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On violations of Le Chatelier's principle for a temperature change in small systems observed for short times

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Le Chatelier's principle states that when a system is disturbed, it will shift its equilibrium to counteract the disturbance. However for a chemical reaction in a small, confined system, the probability of observing it proceed in the opposite direction to that predicted by Le Chatelier's principle, can be significant. This work gives a molecular level proof of Le Chatelier's principle for the case of a temperature change. Moreover, a new, exact mathematical expression is derived that is valid for arbitrary system sizes and gives the relative probability that a single experiment will proceed in the endothermic or exothermic direction, in terms of a microscopic phase function. We show that the average of the time integral of this function is the maximum possible value of the purely irreversible entropy production for the thermal relaxation process. Our result is tested against computer simulations of the unfolding of a polypeptide. We prove that any equilibrium reaction mixture on average responds to a temperature increase by shifting its point of equilibrium in the endothermic direction. © 2009 American Institute of Physics. [doi:10.1063/1.3261849]

I. INTRODUCTION

Le Chatelier's principle (1884) (Refs. 1 and 2) can be stated: "If a system at equilibrium is disturbed by a change in temperature, pressure, or the concentration of one of the components, the system will shift its equilibrium so as to counteract the effect of the disturbance."³ When this principle is applied to an equilibrium reactive mixture that is subject to a temperature increase, an endothermic reaction will shift its point of equilibrium to increase the concentration of products at the cost of reactants. Because the reaction is endothermic, increasing the concentration of products tends to "resist" (by absorbing heat) the increase in temperature that the system is subject to. If the reaction is exothermic the reverse occurs.

This qualitative principle is known by all chemists, and is extensively applied in the study of chemical reactions. It can be justified using a very simple argument: If the opposite of Le Chatelier's principle held, equilibrium states would not be stable with respect to small fluctuations and thus they would not be observable. Further, this simple argument shows that Le Chatelier's principle applies on average, to systems of arbitrary size.

In this paper we will provide a microscopic derivation of a quantitative statement of Le Chatelier's principle as it applies to changes in temperature. For chemical reactions in small systems, it is not only the average behavior that is of interest. In this situation the probability of observing a reac-

tion proceed in the opposite direction to that found on average (or in the thermodynamic limit) can be significant. Our derivation will allow us to extend the principle to describe the probability, in a small system, that endothermic or exothermic changes occur. We achieve this by applying a fluctuation theorem⁴⁻⁶ (FT) to this process.

Previously we have shown⁷ that the Evans-Searles transient FT (TFT) can be used to produce quantitative results consistent with Le Chatelier's principle as it applies to spatial variations in the number density or concentration. This is a somewhat unusual application of the principle. Here we demonstrate the FT's role in elucidating the response of a system to a temperature change. This is one of the three standard applications of the principle by chemists. The other common applications are changes in pressure or the addition/removal of reactants or products, but we do not cover these applications here.

FTs are analytic relationships that quantify the relative probability of observing opposite values (\pm) of time averages of a property. Their discovery in the early 1990s led to a breakthrough in our understanding of nonequilibrium systems.^{5,6} Demonstration of the first relationship in 1993 by Evans *et al.*,⁸ and the derivation of the Evans-Searles TFT (Ref. 9) and the Gallavotti-Cohen FT (Ref. 10) provided greater insight into the basis of irreversibility and the second law of thermodynamics, and motivated new research in the field. Subsequently, the Jarzynski equality¹¹ and the Crooks FT (Ref. 12) were developed, giving remarkable new expressions for the free energy difference between equilibrium states using path integrals of the work performed along all

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possible nonequilibrium paths that dynamically connect the two different equilibrium states. Since their establishment, FTs have been developed to investigate nonequilibrium states in nanophysics and biophysics where the energies involved are typically small and thermal agitation cannot be neglected.^{13–17}

In the past couple of years it has become apparent that the argument of the Evans–Searles FT, namely, the dissipation function, is also the argument of response theory (both linear and nonlinear)^{18,19} and is the central quantity controlling the relaxation of systems to equilibrium.²⁰ In the present paper we show that the dissipation function is also central to Le Chatelier’s principle—at least for the case studied here and the case we studied previously.⁷

The FT of interest in this paper is the Evans–Searles TFT.^{4–6} The subject of the TFT is the time integral of the dissipation function Ω_τ , which is defined as

$$\begin{aligned}\Omega_\tau(\Gamma) &= \int_0^\tau ds \Omega(\Gamma(s)) \\ &\equiv \ln \left(\frac{f(\Gamma(0), 0)}{f(\Gamma(\tau), 0)} \right) - \int_0^\tau dt \Lambda(\Gamma(t)),\end{aligned}\quad (1)$$

where $f(\Gamma, 0)$ is the phase space distribution function at time 0, the phase space vector is $\Gamma \equiv (\mathbf{q}_1, \dots, \mathbf{q}_N, \mathbf{p}_1, \dots, \mathbf{p}_N)$, and $\Lambda(\Gamma) = (\partial/\partial\Gamma) \cdot \dot{\Gamma}$ is the phase space expansion rate associated with the dynamics. The phase space expansion rate is zero for isolated Hamiltonian systems but nonzero for Hamiltonian systems that gain or lose heat to an external thermostat. The TFT then relates the relative probabilities of observing trajectories of duration τ that are characterized by the time integral taking on values within $A \pm dA$ and $-A \pm dA$, respectively,

$$\frac{P(\Omega_\tau = A)}{P(\Omega_\tau = -A)} = e^A. \quad (2)$$

Here $P(\Omega_\tau = A)$ is the probability that Ω_τ takes on a value within $A \pm dA$. This result is true for any time reversible dynamics where the initial distribution and time reversible dynamics are ergodically consistent⁴ and the initial distribution is an even function of the momenta.⁴ Near equilibrium the identification of the dissipation function with the time integral of the irreversible entropy production^{5,6} has resulted in considerable interest in this relationship. In this paper, we show that when an equilibrium system is subject to a rapid change in temperature, the dissipation function also takes on a simple physical meaning.

The TFT can be integrated to give the second law inequality,²¹

$$\langle \Omega_\tau \rangle \geq 0. \quad (3)$$

When the dissipation function is identified with the extensive entropy production, and the thermodynamic limit is taken, a proof of Eq. (3) constitutes a proof of the second “law” of thermodynamics. It is worth repeating that Eq. (3) does *not* imply that the instantaneous ensemble average dissipation function is positive, i.e., it is not necessary that $\langle \Omega(t) \rangle \geq 0$, $\forall t!$

Most early studies on FTs focused on systems where mechanical fields or forces drove them out of equilibrium.²² In order to generate steady states or to sample specific ensembles, it is necessary to thermostat the systems in order to remove the heat generated on average by the fields. To achieve this in numerical experiments, various reversible, deterministic thermostats have been employed.²³ Moreover, in order to obtain experimentally applicable forms of these theorems that are valid arbitrarily far from equilibrium, it was found to be necessary to introduce a thermal reservoir that is large and remote from the system of interest, and which effectively remains in equilibrium.^{4,24–26} Details of such thermostats were found to be irrelevant to the validity of FTs due to their remoteness from the system of interest.²⁴

Recently some attention from the scientific community has focused on the study of the systems that are driven away from equilibrium by reservoirs whose temperature is changing (see Refs. 26–32 and references therein). It is this type of system that will be relevant to this work.

An interesting system to which Le Chatelier’s principle can be applied is the unfolding of a polypeptide due to a temperature change. The unfolding process is endothermic and therefore, the probability of observing the polypeptide in the unfolded state is expected to become greater when the temperature increases. This relatively simple system will be representative of the behavior of more complex processes such as those involved in folding of more complex proteins.³³

In Sec. II we derive a TFT for a system that is subject to a temperature change. We show that a new expression can be obtained that is applicable to systems of arbitrary size (including microscopic systems), and show how this result leads to Le Chatelier’s principle in the thermodynamic limit. In Sec. III and IV we describe our simulations on a polypeptide and present the results of numerical calculations that verify the applicability of the new results. Finally, in Sec. V, we discuss the implications of this work, the connection of the dissipation function to classical thermodynamics, and we give some generalizations of our main results.

II. THE FLUCTUATION THEOREM FOR A TEMPERATURE CHANGE

Consider an ensemble of trajectories, sampled from a canonical distribution with temperature T_1 and $\beta_1 = 1/(k_B T_1)$ that is subject to a sudden temperature change at $t=0$. In a molecular dynamics (MD) simulation, sampling of a canonical distribution is achieved by selecting points from a trajectory generated with the Nosé–Hoover thermostatted dynamics that introduces an extra degree of freedom to the system and extends the phase space by one degree of freedom.^{34,35} We consider a system of N particles and represent the full phase space vector as $\Gamma' \equiv (\Gamma, \alpha) \equiv (\mathbf{q}, \mathbf{p}, \alpha)$, where \mathbf{q} are the particle coordinates, \mathbf{p} are the particle momenta, and α is the thermostat multiplier. For systems undergoing thermostatted dynamics and which are transient mixing (which implies that transient correlation functions decay

and which are ergodic), we have proved²⁰ that almost any initial distribution will eventually relax to the extended phase space, canonical equilibrium distribution,

$$f(\mathbf{\Gamma}, \alpha) = e^{-\beta_1 E_0(\mathbf{\Gamma}) - (3/2)N_R \alpha^2 \tau_\alpha^2 / Z}, \quad (4)$$

where

$$E_0(\mathbf{\Gamma}) = \sum_{i=1}^N \frac{\mathbf{p}_i \cdot \mathbf{p}_i}{2m_i} + \Phi(\mathbf{q})$$

is the phase variable whose average gives the internal energy and $\Phi(\mathbf{q})$ is the particle interaction potential, N_R is the number of particles in the thermostating reservoir, τ_α is the relaxation time constant associated with the reservoir, and $Z = \int d\mathbf{\Gamma} d\alpha e^{-\beta_1 E_0(\mathbf{\Gamma}) - (3/2)N_R \alpha^2 \tau_\alpha^2}$ is the extended partition function. The Nosé–Hoover thermostatted equations of motion are

$$\begin{aligned} \dot{\mathbf{q}}_i &= \mathbf{p}_i / m_i, \\ \dot{\mathbf{p}}_i &= \mathbf{F}_i - S_i \alpha \mathbf{p}_i, \\ \dot{\alpha} &= \frac{1}{\tau_\alpha^2} \left(\frac{\sum_{i=1}^N S_i \mathbf{p}_i \cdot \mathbf{p}_i / m_i}{3N_R k_B T(t)} - 1 \right), \end{aligned} \quad (5)$$

and these will generate the equilibrium distribution (4) when $T(t) = T_1 \equiv \beta_1^{-1} / k_B$. Here S_i is a switch with a value 1 when the particle is in the thermostating reservoir and 0 when it is not ($\sum_{i=1}^N S_i = N_R$). Note that $\dot{\alpha}$ in Eq. (5) and the distribution function in Eq. (4) both have τ_α as a temperature independent parameter. Furthermore there is no β_1 appearing in the prefactor for the thermostat variable α^2 appearing in the equilibrium distribution (4). This ensures that there is no contribution to the dissipation arising from subjecting the unphysical thermostat variables to a temperature change.²⁶

Consider the trajectories generated by Eq. (5) when the target temperature undergoes a step change at time 0^- (that is the time immediately before $t=0$),

$$\begin{cases} T(t) = T_1, & \beta = \beta_1 \equiv \frac{1}{k_B T_1}, & t < 0 \\ T(t) = T_2, & \beta = \beta_2 \equiv \frac{1}{k_B T_2}, & t \geq 0. \end{cases} \quad (6)$$

Due to the time dependence of $T(t)$, distribution (4) will no longer be preserved by Eq. (5) for $t > 0$. However, provided the system is transient mixing, as $t \rightarrow \infty$ the distribution function $f(\mathbf{\Gamma}, t)$ will approach the equilibrium distribution resembling Eq. (4), but with β_1 replaced by β_2 .²⁰

Noting that the phase space expansion rate for dynamics (5) is $\Lambda(\mathbf{\Gamma}', t) = -3N_R \alpha(\mathbf{\Gamma}, t)$ and the distribution function is given by Eq. (4), the time integral of the dissipation for this system (1) is

$$\begin{aligned} \Omega_\tau(\mathbf{\Gamma}) &= \beta_1 (E_0(\mathbf{\Gamma}(\tau)) - E_0(\mathbf{\Gamma}(0))) \\ &+ \frac{3}{2} N_R \tau_\alpha^2 (\alpha(\tau)^2 - \alpha(0)^2) + 3N_R \int_0^\tau dt \alpha(t). \end{aligned} \quad (7)$$

In order to be applied to experimental situations, an expression for the dissipation function that does not refer to any of

the fictitious Nosé–Hoover variables is essential. By differentiating with respect to time, then substituting the equations of motion (5), it can be shown

$$\frac{d}{dt} \left(\beta_2 E_0(\mathbf{\Gamma}(t)) + \frac{3}{2} N_R \tau_\alpha^2 \alpha(t)^2 \right) = -3N_R \alpha(t).$$

Integration over the period $t=0$ to $t=\tau$ then results in

$$\begin{aligned} \beta_2 E_0(\mathbf{\Gamma}(\tau)) - \beta_2 E_0(\mathbf{\Gamma}(0)) + \frac{3}{2} N_R \tau_\alpha^2 \alpha(\tau)^2 - \frac{3}{2} N_R \tau_\alpha^2 \alpha(0)^2 \\ = -3N_R \int_0^\tau dt \alpha(t), \end{aligned}$$

which can be substituted into Eq. (7) to give

$$\begin{aligned} \Omega_\tau(\mathbf{\Gamma}) &= (\beta_1 - \beta_2) (E_0(\mathbf{\Gamma}(\tau)) - E_0(\mathbf{\Gamma}(0))) \\ &\equiv -\Delta\beta \Delta E_0(\mathbf{\Gamma}, \tau). \end{aligned} \quad (8)$$

The dissipation function satisfies the TFT (2) so

$$\frac{P(-\Delta\beta \Delta E_0(\tau) = A)}{P(-\Delta\beta \Delta E_0(\tau) = -A)} = e^A. \quad (9)$$

This is the TFT for a temperature change and is the central result of this paper. It should be emphasized that β_1 and β_2 refer to the target values for the thermostat and are well defined even though the system is likely to be in a nonequilibrium state at short times $t > 0$ when the true thermodynamic temperature of the system of interest cannot necessarily be defined. Equation (9) can be integrated to give the second law equality (3), which in this case becomes

$$\Delta\beta \langle \Delta E_0(\tau) \rangle \leq 0, \quad \forall \tau > 0. \quad (10)$$

Furthermore, in deriving Eq. (10) from Eq. (9) it is clear that the equality will only hold in the special cases that all trajectories conserve energy (which will not be the case for thermostatted dynamics) or there is no temperature change. If the temperature is raised ($T_2 > T_1; \beta_1 > \beta_2$) then

$$\Delta E = \langle \Delta E_0(\tau) \rangle > 0, \quad \forall \tau > 0. \quad (11)$$

That is, if the temperature increases the reaction will likely proceed in the direction such that $\Delta E > 0$, or the endothermic reaction is favored. Derivation of Eq. (11) constitutes a derivation of Le Chatelier's principle for a temperature change in an isochoric system. Furthermore, Eq. (11) tells us even more since it applies irrespective of the size of the system considered and is applicable for all τ after the temperature change, even when the system has *not* relaxed to the new equilibrium state. If the temperature decreases the reaction will be exothermic on average, $\Delta E < 0$. In both cases Eq. (11) does *not* imply that the average energy is a monotonic increasing or decreasing function of time. There may be time intervals ($t_1, t_2: 0 < t_1 < t_2$) within which the average energy change could be negative $\langle E_0(t_2) - E_0(t_1) \rangle < 0$ in the case where $T_2 > T_1; \beta_1 > \beta_2$. All that Eq. (11) states is that for this case $\langle E_0(t_2) - E_0(0) \rangle > 0$ and $\langle E_0(t_1) - E_0(0) \rangle > 0$.

It is informative to rearrange Eq. (9) and to write it in terms of an intensive quantity, say the change in internal energy per particle (N),

$$\frac{P(\Delta E_0(\tau)/N = A)}{P(\Delta E_0(\tau)/N = -A)} = e^{AN(T_2 - T_1)/(k_B T_1 T_2)}. \quad (12)$$

In this form it becomes evident that as the temperature difference decreases or the number of molecules decrease, the probability ratio becomes closer to unity. In the large system limit $N \rightarrow \infty$, the difference in internal energy will *only* take on positive values when $T_2 > T_1$, or negative values when $T_1 > T_2$.

III. SIMULATION DETAILS

In order to test the TFT (9) derived above, we carried out MD simulations of a polypeptide, poly(L-glutamate) with 21 glutamate units, in water under constant volume and constant temperature (canonical) conditions. The system was initially thermostatted at a temperature of 300 K, the thermostat target temperature was increased instantaneously to 305 K and the change in internal energy over various periods was measured.

The polypeptide, poly(L-glutamate) with 21 glutamate units, was solvated with water in a cubic unit cell large enough to contain the macromolecule and 1.0 nm of solvent on all sides. To balance the negative charges in the glutamate backbone, 21 Na^+ ions were added by replacing the water molecules that were located at the most negative points in the simulation cell. To minimize the edge effects, periodic boundary conditions were applied to the unit cell in all directions.

Simulations were carried out using GROMACS MD package.³⁶ The system was energy minimized with a steepest descent method for 400 steps and a $10 \text{ kJ mol}^{-1} \text{ nm}^{-1}$ energy tolerance for the convergence of the minimization process. This was used as the initial configuration of a 20 ps position restraint simulation in which the protein was harmonically restrained with an isotropic force constant of $1000 \text{ kJ mol}^{-1} \text{ nm}^{-2}$. This allows further equilibration of the polypeptide and solvent while keeping the conformation of the protein unchanged. The whole system, including polypeptide, solvent, and ions, was thermostatted. To simulate the system in a canonical ensemble a fixed volume simulation cell and a Nosé–Hoover thermostat^{34,35} was applied with a Nosé–Hoover relaxation time of $\tau_\alpha = 0.1 \text{ ps}$.

The polypeptide position constraint was then removed and MD simulations performed for 10 ns at a temperature of 300 K and a pressure of 1 bar using the leap-frog algorithm³⁷ to numerically integrate the equations of motion with a time step of 2 fs. For both position restraint and MD simulations the GROMOS 96 force field³⁸ was used with the LINCS algorithm³⁹ to constrain the bond lengths in nonwater molecules and the SETTLE algorithm⁴⁰ for the water molecules to make the 2 fs time step feasible. A fast particle-mesh Ewald electrostatics was used for the calculation of the non-bonded interactions. The short-range cutoff radius was set to 1.0 nm and cutoff radius for both Coulombic and Lennard-Jones interactions of 1.4 nm. Interactions within the short-range cutoff were updated every time step whereas interactions within the long-range cutoff were updated every ten time steps using a neighbor list and gridding of the simulation cell. All atoms were given an initial velocity obtained

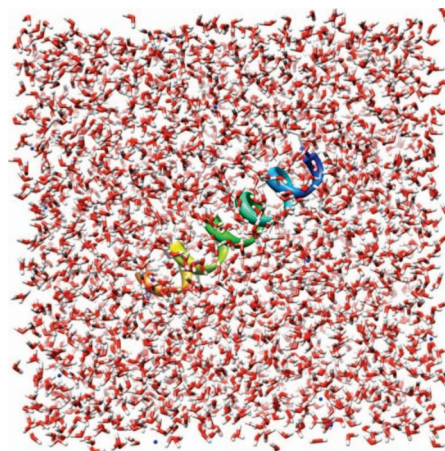


FIG. 1. A typical snapshot of the unit cell containing a polypeptide (poly-L-glutamate with 21 glutamate units), water, and sodium ions, equilibrated at 300 K. The simulation cell is cubic with 5.45 nm sides and has periodic boundaries. The shading of the polypeptide is just to highlight the folding along its length.

from a Maxwell distribution at the desired initial temperature. Employing the above-mentioned procedures, 6250 structures were taken from this main trajectory by sampling every picosecond.

To simulate the response of the systems to the temperature increase protocol described above, all structures are then subjected to a further 5 ps MD run at 300 K followed by an instantaneous temperature jump to 305 K. The nonequilibrium response of all structures was investigated from their trajectories for 10 ps time after the excitation. The computations were performed on a 40-CPU grid, CBCL-DUBS 1 workstation by parallel computing using the GROMACS MD package³⁶ running CENTOS 5 LINUX.

IV. RESULTS

A typical configuration of the polypeptide in water, equilibrated system at 300 K, is shown in Fig. 1. The polypeptide is almost fully folded, with a root-mean-squared deviation (RMSD) from its fully folded structure of 0.22 nm and an average internal energy of $-195\,313 \text{ kJ mol}^{-1}$. The equilibrated structure at 305 K is slightly less folded with a RMSD from the fully folded structure of 0.27 nm, and an average internal energy of $-193\,154 \text{ kJ mol}^{-1}$. This result is clearly consistent with Le Chatelier's principle and Eq. (11), which indicates that a temperature increase will result in an increase in the internal energy, and corresponds to unfolding of the polypeptide.

This result for the averages is not surprising or new, however, in this manuscript we have obtained a new TFT that provides, in addition, information on the probability distribution of the change in internal energy through Eq. (9). In order to test this, 6250 trajectories of length 10 ps were simulated and the difference in the internal energy over various periods were measured. Figure 2 shows the time evolution of the instantaneous kinetic temperature and the internal energy of the system for sample trajectories for a period 0.1 ps before the target temperature changed (at $t=0$) until 1.0 ps afterward. Clearly the temperature change and system

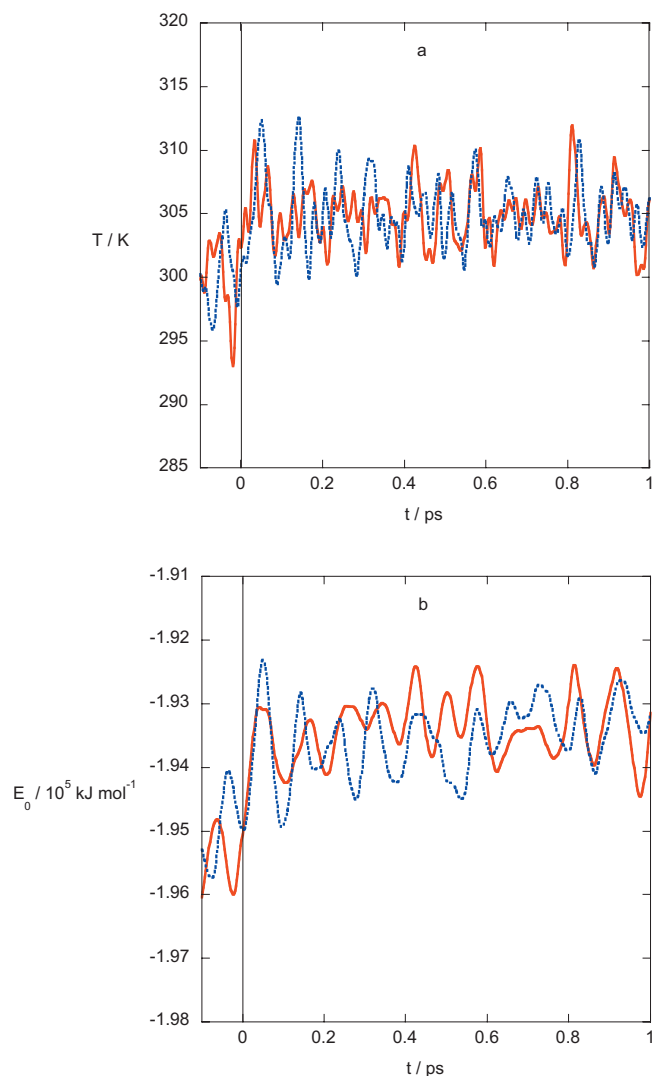


FIG. 2. Time-evolution of (a) kinetic temperature and (b) internal energy for two simulation trajectories of a polypeptide in water subject to a temperature change from 300 to 305 K at $t=0$.

size are sufficiently small that fluctuations in the internal energy can lead to either increases or decreases in the internal energy after the target temperature is changed. Histograms of the change in internal energy over the first 0.1 ps and the first 10.0 ps after the temperature change are plotted in Fig. 3. These demonstrate that a small proportion of the trajectories do indeed respond to the increase in temperature by an overall decrease in the internal energy over a period of 0.1 ps, and an even smaller proportion over the period of 10 ps. Eventually the histogram will converge to its limiting shape with the proportion of trajectories with negative values of the dissipation function depending on the initial and final temperatures, and the system size. The error bars shown in Fig. 3 represent one standard error about the mean probability for each histogram bin of width dA . The standard errors were calculated from ten independent simulations of 625 trajectories for the 0.1 ps data and 561 trajectories for the 10 ps data.

Figure 4 tests Eq. (9) by plotting $\ln(P(\Omega_\tau=A)/P(\Omega_\tau=-A))$ versus A . If Eq. (9) is valid, then a straight line of unit slope would be obtained. The relative errors in the

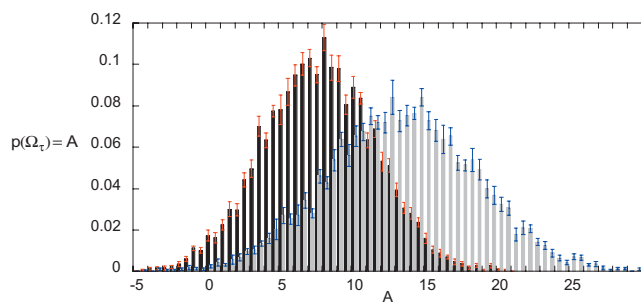


FIG. 3. Histograms of the time-integrated dissipation function for an instantaneous temperature change from 300 to 305 K. The system is a polypeptide in water and the dissipation function was monitored for periods of 0.1 ps (black bars) and 10 ps (gray bars) after the temperature change. The error bars show one standard error determined from ten independent runs.

probabilities of observing extreme values of the dissipation function are large, and therefore in order to obtain an accurate measurement of the slope in Fig. 4, a careful error analysis of the data was required. The data in Fig. 4 was obtained for the range of values of dissipation function where there were at least two trajectories out of the 6250 in each histogram bin. The error bars in Fig. 4 were calculated as

$$\left| \frac{\Delta P(\Omega_\tau=A)}{P(\Omega_\tau=A)} \right| + \left| \frac{\Delta P(\Omega_\tau=-A)}{P(\Omega_\tau=-A)} \right|.$$

A weighted least-squares fit was then carried out and the slope was found to be 1.04 ± 0.05 where the error represents one standard error. This demonstrates agreement with the predictions of Eq. (9), and our central result is therefore verified by these numerical results on a polypeptide.

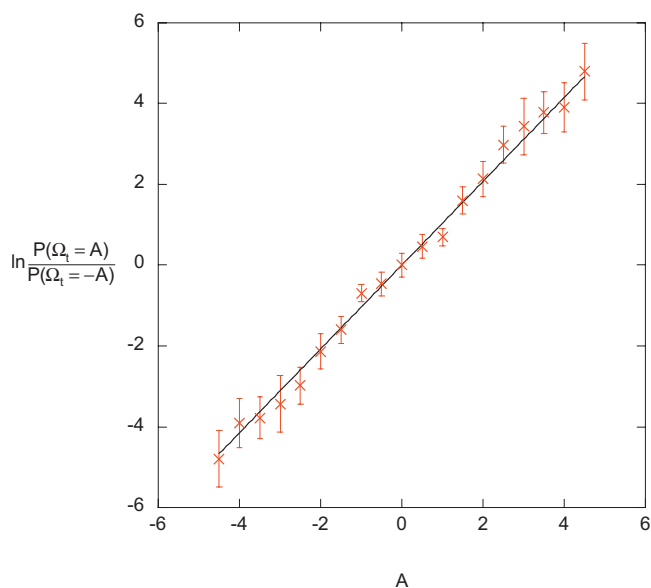


FIG. 4. Logarithm of the ratio of number of trajectories in histogram bins, $\ln[P(\Omega_\tau=A)/P(\Omega_\tau=-A)]$ vs A , where Ω_τ was evaluated for trajectories of length $\tau=0.1$ ps. The error bars represent one standard error calculated from propagation of the errors in Fig. 3. The weighted line of best fit has a slope of 1.04 ± 0.05 .

V. DISCUSSION AND CONCLUSIONS

In Secs. II–IV we considered a constant volume system. It is straightforward to apply the same treatment to a system at constant pressure, P . In that case, the distribution of interest is the isothermal-isobaric distribution function $f(\mathbf{\Gamma}, V) = e^{-\beta_1 H_0(\mathbf{\Gamma}, V)} / \int d\mathbf{\Gamma} \int_0^\infty dV e^{-\beta_1 H_0(\mathbf{\Gamma}, V)}$, where $H_0(\mathbf{\Gamma}, V) = E_0(\mathbf{\Gamma}) + PV$ is the phase variable whose average is the enthalpy of the system. In a similar manner to the isothermal constant volume case, the extended isothermal-isobaric ensemble can be generated using a Nosé–Hoover thermostat and barostat,²⁵ and using the treatment above the dissipation function is found to be $\Omega_\tau = -\Delta\beta\Delta H_0(\tau)$. The TFT becomes

$$\frac{P(-\Delta\beta\Delta H_0(\tau) = A)}{P(-\Delta\beta\Delta H_0(\tau) = -A)} = e^A. \quad (13)$$

If we assume that $T_2 > T_1$ and integrate, we find that if the temperature increases $\Delta H = \langle H_0(\mathbf{\Gamma}(t)) - H_0(\mathbf{\Gamma}(0)) \rangle > 0$, and if the temperature decreases $\Delta H < 0$. As in the isochoric case the average enthalpy change need not be a monotonic function of time. These results correspond to Le Chatelier's principle for a temperature change in a constant pressure system.

In both the isochoric and the isobaric cases the time integral of the dissipation function is recognizable as a purely irreversible entropy change divided by Boltzmann's constant. For example in Eq. (8) for the isochoric case we see that since no work is being done on the system, $\Delta E_0(\tau) = \Delta Q(\tau)$, therefore $\Omega_\tau = \Delta Q(\tau) / k_B T_1 - \Delta Q(\tau) / k_B T_2$. It is the entropy change that would occur if the heat was transferred isothermally at the initial temperature, minus the entropy change that would occur if the process was completely reversible (i.e., at the final temperature, T_2). Within the context of classical thermodynamics given a fixed heat transfer $\Delta Q(\tau)$, this difference is the maximum possible purely irreversible entropy change for all thermodynamically possible temperature profiles $T(t)$, for the thermal relaxation process. If the temperature difference was sufficiently small that the transient states could be regarded as being in local thermodynamic equilibrium, the actual purely irreversible entropy change for an actual temperature profile $T(t)$ would be somewhat less than the value given by the dissipation function. This is because the transient temperature would vary continuously in time from the initial to the final temperature. The maximum irreversible entropy change is zero for reversible processes and positive for irreversible processes showing once again the consistency of the FT, the second law inequality, and macroscopic thermodynamics.⁶

The treatment above only refers to a step change in the temperature, but Eq. (9) would be expected to apply approximately in all cases where the change in temperature is fast compared to the response of the system. Furthermore, if τ is sufficiently long that the system has relaxed to its final equilibrium state, we observe that Eq. (10) refers to the difference in the value of a state function, and therefore this result will apply irrespective of the protocol used to produce the change. However, it would be of interest to treat other protocols for the change in temperature. If the change is made in a series of M steps with the time between steps being sufficiently long that the system is able to relax to equilibrium at

the new temperature, it can be shown that the total dissipation function is the sum of the individual steps,

$$\Omega_{M\tau} = \sum_{i=1}^M [\beta_i - \beta_{i+1}] [E_0(\mathbf{\Gamma}(i\tau)) - E_0(\mathbf{\Gamma}([i-1]\tau))],$$

and that this dissipation function satisfies a fluctuation relation of the form given by Eq. (2). Interestingly, in this case if the set of reciprocal temperatures is monotonic the set of average energies must also be monotonic. This contrasts the single step case discussed earlier in this paper. Further work is required to obtain a TFT for the more general protocols.

We should note that for the temperature change and time scales considered in the numerical work of this manuscript, the degree of unfolding of the polypeptide is small. The choice of these parameters was made to ensure that a significant number of negative values of the dissipation function could be obtained. However, the theory will still apply if larger temperature changes and time scales are considered. While longer time scales are hard to achieve computationally, these can be achieved experimentally and it would be of great interest to obtain experimental results for such cases.

Finally we note that the fluctuation relation (9) is for the dissipation function. However, as shown previously,⁴¹ for any phase variable that is odd under time reversal, there is an exact generalized FT. For the temperature change considered here this becomes

$$\frac{Pr(\phi_\tau = A)}{Pr(\phi_\tau = -A)} = \langle e^{-\Omega_\tau} \rangle_{\phi_\tau(\mathbf{\Gamma})=A}^{-1} = \langle e^{\Delta\beta\Delta E_0(\tau)} \rangle_{\phi_\tau(\mathbf{\Gamma})=A}^{-1}, \quad (14)$$

where ϕ is the phase variable that is odd under time-reversal symmetry and $\langle \dots \rangle_{\phi_\tau(\mathbf{\Gamma})=A}$ is a conditional ensemble average. The treatment can therefore be extended to various properties such as the rate of extension of the polypeptide (in which case ϕ_τ corresponds to the change in length over a time interval τ) or the change in internal energy of the polypeptide and its solvation shell.

With growing interest in the study of reactions in small systems (see Ref. 42 and references therein), development of an exact relation for the statistics of processes occurring within them seems of utmost importance. In addition, very few exact relations for process that occur under nonequilibrium conditions are available. The fluctuation relation developed in this paper for a small system subject to a temperature change is one of the few exact results available for such systems. It is anticipated that this result will assist in understanding processes such as protein unfolding and chemical reactions in small systems.

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