The Work-Hamiltonian Connection and the Usefulness of the Jarzynski Equality for Free Energy Calculations *

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The connection between work and changes in the Hamiltonian for a system with a time-dependent Hamiltonian has recently been called into question, casting doubt on the usefulness of the Jarzynski equality for calculating free energy changes. In this paper, we discuss the relationship between two possible definitions of free energy and show how some recent disagreements regarding the applicability of the Jarzynski equality are the result of different authors using different definitions of free energy. Finally, in light of the recently raised doubts, we explicitly demonstrate that it is indeed possible to obtain physically preprintrelevant free energy profiles from molecular pulling experiments by using the Jarzynski equality and the results of Hummer and Szabo.

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Single molecule experiments, such as the stretching of a polymer molecule using an atomic force microscope or laser tweezers, have become common in the last decade [1, 2]. The goal is often the determination of the free energy surface along some coordinate of the molecular potential energy surface. In order to proceed, one invokes the Jarzynski equality using the extension derived by Hummer and Szabo [3].

Although there has been some controversy about these theoretical advances, it is fair to say that their use in interpreting nano-scale single molecule experiments is widespread. Thus any question that they may be fundamentally in error must be carefully examined.

Recently, questions have been raised about the connection between work and changes in the Hamiltonian for a system with a time-dependent Hamiltonian, casting doubt on the applicability of the Jarzynski equality for computing free energy changes [4]. Here, we discuss these questions and show that the Jarzynski equality can be usefully applied to determine physically relevant free energy changes.

Consider a system with Hamiltonian $\mathcal{H}_0(x)$, where x represents the microstate of the system, and suppose that this system is subject to a time-dependent force $f(t)$ acting along some coordinate $z(x)$. From the perspective of classical mechanics, we have two options for treating the force. We may consider it as an external force not included in the Hamiltonian of the system and study the evolution of a system governed by $\mathcal{H}_0(x)$ under the effect of the external force $f(t)$ acting along $z(x)$. Alternatively, we may include the force in the Hamiltonian of the system and study the evolution of a system governed by $\mathcal{H}(x,t) = \mathcal{H}_0(x) - z(x)f(t)$.

In the first case, we are considering a time-independent Hamiltonian under the effect of an external force $f(t)$.

According to classical mechanics, the work done by the external force up to time τ is

$$W(\tau) = \int_{t=0}^{t=\tau} f(t)d\{z[x(t)]\} \qquad (1)$$

and we have the usual result that the work done on the system equals its energy change,

$$\mathcal{H}_0[x(t_2)] - \mathcal{H}_0[x(t_1)] = W(t_2) - W(t_1). \qquad (2)$$

The free energy change appropriate for this first description of the system is

$$G(z_2) - G(z_1) = -\log\left[\frac{\int dx\delta[z(x) - z_2]e^{-\mathcal{H}_0(x)}}{\int dx\delta[z(x) - z_1]e^{-\mathcal{H}_0(x)}}\right] \qquad (3)$$

($k_B T = 1$ throughout).

In the second case, we consider the time-dependent Hamiltonian $\mathcal{H}(x,t) = \mathcal{H}_0(x) - z(x)f(t)$. In this description of the system, $f(t)$ is an internal force and there should be no expectation that the work done by $f(t)$ equals the change in energy of the system. Here we consider the *thermodynamic work*,

$$W_t(\tau) = \int_0^\tau dt\frac{\partial\mathcal{H}}{\partial t}, \qquad (4)$$

which by definition equals the change in energy of the system. The appropriate free energy change to consider for this description of the system is

$$\Delta G_t(\tau) = G_t(\tau) - G_t(0) = -\log\left[\frac{\int dx e^{-\mathcal{H}(x,\tau)}}{\int dx e^{-\mathcal{H}(x,0)}}\right]. \qquad (5)$$

We note, as suggested by Vilar and Rubi (VR) [4], that this second description of the system is not unique – adding a term $g(t)$ to the Hamiltonian has no effect on the dynamics of the system but changes the values of W_t and ΔG_t.

In considering the effect of a force f on a harmonic spring of force constant k, VR describe the system according to the first picture and obtain $\Delta G = W = f^2/2k$

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while Horowitz and Jarzynski (HJ) use the second picture and obtain $\Delta G_t = W_t = -f^2/2k$ [5, 6]. Both of these results are correct in their respective descriptions, and mean different things. In particular, VR are describing the free energy change associated with changing the length of the spring in the absence of an external force; the force is only a tool used to measure the free energy profile of the free spring. Meanwhile, HJ are describing the free energy change of the combined force-spring system as a function of the force.

The Jarzynski equality is framed in the second of our descriptions and expresses a relation between W_t and ΔG_t [7],

$$e^{-\Delta G_t} = \langle e^{-W_t} \rangle. \tag{6}$$

The validity of this expression is not in question – only its utility in describing free energy changes in a system. VR point out that ΔG_t depends on the arbitrary choice of $g(t)$ in the Hamiltonian and leads to arbitrary free energy changes. If all that can be extracted from the Jarzynski equality is this arbitrary ΔG_t, then the Jarzynski equality seems to be of little use. We shall show, however, that this is not the case.

Consider a single-molecule pulling experiment, for which the Jarzynski equality has frequently been applied [1, 2]. In studying the unfolding of a biomolecule, one is often interested in the free energy profile $G(z)$ as a function of end-to-end distance z. We could map the free energy by reversibly pulling the ends of the molecule and measuring the work exerted by the external force as a function of z. This is of course the classic method and corresponds to VR's analysis of the harmonic spring.

We could also try to get the free energy profile using the Jarzynski equality. Direct application of the Jarzynski equality to yield ΔG_t gives the free energy difference between the free molecule and the molecule with a certain force applied to it. This is not in itself a particularly useful quantity and is not the free energy profile. Hummer and Szabo have, however, shown how to obtain free energy profiles from single-molecule pulling experiments [3].

Consider an unperturbed system described by a Hamiltonian $\mathcal{H}_0(x)$. When a time-dependent perturbation is applied along some coordinate $z(x)$, we write the new Hamiltonian as $\mathcal{H}_0(x) + \mathcal{H}'(z, t)$. Hummer and Szabo have shown that the unperturbed free energy profile along coordinate z can then be reconstructed as

$$G(z_0) = -\log\langle \delta[z(t) - z_0]e^{-W_t + \mathcal{H}'(z,t)} \rangle, \tag{7}$$

where the average is over all trajectories of the system in the presence of the perturbation [3].

We now apply this result to a macroscopic, deterministic spring and show how the Jarzynski equality can be used to calculate $G(z)$, thereby reconciling the results of HJ and those of VR. In this case, there is only one degree of freedom so the microstate x is simply the length

of the spring. Our model is $\mathcal{H}_0(x) = p^2 + kx^2/2$ and $\mathcal{H}(x, t) = p^2 + kx^2/2 - f(t)x$, where $f(t)$ switches from 0 to f_0 over time $0 < t < \tau$. The pulling process is finished at $t = \tau$, at which time $f(\tau) = f_0$ and from classical mechanics $x(\tau) = f_0/k$.

Inserting this into Hummer and Szabo's result,

$$G(z) = -\log\langle \delta[x(\tau) - z]e^{-W_t - f_0 x(\tau)} \rangle, \tag{8}$$

where we have used the fact that in this case our coordinate of interest $z(x)$ is just x.

In this deterministic case only $z = f_0/k$ contributes to the average and we have

$$G(z = f_0/k) = -\log\langle e^{-W_t - f_0^2/k} \rangle = -\log\left[\langle e^{-W_t} \rangle e^{-f_0^2/k}\right]. \tag{9}$$

For reversible pulling, HJ calculate that the work distribution is sharply peaked at $W_t = -f_0^2/2k$, so we finally obtain

$$G(z = f_0/k) = -\log\left[e^{f_0^2/2k}e^{-f_0^2/k}\right] = +f_0^2/2k, \tag{10}$$

which agrees with VR and is the expected result for the free energy profile of a Hookean spring.

Consider the effect of adding an arbitrary $g(t)$ to the general Hamiltonian. The effect on ΔG_t is easily seen from Eq. (5) to be

$$\Delta G_t^{new}(\tau) = \Delta G_t(\tau) + [g(\tau) - g(0)]. \tag{11}$$

Since the term $g(t)$ redefines the zero of energy at each point in time, it is expected that $\Delta G_t(\tau)$ will be affected as it is comparing free energies at two different times. Before ascribing a physical interpretation to ΔG_t, it must be corrected by subtracting this arbitrary change in the zero of energy.

We now examine the effect of an arbitrary $g(t)$ on the free energy profile $G(z)$ computed via Jarzynski's equality. We then have

$$\mathcal{H}'^{new}(x, t) = \mathcal{H}'(x, t) + g(t) \tag{12}$$
$$W_t^{new} = W_t + g(\tau) - g(0) \tag{13}$$

and Eq. (7) becomes

$$G^{new}(z_0) = -\log\langle \delta[z(t) - z_0]e^{-W_t + \mathcal{H}'(z,t) + g(0)} \rangle, \tag{14}$$

which can be simplified to

$$G^{new}(z_0) = G(z_0) - g(0). \tag{15}$$

So adding a time-dependent term $g(t)$ shifts the overall free energy profile $G(z)$ by an additive constant, but has no effect on relative free energies.

We can consider the same situation from the perspective of thermodynamics in one dimension. The internal energy of the system is given by $U = \mathcal{H}_0$ and its enthalpy

by the Legendre transform $\mathcal{H}_0 - fz$. We can then define two free energies, $G = U - ST$ and $G_t = U - fz - ST$.

The method of VR is constructed to measure G as a function of position, $G(z)$, while HJ are calculating G_t as a function of f, $G_t(f)$. As long as the fluctuations in x are small at a given f (ie, we are in the thermodynamic limit), we can use the simple relation $G(z) = G_t(f) + fz$ to convert between the two quantities. Outside of this limit, there is not a simple relation between the two quantities but the method of Hummer and Szabo discussed above can be used to reconstruct $G(z)$ from pulling experiments.

In conclusion, we have shown that by properly applying the Jarzynski equality, the textbook result for the free energy profile of a spring is correctly recovered. More importantly in light of recent doubts, we have reaffirmed the applicability of the Jarzynski equality to the analysis of single-molecule pulling data.

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