Equalities and Inequalities: Irreversibility and the Second Law of Thermodynamics at the Nanoscale

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Abstract

The reason we never observe violations of the second law of thermodynamics is in part a matter of statistics: When $\sim 10^{23}$ degrees of freedom are involved, the odds are overwhelmingly stacked against the possibility of seeing significant deviations away from the mean behavior. As we turn our attention to smaller systems, however, statistical fluctuations become more prominent. In recent years it has become apparent that the fluctuations of systems far from thermal equilibrium are not mere background noise, but satisfy strong, useful, and unexpected properties. In particular, a proper accounting of fluctuations allows us to rewrite familiar inequalities of macroscopic thermodynamics as equalities. This review describes some of this progress, and argues that it has refined our understanding of irreversibility and the second law.

1. INTRODUCTION

On anyone's list of the supreme achievements of nineteenth-century science, both Maxwell's equations and the second law of thermodynamics surely rank high. Yet whereas Maxwell's equations are widely viewed as done, dusted, and uncontroversial, the second law still provokes lively arguments, long after Carnot published his *Reflections on the Motive Power of Fire* (1824) and Clausius articulated the increase of entropy (1865). The puzzle at the core of the second law is this: How can microscopic equations of motion that are symmetric with respect to time reversal give rise to macroscopic behavior that clearly does not share this symmetry? Of course, quite apart from questions related to the origin of time's arrow, there is a nuts-and-bolts aspect to the second law. Together with the first law, it provides a set of tools that are indispensable in practical applications ranging from the design of power plants and refrigeration systems to the analysis of chemical reactions.

The past few decades have seen growing interest in applying these laws and tools to individual microscopic systems, down to nanometer length scales. Much of this interest arises at the intersection of biology, chemistry, and physics, where there has been tremendous progress in uncovering the mechanochemical details of biomolecular processes (1). For example, it is natural to think of the molecular complex $\phi29$—a motor protein that crams DNA into the empty shell of a virus—as a nanoscale machine that generates torque by consuming free energy (2). The development of ever more sophisticated experimental tools to grab, pull, and otherwise bother individual molecules, and the widespread use of all-atom simulations to study the dynamics and the thermodynamics of molecular systems, have also contributed to the growing interest in the thermodynamics of small systems (3).

Because the rigid, prohibitive character of the second law emerges from the statistics of huge numbers, we might expect it to be enforced somewhat more leniently in systems with relatively few degrees of freedom. To illustrate this point, consider the familiar gas-and-piston setup, in which the gas of $N \sim 10^{23}$ molecules begins in a state of thermal equilibrium inside a container enclosed by adiabatic walls. If the piston is rapidly pushed into the gas and then pulled back to its initial location, there will be a net increase in the internal energy of the gas. That is,

$$W > 0, \qquad 1.$$

where W denotes the work performed by the agent that manipulates the piston. This inequality is not mandated by the underlying dynamics: There certainly exist microscopically viable N-particle trajectories for which $W < 0$. However, the probability to observe such trajectories becomes fantastically small for large N. By contrast, for a gas of only a few particles, we would not be surprised to observe—once in a rare while, perhaps—a negative value of work, although we still expect Equation 1 to hold on average

$$\langle \mathrm{W} \rangle > 0. \qquad 2.$$

The angular brackets here and below denote an average over many repetitions of this hypothetical process, with the tiny sample of gas re-equilibrated prior to each repetition.

This example suggests the following perspective: As we apply the tools of thermodynamics to ever-smaller systems, the second law becomes increasingly blurred. Inequalities such as Equation 1 remain true on average, but statistical fluctuations around the average become ever more important as fewer degrees of freedom come into play.

This picture is accurate, but incomplete. It encourages us to dismiss the fluctuations in W as uninteresting noise that merely reflects poor statistics (small N). As it turns out, these fluctuations themselves satisfy rather strong, interesting, and useful laws. For example, Equation 2 can be replaced by the equality,

$$\langle e^{-W/k_B T} \rangle = 1, \qquad 3.$$

where T is the temperature at which the gas is initially equilibrated, and k_B is Boltzmann's constant. If we additionally assume that the piston is manipulated in a time-symmetric manner, for example, pushed in at a constant speed and then pulled out at the same speed, then the statistical distribution of work values $\rho(W)$ satisfies the symmetry relation

$$\frac{\rho(+W)}{\rho(-W)} = e^{W/k_B T}. \qquad 4.$$

The validity of these results depends neither on the number of molecules in the gas, nor (surprisingly!) on the rate at which the process is performed.

I have used the gas and piston out of convenience and familiarity, but the predictions illustrated by Equations 3 and 4—and expressed more generally by Equations 15 and 30 below—are not specific to this particular example. They apply to any system that is driven away from equilibrium by the variation of mechanical parameters, under relatively standard assumptions regarding the initial equilibrium state and the microscopic dynamics. Moreover, they belong to a larger collection of recently derived theoretical predictions, which pertain to fluctuations of work (4–9), entropy production (10–18), and other quantities (19, 20) in systems far from thermal equilibrium. Although these predictions go by various names, both descriptive and eponymous, the term "fluctuation theorems" has come to serve as a useful label encompassing the entire collection of results. There is by now a large body of literature on fluctuation theorems, including reviews and pedagogical treatments (3, 21–38).

In my view, these are not results that one might naturally have obtained by starting with a solid understanding of macroscopic thermodynamics and extrapolating down to small system size. Rather, they reveal genuinely new, nanoscale features of the second law. My aim in this review is to elaborate on this assertion. Focusing on those fluctuation theorems that describe the relationship between work and free energy—these are sometimes called nonequilibrium work relations—I argue that they have refined our understanding of dissipation, hysteresis, and other hallmarks of thermodynamic irreversibility. Most notably, when fluctuations are taken into account, inequalities that are related to the second law (e.g., Equations 5, 24, 28, 35) can be rewritten as equalities (Equations 15, 25, 30, 31). Among the take-home messages that emerge from these developments are the following:

1. Equilibrium information is subtly encoded in the microscopic response of a system driven far from equilibrium.
2. Surprising symmetries lurk beneath the strong hysteresis that characterizes irreversible processes.
3. Physical measures of dissipation are related to information-theoretic measures of time-asymmetry.
4. The ability of thermodynamics to set the direction of time's arrow can be quantified.

Moreover, these results have practical applications in computational thermodynamics and in the analysis of single-molecule manipulation experiments, as discussed briefly in Section 8.

Section 2 introduces definitions and notation, and specifies the framework that will serve as a paradigm of a thermodynamic process. Sections 3–6 address the four points listed above, respectively. Section 7 discusses how these results relate to fluctuation theorems for entropy production. Finally, I conclude in Section 8.

2. BACKGROUND AND SETUP

This section establishes the basic framework that will be considered, and introduces the definitions and assumptions used in later sections.

2.1. Macroscopic Thermodynamics and the Clausius Inequality

Throughout this review, the following serves as a paradigm of a nonequilibrium thermodynamic process.

Consider a finite, classical system of interest in contact with a thermal reservoir at temperature T (for instance, a rubber band surrounded by air), and let λ denote some externally controlled parameter of the system (the length of the rubber band). I refer to λ as a work parameter, because by varying it we perform work on the system. The notation $[\lambda, T]$ specifies an equilibrium state of the system. Now imagine that the system of interest is prepared in equilibrium with the reservoir, at fixed $\lambda = A$; that is, in state $[A, T]$. Then from time $t = 0$ to $t = \tau$ the system is perturbed, perhaps violently, by varying the parameter with time, ending at a value $\lambda = B$. (The rubber band is stretched rapidly.) Finally, from $t = \tau$ to $t = \tau^*$ the work parameter is held fixed at $\lambda = B$, allowing the system to re-equilibrate with the thermal reservoir and thus relax to the state $[B, T]$.

In this manner, the system is made to evolve from one equilibrium state to another, but in the interim it is generally driven away from equilibrium. The Clausius inequality of classical thermodynamics then predicts that the external work performed on the system is no less than the free-energy difference between the terminal states:

$$W \geq \Delta F \equiv F_{B,T} - F_{A,T}. \qquad 5.$$

Here $F_{\lambda,T}$ denotes the Helmholtz free energy of the state $[\lambda, T]$. When the parameter is varied slowly enough that the system remains in equilibrium with the reservoir at all times, then the process is reversible and isothermal, and $W = \Delta F$.

Throughout most of this review, Equation 5 serves as the essential statement of the second law of thermodynamics. Of course, not all thermodynamic processes fall within this paradigm, nor is Equation 5 the broadest formulation of the Clausius inequality. However, because complete generality can impede clarity, I focus on the class of processes described above. Most of the results presented in the following sections can be extended to more general thermodynamic processes—such as those involving multiple thermal reservoirs or nonequilibrium initial states—as I briefly discuss in Section 7.

Three comments are now in order, before proceeding to the nanoscale:

1. As the system is driven away from equilibrium, its temperature may change or become ill-defined. The variable T, however, always denotes the initial temperature of the system and thermal reservoir.
2. No external work is performed on the system during the re-equilibration stage, $\tau < t < \tau^*$, as λ is held fixed. Therefore Equation 5 remains valid if the process is considered to end at $t = \tau$—even if the system has not yet reached equilibrium with the reservoir!—provided we agree to define ΔF to be a free-energy difference between the equilibrium states $[A, T]$ and $[B, T]$. In this sense the re-equilibration stage is somewhat superfluous.
3. Although in general it is presumed that the system remains in thermal contact with the reservoir for $0 < t < \tau$, the results discussed in this review are also valid if the system is isolated from the reservoir during this interval. (This is not surprising, given that an isolated system can be viewed as a limiting case of a system in contact with a reservoir, if we imagine that the interaction between the two is so weak that the effects of thermal contact are negligible over a time interval of duration τ.)

2.2. Microscopic Definitions of Work and Free Energy

Now let us scale down this paradigm to small systems, with an eye toward incorporating statistical fluctuations. Consider a framework in which the system of interest and the thermal reservoir are represented as a large collection of microscopic, classical degrees of freedom. The work parameter λ is an additional coordinate describing the position or orientation of a body—or some other mechanical variable such as the location of a laser trap in a single-molecule manipulation experiment (27)—that interacts with the system of interest, but is controlled by an external agent. This framework is illustrated with a toy model in **Figure 1**. Here the system of interest consists of the three particles represented as open circles, whose coordinates z_i give distances from the fixed wall. The work parameter is the fourth particle, depicted as a shaded circle at a distance λ from the wall.

Let the vector $\mathbf{x}$ denote a microscopic state of the system of interest, that is the configurations and momenta of its microscopic degrees of freedom; let $\mathbf{y}$ similarly denote a microstate of the thermal reservoir. The Hamiltonian for this collection of classical variables is assumed to take the form

$$\mathcal{H}(\mathbf{x},\mathbf{y};\lambda) = H(\mathbf{x};\lambda) + H_{\mathrm{env}}(\mathbf{y}) + H_{\mathrm{int}}(\mathbf{x},\mathbf{y}), \qquad 6.$$

where $H(\mathbf{x};\lambda)$ represents the energy of the system of interest—including its interaction with the work parameter—$H_{\mathrm{env}}(\mathbf{y})$ is the energy of the thermal environment, and $H_{\mathrm{int}}(\mathbf{x},\mathbf{y})$ is the energy of interaction between system and environment. For the toy model in **Figure 1**, $\mathbf{x} = (z_1, z_2, z_3, p_1, p_2, p_3)$ and we assume

$$H(\mathbf{x};\lambda) = \sum_{i=1}^{3} \frac{p_i^2}{2m} + \sum_{k=0}^{3} u(z_{k+1} - z_k), \qquad 7.$$

where $u(\cdot)$ is a pairwise interaction potential, $z_0 \equiv 0$ is the position of the wall, and $z_4 \equiv \lambda$ is the work parameter.

Now imagine a process during which the external agent manipulates the work parameter according to a protocol $\lambda(t)$. As the parameter is displaced by an amount $\mathrm{d}\lambda$, the change in the value of H due to this displacement is

$$đW \equiv \mathrm{d}\lambda \frac{\partial H}{\partial \lambda}(\mathbf{x};\lambda). \qquad 8.$$

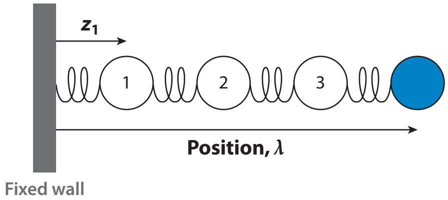

Figure 1

Illustrative model. The numbered circles constitute a three-particle system of interest, with coordinates (z_1, z_2, z_3) giving the distance of each particle from the fixed wall, as shown for z_1. The blue particle is the work parameter, whose position λ is manipulated externally. The springs represent particle-particle (or particle-wall) interactions. The system of interest interacts with a thermal reservoir whose degrees of freedom are not shown.

Because $\mathrm{d}\lambda \cdot \partial H / \partial\lambda$ is the work required to displace the coordinate λ against a force $-\partial H / \partial\lambda$, we interpret Equation 8 to be the work performed by the external agent in bringing about this small displacement (39). Over the entire process, the work performed by the external agent is

$$W = \int đW = \int_0^\tau \mathrm{d}t \dot{\lambda} \frac{\partial H}{\partial\lambda}(\mathbf{x}(t); \lambda(t)), \qquad 9.$$

where the trajectory $\mathbf{x}(t)$ describes the evolution of the system of interest. This is the microscopic definition of work that is used throughout this review. (For discussions and debates related to this definition, see References 37, 39–48.)

Let us now focus on the free-energy difference ΔF appearing in Equation 5. In statistical physics an equilibrium state is represented by a probability distribution rather than by a single microscopic state. If the interaction energy H_{int} in Equation 6 is sufficiently weak—as usually assumed in textbook discussions—then this distribution is given by the Boltzmann-Gibbs formula,

$$p^{\mathrm{eq}}_{\lambda,T}(\mathbf{x}) = \frac{1}{Z_{\lambda,T}} \exp[-H(\mathbf{x}; \lambda)/k_B T], \qquad 10.$$

where

$$Z_{\lambda,T} = \int \mathrm{d}\mathbf{x} \, \exp[-H(\mathbf{x}; \lambda)/k_B T] \qquad 11.$$

is the classical partition function. If H_{int} is too large to be neglected, then the equilibrium distribution takes the modified form

$$p^{\mathrm{eq}}_{\lambda,T} \propto \exp(-H^*/k_B T) \quad , \quad H^*(\mathbf{x}; \lambda) = H(\mathbf{x}; \lambda) + \phi(\mathbf{x}; T), \qquad 12.$$

where $\phi(\mathbf{x}; T)$ is the free-energetic cost of inserting the system of interest into its thermal surroundings. For the purpose of this review, the distinction between Equations 10 and 12 is not terribly relevant. I will use the more familiar Equation 10, which applies to the weak-coupling limit (small H_{int}), with the understanding that all the results discussed below are equally valid in the case of strong coupling, provided H is replaced by H^*. (See Reference 49 for a more detailed discussion.) The free energy associated with this equilibrium state is

$$F_{\lambda,T} = -k_B T \ln Z_{\lambda,T}. \qquad 13.$$

With these elements in place, imagine a microscopic analog of the process described in Section 2.1. The system of interest is prepared in equilibrium with the reservoir, at $\lambda = A$. From $t = 0$ to $t = \tau$, the system evolves with time as the work parameter is varied from $\lambda(0) = A$ to $\lambda(\tau) = B$. By considering infinitely many repetitions of this process, we arrive at a statistical ensemble of realizations of the process, which can be pictured as a swarm of independently evolving trajectories, $\mathbf{x}_1(t)$, $\mathbf{x}_2(t)$,$\cdots$. For each of these we can compute the work, W_1, W_2,$\cdots$ (Equation 9). Letting $\rho(W)$ denote the distribution of these work values, it is reasonable to expect that Equation 5 in this case becomes a statement about the mean of this distribution, namely

$$\langle W \rangle \equiv \int \mathrm{d}W \, \rho(W) W \geq \Delta F. \qquad 14.$$

As suggested earlier, this inequality is correct, but it is not the entire story.

2.3. The Need to Model

Although the laws of macroscopic thermodynamics can be stated without reference to underlying equations of motion, when we study how these laws might apply to a microscopic system away from equilibrium, we must typically specify the equations we use to model its evolution. These equations represent approximations of physical reality, and the choice inevitably reflects certain assumptions. Equation 6 suggests one approach: Treat the system and reservoir as an isolated, classical system evolving in the full phase space $(\mathbf{x}, \mathbf{y})$ under a time-dependent Hamiltonian $\mathcal{H}(\mathbf{x}, \mathbf{y}; \lambda(t))$. The results discussed in Sections 3–6 can all be obtained within this framework. Alternatively, we can treat the reservoir implicitly, by writing down effective equations of motion for just the system variables, $\mathbf{x}$. Examples include Langevin dynamics, the Metropolis algorithm, Nosé-Hoover dynamics and its variants, the Andersen thermostat, and deterministic equations based on Gauss's principle of least constraint (23, 34). As with the Hamiltonian approach, the results discussed below can be derived for each of these model dynamics. This suggests that the results themselves are rather robust: They do not depend sensitively on how the microscopic dynamics are modeled.

In this review, full-blown derivations of fluctuation theorems and work relations are not provided. However, in Sections 3 and 4, in addition to describing various work relations and their connections to the second law, I sketch how several of them can be derived for the toy system shown in **Figure 1**, in the physical context mentioned by the final comment in Section 2.1: The system is thermally isolated during the interval $0 < t < \tau$. The aim here is to convey some idea of the theoretical foundations of these results, without exploring the technical details that accompany an explicit treatment of the reservoir (50).

3. EQUILIBRIUM INFORMATION FROM NONEQUILIBRIUM FLUCTUATIONS

Thermodynamics accustoms us to the idea that irreversible processes are described by inequalities, such as $W \geq \Delta F$. One of the surprises of recent years is that if we pay attention to fluctuations, then such relationships can be recast as equalities. In particular, the nonequilibrium work relation (6, 7) states that

$$\langle e^{-W/k_B T} \rangle = e^{-\Delta F/k_B T}, \qquad 15.$$

where (as above) T is the initial temperature of the system and thermal reservoir, and angular brackets denote an ensemble average over realizations of the process. This result has been derived in various ways, using an assortment of equations of motion to model the microscopic dynamics (6–9, 17, 18, 49–62), and has been confirmed experimentally (63–66). In the following paragraph I sketch how it can be obtained for the toy model of **Figure 1**.

Imagine that after preparing the system in equilibrium at $\lambda = A$ we disconnect it from the thermal reservoir. Then from $t = 0$ to $t = \tau$ the three-particle system of interest evolves under the Hamiltonian $H(\mathbf{x}; \lambda(t))$ (Equation 7), as we displace the fourth particle from $\lambda = A$ to B using a protocol $\lambda(t)$. A realization of this process is described by a trajectory $\mathbf{x}_t \equiv \mathbf{x}(t)$ obeying Hamilton's equations. Combining Equation 9 with the identity $\mathrm{d}H/\mathrm{d}t = \partial H / \partial t$ (see Reference 67, section 8–2), we get $W = H(\mathbf{x}_\tau; B) - H(\mathbf{x}_0; A)$. We then evaluate the left side of Equation 15 by averaging over initial conditions, using Equation 10:

$$\begin{aligned} \langle e^{-W/k_B T} \rangle &= \int \mathrm{d}\mathbf{x}_0 \, p^{\mathrm{eq}}_{A,T}(\mathbf{x}_0) e^{-W/k_B T} \\ &= \frac{1}{Z_{A,T}} \int \mathrm{d}\mathbf{x}_\tau \left| \frac{\partial \mathbf{x}_\tau}{\partial \mathbf{x}_0} \right|^{-1} e^{-H(\mathbf{x}_\tau; B)/k_B T} = \frac{Z_{B,T}}{Z_{A,T}}. \end{aligned} \qquad 16.$$

On the second line, the variables of integration have been changed from initial conditions to final conditions. By Liouville's theorem, the associated Jacobian factor is unity, $|\partial \mathbf{x}_\tau / \partial \mathbf{x}_0| = 1$, which brings us to the desired result, $Z_{B,T}/Z_{A,T} = e^{-\Delta F/k_B T}$ (Equation 13).

This gist of the calculation can be extended to the more general case in which the system and reservoir remain in contact during the interval $0 < t < \tau$ (6, 49). The steps are essentially the ones in Equation 16, only carried out in the full phase space $(\mathbf{x}, \mathbf{y})$, and care must be taken if the interaction energy $H_{\text{int}}(\mathbf{x}, \mathbf{y})$ is strong (49). For alternative derivations of Equation 15 in which the presence of the reservoir is modeled implicitly, using non-Hamiltonian equations of motion, see References 6–8, 17, 18, 32, 51–62.

Recall that the work performed during a reversible, isothermal process depends only on the initial and final states, $W = \Delta F \equiv F_{B,T} - F_{A,T}$, and not on the sequence of equilibrium states that mark the journey from $[A,T]$ to $[B,T]$. The nonequilibrium work relation extends this statement to irreversible processes:

$$-k_B T \ln \langle e^{-W/k_B T} \rangle = \Delta F. \qquad 17.$$

That is, the value of the nonlinear average on the left depends only on equilibrium states $[A,T]$ and $[B,T]$ (because these determine ΔF), and not on the intermediate, out-of-equilibrium states visited by the system. This implies that we can determine an equilibrium free-energy difference by observing a system driven away from equilibrium, provided we repeat the process many times: The value of ΔF is to be found not in a single measurement of work, but in its statistical fluctuations. The idea that far-from-equilibrium fluctuations encode useful equilibrium information is further extended by Equations 25, 30, and 31 below, but before getting to those results I briefly draw attention to a few points related to Equation 15.

First, Equation 15 is closely related, but not equivalent, to an earlier work relation derived by Bochkov & Kuzovlev (4, 5, 68, 69), which can be written as

$$\langle e^{-W_0/k_B T} \rangle = 1. \qquad 18.$$

This result does not involve ΔF and uses a definition of work that differs from Equation 9. References 32, 41, and 70 contain a more detailed discussion of the relationship between Equations 15 and 18, as well as between Equations 25, 30, and their counterparts in References 4, 5, 68, and 69.

With minimal effort, we can use Equation 15 to obtain two inequalities that are closely related to the second law of thermodynamics. Combining Equation 15 with Jensen's inequality (72), $\langle \exp x \rangle \geq \exp\langle x \rangle$, we get

$$\langle W \rangle \geq \Delta F, \qquad 19.$$

as already anticipated (Equation 14). A stronger and less expected result follows almost as immediately from Equation 15 (31):

$$\begin{aligned} P[W < \Delta F - \zeta] &\equiv \int_{-\infty}^{\Delta F - \zeta} \mathrm{d}W \rho(W) \\ &\leq \int_{-\infty}^{\Delta F - \zeta} \mathrm{d}W \rho(W) e^{(\Delta F - \zeta - W)/k_B T} \\ &\leq e^{(\Delta F - \zeta)/k_B T} \int_{-\infty}^{+\infty} \mathrm{d}W \rho(W) e^{-W/k_B T} \\ &= e^{-\zeta/k_B T}. \end{aligned} \qquad 20.$$

Here, P is the probability to observe a value of work that falls below $\Delta F - \zeta$, where ζ is an arbitrary positive value with units of energy. Equation 20 reveals that the left tail of the distribution $\rho(W)$ becomes exponentially suppressed in the thermodynamically forbidden region $W < \Delta F$, a bit like the evanescent piece of a quantum-mechanical wave function in a classically forbidden region. Thus, we have no reasonable hope to observe a value of work that falls much more than a few $k_B T$ below ΔF. This is gratifyingly consistent with experience, which teaches us that the second law is never violated on a macroscopic scale.

For sufficiently slow variation of the work parameter, the central limit theorem suggests that $\rho(W)$ is approximately Gaussian. In this case Equation 15 implies (6)

$$\Delta F = \langle W \rangle - \frac{\sigma_W^2}{2k_B T}, \qquad 21.$$

where σ_W^2 is the variance of the work distribution. This is the result that one expects from linear response theory (72–75).

When Equation 15 is applied to processes involving the motion of perfectly hard walls or other hard constraints, then interesting subtleties can arise that are related to the ordering of limits (76, 77).

Because Equation 15 unequivocally implies that $\langle W \rangle \geq \Delta F$, it might at first glance appear that this represents a microscopic, first-principles derivation of the second law, and thus clarifies the microscopic origins of irreversibility. This is not the case, however. In all derivations of Equation 15 and related work relations (e.g., Equations 25, 30, and 31), the arrow of time is effectively inserted by hand. Specifically, a quite special statistical state (the Boltzmann-Gibbs distribution, p^{eq}) is assumed to describe the system at a particular instant in time ($t = 0$), and attention is then focused on the system's evolution at later times only ($t > 0$). If instead the evolution of the system leading up to the equilibrium state at $t = 0$ had been considered, then all the inequalities associated with the second law would have been obtained, but with their signs reversed. This emphasizes the importance of boundary conditions (in time), and touches on the deep connection between irreversibility and causality (78–80).

Gibbs already recognized that if one accepts an initial equilibrium state given by $p^{\mathrm{eq}} \propto e^{-H/k_B T}$, then various statements of the second law follow from properties of Hamiltonian dynamics (see Chapter XIII of Reference 81). Similar results can be obtained if the initial equilibrium state is represented by any distribution that is a decreasing function of energy (82). Interestingly, however, for a microcanonical initial distribution, inequalities related to the second law of thermodynamics can be violated, at least for systems with one degree of freedom (83, 84).

Let us now return to the picture of our ensemble as a swarm of trajectories, $\mathbf{x}_1(t), \mathbf{x}_2(t), \cdots$ described by the time-dependent phase-space density,

$$f(\mathbf{x}, t) \equiv \langle \delta[\mathbf{x} - \mathbf{x}_k(t)] \rangle, \qquad 22.$$

and let us define a weighted density

$$g(\mathbf{x}, t) \equiv \langle \delta[\mathbf{x} - \mathbf{x}_k(t)] e^{-w_k(t)/k_B T} \rangle, \qquad 23.$$

where $w_k(t)$ is the work performed up to time t during the k-th realization. If we visualize each trajectory $\mathbf{x}_k(t)$ as a particle moving through many-dimensional phase space, and $\mu_k(t) = \exp[-w_k(t)/k_B T]$ as a fictitious, time-dependent mass that the particle carries on its journey, then $f(\mathbf{x}, t)$ and $g(\mathbf{x}, t)$ can be interpreted as a normalized particle density and mass density, respectively. Both are initially described by the canonical distribution, $f = g = p^{\mathrm{eq}}_{A,T}$, but for $t > 0$ the system is no longer in equilibrium:

$$f_t \equiv \langle \delta[\mathbf{x} - \mathbf{x}_k(t)] \rangle \neq p^{\mathrm{eq}}_{\lambda(t),T}(\mathbf{x}, t) \quad , \quad t > 0. \qquad 24.$$

By the simple trick of reweighting each trajectory by $\mu_k(t)$, however, this inequality is transformed into an equality, namely (9)

$$g_t \equiv \langle \delta[\mathbf{x} - \mathbf{x}_k(t)] e^{-w_k(t)/k_B T} \rangle = \frac{1}{Z_{A,T}} e^{-H(\mathbf{x};\lambda(t))/k_B T}. \qquad 25.$$

Note that the right side is proportional to $p^{\rm eq}_{\lambda(t),T}$ and that we recover Equation 15 by setting $t = \tau$ and integrating over phase space.

To sketch a derivation of Equation 25 for our toy model (**Figure 1**), we begin by recalling that the ordinary density $f(\mathbf{x}, t)$ satisfies the Liouville equation, $\partial f/\partial t + \{f, H\} = 0$, using Poisson bracket notation (67) and assuming that the system is isolated from the reservoir. The left side of the Liouville equation is just the total time derivative of $f(\mathbf{x}(t), t)$ along a Hamiltonian trajectory. For the weighted density $g(\mathbf{x}, t)$, an additional term accounts for the time-dependent weight (7, 9):

$$\frac{\partial g}{\partial t} + \{g, H\} = -\frac{\dot{w}}{k_B T} g, \qquad 26.$$

where $\dot{w} = \dot{\lambda}\partial H/\partial\lambda$. It is now a matter of substitution to show that for the initial conditions $g_0 = p^{\rm eq}_{A,T}$, the right side of Equation 25 solves Equation 26. For derivations of Equation 25 (or equivalent results) in which the reservoir is modeled using stochastic and other non-Hamiltonian dynamics, see References 7, 9, 18, 26, 32, and 59.

Equation 25 reveals the following: Even as it is driven away from equilibrium, the swarm of trajectories retains information about the equilibrium state $p^{\rm eq}_{\lambda(t),T}$, and the key to unlocking this information is to attach a statistical, time-dependent weight $\exp[-w_k(t)/k_B T]$ to each realization. This reweighting procedure was described and illustrated by Jarzynski (7, 85), and obtained in terms of path averages by Crooks (18); however, the elegant formulation given by Equation 25 is due to Hummer & Szabo (9, 26), who recognized it as a consequence of the Feynman-Kac theorem of stochastic processes. This naturally brings to mind an analogy with the path-integral formulation of quantum mechanics, in which a wave function is constructed as a sum over paths, each contributing a phase $\exp(iS/\hbar)$. The reweighting procedure outlined above has a similar flavor, but with real weights $\exp[-w_k(t)/k_B T]$ rather than complex phases. In the quantum-mechanical case, the sum over paths produces a solution to the Schrödinger equation, whereas here we get the construction of an equilibrium distribution from nonequilibrium trajectories. Hummer & Szabo (9) have used Equation 25 to derive a method of constructing an equilibrium potential of mean force from nonequilibrium data. This method has been confirmed experimentally by Berkovich et al. (86).

4. MACROSCOPIC HYSTERESIS AND MICROSCOPIC SYMMETRY

The second law of thermodynamics is manifested not only by inequalities such as $W \geq \Delta F$, but also by the time asymmetry inherent to irreversible processes. Hysteresis loops neatly depict this asymmetry. As an example, imagine that we rapidly stretch an ordinary rubber band, then after a sufficient pause we contract it, returning to the initial state. For this process we get a classic hysteresis loop by plotting the tension $\mathcal{T}$ versus the length L of the rubber band (**Figure 2**). Hysteresis conveys the idea that the state of the rubber band follows one path during the stretching stage, but returns along a different path during contraction. The second law implies that the enclosed area is nonnegative, $\oint \mathcal{T}\, dL \geq 0$.

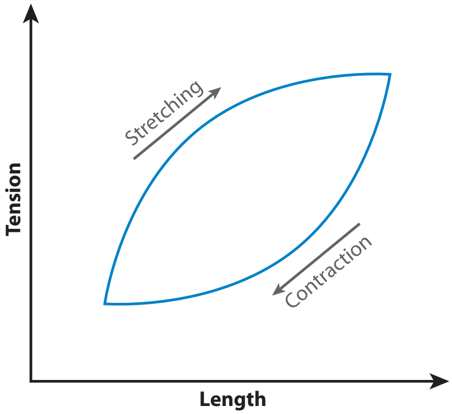

Figure 2

Schematic hysteresis loop for the irreversible stretching and contraction of a rubber band. During the stretching stage, the temperature and tension of the rubber band are higher than would have been the case if the process were performed reversibly, whereas during the contraction stage they are lower. As a result, $W > 0$ over the entire cycle. The hysteresis loop illustrates the idea that the system evolves through one sequence of states during the forward process, but follows a different path back during the reverse process. The statistical expression of this statement is given by Equation 35.

Similar considerations apply to the analogous stretching and contraction of single molecules (87), only now statistical fluctuations become important: The random jigglings of the molecule differ from one repetition of the process to the next. In the previous section we saw that when fluctuations are taken into account, the relationship between work and free energy can be expressed as an equality rather than the usual inequality. The central message of the present section has a similar ring: With an appropriate accounting of fluctuations, the two branches of an irreversible thermodynamic cycle (e.g., the stretching and contraction of the single molecule) are described by unexpected symmetry relations (Equations 30, 31) rather than exclusively by inherent asymmetry (Equations 28, 35).

To develop these results, it is useful to imagine two distinct processes, designated the forward and the reverse process (8). The forward process is the one defined in Section 2, in which the work parameter is varied from A to B using a protocol $\lambda_F(t)$ (the subscript F has been attached as a label). During the reverse process, λ is varied from B to A using the time-reversed protocol,

$$\lambda_R(t) = \lambda_F(\tau - t). \tag{27}$$

At the start of each process, the system is prepared in the appropriate equilibrium state, corresponding to $\lambda = A$ or B, at temperature T. If we perform the two processes in sequence (the forward followed by the reverse), allowing the system to equilibrate with the reservoir at the end of each process, then we have a thermodynamic cycle that exhibits hysteresis. The Clausius inequality applies separately to each stage:

$$-\langle W \rangle_R \leq \Delta F \leq \langle W \rangle_F, \tag{28}$$

where ΔF is defined as before (Equation 5) and the notation now specifies separate averages over the two processes. Of course, Equation 28 implies that the average work over the entire cycle is nonnegative:

$$\langle W \rangle_F + \langle W \rangle_R \geq 0. \tag{29}$$

This illustrates the Kelvin-Planck statement of the second law: No process is possible whose sole result is the absorption of heat from a reservoir and the conversion of all of this heat into work (88).

Statistically, the forward and reverse processes are described by work distributions $\rho_F(W)$ and $\rho_R(W)$. Whereas Equation 28 applies to the means of these distributions, Crooks (17) has shown that their fluctuations satisfy

$$\frac{\rho_F(+W)}{\rho_R(-W)} = e^{(W-\Delta F)/k_B T}. \qquad 30.$$

As with Equation 15 (which is an immediate consequence of Equation 30), this result remains valid even when the system is driven far from equilibrium and has been verified experimentally (64–66, 87, 89).

Crooks's fluctuation theorem (Equation 30) is a statement about distributions of work values, but at its heart is a stronger result about distributions of trajectories (8):

$$\frac{\mathcal{P}_F[\gamma_F]}{\mathcal{P}_R[\gamma_R]} = e^{(W_F-\Delta F)/k_B T}. \qquad 31.$$

Here, the notation $\gamma_F \equiv \{\mathbf{x}_F(t);0\leq t\leq\tau\}$ denotes a trajectory that might be observed during a realization of the forward process, and γ_R is its conjugate twin,

$$\mathbf{x}_R(t) = \mathbf{x}_F^*(\tau - t), \qquad 32.$$

where $\mathbf{x}^*$ is the microscopic state obtained by reversing all the momenta of $\mathbf{x}$, as is illustrated schematically in **Figure 3**. Simply put, the trajectory γ_R represents what we would see if we were to film the trajectory γ_F, and then run the movie backward. Equation 31 then states that the probability of observing a particular trajectory when performing the forward process ($\mathcal{P}_F[\gamma_F]$) relative to that of observing its conjugate twin during the reverse process ($\mathcal{P}_R[\gamma_R]$) is given by the right side of the equation, where $W_F \equiv W[\gamma_F]$ is the work performed in the forward case.

To derive Equation 31 for our toy model, let us assume as before that the reservoir is removed for $0 < t < \tau$. The ratio of probabilities to observe the Hamiltonian trajectories γ_F and γ_R is simply the ratio of probabilities to sample their respective initial conditions from equilibrium (80). Thus,

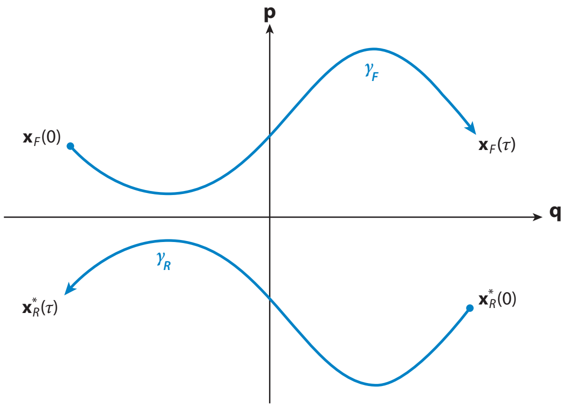

Figure 3

A conjugate pair of trajectories, γ_F and γ_R.

$$
\begin{aligned}
\frac{\mathcal{P}_F[\gamma_F]}{\mathcal{P}_R[\gamma_R]} &= \frac{Z_{B,T}}{Z_{A,T}} e^{[H(\mathbf{x}_R(0);B)-H(\mathbf{x}_F(0);A)]/k_B T} \\
&= \frac{Z_{B,T}}{Z_{A,T}} e^{[H(\mathbf{x}_F(\tau);B)-H(\mathbf{x}_F(0);A)]/k_B T} = e^{(W_F-\Delta F)/k_B T},
\end{aligned}
\qquad 33.
$$

using Equations 32 and 7 to replace $H(\mathbf{x}_R(0);B)$ by $H(\mathbf{x}_F(\tau);B)$. We get to the final result by observing that the quantity inside square brackets on the second line is the net change in H during the forward process, which (for a thermally isolated system) is the work performed on the system. As with the results of Section 3, numerous derivations of Equations 30 and 31 exist in the literature, corresponding to various models of the system and reservoir (8, 17, 18, 32, 51, 53, 57, 58, 60–62, 90).

To gain some appreciation for this result, recall that a system in equilibrium satisfies microscopic reversibility (91) [closely related to detailed balance (17)]: Any sequence of events is as likely to occur as the time-reversed sequence. Using notation similar to Equation 31, this condition can be written as

$$\mathcal{P}^{\mathrm{eq}}[\gamma] = \mathcal{P}^{\mathrm{eq}}[\gamma^*], \qquad 34.$$

where γ and γ^* are a conjugate pair of trajectories (of some finite duration) for a system in equilibrium. By contrast, as depicted by the two branches of a hysteresis loop, an essential feature of thermodynamic irreversibility is that the system does not simply retrace its steps when forced to return to its initial state. This idea is expressed statistically by the inequality

$$\mathcal{P}_F[\gamma_F] \neq \mathcal{P}_R[\gamma_R]; \qquad 35.$$

that is, the trajectories we are likely to observe during one process are not the conjugate twins of those we are likely to observe during the other process. Equation 31, which replaces this inequality with a stronger equality, can be viewed as an extension of the principle of microscopic reversibility, to systems that are driven away from equilibrium by the variation of external parameters.

5. RELATIVE ENTROPY AND DISSIPATED WORK

Information theory and thermodynamics enjoy a special relationship, evidenced most conspicuously by the formula,

$$I[p^{\mathrm{eq}}] = S/k_B, \qquad 36.$$

where $I[p] \equiv -\int p \ln p$ is the information entropy associated with a statistical distribution p. When p describes thermal equilibrium (Equation 10), its information entropy I coincides with the thermodynamic entropy, S/k_B (Equation 36). This familiar but remarkable result relates a measure of our ignorance about a system's microstate (I), to a physical quantity defined via calorimetry (S).

In recent years, another set of results have emerged that, similarly, draw a connection between information theory and thermodynamics, but these results apply to irreversible processes rather than equilibrium states. Here the relevant information-theoretic measure is the relative entropy (92, 93) between two distributions (Equation 37), and the physical quantity is dissipated work, $W - \Delta F$. This section describes these results in some detail, but the central idea can be stated succinctly as follows. The irreversibility of a process can be expressed as an inequality between a pair of probability distributions, either in trajectory space or in phase space (Equations 35, 40, 24). Using the relative entropy to quantify the difference between the two distributions, we find in each case that this information-theoretic measure relates directly to dissipated work (Equations 38, 41, 43).

For two normalized probability distributions p and q on the same space of variables, the relative entropy [or Kullback-Leibler divergence (92)]

$$D[p|q] \equiv \int p \ln\left(\frac{p}{q}\right) \geq 0 \qquad 37.$$

quantifies the extent to which one distribution differs from the other. $D = 0$ if and only if the distributions are identical, and $D \gg 1$ if there is little overlap between the two distributions.

Because relative entropy provides a measure of distinguishability, it is a handy tool for quantifying time-asymmetry. For example, recall that hysteresis can be expressed statistically by the inequality $\mathcal{P}_F[\gamma_F] \neq \mathcal{P}_R[\gamma_R]$ (Equation 35), where the trajectory-space distributions $\mathcal{P}_F$ and $\mathcal{P}_R$ represent the system's response during the forward and reverse processes. We can then use the relative entropy $D[\mathcal{P}_F|\mathcal{P}_R]$ to assign a value to the extent to which the system's evolution during one process differs from that during the other. From Equation 31, it follows that (80)

$$D[\mathcal{P}_F|\mathcal{P}_R] = \frac{W_F^{\text{diss}}}{k_B T}, \qquad 38.$$

where

$$W_F^{\text{diss}} \equiv \langle W \rangle_F - \Delta F \qquad 39.$$

is the average amount of work that is dissipated during the forward process. Similarly, $D[\mathcal{P}_R|\mathcal{P}_F] = W_R^{\text{diss}}/k_B T$.

Distributions in trajectory space are abstract and difficult to visualize. However, a result similar to Equation 38 can be placed within the more familiar setting of phase space. Let $f_F(\mathbf{x}, t)$ denote the time-dependent phase-space density describing the evolution of the system during the forward process (Equation 22), and define $f_R(\mathbf{x}, t)$ analogously for the reverse process. Then the densities $f_F(\mathbf{x}, t_1)$ and $f_R(\mathbf{x}, \tau - t_1)$ are snapshots of the statistical state of the system during the two processes, both taken at the moment the work parameter achieves the value $\lambda_1 \equiv \lambda_F(t_1) = \lambda_R(\tau - t_1)$. The inequality

$$f_F(\mathbf{x}, t_1) \neq f_R(\mathbf{x}^*, \tau - t_1) \qquad 40.$$

then expresses the idea that the statistical state of the system is different when the work parameter passes through the value λ_1 during the forward process, than when it returns through the same value during the reverse process. [The reversal of momenta in $\mathbf{x}^*$ is related to the conjugate pairing of trajectories (Equation 32).] Evaluating the relative entropy between these distributions, Kawai et al.(94) showed that

$$D[f_F|f_R^*] \leq \frac{W_F^{\text{diss}}}{k_B T}, \qquad 41.$$

where the arguments of D are the distributions appearing in Equation 40, for any choice of λ_1. This becomes an equality if the system is isolated from the thermal environment as the work parameter is varied during each process. As with Equation 38, we see that an information-theoretic measure quantifying time-asymmetry (the left side of Equation 41) is related to a physical measure of dissipation, $W_F^{\text{diss}}/k_B T$.

Equations 38 and 41 are closely related. The phase-space distribution $f_F = f_F(\mathbf{x}, t_1)$ is the projection of the trajectory-space distribution $\mathcal{P}_F[\gamma_F]$ onto a single time slice, $t = t_1$, and similarly for f_R^*. Because the relative entropy between two distributions decreases when they are projected onto a smaller set of variables (92, 94)—in this case, from trajectory space to phase space—we have

$$D[f_F|f_R^*] \leq D[\mathcal{P}_F|\mathcal{P}_R] = \frac{W_F^{\text{diss}}}{k_B T}. \tag{42.}$$

In the above discussion, relative entropy has been used to quantify the difference between the forward and reverse processes (hysteresis). It can equally well be used to measure how far a system lags behind equilibrium at a given instant in time, leading again to a link between relative entropy and dissipated work (Equation 43 below).

For the process introduced in Section 2, let $f_t \equiv f(\mathbf{x}, t)$ denote the statistical state of the system at time t, and let $p_t^{\text{eq}} \equiv p_{\lambda(t),T}^{\text{eq}}(\mathbf{x})$ be the equilibrium state corresponding to the current value of the work parameter. It is useful to imagine that f_t continually chases p_t^{eq}: As the work parameter is varied with time, the state of the system (f_t) tries to keep pace with the changing equilibrium distribution (p_t^{eq}), but is unable to do so. Vaikuntanathan & Jarzynski (95) have shown that

$$D[f_t|p_t^{\text{eq}}] \leq \frac{\langle w(t)\rangle - \Delta F(t)}{k_B T}, \tag{43.}$$

where $\Delta F(t) \equiv F_{\lambda(t),T} - F_{A,T}$. In other words, the average work dissipated up to time t, in units of $k_B T$, provides an upper bound on the degree to which the system lags behind equilibrium at that instant. This result can be obtained from either Equation 25 or Equation 41 (95). If we take $t = \tau^*$, allowing the system to relax to a final state of equilibrium (see Section 2.1), then the left side of Equation 43 vanishes and we recover the Clausius inequality.

Relative entropy is an asymmetric measure: In general $D[p|q] \neq D[q|p]$. Feng & Crooks (96) have discussed the use of two symmetric measures of distinguishability to quantify thermodynamic irreversibility. The first is the Jeffreys divergence, $D[p|q] + D[q|p]$. When applied to forward and reverse distributions in trajectory space, this gives the average work over the entire cycle (see Equation 38):

$$\text{Jeffreys}(\mathcal{P}_F;\mathcal{P}_R) = \frac{W_F^{\text{diss}} + W_R^{\text{diss}}}{k_B T} = \frac{\langle W\rangle_F + \langle W\rangle_R}{k_B T}. \tag{44.}$$

The second measure is the Jensen-Shannon divergence,

$$\text{JS}(p;q) = \frac{1}{2}(D[p|m] + D[q|m]), \tag{45.}$$

where $m = (p+q)/2$ is the mean of the two distributions. When evaluated with $p = \mathcal{P}_F$ and $q = \mathcal{P}_R$, this leads to a more complicated, nonlinear average of W_F^{diss} and W_R^{diss} (see equation 7 of Reference 96). Feng and Crooks nevertheless argue that the Jensen-Shannon divergence is the preferred measure of time asymmetry, as it has a particularly nice information-theoretic interpretation. I return to this point at the end of the following section.

6. GUESSING THE DIRECTION OF TIME'S ARROW

Sir Arthur Eddington introduced the term "arrow of time" to describe the evident directionality associated with the flow of events (97). While time's arrow is familiar from daily experience—everyone recognizes that a movie run backward looks peculiar!—Eddington (among others) argued that it is rooted in the second law of thermodynamics. For a macroscopic system undergoing an irreversible process of the sort described in Section 2.1, the relationship between the second law and the arrow of time is almost tautological: $W > \Delta F$ when events proceed in the correct order, and $W < \Delta F$ when the movie is run backward, so to speak. For a microscopic system, fluctuations blur this picture, because we can occasionally observe violations of the Clausius inequality (Equation 5). Thus, the sign of $W - \Delta F$, although correlated with the direction of time's arrow, does not fully determine it. These general observations can be made precise; that is, the ability to determine the direction of time's arrow can be quantified.

To discuss this point, it is convenient to consider a hypothetical guessing game (80). Imagine that I show you a movie in which you observe a system undergoing a thermodynamic process as λ is varied from A to B. Your task is to guess whether this movie depicts the events in the order in which they actually occurred, or whether I have filmed the reverse process (varying λ from B to A) and am now (deviously) showing you the movie of that process, run backward. In the spirit of a Gedanken experiment, assume that the movie gives you full microscopic information about the system—you can track the motion of every atom—and that you know the Hamiltonian function $H(\mathbf{x};\lambda)$ and the value $\Delta F = F_{B,T} - F_{A,T}$. Assume moreover that in choosing which process to perform, I flipped a fair coin: Heads = F, tails = R.

We can formalize this task as an exercise in statistical inference (96). Let $L(F|\gamma)$ denote the likelihood that the movie is being shown in the correct direction (the forward process was performed), given the microscopic trajectory γ that you observe in the movie. Similarly, let $L(R|\gamma)$ denote the likelihood that the reverse process was in fact performed and the movie is now being run backward. The likelihoods associated with the two hypotheses (F, R) sum to unity:

$$L(F\,|\,\gamma) + L(R\,|\,\gamma) = 1. \qquad 46.$$

Now let W denote the work performed on the system, for the trajectory depicted in the movie. If $W > \Delta F$, then the first hypothesis (F) is in agreement with the Clausius inequality and the second hypothesis (R) is not; if $W < \Delta F$, it is the other way around. Therefore for a macroscopic system the task is easy. Formally,

$$L(F\,|\,\gamma) = \theta(W - \Delta F), \qquad 47.$$

where $\theta(\cdot)$ is the unit step function.

For a microscopic system we must allow for the possibility that Equation 5 might be violated now and again. Bayes' Theorem then provides the right tool for analyzing the likelihood:

$$L(F\,|\,\gamma) = \frac{P(\gamma\,|\,F)P(F)}{P(\gamma)}. \qquad 48.$$

Here $P(F)$ is the prior probability that I carried out the forward process, which is simply 1/2 given that I flipped a fair coin to make my choice, and $P(\gamma|F)$ is the probability to generate the trajectory γ when performing the forward process; in the notation of Section 4, this is $P_F[\gamma]$. Finally, $P(\gamma)$ is (effectively) a normalization constant (see Equation 46). Writing the analogous formula for $L(R\,|\,\gamma)$, then combining these with the normalization condition Equation 46 and invoking Equation 31, we get (31, 98, 99)

$$L(F\,|\,\gamma) = \frac{1}{1 + e^{-(W-\Delta F)/k_B T}}. \qquad 49.$$

This result quantifies your ability to determine the arrow of time from the trajectory depicted in the movie. The expression on the right is a smoothed step function. If the value of W surpasses ΔF by many units of $k_B T$, then $L(F\,|\,\gamma) \approx 1$, and you can say with high confidence that the movie is being shown in the correct direction; in the opposite case, you can be equally confident that the movie is being run backward. The transition from one regime to the other—where time's arrow gets blurred, in essence—occurs over an interval of work values whose width is a few k_BT. What is remarkable is that this transition does not depend on the details of either the system or the protocol $\lambda(t)$. Equation 49 was derived by Shirts et al. (98) and later by Maragakis et al. (99) in the context of free-energy estimation, where the interpretation is somewhat different from the one discussed here.

Returning to the point mentioned at the end of the previous section, the Jensen-Shannon divergence has the following interpretation in the context of our hypothetical guessing game: $\mathrm{JS}(\mathcal{P}_F;\mathcal{P}_R)$ is the average gain in information (regarding which process was performed) obtained from observing the movie (96). When the processes are highly irreversible, this approaches its maximum value, $\mathrm{JS} \approx \ln 2$, corresponding to one bit of information. This makes sense: By watching the movie, you are able to infer with confidence whether the coin I flipped turned up heads (F) or tails (R). Feng & Crooks (96) have argued that this interpretation has surprisingly universal implications for biomolecular and other nanoscale machines. Namely, approximately $4-8\ k_BT$ of free energy must be dissipated per operating cycle to guarantee that the machine runs reliably in a designated direction (as opposed to taking backward and forward steps with equal probability, as would necessarily occur under equilibrium conditions).

Finally, time's arrow has unexpected relevance for the convergence of the exponential average in Equation 15. Namely, the realizations that dominate that average are precisely those "during which the system appears as though it is evolving backward in time" (80, p. 046105–8). A detailed analysis of this assertion involves both hysteresis and relative entropy, thus nicely tying together the four strands of discussion represented by Sections 3–6 (80).

7. ENTROPY PRODUCTION AND RELATED QUANTITIES

This review has focused on far-from-equilibrium predictions for work and free energy (Equations 15, 25, 30, 31) and how these inform our understanding of the second law of thermodynamics. Because the second law is often taken to be synonymous with the increase of entropy, we might well wonder how these predictions relate to statements about entropy.

As a point of departure, for macroscopic systems we can use the first law ($\Delta U = W + Q$) and the definition of free energy ($F = U - ST$) to write

$$\frac{W - \Delta F}{T} = \Delta S - \frac{Q}{T} = \Delta S_{\mathrm{tot}}, \qquad 50.$$

where ΔS_{tot} is the combined entropy change of the system and reservoir. If we extend this result to microscopic systems, accepting $(W - \Delta F)/T$ as the definition of ΔS_{tot} for a single realization of a thermodynamic process, then the results discussed in Sections 3–6 can formally be rewritten as statements about the fluctuations of entropy production.

When multiple thermal reservoirs are involved, one can generalize Equation 6 in an obvious way by including terms for all the reservoirs, $\mathcal{H} = H + \sum_k (H_{\mathrm{env}}^k + H_{\mathrm{int}}^k)$. Working entirely within a Hamiltonian framework, the results of Section 3, notably Equations 15, 19, and 20, can then be written in terms of entropy production, and generalized further by dropping the assumption that the system of interest begins in equilibrium (100). Esposito et al. (101) have recently shown that in this situation the value of $\langle \Delta S_{tot} \rangle$ is equal to the statistical correlation that develops between the system and the reservoirs, as measured in terms of relative entropy.

Although the Hamiltonian framework has many advantages, it is often inconvenient for studying irreversible processes, particularly those involving nonequilibrium steady states. Among the many tools that have been introduced as alternatives to the Hamiltonian approach, Gaussian thermostats—the term refers to a method of modeling nonequilibrium systems on the basis of Gauss's principle of least constraint (102)—have played a prominent role in recent developments in nonequilibrium thermodynamics. The term fluctuation theorem was originally applied to a property of entropy production, observed in numerical investigations of a sheared fluid simulated using a Gaussian thermostat (10–13). Because fluctuation theorems for entropy production have been reviewed elsewhere (21, 22, 24, 29, 30, 32, 33, 35, 36), I limit myself to a brief summary of how these results connect to those of Sections 3–6.

The transient fluctuation theorem of Evans & Searles (11) applies to a system that evolves from an initial state of equilibrium to a nonequilibrium steady state. Letting $p_\tau(\Delta s)$ denote the probability distribution of the entropy produced up to a time $\tau > 0$, it states that

$$\frac{p_\tau(+\Delta s)}{p_\tau(-\Delta s)} = e^{\Delta s/k_B}. \qquad 51.$$

This is clearly similar to Equation 30, although it pertains to a single thermodynamic process, rather than a pair of processes (F and R). Equation 51 implies an integrated fluctuation theorem,

$$\langle e^{-\Delta s/k_B} \rangle = 1, \qquad 52.$$

that is analogous to Equation 15, and from this we in turn get analogs of Equations 19 and 20:

$$\langle \Delta s \rangle \geq 0 \qquad , \qquad P[\,\Delta s < -\xi] \leq e^{-\xi/k_B}. \qquad 53.$$

Now consider a system that is in a nonequilibrium steady state from the distant past to the distant future, such as a fluid under constant shear (10), and let $\sigma \equiv \Delta s\,/\,\tau$ denote the entropy production rate, time averaged over a single, randomly sampled interval of duration τ. The steady-state fluctuation theorem of Gallavotti & Cohen (12, 13) asserts that the probability distribution $p_\tau(\sigma)$ satisfies

$$\lim_{\tau\to\infty} \frac{1}{\tau} \ln \frac{p_\tau(+\sigma)}{p_\tau(-\sigma)} = \frac{\sigma}{k_B}. \qquad 54.$$

The integrated form of this result is (21)

$$\lim_{\tau\to\infty} \frac{1}{\tau} \ln \langle e^{-\tau\sigma/k_B} \rangle_\tau = 0, \qquad 55.$$

where the brackets denote an average over intervals of duration τ, in the steady state. Formal manipulations then give us

$$\langle \sigma \rangle_\tau \geq 0 \qquad , \qquad \lim_{\tau\to\infty} \frac{1}{\tau} \ln P_\tau[\sigma < -\epsilon] \leq -\epsilon, \qquad 56.$$

where $P_\tau[\sigma < -\epsilon]$ is the probability to observe a time-averaged entropy production rate less than $-\epsilon$, during an interval of duration τ. The resemblance between Equations 54–56, and Equations 30, 15, 19, 20, respectively, should be obvious; although, viewed as mathematical statements they are different.

The microscopic definition of entropy production in Equations 51–56 depends on the equations of motion used to model the evolution of the system. In the early papers on fluctuation theorems, entropy production was identified with phase-space contraction along a deterministic but non-Hamiltonian trajectory (10–13). These results were then extended to encompass stochastic dynamics, first by Kurchan (14) for diffusion, then by Lebowitz & Spohn (15) for Markov processes in general. Maes (16) subsequently developed a unified framework based on probability distributions of space-time histories; that is, trajectories. In all these cases, the validity of the fluctuation theorem ultimately traces back to the idea that trajectories come in pairs related by time reversal, and that the production of entropy is intimately linked with the probability of observing one trajectory relative to the other, in a manner analogous with Equation 31.

It is intriguing to note that multiple fluctuation theorems can be valid simultaneously, in a given physical context. This idea was mentioned in passing by Hatano & Sasa (19) in the context of transitions between nonequilibrium states, and it has been explored in greater detail by a number of authors since then (32, 53, 103, 104).

Finally, for nonequilibrium steady states there exist connections between entropy production and relative entropy, analogous to those discussed in Section 5. If relative entropy is used to quantify the difference between distributions of steady-state trajectories and their time-reversed counterparts, then the value of this difference can be equated with the thermodynamic production of entropy. This issue has been studied by Maes (16), Maes & Netočný (105), and Gaspard (106).

8. CONCLUSIONS AND OUTLOOK

The central message of this review is that far-from-equilibrium fluctuations are more interesting than one might have guessed. They tell us something new about how the second law of thermodynamics operates at the nanoscale. In particular, they allow us to rewrite thermodynamic inequalities as equalities, revealing that nonequilibrium fluctuations encode equilibrium information.

The last observation has led to practical applications in two broad settings. The first is the development of numerical methods for estimating free energy differences, an active enterprise in computational chemistry and physics (23). Whereas traditional strategies involve equilibrium sampling, Equations 15, 25, and 30 suggest the use of nonequilibrium simulations to construct estimates of ΔF. This is an ongoing area of research (107, 108–110), but nonequilibrium methods have gradually gained acceptance into the free energy estimation toolkit and are being applied to a variety of molecular systems; see Reference 111 for a recent example.

Nonequilibrium work relations have also been applied to the analysis of single-molecule experiments, as originally proposed by Hummer & Szabo (9) and pioneered in the laboratory by Liphardt et al. (63). Individual molecules are driven away from equilibrium using optical tweezers or atomic-force microscopy, and from measurements of the work performed on these molecules, one can reconstruct equilibrium free energies (27, 112). For recent applications of this approach, see References 113–116.

It remains to be seen whether the understanding of far-from-equilibrium fluctuations that has been gained in recent years will lead to the formulation of a unified thermodynamics of small systems; that is, a theoretical framework based on a few propositions, comparable to classical thermodynamics. Some progress, in any case, has been made in this direction.

For stochastic dynamics, Seifert and colleagues (32, 53, 117–119)—building on earlier work by Sekimoto (37, 120)—have developed a formalism in which microscopic analogs of all relevant macroscopic quantities are precisely defined. Many of the results discussed in this review follow naturally within this framework, and this has helped considerably to clarify the relations among these results (32). Evans & Searles (22) have championed the view that fluctuation theorems are elegantly unified in terms of a dissipation function, Ω, whose properties are (by construction) independent of the dynamics used to model the system of interest. More recently, Ge & Qian (121) have proposed a unifying framework for stochastic processes, in which both the information entropy $-\int p \ln p$ and the relative entropy $\int p \ln (p/q)$ play key roles.

References 32 and 121 make a connection to earlier efforts by Oono & Paniconi (122) to develop a steady-state thermodynamics organized around nonequilibrium steady states. Although the original goal was a phenomenological theory, the derivation by Hatano and Sasa of fluctuation theorems for transitions between steady states (19, 123) has encouraged a microscopic approach to this problem (124, 125). In the absence of a universal statistical description of steady states analogous to the Boltzmann-Gibbs formula (Equation 10), this has proven to be highly challenging.

This review has focused exclusively on classical fluctuation theorems and work relations, but the quantum case is also of considerable interest. Quantum versions of these results have been studied for some time (126–129), and the past two to three years have seen a surge of interest in this topic (130–139, 140, 141, 142). Quantum mechanics of course involves profound issues of interpretation. It can be hoped that in the process of trying to specify the quantum-mechanical definition of work (134), dealing with open quantum systems (133, 139, 140, 141, 142), analyzing exactly solvable models (132, 135, 137, 138), or proposing and ultimately performing experiments to test far-from-equilibrium predictions (136), important insights will be gained. Applications of nonequilibrium work relations to the detection of quantum entanglement (143) and to combinatorial optimization using quantum annealing (144) have very recently been proposed.

Finally, there has been a rekindled interest in recent years in the thermodynamics of information-processing systems and closely related topics such as the apparent paradox of Maxwell's demon (145). Making use of the relations described in this review, a number of authors have investigated how nonequilibrium fluctuations and the second law are affected in situations involving information processing, such as occur in the context of memory erasure and feedback control (146–150).

DISCLOSURE STATEMENT

The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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Errata

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