different ways on the work-Hamiltonian connection, which as we show below prevents them from giving general estimates of thermodynamic free energies.

The free-energy difference between two states is defined as $\Delta G = \langle W_{\text{rev}} \rangle$, where W_{rev} is the work required to bring the system from the initial to the final state over a quasi-static, reversible trajectory [2]. Note that, if the system is not macroscopic, W_{rev} is in general a fluctuating quantity and $\Delta G = \langle W_{\text{rev}} \rangle \neq -\frac{1}{\beta} \ln \langle e^{-\beta W_{\text{rev}}} \rangle$. At quasiequilibrium, the external force $f(t)$ balances with the system force $-\partial H(x)/\partial x$. After integration by the displacement, the work done on the system over a reversible trajectory is given by $W_{\text{rev}} = H_0(x_t) - H_0(x_0)$. Therefore, the free-energy follows from

$$\Delta G = \iint W_{\text{rev}} P_{\text{eq}}(x_t, t) P_{\text{eq}}(x_0, 0) dx_t dx_0, \quad (3)$$

where the equilibrium probabilities P_{eq} are obtained, in the usual way, from the Boltzmann distribution $P_{\text{eq}}(x_t, t) = \frac{1}{Z(t)} e^{-\beta H(x_t, t)}$. To be explicit, let us consider a system in a parabolic potential described by $H_0(x) = \frac{1}{2} k x^2$ and $g(t) = 0$, with k a constant. In this case, we can compute exactly the free-energy change,

$$\Delta G = \frac{1}{2} k x_{\text{eq}}^2, \quad (4)$$

where $x_{\text{eq}} = f(t)/k$, which is positive as required for non-spontaneous processes.

One might have been tempted to use the partition function to estimate changes in free energy according to the expression $\Delta G_Z = -\frac{1}{\beta} \ln[Z(t)/Z(0)]$, where $Z(t) = \int e^{-\beta H(x,t)} dx$ is the time-dependent quasiequilibrium partition function [3,4]. However, this relation is not thermodynamically valid when changes in the Hamiltonian cannot be associated with the work performed on the system. As a straightforward example, consider the Hamiltonian $H(x, t) = H_0(x) + g(t)$. This Hamiltonian would lead to arbitrary free-energy changes, $\Delta G_Z = g(t) - g(0)$, when in fact the system remains unaltered. In this case, changes in ΔG_Z are not the result of any physical process but a consequence of the mathematical description. In the case of the parabolic potential, the use of the time-dependent partition function leads to $\Delta G_Z = -\frac{1}{2} k x_{\text{eq}}^2$, a negative value inconsistent with a nonspontaneous process. More generally, the Hamiltonian $H(x, t) = \frac{1}{2} k x^2 - f(t)(x - \gamma)$, where γ is a constant parameter that does not affect the dynamics of the system, leads to $\Delta G_Z = k x_{\text{eq}} (\gamma - \frac{1}{2} x_{\text{eq}})$, which can be positive or negative depending on the value of γ. Therefore, the estimates ΔG_Z are not suitable to obtain typical thermodynamic properties, such as whether or not a process happens spontaneously.

To what extent does the failure of the work-Hamiltonian connection impact nonequilibrium work equalities? In the case of the sudden perturbation and parabolic potential discussed previously, it follows straightforwardly that

$$\langle e^{-\beta W} \rangle = \iint e^{-\beta f_0(x_t - x_0)} P_{\text{eq}}(x_t) P_{eq}(x_0) dx_t dx_0 = 1, \quad (5)$$

which is different from $e^{-\beta \Delta G}$. The reason for this discrepancy is that, under these circumstances, because of the failure of the work-Hamiltonian connection, the identity used to derive nonequilibrium work equalities [3],

$$\left\langle \exp\left(-\beta \int_0^t [\partial H(x_{t'}, t')/\partial t'] dt'\right)\right\rangle = \frac{Z(t)}{Z(0)} = \exp(-\beta \Delta G_Z), \quad (6)$$

is not equivalent to $\langle e^{-\beta W} \rangle = e^{-\beta \Delta G}$. It is important to emphasize that Eq. (6) can be very useful to obtain equilibrium partition functions from nonequilibrium changes in the Hamiltonian, but trying to enforce the work-Hamiltonian connection by *ad hoc* redefinition of work as $\int_0^t [\partial H(x_{t'}, t')/\partial t'] dt'$ [10] does not solve the physical inconsistencies arising from the general association of ΔG_Z with free-energy changes, such as the dependence of ΔG_Z on arbitrary parameters [11]. Along these lines, it has recently been shown that although Eq. (6) holds rigorously for an expanding one-dimensional ideal gas, the free-energy change obtained from it, ΔG_Z, does not equal the actual free-energy change of the system at any time [12]. In this regard, nonequilibrium work equalities [3] hold in terms of partition functions and Hamiltonian changes, as expressed by Eq. (6), but they cannot be interpreted in general in terms of thermodynamic free energies and work.

In the case of the Hamiltonian of Eq. (1), because the force $f(t)$ is constant after it is instantaneously switched on, the work performed on the system is a function of just the initial and final equilibrium states and does not depend explicitly on the dynamics of the system. Therefore, our results apply to a broad variety of systems, as for instance those that follow a Langevin dynamics given by

$$\frac{dx}{dt} = -\frac{\partial H}{\partial x} + \xi(t) = -kx + f_0 \Theta(t) + \xi(t), \quad (7)$$

where $\xi(t)$ is Gaussian white noise with zero mean and correlation $\langle \xi(t) \xi(t') \rangle = \frac{2}{\beta} \delta(t - t')$. This type of stochastic dynamics for a degree of freedom, known as the Ornstein-Uhlenbeck process, has been shown to describe systems as diverse as macromolecules that follow Hooke's law, Brownian particles, electronic devices, and mesoscopic chemical reactions [13]. After the force $f(t)$ is instantaneously switched on, the system relaxes its motion around $x_{\text{eq}} = 0$ towards its new equilibrium position $x_{\text{eq}} = f_0/k$ (Fig. 1). The results of numerically integrating the Langevin equation (Fig. 2) corroborate both the change in free energy given by Eq. (4) and the failure of the nonequilibrium work equality shown by Eq. (5).
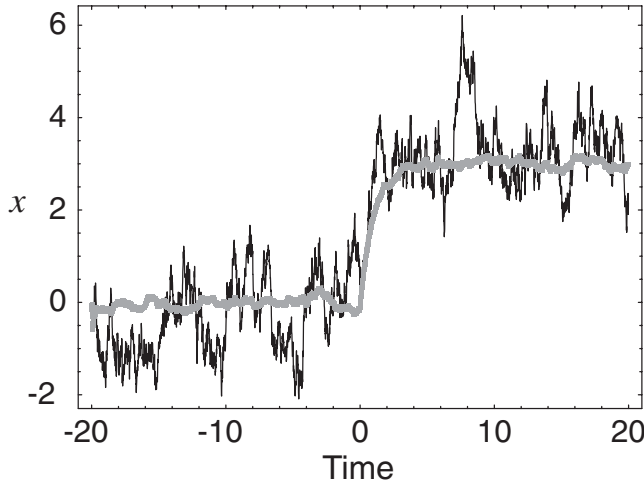
FIG. 1.   Temporal behavior of the degree of freedom x obtained from numerical simulations of Eq. (7). The black line is a representative trajectory. The gray line is the average over 100 trajectories. The values of the parameters (in arbitrary units) are $k = 1$, $\beta = 1$, and $f_0 = 3$. The simulations have been performed by integrating the Langevin equation with a standard second-order Runge-Kutta method for stochastic differential equations [15].

An important question then arises: why do experiments and computer simulations sometimes lead to results that agree with nonequilibrium work equalities? Let us consider a situation closer to the experimental and computational setups, with a parabolic time-dependent potential that constrains the motion on the coordinate x:

$$H(x, t) = H_0(x) + \frac{1}{2}K(x - X_t)^2. \quad (8)$$

Here, K is a constant, and X_t is the time-dependent equilibrium position for the constraining force. In this case, with $H_0(x) = \frac{1}{2}kx^2$ and $X_0 = 0$, we also have

$$\Delta G = \langle W_{\text{rev}} \rangle = \frac{1}{2}kx_{\text{eq}}^2, \quad (9)$$

where now $x_{\text{eq}} \equiv \frac{K}{k+K}X_t$.

For quasiequilibrium displacements of X_t, so that the work is performed over reversible trajectories and $W = W_{\text{rev}} = H_0(x_t) - H_0(x_0)$, we have

$$\langle e^{-\beta W_{\text{rev}}} \rangle = \iint e^{-\beta[H_0(x_t)-H_0(x_0)]}P_{\text{eq}}(x_t, t)P_{\text{eq}}(x_0, 0)dx_t dx_0, \quad (10)$$

which leads to

$$\langle e^{-\beta W_{\text{rev}}} \rangle = \frac{e^{-\beta[k(k+K)/2(2k+K)]x_{\text{eq}}^2}(k + K)}{\sqrt{K(2k + K)}}. \quad (11)$$

This result indicates that quasiequilibrium does not guarantee the accuracy of the exponential estimate of the free energy from nonequilibrium work relations. The free-
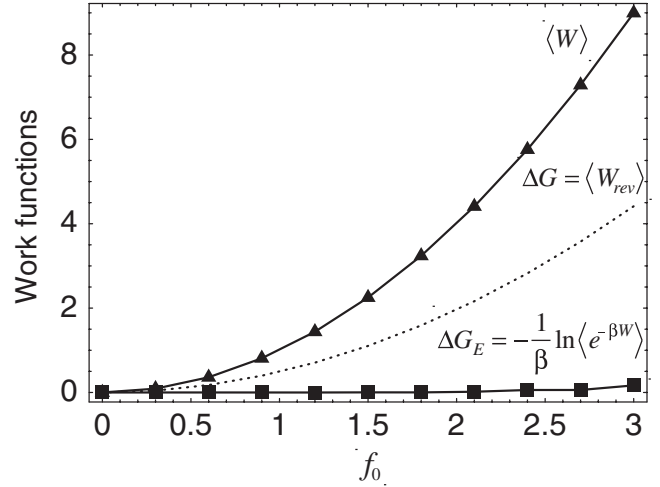

FIG. 2.   Work functions [$\langle W \rangle$ (triangles), $\Delta G_E = -\frac{1}{\beta}\ln\langle e^{-\beta W} \rangle$ (squares), and $\Delta G = \langle W_{\text{rev}} \rangle$ (dotted line)] for the switching-on of a force in a system described by a parabolic potential with Langevin dynamics given by Eq. (7). All the averages have been performed over 10^6 trajectories obtained by integrating the Langevin equation with a standard second-order Runge-Kutta method for stochastic differential equations [15]. The nonequilibrium work performed over a trajectory for a given force strength f_0 is computed as $W = \sum_{0 \leq n\Delta t < 10}(x_{(n+1)\Delta t} - x_{n\Delta t})f_0$ with time step $\Delta t = 10^{-2}$. The work over a reversible trajectory is estimated as $W_{\text{rev}} = \sum_{0 \leq n\Delta t < 10}(x_{(n+1)\Delta t} - x_{n\Delta t})\frac{f_0 n\Delta t}{10}$ by replacing $f_0\Theta(t)$ in Eq. (7) with $f_0 t\Theta(t)/10$, a force that increases slowly with time. The values of the parameters (in arbitrary units) are $k = 1$ and $\beta = 1$.

energy change ΔG and its exponential estimate ΔG_E agree with each other only for large values of K. The reason is that, in this case, work and Hamiltonian are connected to each other when both quasiequilibrium and large K conditions are fulfilled simultaneously. Under such conditions, the work-Hamiltonian connection is valid because $x \approx x_{\text{eq}} \approx X_t$ implies that the rate of change of the Hamiltonian, $\partial H(x, t)/\partial t = -K(x - X_t)dX_t/dt$, equals the power associated with the external force, $dW/dt = -K(x - X_t)dx/dt$. Interestingly, large values of K suppress fluctuations and lead to quasideterministic dynamics. Indeed, a closer look at the experimental data [6] and computer simulations [7] indicate that the agreement between the free-energy change ΔG and its exponential estimate ΔG_E occurs mainly for relatively slow perturbations that lead to quasideterministic trajectories.

Bringing thermodynamics to nonequilibrium microscopic processes [14] is becoming increasingly important with the advent of new experimental and computational techniques able to probe the properties of single molecules [6,7]. Our results show that the classical connection between work and changes in the Hamiltonian cannot be applied straightforwardly to time-dependent systems. As a result, quantities that are based on the work-Hamiltonian connection, such as those obtained from nonequilibrium

work relations and time-dependent partition functions, cannot generally be used to estimate thermodynamically consistent free-energy changes. A possible avenue to overcome these limitations, as we have shown here, is to identify the particular conditions for which work and changes in the Hamiltonian are connected to each other.

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