Comment on "Transient-state fluctuationlike relation for the driving force on a biomolecule"

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Phys. Rev. E **85**, 053103 — Published 17 May 2012

DOI: 10.1103/PhysRevE.85.053103

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Two analytically tractable systems, Brownian particles in (i) moving harmonic oscillator or (ii) with a time-dependent natural frequency, obey a force fluctuation theorem similar to that proposed by Ponmurugan and Vemparala. Many of their results can be explained by using the former case as a model.

Based on force distributions observed in biomolecular simulations of two systems, Ponmurugan and Vemparala proposed [1], without derivation, an intriguing relation in the form of a fluctuation theorem,

$$\frac{P_v(+f)}{P_v(-f)} = e^{\gamma(T,v)f}, \tag{1}$$

where $P_v(\pm f)$ is the velocity-dependent probability of observing a positive or negative force f acting upon a system by a harmonic spring moving at a constant velocity v and $\gamma(T,v)$ is a proportionality constant with a power-law dependence on the temperature T and v.

In this comment, I point out that by using histograms that combine data from different time points, Ponmurugan and Vemparala implicitly assumed time-independence of the force distribution. This may be a reasonable approximation in some cases, but it cannot be rigorously true that the force distribution at $t = 0$, where the system is in equilibrium, is equivalent to the distribution at an arbitrary later time of an nonequilibrium driven process.

As counterexamples, I present two analytically tractable models for which a similar relation holds. The force fluctuation theorem has the form,

$$\frac{P_v(+f,t)}{P_v(-f,t)} = e^{\gamma(\lambda)f}, \tag{2}$$

in which $\gamma(\lambda)$ is a function of a vector of parameters λ that describe the state of the system (including t). The model systems are a Brownian particle in a harmonic oscillator (i) moving at a constant velocity or (ii) with a time-dependent natural frequency. In both cases, the potential energy has the form $U(x,t) = k(t)(x-\bar{x}(t))^2/2$. The systems are prepared in their respective equilibrium distributions and are driven out of equilibrium either by changing $\bar{x}(t)$ or $k(t)$. In case (i), $\bar{x} = vt$ and $k(t) = k$ is a constant. In case (ii), $\bar{x} = 0$ is a constant and $k(t)$ varies with time.

As previously derived [2, 3], the nonequilibrium probability $p_{neq}(x,t)$ of observing position x at time t is Gaussian with a time-dependent mean $x_T(t)$ and variance $\sigma_x^2(t)$. (Note that $x_T(t)$ is *not*, in general, the equilibrium position of the oscillator $\bar{x}(t)$.) Since the force applied by the harmonic oscillator is $-k(t)(x-\bar{x}(t))$, the distribution of force is also Gaussian, with mean $\bar{f}(t) = -k(t)(x_T(t) - \bar{x}(t))$ and variance $\sigma_f^2(t) = k(t)^2\sigma_x^2(t)$. Thus, the ratio of positive and negative force probabilities is,

$$\begin{aligned}\frac{P(+f,t)}{P(-f,t)} &= \exp\left[-\frac{(f-\bar{f}(t))^2}{2\sigma_f^2(t)} + \frac{(f+\bar{f}(t))^2}{2\sigma_f^2(t)}\right] \\ &= \exp\left[\frac{2\bar{f}(t)}{\sigma_f^2(t)}f\right].\end{aligned} \tag{3}$$

Using the analytical $x_T(t)$ and $\sigma_x^2(t)$ [3], the mean and variance of the force in case (i) is,

$$\bar{f}(t) = \frac{v}{\beta D}\left(1 - e^{-\beta Dkt}\right) \tag{4}$$

$$\sigma_f^2(t) = \frac{k}{\beta}, \tag{5}$$

where $\beta = (k_BT)^{-1}$ is the inverse of Boltzmann's constant times the Kelvin temperature and D is the diffusion coefficient. In case (ii), $\bar{f}(t) = 0$ and $\sigma_f^2(t)$ may be obtained from Eq. (6) in Minh [3], leading to a complex expression that shall be omitted here. Notably, both cases have time-dependent force distributions and fit into the form of Eq. (2).

Although it is a simple model, case (i) is surprisingly relevant to biomolecular single-molecule pulling experiments. With a sufficiently stiff spring constant, the dynamics of a complex system subject to a moving harmonic oscillator potential are well-described by those of the harmonic oscillator [4]; this is the *stiff spring approximation.*

For lower pulling rates, Ponmurugan and Vemparala's results appear to fall under the aegis of the stiff spring approximation. At a pulling rate of 10 Å/ns, a spring constant as low as 250 pN/Å was found to be sufficiently stiff to accurately recapitulate free energies with the stiff spring approximation [5]. Ponmurugan and Vemparala's slowest pulling rates were comparable, at 2.5 and 25 Å/ns, and they used a stiffer spring constant of 10 kcal/mol/Å^2 = 695 pN/Å. Indeed, Fig. 2, panels (c) and (d) appear to be roughly Gaussian distributions with variance close to $\sigma_f^2 = k/\beta$ = (695 pN/Å)(0.138 pN Å/K)(300 K) = 2.87×10^4 pN^2 or standard deviation σ_f = 170 pN. Furthermore, the fact that the fast pulling rate leads to an increased mean force is consistent with Eq. 4. The stiff spring approximation, however, fails to predict the powers of the phenomenological power laws.

Because of the one-to-one mapping between position and force, Hummer and Szabo's relation [6] between the work-weighted nonequilibrium position on the pulling coordinate and the equilibrium probability of the same position is relevant to force distributions. Nonetheless, in spite of results presented here, I am skeptical that a more general force fluctuation relation in the form of Eq. 2 will be derived. I hope to be pleasantly surprised.

ACKNOWLEDGEMENT

The author thanks David Beratan for being a supportive postdoctoral advisor. This research was funded by NSF CHE10-57953, NIH 2P50 GM-067082-06-10, and N00014-11-1-0729.

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