

# Nonequilibrium fluctuation-dissipation theorem of Brownian dynamics

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Studying the Brownian motion of a system driven by an external control from one macroscopic state to another macroscopic state, this paper presents the derivation of a nonlinear fluctuation-dissipation theorem (FDT). The new FDT relates the nonequilibrium work to the equilibrium free-energy difference in a very simple manner. It is valid wherever the Brownian dynamics is applicable. It recovers the well-known Crooks fluctuation theorem (CFT) within the quasiequilibrium regime where the dissipative work is nearly zero. It will also be shown that the CFT's fundamental assumption of microscopic reversibility is not obeyed in experiments such as mechanically unfolding biological molecules, in which the external driving forces depend on the system's coordinates. © 2008 American Institute of Physics. [DOI: 10.1063/1.2992153]

The bridge from the nonequilibrium work to the equilibrium free-energy difference has been a subject of much interest in recent years. Such a bridge is necessary to relate the experimental data of forces and displacements to the intrinsic properties of the system in the unfolding studies of proteins and nucleic acids.<sup>1</sup> It also serves as an effective and efficient method in the computations of free energy.<sup>2</sup> In the current literature, Jarzynski equality<sup>3</sup> (JE) and the undergirding Crooks fluctuation theorem<sup>4</sup> (CFT) are taken as the bridge while questions have been raised<sup>5–7</sup> about their applicability and range of validity. The self-consistency check of the CFT has suggested<sup>8</sup> that the CFT and JE are valid only in the quasiequilibrium or linear response regime. In this paper, I will present the derivation of a new fluctuation-dissipation theorem (FDT) without invoking any assumption beyond the Brownian dynamics. I will also show that the assumption of microscopic reversibility, on which the CFT is based, is generally invalid outside the quasiequilibrium regime. This will establish that the CFT and JE are applicable only within the quasiequilibrium regime where the dissipative work is nearly zero. However, the new FDT is valid wherever the Brownian dynamics is applicable.

Let us start with the Langevin equation for the Brownian dynamics as follows:<sup>9</sup>

$$m_i \gamma \frac{dx_i}{dt} + \frac{\partial}{\partial x_i} V = F_i + \xi_i. \quad (1)$$

Here  $m_i$  and  $x_i$  are the atomic mass and coordinate of the  $i$ th degree of freedom, respectively.  $\gamma$  is the damping (frictional) constant.  $V$  is the potential energy of the system that is a function of all coordinates.  $\xi_i$  is the stochastic force acting on the  $i$ th degree of freedom. It is assumed to be Gaussian with the following characteristics:

$$\langle \xi_i(t) \rangle = 0, \quad \langle \xi_i(t) \xi_j(t') \rangle = 2m_i \gamma k_B T \delta_{ij} \delta(t - t'). \quad (2)$$

Here  $k_B$  is the Boltzmann constant.  $T$  is the absolute temperature.  $\delta_{ij}$  is the Kronecker delta and  $\delta(t - t')$  is the Dirac delta function.  $F_i$  is the external force component acting on the  $i$ th degree of freedom. The external force drives the system from state  $A$  at time  $t=0$  to state  $B$  at time  $t=\tau$ . For example, in a mechanical unfolding experiment, the two terminus atoms are subject to the external forces that are functions of the atomic coordinates and time. In general,  $F_i = F_i(x, t)$ , where  $x = \{x_j\}$  is the collection of the atomic coordinates.

Now, we divide the time interval  $[0, \tau]$  into  $N$  equal slices of width  $dt = \tau/N$ . In this, we have  $t_n = ndt$  with  $n = 0, 1, \dots, N$ . For clarity, we omit the index for the degree of freedom and denote  $x_n \triangleq x_i(t_n)$ ,  $\partial V_n \triangleq \partial V(x(t_n)) / \partial x_i$ , and  $F_n \triangleq F_i(x(t_n), t_n)$ . Then the discrete form of the Langevin equation (1) is

$$m \gamma (x_{n+1} - x_n) + \partial V_n dt - F_n dt = \int_{t_n}^{t_{n+1}} dt' \xi(t'). \quad (3)$$

Noting the statistical characteristics of the stochastic term on the right hand side of Eq. (3), we have the transition probability between state  $x_n$  at time  $t_n$  and state  $x_{n+1}$  at time  $t_{n+1}$ , namely, the probability for the system to be in state  $x_{n+1}$  at time  $t_{n+1}$  given that it is in state  $x_n$  at time  $t_n$  as follows:

$$P(x_n, t_n | x_{n+1}, t_{n+1}) = \frac{1}{\Omega} \exp\left(-\frac{(m \gamma (x_{n+1} - x_n) + \partial V_n dt - F_n dt)^2}{4m \gamma k_B T dt}\right). \quad (4)$$

Here the normalization factor  $\Omega = (2k_B T dt / m \gamma)^{1/2}$ , which is independent of the system's coordinates. Note that the Ito scheme is adopted in this paper for the discrete form of the

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Langevin equation in Eq. (3). If the Stratonovich scheme were adopted,  $\Omega$  would have a very complex dependence on the coordinates through  $\partial V_{n+1}$  and  $F_{n+1}$ . When that complex dependence is correctly accounted for, the Stratonovich scheme should agree exactly with the Ito scheme.<sup>9</sup>

Considering the dynamics of the system is Markovian, we have the probability for transition along a given path  $(x(t))=(x_0, x_1, \dots, x_N)$  from state  $A$  ( $x_0=x_A$ ) to state  $B$  ( $x_N=x_B$ ) as follows:

$$\begin{aligned} P(x_0, t_0 | x_1, t_1 | \dots | x_N, t_N) \\ &= p_e(x_A) \prod_{n=0}^{N-1} P(x_n, t_n | x_{n+1}, t_{n+1}) \\ &= \frac{1}{\Omega^N} p_e(x_A) \exp\left(-\sum_{n=0}^{N-1} \frac{(m\gamma(x_{n+1}-x_n) + \partial V_n dt - F_n dt)^2}{4m\gamma k_B T dt}\right), \end{aligned} \quad (5)$$

where  $p_e(x_A)=\exp(-\beta V(x_A))/Z_A$  is the equilibrium probability distribution of the system when it is constrained to the

macroscopic state  $A$ .  $Z_A=\exp(-\beta G_A)$  is the partition function and  $G_A$  is the free energy of that macroscopic state.  $\beta \triangleq 1/k_B T$ . The system is driven from state  $A$  to state  $B$  by the external force  $(F(t))=(F_0, F_1, \dots, F_N)$ .

The following question has been asked but not answered correctly in the current literature: What is the probability for the system to take the exact reverse path  $(\tilde{x}(t))=(x_N, x_{N-1}, \dots, x_0)$  if the external driving force is tuned backward in time,  $(\tilde{F}(t))=(F_N, F_{N-1}, \dots, F_0)$ ? Answering this question correctly requires particular attention to the subtle stochastic nature of the Brownian dynamics. Resembling exactly Eq. (4), the transition probability between state  $x_{N-n}$  at time  $t_n$  and state  $x_{N-n-1}$  at time  $t_{n+1}$  is

$$\begin{aligned} P(x_{N-n}, t_n | x_{N-n-1}, t_{n+1}) \\ &= \frac{1}{\Omega} \exp\left(-\frac{(m\gamma(x_{N-n-1}-x_{N-n}) + \partial V_{N-n} dt - F_{N-n} dt)^2}{4m\gamma k_B T dt}\right). \end{aligned} \quad (6)$$

The probability for transition along the reverse path  $(\tilde{x}(t))=(x_N, x_{N-1}, \dots, x_0)$  is

$$P(x_N, t_0 | x_{N-1}, t_1 | \dots | x_0, t_N) = p_e(x_B) \prod_{n=0}^{N-1} P(x_{N-n}, t_n | x_{N-n-1}, t_{n+1}) = \frac{1}{\Omega^N} p_e(x_B) \exp\left(-\sum_{n=0}^{N-1} \frac{(m\gamma(x_{N-n-1}-x_{N-n}) + \partial V_{N-n} dt - F_{N-n} dt)^2}{4m\gamma k_B T dt}\right), \quad (7)$$

where  $p_e(x_B)=\exp(\beta G_B - \beta V(x_B))$  is the equilibrium probability of the system when constrained to the macroscopic state  $B$ . The relationship between the probabilities along the forward and reverse paths will become clear once we substitute the dummy index  $n$  in the sum on the second line of Eq. (7),  $l=N-n-1$ . Then,

$$P(x_N, t_0 | x_{N-1}, t_1 | \dots | x_0, t_N) = \frac{1}{\Omega^N} p_e(x_B) \exp\left(-\sum_{l=0}^{N-1} \frac{(m\gamma(x_l - x_{l+1}) + \partial V_{l+1} dt - F_{l+1} dt)^2}{4m\gamma k_B T dt}\right). \quad (8)$$

Note that the indices are in different order than those of Eq. (5). The ratio between the two probabilities can be found as

$$\frac{P(x_0, t_0 | x_1, t_1 | \dots | x_N, t_N)}{P(x_N, t_0 | x_{N-1}, t_1 | \dots | x_0, t_N)} = \frac{p_e(x_A)}{p_e(x_B)} \exp\left(-\sum_{n=0}^{N-1} \frac{(x_{n+1}-x_n)(\partial V_n - F_n) - (x_n - x_{n+1})(\partial V_{n+1} - F_{n+1})}{2k_B T}\right). \quad (9)$$

In deriving the above equation, we made use of the fact that  $dt$  is infinitesimal so that

$$\exp\left(-\frac{(\partial V_N - F_N)^2 - (\partial V_0 - F_0)^2}{4m\gamma k_B T} dt\right) \Big|_{dt \rightarrow 0} = 1. \quad (10)$$

Examining the differentials in the exponent on the right hand side of Eq. (9), we note that the internal force  $\partial V$  terms lead to the potential energy differences between states  $A$  and  $B$  as follows:

$$\sum_{n=0}^{N-1} (x_{n+1} - x_n) \partial V_n = \sum_{n=0}^{N-1} (V(x_{n+1}) - V(x_n)) = V(x_B) - V(x_A), \quad (11)$$

$$\sum_{n=0}^{N-1} (x_n - x_{n+1}) \partial V_{n+1} = \sum_{n=0}^{N-1} (V(x_n) - V(x_{n+1})) = V(x_A) - V(x_B).$$

However, the external driving forces are not conservative and their terms have to be dealt with explicitly. Now we have

$$\begin{aligned}
& \frac{P(x_0, t_0 | x_1, t_1 | \cdots | x_N, t_N)}{P(x_N, t_0 | x_{N-1}, t_1 | \cdots | x_0, t_N)} \\
&= \frac{p_e(x_A)}{p_e(x_B)} \exp\left(\frac{V(x_A) - V(x_B)}{k_B T}\right) \\
&\quad \times \exp\left(\sum_{n=0}^{N-1} \frac{(x_{n+1} - x_n)F_n - (x_n - x_{n+1})F_{n+1}}{2k_B T}\right) \\
&= \exp[-\beta\Delta G] \exp\left(\frac{1}{2}\beta W[x_0, x_1, \dots, x_N]\right) \\
&\quad \times \exp\left(-\frac{1}{2}\beta W[x_N, x_{N-1}, \dots, x_0]\right). \quad (12)
\end{aligned}$$

Here  $\Delta G \triangleq G_B - G_A$  is the free-energy difference between the macroscopic states  $A$  and  $B$ .

$$W[x_0, x_1, \dots, x_N] \triangleq \sum_{n=0}^{N-1} (x_{n+1} - x_n)F_n \quad (13)$$

is the work done to the system along the transition path  $(x(t)) = (x_0, x_1, \dots, x_N)$  and

$$W[x_N, x_{N-1}, \dots, x_0] = \sum_{n=0}^{N-1} (x_n - x_{n+1})F_{n+1} \quad (14)$$

is the work done to the system along the transition path  $(\tilde{x}(t)) = (x_N, x_{N-1}, \dots, x_0)$ , which is the exact reverse of  $(x(t))$ . Now we see that the probability for a given path is related to that for the exact reverse path in a very simple formula

$$\begin{aligned}
& P(x_0, t_0 | x_1, t_1 | \cdots | x_N, t_N) \exp\left(-\frac{1}{2}\beta W[x_0, x_1, \dots, x_N]\right) \\
&= \exp[-\beta\Delta G] P(x_N, t_0 | x_{N-1}, t_1 | \cdots | x_0, t_N) \\
&\quad \times \exp\left(-\frac{1}{2}\beta W[x_N, x_{N-1}, \dots, x_0]\right). \quad (15)
\end{aligned}$$

Integrating both sides of Eq. (15) with respect to all coordinates  $x_0, x_1, \dots, x_N$  at all time points, we find a new formula that relates the nonequilibrium work to the equilibrium free-energy difference

$$\exp(-\beta\Delta G) = \langle \exp(-\frac{1}{2}\beta W_{A \rightarrow B}) \rangle_F / \langle \exp(-\frac{1}{2}\beta W_{B \rightarrow A}) \rangle_R. \quad (16)$$

Here  $W_{A \rightarrow B(B \rightarrow A)}$  denotes the work done to the system when it is driven from state  $A$  to state  $B$  (driven back from state  $B$  to state  $A$ ). The angular brackets in the numerator represent the statistical mean among all the forward paths (from state  $A$  to state  $B$ ), and their counterparts in the denominator represent the same among the reverse paths (from state  $B$  to state  $A$ ). This new FDT is valid as long as the Brownian dynamics is applicable because its derivation does not require any additional assumptions.

The microscopic reversibility required by the CFT assumes that

$$W[x_0, x_1, \dots, x_N] = -W[x_N, x_{N-1}, \dots, x_0]. \quad (17)$$

When this is valid or a good approximation, Eq. (15) can be rearranged into the following form:

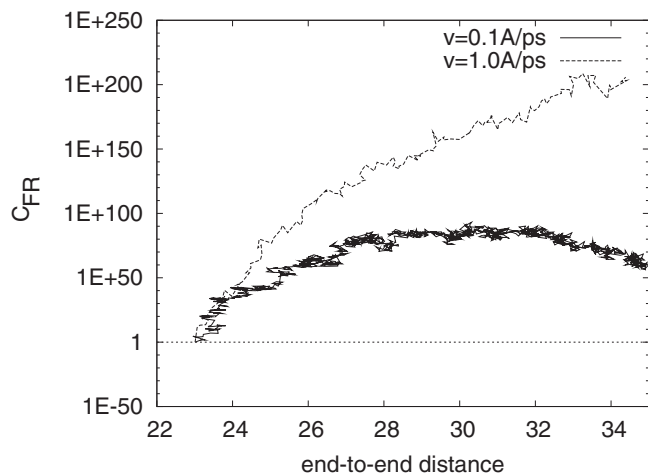


FIG. 1. The self-consistency factor  $C_{FR}$  vs the distance ( $\text{\AA}$ ) between the terminus  $N$  atom (that is fixed) and the terminus  $C$  atom (that is pulled at constant velocity  $v$ ).

$$\begin{aligned}
& P(x_0, t_0 | x_1, t_1 | \cdots | x_N, t_N) \\
&= \exp(-\beta\Delta G) P(x_N, t_0 | x_{N-1}, t_1 | \cdots | x_0, t_N) \\
&\quad \times \exp(-\beta W[x_N, x_{N-1}, \dots, x_0]). \quad (18)
\end{aligned}$$

Multiplying the two sides of Eq. (18) with an arbitrary but finite function  $f(W[x_0, x_1, \dots, x_N])$ , integration over coordinates at all times immediately leads to the CFT in the following form:

$$\exp(-\beta\Delta G) = \langle f(W_{A \rightarrow B}) \rangle_F / \langle f(-W_{B \rightarrow A}) \exp(-\beta W_{B \rightarrow A}) \rangle_R. \quad (19)$$

At this point, it is appropriate briefly look into the CFT's self-consistency. Choosing  $f(W) = 1$ , Eq. (19) gives the free-energy difference through  $\exp(-\beta\Delta G) = 1 / \langle \exp(-\beta W_{B \rightarrow A}) \rangle_R$ . Choosing  $f(W) = e^{-\beta W}$ , it leads to the well-known JE,  $\exp(-\beta\Delta G) = \langle \exp(-\beta W_{A \rightarrow B}) \rangle_F$ . The self-consistency and thus the validity of the CFT and JE demand that

$$C_{FR} \triangleq \langle \exp(-\beta W_{A \rightarrow B}) \rangle_F \langle \exp(-\beta W_{B \rightarrow A}) \rangle_R = 1. \quad (20)$$

Equation (20) is a very strong constraint and therefore severely limits the CFT's applicability. It has been shown<sup>8</sup> that, for near-equilibrium processes, Eq. (20) is simply the linear FDT. For processes that are not near equilibrium; the self-consistency requirement, Eq. (20), is far from being satisfied. I have done *in silico* experiments of unfolding titin (1TIT) in vacuum. The CHARMM27 force fields are used for the interatomic interactions. NAMD/SMD (Ref. 10) is used for the numerical undertakings. I sampled ten unfolding and ten refolding paths to compute the consistency factor  $C_{FR}$  defined in Eq. (20). The consistency  $C_{FR}$  is plotted in Fig. 1 as a function of the end-to-end distance for two unfolding/refolding speeds. As expected,  $C_{FR}$  is closer to 1 for the speed of 0.1  $\text{\AA}/\text{ps}$  than for the speed of 1.0  $\text{\AA}/\text{ps}$ . Even in the case of 0.1  $\text{\AA}/\text{ps}$ , though,  $C_{FR}$  is still very far from 1, which means CFT is not self-consistent for these far nonequilibrium processes.

Now it is time to examine whether or not the assumption of microscopic reversibility is valid. From the definition of work, we have

$$\begin{aligned}
 &W[x_0, x_1, \dots, x_N] + W[x_N, x_{N-1}, \dots, x_0] \\
 &= - \sum_{n=0}^{N-1} (x_{n+1} - x_n)(F_{n+1} - F_n). \quad (21)
 \end{aligned}$$

The assumption of microscopic reversibility means that the right hand side of Eq. (21) is equal to zero. Now one might be attempted to conclude that the right hand side of Eq. (21) vanishes as  $dt \rightarrow 0$  because  $(x_{n+1} - x_n) \sim dt$  and  $(F_{n+1} - F_n) \sim dt$ . But that conclusion is invalid. In fact, it does not vanish as long as the external force  $F(x, t)$  is not independent of the system's coordinates. In general, we have

$$\begin{aligned}
 &W[x_0, x_1, \dots, x_N] + W[x_N, x_{N-1}, \dots, x_0] \\
 &= - \sum_{n=0}^{N-1} (x_{n+1} - x_n)^2 \partial F_n, \quad (22)
 \end{aligned}$$

where  $\partial F_n \triangleq \partial F(x(t_n), t_n) / \partial x_i$ . The right hand side of Eq. (22) would be zero if  $(x_{n+1} - x_n)^2$  were proportional to  $dt^2$ , but the stochastic nature of the system makes  $(x_{n+1} - x_n)^2$  proportional to  $dt$  instead of  $dt^2$ . Therefore the right hand side of Eq. (22) does not vanish in the  $dt \rightarrow 0$  limit. It is equal to twice the dissipative work instead. This means that the CFT and JE are invalid unless the dissipative work is vanishingly small.

Now one more question needs to be asked: What about the case when the external force is independent of the system's coordinates? In such a case, the right hand side of Eq. (22) does vanish. However, with such kind of external forces, the system may not transition from state  $A$  to state  $B$  because of the stochastic nature of its dynamics. In the experiments of mechanically unfolding biological molecules at constant speed, the forces acting on the system are indeed functions of the coordinates of the terminus atoms attached

to the tips of the atomic force microscope or the optical tweezers. CFT and JE are inapplicable to those experiments unless the pulling speeds are slow enough that the system is always near equilibrium.

In summary, a new FDT has been derived from the Brownian dynamics without invoking any assumption. This new FDT is valid in the near-equilibrium or far nonequilibrium regime, wherever the Brownian dynamics is valid. It is also shown that the CFT and the JE are valid only in the near-equilibrium regime where the dissipative work is nearly zero.

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